PNL-5000 PT1
UC-48

Pacific Northwest Laboratory Annual Report for 1983 to the DOE Office of Energy Research

Part 1 Biomedical Sciences February 1984

Prepared for the U.S. Department of Energy
under Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
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J. F. Park and Staff Members
of Pacific Northwest Laboratory

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Pacific Northwest Laboratory
Richland, Washington 99352

PREFACE

This 1983 annual report from Pacific Northwest Laboratory (PNL) to the Department of Energy (DOE) describes research in environment, health, and safety conducted during fiscal year 1983. The report again consists of five parts, each in a separate volume.

The five parts of the report are oriented to particular segments of our program. Parts 1 to 4 report on research performed for the DOE Office of Health and Environmental Research in the Office of Energy Research. Part 5 reports progress on all research performed for the Assistant Secretary for Environmental Protection, Safety and Emergency Preparedness. In some instances, the volumes report on research funded by other DOE components or by other governmental entities under interagency agreements. Each part consists of project reports authored by scientists from several PNL research departments, reflecting the multidisciplinary nature of the research effort.

The parts of the 1983 Annual Report are:

Part 1: Biomedical Sciences Program Manager - J. F. Park	D. L. Felton, Report Coordinator and Editor
Part 2: Ecological Sciences Program Manager - B. E. Vaughan	B. E. Vaughan, Report Coordinator C. M. Novich, Editor
Part 3: Atmospheric Sciences Program Manager - C. E. Elderkin	N. S. Laulainen, Report Coordinator J. L. Downs-Berg, Editor
Part 4: Physical Sciences Program Manager - J. M. Nielsen	R. M. Garcia, Report Coordinator J. E. Danko, Editor
Part 5: Overview and Assessment Program Managers - S. Marks W. A. Glass	R. W. Baalman, Report Coordinator and Editor

Activities of the scientists whose work is described in this annual report are broader in scope than the articles indicate. PNL staff have responded to numerous requests from DOE during the year for planning, for service on various task groups, and for special assistance.

Credit for this annual report goes to many scientists who performed the research and wrote the individual project reports, to the program managers who directed the research and coordinated the technical progress reports, to the editors who edited the individual project reports and assembled the five parts, and to Ray Baalman editor in chief, who directed the total effort.

W. J. Bair, Manager
S. Marks, Associate Manager
Environment, Health and Safety Research Program

Previous reports in this series:

Annual Report for

1951	W-25021, HW-25709
1952	HW-27814, HW-28636
1953	HW-30437, HW-30464
1954	HW-30306, HW-33128, HW-35905, HW-35917
1955	HW-39558, HW-41315, HW-41500
1956	HW-47500
1957	HW-53500
1958	HW-59500
1959	HW-63824, HW-65500
1960	HW-69500, HW-70050
1961	HW-72500, HW-73337
1962	HW-76000, HW-77609
1963	HW-80500, HW-81746
1964	BNWL-122
1965	BNWL-280; BNWL-235, Vol. 1-4; BNWL-361
1966	BNWL-480, Vol. 1; BNWL-481, Vol. 2, Pt. 1-4
1967	BNWL-714, Vol. 1; BNWL-715, Vol. 2, Pt. 1-4
1968	BNWL-1050, Vol. 1, Pt. 1-2; BNWL-1051, Vol. 2, Pt. 1-3
1969	BNWL-1306, Vol. 1, Pt. 1-2; BNWL-1307, Vol. 2, Pt. 1-3
1970	BNWL-1550, Vol. 1, Pt. 1-2; BNWL-1551, Vol. 2, Pt. 1-2
1971	BNWL-1650, Vol. 1, Pt. 1-2; BNWL-1651, Vol. 2, Pt. 1-2
1972	BNWL-1750, Vol. 1, Pt. 1-2; BNWL-1751, Vol. 2, Pt. 1-2
1973	BNWL-1850, Pt. 1-4
1974	BNWL-1950, Pt. 1-4
1975	BNWL-2000, Pt. 1-4
1976	BNWL-2100, Pt. 1-5
1977	PNL-2500, Pt. 1-5
1978	PNL-2850, Pt. 1-5
1979	PNL-3300, Pt. 1-5
1980	PNL-3700, Pt. 1-5
1981	PNL-4100, Pt. 1-5
1982	PNL-4600, Pt. 1-5

FOREWORD

This report summarizes progress on OHER biomedical and health effects research conducted at PNL in FY 1983 to develop the information required for a comprehensive understanding of the interaction of energy-related pollutants with living organisms. Our continuing emphasis on the evaluation of the risk to man from existing and/or developing energy-related technologies supports the DOE goal of increasing and diversifying national energy resources and decreasing risks to human health.

The report is arranged to reflect the PNL program relative to OHER programmatic needs and budget categories. Thus, the first section is devoted to an evaluation of possible health effects among nuclear workers. The next three sections, which contain reports of health effects research in biological systems, are grouped according to the major endpoint being studied: carcinogenesis, mutagenesis, and systems damage. Since some projects have multiple objectives, a section may contain data concerning other endpoints as well.

The section on carcinogenesis presents results from laboratory animal dose-effect relationship studies from both nuclear and synfuels materials. These data, along with metabolism and modeling studies, provide a basis for predicting human risks in the absence of relevant human exposure. This year we include a report on our 22nd Hanford Life Sciences Symposium, which dealt with this problem of extrapolating the results of animal studies to man. Of particular importance in carcinogenesis has been the demonstration that the carcinogenic potencies of complex organic synfuel mixtures may be much lower (or, occasionally, higher) than the sum of the potencies of the individual components.

The mutagenesis section is primarily concerned with the results of microbial mutagenesis studies with synfuel materials. These studies provide valuable information on the carcinogenic potential of these complex organic mixtures. With results from studies reported in the carcinogenesis section, they are also being used to establish an adequate data base for determining the correlation between mutagenic and carcinogenic processes.

A variety of studies relating to noncarcinogenic and nonmutagenic endpoints are summarized in the section entitled "Systems Damage," including prenatal (teratology) and neonatal studies with both synfuel materials and radionuclides. Pharmacokinetic studies to determine the absorption, metabolism, and distribution of pollutants are also reported here. The results of these studies are being used to establish doses to critical tissues and organs involved in growth and development. Pathogenesis of effects produced in target organs is also examined.

The biomedical and health effects research at PNL is an interdisciplinary effort requiring scientific contributions from many research departments at PNL. The personnel in the Biology and Chemistry Department are the principal contributors to this report. Requests for reprints from the list of publications for 1983 will be honored while supplies last.

CONTENTS

Human Health Effects From Energy Generations

• Statistical Health-Effects Study

Principal Investigators: E. S. Gilbert and L. E. Sever

Other Investigators: J. A. Buchanan, S. Marks, and H.D. Tolley

The principal objective of this program is to analyze the mortality of Hanford workers and to determine the effects of radiation exposure in this population. A secondary purpose is to improve methodology for assessing health effects of chronic, low-level exposure to harmful agents or substances, particularly in an occupational setting. In the past year, results of updated mortality analyses have been published; documentation of the computer program used for these analyses has been completed; and an article encouraging the type of methodology used by the program is near completion. Research methods to better characterize uncertainties in the analysis and limitations in the use of the Hanford mortality data have been initiated. In addition, identification of cases for the birth-defects case-control study has been completed.

The primary objective of this program is to analyze the mortality of Hanford workers and, particularly, to assess the effect of radiation exposure in this population. Mortality data have been updated to include deaths up to January 1, 1979, and results of analysis of the updated file have been published in Radiation Research. The most interesting result in our latest update is the lack of statistical significance in the trend of mortality from cancer of the pancreas with increasing radiation dose; multiple myeloma remains the only cancer-type of interest that shows a significant trend.

Because the methods used to analyze the Hanford data should be applicable to other populations exposed to radiation and other substances, the computer program used for this project has recently been generalized and refined to permit easy use by other investigators. This program, MOX (Mortality and Occupation Exposure Analysis), differs from other software tools available for analyzing occupational mortality data in that comparisons are internal, and the statistical tests employed take full advantage of whatever quantitative exposure data are available. Documentation of MOX has been completed, and a detailed User's Manual has been prepared. The program will soon be made available to other investigators.

The standard method of analysis for most occupationally exposed populations is to compare death rates of the exposed populations with those of an external control by calculating standardized mortality ratios (SMRs). This method is an important first step in analysis and may be the only option for populations with limited exposure data. However, this standard method is limited in a number of ways, and in many populations the type of internal comparisons that have been conducted on the Hanford data should enhance the analysis. One major goal for 1983 has been to encourage the use of this method of analysis by writing an article illustrating the limitations of the SMR approach and describing the potential of internal comparisons as well as the availability of the software (MOX) to carry them out. This article is near completion and will soon be submitted for publication.

Efforts have been initiated to better delineate both the potential and the limitations of the Hanford data for learning about radiation effects. This effort has included preliminary calculation of power for detecting radiation-induced leukemia and for detecting radiation-induced cancer of all other types combined, both at the present time and after various additional follow-up times. These calculations, which are based on exposure received through 1978, indicate that an additional 10 or 15 yr of follow-up will increase the potential of this study, but that not a great deal is gained by extending follow-up for a longer period. Calculations of this type are needed to make decisions regarding the length of time the population should be followed and whether or not we should continue to add new workers to the study population. In addition to power calculations, methods of calculating confidence limits for effects are being explored. Even though this data set cannot be used to obtain precise estimates of effects, it may be possible to state that the data are inconsistent with certain effects of considerable magnitude.

During FY 1983, we completed identification of cases of birth defects for a case-control study. Cases born in the three Tri-Cities hospitals during the period 1956-1980 were identified through hospital records and birth, death and fetal death certificates. Using hospital delivery

room records, controls have been selected. Currently, data on controls are being collected from hospital records. For all cases and controls, information on parental employment at Hanford is being obtained from records at the Hanford Environmental Health Foundation (HEHF). Occupational exposure of parents of cases and controls to radiation and to other hazardous substances will be determined from records at HEHF. Proposed analyses will compare parents of cases and controls in terms of history of employment at Hanford, occupational radiation exposure prior to conception or during gestation, and exposure to other hazardous substances.

Carcinogenesis

• Synfuels Biostudies

Principal Investigator: D. D. Mahlum

Other Investigators: M. E. Frazier, R. H. Lovely, R. A. Pelroy, H. A. Ragan, and D. L. Springer

Technical Assistance: J. A. Cushing, R. B. Lucke, L. W. McGee, and D. L. Stewart

Additional coal-derived liquids from several processes have been evaluated using the Chinese hamster ovary (CHO), Syrian hamster embryo (SHE), and initiation-promotion (I/P) systems. The data indicate that there may be substantial differences in biological activity among the processes evaluated. The results also indicate that liquids boiling above 800°F from all processes are more active than those boiling at <800°F; liquids boiling below 700°F have minimal activity. The neutral polyaromatic hydrocarbon fraction from the SRC-II 750-800° distillate is the most active initiator of skin tumorigenesis, a finding similar to that obtained with chemical fractions prepared with SRC-II 800-850 and >850°F distillates.

Inhalation studies in which rats and mice were exposed to aerosols of SRC-II heavy distillate for 1, 4 or 12 weeks are continuing. These studies are showing changes in survival, hematology, and tumor incidence in animals exposed to the highest aerosol concentration for 4 or 12 weeks.

Neurotoxicity studies showed that oral administration of SRC-1 wash solvent induced taste-aversion learning at doses between 20 and 40 mg/kg body weight. Larger doses of wash solvent facilitated shock-avoidance performance while inhibiting the learning and memory of an adversive event.

Mammalian-Cell Assays

Mammalian-cell assays measuring mutation (CHO/HGPRT) and transformation (Syrian hamster ovary [SHE]) have been used to evaluate crude synfuel and petroleum products (Figure 1). Results from both mammalian-cell assays indicate that products from SRC-I, SRC-II, and oil shale contain considerable genetic activity. Materials from both the H-coal and the finer feed from two-stage coal liquefaction processes contain intermediate levels of genetic activity. The genotoxicity level of the two-stage liquefaction product approaches that found with Wilmington crude petroleum.

Analyses of boiling-point cuts from three different coal-liquefaction processes show a pattern consistent with results from microbial mutation assays and animal skin-painting studies. The mutagenic and cell-transforming potential of the tested synfuels decreases as the boiling point of the material decreases (Figure 2). The activity of low-boiling (<700°F) distillates is comparable to that of naturally derived crude petroleum.

Based on examination of mammalian-cell-assay data from fractionated synfuels, the mutagenic and transforming activities do not appear to be associated with any single chemical class (Figures 3A and 3B). Instead, almost all fractions are genetically active. However, the polycyclic aromatic hydrocarbon (PAH)-containing fraction (Fraction 2) is consistently the most active. Fractionation of synfuels also allows an opportunity to compare the activities of the various chemical classes to the activities of the crudes. The results indicate the possibility of antagonism between chemicals which may inhibit expression of their full mutagenic potential. These antagonistic effects appear to increase as boiling point decreases.

Initiation/Promotion (I/P) Studies

As shown in previous Annual Reports (1981 and 1982), skin-tumor-initiating activity increased with increased boiling-point ranges for both SRC-I and -II coal liquids. Chemical-class-fractionation studies with liquids boiling above 800°F showed that the initiating activity was confined to the neutral PAH and nitrogen-containing polycyclic aromatic compound (NPAC) fractions. Of the two, the highest activity was associated with the PAH fraction. These studies also suggested that total initiating activity increased as materials were further fractionated. A number of experiments have therefore been performed to extend previously reported studies to include boiling-point cuts from the EDS process to determine if activity also increases with boiling point for

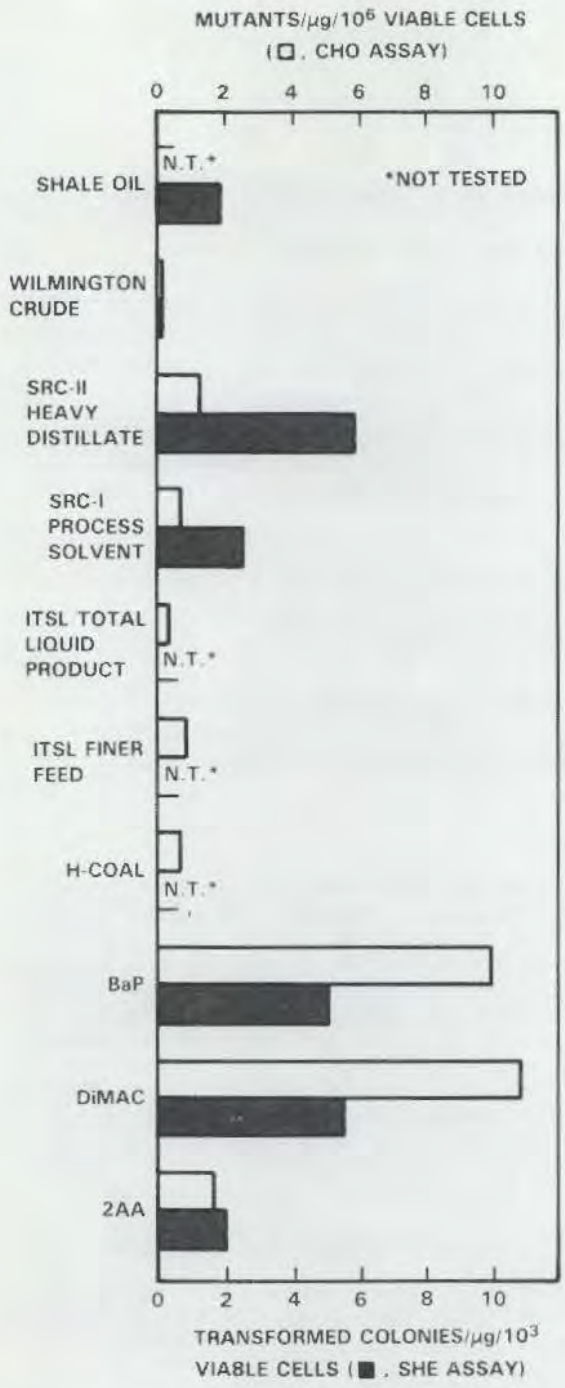

FIGURE 1. Mutagenic and Transforming Potential of Crude Petroleums, Synfuels and Known Carcinogens. ITSL = integrated, two-stage liquefaction; BaP = benzo[a]pyrene; DiMAC = dimethyl acridine; 2AA = aminoanthracene.

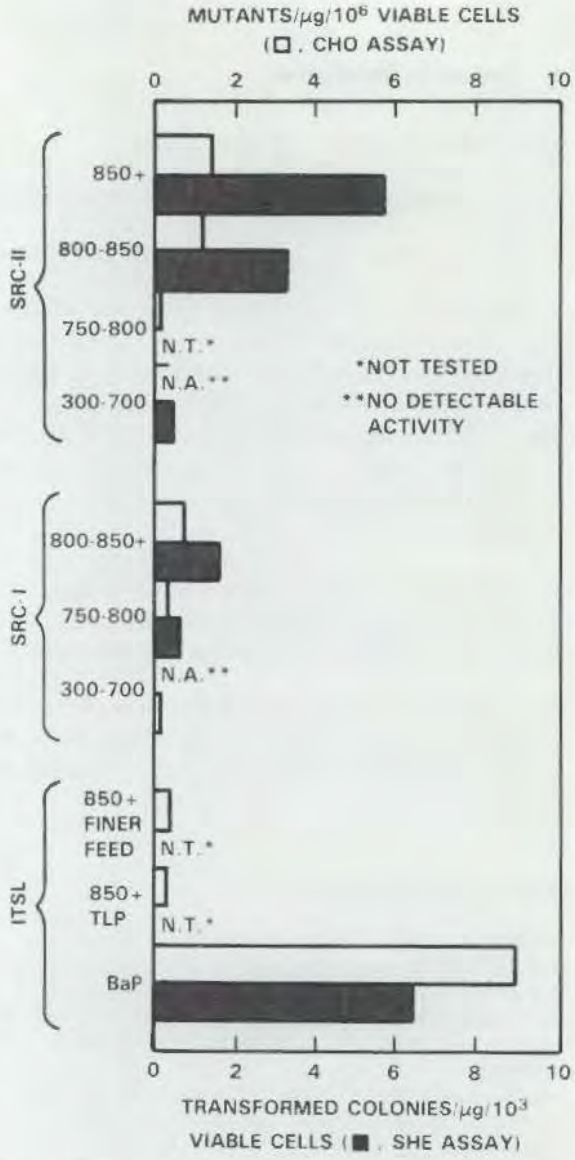

FIGURE 2. Effect of Process Temperature on Mutagenic and Transforming Activity of Synfuels. ITSL = integrated, two-stage liquefaction; TLP = total liquid product; BaP = benzo[a]pyrene.

these materials. We also examined chemical-class fractions from the SRC-II 750-800°F material to determine if the skin-tumor-initiation activity is still dominated by the PAH as we move downward in boiling range. We also further fractionated the PAH fraction from the >850° SRC-II distillate, using high-performance liquid chromatography (HPLC), in an attempt to isolate the components responsible for initiating activity.

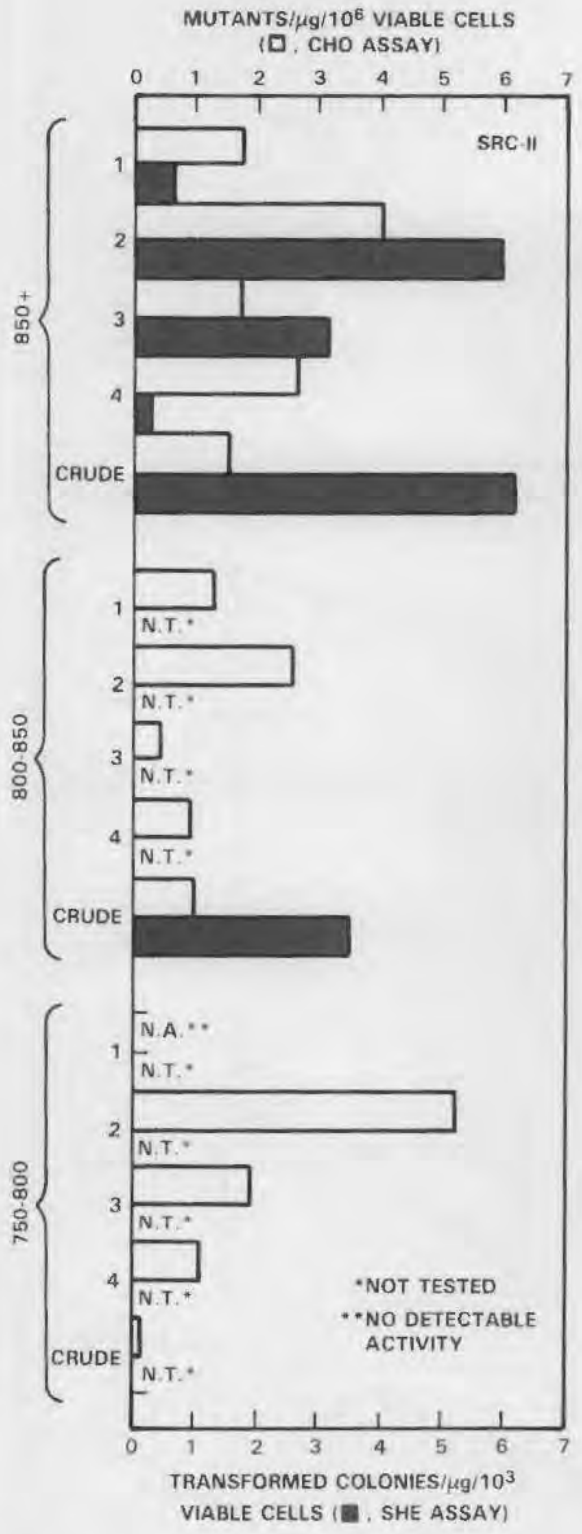

FIGURE 3a. Mutagenic and Transforming Activity of Alumina Fractions from Boiling-Point Cuts of SRC-II Materials. Fractions are: 1) aliphatic, 2) neutral polycyclic aromatic hydrocarbon (PAH), 3) nitrogen-containing polycyclic aromatic compounds, and 4) hydroxy-PAH.

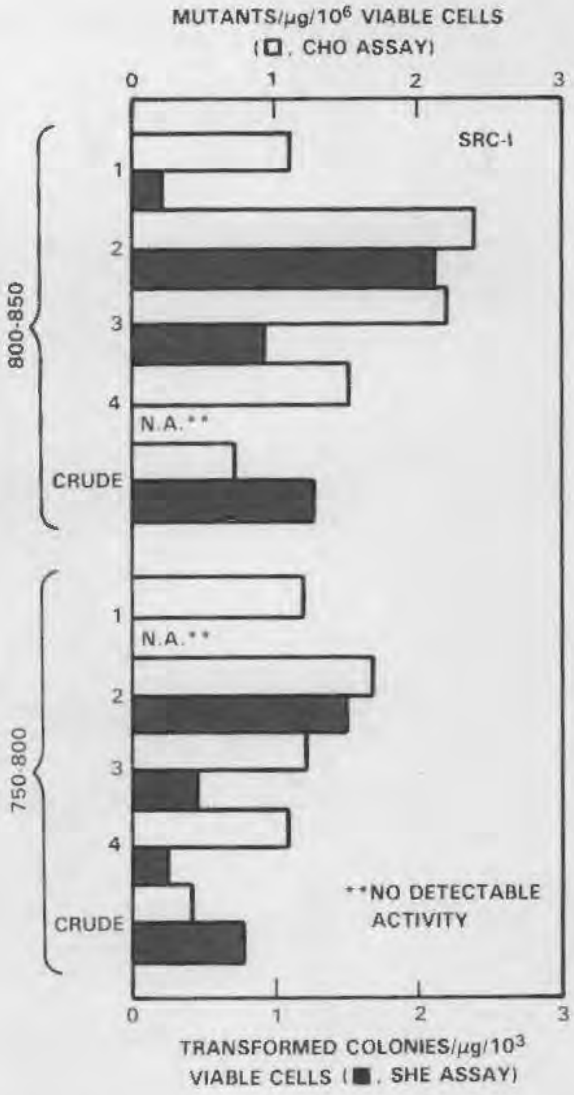

FIGURE 3b. Mutagenic and Transforming Activity of Alumina Fractions from Boiling-Point Cuts of SRC-I Materials.

The data in Figure 4 illustrate that the initiating activity of the >800°F EDS material was approximately three times as high as that of the 750-800° distillate. These results are consistent with the data obtained with SRC-I and -II materials. Class fractions prepared by alumina chromatography from the SRC-II 750-800°F distillate were tested for their initiating activity. The neutral PAH fraction was about twice as active as the NPAC fraction (Figure 5), results which were similar to those obtained with the PAH and NPAC fractions from the SRC-II 800-850° and >850°F distillates. Unlike the results obtained with those materials, the hydroxy PAH fraction showed substantial activity.

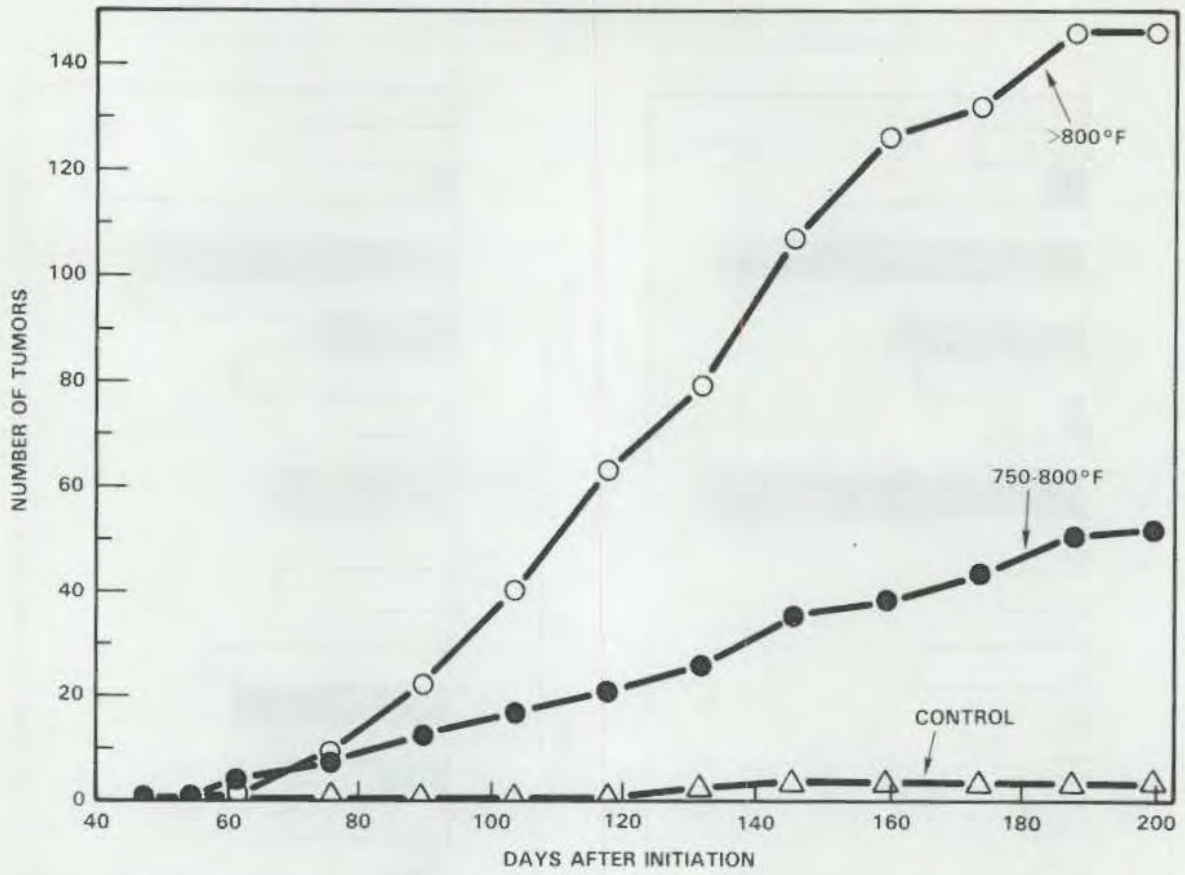

FIGURE 4. Skin-Tumor-Initiating Activity of 750-800° and >800°F EDS Distillates.

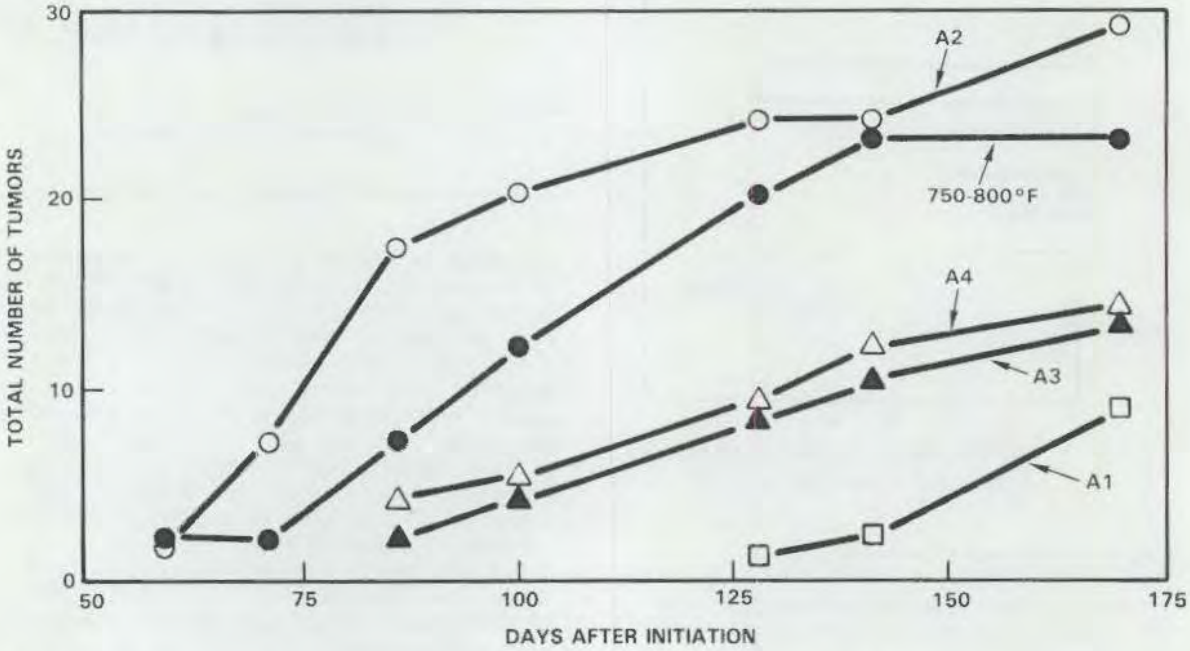

FIGURE 5. Skin-Tumor-Initiating Activity of the SRC-II 700-750°F Distillate and its Chemical Fractions.

In another experiment, the neutral PAH fraction from SRC-II >850°F material was further fractionated using reverse-phase HPLC. The eluents were pooled to form four fractions. These fractions were then tested for initiating activity by applying them to the skin of female CD-1 mice in the same proportion as they were found in the PAH fraction from which they were derived. Subsamples were also tested for mutagenic activity in the Ames system. The data obtained indicate that the highest I/P activity was located in HPLC Fraction #1, which was almost as active as the parent material, even though it represented only about 3% of the total mass of the parent PAH fraction (Figure 6). However, substantial activity was also found in the other three HPLC fractions. The total activity recovered in the HPLC fractions appeared to be greater than that of the parent material, suggesting that some of the initiating activity was suppressed in the cruder material. The mutagenic activity was also highest for HPLC Fraction #1 (Figure 7). If the I/P activity is adjusted by dividing the total number of tumors by the weight of the fraction and comparing the result to the mutagenic activity (revertants/μg), the relative activities of the four fractions appear to be similar in both assay systems.

Inhalation Studies

Last year we described the results of a subchronic (13-wk) inhalation study for SRC-II heavy distillate (HD). The purpose of this study was to obtain survival, growth, hematology, blood chemistry, and histopathology data from exposed animals. In addition, other animals were exposed for either 1, 4, or 12 wk (Groups 1, 2, and 3, respectively), then observed for onset of adverse effects throughout the remainder of their lives. Each of these groups contained 160 male and 160 female Fischer-344 rats and 120 female CD-1 mice, distributed equally over four treatment groups. The mice and rats were 9 and 12 wk of age, respectively, at the beginning of the exposure. The data presented in this report are for these animals, which are currently about 21 mo of age and have been without exposure for 15-18 mo. Mean aerosol concentrations ($\bar{x} \pm SEM$) during the exposure were 0.68 ± 0.03, 0.14 ± 0.01, 0.03 ± 0.003, and 0.0 mg/L of air for the high, middle, and low treatments, and controls, respectively. Particle size for the exposures was 1.7 μm (mass median aerodynamic diameter) with a geometric standard deviation of 2.2.

Since in blood-cell counts were altered from normal in samples taken from animals immediately following exposure, samples from Group 3 male rats were collected 6 mo after the end of the exposure and were then evaluated (Table 1). The results indicated that the number of RBC was still significantly below those for controls, although the differences between control and high-treatment-group animals were considerably less than were observed immediately after exposure. Rats from the high-treatment group had significantly fewer WBC than controls 6 mo after completion of exposure; however, the difference between the high-treatment group and controls was similar to that observed immediately after exposure. These results indicate that the ability of exposed animals to replace their peripheral RBC pool had recovered substantially in the 6-mo postexposure period; however, this kind of recovery was not apparent with respect to WBC.

Survival was greater for rats than for mice. Among treated animals the poorest survival was for mice from high-treatment groups 2 and 3 (Table 2). Currently, 75-95% of the rats are alive. Our plan is to sacrifice the remaining animals once mortality has reached 67%. This will provide adequate data to evaluate the effect of the exposure on longevity and will also provide tissue samples for histopathological examination.

Skin tumors were also observed in mice, but not in rats, following exposure. The greatest number of tumors occurred in animals from high-treatment groups 2 and 3; 40 and 27%, respectively, of these animals developed tumors (Table 3). The first tumor appeared in a high-treatment group 3 animal 4 mo after completion of exposure. A few tumors were observed in animals from high-treatment group 1. Since these animals were exposed for only 1 wk, it is apparent that a limited number of treatments is sufficient to cause the development of skin tumors.

In addition to skin tumors, at necropsy we observed lung tumors in mice. Most occurred in mice from high-treatment groups 2 and 3: 53 and 59%, respectively, of those that died had lung tumors (Table 4). A few tumors were also observed in the other treatment groups. This diagnosis will be confirmed and extended by histopathological examination during FY 1984.

If these diagnoses indicate malignant neoplasms, the results obtained from this study will provide data for risk assessment in humans, both in terms of the exposure concentrations and time-dose relationships.

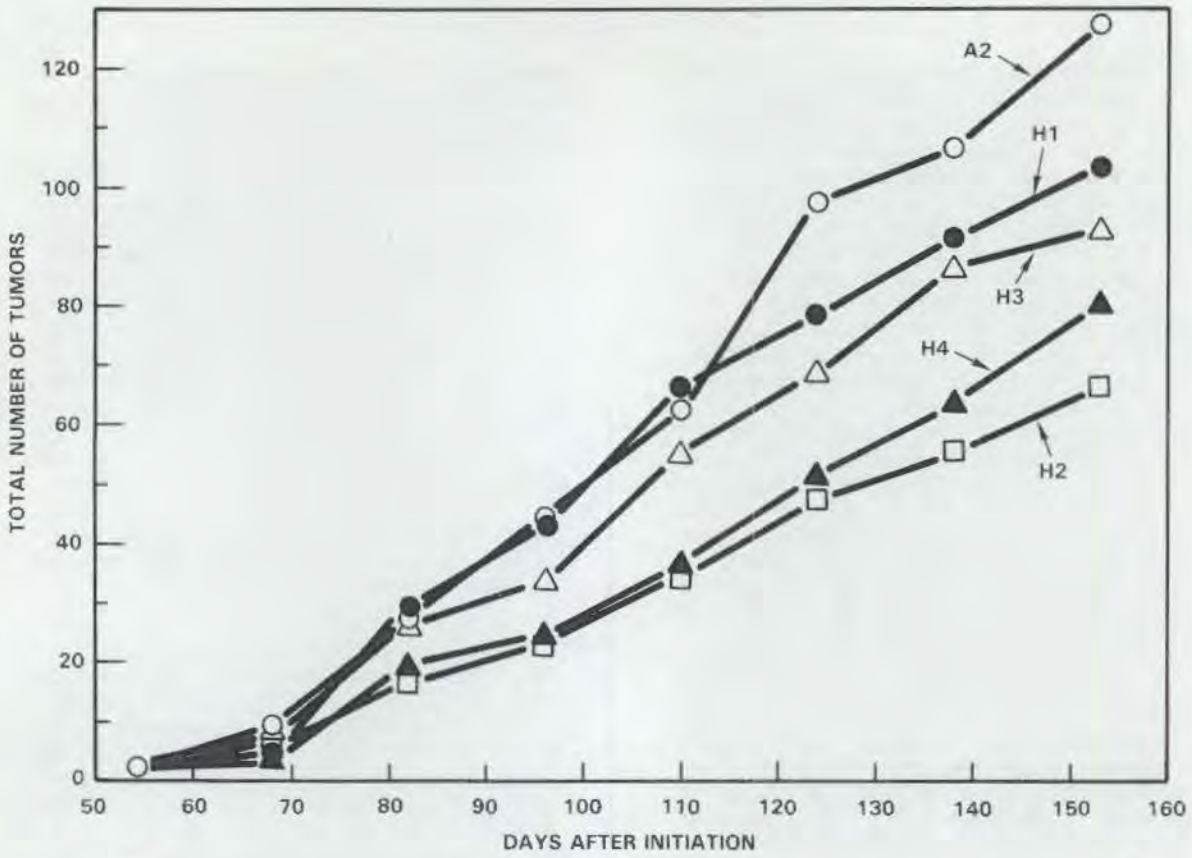

FIGURE 6. Skin-Tumor-Initiating Activity of the SRC-II >850°F Neutral PAH (A2) Fraction and its Subfractions (H-Fractions) Prepared by High Performance Liquid Chromatography.

Neurotoxicity Studies

If a rat ingests a novel taste and then experiences adversive consequences, (e.g., nausea), it rejects that taste when it is subsequently offered. This taste-aversion (TA) learning is a close laboratory analog of the "bait-shyness" found in wild animals. In two experiments we used a standardized protocol to induce TA learning in order to assess the dose-dependent, adversive properties of SRC-I wash solvent. In a third study, data were obtained which suggest that a single gavage of wash solvent (500 mg/kg) can: 1) significantly retard learning and memory of an adversive event, and 2) alter shuttle-box avoidance performance up to 10 days after wash solvent administration.

In the first study, naive female rats were trained to drink water on a 20-min/day watering schedule. After 2 wk training, the rats were given 0.1% sodium-saccharin-flavored water for their 20-min drinking period. They were then dosed with 1.2, 0.9, 0.6, 0.3, or 0 g/kg wash solvent. After 2 days of "water recovery," the rats were given a choice between tap water and saccharin-flavored water to assess TA learning as a result of wash solvent administration (learning trial). All groups dosed with wash solvent showed nearly maximal TA learning, like rats administered X-rays, toxic drugs or chemicals. A second study was conducted to investigate a dose-response relationship. The protocol was the same as in the first study, except that there were four learning trials because lower doses of the wash solvent were administered: 300, 150, 80, 40, 20, 10 or 0 mg/kg. A two-bottle preference test revealed that the threshold for statistically significant TA learning was between 20 and 40 mg/kg. However, evaluation of saccharin-flavored water consumption over the four conditioning trials (1-bottle data) suggests that little learning occurred after the first trial, when rats administered wash solvent were compared to a positive control group gavaged with cyclophosphamide. A third study was therefore conducted to determine if wash solvent affected the rats' TA learning behavior.

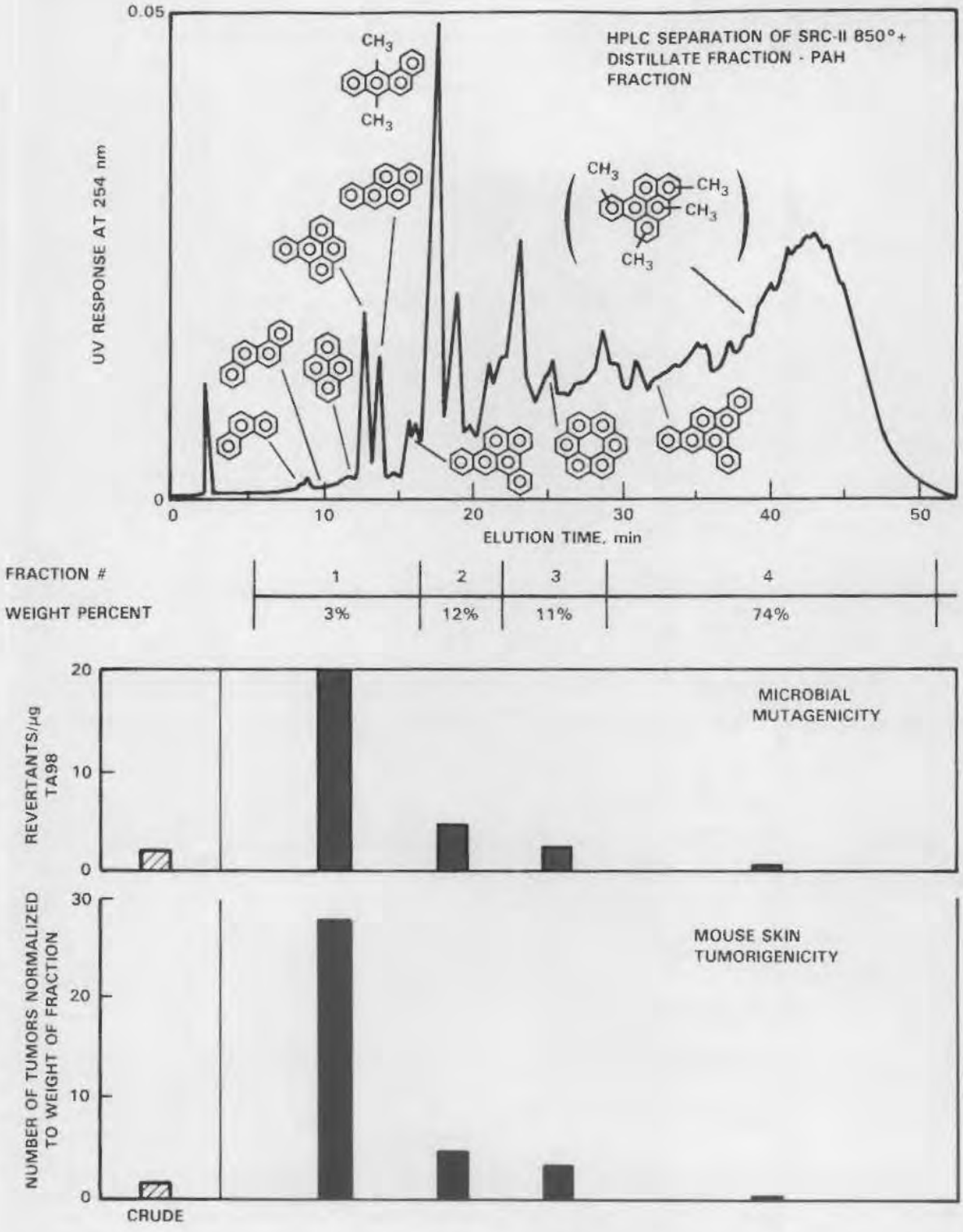

FIGURE 7. Comparative Biological Activity of HPLC Fractions from SRC-II >850°F PAH

TABLE 1. Hematology Data for Male Rats 26 wk after Completion of 12-wk Exposures to SRC-II Heavy Distillate (N = 10).

Mean Erythrocyte Parameters (x ± SEM) for Rats after Exposure to Heavy Distillate

	Male			
	Control	Low	Middle	High
VPRC (%)	44.0 ± 0.38	44.0 ± 0.29	43.6 ± 0.39	43.7 ± 0.16
Hgb (g/100 ml)	17.5 ± 0.11	17.5 ± 0.12	17.3 ± 0.12	17.2 ± 0.07
RBC (10^6/mm^3)	9.2 ± 0.06	9.1 ± 0.05	8.9 ± 0.09	8.5 ± 0.05[b]
Reticulocytes (10^3/mm)	157 ± 11	173 ± 11	157 ± 13	133 ± 10

Mean White Blood Cell Counts (x ± SEM) for Rats after Exposure to Heavy Distillate[a]

	Male			
	Control	Low	Middle	High
Total WBC	9.68 ± 0.51	9.06 ± 0.32	10.3 ± 1.14	7.17 ± 0.41[b]
Lymphocytes	5.66 ± 0.46	6.34 ± 0.30	6.45 ± 0.52	4.34 ± 0.25
Neutrophils	3.77 ± 0.65	2.41 ± 0.23	3.60 ± 0.70	2.71 ± 0.41
Eosinophils	116 ± 33	134 ± 29	71 ± 44	14 ± 9
Monocytes	108 ± 37	136 ± 45	122 ± 38	71 ± 30

[a] Total WBC, lymphocytes, and neutrophil data $\times 10^3$ gives the number of cells per mm^3; eosinophils and monocytes are shown as cells/mm^3.
[b] Significantly different from control means by Duncan's multiple range test ($P < 0.05$)
[c] Significant dose-related trend

TABLE 2. Survival of Mice after Inhalation Exposure to SRC-II Heavy Distillate.

	Percent Surviving			
	Group			
Exposure Duration, wk	Control	Low	Middle	High
1	80	77	80	70
4	70	93	73	46
12	77	57	73	46

TABLE 3. Skin Tumors Observed in Mice after Whole-Body Inhalation Exposure to SRC-II Heavy Distillate. Groups of 30 mice were exposed for either 1, 4, or 12 wk, then observed for onset of adverse effects through the remainder of their lives.

	No. Tumors			
Exposure Duration, wk	Control	Low	Middle	High
1	--	--	--	4/2[a]
4	--	2/2	2/2	23/12
12	--	3/2	2/1	27/8

[a] Number of tumors/number of mice with tumors

TABLE 4. Lung Tumors Observed at Necropsy for Mice after Inhalation Exposure to SRC-II Heavy Distillate.

