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Pacific Northwest Laboratory Annual Report for 1984 to the DOE Office of Energy Research

Part 1 Biomedical Sciences
February 1985

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 1984 annual report from Pacific Northwest Laboratory (PNL) to the Department of Energy (DOE) describes research in environment, health, and safety conducted during fiscal year 1984. 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 Policy, Safety, and Environment. 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 1984 Annual Report are:

Part 1: Biomedical Sciences	
Program Manager - J. F. Park	D. L. Felton, Report Coordinator and Editor
Part 2: Environmental 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 E. L. Owczarski, 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 Manager - 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 progresss 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
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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
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1981	PNL-4100, Pt. 1-5
1982	PNL-4600, Pt. 1-5
1983	PNL-5000, Pt. 1-5

FOREWORD

This report summarizes progress on OHER biomedical and health-effects research conducted at PNL in FY 1984 to develop the information required for a comprehensive understanding to 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 programs 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 with both nuclear materials and complex mixtures. Many of the investigations with nuclear materials are lifespan studies in various stages of completion. These include major studies of inhaled plutonium in dogs and rats. Studies directed toward radionuclide effects in fetal and juvenile mammals are included in this section. Of particular current interest are studies with radon and radon daughters, originally designed to explore exposure problems in uranium mines, which also provide information for evaluation of radon-daughter exposure in energy-efficient housing. Carcinogenesis studies of various fractions of complex organic mixtures are reported for the dermal and inhalation routes of exposure in mice and rats. These animal studies are integrated with in vitro studies of mutagenesis to obtain correlations between mutagenic and carcinogenic processes.

The mutagenicity section describes microbial mutagenesis studies with 6-aminochrysene (6-AC) and benzo[a]pyrene (BaP) in coal-derived complex mixtures. These studies, along with the studies of mammalian-cell mutagenesis and BaP binding to mouse-skin deoxyribonucleic acid (DNA) reported in the carcinogenesis section and the studies of DNA damage in cultured mouse skin and metabolism of 6-AC and BaP in mouse skin reported in the systems damage section, are aimed at understanding how the interaction of various components of coal-derived complex mixtures influences mutagenicity and carcinogenicity.

A variety of studies relating to noncarcinogenic and nonmutagenic endpoints are included in the section entitled "Systems Damage," including teratology and perinatal studies and studies to determine absorption, metabolism, and doses to critical tissues and organs of coal-derived mixtures and radionuclides. Studies of factors affecting the gastrointestinal absorption of actinides have demonstrated the variability and complexity of this critical link in the toxicity of these radionuclides, and promise to provide an improved basic understanding of intestinal absorption mechanisms.

Results are reported on the reproductive capability, neurotoxicity, and cardiovascular effects in rats exposed to various fractions of coal-derived complex mixtures. The initial results of a lifetime study of mice exposed to magnetic fields are also reported.

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 publcations for 1984 will be honored while supplies last.

CONTENTS

Human Health Effects From Energy Generation

• Statistical Health Effects Study

Principal Investigator: E. S. Gilbert

Other Investigators: J. A. Buchanan and S. Marks

The overall objective of this program is to provide data required to evaluate the impact of energy-related activities on health. To date, this objective has been met primarily by analyzing mortality data on Hanford workers, particularly in relation to the radiation exposure they have received. In the past year, construction workers have been added to the data base for this study; a lung cancer case-control study has been initiated; confidence limits for radiation risks have been calculated; and recent analyses by other investigators have been critiqued. In addition, we have completed data collection for a case-control study of congenital malformations that have occurred in the Tri-Cities, WA.

The most important objective of this program is to provide data required to evaluate the impact of energy-related activities on health. An important element is the analysis of data on the health of Hanford workers as reflected in their mortality and in congenital malformations in their offspring. The program includes the development of appropriate methodology for assessing health effects of chronic, low-level exposure.

Recently, efforts at the Hanford Environmental Health Foundation (HEHF), which provides data collection for the mortality study, have focused on improving the quality of mortality data by supplementing data from the Social Security Administration with other sources, and by having all causes of death recoded using the computerized system at the National Center for Health Statistics. The revised mortality data have been analyzed, and results have been compared with earlier analyses. No substantive changes resulted; of 17 cancer types tested for an association with radiation exposure, only multiple myeloma exhibits a statistically significant association.

To date, analyses of the Hanford data have included only operations workers. However, in 1980, the decision was made to supplement the data base by adding construction workers. HEHF has now identified about 12,000 construction workers; radiation exposure data are available for about 11,000 of them. We have not yet linked the exposure and mortality data, but we have compared the mortality of construction workers with that of the general U.S. population by calculating standardized mortality ratios (SMR) and have also examined the magnitude of the radiation exposures. The SMRs for this population are lower than those for operations workers, suggesting that incomplete mortality ascertainment may be a problem. The total accumulated exposure for construction workers through 1978 is only about 12,000 rem, less than one-sixth the amount accumulated by operations workers.

In cooperation with HEHF, a lung cancer case-control study has been initiated. Any correlation of radiation exposure and smoking habits could lead to bias in assessing the association of radiation and mortality from lung cancer and, possibly, from other causes as well. Although smoking data are not available for all workers, such data are available (although not in computerized form) for most workers who continued to work at Hanford after 1964. Fortunately, the group with available smoking histories includes most of those with relatively large radiation exposures. Data collection is now under way for a case-control study of lung cancer that will include the use of available smoking data. The primary goal of this study is to investigate the association of lung cancer with radiation exposure, taking smoking into account; a secondary goal is to examine the general association of smoking habits with radiation exposure and other variables.

The computer program MOX (Mortality and Occupational eXposures), which was developed for analysis of the Hanford data, has been made available to others with similar data. Also, the Journal of Occupational Medicine has accepted an article for publication describing the methodology upon which this program is based and advising readers of the availability of software to carry it out.

Since confidence limits on radiation risks provide a useful way of quantifying the uncertainty in the Hanford data, several models for obtaining such limits have been explored, and both estimates and confidence limits have been calculated for several cancer types. These calculations indicate that, although the Hanford data show no evidence of positive correlations

between radiation and most cancer types, the data are consistent with effects several times our currently accepted estimates. It is possible, however, to rule out effects that are orders of magnitude higher than estimates obtained by linear extrapolation from estimates based on populations exposed at relatively high levels of radiation (such as the Japanese A-bomb survivors). Methods for obtaining such limits were described at a meeting, Statistics in Health, in Canterbury, U.K., and at the Joint Statistical Meetings in Philadelphia.

Recent analyses of the Hanford data by Kneale, Mancuso, and Stewart have been used as evidence in Worker Compensation hearings. Results of these analyses are in conflict with our results, in that the risk of radiation-induced cancer is estimated to be 10 or 20 times standard estimates (such as those found in BEIR III, for example). A brief critique of these analyses has been accepted for publication in the British Journal of Industrial Medicine, and a more extensive critique is being prepared.

Medical records on 672 cases of congenital malformations have been obtained, and matched controls for these cases have been identified. Cases include those born during the period 1956-1980 in the three hospitals in Richland, Kennewick and Pasco (Tri-Cities). Hanford employee status and radiation exposure have been determined for parents of cases and controls, and an edited data file is now in place. Analysis of these data is being conducted to determine if there are associations between Hanford employment and/or radiation exposure and congenital malformations. Congenital malformation cases will be compared with controls, and several types of malformations will be analyzed separately.

Carcinogenesis

• Biostudies of Complex Mixtures

Principal Investigator: D. D. Mahlum

Other Investigators: M. E. Frazier, P. L. Hackett, R. H. Lovely, L. B. Sasser, and D. L. Springer

Technical Assistance: C. A. Bolt, J. A. Cushing, K. L. Hopkins, D. G. Jones, R. B. Lucke, R. L. Rommereim, and R. C. Zangar

During the past year, SRC-II-derived coal liquids (CL) were further evaluated using the Chinese hamster ovary cells (CHO) and the mouse-skin initiation/promotion (I/P) assays. Results from the CHO assay indicated that the polycyclic aromatic hydrocarbon (PAH) and nitrogen-containing polycyclic aromatic compound (NPAC) fractions contained most of the mutagenic activity. The CL boiling at 800-850°F and >850°F were the most active; however, those boiling at 750-800°F also showed substantial activity. Direct-acting mutagens were detected in these CL. Data from I/P assays indicate that the CL boiling from 700-750°F was not very active as an initiator when it was applied as a single, 25-mg dose; however, application of 5-mg doses (one dose each day) resulted in higher tumor incidence.

Studies to determine whether exposure of rats to CL causes changes in the cardiovascular system indicated that 6 weeks exposure to SRC-II heavy distillate (HD) produced a 20% increase in blood pressure.

Covalent binding of BaP to mouse skin deoxyribonucleic acid (DNA) in the presence of carcinogenic complex mixtures indicated very low binding levels of BaP, suggesting that compounds other than BaP contribute substantially to the carcinogenic activity of the CL.

In the inhalation studies in which rats and mice were exposed to SRC-II HD for either 1, 4 or 12 weeks, all mice have been sacrificed, and about 20% of the rats remain on study. Results for mice indicate that 4 or 12 weeks exposure to the highest dose (0.7 mg HD/liter of air) resulted in reduced life span and in skin and lung tumors. Results from histopathological evaluation of mouse tissues will be available during FY85; for rats, during FY86.

Exposure of rats to SRC-I wash solvent (WS) inhibited memory and reduced motor activity. Exposure to WS also produced a shift in the circadian distribution of activity.

Mammalian-Cell Assays

The 850°+, 800-850° and 750-800°F distillates from the SRC-II process were fractionated by alumina column chromatography into major compound classes. The resultant fractions were neutral aliphatic hydrocarbons (AH), PAH, NPAC, and hydroxy-containing PAH (HPAH). These fractions were examined, using the CHO/HGPRT mammalian-cell mutation assay, in the presence and absence of an exogenous metabolic activation system that consisted of an Aroclor-induced rat liver homogenate coupled with an NADPH generating system.

Evaluation of these data indicates the following important observations (Figure 1): 1) SRC-II CL contain direct-acting mutagens, or promutagens, which are "activated" (metabolized) by CHO cells without the addition of exogenous enzymes. 2) In most instances, the mutagenic activities (both direct and indirect) of the various chemical subclasses decreased with decreasing boiling point (bp), as for the crude bp cuts. 3) The fraction that contains the neutral PAH compounds contains no direct-acting mutagens, as measured with our assay. 4) Individual chemical fractions of the 750-800°F cut showed considerable activity; however, this activity seemed to be masked by the crude, both in the presence and absence of activating enzymes.

An additional observation from the data in Figure 1 is that there appears to be considerably more mutagenic activity in some of the chemical fractions than was detected in the whole bp cuts. For example, if we weigh the activity of four chemical fractions of the 850+ distillate according to their proportional presence in whole distillate, the cumulative mutagenic activity of the four alumina column fractions is about twice that in the unfractionated CL (Table 1). This suggests that the composition of the total material may antagonize or suppress expression of the

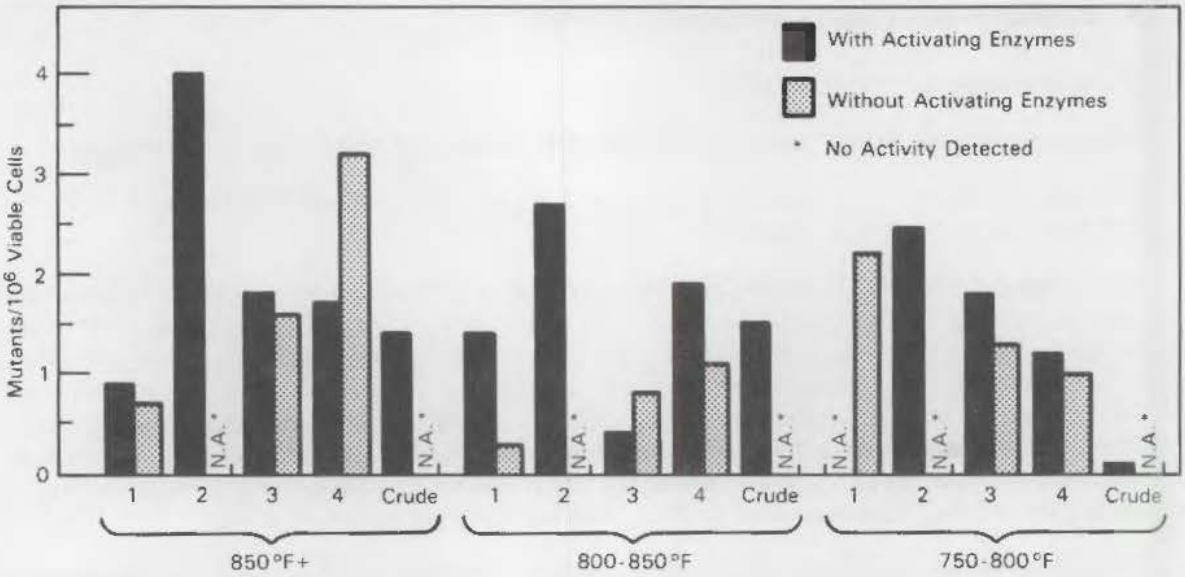

FIGURE 1. Potency in the CHO Assay of Several Discrete Boiling Point Cuts and Their Respective Chemical Fractions, Obtained Using the Alumina Column Separation Techniques of Later et al., Anal. Chem. 53: 1612-1620 (1981). Comparison of mutagenic responses of CHO cells in the presence or absence of a metabolic activation system. The unfractionated distillates are referred to as "crude." Chemical fractions are: 1 = aliphatic hydrocarbon; 2 = neutral polycyclic aromatic hydrocarbon; 3 = nitrogen-containing polycyclic aromatic compounds; and 4 = hydroxy polycyclic aromatic hydrocarbon.