	No. Tumors			
Exposure Duration, wk	Control	Low	Middle	High
1	0/6[a]	0/7	1/7	2/9
4	1/9	0/2	1/8	9/17
12	0/7	0/13	3/8	10/17

[a] Number mice with lung tumors/total number dead mice

In the third TA experiment, six groups of eight to nine rats each were trained to drink water on a 20-min/day watering schedule. Following water consumption on the ninth day of training, two groups of rats were gavaged with corn oil (vehicle), and one group was gavaged with wash solvent (500 mg/kg). On the 12th day of the experiment, the group receiving solvent and one of the groups receiving corn oil were given access to saccharin-flavored water. To induce TA learning, they were then injected, 4½ hr later, with cyclophosphamide. The second group that received corn oil on day 9 was treated similarly but was injected with saline on day

12. Two days later, rats were tested for preference between tap water and saccharin-flavored water. The results are plotted on the left side of Figure 8. It is clear from the data that rats pretreated with wash solvent failed to exhibit TA learning, as did the group pretreated with corn oil. The data on the right side of Figure 8 are from the other three groups in the same study. The first two groups received water on the 12th day and were then immediately gavaged with either wash solvent (500 mg/kg) or corn oil. Thirty minutes later, their mouths were flushed with 0.1 ml saccharin-flavored water; 4½ hr later they were dosed with cyclosphosphamide to induce TA learning for saccharin. Taste-aversion learning occurred in both groups. The data on the far right of the figure are from rats that received saccharin-flavored water on day 12 and were gavaged with wash solvent 4½ hr later. It is clear that wash solvent produced TA learning even when it was delayed 4½ hr. However, it is also clear that exposure to wash solvent on day 9 effectively blocked TA learning for the relationship between saccharin and cyclophosphamide on day 12 (anterograde amnesia).

Four days after the preference testing, three of the six groups of rats were assessed for shuttlebox avoidance performance over 100 training trials. In the shuttlebox task a rat must learn to avoid shock to the feet by running when an audible tone is presented. The tone precedes shock onset by 10 sec. The groups assessed in the shuttlebox task are designated "S" above the standard error bars in Figure 8. We also assessed the avoidance performance of experimentally naive control rats that were housed and weighed daily at the same time as the rats in the TA experiment. The results of the shuttlebox-avoidance experiment are shown in Figure 9. The avoidance performance of the corn-oil-treated (vehi-

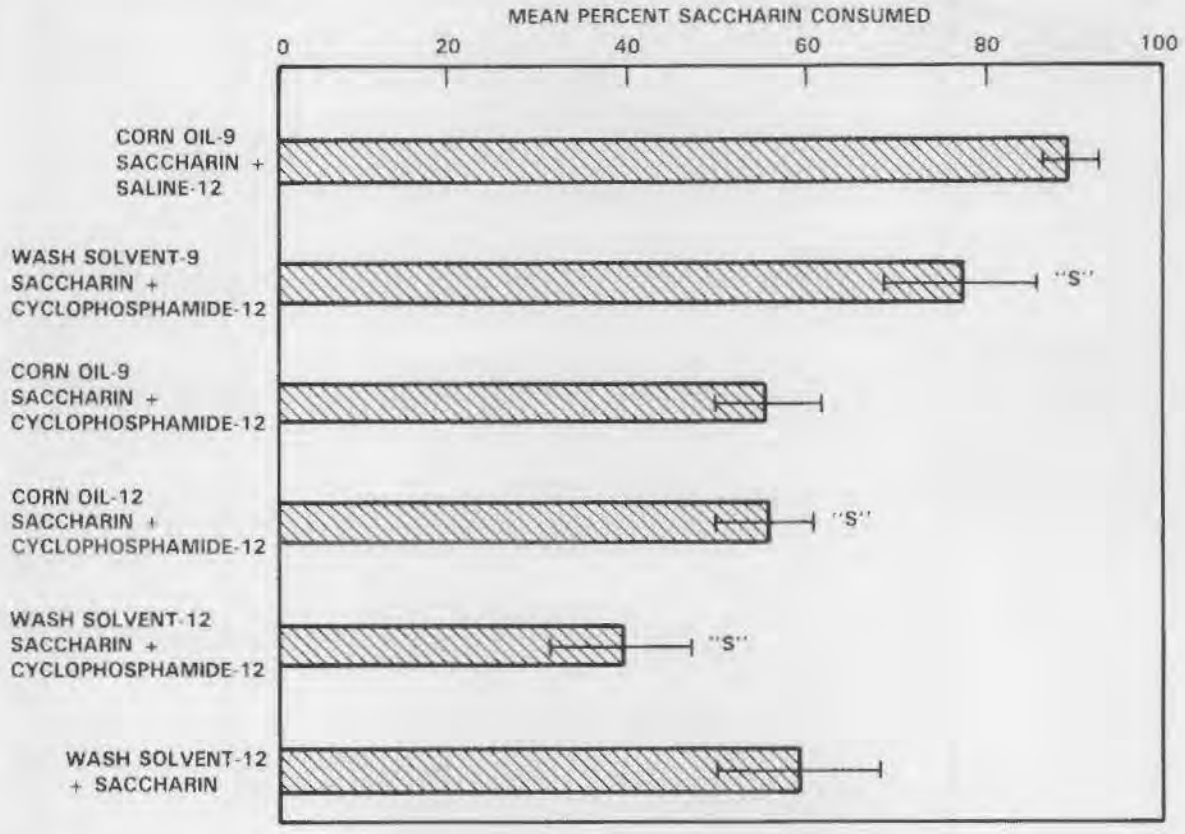

FIGURE 8. Mean Percent Consumption (± SEM) of Saccharin-Flavored Water in Two-Bottle Preference Test. From top to bottom, groups are: A. Gavaged with corn oil on day 9; saccharin-flavored water followed by saline, day 12. B. Gavaged with wash solvent on day 9; saccharin-flavored water, followed by cyclophosphamide on day 12. C. Gavaged with corn oil on day 9; saccharin-flavored water, followed by cyclophosphamide on day 12. D. Gavaged with corn oil on day 12; followed by saccharin (1/2 hr), then cyclophosphamide (4 1/2 hr). E. Gavaged with wash solvent on day 12; followed by saccharin (1/2 hr), then cyclophosphamide (4 1/2 hr). F. Gavaged with wash solvent 4 1/2 hr after saccharin consumption.

cle) control group was not different from that of the naive, cage-control group. Thus, except for the rats administered wash solvent, the manipulations of the first experiment had no apparent effect on avoidance performance. By contrast, the two groups dosed with wash solvent show facilitated performance in this task, possibly as a result of effects on the hippocampus which increased the general activity of the animals. Furthermore, the group tested 7 days following wash solvent administration showed greater facilitation than the group tested at 10 days.

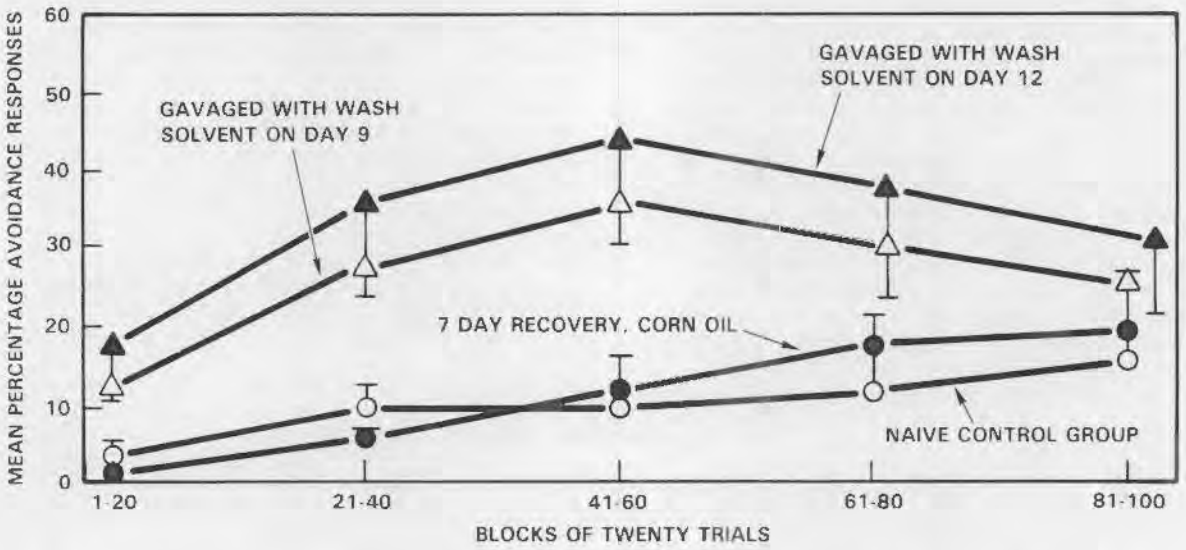

FIGURE 9. Mean Percent Avoidance Performance for the Four Groups of Rats Tested. Performance is plotted by 20-trial blocks. (SEM is plotted for the 7-day-recovery group (wash solvent) and for the experimentally naive control group.)

• Inhaled Plutonium Oxide in Dogs

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This project is concerned with long-term experiments to determine the lifespan dose-effect relationships of inhaled $^{239}PuO_2$ and $^{238}PuO_2$ in beagles. The data will be used to estimate the health effects of inhaled transuranics.

Beagle dogs given a single exposure to $^{239}PuO_2$ or $^{238}PuO_2$ aerosols to obtain graded levels of initial lung burdens are being observed for lifespan dose-effect relationships. Mortality due to radiation pnuemonitis and lung tumor increased in the three highest dose-level groups exposed to $^{239}PuO_2$ during the 12-yr postexposure period. During the 9½ yr after exposure to $^{238}PuO_2$, mortality due to lung and/or bone tumors increased in the two highest dose-level groups. Chronic lymphopenia, occurring 0.5 to 2 yr after exposure, was the earliest observed effect after inhalation of either $^{239}PuO_2$ or $^{238}PuO_2$ in the four highest dose-level groups that had initial lung burdens ≥80 nCi.

To determine the lifespan dose-effect relationships of inhaled plutonium, 18-mo-old beagle dogs were exposed to aerosols of $^{239}PuO_2$ (mean AMAD, 2.3 μm; mean GSD, 1.9), prepared by calcining the oxalate at 750°C for 2 hr; or to $^{238}PuO_2$ (mean AMAD, 1.8 μm; mean GSD, 1.9), prepared by calcining the oxalate at 700°C and subjecting the product to $H_2{}^{18}O$ steam in argon exchange at 800°C for 96 hr. This material, referred to as pure plutonium oxide, is used as fuel in space-nuclear power systems.

One hundred thirty dogs exposed to $^{239}PuO_2$ in 1970 and 1971 were selected for long-term studies; 22 will be sacrificed to obtain plutonium distribution and pathology data; 108 were assigned to lifespan dose-effect studies (Table 1). One hundred thirteen dogs exposed to $^{238}PuO_2$ in 1973 and 1974 were selected for lifespan dose-effect studies (Table 2). Twenty-four additional dogs were exposed for periodic sacrifice. The appendix (following the entire Annual Report) shows the status of the dogs on these experiments.

TABLE 1. Lifespan Dose-Effect Studies with Inhaled $^{239}PuO_2$ in Beagles.

Dose Level Group	Number of Dogs		Initial Average Deposition[b]	
	Male	Female	nCi[c]	nCi/kg[c,d]
Control	30	30	0	0
1	10	10	3.5 ± 3	0.029 ± 0.011
2	10	10	22 ± 4	0.18 ± 0.04
3	10	10	79 ± 14	0.66 ± 0.13
4	10	10	300 ± 62	2.3 ± 0.4
5	10	10	1200 ± 170	9.3 ± 1.4
6	3	3	5800 ± 1300	50 ± 22
	63	63		

[a] Exposed in 1970 and 1971.

[b] Estimated from external chest counts at 14 and 30 days postexposure and estimated lung weights and body weights.

[c] Mean ± 95% confidence intervals around the means.

Table 3 summarizes, by dose-level group, the mortality and lesions associated with deaths through 12 yr after exposure to $^{239}PuO_2$. During this period, all of the dogs in the highest-level dose group and in Dose Level Group 5, nineteen in Group 4, six in Group 3, five in Group 2, eight in Dose Level Group 1 and eight in the control group were euthanized when death was imminent. Fourteen dogs were sacrificed for comparison of plutonium tissue distribution. Table 4 and Figure 1 show the primary causes of death and the distribution of ^{239}Pu in the tissues of these animals.

TABLE 2. Lifespan Dose-Effect Studies with Inhaled $^{238}PuO_2$ in Beagles.

Dose Level Group	Number of Dogs		Initial Alveolar Deposition[b]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Contrs.	40	28	0	0
1	10	10	2.3 ± 0.8	0.0016 ± 0.0007
2	10	10	18 ± 4	0.13 ± 0.03
3	10	10	77 ± 11	0.56 ± 0.07
4	10	10	350 ± 80	3.0 ± 0.5
5	10	10	1300 ± 270	10 ± 1.9
6	7	6	5200 ± 1400	43 ± 12
	97	66		

[a] Exposed in 1973 and 1974.
[b] Estimated from external thorax counts at 14 and 40 days postexposure and estimated lung weights (0.01 x body weight).
[c] Mean ± 95% confidence intervals around the means.

As survival time increased, the fraction of plutonium in the lung decreased to ~12% of the final body burden by 11 to 12 yr after exposure. During the first year after exposure, plutonium was translocated primarily to the thoracic lymph nodes; little plutonium was translocated to other tissues. Plutonium content of the thoracic lymph nodes was ~63% of the final body burden at 11 to 12 yr after exposure; the abdominal lymph nodes, principally the hepatic nodes, contained ~6%. The fraction of plutonium in liver increased, accounting for ~31% of the final body burden at 11 to 12 yr after exposure in the higher (0.1- to 0.2-μCi body burden) dose-level groups. The organ distribution of plutonium in the periodically sacrificed dogs was generally similar to that of the high-dose-level dogs euthanized when death was imminent during the first 2 yr after exposure. The lower-dose-level dogs (0.001- to 0.1-μCi final body burden) sacrificed or euthanized during the 4th to 12th postexposure years had a much smaller fraction of the final body burden in the liver, with a larger fraction retained in the lungs and/or thoracic lymph nodes. About 2% of the final body burden was in the skeleton at 11 to 12 yr after exposure.

The dogs euthanized because of respiratory insufficiency during the 3-yr postexposure period had increased respiration rates, and hypercapnia and hypoxemia associated with lesions in the lungs. Intermittent anorexia and body weight loss accompanied the respiratory insufficiency. Histopathologic examination of the lungs showed radiation pneumonitis, characterized by focal interstitial and subpleural fibrosis, increased numbers of alveolar macrophages, alveolar epithelial hyperplasia, and foci of squamous metaplasia. Autoradiographs showed activity primarily composed of large stars, more numerous in areas of interstitial and subpleural fibrosis. Dog 804M also had a pulmonary tumor, classified as a bronchiolar-alveolar carcinoma.

TABLE 3. Summary of Lesions in Dogs Euthanized During the 12-yr Period after Inhalation of $^{239}PuO_2$.

Dose Group	No. Dogs/ Group	No. Dead Dogs/ Group	Number of Dogs/Lesion Associated with Death																										
			Radiation Pneumonitis	Lung Tumor	Esophagus, Leiomyoma, Lung Tumor	Bone Tumor	Malignant Lymphoma	Hemangiosarcoma	Reticulum Cell Sarcoma	Pituitary Tumor Cushing's	Ovarian Tumor	Oral Tumor	Round Cell Sarcoma	Malignant Melanoma	Pneumonia	Pheochromocytoma	Liver Cirrhosis, Addison's	Nephrosclerosis	Thromboembolism	Septicemia	Epilepsy	Epilepsy, Nephrosclerosis	Pyometra	Cardiac Insufficiency	Unknown
6	8	8	7	1																									
5	21	21	1	20																									
4	22	19		12	1				1	1					2		1						1						
3	20	6		2			1												1				1	1					
2	21	3									1			1		1					1				1				
1	24	8				1	1	2		1			1							1						1			
Control	20	8		3				1				1						1	1			1							

TABLE 4. Tissue Distribution of Plutonium in Beagles after Inhalation of $^{239}PuO_2$.

Dog Number	Time After Exposure, mo	Final Body Burden, μCi	Percent of Final Body Burden					Cause of Death
			Lungs	Thoracic Lymph Nodes[a]	Abdominal Lymph Nodes[b]	Liver	Skeleton	
478M	0.25	0.293	98	0.15	0.02	0.24	0.18	Sacrifice
435F	0.25	3.841	99	0.11	0.01	0.00	0.03	Sacrifice
816M	0.50	0.399	99	0.12	0.01	0.00	0.03	Sacrifice
918M	1	0.074	99	0.82	0.02	0.11	0.08	Sacrifice
920F	1	0.011	94	0.47	0.03	0.08	0.61	Sacrifice
913M	1	4.849	98	1.1	0.00	0.03	0.05	Sacrifice
702F	5	1.682	94	5.7	0.00	0.01	0.09	Sacrifice
709M	5	1.726	97	2.2	0.00	0.00	0.05	Sacrifice
734M	5	0.914	96	3.4	0.00	0.01	0.05	Sacrifice
739F	5	1.511	95	4.7	0.03	0.00	0.00	Sacrifice
910M	11	12.229	84	15	0.01	0.06	0.05	Radiation Pneumonitis
747F	12	5.434	71	29	0.03	0.07	0.07	Radiation Pneumonitis
906F	12	6.154	88	12	0.00	0.03	0.05	Radiation Pneumonitis
849F	13	0.0007	80	15	0.20	0.04	1.6	Sacrifice
896F	15	4.115	81	15	0.92	0.23	0.12	Radiation Pneumonitis
817M	21	3.794	64	34	0.13	1.4	0.19	Radiation Pneumonitis
815M	25	0.074	64	32	—	0.08	0.10	Sacrifice
829M	26	3.198	75	19	0.79	4.2	0.45	Radiation Pneumonitis
760M	31	0.978	71	23	0.57	3.7	0.28	Radiation Pneumonitis
890F	31	2.012	55	28	2.2	13	0.26	Radiation Pneumonitis
804M	37	1.101	62	29	0.19	7.9	0.36	Radiation Pneumonitis, Lung Tumor
798F	43	0.0056	55	44	0.02	0.17	0.43	Sacrifice
772M	53	1.821	42	23	0.88	29	0.69	Lung Tumor
759M	53	0.707	43	27	12	15	0.65	Lung Tumor
796F	55	0.671	40	31	4.1	21	1.0	Lung Tumor
783M	59	1.377	59	11	1.8	26	0.67	Lung Tumor
873M	62	1.746	45	27	6.4	16	0.76	Lung Tumor
753F	69	1.171	35	31	0.09	24	0.64	Lung Tumor
761M	69	1.064	36	37	6.3	19	0.53	Lung Tumor
727M	72	0.585	39	24	12	23	0.76	Lung Tumor
762M	72	0.0017	51	42	0.34	0.71	0.66	Sacrifice
837M	72	1.034	42	38	0.70	14	0.46	Lung Tumor
863F	76	0.617	33	12	1.3	47	1.4	Lung Tumor
852F	77	1.067	33	35	0.88	26	0.94	Lung Tumor
803M	79	0.415	20	46	11	20	1.4	Interstitial Pneumonitis
875M	83	0.0026	24	66	0.34	0.64	6.3	Malignant Lymphoma, Kidney
754M	84	0.0046	29	66	0.23	0.39	1.2	Status Epilepticus
835F	86	0.099	27	65	0.95	3.1	1.7	Reticulum Cell Sarcoma
880F	86	0.468	19	31	13	34	0.37	Lung Tumor
769F	90	0.019	36	57	0.32	1.7	1.8	Ovarian Tumor
888M	93	0.179	32	40	10	12	2.1	Lung Tumor
856F	94	0.306	40	45	0.78	9.0	3.9	Lung Tumor
889F	94	0.613	14	27	6.9	41	8.1	Lung Tumor
787M	95	0.473	24	19	12	39	2.7	Lung Tumor
820F	96	0.387	14	40	7.6	29	1.4	Lung Tumor
834F	97	0.025	30	46	17	3.5	0.91	Pyometra
752M	98	0.055	24	62	1.2	7.7	0.98	Lung Tumor
864F	100	0.616	18	22	2.9	50	2.9	Lung Tumor
908F	101	0.0073	14	72	0.049	0.56	0.93	Unknown
778M	102	0.065	11	85	1.3	1.0	0.52	Pulmonary Thromboembolism
812M	103	0.288	15	36	29	16	2.2	Lung Tumor
814F	104	0.054	49	33	4.1	10	1.6	Lung Tumor
840F	107	0.389	17	35	5.8	37	2.0	Lung Tumor
777M	109	0.392	11	52	7.8	24	1.7	Lung Tumor
857M	109	0.333	20	39	9.4	27	2.4	Lung Tumor
898F	111	0.333	10	34	28	21	3.4	Lung Tumor
899F	113	0.0066	7.3	87	0.14	0.27	1.6	Hemangiosarcoma, Heart
697M	114	0.141	15	64	8.1	9.9	1.4	Cardiac Insufficiency
909M	115	0.444	16	46	11	25	1.2	Lung Tumor
824F	116	0.178	21	75	0.50	2.3	0.70	Pneumonia
891M	116	0.0023	11	84	0.064	0.48	1.5	Septicemia
836M	117	0.333	12	63	15	7.4	0.97	Lung Tumor
892M	120	0.348	10	47	18	20	3.7	Lung Tumor
794M	120	0.397	13	33	14	31	3.5	Pituitary Tumor, Cushing's
781F	122	0.034	37	59	0.25	1.1	0.72	Lung Tumor, Kidney Tumor
809F	123	0.120	12	36	18	28	3.3	Liver Cirrhosis, Thyroid Tumor, Addison's
854M	124	0.435	12	66	15	3.8	1.3	Lung Tumor
807F	125	0.0021	10	71	0.55	1.2	1.3	Pituitary Tumor, Cushing's
810F	126	0.219	5.9	43	20	22	1.8	Lung Tumor
900M	126	0.0016	13	60	2.3	9.0	2.9	Round Cell Sarcoma
748F	127	0.0015	10	50	0.87	0.33	1.2	Unknown
860M	133	0.335	8.2	68	8.0	11	2.5	Lung Tumor
805F	134	0.169	5.8	55	8.9	21	2.8	Esophageal Leiomyoma, Lung Tumor
780F	135	0.0074	28	69	0.37	0.02	0.79	Pheochromocytoma
905F	135	0.060	13	50	10	19	1.7	Malignant Lymphoma
825F	137	0.0020	9.5	85	0.74	0.54	2.7	Hemangiosarcoma, Spleen
764F	139	0.081	15	75	3.9	4.9	0.73	Lung Tumor
808F	139	0.206	11	30	1.8	53	3.0	Lung Tumor
806F	140	0.010	11	78	1.8	5.1	2.3	Malignant Melanoma, Palate
850F	140	0.00062	12	82	0.61	0.11	2.0	Bone Tumor
833F	143	0.157	3.1	40	22	31	1.1	Metritis, Adrenal and Thyroid Carcinoma

[a] Includes tracheobronchial, mediastinal and sternal lymph nodes
[b] Includes hepatic, splenic and mesenteric lymph nodes

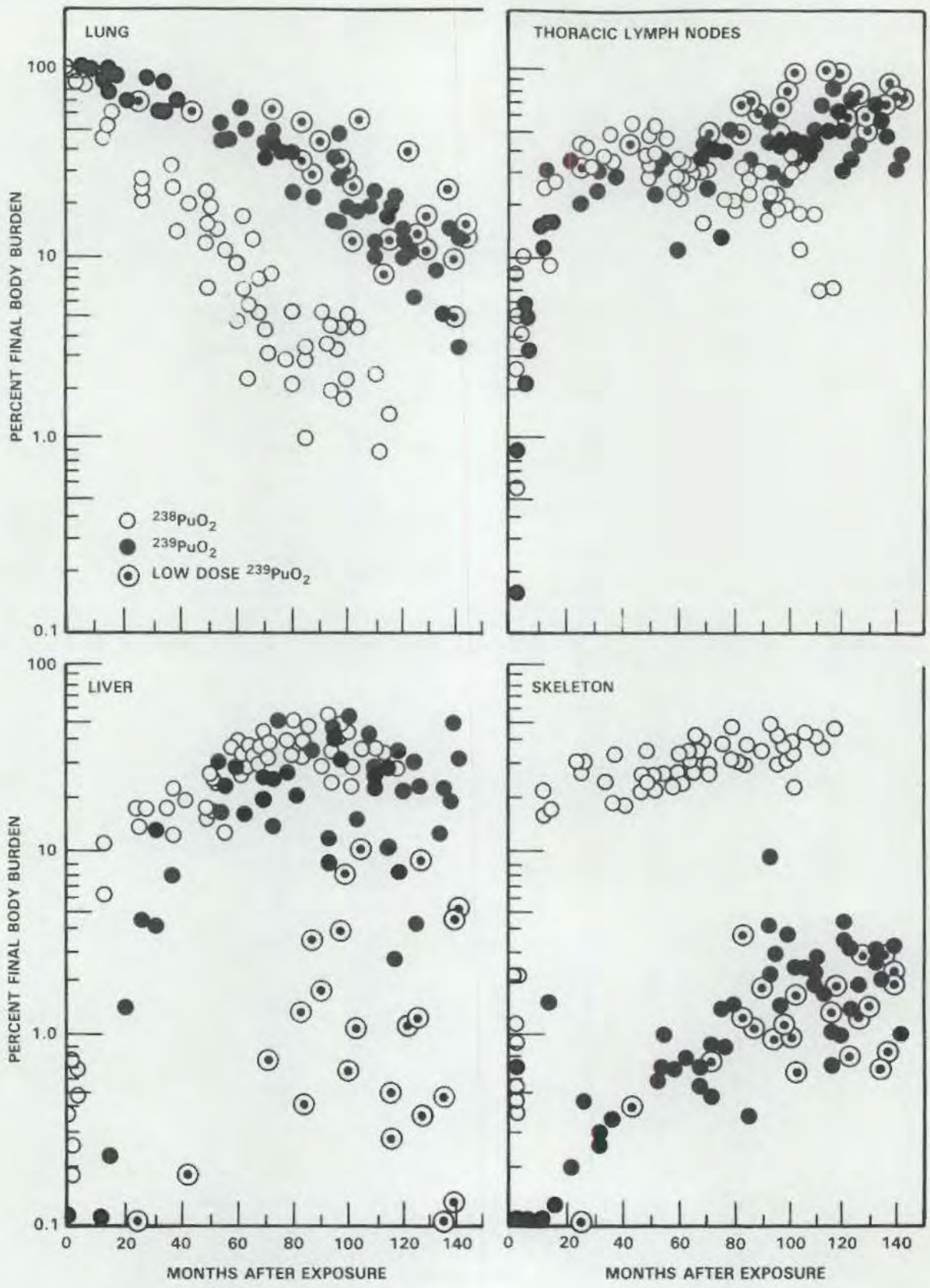

FIGURE 1. Plutonium in Tissues of Dogs after Inhalation of PuO_2.

Thirty-six of the 59 exposed dogs euthanized 3 to 12 yr after exposure had lung tumors. Radiographic evidence of pulmonary neoplasia was observed before respiratory insufficiency developed. Radiographic evidence of pulmonary neoplasia frequently preceded development of respiratory insufficiency. In dogs with neoplasia in the lung, respiratory insufficiency, when it was observed, was usually a late clinical finding that occurred shortly before euthanasia. All of the exposed dogs with lung tumors were in Dose-Level Groups 3, 4, 5, and 6. One dog in Dose Level 1, which was euthanized 11.7 yr after exposure, had an osteosarcoma involving the nasal cavity and maxilla. Three control dogs were euthanized because of lung tumors. Dogs 794M, 803M, 809F, 824F, 833F, and 835F (Dose Level 4), 697M, 778M, 834F, and 905F (Dose Level 3), 748F, 754M, 769F, 780F, and 806F (Dose Level 2), and 807F, 825F, 875M, 891M, 899F, 900M and 908M (Dose Level 1) died during the 7- to 12-yr postexposure period of causes presently thought to be unrelated to plutonium exposure.

In 17 of the dogs, the lung tumors were classified as bronchiolar-alveolar carcinoma; in six dogs as adenosquamous carcinoma; in seven dogs, adenocarcinoma; in two dogs, epidermoid and adenocarcinoma; in one dog, epidermoid carcinoma; in one dog, epidermoid and bronchiolar-alveolar carcinoma; in one dog, adenocarcinoma and bronchiolar-alveolar carcinoma; and in another dog, adenocarcinoma, adenosquamous carcinoma and bronchiolar-alveolar adenocarcinoma. The epidermoid carcinoma metastasized to the skeleton; the bronchiolar-alveolar carcinomas metastasized only to the thoracic lymph nodes in eight dogs, and to several organs (including thoracic lymph nodes, mediastinum, kidney, thyroid, skeleton, heart, adrenal gland, aorta, and axillary, prescapular, cervical, splenic and hepatic lymph nodes) in four other dogs. Three of the adenosquamous carcinomas metastasized to thoracic lymph nodes, mediastinum and thoracic pleura, and one to the hepatic and tracheobronchial lymph nodes. The adenocarcinomas metastasized to the lungs, tracheobronchial lymph nodes, hepatic lymph nodes, splenic lymph nodes, sternal and axillary lymph nodes, heart, kidney and esophagus in three dogs.

The lung tumors in the control dogs were classified as bronchiolar-alveolar adenocarcinomas with metastases to thoracic and abdominal lymph nodes, trachea, esophagus and mediastinum; adenocarcinoma with metastases to the diaphragm and abdominal lymph nodes; and combined epidermoid and adenocarcinoma with metastases to the thoracic lymph nodes, diaphragm, liver and kidney.

Three of the exposed dogs had lesions of secondary hypertrophic osteoarthropathy. Sclerosing lymphadenopathy was associated with the high concentration of plutonium in the thoracic and hepatic lymph nodes of dogs in Dose Level Groups 3, 4, 5 and 6. There was also a generalized lymphoid atrophy that may be related, in the dogs with respiratory insufficiency, to debilitation or to lymphocytopenia. Livers of the dogs in Dose Level Groups 4 and 5, which were euthanized during the 4- to 12-yr postexposure period, showed moderate, diffuse, centrilobular congestion. Liver cells in these areas contained fine, granular, yellow pigment resembling lipofuscin, and were frequently vacuolated. Focal aggregation of vacuolated, lipofuscin-containing cells in the sinusoids was associated with alpha stars on autoradiographs.

Lymphopenia developed after inhalation of $^{239}PuO_2$ in dose level groups with mean initial alveolar depositions of 79 nCi or more (Figure 2). Through 123 mo after exposure, mean lymphocyte values were significantly lower ($P < 0.05$) for Dose Level Groups 3 and 4 than for the control group. At 127 mo after exposure, mean lymphocyte values for Dose Level Groups 3 and 4 were not significantly different than for the control groups. The reduction in lymphocytes was dose-related, both in time of appearance and magnitude. Over the course of this study, there has been a slight age-related decrease in mean lymphocyte values of control dogs. In addition, mean lymphocyte concentrations in Groups 3 and 4 have tended to increase, making the differences between control dogs and these groups less significant than previously. At mean alveolar depositions of 3.5 and 22 nCi, lymphocyte values were within ranges observed in control dogs. A reduction in total leukocytes was evident in the higher dose groups, which were also lymphopenic. No effects have been observed on red-cell parameters following $^{239}PuO_2$ inhalation.

Serum chemistry assays have been performed to detect organ-specific damage from plutonium that translocated from lung to extrapulmonary sites. No consistent, dose-related alterations have occurred in serum constituents (glutamic pyruvic transaminase [GPT], glutamic oxaloacetic transaminase, alkaline phosphatase [ALP], urea nitrogen, and serum protein fractions) of dogs exposed to $^{239}PuO_2$.

Table 5 summarizes, by dose-level group, mortality and lesions associated with

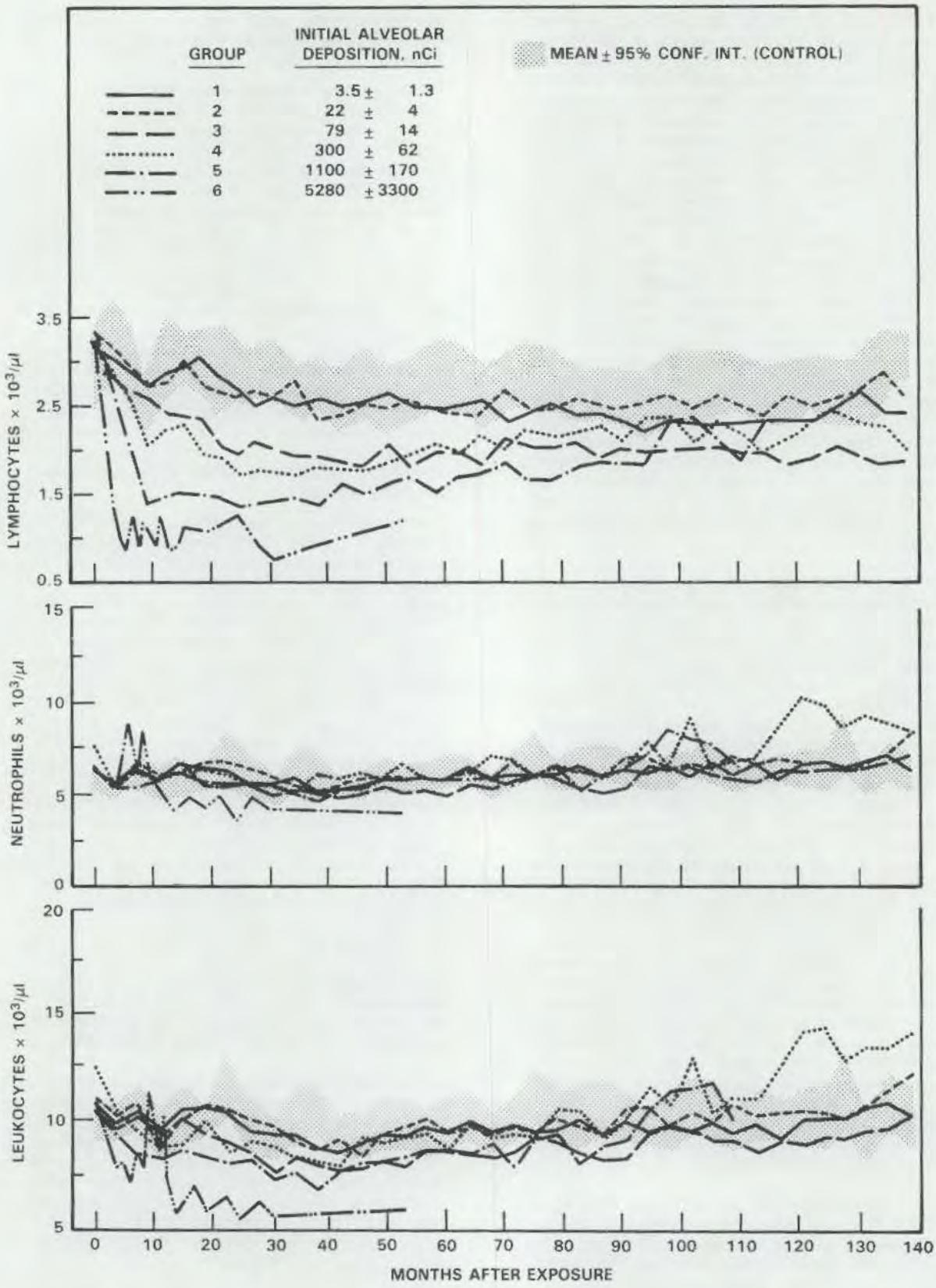

FIGURE 2. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs after Inhalation of $^{239}PuO_2$.

TABLE 5. Summary of Lesions in Dogs Euthanized During the 9.5-yr Period after Inhalation of $^{239}PuO_2$.

			Number of Dogs/Lesion Associated with Death															
Dose Group	No. Dogs/ Group	No. Dead Dogs/ Group	Lung Tumor	Bone Tumor	Bone Tumor & Lung Tumor	Bone Tumor & Addison's Disease	Bone Tumor, Addison's Disease & Lung Tumor	Addison's Disease	Pituitary Tumor (Cushing's)	Hemangiosarcoma, Heart	Malignant Lymphoma	Parathyroid Adenoma	Brain Tumor & Heart Tumor	Spinal Cord Degeneration	Pyometra	Pneumonia	Myocardial Infarction
6	13	13	3	2	6	1		1									
5	20	18		9	3		1	2								1	1
4	20	1								1							
3	22	3							1		1	1					1
2	21	1												1			
1	20	2		1									1				
Control	20	2									1				1		

death through 9½ yr after exposure to $^{239}PuO_2$. During this period, all of the dogs in the highest-level dose group, eighteen dogs in Dose Level Group 5, one dog in Group 4, three dogs in Group 3, one dog in Group 2, and two dogs in Dose Level Group 1 were euthanized when death was imminent. Two control dogs were euthanized during the 9½-yr postexposure period. Twenty-one dogs were sacrificed for comparison of plutonium tissue distribution. Table 6 and Figure 1 show the causes of death and the distribution of ^{239}Pu in the tissues of these animals.

Of the 38 exposed dogs euthanized, 23 were killed due to bone tumors (osteosarcoma), 3 due to lung tumors, and 3 due to Addison's disease. Eleven of the dogs euthanized due to osteosarcoma also had lung tumors; two also had Addison's disease. All of the exposed dogs with osteosarcomas, lung tumors and Addison's disease were in Dose Level Groups 5 and 6. One Dose-Level-Group-1 dog (989F) had a fibrosarcoma in the ilium. Eleven of the 23 osteosarcomas were in vertebrae; 2 in femora, 3 in ribs, 2 in the scapulae, 3 in the pelvis, 1 in the tibia and 1 in the humerus. Dogs 1047M and 1191F (Dose Level 5), 1081M (Dose Level 4), 960M, 1040M and 1043F (Dose Level 3), 1062M (Dose Level 2) and 1063M (Dose Level 1) died during the 3- to 9½-yr postexposure period of causes presently thought to be unrelated to plutonium exposure.

The lung tumors were classified as bronchiolar-alveolar carcinomas in ten dogs, bronchiolar-alveolar adenoma in one dog, and adenosquamous carcinoma in two dogs. In one dog, three lung-tumor types were observed: bronchiolar-alveolar, adenocarcinoma and fibrosarcoma. Lung-tumor metastases were not observed. Bone-tumor metastases were found in the lungs of six dogs; in three dogs, the bone tumor metastasized to lungs, thoracic lymph nodes, liver, spleen and heart; and in one dog, the bone tumor metastasized to the iliac lymph nodes. The five dogs with Addison's disease had adrenal cortical atrophy.

In addition to the lesions associated with the cause of death, lesions in the lungs of the Dose Level Groups 5 and 6 dogs included focal alveolar histocytosis, alveolitis, alveolar epithelial cell hyperplasia, alveolar emphysema, pleural fibrosis, and interstitial fibrosis. Numerous alpha stars were observed, mainly in foci of fibrosis, and single alpha tracks were scattered throughout sections in foci of alveolar histocytosis and in alveolar septa. The tracheobronchial and mediastinal lymph nodes were completely obliterated by necrosis and scarring, associated with high concentrations of plutonium observed as alpha stars. Similar but less severe lesions were seen in the hepatic lymph nodes. There were extensive alterations in bone, including multiple areas of focal atrophy of bone; endosteal, trabecu-

TABLE 6. Tissue Distribution of Plutonium in Beagles after Inhalation of $^{238}PuO_2$.

Dog Number	Time After Exposure, mo	Final Body Burden, μCi	Percent of Final Body Burden					Cause of Death
			Lungs	Thoracic Lymph Nodes[a]	Abdominal Lymph Nodes[b]	Liver	Skeleton	
1032M	0.25	0.150	97	0.34	0.20	1.7	0.16	Sacrifice
921F	1	0.0044	93	0.65	0.04	0.38	2.1	Sacrifice
930F	1	0.052	99	0.63	0.01	0.07	0.35	Sacrifice
931F	1	0.347	96	1.9	0.01	0.05	0.36	Sacrifice
929F	2	0.017	91	7.5	0.002	0.26	0.58	Sacrifice
932F	2	0.382	96	2.5	0.01	0.18	0.39	Sacrifice
923F	2	0.0023	88	9.4	0.03	0.09	0.44	Sacrifice
925M	3	0.0064	91	4.1	0.04	0.04	1.2	Sacrifice
926M	3	0.078	87	11	0.23	0.65	1.1	Sacrifice
934M	3	0.902	92	4.8	1.7	0.45	0.95	Sacrifice
1318M	12	0.030	45	27	0.08	10	15	Sacrifice
1319M	12	0.077	41	26	0.03	11	20	Sacrifice
1214M	13	0.014	52	9.2	0.32	6.2	16	Sacrifice
1310M	25	0.026	19	36	0.08	15	28	Sacrifice
1317M	25	0.041	20	33	0.16	17	26	Sacrifice
1315M	25	0.047	22	31	0.04	17	28	Sacrifice
1191F	35	0.658	26	32	0.13	18	22	Pneumonia
1215M	36	0.011	21	43	0.17	13	21	Sacrifice
1311M	37	0.036	13	31	0.22	21	32	Sacrifice
994F	42	5.024	17	45	0.50	18	18	Addison's Disease
970F	48	0.0022	20	34	0.36	16	24	Sacrifice
1312M	49	0.035	6.8	29	0.26	25	35	Sacrifice
1143M	49	6.331	11	43	2.0	15	22	Bone Tumor, Lung Tumor
1025M	50	10.033	16	27	7.1	24	23	Lung Tumor
1064M	51	8.427	13	48	1.9	15	20	Bone Tumor, Lung Tumor
1175F	52	3.641	14	31	0.08	25	26	Lung Tumor
1079M	56	2.182	9.8	40	4.3	13	25	Addison's Disease
1096F	59	1.204	4.3	22	2.7	36	24	Addison's Disease
1189M	60	0.044	8.9	25	0.16	35	25	Sacrifice
1115F	61	1.534	5.0	32	2.3	26	33	Bone Tumor
1162F	61	3.663	12	32	5.9	27	25	Bone Tumor, Addison's Disease
1009M	62	4.360	15	25	2.4	33	23	Lung Tumor
974F	64	1.465	5.1	24	5.9	33	29	Bone Tumor
1092M	65	1.515	2.1	26	9.1	29	30	Bone Tumor
975F	66	3.749	11	30	2.1	28	25	Bone Tumor, Lung Tumor
1042F	69	1.494	4.7	25	2.9	32	33	Bone Tumor, Lung Tumor
1037M	69	2.417	7.1	27	7.8	28	27	Bone Tumor
1027M	70	2.546	3.8	15	7.0	40	31	Bone Tumor, Lung Tumor
1006F	72	2.826	7.5	30	3.4	29	26	Bone Tumor, Lung Tumor
1057M	72	1.748	3.0	35	2.2	33	24	Bone Tumor
1082M	78	0.0083	2.4	20	0.81	40	34	Paralysis
1081M	80	0.361	4.6	15	0.48	47	29	Hemangiosarcoma, Heart
1058F	80	1.000	2.0	18	4.4	31	41	Bone Tumor, Adrenal Tumor
1002M	84	1.786	2.9	31	2.0	31	28	Bone Tumor, Lung Tumor
1109F	86	0.885	0.93	23	4.0	34	35	Bone Tumor, Addison's Disease, Lung Tumor
1218F	86	0.678	2.7	23	4.1	42	25	Bone Tumor
1071M	91	1.088	5.4	28	3.4	27	33	Bone Tumor, Lung Tumor
1063M	94	0.00060	3.4	15	1.3	22	43	Bone Tumor, Heart Tumor
1160F	95	0.956	1.6	21	0.91	43	30	Bone Tumor, Lung Tumor
960M	95	0.036	4.0	21	0.49	33	39	Malignant Lymphoma
1040M	96	0.059	3.0	17	0.96	40	35	Parathyroid Adenoma
1140M	97	0.504	3.8	18	7.7	37	30	Bone Tumor
989F	99	0.0017	5.1	11	1.2	22	29	Bone Tumor (Fibrosarcoma)
1211M	99	0.895	1.3	29	4.7	39	23	Bone Tumor
1173M	99	0.462	2.0	33	7.5	21	33	Bone Tumor
1043F	103	0.037	3.5	16	0.57	33	42	Empyema, Pituitary Tumor, Cushing's
1192F	109	0.345	2.4	7.3	4.6	36	46	Bone Tumor
1178M	110	0.594	0.86	17	2.0	33	42	Bone Tumor, Lung Tumor
1147M	115	0.241	1.4	7.8	11	28	48	Herniated Vertebral Disc

[a] Includes tracheobronchial, mediastinal and sternal lymph nodes
[b] Includes hepatic, splenic and mesenteric lymph nodes

lar and peritrabecular bone fibrosis; and osteolysis of cortical, endosteal, and trabecular bone. One dog had lesions of secondary hypertrophic osteoarthropathy. Radioactivity in the bone was present as single tracks, generally scattered throughout the bone, cartilage, and bone marrow. The liver contained foci of hepatocellular fatty change, where small clusters of single tracks were seen. There was also mild, focal, nodular hyperplasia of hepatocytes. Elevated serum GPT levels, suggestive of liver damage, were observed in the Dose Level Groups 5 and 6 dogs.

Dose-related lymphopenia was observed in groups with mean alveolar $^{238}PuO_2$ deposition of 77 nCi or more (Figure 3). The lymphocyte depression was more pronounced in magnitude and appeared earlier than in dogs exposed to similar doses of $^{239}PuO_2$. Through 118 mo after exposure, mean lymphocyte values were significantly lower ($P < 0.05$) for Dose Level Groups 4 and 5 than for the control group. However, lymphocyte values in the $^{238}PuO_2$-exposed dogs tended to increase sooner after reaching a minimum than in $^{239}PuO^2$-exposed dogs, and mean lymphocyte concentrations in Group 3 dogs were not significantly different from values of control dogs 86 to 94 mo following exposure. As with ^{239}Pu, lymphocyte values in the two lowest exposure groups (2.3 and 18 nCi) were not different from control values. A dose-related reduction in total leukocytes was evident, primarily because of lymphopenia, except in Groups 5 and 6, in which neutropenia was also observed. Through 118 mo after exposure, mean leukocyte and neutrophil values were significantly lower ($P < 0.05$) for Dose Level Group 5 than for the control group. No difference in monocyte values was seen in relation to dose levels. A significant and progressive reduction in eosinophils was evident only in Group 6 dogs following $^{238}PuO_2$ inhalation. No chronic effects have been observed in red-cell parameters.

Lymphopenia, the earliest observed effect after inhalation of either $^{239}PuO_2$ or $^{238}PuO_2$, occurred after deposition of ~80 nCi plutonium in the lungs. On a concentration basis, the 80-nCi dose level is about 40 times the 16-nCi maximum permissible human lung deposition, based on 0.3 rem/wk to the lung.

In serum chemistry assays of $^{238}PuO_2$ dogs, performed more than 118 mo following exposure, ALP and GPT values were higher than those of the control group only in Dose Level Group 3, 4 and 5 dogs. Elevations in GPT are consistent with liver histopathologic findings and radiochemical analyses indicating ^{238}Pu translocation to the liver. Alkaline phosphatase elevations occurred in some of the dogs with primary bone tumors and in others in which the increase was attributable to the liver (by heat inactivation of ALP) as the source of the largest portion of the ALP.

At 8½ to 9½ yr after exposure, the fraction of the final body burden in the lungs of the ^{238}Pu-exposed dogs was about 2%, compared to 18% in the ^{239}Pu-exposed dogs (Figure 1). At that time, ~11% of the ^{238}Pu was in the thoracic lymph nodes, compared to ~48% of the ^{239}Pu. Livers of the ^{238}Pu-exposed dogs contained ~32% of the plutonium burden, compared to 21% in the livers of the ^{239}Pu-exposed dogs. About 45% of the final body burden was in the skeletons of the ^{238}Pu-exposed dogs, at that time, compared to ~2% in the ^{239}Pu-exposed dogs. Tissue distribution of ^{238}Pu in low-dose-level dogs did not differ from that in high-dose-level dogs.

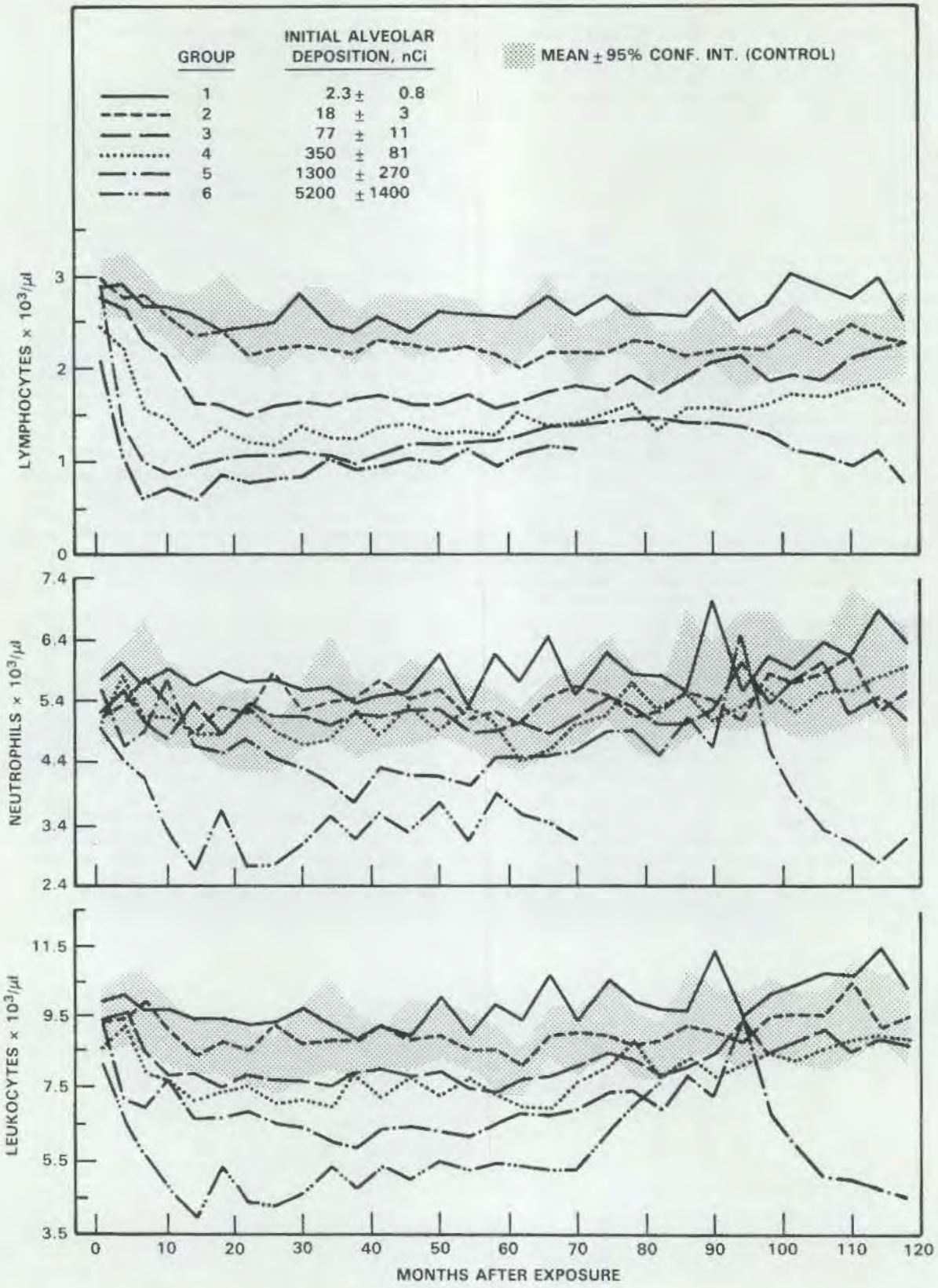

FIGURE 3. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs after Inhalation of $^{238}PuO_2$.

• Inhaled Plutonium Nitrate in Dogs

Principal Investigator: G. E. Dagle

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The major objective of this project is to determine dose-effect relationships of inhaled plutonium nitrate in dogs to aid in predicting health effects of accidental exposure in man. For lifespan dose-effect studies, beagle dogs were given a single inhalation exposure to $^{239}Pu(No_3)_4$, in 1976 and 1977. The earliest biological effect was on the hematopoietic system; as described in previous Annual Reports, lymphopenia and neutropenia occurred at the two highest dose levels. We have also observed radiation pneumonitis, lung cancer, and bone cancer at the highest dose levels.

The skeleton and liver are generally considered the critical tissues after inhalation of "soluble" plutonium (e.g., plutonium nitrate), on the assumption that the plutonium will be rapidly translocated from the lung to skeleton and liver. In several rodent studies, however, inhalation of "soluble" plutonium has resulted in lung tumors as well as skeletal tumors. Lifespan studies are necessary to evaluate the complex interactions between tissues and organ systems directly or indirectly impaired by lower levels of exposure. Beagle dogs were chosen to correlate relative risks, determined in other studies, with different forms and routes of exposure to plutonium.

Six dose groups (105 dogs) were exposed, in 1976 and 1977, to aerosols of $^{239}Pu(NO_3)_4$ for lifespan observations (Table 1). In addition, 20 dogs were exposed to nitric acid aerosols as vehicle controls, 25 dogs were exposed to aerosols of $^{239}Pu(NO_3)_4$ for periodic sacrifice to study plutonium metabolism and the pathogenesis of developing lesions; 7 dogs were selected as controls for periodic sacrifice; and 20 dogs were selected as untreated controls for lifespan observations. The dogs were exposed in aerosol chambers, using techniques described in previous reports. The Appendix (following the entire Annual Report) shows the current status of each dog on these experiments.

The initial deposition and early clearance of inhaled $^{239}Pu(NO_3)_4$ aerosols were discussed in previous Annual Reports. The average amount of plutonium in the lung decreased to less than 1% of the final body burden in dogs surviving 5 yr or more (Table 2). There was early translocation to the liver and skeleton, with an average

TABLE 1. Lifespan Dose-Effect Studies With Inhaled $^{239}Pu(NO_3)_4$ in Beagles.[a]

Dose Level Group	Number of Dogs		Initial Alveolar Deposition[c]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Control	10	10	0	0
Vehicle	10	10	0	0
1	10	10	2 ± 2	0.02 ± 0.02
2	10	10	8 ± 4	0.06 ± 0.04
3	10	10	36 ± 17	0.5 ± 0.2
4	10	10	295 ± 67	2 ± 0.8
5	10	10	1709 ± 639	14 ± 6
6	3	2	5445 ± 1841	47 ± 17

[a] Exposed in 1976 and 1977

[b] Estimated from external thoracic counts at 2 weeks post-exposure and estimated lung weights (0.011 × body weight)

[c] Mean ± standard deviation

of 42% and 50%, respectively, of final body burden present in these tissues in dogs surviving 5 yr or more. Only minimal amounts were translocated to thoracic or abdominal lymph nodes. This was in contrast to dogs that inhaled $^{239}PuO_2$, in which a considerable amount translocated to the thoracic lymph nodes, but only minimal amounts translocated to liver or skeleton at these time periods. In a pilot study reported previously (Annual Report, 1979), $^{238}Pu(NO_3)_4$ translocated more rapidly to liver and skeleton than did $^{239}Pu(NO_3)_4$, but both reached a similar plateau at 1 yr after exposure.

The earliest observed biological effect was on the hematopoietic system: lymphopenia occurred at the two highest dose levels at 4 wk after exposure to

TABLE 2. Tissue Distribution of Plutonium in Beagles After Inhalation of $^{239}Pu(NO_3)_4$.

Dog Number	Time After Exposure, mo	Final Body Burden, μCi	Percent of Final Body Burden					Cause of Death
			Lungs	Thoracic Lymph Nodes[a]	Abdominal Lymph Nodes[b]	Liver	Skeleton	
1329F	1	0.485	70.05	0.16	0.04	8.28	18.79	Sacrifice
1346M	1	0.902	76.81	0.32	0.03	10.45	10.30	Sacrifice
1347F	1	0.699	71.71	0.36	0.08	9.33	14.09	Sacrifice
1336M	1	0.032	71.38	0.22	0.05	5.72	19.73	Sacrifice
1341F	1	0.022	64.43	0.29	0.10	12.92	18.63	Sacrifice
1344F	1	0.052	58.68	0.25	0.04	21.87	16.09	Sacrifice
1335M	1	0.003	19.52	0.07	0.06	6.68	25.04	Sacrifice
1339F	1	0.001	19.08	0.13	0.08	20.92	45.47	Sacrifice
1351M	1	0.002	40.68	1.22	0.09	17.09	28.89	Sacrifice
1522F	3	0.059	54.68	0.57	0.10	11.52	28.24	Sacrifice
1529F	3	0.049	51.68	0.40	0.07	18.48	23.74	Sacrifice
1539M	3	0.072	52.45	0.31	0.05	18.58	25.03	Sacrifice
1564F	12	0.037	18.00	1.27	0.11	33.53	42.63	Sacrifice
1571F	12	0.053	22.37	1.47	0.11	28.76	42.91	Sacrifice
1588M	12	0.053	13.14	0.40	0.12	35.85	46.18	Sacrifice
1424M	14	4.625	33.10	1.43	0.16	26.49	36.88	Radiation Pneumonitis
1517F	16	4.025	18.99	0.94	0.18	29.51	47.88	Radiation Pneumonitis
1510F	17	4.048	22.00	1.15	0.05	20.71	52.00	Radiation Pneumonitis
1420M	25	1.616	16.51	0.86	0.20	7.77	70.06	Radiation Pneumonitis
1471M	34	1.375	9.25	0.73	0.12	26.92	58.34	Radiation Pneumonitis
1518M	42	1.880	6.87	0.24	0.07	21.34	67.51	Radiation Pneumonitis + Lung Tumor
1512M	42	2.136	4.31	0.60	0.08	49.93	42.66	Bone Tumor
1508M	43	1.730	3.24	0.62	0.08	41.53	52.70	Bone Tumor
1459F	51	1.567	4.40	0.15	0.12	30.86	61.41	Radiation Pneumonitis + Lung Tumor
1492F	52	1.202	2.81	0.20	0.17	27.02	66.38	Bone Tumor
1502F	54	3.113	0.80	0.39	0.09	33.33	62.51	Bone Tumor, Lung Tumor
1485F	55	1.052	0.82	0.35	0.07	31.13	63.94	Bone Tumor
1387F	55	0.167	1.41	0.22	0.12	45.48	49.10	Bone Tumor
1429M	59	1.159	4.14	0.35	0.10	37.06	54.70	Bone Tumor, Lung Tumor
1646F	61	0.806	0.72	0.20	0.40	46.92	48.42	Bone Tumor
1619F	62	1.361	0.55	0.59	0.13	37.87	58.63	Bone Tumor
1636M	66	0.634	1.21	0.27	0.52	53.97	39.09	Bone Tumor
1498F	69	0.845	0.59	0.32	0.13	26.63	53.37	Bone Tumor, Lung Tumor
1419M	76	0.873	0.69	0.28	0.39	44.06	50.70	Bone Tumor, Lung Tumor

[a] Includes tracheobronchial, mediastinal and sternal lymph nodes
[b] Includes hepatic, splenic and mesenteric lymph nodes

$^{239}Pu(NO_3)_4$. The results of these continuing evaluations are shown in Figure 1. Total leukocyte concentrations were reduced significantly in the two highest dose groups, i.e., Group 5 (mean initial alveolar deposition, ~1700 nCi), and Group 6 (~5500 nCi). The reduction in white cells in Groups 5 and 6 is due to an effect on most leukocyte types (neutrophils, lymphocytes, monocytes and eosinophils). This is in contrast to the effects of both $^{239}PuO_2$ and $^{238}PuO_2$, which significantly depressed lymphocyte concentrations by 21 mo after exposure to initial lung burdens of ~80 nCi or more. The lymphocytopenia at lower dose levels of plutonium oxides may be related to the more-extensive translocation of plutonium oxide to the tracheobronchial lymph nodes.

All five dogs at the highest dose level and two of 20 dogs at the medium-high dose

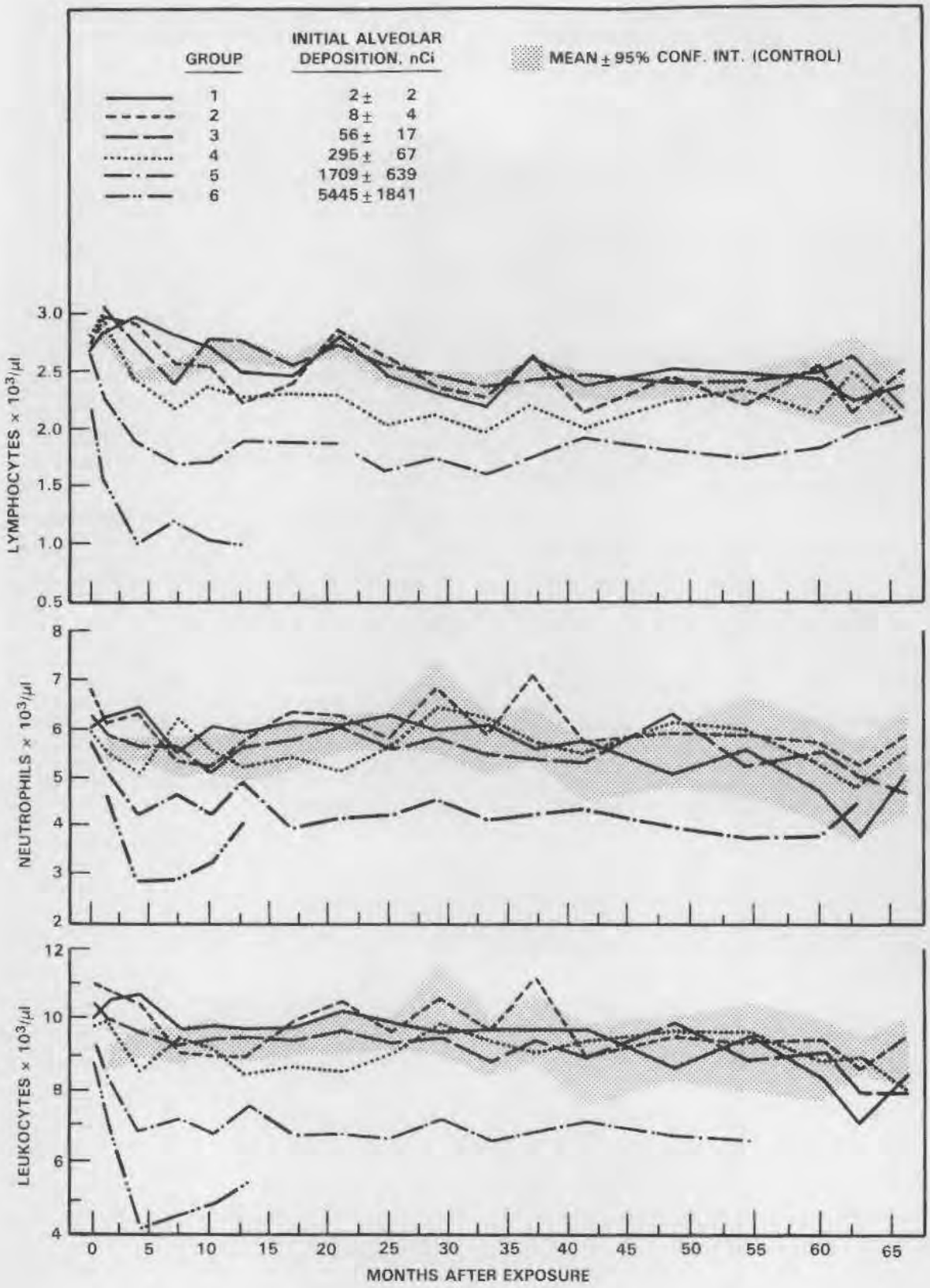

FIGURE 1. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs after Inhalation of $^{239}Pu(NO_3)_4$.

level died from radiation pneumonitis 14 to 51 mo after exposure. Histopathologic examination of these dogs' lungs revealed interstitial fibrosis, alveolar epithelial hyperplasia, increased numbers of alveolar macrophages, occasional small emphysematous cavities and, at times, very small nodules of squamous metaplasia at the termini of respiratory bronchioles.

Lung tumors occurred in two dogs with radiation pneumonitis and in five additional dogs euthanized because of osteosarcomas. Typically, these arose in subpleural areas in proximity to areas of interstitial fibrosis or small cavities communicating with bronchioles. They consisted of bronchiolo-alveolar carcinomas in four dogs, a papillary adenocarcinoma in one dog, both bronchiolo-alveolar carcinoma and papillary adenocarcinma in one dog, and bronchiolo-alveolar carcionoma, papillary adenocarcinoma, and mixed lung tumor in one dog. No metastases or invasions of nonpulmonary parenchyma were observed.

All the dogs that died or were euthanized after more than 51 mo of plutonium exposure had osteosarcomas. Osteosarcomas were present in 13 dogs euthanized 42 to 76 mo after exposure: 12 dogs from the Group 5 dose level and one dog at the Group 4 dose level. The osteosarcomas occurred in a lumbar vertebra (three dogs), thoracic vertebra (two dogs), cervical vertebra (two dogs), a humerus (two dogs), sacrum (one dog), pelvis (one dog), facial (maxillary) bone (one dog), and in both a humerus and rib of one dog. Metastases to the lung occurred in four dogs. These dogs also had radiation osteosis, generally characterized by peritrabecular fibrosis.

Autoradiographs of liver sections from dogs euthanized 3 to 5 yr after inhalation exposure to the higher dose levels of $^{239}Pu(NO_3)_4$ were compared with liver sections from dogs exposed to levels of $^{239}PuO_2$ that yielded similar concentrations of plutonium in the liver at similar intervals after exposure. The autoradiographs showed that the nitrate-exposed dogs had >99% of plutonium activity in diffusely distributed single tracks (only rarely in alpha stars), whereas the oxide-exposed dogs had >99% of the plutonium activity concentrated in alpha stars (only rarely in single tracks). The character of the alpha activity probably influenced the increased prominence of hepatic adenomatous hyperplasia in the $^{239}Pu(NO_3)_4$-exposed dogs compared to the $^{239}PuO_2$-exposed dogs.

Serum enzyme assays have been performed throughout the postexposure period in an attempt to diagnose specific damage to liver and/or bone by plutonium translocated from the lung. Prior evaluations revealed periodic elevations in mean values for glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase, and alkaline phosphatase (ALP); however, there were no consistent dose-related elevations in these values. Currently (more than 74 mo following exposure), ALP values in Dose Level Groups 4 and 5 are significantly ($P < 0.05$) higher than those for the control group.

• Inhaled Transuranics in Rodents

Principal Investigator: C. L. Sanders

Other Investigators: J. K. Briant, and K. Rhoads

This project examines the interactions of external and internal radiation from mixtures of radionuclides that might be released from the nuclear fuel inventory.

Accidental inhalation of radionuclides rarely involves exposure to only a pure material but, instead, is complicated by the presence of numerous radionuclides and may be exacerbated by exposure to external irradiation. To investigate such potential effects, groups of Wistar rats were exposed to aerosols of high-fired $^{239}PuO_2$, $^{244}CmO_2$, and a PuO_2-CmO_2 mixture (1:1 activity ratio and 1355:1 mass ratio). Some groups also received acute, whole-body exposure to ^{60}Co gamma rays (440 R) immediately prior to inhalation exposure.

There were no significant differences in clearance of ^{239}Pu or ^{244}Cm from the lungs or the body between groups exposed to ^{60}Co irradiation and those that were not (Table 1). Nor was translocation of plutonium or curium to thoracic lymph nodes or skeleton significantly altered by gamma irradiation just prior to transuranic inhalation.

Chain-aggregate aerosols result from high-temperature vaporization of liquid metal fast breeder reactor (LMFBR) fuels. The behavior of these aerosols in the respiratory tract may be different from that seen for single-particle fuel aerosols.

In a recently completed graduate research project by J. K. Briant, young adult rats were exposed to an aerosol produced by laser vaporization of LMFBR fuel that was, by weight, 17.3% $^{239}PuO_2$ and 79.7% $^{238}UO_2$. The AMAD was 0.7 μm; GSD was 1.4. The aerosol was composed of a branched-chain aggregate. The initial body burden was 568 ± 100 nCi alpha activity, and the initial lung burden (ILB) was 112 ± 31 nCi alpha activity. Upper-airway (larynx, trachea, bronchi and carinae) retention accounted for about 1% of the ILB during the first week after exposure. Upper-airway clearance half-life (2 days after exposure) for the plutonium/uranium aerosol was about 30 days; deep-lung (alveolar) clearance half-time was about 100 days (Figure 1). These data indicate that deposition and respiratory-tract clearance of a branched-chain nuclear fuel aerosol is not substantially different from that of similar-sized spherical particles.

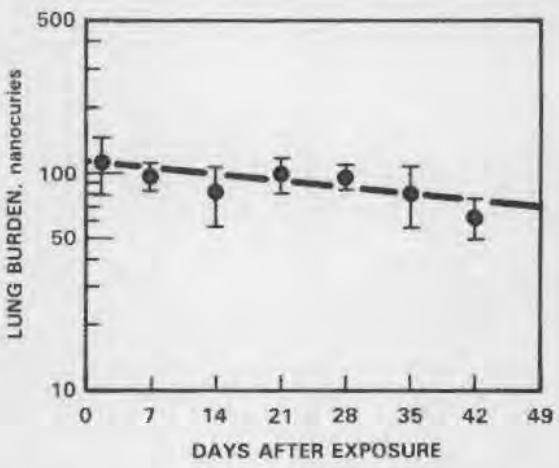

FIGURE 1. Clearance of Initial Lung burden for Rats Exposed to a Single Dose of Branched-Chain-Aggregate Plutonium/Uranium Fuel Aerosol.

TABLE 1. Lung and Whole-Body Clearance Functions for Plutonium and Curium Oxides with or Without External Gamma-Irradiation (440 R).

	Lung Clearance					Whole-Body Clearance				
Treatment	A1[a]	T1[a]	A2[a]	T2[a]	r[a]	1	T1	A2	T2	r
Pu Only	40	32			0.85	37	23	7.3	74	0.87
Pu + Gamma	36	48			0.77	32	18	16	100	0.88
Cm Only	79	6.2	23	58	0.98	93	13	31	1638	0.93
Cm + Gamma	30	2.4	68	22	0.95	116	37			

[a]A1 and A2 = amounts (nCi) cleared with half times T1 and T2 (days), respectively

• Low-Level $^{239}PuO_2$ Lifespan Studies

Principal Investigator: C. L. Sanders

Other Investigators: B. W. Killand, J. A. Mahaffey, K. E. McDonald, and K. Rhoads

This project will produce data to generate a dose-response curve for lung-tumor incidence in rats following inhalation of $^{239}PuO_2$ at levels producing a lifespan radiation dose to the lung of <5 to >2000 rad. A total of 2138 exposed rats and 1070 sham-exposed rats are on lifespan study. Individual initial alveolar depositions and radiation doses are estimated determined from ^{169}Yb whole-body counts, using a ^{239}Pu master lung-clearance curve and correcting for early differences in lung weight.

This study was designed to provide data for estimating the dose-response relationships of lung-tumor incidence in rats exposed by inhalation to $^{239}PuO_2$. The sizes of the exposure groups were determined by statistical analysis of previous higher-dose-level studies and the historical frequency of spontaneous lung tumors in Wistar rats.

All inhalation exposures have been completed. Initial alveolar depositions (IAD) were close to targeted values (0.5 nCi ^{239}Pu in the lowest group, increasing by a factor of two up to 128 nCi), ranging from a low IAD of 0.60 ± 0.15 nCi to a high of 150 ± 37 nCi (Table 1). The activity ratio of $^{169}Yb/^{239}Pu$ was about 14 for the lowest IAD groups, about 5 for the middle groups and 0.4 for the highest groups. Particle sizes (activity median aerodynamic diameters, AMAD) for inhaled ^{169}Yb or $^{239}PuO_2$ were smallest for the dose groups with an IAD up to 32 nCi, ranging from an AMAD of 1.0 to 1.6 μm. The AMAD of particles for the highest-dose groups was 1.9 to 2.6 μm (Table 1).

The mean IAD in the ^{239}Pu master lung-clearance curve study was about 9 nCi. Analysis of lung contents of rats to 441 days after exposure indicated that 76% of the inhaled ^{239}Pu was cleared from the lung with a half-time of 20 ± 4.9 days; the remaining 24% was cleared with a half-time of 180 ± 130 days. The effective half-time of ^{169}Yb in the lung was 14 days.

Lung weights increased during the first 2 mo after exposure (at 70 days of age), usually remaining constant in healthy rats, at about 1.6 to 1.8 g thereafter. About 80% of the total radiation dose was delivered during the first 2 mo after exposure. The relationship between age, body weight and lung weight was established by regression, allowing age and body weight to be used to predict lung weight during the first 4 mo of life. The

TABLE 1. Aerosol Characteristics of Inhaled ^{169}Yb, $^{239}PuO_2$ Particles. Values are mean ± standard deviation.

	Aerosol Characteristics		
IAD, nCi	AMAD, μm	GSD	Activity Ratio $^{169}Yb/^{239}Pu$
0.60 ± 0.15	1.10 ± 0.11	2.40 ± 0.39	14.50 ± 2.68
0.98 ± 0.25	1.00 ± 0.09	2.40 ± 0.22	14.10 ± 0.15
2.4 ± 0.69	1.60 ± 0.13	2.00 ± 0.06	5.19 ± 0.04
5.7 ± 1.2	1.40 ± 0.08	2.10 ± 0.10	5.28
7.5 ± 2.0	1.5 ± 0.08	2.30 ± 0.12	5.20
17 ± 7.6	1.50 ± 0.15	2.30 ± 0.27	0.39
32 ± 7.2	1.60 ± 0.09	2.20 ± 0.11	0.39
82 ± 20	1.90 ± 0.11	2.00 ± 0.03	0.42
150 ± 37	2.60 ± 0.04	2.50 ± 0.08	0.40

coefficient of determination for lung weight predicted by age and body weight was 72%. For individual rats, lung clearance of ^{239}Pu was similar to that of the groups (Figure 1), indicating that a master lung-clearance curve can be used to accurately predict radiation dose to lung.

A consistent and significant relationship was observed between actual ^{239}Pu in lung (measured by liquid scintillation counting) and levels estimated by ^{169}Yb whole-body counting at 7 and 14 days after exposure (Table 2). "System check" animals provided the basis for these analyses; there were four or five of these rats for every exposure group of 35. Even at the lowest IAD levels, good correlations were obtained between actual ^{239}Pu and estimated ^{239}Pu levels in the lung.

The cumulative radiation dose to the lung at time t for inhaled ^{239}Pu is estimated by the equation:

$$R_t = \frac{(51.23)(5.15)(1.11\ WBC_{14})}{(1000)\ L_t} \int_0^t Y(t)\ dt$$

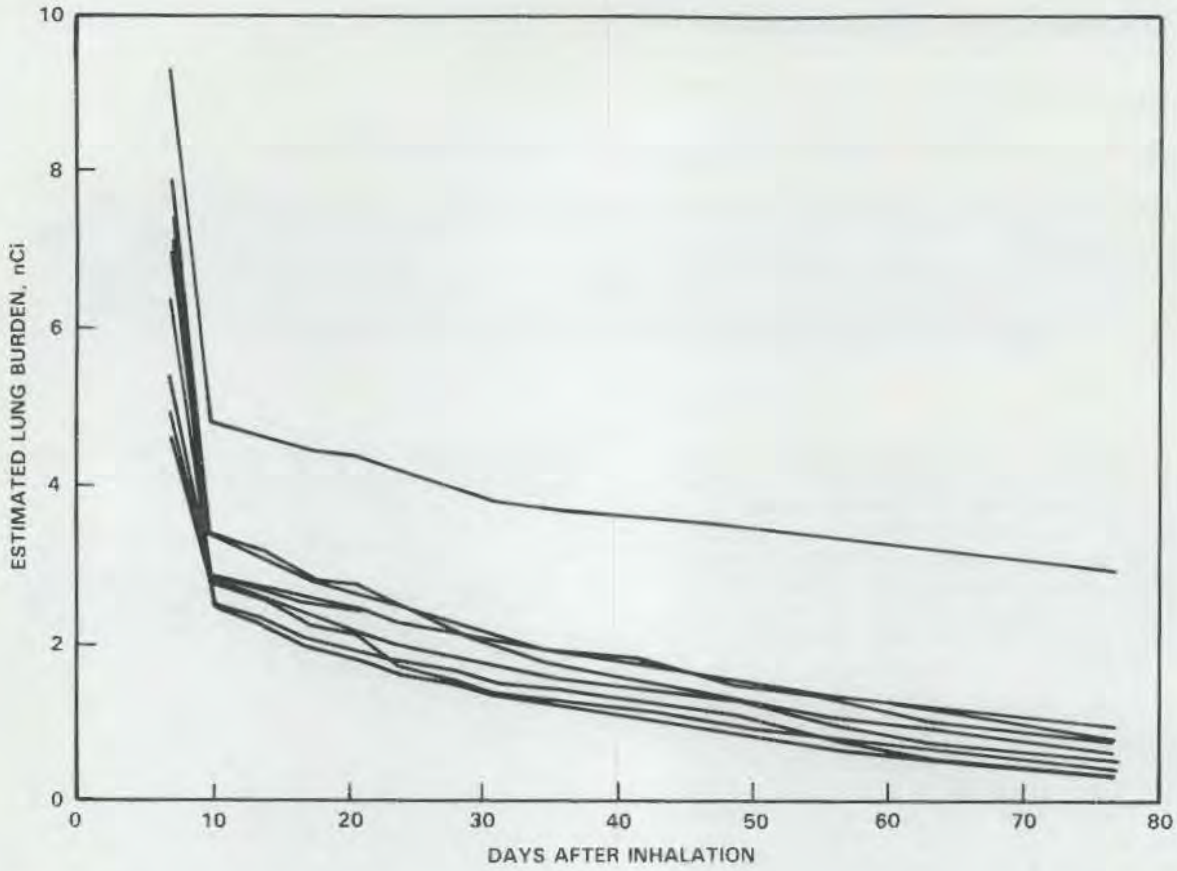

FIGURE 1. Clearance of Inhaled ^{239}Pu from the Lungs of Nine Rats Following Inhalation of ^{169}Yb, $^{239}PuO_2$. Lung ^{239}Pu levels were determined by whole-body counting of ^{169}Yb activity. Each curve is for an individual rat.

TABLE 2. Regression Characteristics of Prediction of ^{239}Pu Lung Contents, Using Liquid Scintillation Counting from Whole-Body Counting for ^{169}Yb at 14 Days after Exposure.

Target IAD	n	Regression Slope $\hat{\beta} \pm \hat{s}_{\beta}$	Residual Standard $\hat{s}$	Coefficient of Determination R^2
0.5	40	0.79 ± 0.012[a]	0.038	0.82
1	60	0.72 ± 0.0091[a]	0.057	0.84
2	34	0.86 ± 0.0087[a]	0.12	0.97
4	5	0.72 ± 0.015[a]	0.16	0.95
8	8	0.74 ± 0.011[a]	0.20	0.96
16	10	0.78 ± 0.017[a]	0.92	0.98
32	10	0.97 ± 0.012	0.87	0.96
64	9	0.83 ± 0.024	5.7	0.91
128	4	0.88 ± 0.010	2.9	0.96

[a]Not significantly different based on likelihood ratio test. Pooled estimate is 0.78 ± 0.022.

where R_t is the radiation dose in rad at time t; 51.23 is a constant; 5.15 is meV per alpha disintegration; 1.11 WBC_{14} is the estimated IAD based on whole-body counts at 14 days after exposure (WBC_{14}) and corrected for alveolar clearance from 0 to 14 days after exposure by the factor 1.11;

$$Y(t) = 0.764e^{-0.0237t} + 0.236e^{-0.00227t},$$

the lung clearance of ^{239}Pu; and

$$L_t = -1.23 + 0.0361t + 0.00647B_t - 0.000117B_t,$$

the lung weight based upon changes in age after exposure and body weight, B_t. A lung weight of 1.6 g was used subsequent to 2 mo after exposure.

About 85% of the radiation dose was delivered during the first year after exposure, most of it during the first few months. R_t ranged from 8.3 rad for an IAD of 0.6 nCi at 3 yr after exposure to 2100 rad for an IAD of 150 nCi (Figure 2). The dose contributed to the lung by ^{169}Yb was 0.1 rad at the lowest IAD, or 83 times less than the dose from ^{239}Pu (830 times less

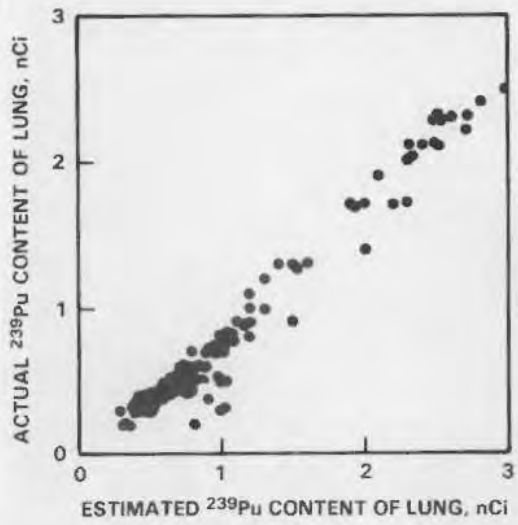

FIGURE 2. Correlation of Actual and Estimated ^{239}Pu Levels in the Lungs of Individual Rats in 0.60- to 2.4-nCi IAD Exposure Groups. Each point represents an individual rat.

on a dose-equivalent basis, employing a quality factor of 10 for alphas). Other groups exhibited ^{169}Yb doses of 0.08 to 0.69 rad, depending upon the ^{169}Yb IAD and $^{169}Yb/^{239}Pu$ ratio. The contribution of ^{169}Yb was considered insignificant with respect to expected biological effects from inhaled ^{239}Pu.

The status of the lifespan study, as of September 1983, is shown in Table 3. Most deaths in the highest-dose groups are due to lung tumors. Radiation pneumonitis and fibrosis were significant factors in mortality only in the 150-nCi group.

TABLE 3. Status of the Lifespan Study as of September 1983.

	No. Rats on Lifespan Study		No. Control Rats	
IAD, nCi	Alive	Dead	Alive	Dead
0.60	994	6	499	1
0.98	530	1	269	1
2.4	203	6	105	0
5.7	96	2	44	1
7.5	58	2	30	0
17	59	1	29	1
32	49	11	28	2
82	57	3	30	0
150	35	25	29	1

• Cigarette Smoke and Plutonium

Principal Investigator: R. E. Filipy

Other Investigators: W. J. Bair, and R. L. Buschbom

Technical Assistance: S. D. Harris, K. E. Lauhala, and B. G. Moore

Cigarette-smoke-exposed rats and beagle dogs retain greater amounts of inhaled $^{239}PuO_2$ in their lungs than do animals with no smoke exposure. Autoradiographic techniques with liquid photographic emulsion and cellulose nitrate track-etch film are being used to determine what effect cigarette-smoke exposure has on spatial distribution of plutonium particles in the lung.

The major objective of this project is to obtain experimental data on whether cigarette smokers are at greater risk than nonsmokers to potential health effects of inhaled plutonium. Because cigarette smokers constitute a large fraction of the population, a synergistic effect of plutonium and cigarette smoke might influence estimates of the health risk for plutonium and other transuranics released to the environment.

Prolonged exposure to cigarette smoke caused a significant reduction in the clearance rate of $^{239}PuO_2$ from the lungs of rats within the first 6 wk after inhalation of the radionuclide. Smoke-exposed rats and sham-exposed rats that inhaled the plutonium aerosol retained approximately 65 and 40%, respectively, in their lungs at the end of the 6-wk period. Autoradiographs of rat lung sections indicated that the parenchyma was the primary site of retained plutonium in both groups. Autoradiographs of the inner surfaces of pulmonary airways indicated that at the time of death of sham-exposed rats, nearly eight times more plutonium was being cleared from the lungs via the mucociliary clearance pathway than in smoke-exposed rats. These data and the methods used were summarized in the 1982 Annual Report.

Groups of beagle dogs were exposed to cigarette smoke or were sham-exposed for approximately 60 wk after exposure to an aerosol of $^{239}PuO_2$. Based on in vivo determination of lung burdens, the smoke-exposed dogs retained more plutonium in their lungs than did the sham-exposed dogs, although the difference between groups was not as great as for rats.

We are now developing an autoradiographic procedure for location and quantitation of plutonium particles in the airways of dogs. At necropsy, individual lobes of the lungs are filled with air, and 1.5% cacodylate-buffered glutaraldehyde is perfused through the pulmonary vasculature to avoid displacement of plutonium particles within the airways. The lung parenchyma is stripped from the major airways of the fixed lung lobe to approximately the level of the secondary bronchioles (Figure 1). The isolated airways are cut into sections, as indicated in Figure 1, split, and flattened against sheets of cellulose nitrate track-etch film so that the film is exposed to what had been the inner surfaces of the airways. After 6 wk of exposure, the film is removed from the tissue and immersed, with agitation, in a 4 N NaOH solution at 60°C for 150 min. The film is then washed in water, dried, and mounted on glass microscope slides for viewing.

Figures 2 and 3 are backlighted photomicrographs of the film after etching. Each point of light in Figure 2 represents the path of one alpha particle. The film in Figure 3 was exposed to the inner surface of the bronchiole section numbered "1" in Figure 1. There was a relatively dense concentration of plutonium particles in that section, shown on the film as clusters of alpha tracks (Figure 3).

The concentration of plutonium particles on the inner surface of the airways of the dog was difficult to quantitate because individual particles were not as easily distinguishable on the track-etch film as on liquid-emulsion autoradiographs of rat pulmonary airways. As a first approach, the concentrations of etched "holes" in the films were subjectively graded from 1 through 5; those grades are indicated in parentheses following section identification numbers in Figure 1. Particle densities were generally highest in the smallest airways; e.g., sections 1, 3, 6, 14, 15 and 17. Sections which included major bifurcations in the airways (10, 16 and 19) did not have markedly high concentrations.

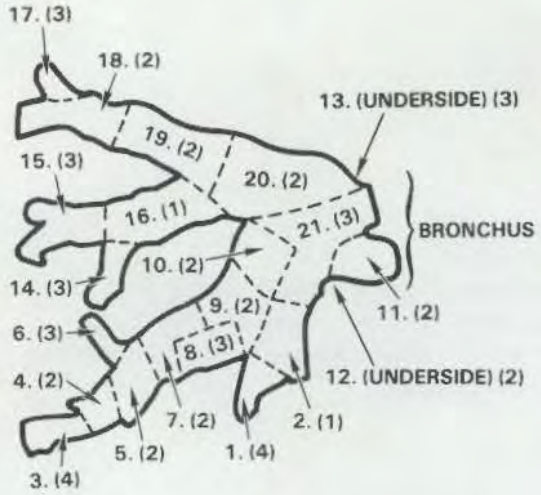

FIGURE 1. Diagram of Pulmonary Airways From the Left Apical Cardiac Lobe of a Dog Lung. See text for further explanation.

FIGURE 2. Track-Etch Film Autoradiograph of Two Plutonium Particles (Photomicrograph).

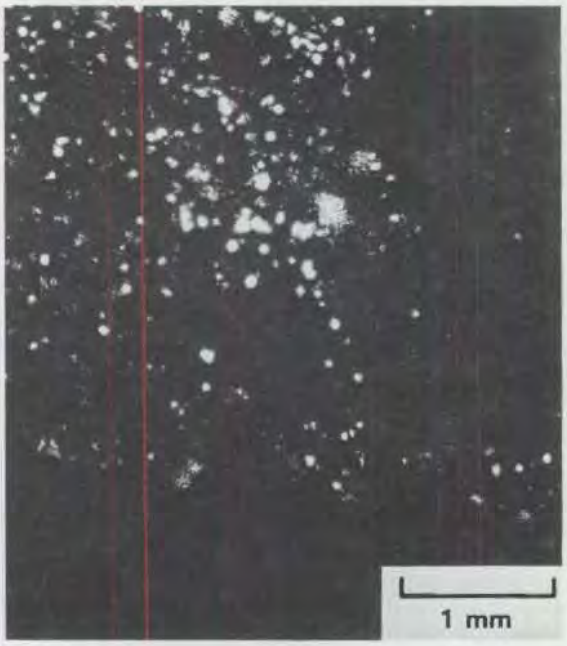

FIGURE 3. Track-Etch Film Autoradiograph of a Portion of Bronchial Section 1 (See Figure 1). (Photomicrograph).

Since the tissue is not destroyed by this kind of autoradiography, it should be possible to reconstitute the specimen by immersion in fixative, to process it by routine histotechnical methods, and to produce liquid-photographic-emulsion autoradiographs from cross-sections of the same airways from which the track-etch autoradiographs were made. Our efforts along these lines have thus far been unsuccessful.

We plan to apply these procedures to the lungs from 12 smoke-exposed dogs (six of which had also inhaled plutonium) and lungs from 5 dogs that inhaled plutonium but were not smoke-exposed. First, a single lobe from each lung will be used for comparing plutonium deposition in smokers and nonsmokers. Track-etch film autoradiographs and cross-sectional, liquid-emulsion autoradiographs will be made from immediately adjacent portions of each airway section. We hope that these preparations will reveal the concentration of particles as well as their location within the tissues.

• Toxicology of Krypton-85

Principal Investigator: J. E. Ballou

Other Investigators: G. E. Dagle, H. S. DeFord, D. W. Murphy, M. R. Sikov, H. D. Tolley, and D. H. Willard

The purpose of this research is to obtain biological data to supplement earlier evaluations of the hazards of ^{85}Kr exposure. The studies include both short-term and chronic exposures of rats, dogs and sheep to determine tissue distribution and retention kinetics for metabolic modeling. We have also included dose-effect studies in rats exposed acutely as newborns or chronically for most of their life span to identify tissues at risk and determine tumorigenic potency.

This is the final report for this project, which terminated at the end of FY 1983. Progress Reports were presented in Annual Reports for 1975 through 1982.

Highlights of the research include the following: 1) the demonstration of placental transfer and fetal incorporation of inhaled ^{85}Kr in pregnant sheep (Toxicol. Appl. Pharmacol. 45: 290, 1978); 2) a description of ^{85}Kr distribution and retention in the rat (Health Phys. 43: 669, 1982); 3) the demonstration of a low hazard potential for the fetus associated with ^{85}Kr exposure during pregnancy (submitted to Health Phys.); 4) the identification of basal cell carcinoma of the skin as the primary malignancy associated with exposure of newborn rats to ^{85}Kr atmospheres (submitted to Health Phys.; the threshold for induction of this lesion appears to be less than 1000 rad to the skin surface); and 5) the determination that chronic exposure to ^{85}Kr levels up to 10,000 times the MPC for the general population did not influence ^{85}Kr distribution, weight gain or tumor incidence in rats exposed for 808 days. Significant ($P = 0.05$) lifeshortening in the 10^4-times MPC group was suggested by one statistical test and rejected by another (submitted to Health Phys.). Findings from these studies support the adequacy of the recommended MPC for ^{85}Kr and indicate that a negligible hazard is associated with the present environmental level of ^{85}Kr.

• Toxicology of Thorium Cycle Nuclides

Principal Investigator: J. E. Ballou

Other Investigators: A. C. Case, G. E. Dagle, R. A. Gies, D. L. Haggard, D. W. Murphy, J. L. Ryan, and H. D. Tolley

The purpose of this project is to investigate the biological hazards associated with uranium-thorium breeder fuels and fuel recycle process solutions. Initial studies emphasize the metabolism and long-term biological effects of inhaled ^{235}U-^{232}U nitrate and oxide fuel materials and of ^{231}Pa, a major, long-lived, radioactive waste product.