TABLE 1. Mutagenic Activities of Chemical Class Fractions Prepared from SRC-II 850°F+ Distillate.

Test Material	Percent Total by Weight	Mutants/μg	Total Mutants/100 μg	Percent Mutagenic Activity
SRC-II 850°F+	100	1.4	140	100
Alumina Column Fractions				
1 (AH)[a]	1.6	0.9	1.4	1.0
2 (PAH)[b]	47.3	4.0	189.0	135.0
3 (NPAC)[c]	34.1	1.8	61.4	43.9
4 (HPAH)[d]	17	1.7	28.9	20.6
Totals	100	--	280.7	200.5

(a) Aliphatic hydrocarbons
(b) Polyaromatic hydrocarbons
(c) Neutral polyaromatic compounds
(d) Hydroxy polycyclic aromatic hydrocarbons

mutagenic potential of the whole mixture. This same phenomenon is even more apparent with direct-acting mutagenic activity. In the absence of the activating enzyme, no mutagenic activity was detected in any of the three distillates assayed; however, the AH, NPAC, and HPAH fractions of all three distillates had considerable direct-acting mutagenic activity.

I/P Studies

We have examined a number of coal-derived liquids for their skin-tumor-initiating activity. Crude liquids that have shown significant activity have been fractionated into chemical class fractions in attempts to isolate and identify components responsible for the activity. These studies showed that initiating activity was associated with the neutral PAH and NPAC chemical fractions. We extended these studies to the 700-750°F distillate to determine whether initiating activity was also associated with these chemical class fractions in the lower-boiling cuts. The AH, PAH, NPAC, and HPAH fractions were tested by applying them to the skin of

female, Charles River CD-1 mice in the same proportions in which they were found in the parent distillate. A subsample of the NPAC fraction was treated with nitrous acid to destroy the primary aromatic amines (PAA), then tested for initiating activity. All animals were treated twice-weekly with 12-O-tetradecanoylphorbol-13-acetate (TPA) to promote tumor development; promotion continued for 24 weeks. Table 2 shows the tumor incidence and the tumor yield (tumors per group of 30 mice). As in previous experiments with higher-boiling distillates, the neutral PAH had the highest activity, followed by the NPAC fraction. There was no significant activity in the AH or HPAH fractions. Interestingly, the tumor response with the nitrosated NPAC fraction was not above background, suggesting that activity of the NPAC fraction was probably due to the PAA.

TABLE 2. Skin-Tumor-Initiating Activity of SRC-II 700-750°F Distillate and Its Chemical Class Fractions.

Initiator	Incidence	No. of Tumors[a]
Vehicle	5/30	5
700-750°F Distillate	17/30	30
Aliphatic Fraction	9/30	11
Neutral PAH	20/30	31
NPAC	11/30	13
HPAH	4/30	4
Nitrosated NPAC	5/30	5
A1 + A2 + A3 + A4	23/30	32

[a]Total number of tumors per group of 30 mice

When we tested several 50°F distillates from an SRC-II process solvent, the initiating activity of the 700-750°F cut relative to that of the >850°F material appeared to be lower than when these same materials were tested in a chronic skin-painting assay. To test our hypothesis that this difference might disappear if multiple initiating doses were used in the I/P assay, we applied one, three, or nine daily 25-mg doses of the distillate. We also initiated another group with five 5-mg doses applied on different days. Again, all mice were promoted with TPA for 24 weeks. The results of this experiment (Table 3) show that multiple 25-mg doses produced responses, but that the highest response was found in the group initiated with five 5-mg doses. This suggests that the 25-mg dose was somewhat toxic to mouse skin, thereby preventing full expression of the activity.

TABLE 3. Effect of Dosing Modality on the Skin-Tumor-Initiating Activity of SRC-II 700-750°F Distillate.

Initiator	Dose	Incidence	No. of Tumors[a]
Vehicle		5/30	5
700-750°F Distillate	1 × 25 mg	17/30	30
700-750°F Distillate	3 × 25 mg	22/30	51
700-750°F Distillate	9 × 25 mg	25/30	72
700-750°F Distillate	5 × 5 mg	29/30	90

[a]Total number of tumors per group of 30 mice

In previous studies we have shown that hydrotreatment of CL results in decreased mutagenicity and carcinogenicity, possibly due entirely to hydrogenation of aromatic mutagens and/or carcinogens; for example, hydroaromatics from compounds such as BaP might be inactive. However, activity could also be lost if the hydroaromatics that are formed interfere with expression of activity by the remaining mutagens and carcinogens (antagonism). Since we had access to hydrogenated derivatives of BaP, we tested these materials for both initiating activity and their effect on the intitiating activity of BaP. The materials used were 4,5-dihydro BaP, 7,8,9,10-tetrahydro BaP, and a mixture of products resulting from the catalytic hydrogenation of BaP. The dihydro and tetrahydro derivatives were tested for initiating activity at doses of 25 and 125 µg; BaP was tested only at a dose of 25 µg. The dihydro BaP produced a dose-dependent response that was from one-half to one-fifth that of BaP; the tetrahydro BaP showed the same slight activity for both doses. When a 25-µg dose of BaP was applied in the presence of 125 µg of either the dihydro or tetrahydro derivatives, the response was no greater than for the same dose of BaP only. It is not clear whether this indicates antagonism between BaP and its hydrogenated derivatives, or that the affected cells have reached a maximum response for these types of materials. An additional experiment will be performed in which a group is separately initiated with BaP and the hydrogenated material, perhaps 3 to 7 days apart.

DNA Binding and Adducts Studies

Previous studies have examined the effects of complex mixtures on the activity of indirect mutagens, using bacterial assays. Results from those studies indicated that the mutagenic activities of individual compounds were reduced substantially when they were presented to the bacteria in a complex mixture. Similar interactions

were observed with animal carcinogenesis studies. For example, when BaP was mixed with a carcinogenic CL (50 µg BaP + 50 mg CL) and applied once to the shaved backs of mice, fewer tumors were observed in mice receiving BaP in CL than in mice receiving BaP only. In another experiment, mice were initiated with complex mixtures from the SRC process; animals treated with the >850°F fraction developed 2.5 times as many tumors as those initiated with the 800-850°F, even though both CL contained equal amounts of BaP. These data demonstrate that the initiating activity of BaP was suppressed when presented in a complex chemical matrix. To extend these studies, in vivo experiments were conducted to determine the extent of DNA binding of BaP alone or BaP in complex mixtures.

For these studies, tritiated BaP (50 µg, 375 µCi) in dichloromethane or tritiated BaP (50 µg, 375 µCi) in dichloromethane containing 500 µg or 25 mg of CL was applied to the shaved backs of CD-1 mice (three treatment groups). Twenty-four hours after dosing, the area covered by the dosing solution was identified with ultraviolet (UV) light and removed. The skin was digested with proteinase K, and the DNA was extracted once with phenol-chloroform-isoamyl alcohol and once with chloroform-isoamyl alcohol. After precipitation with ethanol, the DNA was rehydrated in buffer, and the amount of DNA was estimated, using the absorbance at 260 nm. The ratio of absorbance at 260 to 280 nm was used to evaluate the DNA purity. Radioactivity associated with the DNA was determined by solubilizing the DNA and using liquid scintillation counting procedures.

In Vitro DNA Binding

Results for the binding of BaP to mouse-skin DNA are shown in Table 4. In the absence of CL, binding to DNA was 5.5 pg BaP/µg DNA. When the CL were applied at amounts similar to those used in the skin-painting assay (i.e., 25 mg CL), binding of BaP was not detected. These effects were observed at ratios of BaP to CL of 1:500. When the amount of CL was reduced so that the ratio of BaP to CL was 1:10, binding of BaP was about 25% of that for BaP alone. In addition, the binding of BaP in the presence of the >850°F cut was slightly greater than for the 800-850°F distillate.

The biochemical mechanisms responsible for differences in the carcinogenic activity of individual compounds, compared to those of complex mixtures, are unclear. Since a large portion (~45%) of each CL was neutral PAH, the reduced DNA-binding of BaP

TABLE 4. In Vivo Binding of Tritiated Benzo[a]pyrene to Mouse-Skin DNA in the Presence or Absence of Two Coal Liquids (CL).

Substrate	Dose, µg	Ratio, BaP:CL	DNA Binding, %
BaP	50	---	100
Bap+ 800-850°F	50 25,000	1:500	<2
BaP+ >850°F	50 25,500	1:500	<2
BaP+ 800-850°F	50 500	1:10	22
BaP + >850°F	50 500	1:10	31

may be due to mass action. Assuming that PAH in the complex mixture compete for the same binding site(s) on the mixed-function oxidase enzymes, mass action laws dictate that the rates and extent of BaP metabolism were reduced by competition from other PAH. Presumably, many of these PAH are noncarcinogenic, yet most (if not all) are metabolized by mixed-function oxidase enzymes to more water-soluble products. We do not know whether similar competition occurs for components from other chemical classes, such as the aliphatic, NPAC or HPAH.

Other mechanisms may also be responsible for the results observed. For example, it has been shown that as the concentration of BaP increases, the route of BaP metabolism shifts away from the pathway that produced the diol-epoxide metabolite, which is the ulitmate carcinogenic form of BaP. Both carcinogenic and noncarcinogenic compounds present in the CL might cause similar pathway shifts, thereby reducing the amount (and/or rate) of BaP diol-epoxide available for binding to DNA.

Inhalation Studies

Lifespan studies for animals after exposure to SRC-II HD have also been conducted to determine whether short- to moderate-term exposures to a high-boiling CL resulted in shorter than normal lifespans, tumor development, and/or other undesirable effects. In addition, we wanted to determine whether short-term exposures to this material at relatively high doses resulted in adverse effects similar to those observed after longer exposures.

Animals (40 rats of each sex and 30 female mice in each treatment group) were exposed 6 hours/day, 5 days/week for either 1 (Group 1), 4 (Group 2), or 12 weeks (Group 3) at aerosol concentrations of 0.68 + 0.03, 0.14 + 0.01, 0.03 + 0.003,

and 0.0 mg HD/L of air for the high, middle, low and control groups, respectively. Particle sizes were 1.7 to 1.8 μm mass median aerodynamic diameter (MMAD), with geometric standard deviations of 2.0 to 2.3. After exposure, animals were observed daily, weighed weekly for several weeks, then monthly for the remainder of their lives. Animals found dead were necropsied immediately. Currently, 10% of the rats remain alive; all mice have died or were sacrificed.

Body weights for mice are shown in Figure 2. Data for animals exposed for 1 week indicate that they lost weight during exposure, then regained weight and grew at a uniform rate through the remainder of their lives. Weights for the low-dose group tend to be lower than for the other groups; the reason is not readily apparent. Group 2 and 3 animals, like those of Group 1, lost weight during the first week of exposure. Both treated and control groups then gained weight at a constant rate until the last few weeks of their lives, when weights tended to decline.

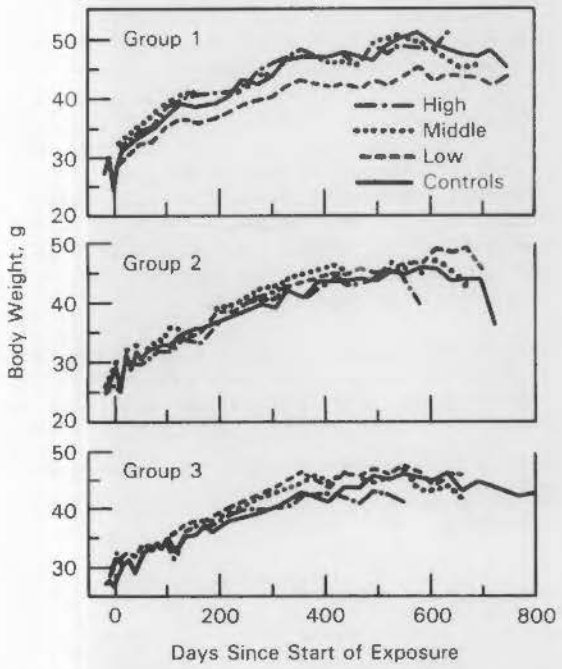

FIGURE 2. Body Weights of Mice Exposed to Low (0.03 mg/L); Middle (0.14 mg/L) or High (0.68 mg/L) Levels of SRC-II Heavy Distillate for 1 Week (Group 1), 4 Weeks (Group 2) or 12 Weeks (Group 3).

Data for median survival age of mice (age when mortality reached 50%) are shown in Table 5. For controls, the median survival age in Groups 1, 2, and 3 averaged 110 weeks. Generally, median survival ages were lower with longer exposure and higher exposure concentrations. Survival ages for low-dose animals from Groups 1 and 2 were about the same as those of controls. Median survival age was the lowest (approximately 30%) for animals that received the highest dose for the greatest length of time.

TABLE 5. Median Survival Ages of Female Mice Exposed to SRC-II Heavy Distillate.

	Weeks of Age			
Dose, mg/L:	0.0	0.03	0.14	0.68
Groups	Control	Low Dose	Middle Dose	High Dose
1	111	109	101	95
2	106	107	94	86
3	114	90	93	80

In addition to shortened life span, exposure produced skin tumors in the mice from all exposure groups except the low-dose animals from Group 1 (Table 6). In general, the number of animals with tumors and the total number of tumors per treatment group increased with the length of exposure and concentration. Tumor incidence for high-dose animals in Groups 2 and 3 was similar: about 40% of the mice had tumors, with an average of ~2.5 tumors per mouse. Since tumors were observed in middle- and high-dose mice from Group 1, it is apparent that a limited number of exposures to HD is sufficient to cause tumor development.