Male Wistar rats exposed to graded doses of ^{231}Pa citrate aerosols (1, 17 or 56 nCi initial lung burden; ILB) have been observed for their life span. Retention in the lungs, liver and skeleton (data for the three dose groups were combined) is shown in Figure 1, together with previously reported data on retention of ^{233}U (Annual Report, 1982). The curves were constructed using data from both sacrificed and lifespan rats, as indicated. After 7 days, retention was described by either one- or two-exponential functions as detailed in Table 1, which also shows ^{233}U retention parameters for comparison. The short-lived lung-clearance component usually associated with absorption and mucociliary processes was not included in these data, i.e., only retention intervals for 7 to 200 days and >200 days are shown.

Cumulative radiation dose to the tissues was calculated assuming clearance according to the equations shown in Figure 1 and summing over the individual rat's life span. The estimated lung doses were divided into dose ranges for presentation in Table 2 and are shown with the corresponding malignant-lung-tumor incidence. The overall incidence of malignant tumors is given in detail in Table 3.

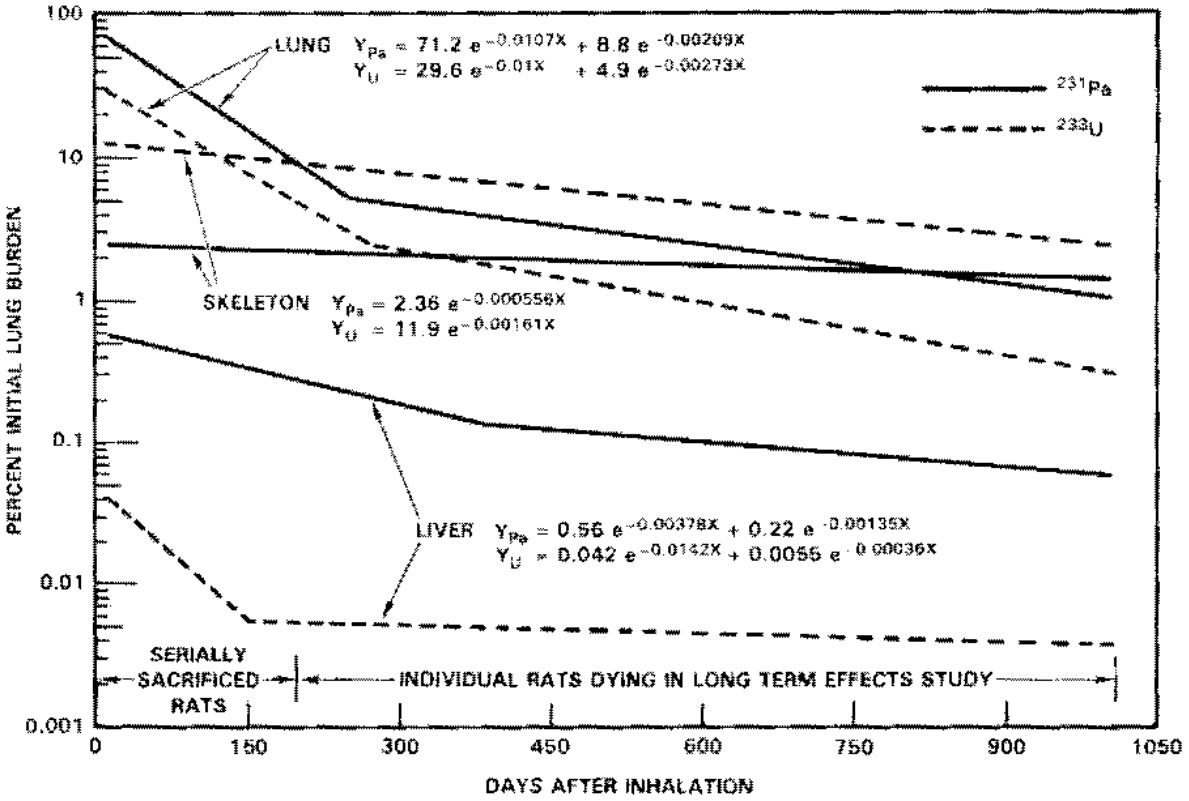

FIGURE 1. Retention of Inhaled ^{231}Pa Citrate and ^{233}U Nitrate in Major Tissues of Rats.

TABLE 1. Tissue Retention Kinetics for Inhaled ^{231}Pa Citrate and ^{233}U Nitrate in the Rat.

Retention Interval, days	Retention Parameters in Major Tissues[a]					
	Lung		Skeleton		Liver	
	% ILB	$T_{1/2}$, days	% ILB	$T_{1/2}$, days	% ILB	$T_{1/2}$, days
7-200	71	65	--	--	0.6	180
	(30)[b]	(69)			(0.04)	(50)
>200	9	340	2.4	1200	0.2	510
	(5)	(230)	(1.2)	(430)	(0.006)	(2000)

[a] Retention in lung and liver was described by two exponential functions covering the time intervals 7-200 days and times >200 days. Skeletal retention was described by a single exponential for the time period 7 to ~1000 days after exposure.
[b] Values in parentheses are for ^{233}U; other values are for ^{231}Pa.

Malignant lung tumors were clearly associated with ^{231}Pa inhalation. The dose-related response for these lesions agrees well with results obtained with inhaled ^{238}Pu, ^{239}Pu, ^{241}Am, ^{253}Es, ^{233}U and ^{232}U nitrate aerosols. The lowest ^{231}Pa dose which produced a lung tumor was ~90 rad, accumulated over time periods of 535 days (one papillary adenocarcinoma) and 683 days (one adenosquamous carcinoma).

Osteosarcomas of the skeleton were uncommon in these rats, reflecting the relatively low (~1 to 2% ILB) translocation of ^{231}Pa from lung to skeleton compared with other actinides we have studied. Protactinium-231 was translocated to the liver in amounts similar to those observed with ^{239}Pu and was similarly ineffective in the induction of liver tumors. Further comparisons of ^{231}Pa and the high-specific-activity uranium isotopes ^{233}U and ^{232}U will be made when radioanalyses are completed.

TABLE 2. Dose-Related Incidence of Malignant Lung Tumors in Rats Exposed to Inhaled ^{231}Pa Citrate Aerosols.

Cumulative Lung Dose, rad	Number of Rats in Dose Range	Percent Incidence of Specific Tumor Type			
		Adenocarcinoma	Squamous Cell Carcinoma	Adenosquamous Carcinoma	Other[a]
≤10	50	0	0	0	0
11-100	17	6	0	6	0
101-1000	85	25	5	4	1
1001-4000	24	71	4	0	8
Control (includes treated controls)	197	0	0	0	0

[a] Includes malignant neoplasms, carcinomas and hemangiosarcomas of the lung.

TABLE 3. Number of Malignant Tumors in Rats Exposed to Inhaled ^{231}Pa Citrate Aerosols.

			Initial Lung Burden, nCi ± SD		
	Control	Treated Control	1 ± 0.5	17 ± 9	56 ± 26
Skeleton					
Osteosarcoma			1		
Synovial Sarcoma		1			
Lung					
Malignant Neoplasm					1
Carcinoma				1	
Squamous Cell Carcinoma				1	4
Adenocarcinoma					8
Bronchiolar Adenocarcinoma				2	3
Papillary Adenocarcinoma				5	21
Adenosquamous Carcinoma				3	1
Fibrous Histiocytoma		2	1	1	1
Hemangiosarcoma					1
Malignant Lymphoma		1	1		
Liver					
Hepatoma	1			2	
Fibrous Histiocytoma	2			1	
Leukemia		1			
Skin					
Squamous Cell Carcinoma		1	1	1	
Basal Cell Carcinoma		1			
Sebaceous Adenocarcinoma		1			
Fibrous Histiocytoma			1		
Subcutaneous Tissue					
Fibrosarcoma			1	1	3
Fibrous Histiocytoma	7	6	4	3	2
Leiomyosarcoma				1	
Osteosarcoma	1				
Neurofibrosarcoma	3	4	1		
Breast					
Adenocarcinoma					1
Endocrine Glands					
Carcinoma		1	1		
Cortical Cell Carcinoma		2	2	1	1
Pheochromocytoma	4		1		1
Osteosarcoma	1				
Malignant Lymphoma	1				
Prostate					
Carcinoma	1				
Salivary Gland					
Adenocarcinoma		1			
Fibrosarcoma		1			
Neurofibrosarcoma	1				
Lymph Node					
Fibrous Histiocytoma	1	2		1	1
Hemangiosarcoma		1			
Malignant Lymphoma	7	2	3	8	
Viscera					
Malignant Neoplasm		1			
Transitional Cell Carcinoma		1			
Adenocarcinoma		1	3		1
Sarcoma			1		
Fibrosarcoma	1				
Fibrous Histiocytoma	1	2		1	
Liposarcoma		1		1	
Leiomyosarcoma					1
Hemangiosarcoma		1			1
Neurofibrosarcoma	1	1			
Malignant Lymphoma	5	5	5	2	3
Leukemia	3	2	1	5	1
Nasal Cavity					
Squamous Cell Carcinoma		1			
NUMBER OF TUMORS/NUMBER OF RATS	41/100	44/97	28/59	41/59	56/60
NUMBER OF RATS WITH TUMORS	38	40	25	37	43
NUMBER OF RATS WITH MULTIPLE TUMORS	2	4	2	5	12

• Inhalation Hazards to Uranium Miners

Principal Investigator: F. T. Cross

Other Investigators: R. L. Buschbom, G. E. Dagle, P. O. Jackson, R. F. Palmer, and H. A. Ragan

Technical Assistance: G. Brodaczynski, C. R. Petty, and W. L. Skinner

This project is investigating levels of uranium mine air contaminants, using both large and small experimental animals to model human respiratory system disease. Lung cancer and deaths by degenerative lung disease have reached epidemic proportions among uranium miners, but the cause-effect relationships for these diseases are based on inadequate epidemiological data. This project identifies agents or combinations of agents (both chemical and radiological), and their exposure levels, that produce respiratory tract lesions, including respiratory epithelial carcinoma, pneumoconiosis, and emphysema.

Small-Animal Studies

Approximately 2000 male, specific-pathogen-free Wistar rats are currently on study; the completed 4000 and 5000 Series experiments (Tables 1 and 2) were designed to clarify the roles of unattached RaA daughters, and the degree of radon daughter disequilibrium, in the development of respiratory system disease. The nearly completed 6000 and 7000 Series experiments (Table 3) are designed to develop the relationships between response and exposure to radon daughters (at two rates of exposure) and carnotite uranium ore dust. The 8000 Series experiments (Table 4) are designed to extend the exposure-response relationships to levels appropriate to current exposure conditions in the mines and to lifetime environmental exposures. The 9000 Series experiments (Table 5) continue the "low-dose" studies at exposure rates comparable to former occupational working levels (10 WL) to further evaluate the hypothesis that the tumor probability per working level month (WLM) exposure increases with decrease in exposure and exposure rate. Concurrent exposure to varying levels of uranium ore dust tests, in addition, the hypothesis that irritants (both specific and nonspecific) act synergistically with radiation exposures, the synergism increasing with decrease in exposure level. The exposures of 9000 Series animals are currently in progress; the exposures of 4000, 5000, 6000, 7000 and 8000 Series animals are completed; some of the 7000 and 8000 Series animals are still living.

TABLE 1. Radon-Daughter Unattachment Fraction Study in Rats (4000 Series experiments).

Exposure Regimen[a]	Total Exposure, WLM[b]
500 WL Radon Daughters Low RaA Unattachment (~2%) ~15 mg/m³ Uranium Ore Dust	5120
500 WL Radon Daughters Intermediate RaA Unattachment (~10%) ~0.7 mg/m³ Uranium Ore Dust	5120
500 WL Radon Daughters High RaA Unattachment (~24%) ~0.4 mg/m³ Uranium Ore Dust	5120
Controls	

[a] 32 animals in each group, exposed 90 hr/wk

[b] Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

TABLE 2. Radon-Daughter Disequilibrium Study in Rats (5000 Series experiments).

Exposure Regimen[a] Daughter Equilibrium Ratios				Average Equilibrium Factor	Total Exposure, WLM[b]
Rn	RaA	RaB	RaC-C'		
1	0.9	0.4	0.2	0.4	5120
1	0.5	0.07	0.01	0.1	5120
Controls					

[a] 32 animals in each group, exposed 90 hr/wk at 500 WL and 15 mg/m³ uranium ore dust

[b] Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

TABLE 3. Exposure-Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (6000 Series experiments).

Number of Animals[a]	Exposure Regimen[b,c]	Total Exposure, WLM[d]
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	10,240
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	5120
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	2560
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	1280
64	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	640
128	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	320
32	Controls	

[a] Number of animals is sufficient to detect the predicted incidence of lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 9200 WLM (see footnote d), and 0.13% spontaneous incidence.

[b] Exposure rate, 90 hr/wk; planned periodic sacrifice.

[c] Study will be repeated @ 100 WL rate (without periodic sacrifice) to augment previous limited exposure-rate data (7000 series experiments).

[d] Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration. Previous exposure at 900 WL for 84 hr/wk to 9200 WLM produced an 80% incidence of carcinoma.

TABLE 4. Low-Exposure Response Relationship Study for Radon-Daughter Carcinogenesis in Rats.

Number of Animals[a]	Exposure Regimen[b]	Total Exposure, WLM[c]
64	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	640[d]
64	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	320[d]
160	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	160
352	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	80
448	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	40
512	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	20
160	Controls	

[a] Number of animals is sufficient to detect lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 640 WLM (see footnote c), and 0.13% spontaneous incidence.

[b] Exposure rate, 90 hr/wk; planned periodic sacrifice of 32 animals from group.

[c] Recent exposures indicate a tumor incidence of 16% at 640 WLM. Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

[d] Repeat exposure is for normalization with Table 3 data.

We have concluded that the most significant lesions related to radon daughter and carnotite ore-dust exposures in the 4000 and 5000 Series experiments are neoplastic and non-neoplastic lesions of the respiratory tract. Histopathologic data for these lesions and survival times were shown in the 1982 Annual Report. Preliminary histopathologic data for the 6000 Series sacrifice animals are shown in Table 6.

The unattachment fraction and disequilibrium studies showed that the risk of primary lung tumors significantly increases with increasing radon-daughter unattachment fraction and disequilibrium. The increase was of borderline significance in the disequilibrium study when the total number of rats with lung tumors was intercompared. One would have expected a stronger significance if equilibrium radon daughters (equilibrium factor = 1) had been compared with the 0.1 equilibrium factor exposure conditions. However, results of the animal exposures concur with modeling predictions of increasing radiation dose with unattachment fraction and disequilibrium of radon daughters. Because tumors commonly occur more peripherally in animals than in humans, radon-daughter disequilibrium, in particular, is thought to be of greater significance in human exposures. When lung lesions are compared, a 0.1 equilibrium factor exposure condition is approximately equivalent to an exposure condition with somewhat less than 10% RaA unattachment.

Nasopharyngeal squamous metaplasia and, generally, carcinoma increased with increase in the RaA unattachment fraction. There was no indication that high disequilibrium radon daughter exposures without concomitant high RaA unattachment produced more nasal carcinoma.

The lung carcinomas in the unattachment fraction and disequilibrium studies were roughly identified as proximal or distal according to the size of associated or neighboring bronchi and bronchioles. They were generally estimated to be about 50% proximal (bronchi-related) and 50% distal (bronchiole-related). The histologic classification was approximately 70% bronchogenic carcinoma and 30% bronchioloalveolar carcinoma. These data are in constrast to the nearly 100% proximal location and bronchogenic classification of human lung cancers.

The preliminary serial sacrifice data shown in Table 6 for the exposure-response relationship study (5000 Series experiments) indicated that, in most cases, the earliest lung tumors occurred approximately 1 yr following completion of exposures. At exposure levels less than 1280 WLM, no lung cancers were noted earlier than 18 mo after exposure.

TABLE 5. Ultralow Exposure Rate Study for Radon-Daughter Carcinogenesis in Rats.

Number of Animals[a]	Exposure Regimen[b]	Total Exposure, WLM[c]
64	10 WL Radon Daughters 15 mg/m³ Uranium Ore Dust	320
64	10 WL Radon Daughters 3 mg/m³ Uranium Ore Dust	320
352	10 WL Radon Daughters 15 mg/m³ Uranium Ore Dust	80
352	10 WL Radon Daughters 3 mg/m³ Uranium Ore Dust	80
312	10 WL Radon Daughters 15 mg/m³ Uranium Ore Dust	20
512	10 WL Radon Daughters 3 mg/m³ Uranium Ore Dust	20
96	Controls	

[a] Number of animals is sufficient to detect lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 640 WLM (tumor incidence is approximately 16% at 640 WLM, and 0.13% spontaneous incidence.

[b] Exposure rate, 90 hr/wk; planned periodic sacrifice of 32 animals in each group.

[c] Working level (WL) is defined as any combination of the short-lived daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

Large-Animal Studies

Thirty-five beagle dogs are currently on study to determine the pathogenic role of inhalation exposure to carnotite uranium ore dust. We are particularly interested in clarifying the role of the ore dust in the production of the massive pulmonary fibrosis observed in an earlier study, in which beagle dogs were exposed to radon daughters and mixtures of uranium ore dust and cigarette smoke. The present study (chronic, head-only exposures) began when the dogs were about 2½ yr old. Along with routine physical examinations and periodic hematologic and clinical chemistry measurements, histopathologic, radiometric, morphometric, renal and pulmonary function evaluations were conducted on these dogs.

The most notable pulmonary lesions observed in dogs exposed for up to 4 yr are vesicular emphysema, peribronchiolitis and focal pneumoconiosis. These lesions, described in the 1981 Annual Report, were contrasted with the lesions observed in the earlier study, in which beagle dogs were exposed to mixtures of radon daughters, uranium ore dust and cigarette smoke. Three animals were killed following 6 yr of exposure to determine any further progression of pulmonary lesions. These data have not yet been analyzed.

Radiometric analyses of lung tissues were performed on two of three animals killed each year (through 4 yr) following the start of uranium-ore-dust exposures. Previous inhalation studies in our laboratory involving three species of animals (rat, hamster and beagle dog) and two varieties of uranium ore dust in secular equilibrium (carnotite and pitchblende) revealed consistent separation of uranium and thorium isotopes in tissues of animals at necropsy. The pattern of higher retention of thorium than uranium was noted shortly after exposures began and suggested that uranium ore, when present as an airborne contaminant, should be regulated on the basis of its constituent radionuclides, making the ^{230}Th level the determining factor in maximum permissible air concentrations. Because the carnotite ore experiments were confounded by the presence of other air contaminants, such as radon daughters, diesel engine exhaust and cigarette smoke, and because subsequent measurements of miners' lungs at the University of Utah revealed that uranium and thorium isotopes remain in near-equilibrium, it was decided to repeat some of these measurements in the lungs of beagle dogs exposed to carnotite ore dust alone. These data were also shown in the 1982 Annual Report. Further analysis on

TABLE 6. Summary of Malignant Lung Tumors in Serially Sacrificed Animals (6000 Series experiments).

Sacrifice Time, mo[a]	Nominal Exposure, WLM[b]	No. of Rats	Adenocarcinoma	Epidermoid Carcinoma	Adenosquamous Carcinoma
6	10,240	6	--	1	--
12	10,240	5	4[c]	1	--
6	5120	6	-	--	--
12	5120	6	1	--	--
18	5120	3	2[c]	1	1
6	2560	6	--	--	--
12	2560	6	--	--	--
18	2560	6	4	--	--
6	1280	6	--	--	--
12	1280	6	--	--	--
18	1280	6	--	--	--
6	640	6	--	--	--
12	640	6	--	--	-
18	640	5	--	--	-
6	320	6	-	--	--
12	320	6	--	--	--
18	320	6	--	--	--
6	Control	6	--	-	--
12	Control	6	--		--
18	Control	6	-	-	-
	Totals	114	31	3	1

[a]Sacrifice times are months from completion of exposures.

[b]Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α energy. Working level months (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

[c]One rat also had an epidermoid carcinoma.

long-lived radionuclides in two dogs exposed for 6 yr to uranium ore dust show qualitatively consistent data, with an average $^{230}Th/^{238}U$ ratio of 17.1. Tissues from two other dogs formerly exposed to mixtures of 4400 WLM radon daughters and uranium ore dust (one with, the other without cigarette smoke) were also analyzed for long-lived radionuclides. The exposures to radon daughters and uranium ore dust terminated in 1974. Radiometric analyses 8 yr later showed an average $^{230}Th/^{238}U$ ratio of 10.5. The smaller of the two ratios (8.4 versus 12.7) was in the dog exposed to cigarette smoke. There is no clearcut evidence from these limited data that the explanation for the near-equilibrium conditions found in the human data might be due to the longer time elapsed between exposures of the miners and autopsy of their lungs. The previous animal data have always reflected the $^{230}Th/^{238}U$ ratios immediately following exposures to uranium ore dust.

We have recently supplemented serum tests with urinalyses to determine the presence of kidney damage in the ore-dust-exposed dogs. Renal function was evaluated on six uranium-ore-dust-exposed and six sham-exposed dogs following 6 yr of exposure for 20 hr/wk to 15 mg/m³ uranium ore-dust concentations. Tests conducted on integrated urine samples were: osmolality, specific gravity, glucose, creatinine, protein, sodium, potassium, chloride, alkaline and acid phosphatases, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and a microscopic examination. With the exception of glucose, results of the battery of tests were equivalent for the exposed and sham-exposed dogs. The mean glucose excreted in 24 hr by the exposed dogs was 27.3 mg, versus 10.1 mg by the sham-exposed dogs ($P < 0.05$). This difference was equally apparent when glucose excretion was expressed as mg/kg of body weight or as mg/ml of urine. However, the ability of the kidneys to concentrate urine following deprivation of water for an extended period was not been compromised by prolonged exposure to uranium ore dust.

• Fetal and Juvenile Radiotoxicity

Principal Investigator: M. R. Sikov

Other Investigators: R. L. Buschbom, W. C. Cannon, D. B. Carr, G. E. Dagle, P. L. Hackett, B. J. Kelman, D. D. Mahlum, B. J. McClanahan, and D. N. Rommereim

Technical Assistance: J. A. Cushing, B. Hogberg, T. A. Pierce, R. L. Rommereim, and S. A. Watson

This project is directed at obtaining detailed comparative information on the deposition, distribution, retention, and toxicity of radionuclides in the prenatal and juvenile mammal. Because quantitative data cannot necessarily be extrapolated to man, emphasis is also directed toward establishing patterns, phenomenologic interactions, and relationships which will be useful in determining appropriate exposure levels for the rapidly growing infant or child and for pregnant women.

An experiment to evaluate the effects of foster-rearing of newborn rats on the lifetime effects of ^{239}Pu exposure has demonstrated that, while longevity is primarily dependent on radiation history, growth rate and adult body weight are related to the exposure and fitness of the foster dam. Results from an ongoing comparison of the dosimetry and embryotoxicity of ^{239}Pu and ^{241}Am confirm that the former has a greater effect on the conceptus, on the basis of dose administered to the dam. Studies in the guinea-pig perfusion system have confirmed that maternal blood flow to the placenta is decreased by intravenous doses of 30 nCi/g ^{239}Pu and suggest that the threshold lies at approximately 5 nCi/g body weight. A dose of 30 nCi/g of ^{241}Am does not affect blood flow. Clearance of the two actinides is similar when blood flow effects are not considered.

The rationale and protocol for an experiment to evaluate the effects of foster-rearing of neonatal rats on the incidence of ^{239}Pu-induced bone tumors were described in previous Annual Reports (1981, 1982). In brief, pregnant rats were injected intravenously at 19 days of gestation (dg) with 60 nCi/g of a citrated (70-fold molar excess) ^{239}Pu solution or with a citrate solution. At 1 day of age, the offspring of some litters were fostered to lactating females that had received the same (or the opposite) exposure as the dams; others were kept with their dams. Thus, six experimental groups were formed, as shown in Table 1. Within each time block, control dams were killed 1 mo after the last exposed dam had died; surviving offspring were killed at 30 mo of age. All animals were necropsied, and lesions (including tumors) were prepared for histopathological examination.

Kaplan-Meier survival curves were computed and plotted, and statistical comparisons were made using the Breslow and the Mantel-Haenszel statistics. Results showed that the longevity of dams was significantly reduced by ^{239}Pu exposure but was not significantly affected by rearing a foster litter of the same (or opposite) exposure group (Table 1). Survival of control and exposed offspring was uniformly greater than that of their dams. Survival curves were significantly depressed in all groups of offspring that were exposed prenatally, but a consistent effect of fostering could not be detected.

Latency to development of grossly detectable mammary tumors was decreased in all groups of exposed pups relative to those which were not exposed prenatally. Latency was shorter in exposed pups fostered to a control mother (XC) than in those kept with their own mother (X) or fostered to an exposed mother (XX). These tumors have not yet been confirmed by histological evaluation.

Following the pattern described in last year's Annual Report for the period through 1 yr of age, weight curves of the offspring continued to more closely reflect postnatal rearing than prenatal exposure. Although the data become less clear at older ages, because of deaths within each group and debilitation prior to death, statistical evaluation using analysis of variance demonstrates that these differences are statistically significant. It is of biological importance that these effects on growth and body weight are dissociated from direct effects on postnatal survival attributable to prenatal/neonatal exposure.

Radioanalysis was performed on tissues from other animals that had received identical exposures, as well as from deced-

TABLE 1. Interactions Between Fostering and ^{239}Pu Exposure on Longevity of Maternal Rats and Their Offspring.

Prenatal Exposure of Offspring	Exposure of Foster Mother	Group Designation	Median Survival, Days of Age		
			F_0 females	F_1 females	F_1 Males
Control	[a]	C	Sac[b]	862	812
Control	Control	CC	Sac[b]	852	844
Control	Exposed	CX	429	843	826
Exposed	[a]	X	294	784	707
Exposed	Exposed	XX	329	734	783
Exposed	Control	XC	Sac[b]	760	733

[a] Not fostered.

[b] Sacrificed unexposed females were killed at 1 month after all exposed females within same four-block were dead.

ents, to allow calculation of radiation doses. Organ burdens and concentrations for representative tissues, shown in Figure 1, are in general agreement with data from previous experiments. Further detailed data analyses are in progress to establish radiation doses to other relevant tissues. Total plutonium content of the offspring in the groups reared by plutonium-exposed females (partially illustrated by liver) increased during the first day of postnatal life, reflecting continued intake and deposition from milk. As a result, postnatal liver (and body) burdens in the XC groups were less than those in the X or XX groups and, to a first-order approximation, summation of body burdens in the XC and CX groups equal those in the X and XX groups. A similar relationship between groups was seen when concentrations in liver were considered. However, the decrease in concentration with time was more precipitous because of the progressive growth of the offspring, and hepatic concentrations were barely significant after 3 mo of age. Clear differences in skeletal deposition could not be detected among the three prenatally exposed groups, although all were markedly higher than in the CX group. The bones of the head tended to have higher initial concentrations than those of the appendicular skeleton (illustrated by the mandible and femur, respectively), and the rate of decrease tended to be lower as the result of slower growth in the postnatal period. Retention was tenacious after the initial rapid decline through 3 mo of age, and the animals of the three prenatally exposed groups received significant skeletal exposures throughout the duration of the study.

Results from our previous experiments suggested that prenatal rats were less affected by intravenous exposures of their dams to ^{241}Am than to ^{239}Pu, on an administered dose basis. Much of the difference was attributable to differences in placental transfer and the resulting radiation dose received by the fetus, but we could not rule out the influence of strain differences, which we had demonstrated with plutonium. To better define these factors, an experiment was initiated to obtain a contemporaneous comparison of embryonic response and to obtain additional dosimetric data. Based on approximate relative fetoplacental concentrations, calculated from the data of our earlier experiments, pregnant rats at 9 or 15 dg were intravenously injected with 10 or 30 nCi/g of ^{239}Pu or with 30 or 90 nCi/g of ^{241}Am. To reduce variability, the animals were bred during a 2-hr period in the morning and are thus approximately 8 hr younger than those used in previous experiments. The study is ongoing, but some interesting relationships are already apparent (Table 2). Prenatal mortality was increased by the highest dose of plutonium or americium when administered at 9 dg; the increase was of similar magnitude in both groups despite the threefold difference in administered dose. Weights of the 20-dg fetuses were affected only by exposure at 9 dg; a significant decrease was seen at 30 nCi/g plutonium and an almost-significant decrease at 90 nCi/g of americium. Placental weight was significantly reduced only after exposure to the highest dose of plutonium at 9 dg. Exposure at 15 dg did not affect prenatal mortality, fetal weight, or placental weight.

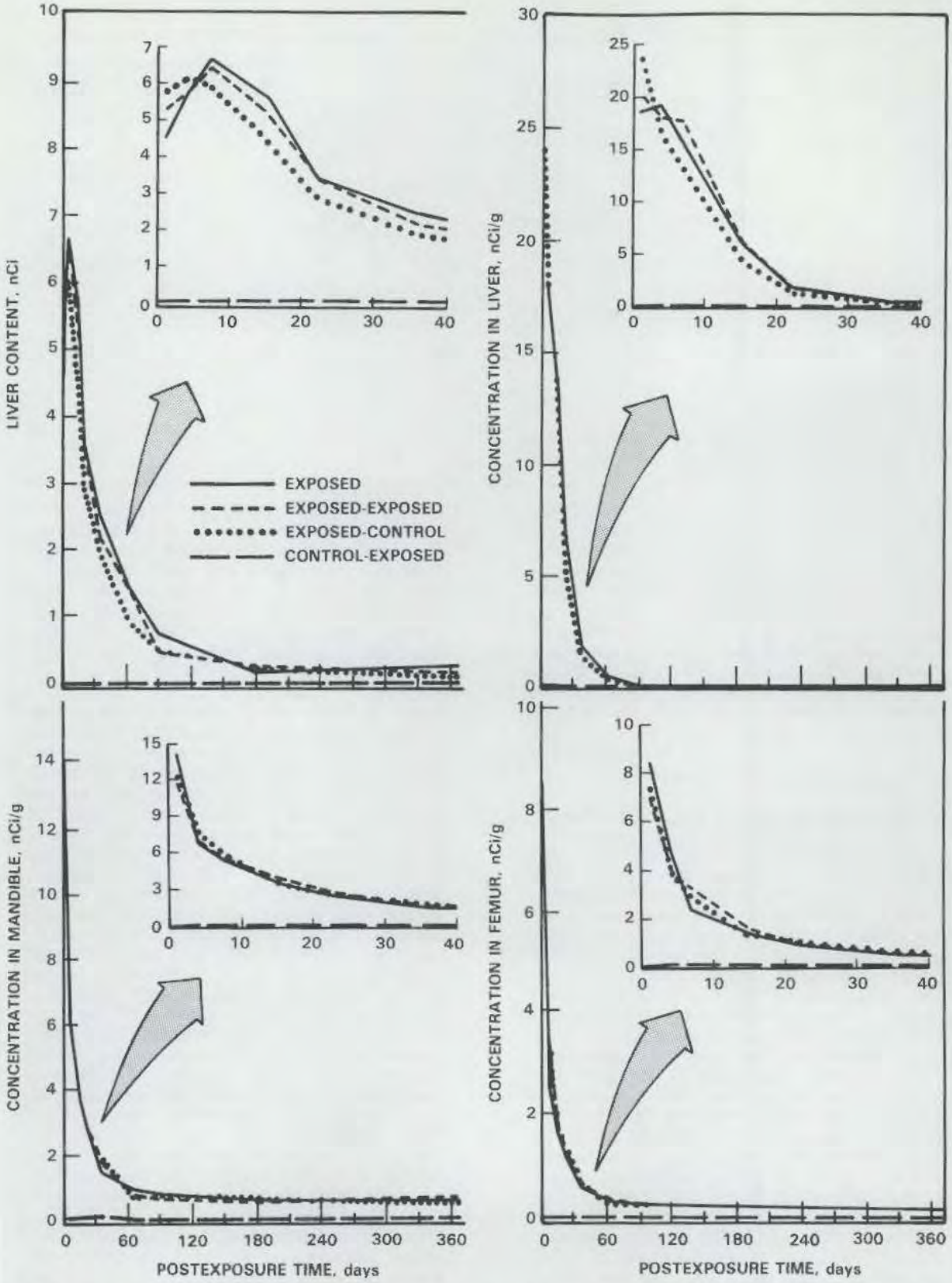

FIGURE 1. Effect of Foster-Rearing on Content and Concentrations of ^{239}Pu in Representative Organs During Prenatal and Postnatal Development of Rats Exposed via Placental Transfer and/or Milk (——— = Exposed; - - - - - = Exposed-Exposed, ••••••••• = Exposed-Control, ——— —— = Control-Exposed; See Table 1 for Further Details).

TABLE 2. Effects of Exposure of Rats to ^{239}Pu or ^{241}Am at 9 or 15 Days of Gestation (dg) on Developmental Measures Evaluated at 20 dg.

	9-dg Exposures					15-dg Exposures			
		^{239}Pu		^{241}Am			^{239}Pu	^{241}Am	
	Control	10 nCi/g	30 nCi/g	30 nCi/g	90 nCi/g	Control	30 nCi/g	30 nCi/g	90 nCi/g
No. Litters	7	16	15	15	12	6	13	6	11
Implants/ Litter[a]	12.4 ±1.4	12.9 ±1.9	12.9 ±1.2	12.1 ±2.5	12.7 ±2.5	12.7 ±1.4	13.1 ±1.5	13.5 ±2.3	12.4 ±1.8
Deaths/ Litter[a]	1.4 ±1.1	1.5 ±2.2	2.1 ±3.8	0.5 ±0.6	2.2 ±3.2	0.3 ±0.5	1.0 ±0.8	1.0 ±1.3	0.7 ±0.9
Fetal Wt. g[b]	3.4 ±0.3[d]	3.2 ±0.3[d]	2.9 ±0.2[c]	3.3 ±0.3[d]	3.0 ±0.4[d,e]	3.3 ±0.2[d]	3.2 ±0.3[d]	3.1 ±0.1[d]	3.1 ±0.4[d]
Placental Wt. g[b]	0.44±0.03[d]	0.46±0.11[d]	0.38±0.03[e]	0.45±0.04[d]	0.44±0.04[d]	0.39±0.04[d]	0.43±0.05[d]	0.39±0.04[d]	0.40±0.05[d]
No. Skeletons Examined	74	167	160	158	114	71	143	69	117
Anomalous Ribs[c]	1/1	33/9	50/8	1/1	7/4	0	2/2	0	0

[a]Mean ± SD
[b]Mean of litter means ± SD
[c]Bent or wavy; expressed as number fetuses/number litters affected.
[d,e]Values with common letter do not differ significantly ($P > 0.05$).

In agreement with our previous findings, exposure to either plutonium or americium was not overtly teratogenic. Under the conditions of the present experiments, however, it appears that there is a dose-dependent increase in the incidence of anomalous (bent or wavy) ribs in the animals exposed to plutonium and a tendency toward an increase in those exposed to the high dose of americium (Table 2). This may be attributable to more-intensive skeletal evaluation, to larger group sizes, or to the slightly earlier stage of gestation at exposure in the present studies.

As described in last year's Annual Report, 30 nCi/g of monomeric ^{239}Pu (maternal plasma concentration of ~100 ng/g) is associated with a decrease in maternal blood flow to the perfused guinea-pig placenta. Further experiments have confirmed that the effect is reproducible and independent of the dosing vehicle (Figure 2), and ongoing experiments suggest that the apparent threshold is in the maternal dose range of approximately 5 nCi/g (82 µg/kg) body weight (Table 3). Because of this usual effect at low chemical concentrations and the indicated differences between plutonium and americium transfer, we employed the same perfusion technique to directly measure the clearance of ^{241}Am from mother to fetus (Am_{MF}). Maternal blood flow to the placenta was again measured indirectly using the clearance of tritiated water. Results indicated that, unlike plutonium, ^{241}Am did not affect maternal blood flow at doses of 30 nCi/g (9 µg/kg). The Am_{MF} measured 3.4 ± 0.7 µl/min (mean ± SE), which was not significantly different from our previous measurements of plutonium (2.3 ± 0.6 µl/min) when uncorrected for blood flow. Am_{MF} from six experiments are shown in Table 3. When corrections were made for the disrupted maternal blood flow observed following plutonium administration, Pu_{MF} was five times greater than Am_{MF}, on a µCi basis.

Based on continuing questions about the movement, coalescence, and localization of particles deposited in the lung, together with a suggestion that areas of bronchiolization were the most susceptible to tumorigenesis, we are developing a model to allow more detailed study. The late-gestation fetal rat is being used because of its high rate of bronchiolization and because the lungs are sufficiently small to be easily examined and photographed, both in whole mounts and in histologic sections. Initial studies involved intratracheal deposition of suspensions, using a glass needle inserted through the uterus and fetal membranes. Reports in the literature indicated that prenatal rats would inhale and ingest particulates present in the amniotic fluid. Accordingly, we have explored the less-demanding procedure of intra-amniotic instillation and have found that extensive deep lung deposition of colloidal carbon suspensions can be obtained by administration as early as 17 dg, although reproducible exposures are not obtainable until 19 dg (Figure 3). Using this exposure method, we are evaluating the deposition of submicron-size particles of metal oxides.

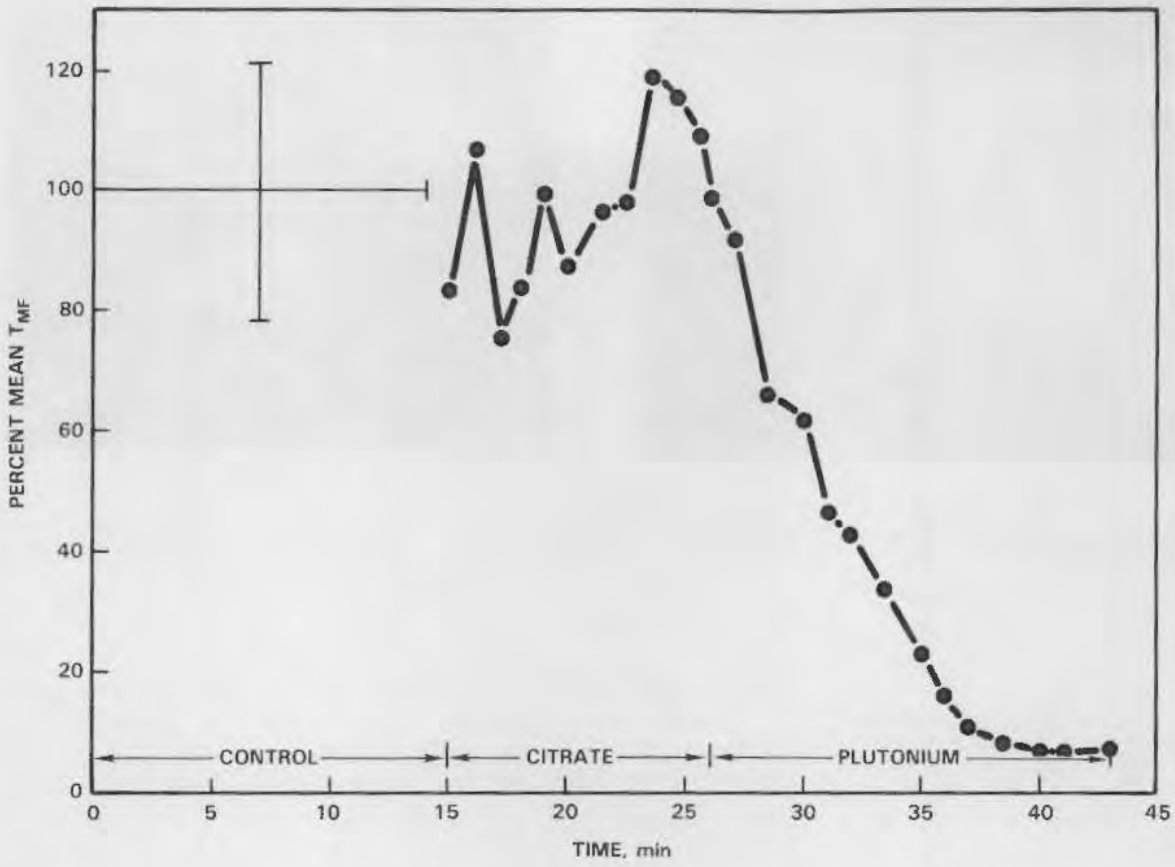

FIGURE 2. Clearance of Tritiated Water (T_{MF}, Expressed as Percent of Mean Control) as a Function of Time and Vehicle/^{239}Pu Exposure in a Typical Experiment.

TABLE 3. Clearance of ^{241}Am from Dam to Fetus (Am_{MF}) and its Relationship to Changes in Maternal Blood Flow to the Placenta, Expressed as the Clearance of Tritiated Water from Dam to Fetus (T_{MF}).

Dam No.	Am_{MF} (µl/min) Mean ± SE	Intercept, A[a] (×10^{-4})	Slope, B[a] (×10^{-4})	P	r[b]
1	13.4 ± 2.5	--	--	NS[c]	NS
2	12.3 ± 2.0	--	--	NS[c]	NS
3	32.4 ± 4.5	−13	48	<0.001	0.98
4	5.7 ± 3.8	−22	393	<0.07	0.47
5	34.4 ± 4.4	−35	78	<0.03	0.38
6	31.2 ± 2.5	5	33	<0.1	0.32

[a] $Y = A + BX$ where $Y = Pu_{MF}$ and $X = T_{MF}$.
[b] Correlation coefficient for the regression
[c] Not significant

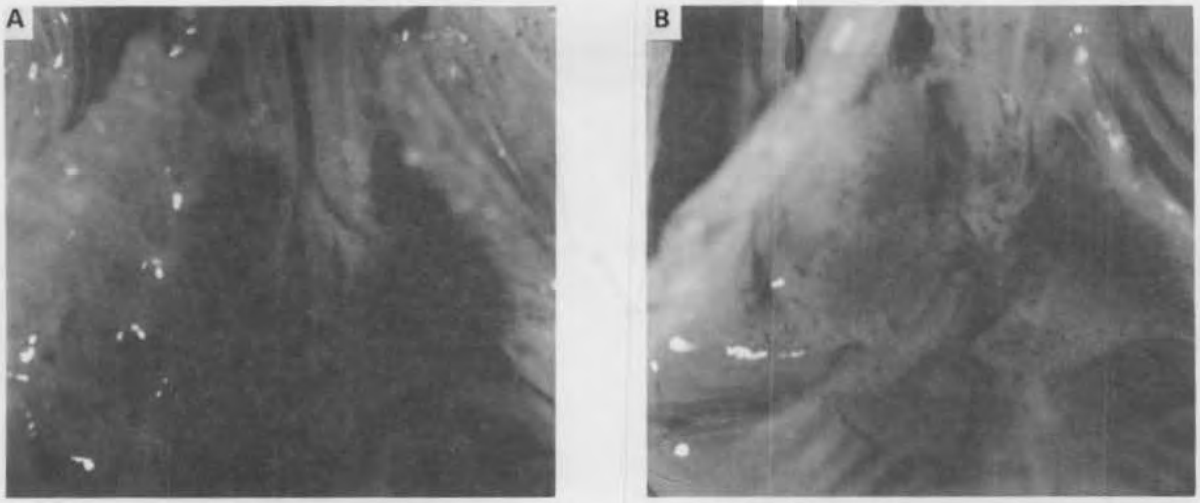

FIGURE 3. Patterns of Colloidal Carbon in Fetal Rat Lungs and Tracheas after Intra-Amniotic Instillation. A. high deposition; B. low deposition.

• Hanford Life Sciences Symposium

Co-Chairpersons: R. C. Thompson and J. A. Mahaffey

The 22nd Annual Hanford Life Sciences Symposium, on the topic "Life-Span Radiation Effects Studies in Animals: What Can They Tell Us?," was held in Richland, Washington, September 27-29, 1983. It was attended by approximately 150 registrants from 7 countries, representing more than 30 laboratories and funding agencies. Fifty papers and more than 5 hr of discussion were packed into a very full 3 days.

A panel of three eminent statisticians critiqued papers as they were presented and led summary discussions. This was an acclaimed feature of the Symposium, and these discussions will be included in the published Proceedings. The statisticians on this panel were: Dr. Marvin Schneiderman of Clement Associates, Arlington, Virginia--for many years at the U.S. National Cancer Institute; Dr. Kenny Crump of Science Research Systems, Rustin, Louisiana; and Dr. Leon Rosenblatt of Geneticon, Inc., Walnut Creek, California.

The first session of the Symposium included eight overview papers summarizing work in progress in major laboratories conducting lifespan radiation effects studies. Additional papers included ten from Pacific Northwest Laboratory, seven from the University of Utah, six from Lovelace Inhalation Toxicology Research Institute, three from the University of California at Davis, three relating to French studies, two each from Colorado State University, George Washington University, and from the laboratories in Mol, Belgium; and single papers from Japan, Australia, West Germany, England, Argonne National Laboratory, Lawrence-Livermore Laboratory, Oak Ridge Associated Universities, the University of Chicago, and the U.S. Air Force School of Aviation Medicine.

The Symposium also heard opening remarks from Dr. Alvin Trivelpiece, Director of the Office of Energy Research, U.S. Department of Energy (DOE); and a description, by Dr. G. B. Gerber, of radiation protection studies sponsored by the Commission of the European Communities, with special emphasis on the potential for cooperative studies involving U.S. programs and European scientists. Special recognition was given at the Banquet to Harry A. Kornberg, who initiated the Hanford Life Sciences Symposia in 1962; and to Herbert M. Parker, who, as Director of the Hanford Laboratories, gave continuing support to the development of the Symposia.

If there could be said to be a recurrent theme it might have been the importance of not neglecting the factor of time in the evaluation of dose-response relationships. The day has passed when raw incidence data can be reported, even as preliminary data, without raising critical questions of when, in relation to exposure, the effect occurred.

Many cautions were expressed concerning the myriad of unforeseen and possibly unappreciated biases that may influence an experimental result. The lesson to be learned is not that all such biases can be avoided--the important thing is that these biases be recognized, and acknowledged, and allowance made for them in the interpretation of results. The problem of unappreciated bias is particularly prevalent when, as often happens in these studies, data are interpreted by persons or groups not involved in the collection of the data. Every effort should be made to involve the data collector in such interpretations.

The complete Proceedings of the Symposium, edited by Roy C. Thompson and Judith A. Mahaffey, will be published by DOE as a volume in their DOE Symposium Series, and should be available before the end of 1984.

Mutagenesis

• Mutagenicity of Synfuel Materials

Principal Investigator: R. A. Pelroy

Other Investigator: D. L. Stewart

Salmonella typhimurium TA-98 was used to determine the effect of complex coal liquids on the mutagenicity of 6-aminochrysene and benzo[a]pyrene. The potency of the amino-PAH was markedly increased in the presence of the SRC-II 800-850°F and 800+°F distillate cuts. On the other hand, the potency of benzo[a]pyrene decreased sharply under the same conditions. Evidently, the chemically complex liquids are capable of exerting opposite effects on mutagenicity in these two types of compounds.

The high-boiling coal liquids are mutagenically and carcinogenically active in in vitro cellular and small-animal (rodent) skin-painting assays. Most of the activity associated with these materials appears to reside in the neutral polycyclic hydrocarbon (PAH) and amino-PAH constituents of the nitrogen polycylics. The skin-painting (carcinogenesis and tumorigenesis) assay systems respond more strongly to the former, while the microbial in vitro assays are more responsive to the amino PAH.

Chemical evidence, in conjunction with the results from mutagenesis with Salmonella typhimurium suggested that the composition of the coal liquids suppressed activity of mutagens/carcinogens such as benzo[a]pyrene (BaP). A direct test of this hypothesis for S. typhimurium TA-98 is shown by the data presented in Figure 1. In this experiment, the mutagenicity of BaP was measured both in the presence, and absence, of a fixed amount of an SRC-II distillate cut. Mutagenicity was expressed as the slope of the dose-response curves for benzo[a]pyrene (Figure 1, right panel). As can be seen, the mutagenic potency of BaP decreased in the presence of the coal liquids; the highest degree of inhibition was induced by the 800-850°F distillate cut (Figure 1, left panel).

The same type of experiment was also carried out with 6-aminochrysene (6-AC) in place of BaP. In this case the results (Figure 2) were opposite those found for BaP. Both the distillate cuts enhanced the potency of the amino PAH. This is shown in the dose-response data for 6-AC in the presence of the 850°+F distillate cut (Figure 2, right panel), where the potency of the amino PAH increased several-fold in the presence of the 850°+F distil-

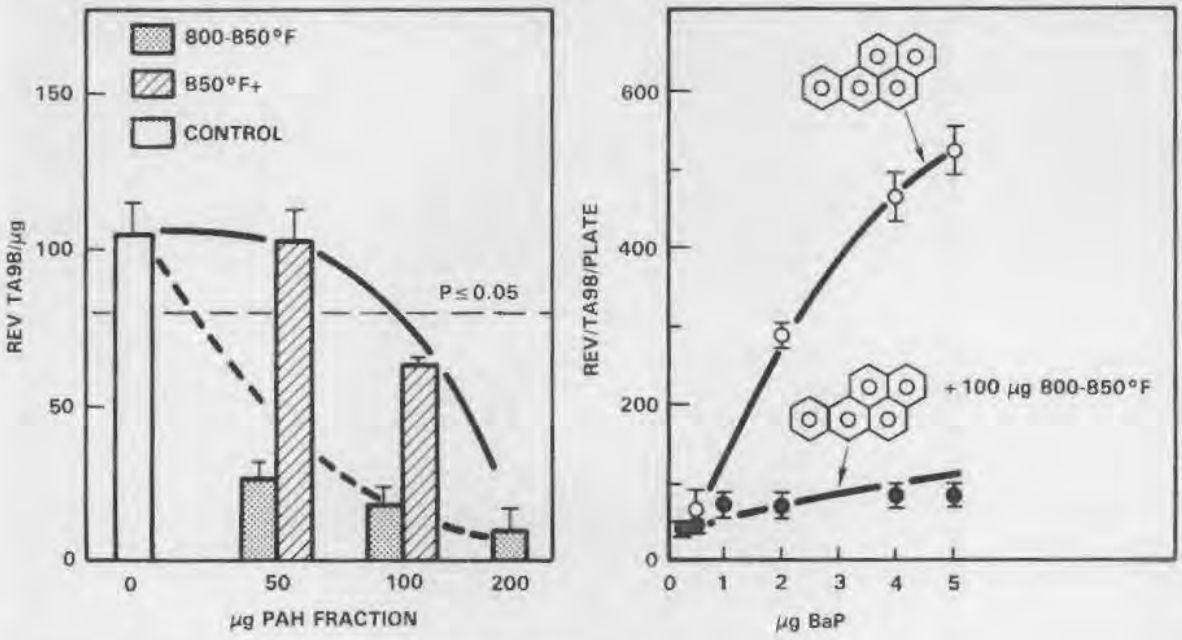

FIGURE 1. Effect of Coal Liquids on the Activity of Benzo[a]pyrene.

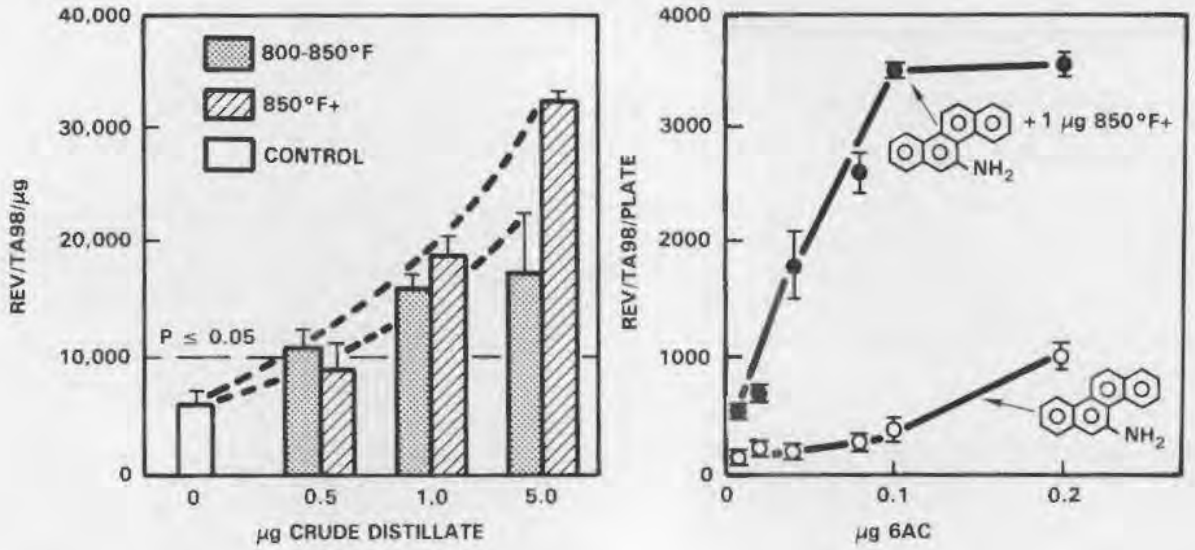

FIGURE 2. Effect of Coal Liquids on the Activity of 6-Aminochrysene.

late (shown by increases in the slope of the dose-response curve). The potency of 6-AC was less enhanced by the 800-850°F distillate (Figure 2, left panel); however, the synergistic effects were still highly significant in comparison with those of the controls.

A similar experiment was performed to determine if the skin-tumor-initiating activities of BaP and 6-AC would be affected by the matrix in which they were applied to the skin. To test this question, BaP (50 µg/mouse) was applied to mouse skin in either 50 µl of acetone or 50 µl of a wide-boiling-range coal liquid (boiling point, 300 to >850°F); coal liquid alone was also administered. After 2 wk, the treated area was promoted twice weekly with 5 µg of phorbol myristate acetate. The tumor yield per group of 30 mice was used as a measure of the initiating activity of the test material. Similarly, 6-AC was tested by applying a 25-µg dose either in acetone or in the nitrogen-containing polycyclic aromatic compound (NPAC) fraction prepared from the >850°F distillate. The results (Figure 3) indicate that the initiating activities of both BaP and 6-AC were suppressed by the presence of the coal-derived liquid. Results for 6-AC are in contrast to those obtained in the microbial mutagenesis assay; those for BaP were similar for both assays.

In summary, the SRC-II distillate cuts appeared to exert opposite effects on the mutagenicity of 6-AC and BaP, enhancing the potency of the former and inhibiting the potency of the latter in the S. typhimurium microsome mutagenicity (Ames) assay system.

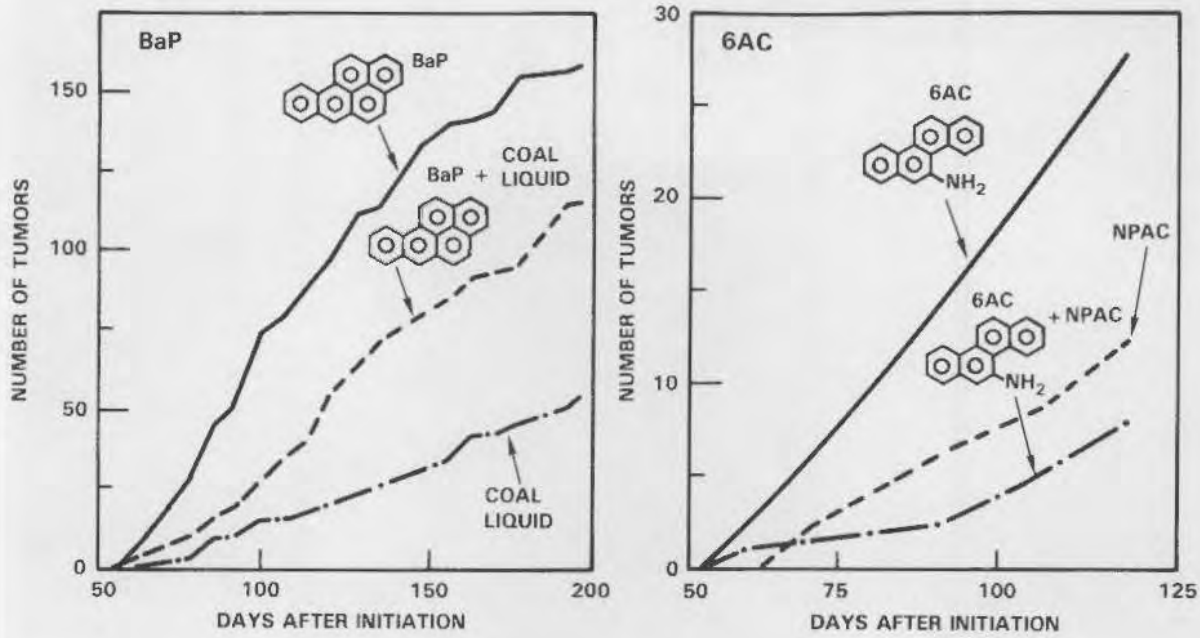

FIGURE 3. Skin-Tumor-Initiating Activities of Benzo[a]pyrene and 6-Aminochrysene.

Systems
Damage

• Gut-Related Studies of Radionuclide Toxicity

Principal Investigator: M. F. Sullivan

Other Investigators: R. L. Buschbom, R. A. Miller, P. S. Ruemmler, and J. L. Ryan

This project is concerned with the behavior of radioactive materials that may be ingested as a consequence of a reactor accident, unavoidable occupational exposure, or after release to the environment and incorporation into the food chain. Current emphasis is on evaluating hazards from ingested actinides as a function of animal age, species, nutrition, and diet, or chemicophysical state of the actinide. We are also concerned with the behavior of actinides that are inhaled and pass through the gastrointestinal (GI) tract after clearance from the lungs.

Recent experiments have shown that the dose dependency of the transfer factor, f_1, for absorption of neptunium, which we reported earlier, is due to the reducing effect of the intestinal content on Np(V). The Np(V) is presumably changed to Np(IV), an oxidation state that is less well absorbed from the gastrointestinal (GI) tract than Np(V). By restricting food consumption or by supplementing doses of Np(V) administered to either adult or neonatal rodents with oxidizing or reducing chemicals we were able to stimulate or prevent the influence of the GI content on the Np(V) administered. We have also shown that these supplemental chemicals influence the GI absorption of ^{233}U in the same way. Results of other experiments have shown that ^{238}Pu absorption is increased in animals that are anemic because of an iron-deficient diet or age.

We have demonstrated that the marked plutonium absorption in neonatal or weanling rats gavaged with ^{238}Pu is a result of the maturity of the intestine and is not dependent on the ingestion of milk at the time of gavage.

An inhalation study with rats that received ^{237}Np nitrate aerosols showed that clearance from the lung was quite rapid ($T_{\frac{1}{2}}$ = 28 days) and that retention in the skeleton was protracted. No bone tumors were found during the 2 yr these animals were observed for the ocurrence of late effects. The only neoplasm, other than mammary or pituitary tumors, was a single lung carcinoma in a rat exposed to 0.15 μCi of ^{237}Np.

Influence of Fasting and/or Oxidizing or Reducing Agents on the GI Absorption of ^{237}Np

Results reported earlier (Annual Report, 1982) demonstrated that neptunium absorption was dose-dependent. Since neptunium can exist as Np(IV), Np(V) or Np(VI) and has been shown by others in this laboratory to be absorbed from the GI tract at various rates, depending on the oxidation state of the neptunium administered, it seemed plausible that such a change in the GI tract might be responsible for the unexpected dose-dependency for absorption.

To determine if the GI contents were responsible, groups of rats and mice were fasted 24 hr before and 4 hr after gavage with either ^{237}Np or ^{235}Np nitrate. Other groups of rats and mice that were either fed ad libitum or fasted were given doses of the oxidizing agent ferric nitrate as a supplement to ^{237}Np. This agent is known to maintain neptunium in its pentavalent state but does not oxidize Np(V) to Np(VI). The results obtained when the animals were killed a week later are shown in Table 1. It is apparent from the absorption and retention data that fasting resulted in a 5-fold increase in rats and an 18-fold increase in mice. Ferric iron caused an even greater increase (80-fold in rats and 150-fold in mice) in absorption. To demonstrate further that the effect of the intestinal content was to alter the valence of neptunium, a reducing agent, ferrous iron ($FeSO_4$), was given as a supplement to Np(V). The results are also shown in Table 1. Administration of ferrous iron resulted in less neptunium absorption by fasted rats and mice than by fed controls; presumably, due to the reduction of $^{237}Np(V)$ to $^{237}Np(IV)$.

The influence of the intestinal content of adult animals in reducing the chemical form of an isotope is well known, but less is known about the influence of the GI content of sucklings. Therefore, sucklings were given ^{237}Np supplemented with various concentrations of either ferric or ferrous iron. The results (Table 2) indicate that absorption was stimulated by ferric iron and depressed by ferrous iron, similarly to the case for adult rats; however, the degree of change was less.

TABLE 1. Influence of Fasting and Oxidizing or Reducing Agents on Neptunium Absorption by Rats Gavaged with ^{237}Np Nitrate or Mice Gavaged with ^{239}Np Nitrate.

	Percent of Gavaged Neptunium							
	Fed Controls		Fasted Controls		Fasting + $Fe(NO_3)_3$		Fasting + $FeSO_4$	
Tissue	Rats (6)[a]	Mice (8)	Rats (25)	Mice (8)	Rats (4)	Mice (9)	Rats (14)	Mice (5)
Carcass	0.07	0.03	0.39	0.66	5.1	4.7	0.03	0.13
Liver	0.002	0.01	0.03	0.32	1.4	1.3	0.001	0.02
Urine	0.03	0.02	0.24	0.29	1.5	0.9	0.05	0.24
Total Absorbed	0.10	0.06	0.65	1.3	8.0	6.9	0.07	0.4

[a]Numbers of animals/group shown in parentheses

TABLE 2. Influence of Oxidizing or Reducing Agents on Gastrointestinal Absorption and Retention of Neptunium Gavaged to 5-Day-Old Rats as ^{237}Np Nitrate, pH 1.5.

	Percent of Gavaged ^{237}Np Dose ± SEM		
Tissue	^{237}Np Control (15)[a]	$^{237}Np + Fe(NO_3)_3$	$^{237}Np + FeSO_4$ (8)
Carcass	0.67	2.7	0.12
Liver	0.02	0.03	0.01
Total Retained	0.89 ± 0.12	2.73 ± 0.50	0.13 ± 0.03

[a]Number of rats shown in parentheses

The Effect of Fasting and/or Oxidizing and Reducing Agents on the GI Absorption of ^{232}U

Although the absorption of uranium by man in industrial contamination accidents is reported to be as high as 10%, our study on the effect of mass on GI absorption by rats (Annual Report, 1982) did not suggest a reason for the contrastingly low absorption, 0.01%, by animals (Annual Report, 1974). Since uranium occurs in several oxidation states, like neptunium and plutonium, we gavaged rats with ^{232}U (IV) nitrate, pH 2, supplemented by either ferric iron, which should maintain the uranium in the VI state, or iron powder which should maintain uranium in the IV state. The data obtained are shown in Table 3. They show that fasting resulted in a threefold increase in GI absorption. Iron powder did not decrease the effect of fasting, but ferric iron caused a 20-fold increase in absorption in comparison to fasted controls and a 50-fold increase in absorption in comparison to rats fed *ad libitum*. These results suggest that the higher reported absorption of uranium is associated with the uranyl (VI) valence state, and the lower absorption commonly seen in rats is associated with the IV valence state.

Effect of Iron Deficiency on Plutonium GI Absorption by Rats

Ragan reported (Annual Report, 1973) that mice fed an iron-deficient diet absorbed more ^{239}Pu from the GI tract and retained more parenterally injected ^{239}Pu (Annual Report, 1974) than mice fed a balanced diet. However, rats fed an iron-deficient diet did not absorb more ^{239}Pu nor retain more when it was injected parenterally than their control group (Annual Reports, 1975, 1976). This suggested a difference in species response to iron deficiency or an effect of an unknown source of dietary iron.

To compare the effect of an iron-deficient diet with that of an iron-replete diet on ^{238}Pu absorption, two groups of rats (Table 4) were fed an iron-deficient diet for 24 days. One-third of their blood was withdrawn to further depress their iron stores. Some of the rats were returned to the balanced diet and gavaged with ^{238}Pu 2 days later. Others remained on an iron-deficient diet until they were killed at a week after ^{238}Pu gavage.

The data in Table 4 demonstrate that ^{238}Pu absorption was increased threefold in rats maintained on the iron-deficient diet un-

TABLE 3. Influence of Fasting and Oxidizing or Reducing Agents on ^{233}U Absorption by Rats Gavaged with ^{233}U (IV) Nitrate, pH 1.5.

Tissue	Percent of Gavaged ^{233}U (IV) ± SEM			
	Fed Controls (6)[a]	Fasted Controls (6)	Fasting + $Fe(NO_3)_3$ (6)	Fasting + Fe Powder (6)
Carcass	0.02	0.06	1.4	0.04
Liver	0.0004	0.001	0.04	0.001
Kidney	0.0004	0.02	0.91	0.13
Urine	0.05	0.09	0.94	0.07
Total Absorbed	0.07 ± 0.02	0.17	3.29	0.24

[a]Number of rats used in parentheses.

TABLE 4. Influence of Anemia Resulting from an Iron-Deficient Diet, and of Blood Sampling, on GI Absorption of Plutonium by Weanling Rats Gavaged with 40 μCi/kg ^{238}Pu Nitrate.

Tissue	Dietary Treatment		
	Iron-Replete (7)[a]	Iron-Deficient (7)	Iron-Deficient and Iron-Replete (6)[a,b]
Blood Hematocrit (%)	46	25	44
	Percent of Gavaged ^{238}Pu Dose × 10^2 ± SEM		
Carcass	1.8	6.0	0.8
Liver	0.2	0.6	0.06
Urine	0.8	1.0	0.4
Total Absorbed	2.8 ± 1.0	9.6 ± 2.0	1.3 ± 0.1

[a]The number of rats gavaged is shown in parentheses. All were killed at 7 days after gavage.
[b]These rats were fed an iron-deficient diet, then returned to a normal, iron-replete diet for 2 days before gavage.

til they were killed. It was not increased in rats that were first given an iron-deficient diet, then returned to an iron-replete diet 2 days before ^{238}Pu gavage. This indicates that in the anemic rats the increased absorption of ^{238}Pu was not dependent on the demand for iron. Instead, it was the result of the availability of the iron carrier system in the intestine that preferentially bound the available iron due to the demand by the erythroid processes.

Influence of Age and Diet on Plutonium GI Absorption by Neonatal Rats

To determine if ingestion of neonatal ^{238}Pu-contaminated excreta by nursing dams contributed, via nursing, to the amount of ^{238}Pu retained by suckling rats gavaged with ^{238}Pu nitrate, part of a litter was separated from their dam and maintained at 35°C, while the remainder of the litter was suckled and killed a day later. The results, shown in Table 5, Groups 1 and 2, indicate that the weaned neonates retained three times as much ^{238}Pu as those that remained with the dam. Although analysis indicated that much of the neonatal excreta was ingested by the dam, fasting or stressing the weanlings resulted in higher ^{238}Pu retention than occurred in sucklings nursed until death.

To determine whether the rapid decrease in plutonium absorption that occurs when rats are weaned is a result of maturation due to dietary change or to age, litters of rats were divided into groups that were approximately equal in sex distribution, and some animals of each litter were weaned at 21 days of age and gavaged with ^{238}Pu nitrate. Others were not gavaged until a week after they were weaned and were then fed rat chow. A third group was not weaned until 28 days, when they were gavaged with ^{238}Pu nitrate. The results, shown in Table 5, Groups 3-5, indicate that absorption was highest in the rats gavaged at 21 days. It was lowest in the group suckled until they were 28 days old and then gavaged. Weaning and feeding them rat chow did not enhance maturation of the mucosal epithelium.

To compare the influence of age on plutonium absorption, a group of young adult rats and a group of aged rats were gavaged

TABLE 5. Influence of Age and Diet on Plutonium Absorption by Suckling, Weanling or Adult Rats Gavaged with ^{238}Pu Nitrate, pH 2.

Animal Group No.:	1	2	3	4	5	6	7
Age at Weaning, days	6	5	21	21	28	21	21
Age at Gavage, days	5	5	21	28	28	90	800
Age at Necropsy, days	6	6	28	35	35	97	807
No. of Animals	7	8	11	11	10	8	7
Tissue	Percent of Gavaged ^{238}Pu Dose $\times 10^2$						
Carcass	45	154	4.6	2.0	0.9	1.0	34
Liver	5	12	0.4	0.3	0.1	0.2	0.3
Urine						0.5	0.9
Total Retained	50	166	5.0	2.3	1.0	1.2	34.3
Total Absorbed						1.7	35.2

with ^{238}Pu nitrate after an aliquot of blood was withdrawn for measurement of the volume of packed red blood cells. The hematocrit of the aged rats was depressed to a value below that of the young rats (39 versus 46%), but there was no difference in the retention of ^{238}Pu in liver or femur. However, the quantity measured in the carcasses of aged adults was 34 times higher than in the younger animals. This suggests that if the increased absorption was related to the slightly anemic condition, the femur, which was used to calculate the skeletal ^{238}Pu content, was not the site for ^{238}Pu deposition in aged rats. Further study may determine whether these results are representative of plutonium absorption by an aged population of animals and, perhaps, by man.

Behavior and Toxicity of Inhaled ^{237}Np

An experiment designed to study the lung-clearance dynamics and toxicity of inhaled ^{237}Np was recently concluded. One hundred rats were exposed in groups of 25 to ^{237}Np nitrate aerosols. Their deposited doses were 0, 0.1, 0.15 and 0.3 μCi, respectively. The initial lung burdens were 0.03, 0.05 and 0.09 μCi. These doses were the same as in earlier Russian inhalation studies that were reported to have caused numerous skeletal neoplasms. Our clearance data (Figure 1) agreed with their clearance results, following a two-compartment model. The half-times estimated by this model were 28 days for the early period and 8664 days for the deep lung clearance. The early clearance resulted in only 3% remaining in the lung at 90 days. Although the half-time for eliminating ^{237}Np from the skeleton did not occur before the last animals were killed at 730 days after exposure, no bone tumors were observed. This difference from the published Russian data may have been due to the difference in rat strains or to the small number of our animals retained for observation of late effects.

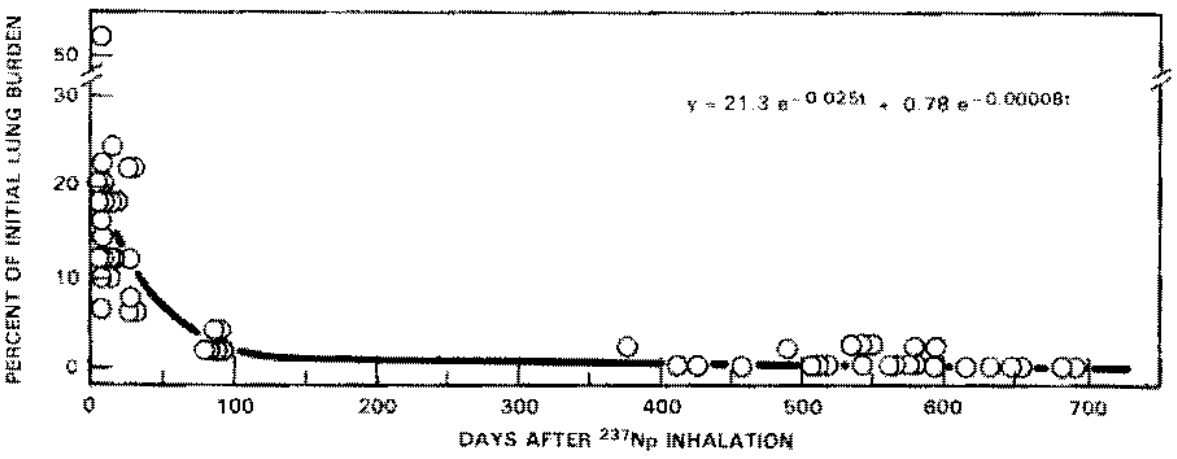

FIGURE 1. Clearance Curve for the Elimination of Neptunium from the Lungs of Rats Exposed by Inhalation to ^{237}Np Nitrate.

• Modifying Radionuclide Effects

Principal Investigator: L. B. Sasser

Other Investigators: D. D. Mahlum

Technical Assistance: R. L. Rommereim

This project involves a study of the relationships of physiological, environmental, and nutritional factors that may affect the metabolism and toxicity of radionuclides, with the aim of identifying segments of the population that may be particularly sensitive to radionuclides. We have studied placental transport and suckling as pathways for americium entry into the newborn or juvenile rat. The relative amount of ^{241}Am reaching the offspring was dependent on the time of dosing in relation to the pregnancy; larger amounts were transferred via nursing than across the placenta.

Data reported previously (Annual Reports, 1979, 1980) demonstrated that the relative amounts of plutonium reaching the offspring via the placenta and by nursing were functions of the temporal relationship between plutonium administration and pregnancy. It is well documented that the behavior of plutonium differs somewhat from that of americium in the adult, and recent data suggest that greater amounts of plutonium are transferred to the fetus compared to americium. Because of these differences, it seemed appropriate to investigate the fate of americium as affected by pregnancy and lactation. Therefore, the objective of these studies was to determine the effect of pregnancy and lactation on the transfer of americium to the offspring of the rat. The experiment was designed so that female rats were dosed while nulliparous (30 days prior to mating), pregnant (19 days of gestation; dg), or lactating (1 day after parturition); the subsequent transfer of americium to the offspring was then measured as a function of offspring age. The protocol describing this experiment and preliminary data were detailed in last year's Annual Report (1983); we now report the completion of the experiment.

Approximately 50% of the injected dose was initially retained in the livers of all rats; however, the biological half-time of ^{241}Am in the liver of rats dosed when nulliparous was only 10.6 days, compared with 25.6 and 27.1 days for the pregnant and lactating groups, respectively. The initial concentration was approximately 5% of the injected dose per gram of liver, whereas the concentrations in all other tissues were 1% (or less) of the dose per gram of tissue. However, retention by kidney, femur, uterus, and muscle was prolonged compared to that of the liver. Americium concentration in spleen and femur actually increased slightly with time after dosing.

The concentration of ^{241}Am in mammary tissue, milk, and placenta (those tissues directly related to exposure of progeny) as well as the amount transferred to progeny are shown in Table 1. The initial concentration in mammary tissue of rats injected while pregnant or lactating was approximately three times greater than that of the group injected while nulliparous. The release of ^{241}Am from mammary tissue appeared to be accentuated during lactation; the half-time of ^{241}Am in the mammary tissue of the "pregnant," "lactating," and "nulliparous" groups was 7, 9, and 17 days, respectively.

The amount of ^{241}Am transferred to the milk was directly correlated to the temporal relationship between exposure and lactation. Even though the concentration of ^{241}Am in the mammary tissue of the rats dosed when pregnant or when lactating was essentially equivalent, the transfer of ^{241}Am to the milk was greatest in animals dosed during lactation. Thus, it appears that the americium concentration of milk was more closely correlated with the circulating blood levels of ^{241}Am rather than with concentrations in mammary tissue. When exposure occurred prepartum, the retained ^{241}Am tended to become bound in various tissues and was less available during milk synthesis. Surprisingly, however, the concentration of ^{241}Am in milk of the nulliparous group was substantial as late as 7 to 10 wk after dosing.

The relative amount of americium reaching the offspring was dependent on the time of dosing in relation to pregnancy. Approximately 0.01% of administered activity was transferred to each pup in utero 1 day after injection, whereas ^{241}Am could not

TABLE 1. The Concentration (Mean ± SE) of Americium in Mammary Tissue, Milk, Placenta, and Progeny after the Intravenous Administration of ^{241}Am Citrate to Rats when Pregnant (19 Days of Gestation), Lactating (1 Day Postpartum), or Nulliparous (~30 Days Before Conception).

				% of Injected Am/g of Tissue			Length of Exposure		
Group	No. Animals	Time After Injecting Dam, days	Time After Parturition, days	Mammary Tissue x 10^{-2}	Milk x 10^{-3}	Placenta x 10^{-2}	In Utero, days	Via Milk, days	% of Injected Am/Pup x 10^{-2}
Pregnant	5	1	−2	17.7 ± 4.38	...	8.65 ± 3.31	1	0	1.08 ± 0.11
	6	4	1	14.4 ± 1.21	4.89 ± 2.20[a]	...	3	1	1.81 ± 0.19[a]
	5	9	6	10.6 ± 1.05	4.54 ± 1.40	...	3	6	2.59 ± 0.26
	5	14	11	7.15 ± 0.33	3.42 ± 0.72	...	3	11	4.04 ± 0.17
	5	21	18	6.99 ± 0.47	3.03 ± 0.48	...	3	18	3.69 ± 0.39
Lactating	5	1	2	14.3 ± 1.57	23.9 ± 5.90	...	0	1	14.9 ± 0.93
	5	4	5	17.7 ± 4.63	9.00 ± 2.96[a]	...	0	4	13.9 ± 1.5
	4	9	10	6.78 ± 0.34	4.23 ± 1.48	...	0	9	9.67 ± 0.15
	4	14	15	5.69 ± 0.62	1.98 ± 0.91	...	0	14	6.90 ± 0.36
	4	21	22	7.51 ± 1.64	1.46 ± 0.48	...	0	21	0.964 ± 0.097
Nulliparous	5	~51	2	5.38 ± 1.69	...	0.138 ± 0.008	22	0	ND
	6	~53	1	5.03 ± 1.79	4.06 ± 1.29	...	22	1	0.0624 ± 0.0023
	5	~37	6	4.77 ± 0.23	5.28 ± 1.38	...	22	6	0.100 ± 0.029
	5	~63	11	3.06 ± 0.46	2.04 ± 0.37[a,b]	...	22	11	0.315 ± 0.066[b]
	5	~70	18	2.51 ± 0.50	2.49 ± 1.22[b]	...	22	18	0.381 ± 0.121[a]

[a] n = 4
[b] n = 3

be detected in fetuses whose dams were injected before conception. When exposure occurred during lactation, approximately 10 times more ^{241}Am was transferred to each offspring from milk than was transferred from the placenta when exposure occurred late in gestation. Furthermore, more ^{241}Am was received by the progeny via milk if exposure of the dam occurred during lactation rather than during pregnancy.

Although it could not be detected in fetuses of dams exposed prior to pregnancy, the ^{241}Am content of the pup increased steadily through 18 days of nursing. Thus, when exposure occurred well in advance of pregnancy, ^{241}Am was apparently not transferred across the placenta but only through the milk.

The amount of ^{241}Am transferred across the placenta was a factor of 10 less than that previously reported for plutonium, whereas the amount transferred via milk 1 day after injection was 10 times greater than that found for plutonium (Annual Report, 1980).

• Synfuels Teratology

Principal Investigator: P. L. Hackett

Other Investigators: D. D. Mahlum and M. R. Sikov

Technical Assistance: R. L. Rommereim

This project was initiated to determine and quantify the developmental toxicity of materials associated with solvent-refined coal (SRC) processes. Previously reported studies demonstrated that some SRC materials were embryotoxic and teratogenic when administered to rats from 12 through 16 days of gestation (dg). The most commonly observed, dose-related, fetal morphologic lesion was "small lung" (as determined by fetal lung weight), which was often accompanied by cleft palate, diaphragmatic hernia, or syndactyly/ectrodactyly. Recent results indicate that the incidence of small lung is highest when exposure to crude material (boiling range, 300 to >850°F) occurs on 12 or 13 dg. No adverse fetal effects have been observed following administration of material boiling below 700°F.

Recent developmental toxicology studies of synfuel materials have had a dual purpose. One goal was to determine the interval in which the embyro is most sensitive to exposure to solvent-refined coal (SRC) materials, as evidenced by adverse effects on viability, growth and development. The second goal was to determine the teratogenic potential of a series of boiling-range cuts of crude material from a process development unit.

Previous studies of maternal and fetal response to an SRC material (designated HPS) indicated that exposure to 0.74 g/kg of HPS from 12 through 16 days of gestation (dg) increased the incidence of small fetal lungs (Annual Report, 1982). Subsequent studies, performed with the same dose level, demonstrated that a shorter dosing interval (12 to 14 dg) resulted in a lower incidence of small fetal lungs and that a single dose of 0.74 g/kg of HPS delivered on 12, 13 or 14 dg produced no observable fetal effects. These effects, suggestive of a dose response, indicated that both the dose level of the complex mixture and the time of administration were critical to the induction of fetal anomalies. We therefore compared the effects of single doses of HPS, ranging from 0.92 to 1.85 g/kg and delivered on 12, 13 or 14 dg, with those resulting from daily doses of 0.74 g/kg delivered between 12 and 14 dg or 15 and 16 dg.

Female rats (Sprague-Dawley, CD, Charles River Laboratories) of known gestational age were assigned to treatment groups by formal randomization based on body weight. On each dosing day, suspensions of HPS in milk were prepared immediately prior to intragastric intubation of a constant-volume dose. All animals were weighed at intervals; at sacrifice (20 dg), the gravid uterus, with products of conception, was also weighed. The contents of the excised uterus were examined for number and location of early and late resorptions and of live and dead fetuses. Live fetuses were weighed and examined for gross defects, visceral malformations and altered morphologic development of the skeleton. Fetal lungs were examined in situ and were then removed and weighed.

Weight gains of maternal rats tended to be lower in animals that received a single dose of 1.11 g/kg or more and in rats that received multiple doses of 0.74 g/kg of HPS (Table 1). Although thymus weights were depressed in all animals dosed with HPS (Table 1), the increase in adrenal weights that had previously been reported as accompanying thymic involution (Annual Report, 1981) was not observed. No significant trends in intrauterine mortality could be attributed to any dosing regimen.

Fetal body weights were significantly lower than those of controls at all dose levels on 14 dg, at the highest dose level on 12 dg and when 0.74 g/kg was delivered from 12 through 14 dg (Figure 1). Fetal lung weights were lower than control values for all dosing regimens except at the lowest dose on 13 dg and following dosing on 15 and 16 dg (Figure 1). Incidences of major fetal malformations (expressed as the percentage of affected fetuses/litter) are shown in Figure 2. Small lungs were observed most frequently following dosing on 12 dg, but a dose-response was observed for each exposure day. Cleft palate tended to occur more frequently after dosing on 13 dg, and diaphragmatic hernia was observed more often in fetuses exposed on 12 dg to the highest dose level.

In summary, teratogenic events were most evident following exposure to high dose

TABLE 1. Maternal Measures (Mean ± SE) Following Administration of Process Solvents on Various Days of Gestation.

Dose, g/kg	Dosing Interval, dg	Number of Aminals	Weight Gain[a], g	Thymus Weight, mg	Late Resorptions, %
0	12-14	16	47 ± 4[b]	215 ± 17[b]	2.2 ± 0.8
0.74	12-14	6	38 ± 8[b,c]	77 ± 10[d]	11.7 ± 7.5
0.92	12	7	42 ± 6[b,c]	114 ± 16[c,d]	1.0 ± 1.0
	13	6	50 ± 3[b]	146 ± 13[c]	0
	14	6	64 ± 6[b]	145 ± 17[b,c,d]	3.0 ± 1.4
1.11	12	7	36 ± 9[b,c]	137 ± 16[c,d]	4.6 ± 2.4
	13	6	24 ± 6[b,c]	128 ± 15[c,d]	1.4 ± 1.4
	14	6	28 ± 6[b,c]	113 ± 15[c,d]	2.1 ± 1.4
1.48	12	7	28 ± 7[b,c]	134 ± 12[c]	8.8 ± 3.3
	13	6	22 ± 5[c]	123 ± 15[c,d]	17.8 ± 16.5
	14	6	31 ± 6[b,c]	90 ± 11[c,d]	1.3 ± 1.3
1.85	12	6	30 ± 4[b,c]	116 ± 38[b,c,d]	23.2 ± 15.5
	13	6	25 ± 7[b,c]	90 ± 10[c,d]	0
	14	6	15 ± 8[c]	103 ± 17[c,d]	5.3 ± 3.4

[a]Extragestational weight (body weight minus weight of gravid uterus) gain from 0-20 dg.
[b-d]Values that do not share a common superscript letter are significantly different ($P < 0.05$).

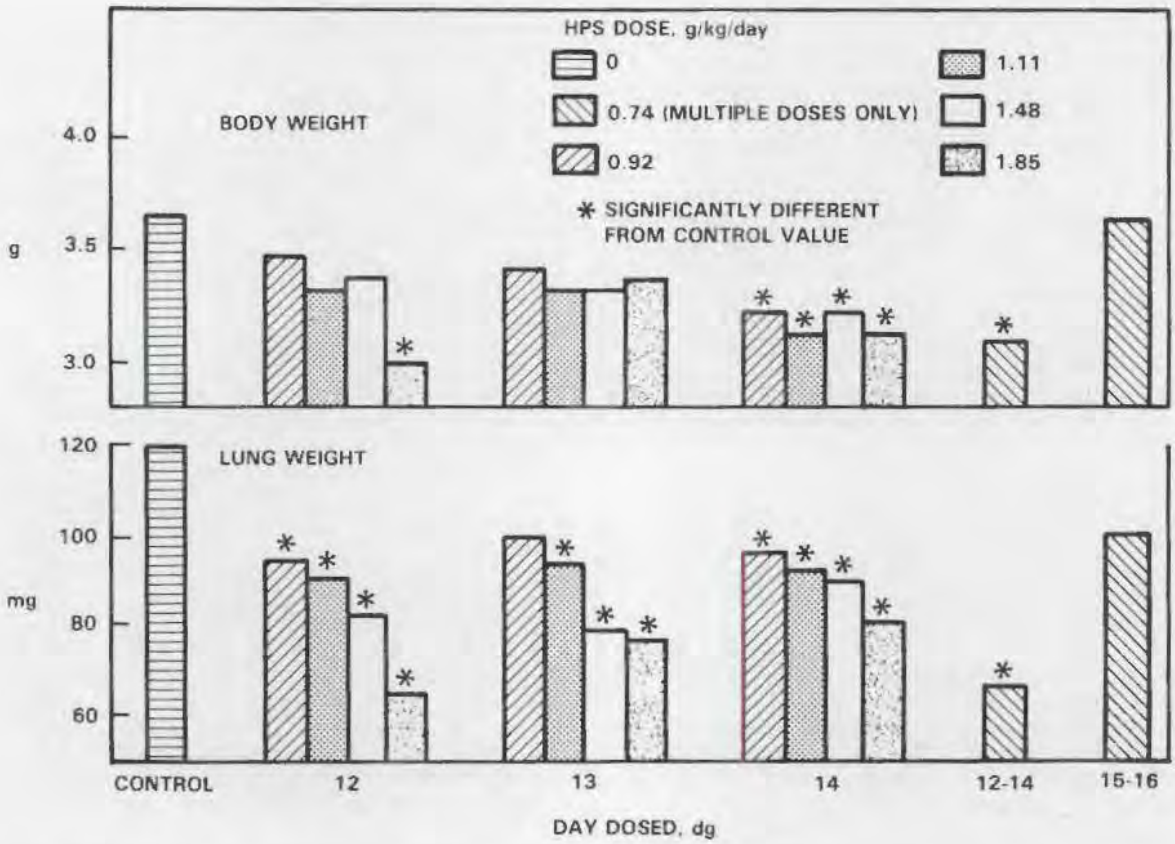

FIGURE 1. Fetal Body and Lung Weights Following in Utero Exposure to SRC Materials During Specific Stages of Development.

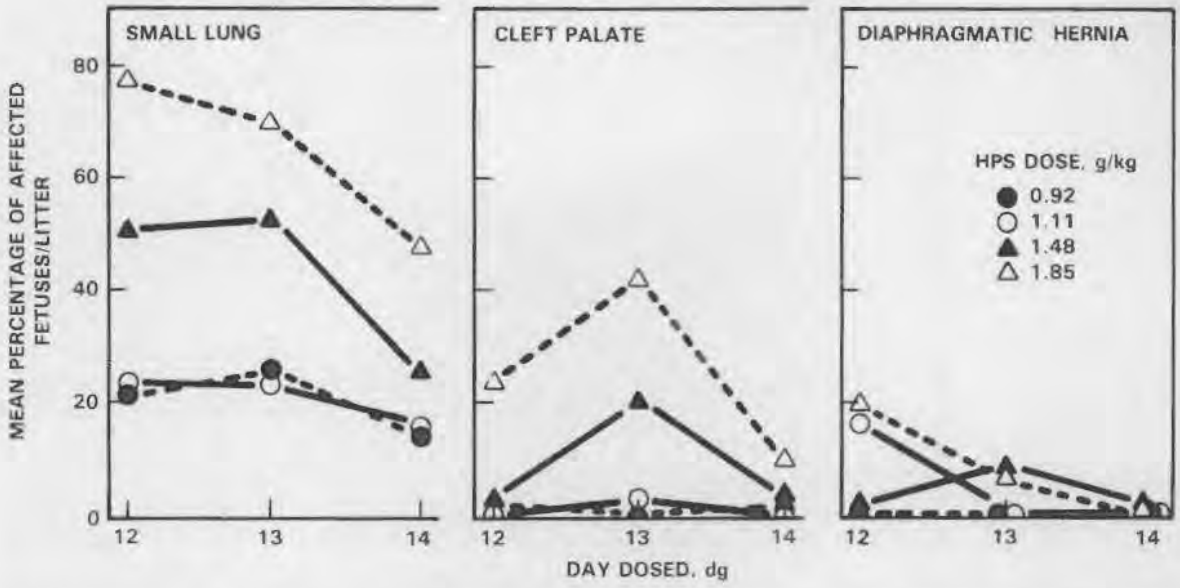

FIGURE 2. Percentage of Fetuses with Malformations Following in Utero Exposure to SRC Materials on 12, 13 and 14 Days of Gestation.

levels of HPS on 12 or 13 dg, and fetal growth depression occurred most often when dosing was performed on, or later than, 14 dg.

The protocol for determining the teratogenic potential of the discrete boiling-range cuts of HPS was similar to that described for the preceding study. For this study, rats were dosed on 13 dg with crude HPS at a dose level of 1.85 g/kg, or with doses of the boiling-point cuts equivalent to 1.85 g/kg, based on the percentage composition of the crude material (Table 2). The low-boiling cut (I, 300-700°F) was added to each higher-boiling cut since our preliminary studies (Annual Report, 1982) indicated that the high-boiling material was not readily dispersible and might have been unavailable for absorption from the gastrointestinal tract.

TABLE 2. Description of Boiling-Range Cuts of a Coal Liquid (HPS) Administered in Developmental Toxicology Studies.

Cut	Boiling Range, °F	Percent of Crude HPS
I	300-700	78.9
II	700-750	5.5
III	750-800	7.4
IV	800-850	3.5
V	>850	4.7
Crude	300->850	100

Maternal mortality was high (50%) following administration of a mixture of boiling-range cuts I, II and III (300-800°F, Table 3). Mortality levels were somewhat lower (20%) when the 750-800°F cut was eliminated and when crude HPS was administered (17%). Thymus weights were most affected by exposure to crude HPS and mixtures of the highest-boiling cuts (IV and V) in the low-boiling material. Significantly increased adrenal weights occurred only after dosing with crude HPS.

Fetal body weights were not significantly altered by in utero exposure to any of the HPS fractions (Table 4). Fetal lung weights tended to be depressed in all HPS-treated litters except for those exposed only to the low-boiling cut (300 to 700°F). Higher incidences of small fetal lungs (Table 5) were observed after administration of boiling-range cuts I + II + III, I + IV + V or crude material. Cleft palates, which were commonly observed following treatment with crude HPS, were observed in only one litter exposed to high-boiling material. The incidence of a physiologic variation, reduced ossification of the nasal bones, appeared to be correlated with the incidence of small lungs.

Although the results of these studies are preliminary, they suggest that no adverse fetal effects are induced by materials boiling below 700°F, but that some equivocal maternal measures of toxicity (less than normal body-weight gains and abnormally low thymus weights) should be studied further.

TABLE 3. Maternal Measures (Mean ± SE) Following Treatment of Pregnant Rats with Various Boiling-Range Cuts of a Coal Liquid (HPS).