TABLE 6. Skin Tumors Observed in Mice After Whole-Body Inhalation Exposure to SRC-II Heavy Distillate.

	Number of Animals with Tumors/Total Number of Tumors			
Dose, mg/L:	0.0	0.03	0.14	0.68
Groups	Control	Low Dose	Middle Dose	High Dose
1	0/0	0/0	1/1	8/4
2	0/0	3/3	6/7	13/28
3	0/0	3/4	7/12	11/31

We anticipate that all rats will be necropsied during the first quarter of FY 85, when we plan to complete histopathological examination of the mice and begin evaluation of the rats. If these evaluations indicate malignancies, the results from this study will provide data for risk assessment in humans in terms of exposure concentrations and time/dose relationships.

Cardiovascular Studies

In recent years, evidence has been obtained that suggests that PAH material may be involved in some aspects of cardiovascular illnesses. Moreover, there is an anecdotal history of increased incidence of disease, especially myocardial infarction, among workers exposed to coal-derived materials. We have therefore investigated the use of an isoproterenol myocardial infarction model to measure cardiovascular function in experimental animals exposed to CL. A strong dose-response relationship for myocardial infarction in young adult rats was established, but we did not find this relationship in mature rats. Using this model, we then examined the susceptibility of the young adult cardiovascular system to SRC-II HD.

Male Fischer rats were exposed to HD by inhalation (0.7 mg/L), 6 hours/day, 5 days/week for 6 weeks. After a 10- to 20-day recovery period, exposed and control rats were injected subcutaneously with 0, 20, 40, or 60 mg of isoproterenol/kg body weight. Approximately 24 hours later, the femoral artery was surgically cannulated under light sodium pentabarbitol anesthesia, and blood pressure, heart rate, and electrocardiogram (ECG) were measured. The animals were injected with ^{99}Tc-pyrophosphate and killed 1 hour later. Increased ^{99}Tc uptake was used as a measure of cardiac damage.

Blood pressure of exposed rats that received no isoproterenol was significantly elevated compared to those of control animals (Table 7). Exposed animals injected with isoproterenol also had higher blood pressure than controls, but this effect was significant only at the 60-mg/kg isoproterenol dose. Except in animals injected with 60 mg/kg isoproterenol prior to HD exposure, isoproterenol generally suppressed elevation of blood pressure in the HD-exposed groups compared with the noninjected group. Administration of isoproterenol before exposure had no effect.

Heart rates of control animals increased with increasing doses of isoproterenol (correlation coefficient = 0.97; Table 7). In contrast, heart rates of HD-exposed animals increased significantly at the 20-mg/kg isoproterenol dose, after which no significant dose-related change occurred. A highly significant difference between control and HD-exposed animals was observed in those that received isoproterenol before HD exposure, suggesting that HD inhibited the normal recovery of the cardiovascular system after exposure to isoproterenol. A trend for this same response occurred for blood pressure, although the results were not significant.

Significant changes in ECG patterns were not induced by HD exposure, but major alterations were recorded in animals that received isoproterenol. A dose-related increase was observed in the uptake of ^{99}Tc by the hearts of both control and HD-exposed animals after isoproterenol injections, and the uptake in control animals was significantly greater than in exposed animals. This suggests that HD had a protective effect against the myocardial infarction caused by the isoproterenol. However, evaluation was complicated by the HD-induced effect on body weight: ^{99}Tc uptake by myocardial tissue of HD-exposed rats and control rats of similar weight was the same.

These data suggest that the cardiovascular system may be at risk from exposure to HD. The isoproterenol infarction model may be useful for sensitizing the cardiovascular

TABLE 7. Blood Pressure and Heart Rates of Rats Exposed to SRC-II Heavy Distillate (HD; Boiling Point, 550-850°F) for 6 Weeks: Isoproterenol, to Induce Myocardial Infarction, was Administered as Indicated.

Isoproterenol, mg/kg body weight	Blood Pressure, mm Hg		Heart Rate, beats/min	
	Control	HD (0.7 mg/L)	Control	HD (0.7 mg/L)
0	100 ± 1.5	122 ± 1.5[a]	367 ± 21	406 ± 19
20	99 ± 2.1	110 ± 5.0	380 ± 8.0	430 ± 14[b]
40	101 ± 5.0	112 ± 1.7	394 ± 11	434 ± 6.1[a]
60	95 ± 1.9	111 ± 3.1[a]	420 ± 12	439 ± 6.3
60[c] (Pre-Exposure)	111 ± 3.6	120 ± 3.6	375 ± 13	435 ± 12[a]

[a] Significantly different from control group ($P < 0.01$)
[b] Significantly different from control group ($P < 0.02$)
[c] Isoproterenol administered 3 days prior to beginning exposure to HD.

system to cardiotoxic agents and measuring effects (e.g., heart rate changes), but the weight-related sensitivity of rats to isoproterenol may limit its use. Plans are now underway to determine whether these effects are transient or permanent and to extend these studies to other complex mixtures.

Neurotoxicity Studies

This year we have continuted to evaluate the hypothesis that SRC-I WS may have direct effects on the neurological basis of memory. Because the taste-aversion (TA) learning task we used last year was highly variable among replicates and because it took nearly 3 weeks to perform, we have assessed memory using a one-trial, learned inhibitory avoidance response. The control group in this task is stable, and the task takes only 2 hours/day for 3 days.

In the first study, rats were placed on the bright white side of a two-compartment apparatus, the other side of which was black. Typically, rats will pass through a portal to the black/darkened side within 5-15 sec. After an initial adaptation trial, rats were again placed on the white side (Day 2); when they passed to the darkened side, they received a foot shock (1 mA, 2-sec duration). Immediately following training, half of the rats (n = 10) were gavaged with corn oil vehicle (CO), and the other half were gavaged with 500 mg/kg body weight WS in CO. Three days later (Day 5), all rats were again tested in the two-compartment task to see if their entry to the darkened (shocking) side of the apparatus was inhibited. The rats were allowed up to 2 minutes to enter the darkened compartment before the memory/retention trial was terminated. The data obtained make it clear that WS, at 500 mg/kg, does not produce retrograde amnesia.

WS	108.3 ± 8.5
CO	103.2 ± 11.4

All rats exposed to WS following learning showed retention of the adversive experience.

In the next experiments, we used the same memory test, but the WS or CO was administered 2 hours before the foot-shock training trials. The rats were then assessed for retention on Day 5. The data show that exposure to WS prior to learning affected subsequent memory processes.

WS	66.2 ± 17.7
CO	113.6 ± 6.4

Either rats were unable to encode and store the learning experience or the WS affected their ability to retrieve it from memory 3 days later.

In the third experiment of this series, we assessed whether the retention deficit in rats exposed to WS was due to state-dependent learning. This sometimes occurs when animals are trained when in one drug state and tested for retention in the normal state, or vice versa. For example, in the experiment described above, it is possible that the rats trained 2 hours after WS exposure might have shown normal retention/memory if they had been re-exposed 2 hours prior to the retention test on Day 5, when they would have been in the same drug state. We evaluated this possibility with four groups of 10 rats each. Half of the rats (n = 10/group) were trained 2 hours following CO exposure. In the retention test (Day 5), half of the WS group (n = 10) was exposed to WS for the second time 2 hours prior to the retention test; the other half of the WS group was exposed to CO prior to the retention test. Similarly, half (n = 10/group) of the rats exposed to CO 2 hours prior to training were re-exposed to CO 2 hours prior to the retention test; the other half that were originally exposed to CO were exposed to WS prior to the retention test. The retention data (Table 8) show that while some of the retention deficit was due to state-dependent learning (groups WS-WS, CO-WS), a significant source of variance was due to a genuine anterograde amnesia (group WS-CO), thus implicating neural dysfunction due solely to WS exposure.

TABLE 8. Mean Latency (Sec ± SEM) of Rats Administered Combinations of Wash Solvent (WS) and Corn Oil Vehicle (CO) to Re-Enter Black Side of Compartment in Test for Anterograde Amnesia and State Dependency. Treatment designations are for days 2 and 5, respectively.

CO - CO	112.5 ± 7.5
WS - CO	70.6 ± 19.5
WS - WS	100.7 ± 15.9
CO - WS	100.6 ± 10.0

At doses of WS above 1.5 g/kg body weight, it is not uncommon to observe motor tremors within 10-15 minutes of gavage. These observations, along with the evidence for disruption of memory formation, suggested that lesions might be found in the central nervous system following exposure to WS. For neurohistological evaluations, both male and female rats were exposed to WS doses ranging from 500 mg/kg to 2 mg/kg. At varying time intervals, ranging from 1 hour to several days after gavage, these rats were sacrificed and perfused trans-

cardially. Coronal sections (25 μm) were taken throughout the brain and spinal cord, and sections of sciatic nerve were also taken. The neural tissue was stained for cell death (Nissil stain) and fiber degeneration (Fink-Heimer). No evidence of cell death or fiber degeneration due to WS exposure was found in any of the tissue preparations.

We have also examined motor activity in a residential maze. Animals were gavaged with 500 mg/kg WS 20 hours before testing. The testing lasted 23 hours, thus allowing us to evaluate the circadian distribution of motor activity. Statistically significant reductions in activity were found in both male and female rats (Table 9). In addition, the male rats showed a shift of about 2 hours in the midnight epoch of activity despite the fact that the animals were well adapated to a 12-hour/12-hour day/night cycle.

TABLE 9. Motor Activity (Mean Number [± SEM] Photocell Breaks in Residential Maze) Over a 23-hr Test Period. Rats were gavaged with Wash Solvent (WS) or Corn Oil Vehicle (CO) before testing.

Males	WS	1722.3 ± 110.1
	CO	2216.9 ± 220.2
Females	WS	2098.3 ± 241.3
	CO	2807.2 ± 343.2

Reproduction Studies

During FY 84, a study was conducted to determine the effect of exposure to high-boiling CL on the reproductive capability of female rats. This study was conducted jointly under the "Biostudies of Complex Mixtures" and "Perinatal Effects of Complex Mixtures" projects (See "Perinatal Effects of Complex Mixtures," this report).

• 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 four highest dose-level groups exposed to $^{239}PuO_2$, during the 13-yr postexposure period. During the 10½ yr after exposure to $^{238}PuO_2$, mortality due to lung and/or bone tumors increased in the three 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-month-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 hours; 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 $H_2{}^{16}O$ steam in argon exchange at 800°C for 96 hours. 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.[a]

Dose Level Group	Number of Dogs		Initial Alveolar Deposition[b]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Control	10	10	0	0
1	10	10	3.5 ± 1.3	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	2.4 ± 0.4
5	10	10	1100 ± 170	9.3 ± 1.4
6	3	5	5800 ± 3300	50 ± 22
	63	65		

[a] Exposed in 1970 and 1971
[b] Estimated from external thorax counts at 14 and 30 days post-exposure and estimated lung weights (0.011 x body weight)
[c] Mean ± 95% confidence intervals around the means

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

Dose Level Group	Number of Dogs		Initial Alveolar Deposition[b]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Control	10	10	0	0
1	10	10	2.3 ± 0.8	0.016 ± 0.007
2	10	10	18 ± 3	0.15 ± 0.03
3	10	10	77 ± 11	0.56 ± 0.07
4	10	10	350 ± 81	2.6 ± 0.5
5	10	10	1300 ± 270	10 ± 1.9
6	7	6	5200 ± 1400	43 ± 12
	67	66		

[a] Exposed in 1973 and 1974
[b] Estimated from external thorax counts at 14 and 30 days post-exposure and estimated lung weights (0.011 x body weight)
[c] Mean ± 95% confidence intervals around the means

Table 3 summarizes, by dose-level group, the mortality and lesions associated with deaths through 13 years 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, 20 in Group 4, 10 in Group 3, 10 in Group 2, 13 in Dose-Level Group 1 and 11 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.

As survival time increased, the fraction of plutonium in the lung decreased to ~16% of the final body burden by 12 to 13 years 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 increased to ~63% of the final body burden at 12 to 13 years after exposure; the abdominal lymph nodes, principally the hepatic nodes, contained ~4%. The fraction of plutonium in liver increased, accounting for ~25% of the final body burden at 12 to 13 years after exposure in the higher 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

TABLE 3. Summary of Lesions in Dogs Euthanized During the 13-yr Period After Inhalation of $^{239}PuO_2$.