Cut	Boiling Range, °F	Number of Dams	Mortality, %	Body Weight Gain, g[a]	Thymus Weight, mg	Adrenal Weight, mg	Late Resorptions, %
Vehicle	---	7	0	36 ± 7	162 ± 18[b]	76 ± 6[b]	2.9 ± 1.4
I	300-700	7	0	19 ± 3	111 ± 16[b,c]	84 ± 7[b]	16.1 ± 6.7
I + II + III	300-800	6	50	27 ± 9	140 ± 42[b,c]	74 ± 7[b]	7.1 ± 7.1
I + IV + V	300-700 800->850	5	20	32 ± 7	96 ± 19[b,c]	69 ± 8[b]	29.3 ± 11.6
I + IV	300-700 800-850	5	0	16 ± 8	98 ± 7[c]	75 ± 2[b]	9.0 ± 5.6
I + V	300-700 >850	4	0	26 ± 4	83 ± 5[c]	89 ± 11[b,c]	5.3 ± 3.2
HPS	300->850	7	17	25 ± 6	90 ± 12[b,c]	110 ± 6[c]	9.6 ± 3.6

[a]Extragestational weight (body weight minus weight of gravid uterus) gain from 0-20 dg
[b-c]Values that do not share a common superscript letter are significantly different ($P < 0.05$)

TABLE 4. Fetal Lung and Body Weights (Mean ± SE) Following in Utero Exposure to Various Boiling-Range Cuts of a Coal Liquid (HPS).

Cut	Boiling Range, °F	No. of Pups/No. of Litters Examined	Body Weight, g	Lung Weight, mg	Lung/Body Weight, %
Vehicle	---	84/7	3.36 ± 0.08	109 ± 4[a]	3.24 ± 0.10[a]
I	300-700	71/7	3.30 ± 0.15	114 ± 7[a]	3.31 ± 0.07[a]
I + II + III	300-800	37/3	3.06 ± 0.28	76 ± 5[b]	2.48 ± 0.14[a,b]
I + IV + V	300-700 800->850	23/4	2.73 ± 0.26	68 ± 10[b]	2.48 ± 0.20[a,b]
I + IV	300-700 800-850	49/5	3.18 ± 0.20	89 ± 6[a,b]	2.79 ± 0.05[b]
I + V	300-700 >850	53/4	3.18 ± 0.15	92 ± 6[a,b]	2.88 ± 0.10[a]
HPS	300->850	72/6	3.40 ± 0.09	77 ± 5[b]	2.28 ± 0.10[b]

[a-b]Values that do not share a common superscript letter are significantly different ($P < 0.05$)

TABLE 5. Incidence of Frequently Observed Fetal Anomalies Following in Utero Exposure to Various Boiling-Range Cuts of a Coal Liquid (HPS).

		Affected Fetuses/Litter, %			
Cut	Boiling Range, °F	Small Lung	Diaphragmatic Hernia	Cleft Palate	Reduced Ossification of Nasal Bones
Vehicle	---	2	0	0	2
I	300-700	4	0	0	14
I + II + III	300-800	69	3	0	72
I + IV + V	300-700 800->850	55	0	5	100
I + IV	300-700 800-850	17	0	0	10
I + V	300-700 >850	14	0	0	24
HPS	300->850	70	6	44	61

• Perinatal Effects of Synfuels

Principal Investigator: D. L. Springer

Other Investigators: L. E. Anderson, R. L. Buschbom, P. L. Hackett, D. D. Mahlum, and R. A. Miller

Technical Assistance: J. A. Brower, C. J. Gerdes, K. M. McCarty, and R. L. Rommereim

Studies were conducted to determine the mortality rate and the cause of death for offspring treated in utero with a high-boiling coal liquid (300 to 850°+F). Pregnant rats were gavaged with 0.74 g/kg body weight/day from 12 to 14 days of gestation (dg); 54% of their pups died within 3 days after birth. Of those dying, 8% had cleft palate, 30% had small lungs, and 31% had both of these malformations; the cause of death for the other 31% was not identified. Lung weights (expressed as percent of body weight) were also decreased in treated pups through 3 days of age, but returned to control levels by 7 days of age. The dose administered resulted in moderate toxicity to the dams.

Rats were treated during pregnancy, and mixed-function oxidase (MFO) enzyme activities were determined in liver preparations from 10-wk-old offspring to determine if prenatal treatment influenced the ability of the animal to metabolize xenobiotics. Permanent changes in the activity of aryl hydrocarbon hydroxylase (AHH) were not observed. An additional group of rats, which were exposed in utero, were examined for evidence of hepatic tumor development by staining tissues for foci of gamma glutamyl transpeptidase (GGT) activity. Few, if any, of the liver tissues of animals exposed to coal liquids were positive for GGT foci.

Exposure of pregnant rats to complex mixtures of synfuel derivation may result in adverse effects to offspring. To evaluate these potential effects, dams were treated during pregnancy, and offspring were evaluated for survival and growth. These data were an extension of teratology studies, which used similar coal liquids (CL). In addition, other experiments were conducted to determine whether the CL act as cross-placental carcinogens and whether prenatal exposure to the CL results in permanent changes in mixed function oxidase (MFO) enzyme activities such as aryl hydrocarbon hydroxylase (AHH) and cytochrome P-450.

Rats (Sprague-Dawley CD, Charles River, Kingston, NY) were caged with males overnight (four females per male), and copulation was detected the next morning by the presence of sperm in vaginal smears. The day that sperm were detected was designated Day 0. Females that copulated were randomized by weight and assigned either to the control or treated group. Pregnant dams were weighed on 0, 9, 15, and 21 days of gestation (dg) and 1 day after delivery. Dams were treated with a material (designated HPS; boiling range 300 to >850°F) from a process development unit at doses of 0.74 mg/kg/day on 12 to 14 dg.

Beginning at 21 dg, dams were observed continually; pups were continually observed from birth through 3 days of age to obtain accurate survival data. Pups were removed from the cages immediately after death and examined for gross abnormalities; body and lung weights were obtained at necropsy, which was performed immediately following death. At birth, all control pups were randomly assigned to groups that were sacrificed at 0.25, 0.5, 1, 3, 7, or 21 days of age. The early sacrifice times were included to obtain body- and lung-weight data for comparison with treated pups that died during these intervals. Surviving treated pups were randomly assigned to groups for sacrifice at 1, 3, 7, and 21 days of age; procedures were similar to those for pups that died. All neonatal measurements for pups that died were pooled at intervals of 0-8, 8-16, 16-37, and 37-72 hr after birth and correspond to measurements made on pups sacrificed at 0.25, 0.5, 1, and 3 days, respectively.

Examination of maternal body-weight data during pregnancy indicated significant decreases for HPS-treated dams relative to those for controls. Since mortality was not observed, these data indicate moderate maternal toxicity to the CL at the doses used in this study.

Within the first 3 days after birth, about 54% of the HPS-treated offspring died (Figure 1). The remaining pups survived through 21 days of age. Body-weight data indicated that pups that died weighed significantly less than those of the control

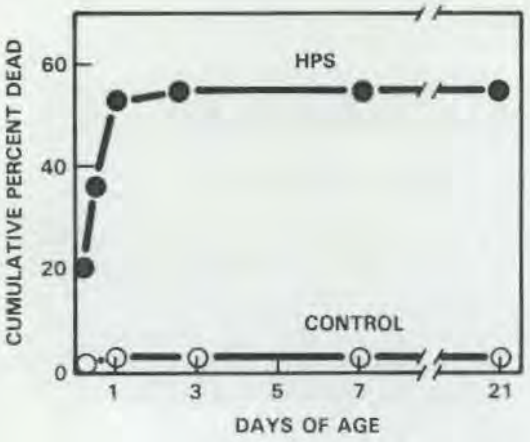

FIGURE 1. Mortality for Offspring Exposed Prenatally to a High-Boiling Coal Liquid (0.74 g/kg Body Weight/Day) on 12 to 14 Days of Gestation.

group. Gross observations indicated that 8% of the dead pups had cleft palates.

Lung weights (expressed as percent of body weight) for HPS-exposed pups were significantly less than those of controls at 0.25 and 0.5 days of age (Figure 2). Randomly selected HPS-exposed pups that were sacrificed also had lungs that weighed significantly less than those of controls at 1 and 3 days after birth. Frequency distributions for lung weights were prepared to develop objective criteria for establishing the incidence of small lungs. Lungs that were more than two standard deviations below the mean for the control group, on both an absolute and relative weight basis, were classified as small. When classified in this manner (Figure 3), none of the lungs from sacrificed control animals were classified as small, whereas 61% of the pups that died had small lungs (Table 1). In addition, 29% of the treated pups that were sacrificed also had lungs classified as small. The incidence of the malformations was greatest between birth and 1 day of age (Figure 3). These data suggest that small lungs contributed to the incidence of mortality through 1 day after birth. The fact that few deaths were observed after 1 day of age, together with the presence of small lungs in treated animals that were sacrificed between 1 and 3 days of age, indicated that some animals with small lungs survived. Furthermore, lack of small lungs in treated pups sacrificed at 7 and 21 days of age demonstrated that lung weights for these animals returned to control levels. These data suggest that recovery was adequate to sustain life; however, it remains to be determined whether lung function for surviving treated pups was normal.

Eight percent of the treated pups that died had cleft palates; 31% had both cleft palate and small lungs. The cause of death for 31% of the pups was not attributable to either small lungs or cleft palate and remains unidentified.

Cross-Placental Carcinogenesis and Enzyme Activities

For these studies, we attempted to determine whether high-boiling CL are cross-placental carcinogens and whether prenatal exposure results in permanent changes in enzyme activities. Reports in the literature indicate that in utero exposure to polyaromatic hydrocarbons such as benzo-[a]pyrene (BaP) resulted in permanent changes in the activities of MFO such as AHH and cytochrome P-450. In these studies, basal levels of AHH activity and P-450 levels from BaP-treated pups were lower than those of controls; after treatment of the offspring with an enzyme inducer such as phenobarbital, activities of these enzymes in exposed pups were higher than for controls. In other studies, lactating dams were exposed to pharmacologically active agents such as phenobarbital. Offspring nursed by these dams showed infertility, delayed onset of puberty and alterations in plasma concentrations of sex hormones. Since xenobiotics and steroid hormones are metabolized by MFO enzymes, and both of these materials are involved in tumor development, we extended our studies to include measurement of MFO enzyme activities after in utero exposure to CL.

For these studies, pregnant rats were treated with a CL boiling from 300 to 850°+F, and the offspring were observed through 10 wk of age. Activity of AHH for male offspring was then determined in liver S9 preparations. The results indicated that the activity of this enzyme was not altered by exposure to the CL (Table 2). In addition, BaP, a positive control, did not produce permanent changes in the enzyme activities. All these results are opposite those in the literature. The reasons are unclear, although it may be significant that the numbers of animals employed in the published literature were much smaller than those in our studies. These results also point to the need to dose animals during lactation and evaluate the effects after exposure by this route.

At weaning, female offspring from this study were placed on a diet containing

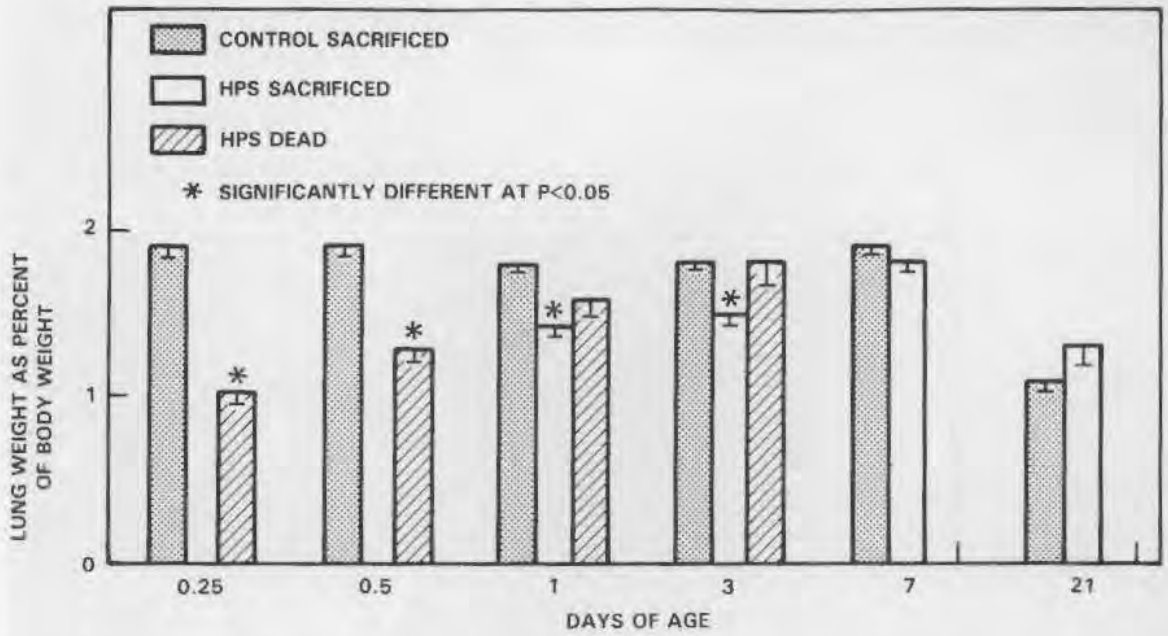

FIGURE 2. Lung Weight as Percent of Body Weight for Offspring Exposed Prenatally to a High-Boiling Coal Liquid on 12 to 14 Days of Gestation.

TABLE 1. Incidence of Malformations in Offspring Exposed Prenatally to a High-Boiling Coal Liquid.

		HPS		
	Control[a]	Sacrificed[a]	Dead	Total
No. Pups/No. Litters Examined	152/14	55/9	64/11	119/12
Gross Observations				
Small Lungs	0/0	16/7	19/10	35/11
Cleft Palate	0/0	0/0	6/9	6/9
Both Small Lungs and Cleft Palate	0/0	0/0	20/8	20/8
No. Affected Pups[b] / Affected Litters	0/0	16/7	44/10	60/11
% Affected Pups per Litter	0	12 ± 3	41 ± 9	53 ± 8

[a] Pups sacrificed at 1, 3, 7 and 21 days of age
[b] Cleft palates and small lungs

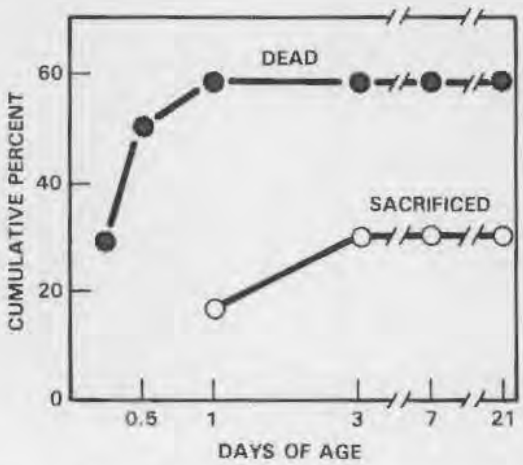

FIGURE 3. Incidence of Small Lungs for Prenatally Exposed Offspring that Died or were Sacrificed.

0.05% phenobarbital, a liver-tumor promoter. After either 10 or 20 wk of promotion, these animals were sacrificed, and the livers were evaluated for the number and frequency of foci that stained positive for the enzyme gamma glutamyl transpeptidase (GGT). Positive results from this study would be suggestive evidence for initiation of the liver toward tumor development. Results from this study will be available during FY 1984.

TABLE 2. Effect of Prenatal Exposure to Phenobarbital, Benzo[a]pyrene or a High-Boiling Coal Liquid on Basal and Induced Activities of Aryl Hydrocarbon Hydroxylase and Cytochrome P-450 Levels.

Activity	Induced or Noninduced	Control	Phenobarbital	BaP	HD (Low)	HD (Mid)	HD (High)
AHH	Noninduced	0.221 ± 0.0094 19	0.232 ± 0.010 19	0.210 ± 0.017 17	0.192 ± 0.019 11	0.204 ± 0.025 10	0.227 --- 1
AHH	Induced	0.728 ± 0.042 19	0.716 ± 0.031 16	0.781 ± 0.068 14	0.644 ± 0.047 11	0.682 ± 0.053 4	---

• Health Effects of Synthetic Fuels

Principal Investigator: R. A. Renne

Other Investigators: R. L. Buschbom, and L. G. Smith

Technical Assistance: V. L. Dedmond, V. L. Madden, S. M. Baze and C. White

The purpose of this project is to study the potential human health hazards associated with synthetic fossil-fuel technologies. Studies in progress are investigating the carcinogenic potential of cutaneous exposure to various boiling-point distillates and chemical-class fractions of materials and products from the solvent-refined coal technology.

Epidermal carcinogenesis studies are in progress on boiling-point distillates and chemical-class fractions of these distillates from the solvent-refined coal (SRC) technology. Exposure is complete, and histopathologic examination is in progress of tissues from animals exposed to boiling-point distillates of process solvent (HPS) from the SRC Process Demonstration Unit at Harmarville, PA. Skin-tumor incidence and latency, based on gross observations of these animals, are presented in Figure 1. These data indicated that the dermal carcinogenic potency of this material increases with boiling point and is due to that portion boiling above 700°F.

Recently begun studies are assaying the dermal carcinogenicity of two chemical fractions from the 750-800°F distillate of HPS. These are the neutral polycyclic aromatic hydrocarbon (PAH) and the nitrogen-containing polycyclic aromatic compounds (NPAC) fractions.

Studies recently completed on recombined PAH and basic fractions of SRC-II heavy distillate (Figure 2) do not indicate synergistic activity in the carcinogenic response to these two fractions; skin-tumor latency is similar to that observed in response to the PAH fraction alone (Annual Report, 1981).

Studies on samples of nitrosated basic tar fractions of SRC-II heavy distillate (Figure 2) indicate that nitrosation does not decrease the carcinogenicity of basic tar. This suggests that primary aromatic amines are not the determinant class of carcinogens in this sample.

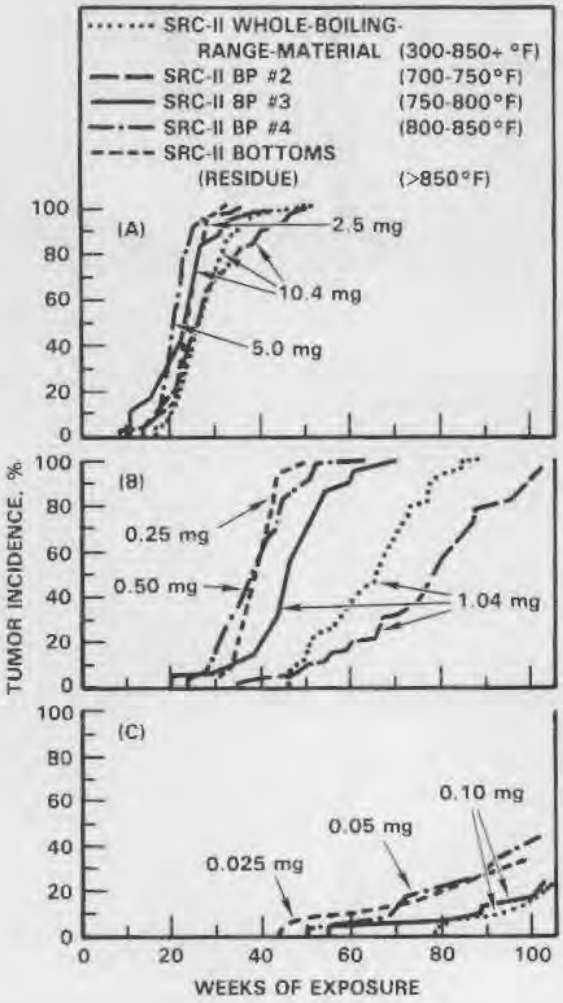

FIGURE 1. Skin-Tumor Response to a Wide-Boiling-Range (300-850+°F) SRC-II Coal Liquid and to its Boiling-Point Cuts. A) High Dose, B) Medium Dose, C) Low Dose.

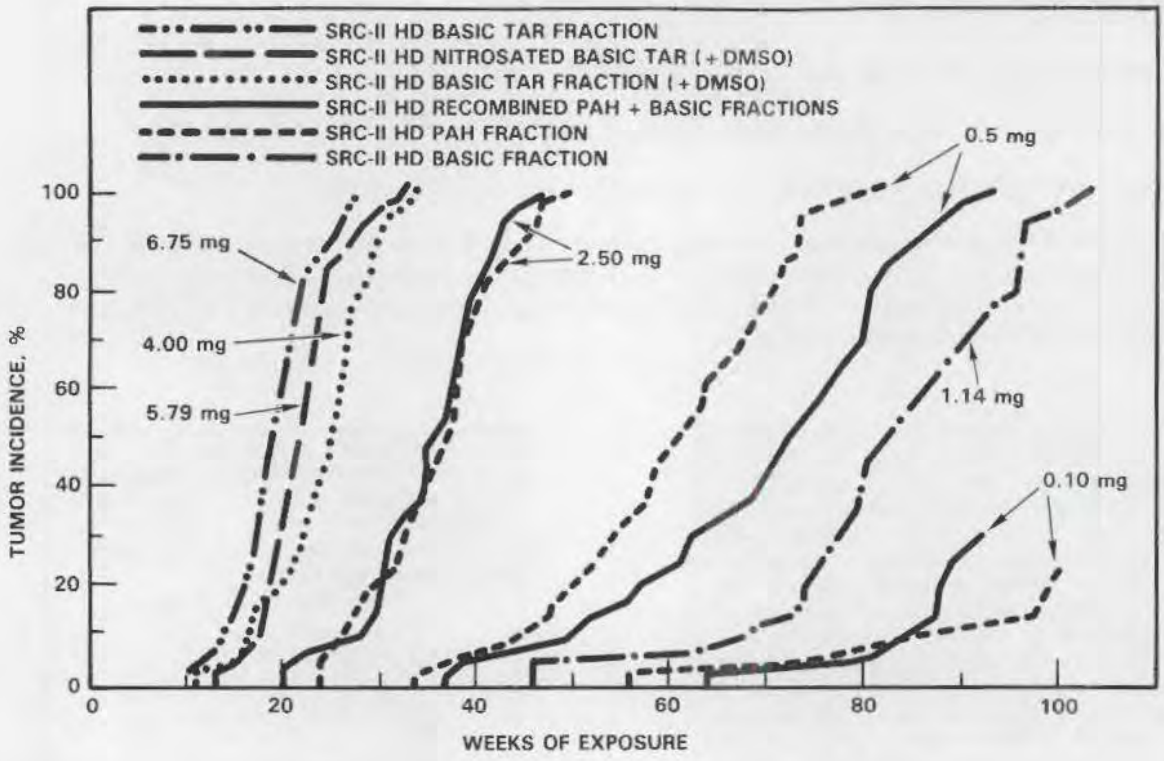

FIGURE 2. Skin-Tumor Response after Nitrosation of Heavy Distillate (HD) Basic Tar Fraction and after Combining Polycyclic Aromatic Hydrocarbon (PAH) and Basic Fractions.

• Tissue Dose in Fossil-Fuel Exposure

Principal Investigator: R. E. Schirmer

Other Investigators: L. J. Felice, B. J. Kelman, D. L. Springer, and R. B. Westerberg

Technical Assistance: C. A. Fankhauser

The half-time for plasma clearance of benzo[a]pyrene (BaP) in the Sprague-Dawley rat is approximately 10 min as estimated from blood levels following intravenous administration. Blood levels of BaP and its polar metabolites rose several hours after percutaneous or intravenous dosing, suggesting that biliary cycling is important. By both routes of administration, the plasma concentration of polar metabolites was greater than the concentration of unchanged BaP at all times. Another observation in the expiriements was that 6-aminochrysene was absorbed much more slowly through the skin than BaP.

Studies of the percutaneous absorption and subsequent disposition of benzo[a]pyrene (BaP) and 6-aminochrysene (6-AC) have been initiated in rats. These compounds were selected as representative of the carcinogenic polynuclear aromatic hydrocarbons and polynuclear aromatic amines present in some synfuel process streams.

The disposition of BaP in the rat was examined by administering 0.46 μmoles of ^{14}C-labeled BaP (10 μCi total activity) in 50 μl of acetone to 10 300-g (nominal) Sprague-Dawley rats by injection into a caudal vein. Another 10 rats were dosed following the same protocol but using dimethylsulfoxide (DMSO) rather than acetone as the vehicle. Blood samples were then collected from the tail vein at intervals up to 24 hr after exposure. A portion of the plasma from each blood sample was extracted with ethyl acetate, followed by 2:1 ethyl acetate:acetone, and both the organic extract and aqueous phases were counted. Counts in the organic phase represent BaP and simple phenolic metabolites; those remaining in the aqueous phase after extraction represent highly polar metabolites such as sulfates, glucuronides, and glutathione conjugates. The plasma concentration of unchanged BaP was then determined by analyzing the organic extract by means of high-performance liquid chromatography (HPLC), using a C-18 reverse-phase column and fluorometric detection. The mobile phase was acetonitrile:water, 80:20. Several of the BaP concentrations were confirmed by independent measurement, using gas chromatography/mass spectrometry.

The percutaneous absorption of BaP was examined by application of 1.15 μmoles (25 μCi) BaP to the shaved backs of rats in 250 μl of DMSO. The dose was increased for this study because the blood levels were expected to be much lower than those found following intravenous (IV) administration. Blood samples from animals dosed percutaneously were collected and analyzed in the same manner as the samples from the IV experiments.

The plasma concentrations measured in these experiments are given in Table 1. A significant proportion of the total BaP-related materials in plasma are present as polar metabolites that do not extract in the ethyl acetate:acetone system. This is true at the earliest times measured and for both IV and percutaneous administration. The initial decline in concentrations of both BaP and polar metabolites was followed by a rise in concentration between 2 and 6 hr after exposure. The rise is most obvious for the metabolites, but is also present, at least as an inflection, in the BaP concentration-versus-time curves. The rise in concentration is believed to be due to biliary recycling of BaP and its metabolites, which has been reported by other investigators. Concentrations of the nonextractable metabolites in the plasma are generally greater than those of parent BaP, with the difference being much greater when the dose is absorbed through the skin rather than injected intravenously.

The half-time for clearance of BaP from plasma is on the order of 10 min, estimated from the initial slope of the plasma-level-versus-time curve. However, biliary recycling makes the effective half-time much longer, resulting in significant levels of BaP in plasma even after 24 hr. A similar effect was observed for the major nonextractable metabolites. The persistence of plasma levels may allow BaP and its metabolites to accumulate in the body under conditions of repeated exposure, even when periods as great as 24 hr separate the exposures.

TABLE 1. Plasma Concentrations of BaP and Polar BaP Metabolites Following Epidermal and Intravenous Administration to Sprague-Dawley Rats.

	Time After Administration										
	1 min	10 min	0.3 hr	1.0 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr	24 hr
0.46 μmoles IV in Acetone											
Concentration BaP[a]	346	325	151	49.6	--	20.6	--	10.7	--	10.7	6.0
Concentration Polar Metabolites[b]	1022	353	207	150		177		130	--	167	55.5
0.46 μmoles IV in Dimethylsulfoxide											
Concentration BaP[a]	--	320	108	74.2	--	56.1	--	54.8	--	21.6	13.1
Concentration Polar Metabolites[b]	--	783	203	181	--	214	--	109	--	104	70.6
1.15 μmoles Percutaneous in Dimethylsulfoxide											
Concentration BaP[a]		4.3	15.8	24.9	23.6	12.9	8.1	4.6	5.6	4.0	1.0
Concentration Polar Metabolites[b]		6.8	25.8	97.0	282	389	353	405	434	339	323

[a]Concentration in picomoles benzo[a]pyrene (BaP)/gram plasma

[b]Concentration in picomoles unextractable BaP metabolites per gram of plasma, calculated from the ^{14}C activity remaining in the aqueous phase after extraction.

The percutaneous absorption of 6-AC was studied following application of 1.6 μmoles of 6-AC in 50 μl of acetone to the shaved backs of rats. The protocol was similar to that described above for the BaP studies, but a serial sacrifice was added to obtain skin samples for direct measurement of the amount of 6-AC remaining at the site of application as a function of time. Plasma samples were taken up in acetonitrile, centrifuged, and analyzed by HPLC on a Zorbax C8 reverse-phase column using methanol/water, 80:20, for the mobile phase, and fluorometric detection. Skin samples were extracted with ethanol, and the extracts analyzed in the same manner as the plasma samples. An attempt was made initially to use an electrochemical detector for this analysis because preliminary results obtained on mouse skin containing 6-AC looked very promising and the detector offers very high sensitivity. However, interfering substances present in the rat tissue and plasma samples prevented application of this detection method until a suitable preseparation procedure can be developed.

The results of the skin analyses are presented in Table 2. The quantity of 6-AC on the skin fell off rapidly during the first 1-2 hr, then became almost constant, with 51% of the dose still present at the site of application after 24 hr. The low rate of removal of 6-AC from the skin resulted in very low blood levels. In spite of the high sensitivity of the fluorometric procedure (limit of detection is less than 4 picomoles/ml plasma) and the relatively high dose, blood levels of 6-AC were not detectable in this experiment. Additional development work will be necessary to achieve high enough analytical sensitivity to complete these measurements.

TABLE 2. Percent of 6-AC Dose Remaining at the Site of Application after Epidermal Application to Sprague-Dawley Rats.

Time after Application											
0	5 min	15 min	30 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr	24 hr
95.0	94.5	83.6	79.0	70.1	75.6	59.3	51.9	67.5	54.4	66.3	51.0

[a]Each value is the average of measurements on four rats.

• Aerosol Technology Development

Principal Investigator: W. C. Cannon and E. F. Blanton

Technical Assistant: B. W. Killand

The objective of this project is to improve techniques and apparatus for generating, sampling and characterizing aerosols and for exposing laboratory animals to airborne pollutants. In the past year we have refined calculations for estimating lung deposition in rodents; evaluated aerosol penetration in new, nose-only chambers; and improved methods of sampling aerosols by eliminating charge effects.

Improving Estimates of Lung Deposition in Rodent Exposures

During rodent exposures, the deposited aerosol activity in the lung (initial lung burden, ILB) is estimated from the product of time-weighted average concentration and exposure time. This quantity, called "the exposure," is calculated by multiplying concentration by time (min·nCi/L), and is symbolized by E. The value of E is updated by periodic measurements of aerosol concentration as the animals are being exposed. Aerosol concentration alone is insufficient to predict lung deposition since the latter is also affected by particle size. However, we have had no adequate method for real-time measurement of the particle size of alpha-emitting aerosols. When the aerosol particle size is different from that used in previous exposures, we need some simple way to modify our estimates of lung burden during exposure.

For some time we have measured total concentration with a real-time monitor, calculating E after each measurement and estimating the activity deposited in the lung at that time. We then terminated the exposure when the estimated ILB reached the target value. In rats, the probability of lung deposition is less for particles larger than 3 μm in aerodynamic diameter than for smaller particles. We hypothesized that we could make more accurate estimates of lung deposition by ignoring particles above some given size, d. We calculated a new exposure value, E_d, which includes only the aerosol particles smaller than d, and based deposition estimates on this value.

We propose to install a preselector in the monitor inlet that will filter out the particles larger than d. By calculating E_d instead of E we will achieve better estimates of the deposited lung burdens. To discover which diameter, d, would result in the best lung deposition estimates we have examined data from past aerosol exposures. These exposures included more than 2000 rats that were exposed, nose-only, to plutonium dioxide aerosols tagged with ytterbium-169. This tag allows us to measure the body burden of each animal by in vivo counting and to calculate ILBs by extrapolating back to the time of exposure. The particle sizes of these aerosols, determined from cascade impactor samples collected during exposures, varied from an AMAD of 0.68 to 2.59 μm. From these cascade impactor data we calculated the fraction of plutonium activity in particles smaller than 2 μm, smaller than 1.5 μm and smaller than 1.0 μm, respectively. Multiplying E by these fractions, we obtain values of $E_{2.0}$, $E_{1.5}$ and $E_{1.0}$, which are "exposures" for the corresponding particle-size cuts.

By dividing, by E, the amount of activity deposited in an animal we obtain a factor relating exposure to deposition. This factor, which has the same units as flow rate, can be interpreted as the effective minute volume of the animal for lung deposition. To determine values of E, we took samples of an exposure aerosol at three ports with filter samplers. Dividing the filter activity by the sampler flow rate provided a direct measure of E. We calculated the mean value of E for each group, then, as explained above, calculated the mean values of $E_{2.0}$, $E_{1.5}$ and $E_{1.0}$.

The body burden of each animal was measured at 7 and 14 days after exposure. The mean values for each exposure group were determined and are symbolized by B_7 and B_{14}, respectively. We then estimated the ILB (B_0) by assuming that the clearance curve between 7 and 14 days could be extrapolated to time 0:

$$B_0 = (B_7)^2/B_{14}$$

The values measured are actually total body burdens but since, by day 7, most of the remaining activity is in the lung, B_7 and B_{14} are essentially lung burdens.

For each exposure group we have three lung burdens and four E values and can calculate a total of 12 effective minute volumes. We then test these values by calculating estimated lung burdens from E values and compare them to the measured lung burdens. Using E_{total}, $E_{2.0}$, $E_{1.5}$ and $E_{1.0}$, our estimates of lung burden were within 10% of the measured value for the number of times indicated in Table 1. The highest scores were achieved using $E_{2.0}$ and $E_{1.5}$. The best cut-off diameter would be approximately 2.0 μm.

TABLE 1. Number of Estimated Lung Burdens Within 10% of the Measured Value. Maximum score possible is 68.

Exposure Fractions:	E_{TOTAL}	$E_{2.0}$	$E_{1.5}$	$E_{1.0}$
Lung Burdens				
B_0	24	37	35	16
B_7	17	30	34	19
B_{14}	13	29	27	20

To further improve estimates, we will also consider using preselectors such as cyclone separators, which have collection efficiencies more closely approximating the upper respiratory tract of the rat.

Aerosol Penetration Factors

One of the more important attributes of an aerosol exposure system is its ability to deliver the aerosol with minimal changes in properties. For this reason we investigated the characteristics of aerosols in the flow-past chamber which we recently developed for nose-only aerosol exposures of rodents. To assess changes in aerosol size distributions caused by the chamber geometry we simultaneously collected cascade-impactor samples at the chamber inlet and at an exposure port. The plutonium activity of the $^{239}PuO_2$ aerosol was analyzed by counting its 17-keV X-rays.

Because the impactors were matched for jet diameters and flow rates we could directly compare stage activities to determine the penetration factor of the chamber for eight aerosol size ranges. These data were collected during 18 rat exposures. Figure 1 shows the mean values of the ratio of the exposure-port impactor-stage activity to the inlet impactor-stage activity, plotted against the midpoint diameter of the stage. Standard deviations of these ratios are plotted as error bars.

From Figure 1 we can estimate that the 50% cut-point of the chamber is 6.5 μm. As an

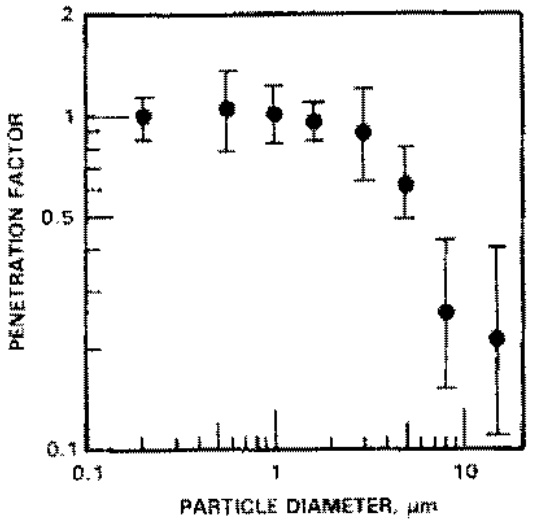

FIGURE 1. Mean (±SD) Penetration Factor (Ratio of Exposure-Port Stage Activity to Inlet Impactor-Stage Activity) Versus Particle-Size Diameter (μm) for a Flow-Past Inhalation Exposure Chamber.

example of how this might affect exposure aerosols, we have estimated the aerosol loss in the chamber for two log-normally distributed aerosols having AMADs of 1.5 and 3.5 μm; both have a geometric standard deviation of 2.5. The loss of the first aerosol would be 13% and of the second, 32%. Although this loss would occur mostly in large particles, for which the probability of lung deposition is very small, in studies involving upper-respiratory-tract deposition, the loss of the larger-size aerosol particles would be quite significant.

Eliminating Charge Effects in Aerosol Sampling

The 10-mm cyclone commonly used to measure respirable particle concentrations of airborne aerosols may underestimate these concentrations because of electrostatic charge. We have demonstrated experimentally (Annual Report, 1982) that such charge effects do not occur when cyclones are coated with a conducting material or are fabricated from conducting nylon.

We have studied theoretical trajectories of charged aerosol particles approaching a charged nylon cyclone to assess the effects of charge on the sampling effiency of the instrument. Figure 2 shows theoretical trajectories calculated for 3.5-μm unit density spheres, each carrying 200 electronic charges, as they approach a nylon cyclone carrying 3 statcoulombs of charge uniformly distributed over its cylindrical surface. None of the particles

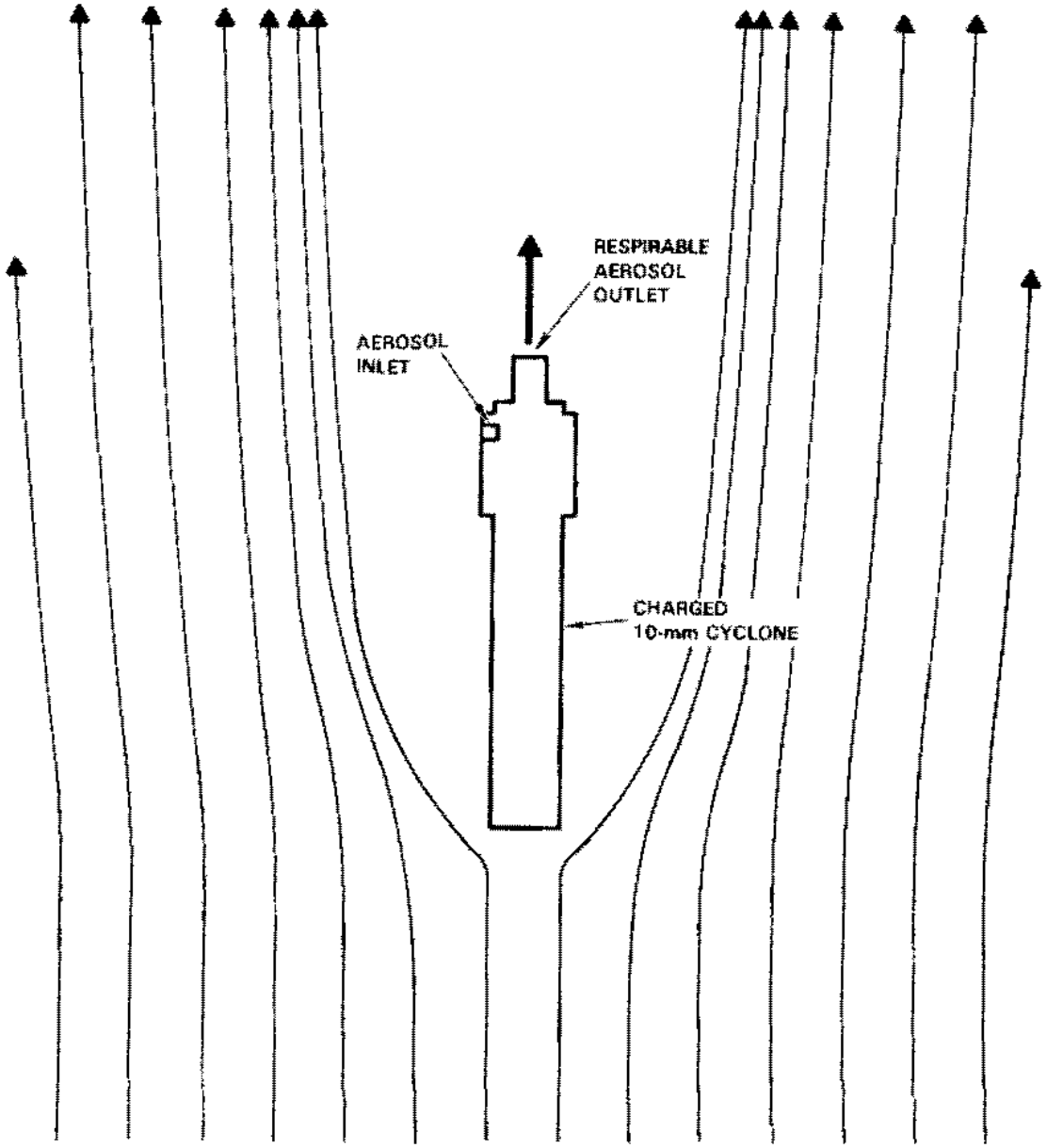

FIGURE 2. Theoretical Trajectories of 3.5-μm-Diameter Unit Density Spheres Approaching a Charged, 10-mm Nylon Cyclone.

that approached the cyclone in a direction parallel to its cylindrical axis would reach the sample inlet, and the collection efficiency would be zero for the case.

Both the theoretical calculations and experimental measurements indicated that estimates of respirable aerosol concentrations may be as much as 20% less than actual values when nonconducting cyclones are used.

Other plastic aerosol samplers may also have adverse charge effects; we will use these methods to see if those samplers also require modification.

• Biological Effects of Magnetic Fields

Principal Investigator: B. J. Kelman

Other Investigators: C. S. Abernethy, D. W. Carlile, J. R. Decker, Jr., D. R. Kalkwarf, E. G. Kuffel, D. D. Mahlum, J. R. Skalski, and J. A. Strand

Technical Assistance: M. Orgill, T. A. Pierce, and R. L. Rommereim

The scope of this project was greatly reduced in the past year. Previously, the objective of this project has been to evaluate the effects of magnetic fields on a variety of biological systems. These systems have included dominant lethal studies in mice, prenatal development in rats, fertilization and embryonic development in trout, synthetic membranes, and long-term exposure of mice. Reports have continued to appear in the literature describing biological effects of magnetic fields, but the current data base remains extremely weak, primarily because of the lack of appropriate controls, especially in whole-animal studies. Our lifetime study in mice, begun in FY 1982, continued this year in a facility which permits exposure and sham-exposure of animals under nearly identical conditions.

Additional studies were carried out to determine the nature of the interaction between rainbow trout ova and sperm and magnetic fields that leads to enhanced fertilization.

Facilities

The primary facility used in lifetime exposures has been described in previous Annual Reports (1979-1982). However, since it is unique (it allows lifetime exposures with concurrent controls), a brief description is included below.

A 1200-ft^2 metal building has been renovated to house two identical beam-bending magnets (type 18D36), which were obtained on loan from the Stanford Linear Accelerator Center (SLAC). These magnets, which we previously used at SLAC, have poles that measure 45.7 x 91.4 cm, with a gap of 17.8 cm. This provides a relatively large cavity with a uniform vertical field. In addition, the space on either side of the poles can be used for exposure to gradient fields.

An environmentally controlled unit, described in a previous Annual Report (1980), has been placed in each magnet to house the animals. The environmental units are matched in size, lighting, temperature, and humidity. The mode of operation has been such that one magnet is energized (to provide the exposure field) while the other is not. This permits control animals to be maintained under conditions which are as similar as possible to those encountered by the exposed groups. Either magnet can be energized, thereby allowing locations of control and exposed groups to be exchanged between magnets, minimizing potential differences between units.

Trout Egg Fertilization

Previous studies conducted in this laboratory confirmed that fertility of trout ova was significantly increased in the presence of 1-T magnetic fields. In order to determine whether this response was dose-related, trout ova and sperm were exposed to field strengths of 0, 0.1, 0.5, and 1.0 T for periods of 5, 15, 20, and 60 min. These exposures were completed in FY 1983 and were evaluated during the remainder of the year. No valid statistical conclusions can be reached until an additional replicate test series is completed. However, inspection of the available data indicates a slight but consistent trend toward increased fertility with increased strength and duration of exposure to a magnetic field.

Lifetime Exposure to Magnetic Fields

Lifetime exposures of female CD1 mice to homogeneous 1-T and gradient 2-T/m fields were continued. This study was begun on April 13, 1982 when mice were 5 mo of age; 25 mice were placed in the gradient field, 50 mice were placed in the homogeneous field, and 75 mice were placed in the control magnet.

Each week the mice have been transferred from the energized magnet to the nonenergized magnet; the nonenergized magnet has then been energized, and the previously energized magnet degaussed. This procedure controls for any slight differences which may be present between the two magnets.

At the initiation of the experiment, the mean weight of the mice used in the study was 31.2 g, with a standard deviation of 0.7 g. Figure 1 shows weights (mean ± SE) of the four groups of mice as a function of exposure duration. Weights of the mice exposed or sham-exposed to the homogeneous field were not different over the period shown. At 536 days of exposure, mice exposed to the gradient field weighed 41 ± 2 g; those exposed to the homogeneous field, 43 ± 1 g. Mice sham-exposed to the gradient field weighed 40 ± 1 g, and those sham-exposed to the homogeneous field, 45 ± 2 g.

Mice exposed or sham-exposed to the gradient fields gained weight more slowly during the first 40 days of exposure than mice exposed or sham-exposed to homogeneous fields. The origin of the difference is not readily apparent, although we strongly suspect it is directly related to crowding among the gradient-exposed animals, a problem which initially went undetected. During the early phases of this experiment, some of the animals housed in the gradient area of the magnets may have escaped from their caging units and joined other animals in the gradient group in their cages. These animals did not cross between gradient and homogeneous parts of the exposure chamber. We have hypothesized that the crowding and consequent deprivation of both water and feed retarded the weight gain of the gradient animals. However, it is clearly evident that no difference exists in the weights of animals comparing exposed groups with their appropriate controls.