			Number of Dogs/Lesion Associated with Death																												
Dose Group	No. Dogs/ Group	No. Dead Dogs/ Group	Radiation Pneumonitis	Lung Tumor	Esophagus, Leiomyoma, Lung Tumor	Bone Tumor	Malignant Lymphoma	Hemangiosarcoma, Heart, Spleen, Liver	Reticulum Cell Sarcoma	Pituitary Tumor, Cushing's	Ovarian Tumor	Hemangioma, Spleen	Oral Tumor	Round Cell Sarcoma	Malignant Melanoma	Pneumonia	Pheochromocytoma	Liver Cirrhosis, Addison's	Urinary Bladder Tumor	Nephrosclerosis	Thromboembolism	Peritonitis	Septicemia	Epilepsy	Neurofibrosarcoma	Pyometra	Cardiac Insufficiency	Unknown	Meningioma
6	8	8	7	1																											
5	21	21	1	20																											
4	22	20		13	1				1	1						2		1								1					
3	20	10		5			1													1	1				1	1	1				
2	21	10				1					1	1			1	1	1		1			1		1				1			
1	24	13				2	1	3		1				1		1							1	1				1	1		
Control	20	11		3			2	2					1							1	1										

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

			Percent of Final Body Burden					
Dog Number	Time After Exposure, mo	Final Body Burden, μCi	Lungs	Thoracic Lymph Nodes[a]	Abdominal Lymph Nodes[b]	Liver	Skeleton	Cause of Death
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

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

TABLE 4. (Continued)

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	
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	22	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	0.78	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	Ovarium 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	7.5	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	0.080	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
862M	145	0.0026	21	56	0.85	4.4	6.9	Peritonitis
904F	145	0.0013	8.9	87	0.30	0.88	1.0	Chondrosarcoma
756M	147	0.0016	15	75	1.0	1.6	4.1	Epilepsy
782M	148	0.043	12	72	4.9	9.0	0.86	Neurofibrosarcoma
886F	149	0.00085	13	51	15	3.6	13	Meningioma
795F	152	0.030	24	26	8.3	38	1.5	Lung Tumor
771F	153	0.019	20	71	1.0	5.8	1.1	Lung Tumor
813F	153	0.036	22	44	4.7	27	1.1	Multilobar Sarcoma, Skull
826F	153	0.0033	8.1	88	0.37	0.94	1.2	Hemangioma, Spleen
859M	154	0.048	19	31	29	7.3	0.79	Urinary Bladder Tumor
870F	154	0.00062	8.2	70	4.9	9.6	4.8	Pneumonia
879M	154				— Processing —			Hemangiosarcoma
884M	155	0.077	13	45	9.4	30	1.6	Lung Tumor
831F	155	0.0087	24	71	0.65	3.3	1.0	Pneumonia
866M	156	0.145	15	41	9.3	34	0.20	Lung Tumor

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

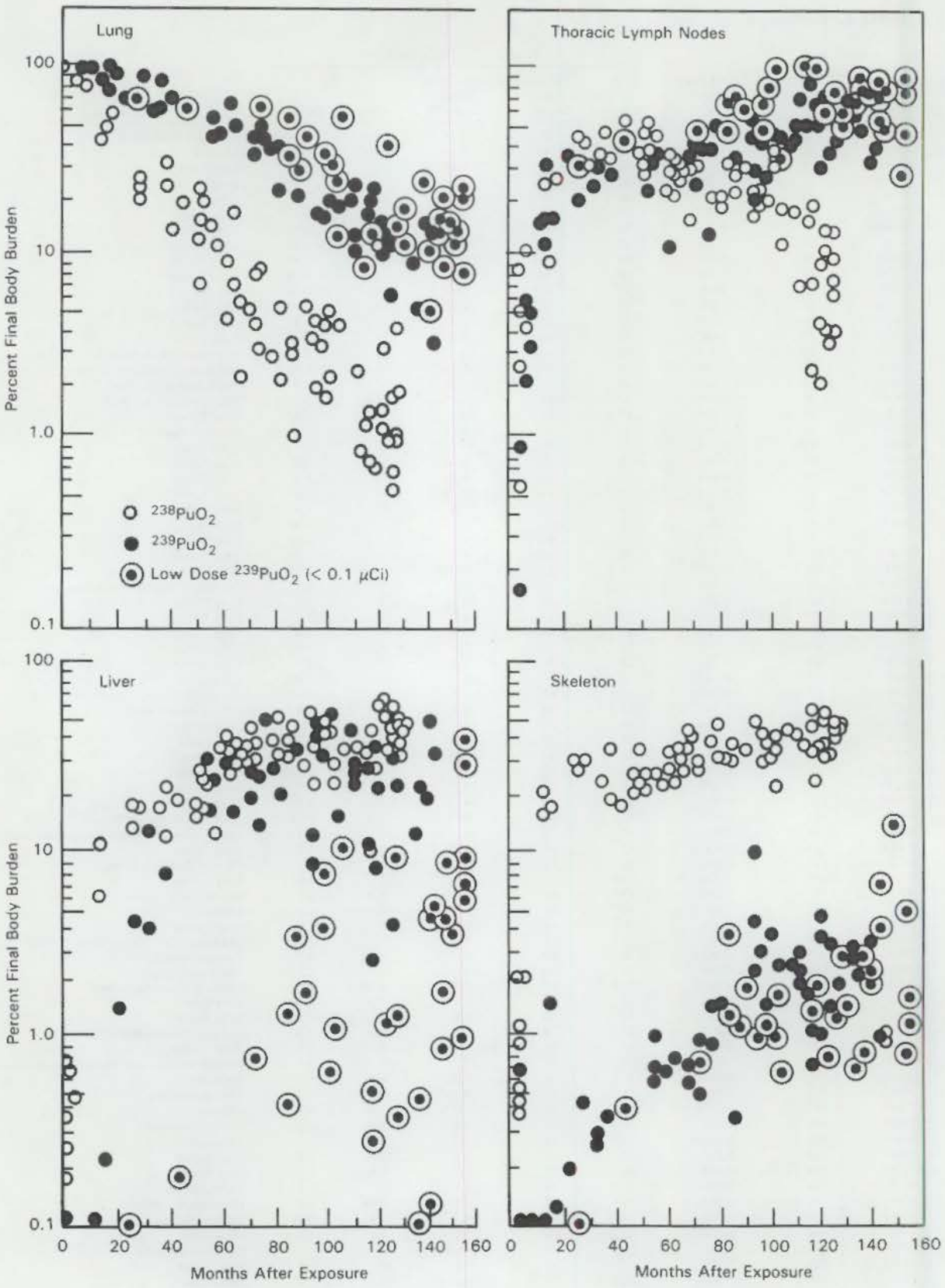

FIGURE 1. Plutonium in Tissues of Dogs After Inhalation of PuO_2.

during the first 2 years after exposure. The lower-dose-level dogs sacrificed or euthanized during the 4th to 13th post-exposure years generally 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 3% of the final body burden was in the skeleton at 12 to 13 years after exposure. Plutonium analyses are still in progress on four of the dogs.

The nine dogs euthanized because of radiation pneumonitis during the 3-year post-exposure 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.

Forty of the 74 exposed dogs euthanized 3 to 13 years after exposure had lung tumors. 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. Two dogs in Dose Level 1 were euthanized 11.7 and 12.1 years, respectively, after exposure: one had an osteosarcoma involving the nasal cavity and maxilla; the other had a chondrosarcoma involving the nasal cavity. One dog in Dose Level 2, euthanized 12.8 years after exposure, had a multilobular sarcoma of the skull. Three control dogs were euthanized because of lung tumors. Dogs 794M, 803M, 809F, 824F, 833F, and 835F (Dose Level 4), 697M, 778M, 782M, 834F and 905F (Dose Level 3), 748F, 754M, 769F, 780F, 806F, 826F, 831F, 859M and 862M (Dose Level 2), and 756M, 807F, 825F, 870M, 875M, 879M, 886F, 891M, 899F, 900M and 908M (Dose Level 1) died during the 7- to 13-years 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 four dogs, epidermoid and adenocarcinoma; in two dogs, epidermoid carcinoma; in one dog, epidermoid and bronchiolar-alveolar carcinoma; in one dog, adenocarcinoma and bronchiolar-alveolar carcinoma; in one dog, epidermoid carcinoma, 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 13-year 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 months after exposure, mean lymphocyte values were sig-

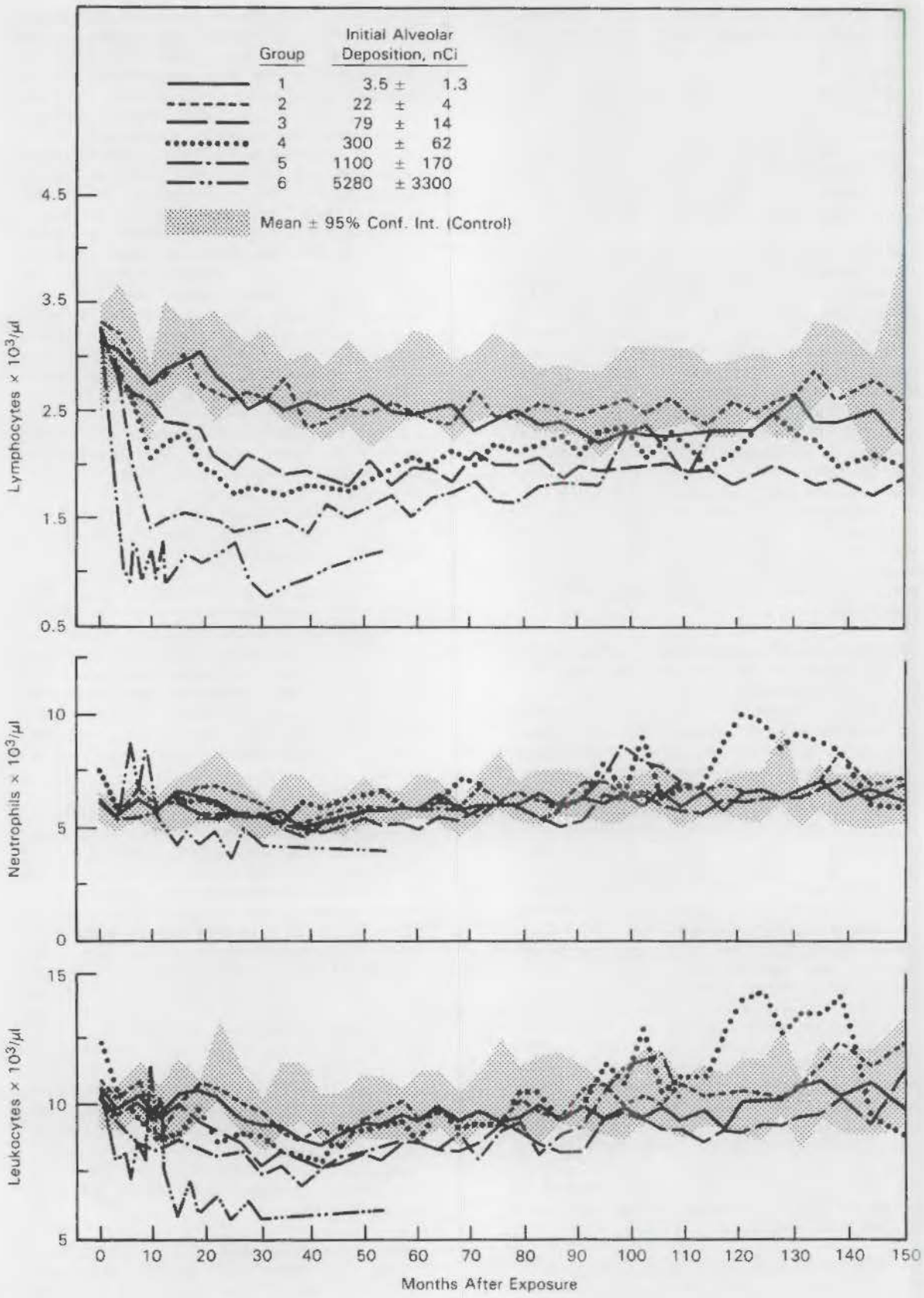

FIGURE 2. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}PuO_2$.

nificantly lower ($P < 0.05$) for Dose-Level Groups 3 and 4 than for the control group. At 127 months 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 death through 10½ years after exposure to $^{238}PuO_2$. During this period, all of the dogs in the highest-level dose group, 19 dogs in Dose-Level Group 5, 5 dogs in Group 4, 6 dogs in Group 3, 5 dogs in Group 2, and five dogs in Dose-Level Group 1 were euthanized when death was imminent. Four control dogs were euthanized during the 10½-year 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 ^{238}Pu in the tissues of these animals.

Of the 53 exposed dogs euthanized, 27 were killed because of bone tumors, three because of lung tumors, and one because of radiation pneumonitis. Twelve of the dogs euthanized because of bone tumors also had lung tumors. Twenty-five of the 27 dogs with bone tumors had osteosarcomas, one Dose-Level Group 1 dog (989F) had a fibrosarcoma in the ilium, and one Dose-Level Group 4 dog (1103F) had a fibrosarcoma in a vertebra. All of the exposed dogs with osteosarcomas and lung tumors were in Dose-Level Groups 4, 5, and 6. Twelve of the 25 osteosarcomas were in vertebrae; two in femora; three in ribs; two in the scapulae; three in the pelvis; one in the tibia; one in the sternum; and one in the humerus. Dog 994F (Dose Level 6); dogs 1030F, 1047M, 1079M, 1096M, and 1191F (Dose Level 5); 991F and 1080M (Dose Level 4); 960M, 1040M, 1043F, 1059F, and 1066M (Dose Level 3); 971F, 1078F, 1082M, 1188M, and 1229M (Dose Level 2); and 951M, 1063M, 1069F, and 1106F (Dose Level 1) died dur-

TABLE 5. Summary of Lesions in Dogs Euthanized During the 10.5-yr Period After Inhalation of $^{238}PuO_2$.

			Number of Dogs/Lesion Associated with Death																						
Dose Group	No. Dogs/ Group	No. Dead Dogs/ Group	Radiation Pneumonitis	Lung Tumor	Lung Tumor, Metastatic	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	Empyema, Pituitary Tumor, Cushing's	Hemangiosarcoma, Heart, Spleen	Malignant Lymphoma	Adrenal Carcinoma, Osteoarthopathy	Parathyroid Adenoma	Brain Tumor	Brain Tumor, Heart Tumor	Spinal Cord Degeneration	Pyometra	Pneumonia	Herniated Vertebral Disc	Urinary Bladder Tumor	Anesthesia
6	13	13		3		2	6	1		1											1	1		
5	20	19				10	4		1	2											1		1	
4	20	5				1	1						1								1			
3	22	6	1									1		3		1								
2	21	5			1								1				1		1		1			
1	20	5				1								1	1			1						1
Control	20	4									1			1						1			1	

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	37	25	Sacrifice
1115F	61	1.534	5.0	32	2.3	26	33	Bone Tumor
1162F	61	3.663	12	32	5.9	21	25	Bone Tumor, Addison's Disease
1009M	62	4.360	15	25	2.4	31	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	0.31	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
1106F	117	0.0029	1.3	16	1.8	9.9	57	Adrenal Carcinoma
1103F	118	0.232	0.76	18	3.1	45	32	Bone Tumor, Lung Tumor
1188M	119	0.0089	0.71	2.5	0.94	68	24	Metastatic Lung Tumor
1066M	121	0.035	1.1	4.4	0.52	57	32	Malignant Lymphoma
1069F	121	0.0022	10	2.1	1.6	51	33	Malignant Lymphoma
1030F	122	0.160	1.5	15	1.1	22	56	Pneumonia
951M	122	0.0023	3.3	8.9	0.77	47	35	Anesthesia
1229M	123	0.0060	0.94	11	0.73	35	49	Pneumonia
1072M	124	0.079	0.65	4.1	1.6	57	34	Radiation Pneumonitis
1157M	124	0.294	0.55	3.5	3.7	41	44	Bone Tumor
971M	125	0.0095	1.7	5.5	0.44	49	41	Hemangiosarcoma, Spleen
1078F	125	0.025	0.98	9.6	0.60	46	41	Meningioma
952F	125	0.106	1.0	4.4	2.1	39	48	Bone Tumor
1059F	126	0.050	4.2	7.4	0.99	45	39	Malignant Lymphoma
991F	126	0.058	1.8	14	0.81	36	41	Urinary Bladder Tumor

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

ing the 10½-year postexposure period of causes presently thought to be unrelated to plutonium exposure.

The lung tumors were classified as bronchiolar-alveolar carcinomas in 11 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; in one dog, the bone tumor metastasized to the iliac lymph nodes; and in one dog, the bone tumor metastasized to the lungs, pleura, diaphragm and heart. 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, trabecular 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 126 months 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 months 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 months 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 months following exposure, ALP and GPT values were higher than those of the control group only in Dose-Level Groups 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 9½ to 10½ years after exposure, the fraction of the final body burden in the lungs of the ^{238}Pu-exposed dogs was about 2%, compared to 15% in the ^{239}Pu-exposed dogs (Figure 1). At that time, ~8% of the ^{238}Pu was in the thoracic lymph nodes, compared to ~57% of the ^{239}Pu. Livers of the ^{238}Pu-exposed dogs contained ~43% of the plutonium burden, compared to 12% in the livers of the ^{239}Pu-exposed dogs. About 40% 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.

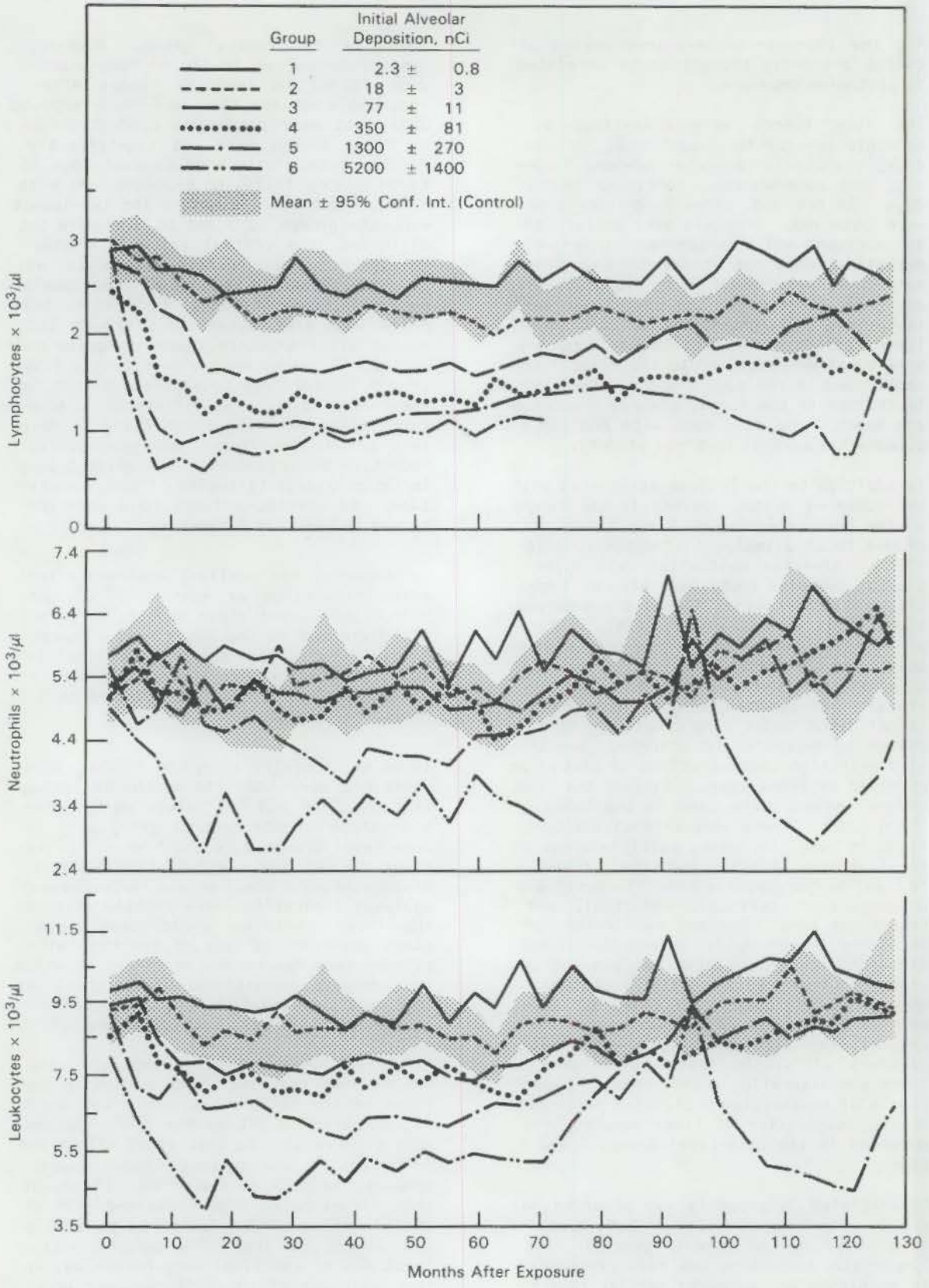

FIGURE 3. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{238}PuO_2$.

• Inhaled Plutonium Nitrate in Dogs

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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 years or more (Table 2). There was early translocation to the liver and skeleton, with only minimal amounts translocated to thoracic or abdominal lymph nodes. This was in contrast to dogs that inhaled $^{239}PuO_2$, where a considerable amount translocated to the thoracic lymph nodes but only small 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 year after exposure.

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[b]	
	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	56 ± 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 x body weight)

[c] Mean ± standard deviation

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
1659	70	0.736	1.14	0.34	0.40	38.90	55.89	Bone Tumor
1419M	76	0.873	0.69	0.28	0.39	44.06	50.70	Bone Tumor, Lung Tumor
1652	87	0.658	1.46	0.23	0.29	50.47	44.32	Bone Tumor, Lung Tumor
1408	93	0.181	0.60	0.19	0.37	49.47	45.52	Bone Tumor

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

The earliest observed biological effect was on the hematopoietic system: lymphopenia occurred at the two highest dose levels at 4 weeks after exposure to $^{239}Pu(NO_3)_4$. 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 months after exposure to initial lung burdens of ~80 nCi or more. The lymphopenia at lower dose levels of plutonium oxides may be related to the more-extensive translocation of plutonium oxide to the tracheobronchial lymph nodes.

Table 3 summarizes, by dose-level group, the mortality and lesions associated wtih deaths through 6½ years after exposure to $^{239}Pu(NO_3)_4$. All five dogs at the highest dose level and two of 20 dogs at the medium-high dose level died from radiation pneumonitis 14 to 51 months 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.

One dog at dose-level Group 4 was euthanized, because of large lung tumors, after 77 months exposure. The lung tumors, both bronchiolo-alveolar carcinoma and combined epidermoid and adenocarcinoma, had metastasized to bone and lymph nodes.

Lung tumors occurred in two additional dogs with radiation pneumonitis and in five dogs euthanized because of osteosarcomas. Typically, the lung tumors 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 in dogs euthanized because of radiation pneumonitis or bone tumors.

Osteosarcomas were the principal reason for euthanizing dogs after more than 51 months of plutonium exposure. Osteosarcomas were present in 14 dogs euthanized 42 to 78 months after exposure: 13 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 (three dogs), sacrum (one dog), pelvis (one dog), maxillary bone (one dog), and in both a humerus and rib of one dog. Metastases to distal sites occurred in six dogs. These dogs also had radiation osteosis, generally characterized by peritrabecular fibrosis.

The average cumulative skeletal dose for dogs with bone tumors was calculated as 202 (SD, 120) rad, based on a logarithmic model of plutonium deposition using final body burdens. The dose was calculated using skeletal mass of 0.1 x initial body weight, and the duration as the time of death minus 60 days.

Autoradiographs of liver sections from dogs euthanized 3 to 5 years 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 6.5 years following exposure), ALP values in Dose Level Groups 4 and 5 are significantly ($P < 0.05$) higher than those for the control group.

The percentage of plutonium deposition in bone present in marrow was determined by ultrasonic cell disruption of selected bones and analysis of bone and bone marrow separately. Table 4 shows that the di-

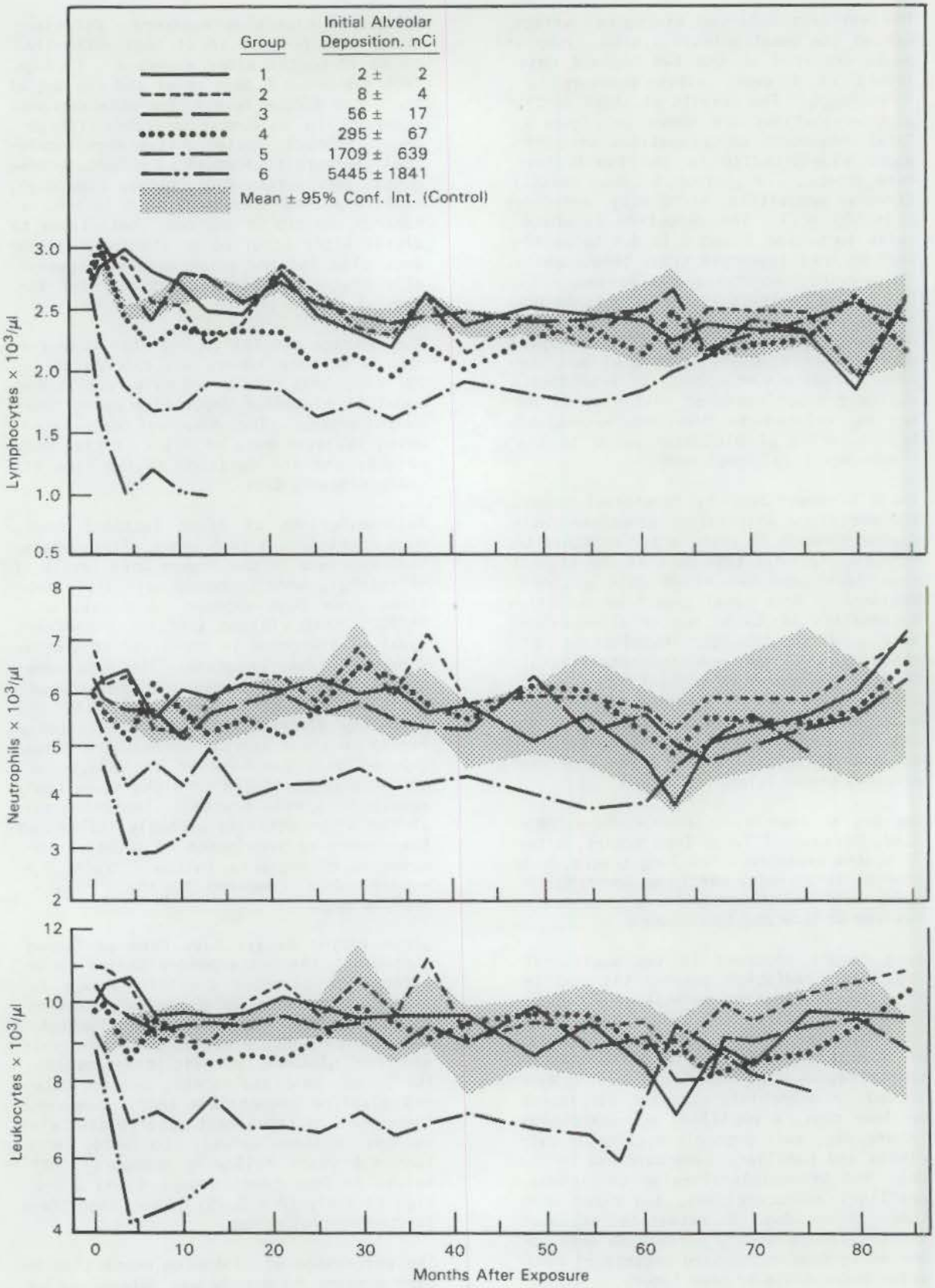

FIGURE 1. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}Pu(NO_3)_4$.

TABLE 3. Summary of Lesions in Dogs Euthanized During the 6.5-Yr Period After Inhalation of $^{239}Pu(NO_3)_4$.