The mortality curves (Figure 2) for exposed and sham-exposed animals do not appear to be significantly different. At 536 days of exposure, mortality was 26% (13 animals) in the exposed homogeneous group, 34% (17 animals) in the sham-exposed homogeneous groups, 20% (5 animals) in the exposed gradient group and 28% (7 animals) in the sham-exposed gradi-

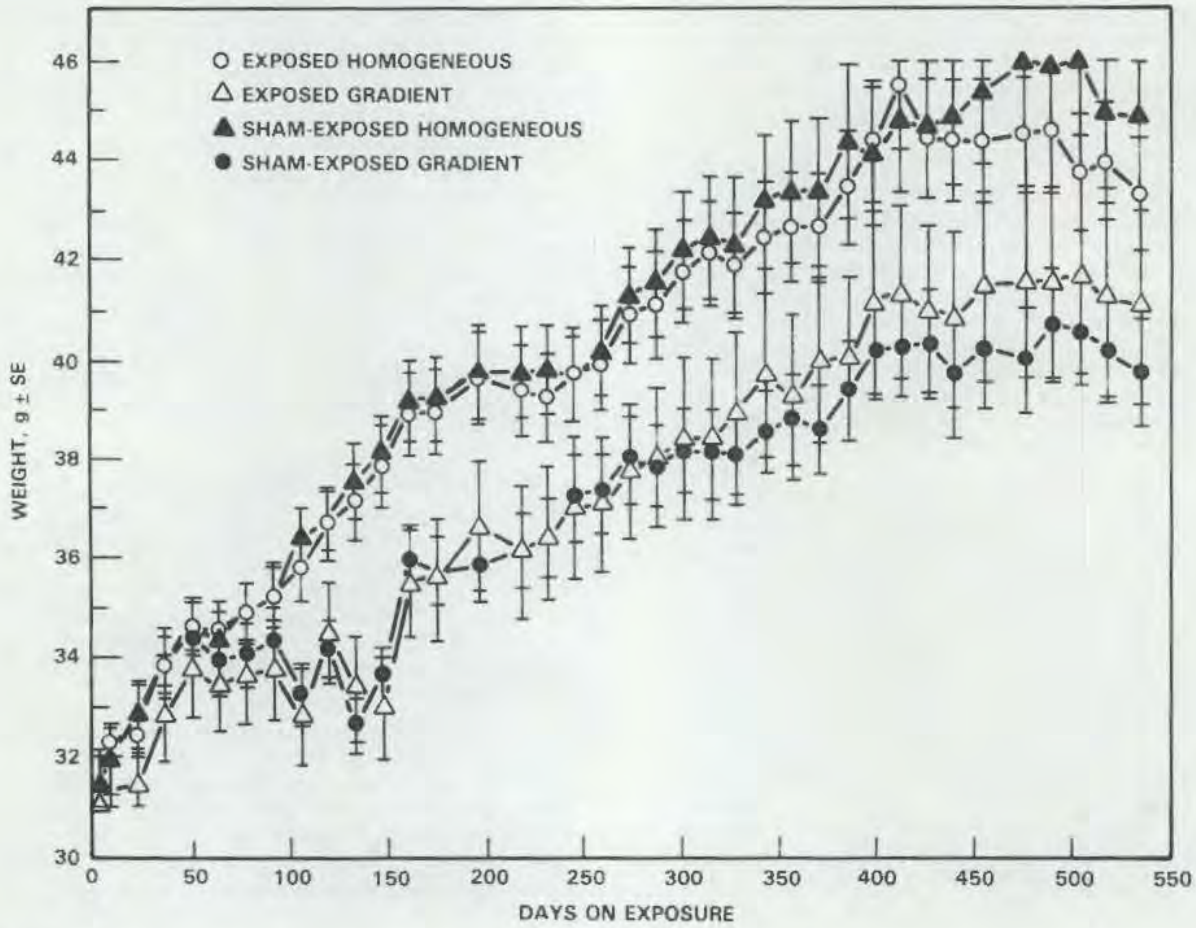

FIGURE 1. Weights of Rats Exposed or Sham-Exposed to Magnetic Fields.

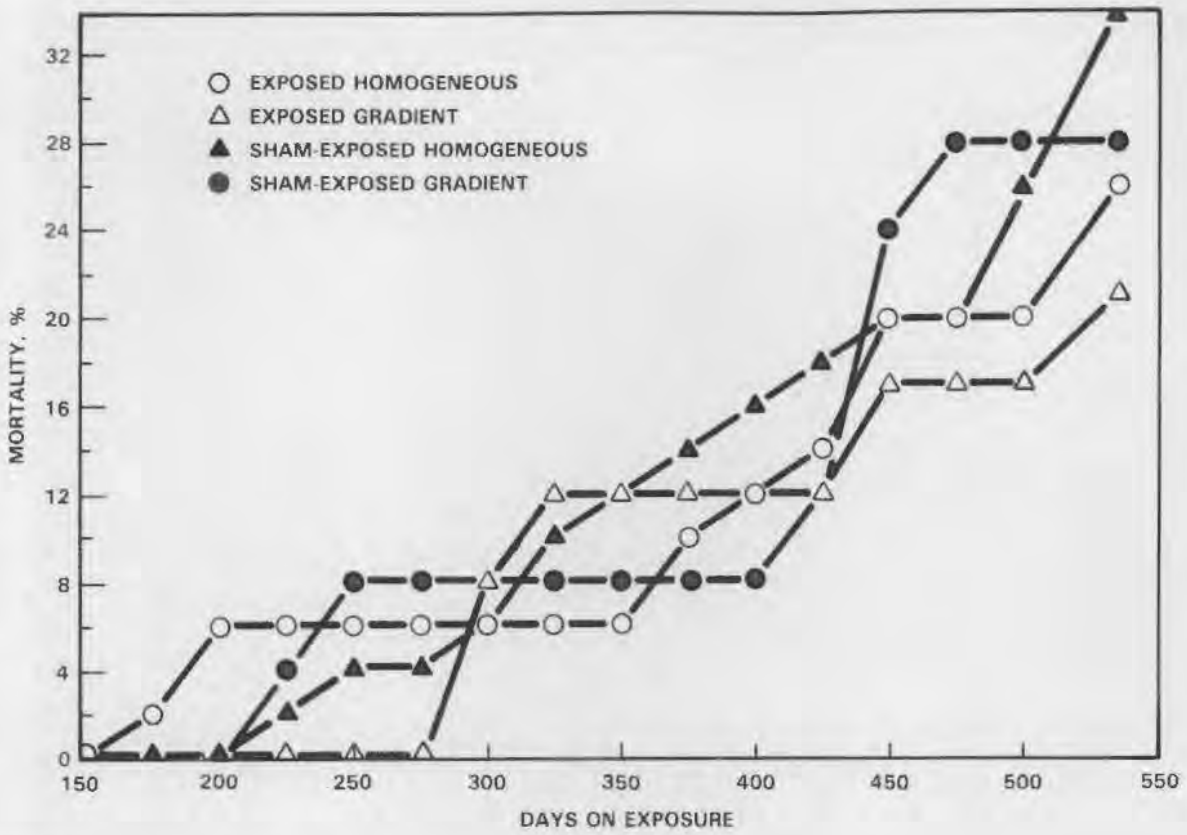

FIGURE 2. Mortality in Rats Exposed or Sham-Exposed to Magnetic Fields.

ent group. No significant differences are apparent between groups if mean time to tumor is considered. In the sham-exposed homogeneous group, mean time to tumor was 331 ± 36 days (±SE). In the exposed homogeneous group, mean time to tumor was 271 ± 51 days. In the sham-exposed gradient group, mean time to tumor was 315 days in the two animals with tumors, and in the exposed gradient group, mean time to tumor was 327 ± 37 days.

Detailed histopathological evaluations have not been completed on all animals that have died. In the sham-exposed homogeneous groups, evaluations have been completed on 11 animals: five died of malignant lymphomas, one of Asner cell carcinoma. Death was not related to carcinomas in five animals. In the exposed homogeneous group, evaluation of 10 animals has been completed: cause of death was malignant lymphoma in three animals, granulocytic leukemia in one, Asner cell carcinoma in one animal, and rhabdomyosarcoma in one animal. Death was not related to carcinoma in four animals. Histopathological evaluations have been completed on six animals from the sham-exposed gradient group: two died of malignant lymphoma; in one animal autolysis was too advanced to allow determination of the cause of death; and three other deaths were unrelated to carcinomas. In the exposed gradient group, five animals have been evaluated for cause of death: three were due to malignant lymphomas and one to Asner cell carcinoma. To date, there does not appear to be a difference in the pattern of tumor type between exposed and sham-exposed groups.

At the present time, no significant differences exist between exposed and sham-exposed animals. Too few animals have died to allow conclusive evaluation of this experiment. However, at the termination of the experiment, we plan to perform extensive necropsies and prepare the tissues for in-depth histopathological evaluations. Electrocardiograms and clinical chemistry results will also be evaluated. Because of the unique applications of lifetime studies hazard evaluation, we plan either to replicate this study or to perform another lifetime study, using another strain of mouse with different genetic characteristics.

General Life
Sciences

• Metal-Membrane Interactions

Principal Investigator: R. P. Schneider

Other Investigators: H. Drucker, R. A. Lindberg, and J. E. Morris

Technical Assistance: M. J. Steele

Using different model systems in *Neurospora crassa*, two studies within this project examine the role of membranes in regulation of metabolism and entry of metals into cells. We studied the regulation of an aspartyl protease secreted by *Neurospora* and found that the enzyme is controlled in a different manner from that of previously investigated proteases. The amount and cellular location of this enzyme varies for each of the three states of derepression under which it is synthesized. Data from zinc-uptake studies suggested that zinc is recognized by the uptake system as zinc citrate but that the citrate does not enter the cell with the zinc. After exposure of cells which have a high zinc-uptake rate because they had been deprived of zinc to 20-mM zinc, the cells lose the ability to transport the metal with a half-time of 12 min. If the cells are transferred to zinc-free medium, the rate of loss of the uptake system is slowed fivefold (half-time of 1 hr). These experiments indicate that *Neurospora* has a sensitive control system for regulating accumulation of zinc.

In spite of the ubiquitous, increasing presence of toxic metals derived from the production of energy in the environment, little is known of their interactions with membrane uptake and regulatory systems. The ionic forms of most toxic metals penetrate cell membranes slowly; therefore, it seems likely that many of their effects are exerted at the membrane level or are determined by membrane-regulated entry into cells. Thus, information on the interaction of metals with defined membrane functions may be expected to aid in predicting potential effects of trace metals from fossil-fuel utilization and processing.

Using different model systems, two studies within this project examine the role of membranes in regulation of metabolism and their role in regulating entry of toxic metals into cells.

Regulation of Extracellular Enzymes in Neurospora crassa

We have investigated the regulation of several extracellular enzymes produced by the fungus Neurospora crassa to better understand how components of the external environment can control gene expression. We have found that N. crassa secretes several proteases and nucleases in response to limitation of the elemental nutrients obtainable from proteins and nucleic acids. We have also found that regulation of an extracellular acid protease is more complex than that of enzymes studied earlier.

Three of the proteases investigated are derepressible for any of the three elemental nutrients that make up protein (i.e., starvation for S, C, or N results in "turning on" the genes for these proteases). However, regulation of the extracellular aspartyl protease, is not coordinated with the other proteases. Figure 1 shows that the protease is derepressible for S but is only present in small amounts when N is limited, and is not detectable when C is limiting. A curve similar to that representing S-derepression is generated for all three states of derepression if the filtrates are assayed for activity from the other N. crassa proteases.

To determine at which level this enzyme is regulated, we examined the intracellular levels created by the various states of derepression. We did this by harvesting mycelia at several time points during derepression, then freeze-drying, grinding and extracting soluble enzymes, and assaying them for activity inhibitable by the specific inhibitor pepstatin. The results are shown in Figure 2. Apparently, derepression occurs with starvation for any of the three elements (C, S or N). High levels of enzyme are synthesized and secreted when S is limiting; however, only small amounts are synthesized under N-starvation. Under C-limitation, high levels of enzyme are found in the cells, but synthesis stops and no secretion takes place. Secretion of this protease would lead to rapid inactivation under C-starvation because of the high pH caused by secretion of ammonia when amino acids are broken down as a C-source. Further work must be done to determine the cellular location and function of C-derepressed acid protease.

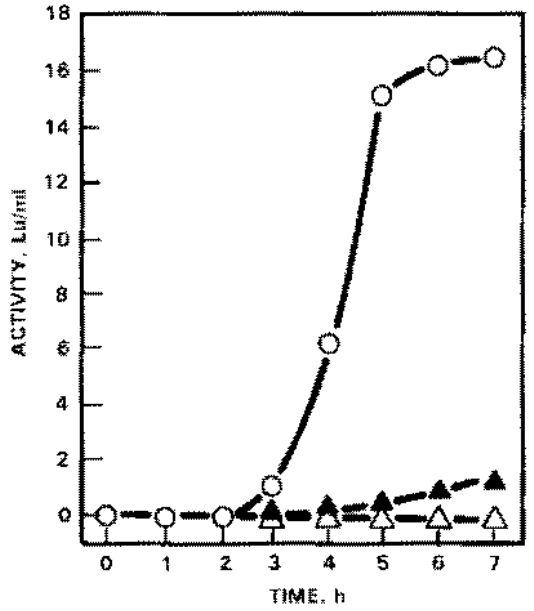

FIGURE 1. Extracellular Appearance of Pepstatin-Inhibitable Protease Activity. Twelve-hour mycelia were transferred to media containing 1% bovine serum albumin and lacking a sulfur (○), a nitrogen (▲), or a carbon source (△).

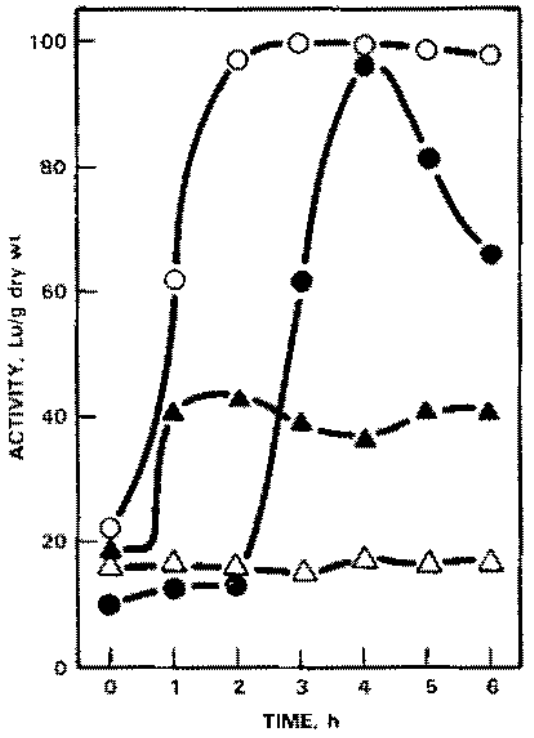

FIGURE 2. Time Course of Accumulation of Intracellular Pepstatin-Inhibitable Activity. Mycelial extracts were prepared from cultures grown under: S- (●), C- (○) and, N- (▲) derepression, and repressing conditions (△).

This protease and its cellular location are regulated in a more complex manner than the other proteases of N. crassa. Cellular location is probably regulated by control of transcriptional initiation site. However, the mechanisms that control the total levels synthesized have not yet been explained. Possibilities include promoter strength, the rate of degradation of newly synthesized mRNA, or the rate of enzyme turnover.

Uptake of Zinc by N. crassa

Previous studies (Annual Report, 1981) have shown that depriving N. crassa of zinc causes it to synthesize a high-affinity uptake system for this element. In addition, we showed that the uptake system has a half-maximal uptake rate at 1.5 nM if free zinc is the substrate and 1.5 μM if the substrate is the zinc-citrate complex.

Last year, additional studies were performed to ascertain the form of the metal recognized and bound by the transport system (i.e., free or chelated zinc). Uptake of zinc was measured as a function of zinc concentration in the presence of two different concentrations of citrate, 1.3 and 8.2 mM. The concentration of free zinc is 6.3 times lower in 8.2- than in 1.3-mM citrate; thus, the uptake rate of zinc at the higher citrate concentration can be predicted from that at the lower concentration of citrate if free zinc is the form recognized by the system. In fact, the uptake rate of zinc, although reduced, was much higher than predicted by the free zinc concentration (Figure 3). The most reasonable explanation is that the transport receptor recognizes zinc citrate as the substrate but transports only the zinc into the cell.

Previous studies showed that the ^{14}C citrate is not taken up in amounts sufficient to account for zinc uptake. The reduction of zinc uptake observed in 8.2-mM citrate (relative to that in 1.3-mM) may be the result of competition with zinc citrate at the recognition site. This information is required for planned studies of the transport of toxic trace metals by the zinc-uptake system, for which potential alternative substrates must be provided in an acceptable chemical form.

We have shown that when 20-mM zinc is added to the medium containing derepressed N. crassa, the cells lose the ability to transport radioactive zinc, with a half-time of 12 min. Furthermore, addition of an inhibitor of protein synthesis to derepressed cultures does not result in the

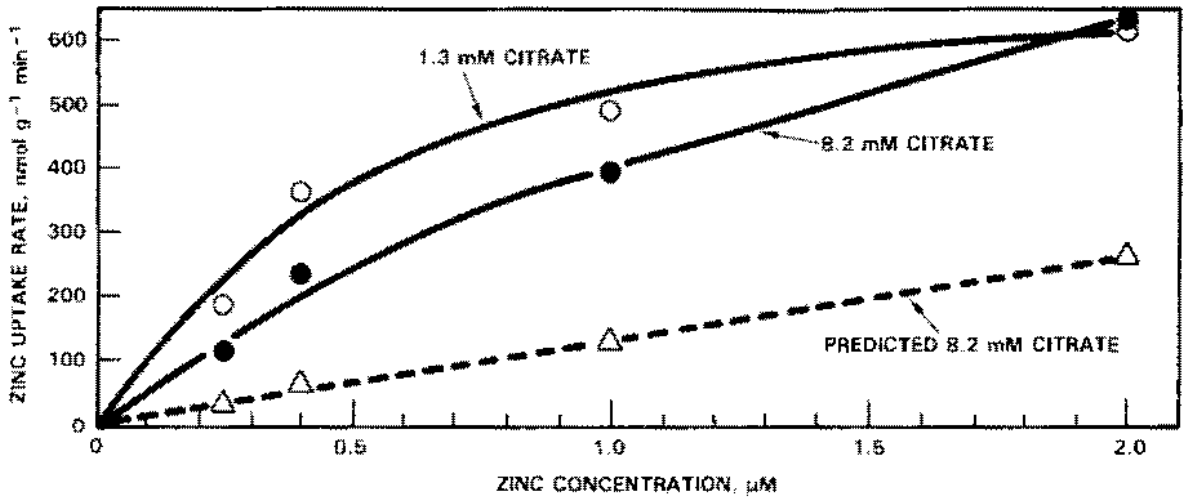

FIGURE 3. The Uptake of Zinc as a Function of Zinc Concentration in 1.3-mM (○) and 8.2-mM (●) Citrate. The dashed line is the predicted available zinc concentration relative to that in 1.3-mM citrate, assuming that unbound zinc is the substrate. The uptake rates used to generate the curve were estimated (interpolated) from the 1.3-mM citrate curve.

loss of uptake ability. This demonstrates that the system is not continuously being synthesized and degraded; i.e., loss is not caused simply by blocking synthesis. Thus, the loss is specifically caused by the presence of zinc and protects the cells from accumulating toxic levels of that element.

We have also conducted studies to examine recovery from the zinc-induced loss of transport ability. We added 20-mM zinc to zinc-starved cells, removed samples of cells from the high-zinc medium, washed them, and measured their ability to transport zinc (as a function of time) in the new zinc-free medium. After only 0.5 min in medium containing 20-mM zinc, the cells continued to lose the transport function for 3 hr (Figure 4). However, the time required for loss of the uptake system was five times slower (half-time = 60 min) than in the presence of external zinc (half-time = 12 min). The rate of loss of the system in zinc-free medium was independent of the length of time the cells were incubated in 20-mM zinc. This suggests that the rate is also independent of the intracellular levels of zinc accumulated during the high-zinc phase. Since the rate-of-transport loss is dependent on the presence of extracellular zinc, when suddenly confronted with high extracellular levels, the uptake system of zinc-deprived cells is rapidly inactivated. If the extracellular zinc disappears (or is all taken up) and the cells contain adequate zinc stores, the uptake system is inactivated five times more slowly. In these conditions, the threat of overaccum-

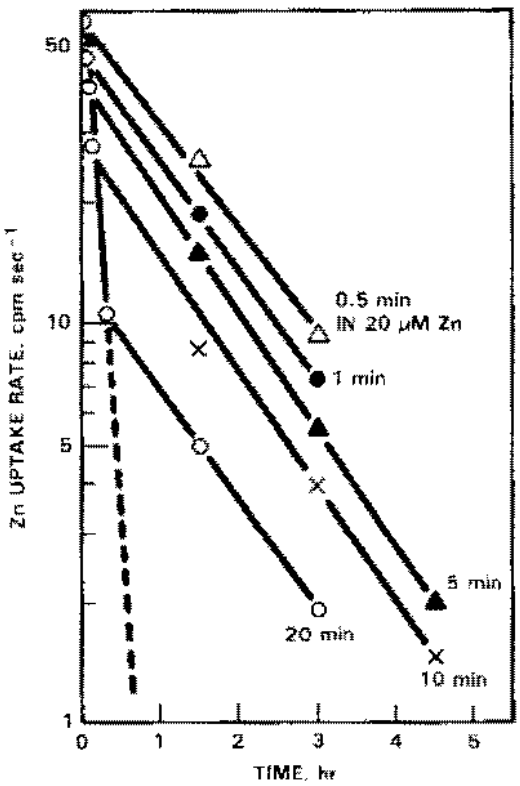

FIGURE 4. Semi Logarithmic Plot of Uptake Rate of Zinc as a Function of Time After the Addition of 20-mM Zinc to Zinc-Deprived Cells. Shown beside each curve is the length of time the cells were incubated in 20-mM zinc-containing medium. They were then transferred to zinc-free medium, and their uptake rates were measured with ^{65}Zn at various intervals. The dashed line indicated the zinc uptake rate if the cells remain in 20-μM zinc for more than 20 minutes. These data were from another experiment.

ulation is removed, and the cells safely retain the ability to accumulate zinc.

In the natural environment, N. crassa probably grows in conditions of extremely low zinc concentration and is at least partially derepressed for zinc uptake in most situations. Exposure to low levels of zinc for as little as 30 sec provides sufficient zinc for the cells for 3 hr. The mechanisms investigated in these studies allow for fine-tuning zinc-uptake ability in conditions of varying availability of the element. These data are required for design of experiments that will permit prediction of the factors affecting bioaccumulation of toxic trace metals by the zinc-uptake system.

Medical Applications of Nuclear Technology

• Blood Irradiator Development

Principal Investigator: F. P. Hungate

Other Investigators: L. R. Bunnell, T. L. Marchioro, W. F. Riemath, and R. E. Weller

Efficacy of chronic blood irradiation in suppressing early rejection of kidney transplants is still being tested. In these new tests, donor kidneys are obtained from strains of dogs other than those in the PNL beagle colony. Assessment of stray radiation dose has indicated a need both for additional shielding and a more efficient distribution of shielding mass. Hardware design is being adapted to provide for effective irradiation of blood volumes in humans, which are greater than those in dogs. Work is in progress to develop analytical techniques in dogs similar to those now available for evaluating lymphocyte populations in mice and in man.

This year, major emphasis was placed on requesting permission from the appropriate Human Subjects Committees to evaluate the efficacy of the blood irradiator in clinical trials. A crucial part of this request is defining radiation doses to the patient and to attending medical staff. An evaluation of such doses was made using TLDs, X-ray film, a gamma analyzer, and a calibrated ionization chamber with its associated electrometer. The results indicated that significant improvement in shielding design will be required. A computer code is being used to evaluate bremsstrahlung doses and identify optimal configurations for placement of shielding.

We identified the presence of energetic gamma radiation from ^{168}Tm, apparently produced by the $n \rightarrow 2n$ reaction. However, the radiation from ^{168}Tm is a minor component compared to bremsstrahlung.

Kidney transplants in dogs continue; we are now using strains other than the beagle as kidney donors in order to maximize the rejection response. In the only test completed at this time, an untreated animal died 9 days after transplant, but the animal with the blood irradiator lived 41 days after transplant, when it was killed. Rejection was evident in both. The treated animal received no blood irradiation during the last 4 wk of its life because shunt flow had stopped, and the irradiator was removed 14 days after transplant. The prolonged delay in rejection following removal of the irradiator provides strong evidence for the effectiveness of chronic irradiation in suppressing rejection. Similar evidence derives from the observed cellular depletion of lymphocytes throughout the dog's body. Two animals died during surgery as a result of defective anesthesia equipment, which is being replaced. Additional animals are being tested as rapidly as they can be scheduled.

To provide radiation intensities suitable for humans, which have about 10 times more blood than dogs, we have designed and initiated fabrication of individual irradiators that have an "active area" twice that of those used on dogs. We are also designing connectors that will permit using two elongated units side-by-side. Such parallel placement will facilitate shielding. The irradator, which will be worn on the arm or leg, can also be more easily connected to the artery and vein of the limb. If higher radiation dose rates are required, they can be achieved by placing more ^{168}Tm in the units and/or prolonging the period of activation. (We now activate the units for 4-5 days; effective activation can be extended up to 25 days.)

At this time there are no suitable means of identifying lymphocyte subsets in dogs, as there are for mice and humans. To develop such a capability, cells from a beagle dog having a lymphoma are being cultured with the expectation that monoclonal antibodies to these cells can be developed. The antibodies will be used in subsequent tests to more suitably evaluate the efficacy of various dose regimens. We hope that data from these tests will also enhance the potential role of blood irradiation for controlling transplant rejection as well as for other clinical applications.

• Radioisotope Customer List

Principal Investigator: M. P. Richards

The purpose of this program is to prepare and distribute the annual document entitled 'List of DOE Radioisotope Customers with Summary of Radioisotope Shipments. This document lists the FY 1982 Commercial radioisotope production and distribution activities of DOE facilities at Argonne National Laboratory, Pacific Northwest Laboratory, Brookhaven National Laboratory, Hanford Engineering Development Laboratory, Idaho Operations Office, Los Alamos Scientific Laboratory, Oak Ridge National Laboratory, Savannah River Plant, and UNC Nuclear Industries. The report (PNL-4759) was published in August 1983.

Appendix

APPENDIX

• Dose-Effect Studies with Inhaled Plutonium in Beagles

On the following pages data are presented for all dogs employed in current life-span dose effect studies with inhaled $^{239}PuO_2$, $^{238}PuO_2$, and ^{239}Pu nitrate. Information is presented on the estimated initial alveolar deposition, based on external thorax counts and on estimated lung weights (0.011 x body weight) at time of exposure. Information is also provided on the current interpretation of the most prominent clinical-pathological features associated with the death of animals. These data represent information presently available, and are presented as reference material for scientists who desire to follow in detail the progress of these experiments.

DOSE-EFFECT STUDIES WITH INHALED PU-239 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
CONTROL	738	F	0	0.00	0.00				08/11/83		171.5*	Processing
CONTROL	740	F	0	0.00	0.00				06/18/83		169.8*	Processing
CONTROL	749	F	0	0.00	0.00					171.9*		
CONTROL	755	M	0	0.00	0.00				12/10/82		162.2*	Status Epilept. Nephrosc
CONTROL	766	M	0	0.00	0.00					171.5*		
CONTROL	775	F	0	0.00	0.00				10/05/81		147.3*	Pul. Thromboembolism
CONTROL	785	M	0	0.00	0.00					170.4*		
CONTROL	789	M	0	0.00	0.00				07/25/83		167.9*	Processing
CONTROL	792	M	0	0.00	0.00				04/28/76		79.5*	Oral Tumor
CONTROL	800	F	0	0.00	0.00					167.3*		
CONTROL	801	M	0	0.00	0.00				02/23/82		148.1*	Lung Tumor
CONTROL	811	F	0	0.00	0.00					166.2*		
CONTROL	846	M	0	0.00	0.00				04/08/83		159.6*	Nephrosclerosis
CONTROL	861	M	0	0.00	0.00					165.0*		
CONTROL	868	F	0	0.00	0.00					163.7*		
CONTROL	872	F	0	0.00	0.00				11/05/82		152.8*	Lung Tumor
CONTROL	878	M	0	0.00	0.00					161.7*		
CONTROL	882	M	0	0.00	0.00				11/06/81		138.7*	Hemangiosarcoma, Liver
CONTROL	885	F	0	0.00	0.00				02/18/83		153.5*	Lung Tumor
CONTROL	903	F	0	0.00	0.00					158.6*		
CONTROL SACRIFICE	701	F	0	0.00	0.00				04/18/79		121.8*	Sacrificed
CONTROL SACRIFICE	703	M	0	0.00	0.00				03/24/77		96.2*	Sacrificed
CONTROL SACRIFICE	724	M	0	0.00	0.00				03/30/78		107.9*	Sacrificed
D-1 LOWEST	756	M	0	0.00	0.00	13.0	19.5	01/19/71	04/21/83		147.0	Processing
D-1 LOWEST	762	M	0	0.00	0.00	11.5	19.3	01/19/71	01/24/77		72.2	Sacrificed
D-1 LOWEST	847	M	0	0.00	0.00	13.0	18.5	07/06/71		146.8		
D-1 LOWEST	858	M	0	0.00	0.00	13.5	18.2	07/06/71		146.8		
D-1 LOWEST	865	F	0	0.00	0.00	9.0	17.4	07/06/71		146.8		
D-1 LOWEST	879	M	0	0.00	0.00	14.5	17.9	10/07/71		143.8		
D-1 LOWEST	886	F	0	0.00	0.00	10.5	18.2	11/10/71		142.7		
D-1 LOWEST	907	F	0	0.00	0.00	11.5	19.9	11/10/71		142.7		
D-1 LOWEST	825	F	1	0.01	0.12	11.5	18.1	06/08/71	11/17/82		137.3	Hemangiosarcoma, Spleen
D-1 LOWEST	849	F	1	0.01	0.10	10.0	21.3	10/07/71	10/26/72		12.6	Sacrificed
D-1 LOWEST	904	F	1	0.01	0.07	9.5	15.9	11/10/71		142.7		
D-1 LOWEST	832	F	2	0.02	0.22	9.0	16.5	04/26/71		149.2		
D-1 LOWEST	900	M	3	0.02	0.22	13.5	16.0	11/10/71	05/21/82		126.3	Round Cell Sarcoma
D-1 LOWEST	870	F	4	0.03	0.32	12.0	16.9	07/06/71		146.8		
D-1 LOWEST	899	F	4	0.03	0.31	11.5	16.0	11/10/71	03/29/81		112.6	Hemangiosarcoma, Heart
D-1 LOWEST	867	M	5	0.04	0.41	11.5	17.4	07/06/71		146.8		
D-1 LOWEST	891	M	6	0.04	0.41	14.0	16.0	11/10/71	06/26/81		115.5	Septicemia
D-1 LOWEST	853	M	8	0.05	0.51	15.0	21.3	10/07/71		143.8		
D-1 LOWEST	875	M	8	0.05	0.54	14.0	16.8	07/06/71	05/21/78		82.5	Kidney:Malignant Lymphoma
D-1 LOWEST	770	F	5	0.06	0.63	9.5	19.1	01/19/71		152.3		

* Indicates age in months since birth, all other ages are in months since exposure.

DOSE-EFFECT STUDIES WITH INHALED PU-239 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION: NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE: WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION: 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-1 LOWEST	788	M	8	0.06	0.62	13.0	18.7	02/09/71		151.7		
D-1 LOWEST	850	F	5	0.06	0.62	8.0	21.3	10/07/71	06/06/83		140.0	Bone Tumor
D-1 LOWEST	893	M	9	0.06	0.61	14.0	14.9	10/07/71		143.8		
D-1 LOWEST	807	F	8	0.07	0.73	11.0	14.6	02/09/71	07/24/81		125.4	Pituitary Tmr, Cushing's
D-1 LOWEST	841	F	6	0.07	0.75	8.0	17.7	06/08/71		147.7		
D-1 LOWEST	908	M	9	0.07	0.77	11.0	15.9	11/10/71	04/01/80		100.7	Unknown, Pul. Hyalinosis
D-2 LOW	776	M	10	0.07	0.74	13.5	20.2	03/04/71		150.9		
D-2 LOW	842	M	10	0.07	0.77	13.5	18.6	07/06/71		146.8		
D-2 LOW	767	M	10	0.08	0.83	12.0	18.2	12/21/70		153.3		
D-2 LOW	920	M	11	0.08	0.92	12.0	16.0	06/08/72	07/07/72		1.0	Sacrificed
D-2 LOW	862	M	13	0.09	1.00	13.0	17.3	06/08/71	06/25/83		144.6	Processing
D-2 LOW	871	M	13	0.09	0.96	13.5	16.9	07/06/71		146.8		
D-2 LOW	874	M	16	0.11	1.24	13.0	16.8	07/06/71		146.8		
D-2 LOW	754	M	22	0.15	1.69	13.0	15.5	01/19/71	01/10/78		83.7	Status Epilepticus
D-2 LOW	845	F	19	0.15	1.63	11.5	17.6	06/08/71		147.7		
D-2 LOW	748	F	14	0.16	1.75	8.0	19.5	01/19/71	08/19/81		127.0	Unknown Cause
D-2 LOW	798	F	16	0.16	1.78	9.0	15.6	02/09/71	08/29/74		42.6	Sacrificed
D-2 LOW	826	F	19	0.17	1.90	10.0	19.1	07/06/71		146.8		
D-2 LOW	831	F	21	0.18	2.00	10.5	17.9	06/08/71		147.7		
D-2 LOW	881	F	19	0.19	2.09	9.0	17.7	10/07/71		143.8		
D-2 LOW	780	F	24	0.22	2.40	10.0	18.2	01/19/71	04/08/82		134.6	Pheochromocytoma
D-2 LOW	859	M	35	0.22	2.41	14.5	18.2	07/06/71		146.8		
D-2 LOW	757	M	36	0.23	2.57	14.0	18.5	12/21/70		153.3		
D-2 LOW	876	F	19	0.24	2.69	7.0	17.9	10/07/71		143.8		
D-2 LOW	806	F	26	0.25	2.74	9.5	15.3	03/04/71	10/29/82		139.9	Palate:Malignant Melanoma
D-2 LOW	813	F	32	0.29	3.20	10.0	15.1	03/04/71		150.9		
D-2 LOW	677	F	34	0.29	3.24	10.5	17.9	10/07/71		143.8		
D-2 LOW	769	F	28	0.32	3.50	8.0	18.2	12/21/70	06/23/78		90.1	Ovarian Tumor
D-2 LOW	802	M	40	0.33	3.64	11.0	18.1	04/26/71		149.2		
D-3 MED-LOW	781	F	48	0.38	4.17	11.5	17.3	12/21/70	02/20/81		122.0	Lung Tumor, Kidney Tumor
D-3 MED-LOW	771	F	44	0.40	4.40	10.0	18.2	01/20/71		152.3		
D-3 MED-LOW	782	M	62	0.42	4.59	13.5	19.0	02/10/71	05/27/83		147.5	Processing
D-3 MED-LOW	786	M	62	0.42	4.59	13.5	19.5	03/04/71		150.9		
D-3 MED-LOW	752	M	62	0.43	4.77	13.0	18.6	12/21/70	02/22/79		98.1	Lung Tumor, Adrenal Tumor
D-3 MED-LOW	823	M	65	0.44	4.81	13.5	16.8	04/26/71		149.2		
D-3 MED-LOW	883	M	63	0.44	4.85	13.0	17.7	10/07/71		143.8		
D-3 MED-LOW	778	M	74	0.46	5.10	14.5	20.2	03/04/71	08/26/79		101.7	Pul. Thromboembolism
D-3 MED-LOW	838	M	56	0.46	5.09	11.0	17.8	06/08/71		147.7		
D-3 MED-LOW	795	F	54	0.49	5.40	10.0	15.0	01/20/71	09/06/83		151.5	Processing
D-3 MED-LOW	815	M	68	0.52	5.67	12.0	16.8	04/26/71	05/22/73		24.9	Sacrificed
D-3 MED-LOW	851	F	53	0.54	5.89	9.0	21.3	10/07/71		143.8		
D-3 MED-LOW	918	M	74	0.58	6.43	11.5	16.0	06/08/72	07/06/72		0.9	Sacrificed
D-3 MED-LOW	834	F	67	0.68	7.44	9.0	17.8	06/08/71	07/05/79		96.9	Pyometra

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DOSE-EFFECT STUDIES WITH INHALED PU-239 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	797	F	85	0.70	7.73	11.0	16.4	03/04/71		150.9		
D-3 MED-LOW	848	F	75	0.72	7.94	9.5	21.3	10/07/71		143.8		
D-3 MED-LOW	827	F	89	0.74	8.09	11.0	16.7	04/26/71		149.2		
D-3 MED-LOW	697	M	140	0.85	9.33	15.0	19.5	10/30/70	05/08/80		114.3	Card. Valve Insufficiency
D-3 MED-LOW	750	M	118	0.93	10.26	11.5	19.6	01/20/71		152.3		
D-3 MED-LOW	884	M	123	1.12	12.30	10.0	17.8	10/08/71		143.7		
D-3 MED-LOW	844	F	135	1.17	12.86	10.5	17.6	06/08/71		147.7		
D-3 MED-LOW	905	F	127	1.36	14.94	8.5	15.9	11/10/71	02/07/83		134.9	Malignant Lymphoma
D-4 MEDIUM	866	M	200	1.35	14.81	13.5	17.4	07/06/71		146.8		
D-4 MEDIUM	809	F	157	1.36	14.95	10.5	15.3	03/04/71	05/28/81		122.8	Lvr Cirr, Thy T., Addison
D-4 MEDIUM	764	F	156	1.37	15.05	10.5	18.2	12/21/70	07/07/82		138.5	Lung Tumor
D-4 MEDIUM	835	F	163	1.48	16.30	10.0	16.4	04/26/71	06/25/78		86.0	Reticulum Cell Sarcoma
D-4 MEDIUM	839	F	189	1.49	16.43	11.5	16.3	04/26/71		149.2		
D-4 MEDIUM	814	F	140	1.50	16.47	8.5	15.1	03/04/71	10/17/79		103.5	Lng Tmr, Thyroid Adenoma
D-4 MEDIUM	836	M	256	1.66	18.29	14.0	17.8	06/08/71	03/16/81		117.3	Lung Tumor
D-4 MEDIUM	819	F	163	1.74	19.18	8.5	18.2	06/08/71		147.7		
D-4 MEDIUM	868	M	274	1.78	19.57	14.0	17.1	10/08/71	07/02/79		92.8	Lung Tumor
D-4 MEDIUM	824	F	227	1.79	19.74	11.5	18.1	06/08/71	01/26/81		115.6	Bronchopneumonia
D-4 MEDIUM	860	M	254	1.85	20.32	12.5	17.3	06/08/71	05/24/82		132.5	Lung Tumor
D-4 MEDIUM	833	F	248	2.37	26.11	9.5	16.5	04/26/71	04/04/83		143.3	Metritis, Adr & Thy Tumor
D-4 MEDIUM	810	F	302	2.39	26.26	11.5	15.3	03/04/71	09/09/81		126.2	Lung Tumor
D-4 MEDIUM	794	M	444	2.60	28.65	15.5	17.7	03/04/71	02/17/81		119.5	Pituitary Tmr, Cushing's
D-4 MEDIUM	854	M	465	2.64	29.06	16.0	21.3	10/08/71	01/25/82		123.6	Lung Tumor
D-4 MEDIUM	478	M	298	2.71	29.80	10.0	64.0	10/09/70	10/16/70		0.2	Sacrificed
D-4 MEDIUM	808	F	270	2.89	31.76	8.5	14.6	02/10/71	09/09/82		138.9	Lung Tumor
D-4 MEDIUM	805	F	257	3.12	34.27	7.5	18.5	06/08/71	07/22/82		133.5	Esophageal & Lung Tumor
D-4 MEDIUM	812	M	638	3.19	35.04	12.5	17.1	04/26/71	11/12/79		102.6	Lung Tumor
D-4 MEDIUM	857	M	486	3.40	37.38	13.0	17.3	06/08/71	07/01/80		108.8	Lung Tumor
D-4 MEDIUM	892	M	494	3.59	39.52	12.5	16.0	11/10/71	10/26/81		119.5	Lung Tumor
D-4 MEDIUM	816	M	398	3.62	39.80	10.0	16.8	04/25/71	05/11/71		0.5	Sacrificed
D-4 MEDIUM	777	M	546	3.97	43.68	12.5	20.2	03/04/71	03/26/80		108.7	Lung Tumor
D-4 MEDIUM	803	M	547	4.32	47.57	11.5	18.1	04/26/71	11/10/77		78.5	Interstitial Pneumonitis
D-5 MED-HIGH	787	M	651	4.73	52.08	12.5	19.5	03/04/71	02/08/79		95.2	Lung Tmr, Intestinal Tmr
D-5 MED-HIGH	840	F	703	4.92	54.08	13.0	17.7	06/08/71	04/29/80		106.7	Lung Tumor
D-5 MED-HIGH	727	M	733	5.33	58.64	12.5	18.8	10/26/70	11/10/76		72.5	Lung Tumor
D-5 MED-HIGH	898	F	711	5.39	59.25	12.0	16.0	11/10/71	02/03/81		110.8	Ori Bladr & Lng & Adr Tmr
D-5 MED-HIGH	856	F	818	5.72	62.92	13.0	18.2	07/07/71	05/02/79		93.8	Lung Tumor
D-5 MED-HIGH	759	M	809	6.13	67.42	12.0	18.3	12/21/70	06/02/75		53.4	Lung Tumor
D-5 MED-HIGH	864	F	801	6.62	72.82	11.0	17.4	07/07/71	11/02/79		99.9	Lung Tumor
D-5 MED-HIGH	909	M	737	6.70	73.70	10.0	15.9	11/10/71	06/04/81		114.8	Lung Tumor
D-5 MED-HIGH	734	M	914	6.92	76.17	12.0	19.2	11/10/70	04/01/71		4.7	Sacrificed
D-5 MED-HIGH	837	M	1283	8.04	88.48	14.5	18.8	07/07/71	07/21/77		72.5	Lung Tumor
D-5 MED-HIGH	863	F	980	8.48	93.33	10.5	17.4	07/07/71	10/21/77		75.5	Lung Tumor

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DOSE-EFFECT STUDIES WITH INHALED PU-239 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-5 MED-HIGH	820	F	847	8.56	94.11	9.0	18.2	06/08/71	06/01/79		95.8	Lung Tumor
D-5 MED-HIGH	852	F	1187	9.38	103.22	11.5	21.3	10/08/71	02/22/78		76.5	Lung Tumor
D-5 MED-HIGH	880	F	840	9.55	105.00	8.0	17.8	10/08/71	12/04/78		85.9	Lung Tumor
D-5 MED-HIGH	889	F	1089	9.90	108.90	10.0	16.0	11/10/71	09/20/79		94.3	Lng Tmr, Osteoarthropathy
D-5 MED-HIGH	783	M	1394	10.14	111.52	12.5	18.9	02/09/71	12/03/75		57.8	Lung Tumor
D-5 MED-HIGH	804	M	1344	10.18	112.00	12.0	20.5	07/07/71	08/18/74		37.4	Lung Tumor, Rad. Pneum.
D-5 MED-HIGH	873	M	1767	10.71	117.80	15.0	16.8	07/07/71	09/03/76		61.9	Lung Tumor
D-5 MED-HIGH	760	M	1378	10.89	119.83	11.5	19.3	01/20/71	08/15/73		30.8	Radiation Pneumonitis
D-5 MED-HIGH	796	F	1318	11.41	125.52	10.5	15.6	02/09/71	09/17/75		55.2	Lng Tmr, Osteoarthropathy
D-5 MED-HIGH	761	M	1460	12.07	132.73	11.0	19.3	01/20/71	11/02/76		69.4	Lung Tumor
D-5 MED-HIGH	709	M	1726	12.55	138.08	12.5	19.6	11/10/70	03/31/71		4.6	Sacrificed
D-5 MED-HIGH	772	M	1896	14.99	164.87	11.5	19.8	02/09/71	06/26/75		52.5	Lng Tmr, Osteoarthropathy
D-5 MED-HIGH	702	F	1682	15.29	168.20	10.0	19.8	11/10/70	03/31/71		4.6	Sacrificed
D-5 MED-HIGH	739	F	1511	17.17	188.88	8.0	18.5	11/10/70	04/01/71		4.7	Sacrificed
D-6 HIGH	753	F	2448	23.43	257.68	9.5	18.5	12/21/70	10/02/76		69.4	Lung Tumor
D-6 HIGH	817	M	3164	23.97	263.67	12.0	19.2	07/07/71	03/26/73		20.6	Radiation Pneumonitis
D-6 HIGH	829	M	3515	24.58	270.38	13.0	19.1	07/07/71	09/13/73		26.3	Radiation Pneumonitis
D-6 HIGH	890	F	3101	31.32	344.56	9.0	16.0	11/10/71	06/13/74		31.1	Radiation Pneumonitis
D-6 HIGH	435	F	3840	33.25	365.71	10.5	75.5	11/05/70	11/12/70		0.2	Sacrificed
D-6 HIGH	913	M	4900	35.64	392.00	12.5	17.4	07/19/72	08/18/72		1.0	Sacrificed
D-6 HIGH	906	F	6632	63.46	698.11	9.5	15.9	11/09/71	11/22/72		12.5	Radiation Pneumonitis
D-6 HIGH	896	F	5515	66.85	735.33	7.5	16.0	11/10/71	02/12/73		15.1	Radiation Pneumonitis
D-6 HIGH	747	F	7476	97.09	1068.00	7.0	19.6	01/20/71	01/13/72		11.8	Radiation Pneumonitis
D-6 HIGH	910	M	14267	103.76	1141.36	12.5	15.9	11/10/71	10/12/72		11.1	Radiation Pneumonitis