Dose Group	No. Dogs/ Group	No. Dead Dogs/ Group	Number of Dogs/Lesion Associated with Death						
			Radiation Pneumonitis	Radiation Pneumonitis and Lung Tumor	Bone Tumor	Bone Tumor and Lung Tumor	Lung Tumor	Pneumonia	Lymphoma
6	5	5	4	1					
5	20	15	1	1	8	5			
4	20	2			1		1		
3	20	0							
2	20	0							
1	20	0							
Vehicle	20	1							1
Control	20	1						1	

TABLE 4. Partition of ^{239}Pu Administered by Inhalation as $^{239}Pu(NO_3)_4$ Between Bone and Bone Marrow in Beagle Dogs.

Months Postexposure:	43	77	81	93	101
	Percent of Plutonium in Marrow[a]				
Humerus					
Proximal	1.55	7.07	3.56	7.40	3.68
Diaphysis	6.26	11.39	6.17	14.79	6.78
Distal	0.41	2.31	0.32	2.85	0.36
Radius					
Proximal	--	--	0.31	0.79	1.82
Diaphysis	0.79	--	1.42	--	--
Distal	--	--	0.93	--	--
Lumbar Vertebrae	2.87	5.77	2.85	5.69	5.62

(a) $\frac{\text{Pu in marrow}}{\text{Pu in intact bone (including marrow)}} \times 100$

aphysis of the humerus consistently had higher percentages of the plutonium in the marrow than proximal or distal portions of the humeri or the lumbar vetebrae. Samples of radius frequently had too little plutonium in the marrow for calculating ratios.

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

Principal Investigator: C. L. Sanders

Other Investigators: J. A. Mahaffey, K. E. McDonald, and S. L. Newton

This project will produce data to generate a dose-response curve (and to evaluate other statistical methods that also incorporate survival time) for lung-tumor incidence in Wistar rats following inhalation of $^{239}PuO_2$ at levels producing lifetime radiation doses to the lung of <5 to >2,000 rad. The lung clearance of ^{239}Pu is best representated by a two-exponential equation, with 78% of the initial alveolar depositions (IAD) cleared with a half-time of 19 days and 22% cleared with a half-time of 180 days. A total of 593 of 2134 exposed and 242 of 1058 sham-exposed rats have died. Among the dead rats, the percent with primary lung tumors was 71% for the 150-nCi group, 70% for the 82-nCi group, and 23% for the 32-nCi group. No lung tumors have been found in controls, and only three have been found at an IAD of <7.5 nCi.

This project was designed to provide data for estimating the time/dose-response relationships of lung-tumor incidence in rats exposed by inhalation to $^{239}PuO_2$. The IAD are determined by whole-body-counting for ^{169}Yb calcined with the $^{239}PuO_2$ particles (Annual Report, 1983). The numbers of rats assigned to each exposure group were based on statistical analysis of previous higher-dose studies and on the historical frequency of primary lung tumors in untreated female, Fischer rats.

A group of 70 rats was exposed to an aerosol of ^{169}Yb, $^{239}PuO_2$, and the clearance of ^{239}Pu from the lung was determined from animals killed at 1, 3, 7, 14, 21, 28, 42, 63, 84, 126, 231, 336, 441 and 546 days after exposure. The group IAD for all rats was estimated to be 9.4 ± 0.4 nCi ^{239}Pu. Analysis of all data indicates that 78% of the inhaled ^{239}Pu was cleared from the lungs with a half-life of 19 ± 4.5 days, and the remaining 22% was cleared with a half-life of 180 ± 110 days (Figure 1). Analysis of lung weights from all rats indicates that a weight of 1.6 g is as useful in calculating radiation dose to the lung as the previous equation used for determining changes in lung weight with age (Annual Report, 1983).

The cumulative radiation dose to the lung from inhaled $^{239}PuO_2$, at time after exposure t, can be estimated by the equation:

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

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 (in nCi), based on whole-body counts for ^{169}Yb at 14 days after exposure and corrected for alveolar clearance from 0 to 14 days by the factor 1.11. L_t is the lung weight, taken to be 1.6 g, and Y(t) is the proportion of IAD in the lung at time t, given as:

$$Y(t) = 0.78e^{-0.037t} + 0.22e^{-0.0039t}.$$

The status of the lifespan study as of October 1984 is shown in Table 1. A total of 598 of 2194 exposed rats and 242 of the 1058 sham-exposed rats have died; histopathological evaluations have been completed on 286 of the exposed and 101 of the sham-exposed rats.

The degree of pulmonary fibrosis is significantly greater than in controls only at the 82- and 150-nCi levels. Nonsignificant increases in pulmonary fibrosis were also seen at the 17- and 32-nCi levels. The incidence was no different from that in controls at all lower exposure levels.

The incidences of squamous cell and adenomatous metaplasias were also related to exposure levels: 33 and 72% at the 82- and 150-nCi levels, respectively, and no different from those of controls at exposure levels of <17-nCi. Adenomatous metaplasias were seen at about the same frequency as squamous cell metaplasias (Table 2).

Other than lung tumors in high exposure levels, the most prevalent tumor types observed in all groups were pituitary adenomas and uterine tumors. Many of the pituitary tumors were large and were the probable cause of death. The uterine tumors were about two-thirds carcinomas and one-third sarcomas (mostly adenocarcinoma and leiomysarcoma, respectively). Irrespective of type, they were highly invasive, metastatic to the lung, and were the probable cause of death. Overall incidences of pituitary adenoma and uterine tumors were, respectively, 36 and 24%, irrespective of exposure group or age.

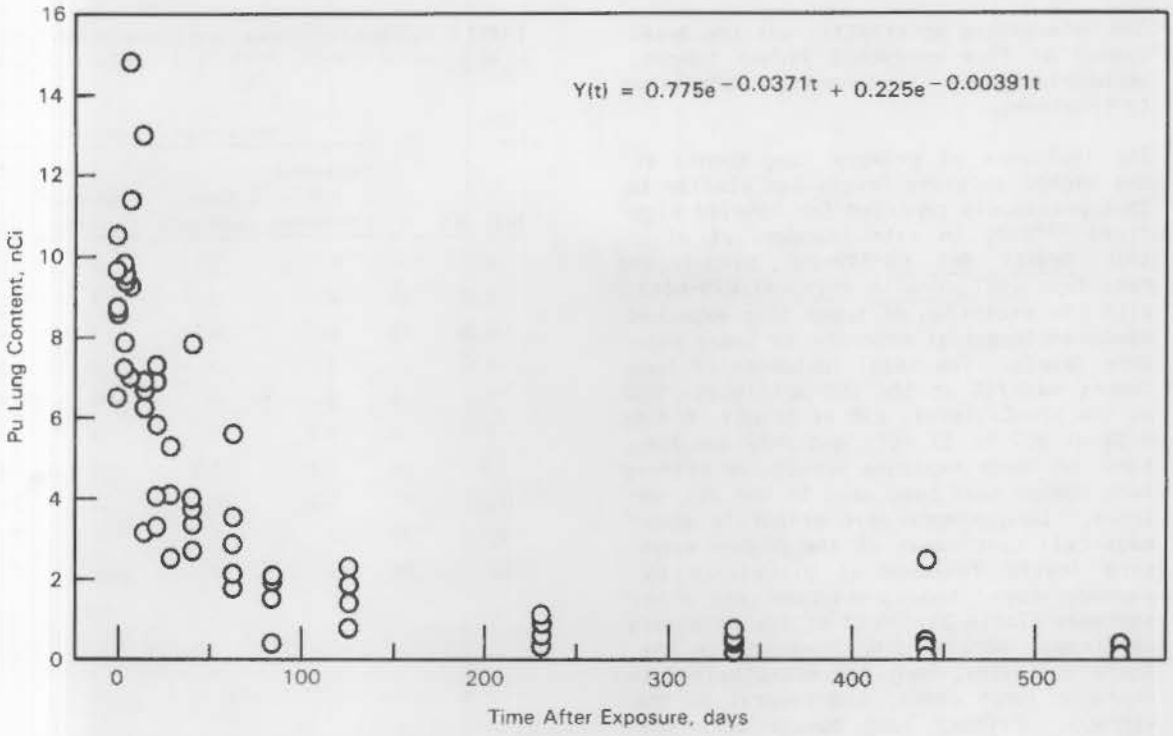

FIGURE 1. Amount of ^{239}Pu Present in Rat Lung as a Function of Time After Exposure. Each point represents the plutonium content in the lung of one animal as determined by liquid scintillation counting. The equation represents the best estimate of the clearance of plutonium from the lung.

TABLE 1. Status of the Inhaled $^{239}PuO_2$ Rat Lifespan Study as of October 1984.

	Number of Rats			
	Exposed		Control	
IAD, nCi	Alive	Dead	Alive	Dead
0.60	876	123	438	60
0.98	446	92	245	24
2.4	92	113	53	50
5.7	54	42	23	21
7.5	28	32	20	9
17	18	41	8	21
32	18	42	10	18
82	9	50	13	16
150	0	58	6	23
Totals	1541	593	816	242

TABLE 2. Incidence of Pulmonary Fibrosis and Metaplasias in Rats Exposed to an Aerosol of $^{239}PuO_2$, ^{169}Yb (N = Number of Animals).

			Percentage of Animals	
			Metaplasia	
IAD, nCi	N	Grade of Pulmonary Fibrosis[a]	Squamous	Adenomatous
0	101	0.17 ± 0.18	0	0
0.6	35	0.09 ± 0.28	2.9	0
0.98	15	0.10 ± 0.30	0	0
2.4	59	0.15 ± 0.40	1.7	1.7
5.7	12	0.27 ± 0.47	0	0
7.5	19	0.16 ± 0.37	0	0
17	30	0.63 ± 0.76	3.3	10
32	31	0.84 ± 0.90	6.5	19
82	27	2.33 ± 0.83	33	63
150	58	2.81 ± 1.00	60	72

[a] 0 = normal, 1 = very slight, 2 = slight, 3 = moderate, 4 = severe, 5 = extreme

One interesting observation was the development of five embryonic kidney tumors, nephroblastomas, in young rats, unrelated to treatment.

The incidence of primary lung tumors at the higher exposure levels was similar to that previously reported for inhaled high-fired $^{239}PuO_2$ in rats (Sanders et al., 1976, Radiat. Res. 68:349-360; Sanders and Mahaffey, 1981, Health Phys. 41:629-644), with the exception of fewer than expected adenocarcinomas at moderate to lower exposure levels. The total incidence of lung tumors was 71% at the 150-μCi level, 70% at the 82-nCi level, 23% at 32 nCi, 5.3 to 8.2% at 5.7 to 17 nCi, and only one lung tumor at lower exposure levels; no primary lung tumors have been seen in the 101 controls. Lung tumors were primarily squamous cell carcinomas at the higher exposure levels followed in prevalence by adenocarinoma, hemangiosarcoma and other sarcomas (Table 3). Most of the pulmonary carcinomas were highly invasive in the thoracic cavity; many had metastasized to thoracic lymph nodes, and several to the kidneys. Primary lung tumors were the probable cause of death in most of the high-level-exposure animals.

TABLE 3. Incidence of Primary Lung Tumors in Rats Exposed to an Aerosol of $^{239}PuO_2$, ^{169}Yb (N = Number of Animals).

		Percentage of Animals			
IAD, nCi	N	Squamous Cell Carcinoma	Adeno-carcinoma	Hemangio-sarcoma	Total
0	101	0	0	0	0
0.60	35	0	0	0	0
0.98	15	0	6.7	0	6.7
2.4	59	0	0	0	0
5.7	12	0	0	0	8.3
7.5	19	5.3	0	0	5.3
17	30	3.3	3.3	0	6.7
32	31	3.2	16	0	23
82	27	48	15	3.7	70
150	58	43	12	10	71

• Cigarette Smoke and Plutonium

Principal Investigator: R. E. Filipy

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

Technical Assistance: R. F. Flores, K. E. Lauhala, and B. G. Moore

Autoradiographic techniques with liquid photographic emulsion and cellulose nitrate track-etch film are being used to investigate the spatial distribution of inhaled plutonium in the lungs of beagle dogs exposed to cigarette smoke or to the plutonium aerosol only. More plutonium than expected was detected on the inner surfaces of bronchi, and particles were observed beneath the bronchial mucosa.

The major objective of this project is to obtain experimental data on whether cigarette smokers are at a greater risk than nonsmokers to potential health effects of inhaled plutonium. Research efforts during the past year have been directed toward determining the effect of cigarette-smoke exposure on the spatial distribution of inhaled plutonium in the lungs of beagle dogs. Differences in deposition and/or retention sites of plutonium particles could result in irradiation of various cell populations within the lung, some of which are more susceptible to malignant transformation than others.

Beagle dogs were exposed to cigarette smoke and/or a plutonium aerosol, as shown in Table 1. The dogs of Groups 1 and 2 were exposed to cigarette smoke daily for approximately 6 months before Group 2 dogs received a single inhalation exposure to plutonium. Cigarette-smoke exposure of Groups 1 and 2 continued for approximately 400 days thereafter. Dogs of Group 3 were also exposed to the plutonium aerosol but received no smoke exposure either before or after the plutonium. On the last day of smoke exposure, the dogs were killed by exsanguination under deep anesthesia, and the lobes of their lungs were fixed individually by vascular perfusion with 1.5% buffered glutaraldehyde.

An autoradiographic technique, developed as part of this program, was used to determine the distribution of plutonium particles in the major pulmonary airways of two lung lobes (left apical and cardiac) from five of the dogs, one dog from Group 1 and two dogs each from Group 2 and 3. The technique was described in a previous report (1983). Briefly, it involved stripping the parenchyma from the airways to the approximate level of the tertiary bronchi, splitting segments of the airways, and pressing the inside surface of each segment against cellulose nitrate track-etch film for 6 weeks. At the end of that time, the pieces of film were

TABLE 1. Protocol to Determine the Effect of Cigarette-Smoke Exposure on Clearance of Plutonium from the Lungs of Beagle Dogs.

Group	Number of Dogs	Exposure
1	6	Smoke Only
2	6	$^{239}PuO_2$ + Smoke
3	6	$^{239}PuO_2$ Only

etched in a 4N NaOH solution at 60°C for 150 minutes and mounted on a glass microscope slide. An example of the exposed and etched film is shown in Figure 1. The number of films (usually, approximately 2 x 2 cm) per bronchial tree varied between 20 and 35, depending on the length of airway that could be isolated from parenchyma.

As a first approach toward quantifying the amount of plutonium detected on the inside surfaces of the pulmonary airways, the films were subjectively graded according to the density of alpha-particle-induced etched pores (tracks) observed by low-power microscopy. A grade of "1" was assigned if only a few alpha tracks were observed; a grade of "5" was assigned to films containing the greatest concentration of tracks. In order to compare the spatial distribution of plutonium within the lung lobes of the five dogs, the airway segments were categorized as follows:

1. primary bronchus only,
2. main lobar bronchi (except the terminal segment) after the first branch,
3. segments of bronchial branches between the terminal segment and the main bronchus,
4. terminal segments of the main bronchi and of the bronchial branches.

FIGURE 1. Photomicrograph of Track-Etch Film to Which a Plutonium Concentration Grade of "2" was Assigned.

Terminal segments were approximately 2 mm in diameter, the smallest size that could be isolated from the parenchyma and split for compression against film.

Average grades assigned to categories of bronchial-tree segments from the left apical and cardiac lung lobes of four plutonium-exposed dogs are listed in Table 2. The data indicate that the smallest bronchi contained the greatest concentrations of plutonium particles, and the main bronchi contained only small concentrations. There is no apparent relationship between particle concentration and lung clearance or exposure to cigarette smoke. The values for Dog #1700 are artificially low, especially for Category 4, because the entire cardiac lobe had very low bronchial concentrations of plutonium. If only the apical lobe was considered, the values in Category 4 and the average grade would be very similar to the corresponding values for the other three dogs. The bronchi of Dog #1736 (cigarette smoke only) contained no detectable radioactivity.

Liquid-emulsion, cross-sectional autoradiographs were made from small portions of each bronchial segment removed before the track-etch film technique was applied. Figure 2, a photomicrograph of one of those sections, shows plutonium particles detected within the lamina propria of a bronchus. Several such instances have been observed in preliminary examination of these autoradiographs. Frequently, the particles were close enough to the epithelial layer so that basal epithelial cells were within range of the alpha radiation. The phenomenon of insoluble particles beneath the mucosa of pulmonary airways has been reported previously in the scientific literature. Speculations about their entry range from penetration through the mucosa to penetration from the parenchymal side of the wall. We cannot deduce the mode of entry from the autoradiographs, nor even whether the particles were contained within macrophages.

Two aspects of the autoradiographic results are of radiological interest: 1) the high concentrations of plutonium particles observed on bronchial surfaces 400 days after a single exposure and 2) the presence of plutonium particles beneath the bronchial mucosa in the lamina propria. These factors are of interest because the basal, dividing cells of the mucosa, which are highly susceptible to malignant transformation, are within range of alpha radiation from particles in both locations.

Future research efforts will be directed toward quantifying of the plutonium contained in the pulmonary airways. One approach will be to make standard track-etch autoradiograms from surfaces, such as filters, containing known amounts of plutonium particles of respirable size. An effort will then be made to compare the bronchial autoradiograms with the standards, using an image-analyzing computer. Also, lungs from the remaining four dogs per group will be processed for track-etch autoradiography.

TABLE 2. Average of the Subjective Grades of Alpha Activity Assigned to Track-Etch Film Pressed Against the Inner Surfaces of Bronchi of Plutonium-Exposed Beagle Dogs.

				Subjective Grade (0-5)				
		Plutonium Lung Burden		Segment of Bronchus				
Dog No.	Group	Initial, nCi	At Death, %	1	2	3	4	Average of All Segments
1736	1	--	--	0	0	0	0	0
1700	2	915	80.3	0.5	0.7	1.8	1.2	1.0
1722	2	1150	86.5	0	0.3	1.8	2.2	1.4
1668	3	1340	67.2	0	0.9	1.5	1.9	1.4
1733	3	1460	68.5	--[a]	1.1	2.6	2.6	2.2

[a]No sample of primary bronchus

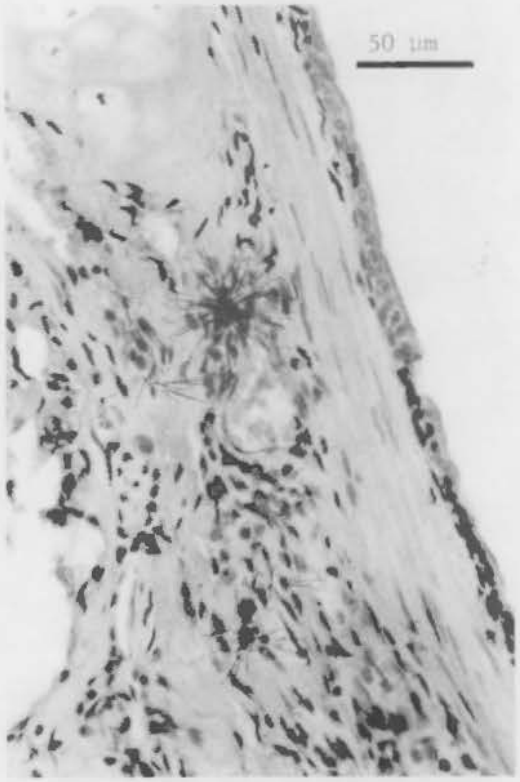

FIGURE 2. Photomicrograph of a Liquid Photographic Emulsion Autoradiograph of Bronchial Wall from a Beagle Dog Exposed to $^{239}PuO_2$.

• Toxicity of Thorium Cycle Nuclides

Principal Investigator: J. E. Ballou

Other Investigators: R. L. Buschbom, A. C. Case, G. E. Dagle, R. A. Gies, and J. L. Ryan

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 ^{233}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 kinetics in major tissues and metabolic data have been presented in previous Annual Reports. Dose-response relationships for malignant lung-tumor induction are discussed below.

Cumulative radiation dose to lung, the tissue most affected by ^{231}Pa inhalation, was calculated from the quantity of ^{231}Pa measured in the lung at death, assuming a generalized lung retention curve for the pooled data. The lung retention curve was derived by fitting a multiexponential function to data for individual rats that died and were analyzed during the lifespan study. Estimated lung doses were divided into dose ranges for presentation in Figure 1. Data points are simply plotted within the indicated order-of-magnitude dose ranges on the abscissa and are not positioned at any specific value within those ranges.

The lung-tumor response to inhaled ^{231}Pa citrate was in good agreement with results we have observed in similar studies with other inhaled actinide nitrates (Figure 1). Peak tumor incidence (73%) for ^{231}Pa was observed in the 24 rats that sustained a cumulative radiation dose >1000 rad to lung; pulmonary adenocarcinomas were the primary lesions induced by these soluble materials.

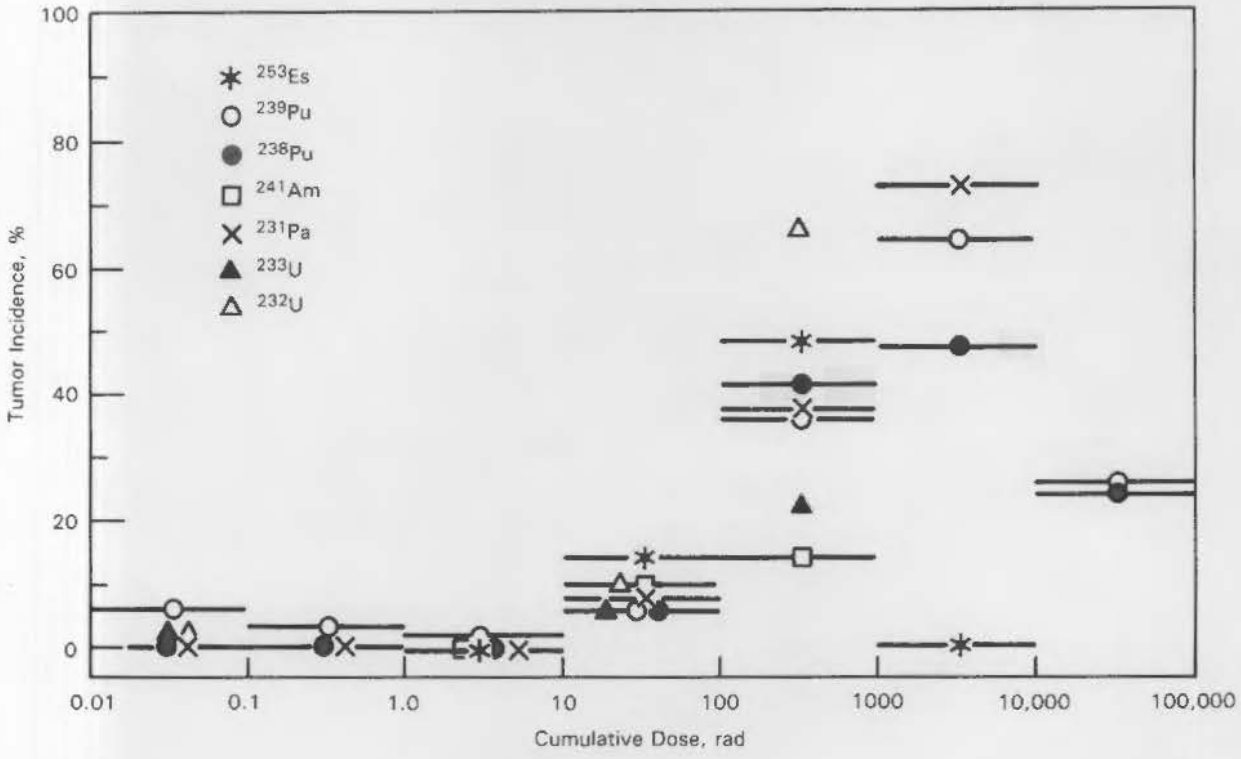

FIGURE 1. Incidence of Malignant Lung Tumors in Rats Exposed to Inhaled Actinide Nitrates.

Malignant lung-tumor incidences are also shown in Figure 1 for male Wistar rats exposed to inhaled $^{233}UO_2(NO_3)_2$ and $^{232}UO_2(NO_3)_2$ aerosols.

The ^{232}U dose indicated in Figure 1 is the minimal lung dose since it includes no contribution from ^{232}U decay products. Studies are now in progress to estimate the steady-state, in vivo concentrations of ^{232}U, ^{228}Th, ^{224}Ra, ^{212}Pb and ^{212}Bi to help define the daughter product dose. Preliminary observations indicate that the overall effect will shift the ^{232}U data points in Figure 1 to the right, perhaps by as much as an order of magnitude, in compensation for the daughter product dose.

The dynamic nature of the in vivo relationships among ^{232}U and its daughter products is illustrated in Figure 2. Rats were intratracheally instilled with $^{232}UO_2(NO_3)_2$ plus daughters and were killed after 1 hour, 1, 7, 28, 56, 112 and 161 days. Tissues (lung, kidney, femur, liver, muscle and/or blood) were removed rapidly at necropsy, sealed in plastic counting vials and analyzed directly by high-resolution gamma spectrometry, using intrinsic germanium detectors. The disposition of the various radioelements in lung (Figure 2) illustrates marked differences in metabolism that are already apparent within the first hour and appear to be maintained up to 56 days after administration. Data beyond 56 days are not yet available.

Similar data for ^{232}U daughter disposition in kidney, skeleton and liver further illustrate the complex nature of the retention curves (Figure 2). Since the short-lived daughters continue to be produced in vivo from their long-lived parents, the usual decreasing functions are often followed by a growth in daughter product activity reflecting this ingrowth from the parent. It is anticipated that the disposition of daughter products after a more prolonged time interval of 100-150 days may more nearly represent the steady-state distribution relationships and should provide information needed for dose calculations.