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DOSE-EFFECT STUDIES WITH INHALED PU-238 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION: NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE: WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION: 9/30/83	DEATH	COMMENTS ON DEAD DOGS
CONTROL	939	M	0	0.00	0.00				10/01/82		136.9*	Processing
CONTROL	949	F	0	0.00	0.00					148.7*		
CONTROL	978	M	0	0.00	0.00					148.5*		
CONTROL	990	F	0	0.00	0.00				07/08/79		97.4*	Pyometra
CONTROL	996	F	0	0.00	0.00					148.9*		
CONTROL	1005	M	0	0.00	0.00					148.0*		
CONTROL	1007	F	0	0.00	0.00					147.9*		
CONTROL	1024	M	0	0.00	0.00					147.5*		
CONTROL	1038	M	0	0.00	0.00					145.4*		
CONTROL	1045	M	0	0.00	0.00					145.3*		
CONTROL	1054	F	0	0.00	0.00					145.1*		
CONTROL	1061	F	0	0.00	0.00				07/07/81		118.2*	Malignant Lymphoma
CONTROL	1093	M	0	0.00	0.00					141.3*		
CONTROL	1097	F	0	0.00	0.00					140.6*		
CONTROL	1112	M	0	0.00	0.00					140.4*		
CONTROL	1116	F	0	0.00	0.00					140.1*		
CONTROL	1186	F	0	0.00	0.00					133.5*		
CONTROL	1197	M	0	0.00	0.00					133.0*		
CONTROL	1209	M	0	0.00	0.00					132.7*		
CONTROL	1225	F	0	0.00	0.00					131.8*		
CONTROL SACRIFICE	966	M	0	0.00	0.00				04/30/77		71.6*	Sacrificed
CONTROL SACRIFICE	1011	F	0	0.00	0.00				06/01/78		83.9*	Sacrificed
CONTROL SACRIFICE	1013	F	0	0.00	0.00				05/29/79		95.8*	Sacrificed
CONTROL SACRIFICE	1087	M	0	0.00	0.00				12/14/76		60.0*	Sacrificed
CONTROL SACRIFICE	1119	M	0	0.00	0.00				01/13/76		47.5*	Sacrificed
CONTROL SACRIFICE	1223	M	0	0.00	0.00				05/15/75		31.9*	Sacrificed
CONTROL SACRIFICE	1227	M	0	0.00	0.00				12/01/76		49.9*	Sacrificed
CONTROL SACRIFICE	1228	M	0	0.00	0.00				10/31/78		72.9*	Sacrificed
D-1 LOWEST	998	M	0	0.00	0.00	10.5	19.6	01/18/73		128.4		
D-1 LOWEST	1003	M	0	0.00	0.00	14.0	19.6	01/18/73		128.4		
D-1 LOWEST	1023	F	0	0.00	0.00	12.5	19.2	01/18/73		128.4		
D-1 LOWEST	1039	M	0	0.00	0.00	11.0	17.0	01/18/73		128.4		
D-1 LOWEST	1044	F	0	0.00	0.00	11.5	17.0	01/18/73		128.4		
D-1 LOWEST	1055	M	0	0.00	0.00	13.0	16.8	01/18/73		128.4		
D-1 LOWEST	1063	M	0	0.00	0.00	14.5	16.7	01/18/73	11/11/80		93.8	Brain Tumor, Heart Tumor
D-1 LOWEST	1105	F	0	0.00	0.00	10.0	16.4	05/31/73		124.0		
D-1 LOWEST	1194	F	0	0.00	0.00	10.5	19.8	04/18/74		113.4		
D-1 LOWEST	1215	M	0	0.00	0.00	15.5	19.3	04/18/74	04/26/77		36.3	Sacrificed
D-1 LOWEST	1230	M	0	0.00	0.00	12.5	18.4	04/18/74		113.4		
D-1 LOWEST	951	M	2	0.01	0.14	14.0	19.3	12/19/72	02/14/83		121.9	Processing
D-1 LOWEST	1008	M	2	0.01	0.15	13.5	19.6	01/18/73		128.4		
D-1 LOWEST	1193	F	2	0.01	0.16	12.5	19.8	04/18/74		113.4		
D-1 LOWEST	959	M	3	0.02	0.22	13.5	19.2	12/19/72		129.3		

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DOSE-EFFECT STUDIES WITH INHALED PU-238 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION: NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE: WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION: 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-1 LOWEST	1069	F	2	0.02	0.24	8.5	18.1	05/31/73	06/24/83		120.8	Processing
D-1 LOWEST	1095	F	2	0.02	0.19	10.5	16.6	05/31/73		124.0		
D-1 LOWEST	921	F	3	0.03	0.31	10.0	19.5	11/30/72	12/27/72		0.9	Sacrificed
D-1 LOWEST	923	F	3	0.03	0.35	8.5	19.5	11/30/72	01/26/73		1.9	Sacrificed
D-1 LOWEST	989	F	3	0.03	0.32	9.5	18.8	12/19/72	03/05/81		98.5	Bone Tumor, Fibrosarcoma
D-1 LOWEST	925	M	5	0.04	0.40	12.5	19.5	11/30/72	02/27/73		2.9	Sacrificed
D-1 LOWEST	1204	M	6	0.04	0.43	14.0	17.7	02/26/74		115.1		
D-1 LOWEST	970	F	6	0.05	0.55	11.0	19.2	12/19/72	01/04/77		48.5	Sacrificed
D-1 LOWEST	993	F	6	0.05	0.50	12.0	18.8	12/19/72		129.3		
D-1 LOWEST	1106	F	5	0.05	0.50	10.0	16.4	05/31/73	03/14/83		117.4	Processing
D-2 LOW	1065	F	6	0.05	0.60	10.0	18.3	05/31/73		124.0		
D-2 LOW	1082	M	11	0.06	0.69	16.0	18.0	05/31/73	12/04/79		78.1	Paralysis, Spinal Crd Deg
D-2 LOW	1188	M	11	0.06	0.71	15.5	18.4	02/26/74		115.1		
D-2 LOW	1084	M	13	0.07	0.76	17.0	17.5	05/31/73		124.0		
D-2 LOW	1090	F	10	0.08	0.83	12.0	17.3	05/31/73		124.0		
D-2 LOW	1222	M	15	0.10	1.07	14.0	19.0	04/18/74		113.4		
D-2 LOW	971	F	13	0.11	1.24	10.5	19.2	12/19/72	05/04/83		124.5	Processing
D-2 LOW	999	F	11	0.11	1.16	9.5	18.7	12/19/72		129.3		
D-2 LOW	1229	M	16	0.11	1.19	13.5	16.8	02/26/74		115.1		
D-2 LOW	1070	M	22	0.12	1.33	16.5	18.1	05/31/73		124.0		
D-2 LOW	1214	M	17	0.12	1.36	12.5	19.3	04/18/74	05/12/75		12.8	Sacrificed
D-2 LOW	955	M	17	0.14	1.55	11.0	19.2	12/19/72		129.3		
D-2 LOW	1033	M	17	0.14	1.55	11.0	19.1	02/22/73		127.2		
D-2 LOW	1036	F	16	0.14	1.52	10.5	18.2	02/22/73		127.2		
D-2 LOW	1216	M	23	0.16	1.77	13.0	19.3	04/18/74		113.4		
D-2 LOW	1060	F	22	0.18	2.00	11.0	17.8	02/22/73		127.2		
D-2 LOW	981	M	30	0.21	2.31	13.0	19.0	12/19/72		129.3		
D-2 LOW	1046	M	27	0.22	2.45	11.0	18.1	02/22/73		127.2		
D-2 LOW	1050	F	22	0.22	2.44	9.0	18.1	02/22/73		127.2		
D-2 LOW	1078	F	29	0.22	2.42	12.0	18.0	05/31/73		124.0		
D-2 LOW	1207	F	22	0.24	2.59	8.5	17.6	02/26/74		115.1		
D-2 LOW	1196	F	28	0.25	2.80	10.0	17.9	02/26/74		115.1		
D-2 LOW	1189	M	38	0.26	2.81	13.5	20.0	04/18/74	04/25/79		60.2	Sacrificed
D-2 LOW	930	M	38	0.27	2.92	13.0	19.2	11/30/72	12/28/72		0.9	Sacrificed
D-3 MED-LOW	1066	M	54	0.31	3.38	16.0	18.3	05/31/73	06/21/83		120.7	Processing
D-3 MED-LOW	1089	F	41	0.31	3.42	12.0	17.3	05/31/73		124.0		
D-3 MED-LOW	972	F	40	0.33	3.64	11.0	19.2	12/19/72		129.3		
D-3 MED-LOW	1310	M	54	0.34	3.72	14.5	18.5	03/04/75	04/01/77		24.9	Sacrificed
D-3 MED-LOW	1312	M	58	0.34	3.74	15.5	18.5	03/04/75	03/26/79		48.7	Sacrificed
D-3 MED-LOW	1311	M	54	0.36	4.00	13.5	18.5	03/04/75	04/03/78		37.0	Sacrificed
D-3 MED-LOW	1219	F	46	0.40	4.38	10.5	19.0	04/18/74		113.4		
D-3 MED-LOW	1317	M	72	0.41	4.50	16.0	18.1	03/04/75	04/01/77		24.9	Sacrificed
D-3 MED-LOW	1158	M	73	0.43	4.71	15.5	17.7	11/06/73		118.8		

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DOSE-EFFECT STUDIES WITH INHALED PU-238 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION: NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURES: WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION: 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	1165	M	76	0.43	4.75	16.0	17.3	11/06/73		118.8		
D-3 MED-LOW	1309	M	60	0.44	4.80	12.5	18.5	03/04/75		102.9		
D-3 MED-LOW	1318	M	67	0.45	4.96	13.5	18.1	03/04/75	03/08/76		12.2	Sacrificed
D-3 MED-LOW	929	F	41	0.50	5.47	7.5	19.2	11/30/72	01/25/73		1.8	Sacrificed
D-3 MED-LOW	1316	M	84	0.53	5.79	14.5	18.1	03/04/75		102.9		
D-3 MED-LOW	960	M	68	0.54	5.91	11.5	19.2	12/19/72	11/07/80		94.6	Malignant Lymphoma
D-3 MED-LOW	1072	M	98	0.54	5.94	16.5	18.1	05/31/73	09/22/83		123.7	Processing
D-3 MED-LOW	1190	F	71	0.54	5.92	12.0	18.1	02/26/74		115.1		
D-3 MED-LOW	926	M	75	0.55	6.00	12.5	19.5	11/30/72	02/28/73		3.0	Sacrificed
D-3 MED-LOW	1315	M	90	0.55	6.00	15.0	18.1	03/04/75	03/31/77		24.9	Sacrificed
D-3 MED-LOW	982	M	76	0.58	6.33	12.0	19.0	12/19/72		129.3		
D-3 MED-LOW	1040	M	84	0.61	6.72	12.5	18.2	02/22/73	03/04/81		96.3	Parathyroid Adenoma
D-3 MED-LOW	1059	F	71	0.65	7.10	10.0	17.8	02/22/73	08/08/83		125.5	Processing
D-3 MED-LOW	1319	M	99	0.67	7.33	13.5	18.1	03/04/75	03/09/76		12.2	Sacrificed
D-3 MED-LOW	1108	F	84	0.69	7.64	11.0	16.4	05/31/73		124.0		
D-3 MED-LOW	1000	F	70	0.71	7.78	9.0	18.7	12/19/72		129.3		
D-3 MED-LOW	1056	M	97	0.71	7.76	12.5	17.9	02/22/73		127.2		
D-3 MED-LOW	1004	M	116	0.73	8.00	14.5	19.6	01/18/73		128.4		
D-3 MED-LOW	1026	M	116	0.78	8.59	13.5	19.2	01/18/73		128.4		
D-3 MED-LOW	1043	F	98	0.89	9.80	10.0	18.1	02/22/73	09/21/81		102.9	Empyema, P.T., Cushing's
D-3 MED-LOW	1031	F	76	0.92	10.13	7.5	19.1	02/22/73		127.2		
D-3 MED-LOW	1212	F	111	1.19	13.06	8.5	17.6	02/26/74		115.1		
D-4 MEDIUM	1176	M	129	0.87	9.56	13.5	15.5	10/06/73		119.8		
D-4 MEDIUM	1221	F	124	1.13	12.40	10.0	19.0	04/18/74		113.4		
D-4 MEDIUM	1195	M	228	1.38	15.20	15.0	18.1	02/26/74		115.1		
D-4 MEDIUM	1032	M	162	1.40	15.43	10.5	16.3	11/30/72	12/08/72		0.3	Sacrificed
D-4 MEDIUM	1053	F	148	1.42	15.58	9.5	17.9	02/22/73		127.2		
D-4 MEDIUM	997	M	203	1.60	17.65	11.5	19.6	01/18/73		128.4		
D-4 MEDIUM	991	F	194	1.76	19.40	10.0	18.8	12/19/72	06/20/83		126.0	Processing
D-4 MEDIUM	1177	M	262	1.76	19.41	13.5	16.6	11/06/73		118.8		
D-4 MEDIUM	932	F	216	1.79	19.64	11.0	19.1	11/30/72	01/25/73		1.8	Sacrificed
D-4 MEDIUM	1103	F	260	1.89	20.80	12.5	16.5	05/31/73	04/08/83		118.2	Processing
D-4 MEDIUM	973	F	271	2.24	24.64	11.0	19.2	12/19/72		129.3		
D-4 MEDIUM	931	F	289	2.39	26.27	11.0	19.1	11/30/72	12/28/72		0.9	Sacrificed
D-4 MEDIUM	1091	F	243	2.60	28.59	8.5	17.3	05/31/73		124.0		
D-4 MEDIUM	1114	M	430	2.70	29.66	14.5	16.4	05/31/73		124.0		
D-4 MEDIUM	1062	M	435	2.93	32.22	13.5	17.8	02/22/73		127.2		
D-4 MEDIUM	934	M	454	3.06	33.63	13.5	19.1	11/30/72	03/01/73		3.0	Sacrificed
D-4 MEDIUM	1081	M	541	3.07	33.81	16.0	18.0	05/31/73	01/18/80		79.6	Hemangiosarcoma, Heart
D-4 MEDIUM	1030	F	340	3.25	35.79	9.5	19.1	02/22/73	04/14/83		121.7	Processing
D-4 MEDIUM	1198	M	539	3.50	38.50	14.0	17.9	02/26/74		115.1		
D-4 MEDIUM	952	F	365	3.69	40.56	9.0	19.2	12/19/72	06/03/83		125.4	Processing
D-4 MEDIUM	1166	M	673	4.08	44.87	15.0	17.3	11/06/73		118.8		

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DOSE-EFFECT STUDIES WITH INHALED PU-238 OXIDE IN BEAGLES

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-4 MEDIUM	1220	F	518	4.28	47.09	11.0	19.0	04/18/74		113.4		
D-4 MEDIUM	992	F	555	4.39	48.26	11.5	18.8	12/19/72		129.3		
D-4 MEDIUM	983	M	617	4.67	51.42	12.0	19.0	12/19/72		129.3		
D-5 MED-HIGH	1191	F	551	4.48	49.25	12.0	19.8	04/18/74	03/21/77		35.1	Interstitial Pneumonitis
D-5 MED-HIGH	1157	M	700	4.71	51.85	13.5	17.7	11/06/73		118.8		
D-5 MED-HIGH	1035	F	571	5.46	60.11	9.5	18.2	02/22/73		127.2		
D-5 MED-HIGH	1192	F	754	6.53	71.81	10.5	18.1	02/26/74	03/29/83		109.0	Bone Tumor
D-5 MED-HIGH	1140	M	1014	6.58	72.43	14.0	18.2	11/06/73	12/14/81		97.2	Bone Tumor
D-5 MED-HIGH	1071	M	1269	6.79	74.65	17.0	18.1	05/31/73	01/09/81		91.3	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1173	M	1023	7.75	85.25	12.0	17.3	11/06/73	02/09/82		99.1	Bone Tumor
D-5 MED-HIGH	1178	M	1125	8.52	93.75	12.0	16.6	11/06/73	01/06/83		110.0	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1047	M	900	8.61	94.74	9.5	18.1	02/22/73	10/05/82		115.4	Vertebral Disk Herniation
D-5 MED-HIGH	1109	F	1119	8.85	97.30	11.5	16.4	05/31/73	08/06/80		86.2	Bone & Lng Tmr, Addison's
D-5 MED-HIGH	1160	F	1344	10.18	112.00	12.0	17.3	11/06/73	09/22/81		94.5	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1211	M	1764	11.06	121.66	14.5	17.6	02/26/74	05/17/82		98.6	Bone Tumor
D-5 MED-HIGH	1096	F	1476	12.20	134.18	11.0	16.6	05/31/73	05/08/78		59.2	Addison's Disease
D-5 MED-HIGH	1218	F	1710	12.95	142.50	12.0	17.3	02/26/74	04/24/81		85.9	Bone Tumor
D-5 MED-HIGH	1092	M	1848	13.44	147.84	12.5	17.3	05/31/73	10/23/78		64.8	Bone Tumor
D-5 MED-HIGH	1027	M	2148	13.95	153.43	14.0	19.2	01/18/73	12/01/78		70.4	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1115	F	1885	14.90	163.91	11.5	16.1	05/31/73	07/11/78		61.3	Bone Tumor
D-5 MED-HIGH	974	F	1718	15.62	171.80	10.0	20.2	01/18/73	05/24/78		64.1	Bone Tumor
D-5 MED-HIGH	1079	M	2620	15.88	174.67	15.0	18.0	05/31/73	02/12/78		56.4	Addison's, G.I. Tumor
D-5 MED-HIGH	1058	F	1907	16.51	181.62	10.5	17.8	02/22/73	11/01/79		80.3	Bone Tumor, Adrenal Tumor
D-6 HIGH	1002	M	2907	18.88	207.64	14.0	19.6	01/10/73	01/21/80		84.1	Bone Tumor, Lung Tumor
D-6 HIGH	1057	M	3116	20.98	230.81	13.5	17.9	02/22/73	03/07/79		72.4	Bone Tumor
D-6 HIGH	1009	M	3630	26.40	290.40	12.5	19.6	01/18/73	04/01/78		62.4	Lng Tmr, Osteoarthropathy
D-6 HIGH	1042	F	2959	28.32	311.47	9.5	18.1	02/22/73	11/10/78		68.6	Bone Tumor, Lung Tumor
D-6 HIGH	994	F	3453	31.39	345.30	10.0	19.6	01/18/73	07/04/76		41.5	Addison's Disease
D-6 HIGH	1006	F	3810	31.49	346.36	11.0	19.6	01/18/73	01/18/79		72.0	Bone Tumor, Lung Tumor
D-6 HIGH	975	F	3968	36.07	396.80	10.0	20.2	01/18/73	07/25/78		66.2	Bone Tumor, Lung Tumor
D-6 HIGH	1037	M	4854	44.13	485.40	10.0	18.2	02/22/73	11/21/78		68.9	Bone Tumor
D-6 HIGH	1143	M	7691	53.78	591.62	13.0	18.2	11/06/73	12/05/77		49.0	Bone Tumor, Lung Tumor
D-6 HIGH	1025	M	8479	57.10	628.07	13.5	19.2	01/18/73	03/17/77		49.9	Lung Tumor
D-6 HIGH	1064	M	9453	63.66	700.22	13.5	16.7	01/18/73	04/14/77		50.8	Bone Tumor, Lung Tumor
D-6 HIGH	1162	F	6959	70.29	773.22	9.0	17.3	11/06/73	12/19/78		51.4	Bone Tumor, Addison's
D-6 HIGH	1175	F	6201	75.16	826.80	7.5	16.6	11/06/73	02/24/78		51.6	Lung Tumor

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
CONTROL	1356	M	0	0.00	0.00					112.7*		
CONTROL	1365	M	0	0.00	0.00					112.6*		
CONTROL	1376	F	0	0.00	0.00				05/11/80		70.8*	Pneumonia
CONTROL	1388	M	0	0.00	0.00				09/11/81		86.7*	Sacrificed
CONTROL	1393	M	0	0.00	0.00					111.3*		
CONTROL	1405	M	0	0.00	0.00					110.9*		
CONTROL	1409	M	0	0.00	0.00					110.8*		
CONTROL	1418	M	0	0.00	0.00					110.5*		
CONTROL	1425	M	0	0.00	0.00				08/02/82		96.5*	Status Epilepticus
CONTROL	1450	F	0	0.00	0.00				11/04/81		87.4*	Sacrificed
CONTROL	1455	F	0	0.00	0.00					109.8*		
CONTROL	1483	F	0	0.00	0.00					108.9*		
CONTROL	1509	M	0	0.00	0.00					108.1*		
CONTROL	1516	F	0	0.00	0.00					107.8*		
CONTROL	1525	M	0	0.00	0.00					107.6*		
CONTROL	1526	M	0	0.00	0.00					107.6*		
CONTROL	1528	F	0	0.00	0.00					107.0*		
CONTROL	1543	M	0	0.00	0.00					106.9*		
CONTROL	1563	F	0	0.00	0.00					96.8*		
CONTROL	1572	F	0	0.00	0.00					96.7*		
CONTROL	1577	M	0	0.00	0.00					96.7*		
CONTROL	1584	F	0	0.00	0.00					96.6*		
CONTROL	1594	F	0	0.00	0.00					96.6*		
CONTROL	1608	M	0	0.00	0.00					96.3*		
CONTROL	1633	F	0	0.00	0.00					89.6*		
CONTROL	1638	F	0	0.00	0.00					89.3*		
VEHICLE	1361	M	0	0.00	0.00	8.5	21.0	02/13/76		91.5		
VEHICLE	1381	F	0	0.00	0.00	9.5	19.8	02/13/76		91.5		
VEHICLE	1392	M	0	0.00	0.00	13.0	22.0	04/22/76		89.3		
VEHICLE	1406	M	0	0.00	0.00	13.5	21.6	04/22/76		89.3		
VEHICLE	1412	F	0	0.00	0.00	9.0	19.0	02/13/76		91.5		
VEHICLE	1421	M	0	0.00	0.00	13.0	23.3	06/23/76		87.2		
VEHICLE	1457	F	0	0.00	0.00	12.0	20.6	04/22/76		89.3		
VEHICLE	1491	F	0	0.00	0.00	8.0	21.6	06/23/76		87.2		
VEHICLE	1504	F	0	0.00	0.00	10.0	20.9	06/23/76		87.2		
VEHICLE	1514	M	0	0.00	0.00	14.0	20.9	06/23/76	08/06/82		73.4	Malignant Lymphoma
VEHICLE	1524	M	0	0.00	0.00	12.0	21.5	07/27/76		86.1		
VEHICLE	1531	F	0	0.00	0.00	9.0	20.9	07/27/76		86.1		
VEHICLE	1542	M	0	0.00	0.00	12.0	20.8	07/27/76		86.1		
VEHICLE	1566	M	0	0.00	0.00	14.0	18.3	03/15/77		78.5		
VEHICLE	1578	M	0	0.00	0.00	10.5	18.2	03/15/77		78.5		
VEHICLE	1593	F	0	0.00	0.00	11.0	18.0	03/15/77		78.5		
VEHICLE	1601	F	0	0.00	0.00	8.5	18.0	03/15/77		78.5		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
VEHICLE	1620	M	0	0.00	0.00	12.0	21.1	12/01/77		69.9		
VEHICLE	1634	F	0	0.00	0.00	10.5	19.6	12/01/77		69.9		
VEHICLE	1651	F	0	0.00	0.00	11.0	19.2	12/01/77		69.9		
D-1 LOWEST	1416	M	0	0.00	0.00	12.0	22.1	05/20/76		88.3		
D-1 LOWEST	1458	F	0	0.00	0.00	10.5	21.5	05/20/76		88.3		
D-1 LOWEST	1489	F	0	0.00	0.00	8.0	20.5	05/20/76		88.3		
D-1 LOWEST	1501	M	0	0.00	0.00	14.0	20.4	05/20/76		88.3		
D-1 LOWEST	1515	M	0	0.00	0.00	13.5	19.8	05/20/76		88.3		
D-1 LOWEST	1573	M	0	0.00	0.00	11.5	19.4	04/19/77		77.4		
D-1 LOWEST	1581	M	0	0.00	0.00	16.5	19.3	04/19/77		77.4		
D-1 LOWEST	1596	M	0	0.00	0.00	14.0	19.2	04/19/77		77.4		
D-1 LOWEST	1600	F	1	0.01	0.11	11.0	19.2	04/19/77		77.4		
D-1 LOWEST	1603	M	2	0.01	0.12	14.0	19.2	04/19/77		77.4		
D-1 LOWEST	1339	F	2	0.02	0.22	9.0	17.5	10/16/75	11/13/75		0.9	Sacrificed
D-1 LOWEST	1519	M	2	0.02	0.18	12.5	19.5	05/20/76		88.3		
D-1 LOWEST	1570	F	2	0.02	0.17	10.5	19.4	04/19/77		77.4		
D-1 LOWEST	1465	F	4	0.03	0.35	12.0	21.0	05/20/76		88.3		
D-1 LOWEST	1470	F	3	0.03	0.29	10.5	21.0	05/20/76		88.3		
D-1 LOWEST	1507	M	4	0.03	0.32	14.0	19.8	05/20/76		88.3		
D-1 LOWEST	1592	F	4	0.03	0.29	13.5	19.2	04/19/77		77.4		
D-1 LOWEST	1607	M	5	0.03	0.35	13.0	19.0	04/19/77		77.4		
D-1 LOWEST	1335	M	5	0.04	0.42	11.5	18.0	10/16/75	11/13/75		0.9	Sacrificed
D-1 LOWEST	1487	F	6	0.04	0.46	13.0	20.5	05/20/76		88.3		
D-1 LOWEST	1583	F	4	0.04	0.40	9.5	19.2	04/19/77		77.4		
D-1 LOWEST	1351	M	7	0.06	0.61	11.0	17.2	10/16/75	11/13/75		0.9	Sacrificed
D-1 LOWEST	1565	F	8	0.06	0.67	11.5	19.4	04/19/77		77.4		
D-2 LOW	1513	M	0	0.00	0.00	11.5	19.8	05/20/76		88.3		
D-2 LOW	1520	M	1	0.01	0.12	10.5	19.5	05/20/76		88.3		
D-2 LOW	1415	M	2	0.02	0.20	11.5	22.2	05/20/76		88.3		
D-2 LOW	1575	M	3	0.02	0.19	14.0	19.4	04/19/77		77.4		
D-2 LOW	1466	F	5	0.03	0.37	14.0	21.0	05/20/76		88.3		
D-2 LOW	1606	F	5	0.04	0.42	12.5	19.0	04/19/77		77.4		
D-2 LOW	1579	M	8	0.05	0.59	14.0	19.3	04/19/77		77.4		
D-2 LOW	1590	F	6	0.05	0.51	12.0	19.2	04/19/77		77.4		
D-2 LOW	1585	F	8	0.06	0.68	12.0	19.2	04/19/77		77.4		
D-2 LOW	1580	F	9	0.07	0.82	11.0	19.3	04/19/77		77.4		
D-2 LOW	1591	M	11	0.07	0.76	15.0	19.2	04/19/77		77.4		
D-2 LOW	1417	M	11	0.08	0.89	12.0	22.1	05/20/76		88.3		
D-2 LOW	1423	M	10	0.08	0.87	11.0	22.1	05/20/76		88.3		
D-2 LOW	1567	M	10	0.08	0.83	12.0	19.4	04/19/77		77.4		
D-2 LOW	1472	F	10	0.09	1.01	10.0	21.0	05/20/76		88.3		
D-2 LOW	1503	F	9	0.09	1.03	8.5	19.8	05/20/76		88.3		
D-2 LOW	1602	M	15	0.09	1.03	14.5	19.2	04/19/77		77.4		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-2 LOW	1484	F	11	0.10	1.08	10.0	20.5	05/20/76		88.3		
D-2 LOW	1599	F	10	0.10	1.14	9.0	19.2	04/19/77		77.4		
D-2 LOW	1490	F	16	0.15	1.65	9.5	20.5	05/20/76		88.3		
D-3 MED-LOW	1336	M	21	0.14	1.52	13.5	18.0	10/16/75	11/13/75		0.9	Sacrificed
D-3 MED-LOW	1341	F	19	0.16	1.78	10.5	17.2	10/16/75	11/13/75		0.9	Sacrificed
D-3 MED-LOW	1605	F	25	0.20	2.19	11.5	17.8	03/15/77	03/24/82		60.3	Sacrificed
D-3 MED-LOW	1386	M	34	0.21	2.36	14.5	22.0	04/20/76		89.3		
D-3 MED-LOW	1389	M	27	0.23	2.54	10.5	21.9	04/20/76	05/04/76		0.5	Sacrificed
D-3 MED-LOW	1413	F	29	0.24	2.68	11.0	18.2	01/20/76		92.3		
D-3 MED-LOW	1445	F	34	0.24	2.60	13.0	21.0	04/20/76	05/05/76		0.5	Sacrificed
D-3 MED-LOW	1568	M	46	0.29	3.17	14.5	18.3	03/15/77		78.5		
D-3 MED-LOW	1595	M	50	0.29	3.23	15.5	18.0	03/15/77		78.5		
D-3 MED-LOW	1390	M	43	0.30	3.29	13.0	21.9	04/20/76	05/04/76		0.5	Sacrificed
D-3 MED-LOW	1391	M	54	0.30	3.26	16.5	21.9	04/20/76		89.3		
D-3 MED-LOW	1587	M	53	0.31	3.40	15.5	18.1	03/15/77		78.5		
D-3 MED-LOW	1359	M	50	0.32	3.57	14.0	20.2	01/20/76	01/23/76		0.1	Sacrificed
D-3 MED-LOW	1540	M	54	0.32	3.51	15.5	20.7	07/22/76		86.3		
D-3 MED-LOW	1344	F	41	0.33	3.60	11.5	17.2	10/16/75	11/14/75		1.0	Sacrificed
D-3 MED-LOW	1589	F	41	0.34	3.75	11.0	18.0	03/15/77	06/08/82		62.8	Sacrificed, Lung Tumor
D-3 MED-LOW	1588	M	50	0.36	3.98	12.5	18.1	03/15/77	03/22/78		12.2	Sacrificed
D-3 MED-LOW	1529	F	43	0.37	4.08	10.5	20.8	07/22/76	10/19/76		2.9	Sacrificed
D-3 MED-LOW	1574	M	46	0.38	4.21	11.0	18.2	03/15/77		78.5		
D-3 MED-LOW	1375	F	50	0.40	4.35	11.5	19.1	01/20/76	01/23/76		0.1	Sacrificed
D-3 MED-LOW	1564	F	40	0.40	4.44	9.0	18.3	03/15/77	03/20/78		12.2	Sacrificed
D-3 MED-LOW	1444	F	49	0.41	4.50	11.0	21.0	04/20/76		89.3		
D-3 MED-LOW	1439	F	53	0.42	4.61	11.5	21.0	04/20/76		89.3		
D-3 MED-LOW	1523	F	55	0.42	4.60	12.0	21.3	07/22/76		86.3		
D-3 MED-LOW	1539	M	65	0.45	4.99	13.0	20.7	07/22/76	10/20/76		3.0	Sacrificed
D-3 MED-LOW	1380	M	63	0.46	5.06	12.5	19.1	01/20/76		92.3		
D-3 MED-LOW	1407	F	50	0.51	5.56	9.0	18.5	01/20/76	01/23/76		0.1	Sacrificed
D-3 MED-LOW	1569	F	58	0.53	5.82	10.0	18.2	03/15/77		78.5		
D-3 MED-LOW	1576	M	70	0.53	5.86	12.0	18.2	03/15/77	03/17/82		60.1	Sacrificed
D-3 MED-LOW	1582	F	57	0.54	5.96	9.5	18.1	03/15/77		78.5		
D-3 MED-LOW	1571	F	68	0.57	6.22	11.0	18.2	03/15/77	03/21/78		12.2	Sacrificed
D-3 MED-LOW	1427	F	68	0.62	6.81	10.0	21.1	04/20/76		89.3		
D-3 MED-LOW	1522	F	78	0.71	7.78	10.0	21.3	07/22/76	10/18/76		2.9	Sacrificed
D-3 MED-LOW	1363	M	85	0.74	8.09	10.5	20.2	01/20/76		92.3		
D-3 MED-LOW	1604	M	85	0.74	8.10	10.5	18.0	03/15/77		78.5		
D-3 MED-LOW	1530	F	72	0.76	8.41	8.5	20.8	07/22/76		86.3		
D-3 MED-LOW	1456	F	61	0.79	8.68	7.0	20.5	04/20/76		89.3		
D-3 MED-LOW	1598	F	93	1.06	11.65	8.0	18.0	03/15/77	03/10/82		59.8	Sacrificed
D-3 MED-LOW	1422	F	99	1.12	12.35	8.0	18.1	01/20/76		92.3		
D-4 MEDIUM	1637	M	192	1.45	15.99	12.0	18.9	11/07/77		70.7		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG NUMBER	SEX	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/83	DEATH	COMMENTS ON DEAD DOGS
D-4 MEDIUM	1404	M	260	1.48	16.25	16.0	21.5	04/20/76		89.3		
D-4 MEDIUM	1521	F	205	1.49	16.37	12.5	21.3	07/22/76		86.3		
D-4 MEDIUM	1656	M	211	1.54	16.90	12.5	18.4	11/07/77		70.7		
D-4 MEDIUM	1379	M	278	1.74	19.16	14.5	19.1	01/20/76		92.3		
D-4 MEDIUM	1362	M	267	1.87	20.54	13.0	20.2	01/20/76		92.3		
D-4 MEDIUM	1639	F	248	2.05	22.57	11.0	18.5	11/07/77		70.7		
D-4 MEDIUM	1647	M	294	2.05	22.58	13.0	18.5	11/07/77		70.7		
D-4 MEDIUM	1640	M	307	2.06	22.71	13.5	18.5	11/07/77		70.7		
D-4 MEDIUM	1645	F	257	2.13	23.39	11.0	18.5	11/07/77		70.7		
D-4 MEDIUM	1534	M	295	2.14	23.57	12.5	20.8	07/22/76		86.3		
D-4 MEDIUM	1414	F	233	2.35	25.86	9.0	18.2	01/20/76		92.3		
D-4 MEDIUM	1618	F	277	2.40	26.36	10.5	20.3	11/07/77		70.7		
D-4 MEDIUM	1385	M	373	2.42	26.63	14.0	19.0	01/20/76		92.3		
D-4 MEDIUM	1408	F	331	2.62	28.77	11.5	18.5	01/20/76		92.3		
D-4 MEDIUM	1428	F	378	3.12	34.36	11.0	21.1	04/20/76		89.3		
D-4 MEDIUM	1535	F	345	3.13	34.48	10.0	20.7	07/22/76		86.3		
D-4 MEDIUM	1446	F	354	3.22	35.40	10.0	21.0	04/20/76		89.3		
D-4 MEDIUM	1364	M	463	3.24	35.65	13.0	20.2	01/20/76		92.3		
D-4 MEDIUM	1387	F	345	4.48	49.30	7.0	19.0	01/20/76	08/13/80		54.8	Bone Tumor
D-5 MED-HIGH	1329	F	363	3.30	36.27	10.0	18.0	10/16/75	11/14/75		1.0	Sacrificed
D-5 MED-HIGH	1346	M	656	4.42	48.59	13.5	17.2	10/16/75	11/14/75		1.0	Sacrificed
D-5 MED-HIGH	1648	M	811	5.90	64.90	12.5	18.5	11/07/77		70.7		
D-5 MED-HIGH	1347	F	688	6.95	76.47	9.0	17.2	10/16/75	11/14/75		1.0	Sacrificed
D-5 MED-HIGH	1659	F	990	7.20	79.22	12.5	18.3	11/07/77		70.7		
D-5 MED-HIGH	1636	M	1212	8.48	93.25	13.0	18.9	11/07/77	05/03/83		65.8	Bone Tumor
D-5 MED-HIGH	1621	M	1334	8.66	95.26	14.0	20.3	11/07/77		70.7		
D-5 MED-HIGH	1646	F	1061	8.77	96.45	11.0	18.5	11/07/77	11/11/82		60.1	Bone Tumor
D-5 MED-HIGH	1429	M	1376	9.62	105.85	13.0	23.2	06/23/76	05/29/81		59.2	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1641	M	1275	9.66	106.24	12.0	18.5	11/07/77		70.7		
D-5 MED-HIGH	1660	M	1518	10.22	112.41	13.5	18.3	11/07/77		70.7		
D-5 MED-HIGH	1508	M	1716	10.76	118.37	14.5	20.9	06/23/76	01/24/80		43.0	Bone Tumor
D-5 MED-HIGH	1655	M	1094	11.05	121.56	9.0	18.4	11/07/77		70.7		
D-5 MED-HIGH	1652	F	1320	12.00	131.95	10.0	18.4	11/07/77	07/20/83		68.4	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1619	F	1490	12.32	135.50	11.0	20.3	11/07/77	01/21/83		62.5	Bone Tumor
D-5 MED-HIGH	1512	M	2411	14.61	160.71	15.0	20.9	06/23/76	12/23/79		42.0	Bone Tumor
D-5 MED-HIGH	1419	M	1559	14.92	164.11	9.5	23.3	06/23/76	10/22/82		76.0	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1496	F	2018	16.68	183.45	11.0	21.5	06/23/76	04/09/82		69.5	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1502	F	3008	20.25	222.80	13.5	20.9	06/23/76	01/21/81		55.0	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1485	F	2330	21.18	233.00	10.0	21.7	06/23/76	12/30/80		54.2	Bone Tumor
D-5 MED-HIGH	1471	F	2508	21.71	238.82	10.5	22.1	06/23/76	05/01/79		34.2	Radiation Pneumonitis
D-5 MED-HIGH	1492	F	2473	24.98	274.82	9.0	21.6	06/23/76	10/16/80		51.8	Bone Tumor
D-5 MED-HIGH	1459	F	2645	26.72	293.89	9.0	22.6	06/23/76	09/25/80		51.1	Rad. Pneumonitis, Lng Tmr
D-6 HIGH	1518	M	3565	29.46	324.09	11.0	20.6	06/23/76	12/18/79		41.8	Rad. Pneumonitis, Lng Tmr

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D-6 HIGH	1420	M	3840	30.36	333.91	11.5	23.3	06/23/76	07/12/78		24.6	Radiation Pneumonitis
D-6 HIGH	1517	F	5185	49.62	545.79	9.5	20.6	06/23/76	11/02/77		16.3	Radiation Pneumonitis
D-6 HIGH	1510	F	6969	55.09	606.02	11.5	20.9	06/23/76	11/09/77		16.6	Radiation Pneumonitis
D-6 HIGH	1424	M	7681	69.83	768.12	10.0	23.2	06/23/76	08/31/77		14.3	Radiation Pneumonitis

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Publications and Presentations

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Ballou, J. E., G. E. Dagle, H. S. DeFord, R. L. Buschbom, and H. D. Tolley. "Toxicology of Krypton-85: Effects of Exposure of Newborn Rats." Health Phys. 45:242 (Abstract).

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Busch, R. H., R. L. Buschbom, W. C. Cannon, K. E. Lauhala, F. J. Miller, J. A. Graham, and L. G. Smith. "Effects of Ammonium Nitrate Aerosol Exposure on Lung Structure of Normal and Elastase-Impaired Rats and Guinea Pigs." Am. Ind. Hyg. Assoc. J. (In press).

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Busch, R. H., K. E. McDonald, J. K. Briant, J. E. Morris, and T. N. Graham. 1983. "Pathologic Effects in Rodents Exposed to Sodium Combustion Products." Environ. Res. 31:138-147.

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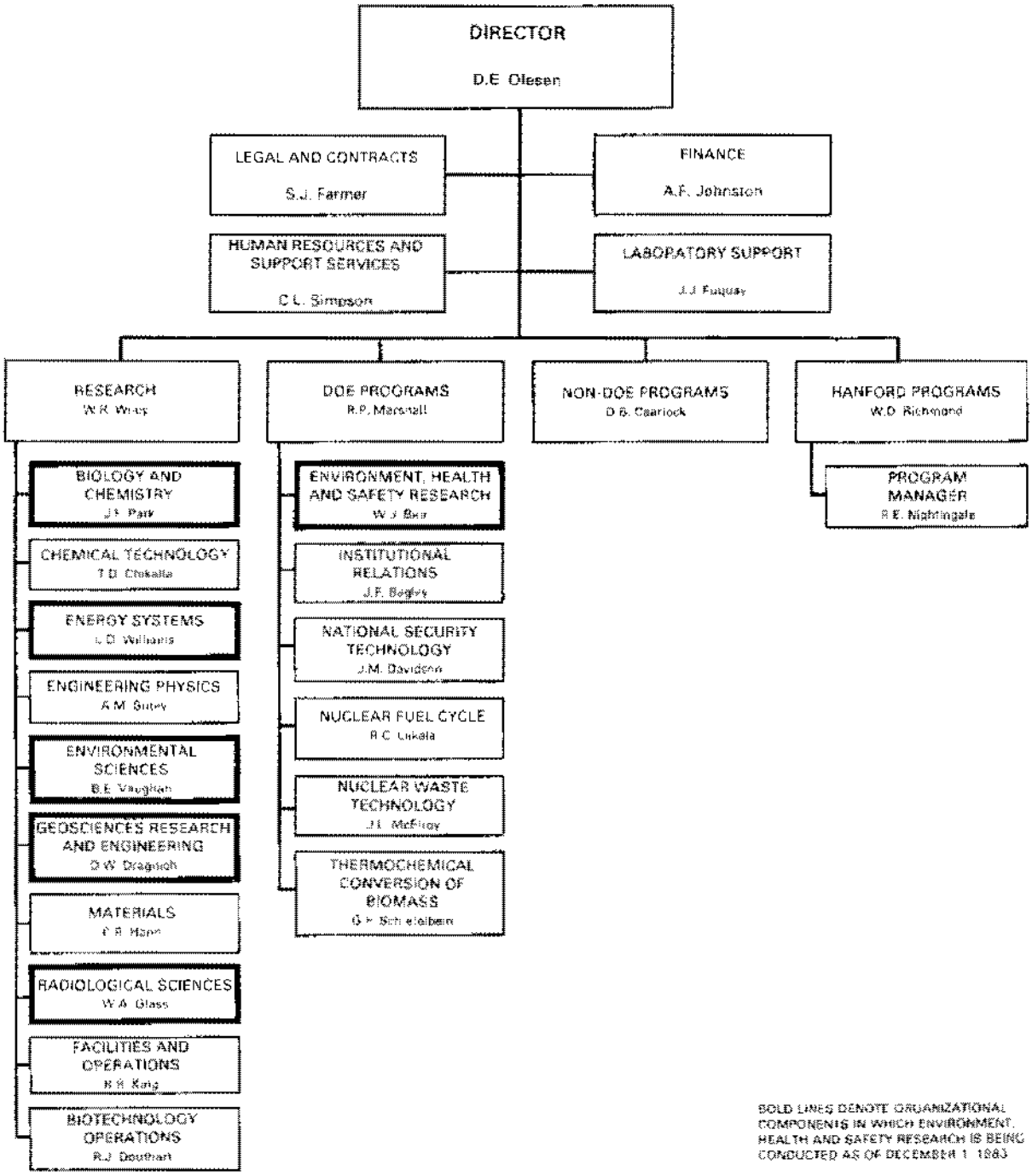

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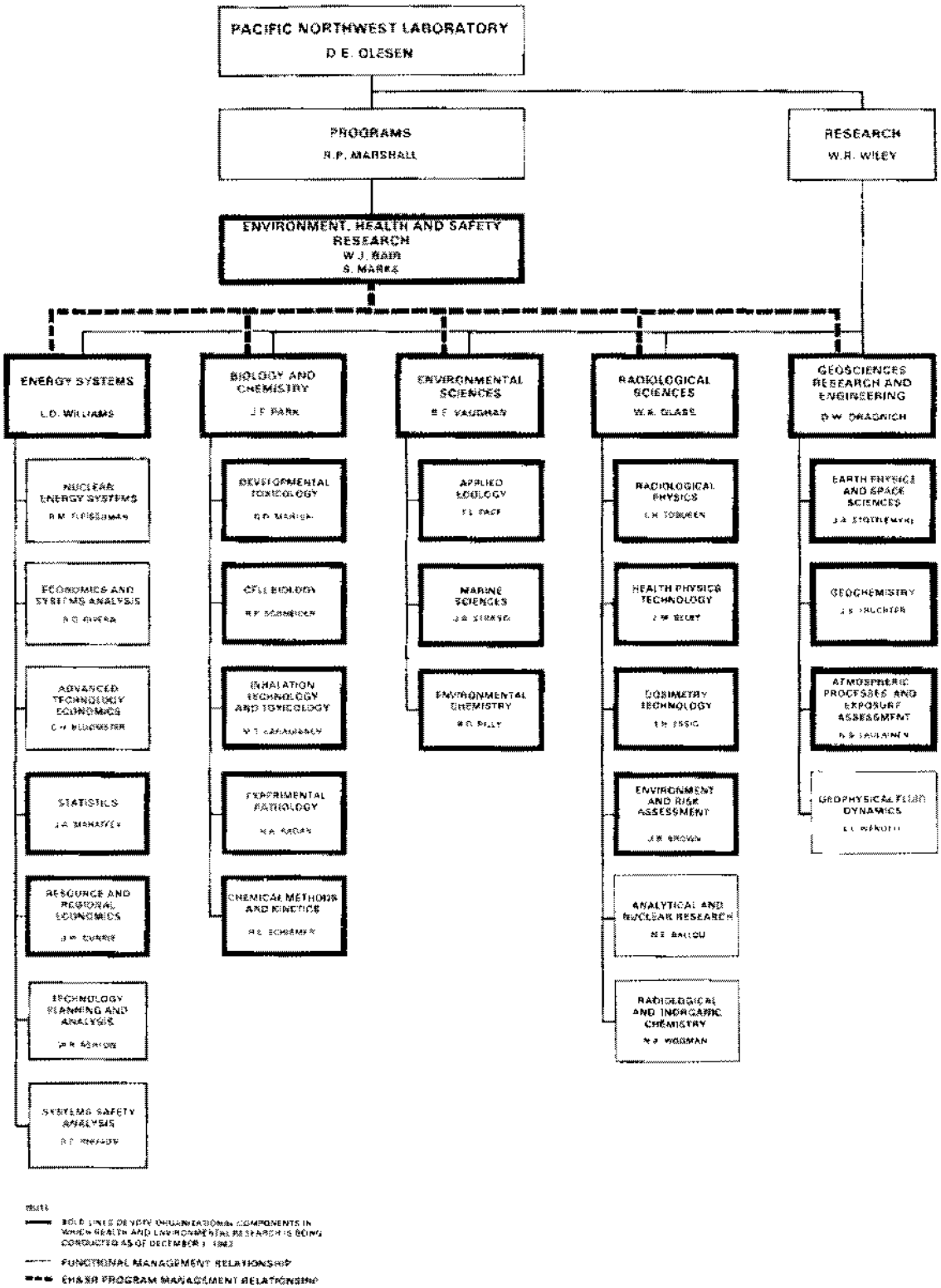

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