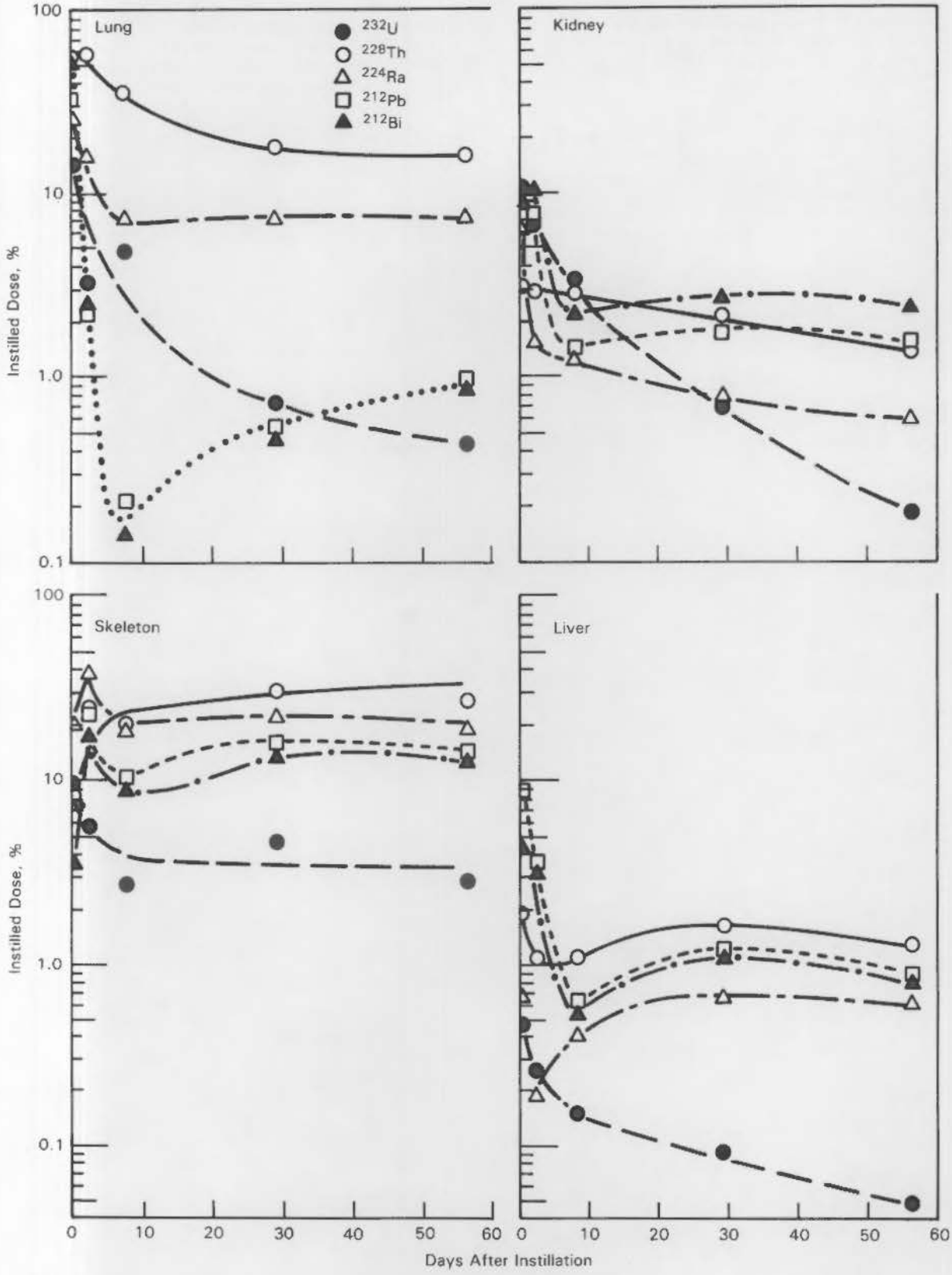

FIGURE 2. Retention of Intratracheally Instilled $^{232}UO_2(NO_3)_2$ Plus Decay Products in Lung, Kidney, Skeleton, and Liver in Rats.

• Inhalation Hazards to Uranium Miners

Principal Investigator: F. T. Cross

Other Investigators: R. L. Buschbom, G. E. Dagle, R. A. Gies, and R. F. Palmer

Technical assistance: R. M. Briones, 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. Histopathologic data from rats are shown for approximately 300- to 10,000-working-level-month (WLM) radon-daughter exposures. Exposure of male rats to radon daughters and uranium ore dust continues, along with exposure of male and female beagle dogs to uranium ore dust alone.

Small-Animal Studies

Approximately 1000 male, specific-pathogen-free, Wistar rats are currently on study; the 6000 and 7000 Series experiments (Table 1) 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 2) are designed to extend the exposure-response relationships to levels appropriate to current conditions in the mines and to lifetime environmental exposures. The 9000 Series experiments (Table 3) continue the "low-dose" studies at exposure rates comparable to former occupational working levels (10 WL). They will help to further evaluate the hypothesis that the tumor probability per WLM exposure increases with decrease in exposure and exposure rate. In addition, concurrent exposure to varying levels of uranium ore dust tests 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 6000, 7000 and 8000 Series animals are completed; some of the 8000 Series animals are still living.

We have concluded that the most significant lesions related to radon-daughter and carnotite-ore-dust exposures in the 6000 Series experiments are neoplastic and nonneoplastic lesions of the respiratory tract. Histopathologic data for these lesions in serially sacrificed animals

TABLE 1. Exposure-Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (6000 and 7000 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	160

[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 2. Low-Exposure Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (8000 Series Experiments).

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.

TABLE 3. Ultralow Exposure Rate Study for Radon-Daughter Carcinogenesis in Rats (9000 Series Experiments).

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

were shown in the 1983 Annual Report. These data indicated that the earliest lung cancers generally occurred approximately 1 year following completion of exposures. At exposure levels less than 1280 WLM, no lung cancers were observed earlier than 18 months after exposure.

The current summary of tumors primary to the rat lung in the 6000 Series experiments is shown in Table 4.

TABLE 4. Current Summary of Primary Tumors of the Respiratory Tract (6000 Series Experiments).

Nominal Exposure, WLM	Animals Examined	Nasal Carcinoma	Lung Tumors: Adenoma	Adenocarcinoma	Epidermoid Carcinoma	Adenosquamous Carcinoma	Sarcoma[a]	No. of Animals with Respiratory Tract Tumors
10,240	52	3	2	27	7	3	2	33
5120	41	1	1	17	1	0	2	21
2560	38	0	0	10	1	0	1	12
1280	38	2	0	10	0	1	0	12
640	70	1	2	5	0	0	0	8
320	68	0	6	1	1	0	0	8
Controls	45	0	0	0	0	0	0	0

[a] Sarcomas include 2 hemangiosarcomas, 1 mesothelioma, 1 undifferentiated sarcoma, and 1 malignant mixed lung tumor.

Large-Animal Studies

Eighteen (nine exposed and nine controls) of 35 beagle dogs remain on study to determine the pathogenic role of carnotite uranium ore dust in inhalation exposure. We are particularly interested in clarifying the role of ore dose 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 years 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 years (a comparable exposure time to the earlier study) are vesicular emphysema, peribronchiolitis and focal pneumoconiosis. These lesions, described in the 1981 Annual Report, are in contrast to the comparatively more severe lesions observed in the earlier study, in which beagle dogs were exposed to mixtures of radon daughters, uranium ore dust and cigarette smoke.

Renal function was evaluated on six uranium-ore-dust-exposed and six sham-exposed dogs following 6 years of exposure for 20 hours/week to 15 mg/m^3 uranium-ore-dust concentrations (1983 Annual Report). With the exception of elevated glucose levels, results of a battery of tests were equivalent for the exposed and sham-exposed dogs, leading to the conclusion that kidney function had not been appreciably compromised by 6 years exposure to uranium ore dust.

The animals, to date, have received 7½ years 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, D. N. Rommereim, and L. B. Sasser

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

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 rapidly growing infants or children and for pregnant women.

Further dosimetry for an experiment to evaluate the effects of foster-rearing of newborn rats on the lifetime effects of ^{239}Pu exposure has demonstrated that most of the lifetime burden is derived from prenatal exposure and that milk contributes little in addition. Other measurements have confirmed our tentative observation that the lifetime burden in offspring is greater with near-term exposure than with exposure earlier in gestation. Additional results from a comparison of the embryotoxicity of ^{239}Pu and ^{241}Am have confirmed that, on the basis of dose administered to the dam, the former has a greater effect on the conceptus. Pilot studies indicate that ^{233}U is teratogenic, acting as a chemical rather than as a radiological teratogen. Studies with ^{239}Pu-exposed pregnant rabbits have shown that maternal distribution differs from that in rodents; concentration patterns in the placenta and membranes also differed.

The protocol and some results from a study to examine the influence of foster-rearing of ^{239}Pu-exposed neonatal rats on late effects were reported in last year's Annual Report. 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, and the offspring from some litters were fostered to other dams at 1 day of age to form six experimental groups. In addition to two control (citrate) groups, there were four groups of exposed offspring: exposed pups that were kept with their natural mother (exposed); pups fostered between exposed mothers (exposed-exposed); exposed pups fostered to a control mother (exposed-control); and control pups fostered to an exposed mother (control-exposed).

The content and concentration of ^{239}Pu in representative organs during prenatal and postnatal development were presented in last year's report. Carcasses from animals that were killed at various times between birth and 22 days of age (and also at 1 year of age) have been subjected to radioanalysis. The resulting values were added to those in structures analyzed separately to obtain the total-body plutonium content, which includes nuclide in the gastrointestinal tract (Figure 1).

The 24-nCi burden at 1 day of age in the exposed, exposed-exposed, and exposed-control groups corresponds to about 0.1% of the injected ^{239}Pu dose and represents the total contribution from placental transfer. (Those in the control-exposed group had not yet received any plutonium.) The low rate of plutonium loss with time in the exposed-control group represents the retention pattern in neonatal rats with a prenatally obtained body burden; i.e., rats in this group received no further plutonium. In both the exposed and the exposed-exposed groups, which received further plutonium via milk, the body content progressively increased (by more than 50%) during the first 2 weeks of age. This appears to be primarily from plutonium contained within the gastrointestinal tract, since the slope of this curve closely paralled that in the control-exposed group, which received plutonium only via milk. The marked loss of activity after 2 weeks of age, when the animals began eating solid food, was similar in these three groups, but body burdens in exposed and exposed-exposed groups were slightly (not statistically significant) greater than that in the exposed-control group. At all time periods studied, the sum of the plutonium contents of the rats in the control-exposed and exposed-control groups approximately equaled those in the exposed and exposed-exposed groups.

In all four age groups, the body burden remaining at weaning was retained quite tenaciously. No attempt was made to fit a

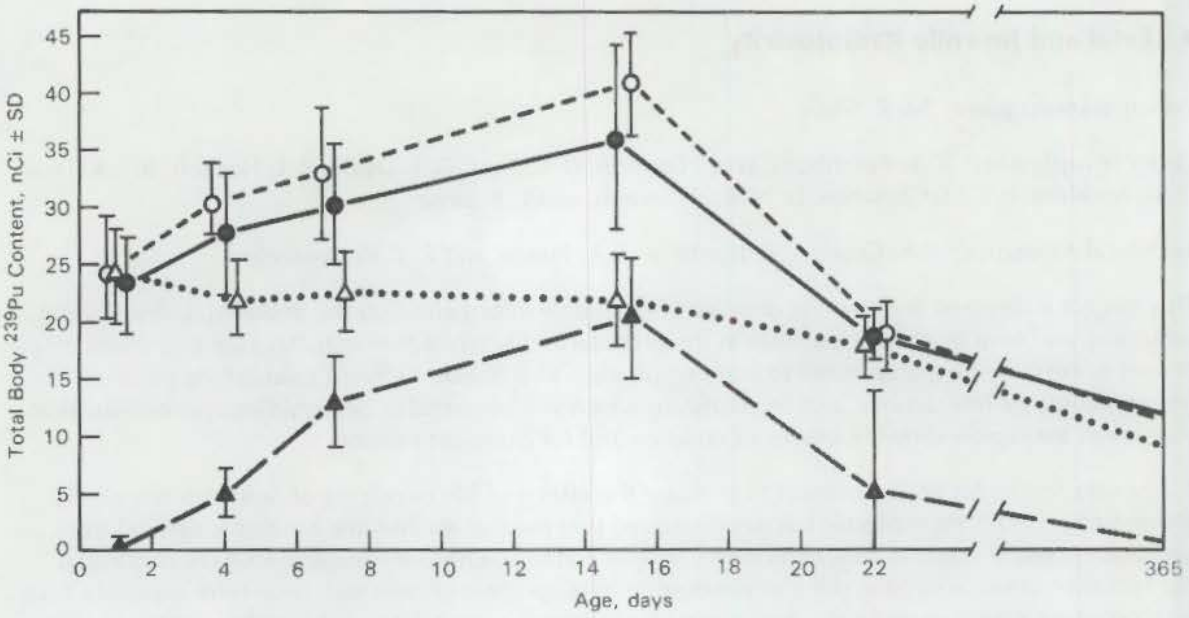

FIGURE 1. Total Body Content of Rats Exposed to ^{239}Pu Via Placental Transfer Only (•••••, Exposed-Control); Milk Only (— — —, Control-Exposed); or Via Placental Transfer and Milk (———, Exposed; — • — •, Exposed-Exposed).

specific relationship to the data since values were not available at intermediate times; nevertheless, the straight line connecting the values at 22 and 365 days of age were parallel for the four groups, reflecting the patterns indicated above.

We previously described (Annual Report, 1978) the prenatal and neonatal distribution and retention of plutonium in offspring from pregnant rats exposed to ^{239}Pu citrate preparations at 9, 15 or 19 dg. These tissues were obtained from animals in a study to evaluate the late effects of ^{239}Pu relative to prenatal stage at exposure, and data were limited for the neonatal period; none were available for the remainder of the first year of life. To obtain additional ^{239}Pu-exposed tissues, pregnant rats at these stages of gestation were injected intravenously with 30 µCi/kg of the same plutonium citrate preparation used previously. Offspring were killed at birth and at several sequential times through 1 year of age (Figure 2).

The concentrations of plutonium in the liver and skeletal elements of rats killed at birth were similar to those reported previously. The present data set, which involved larger group sizes, more clearly defined the suggestive differences among the three age groups: in nearly all instances, concentrations were significantly higher in the animals exposed at 19 dg, less at 15 dg and least at 9 dg. The retention patterns in the skeletal elements were similar to those reported earlier. The questionable liver retention in offspring exposed at the later times was not observed; instead, liver retention tended to decrease with time. Concentrations continued to decrease progressively through 60 days of age, although they were not exponential since they primarily reflected the growth of the offspring. Thereafter, bone concentrations continued a slight progressive decrease, although almost all skeletal elements continued to receive low-dose radiation exposures throughout the 30-month duration of the study.

As part of our continuing effort to obtain comparative data on relative actinide distributions in maternal and fetal placental tissues, stored samples obtained during a study of ^{239}Pu effects in pregnant and fetal rabbits (Annual Report, 1980) were subjected to radioanalysis, and the data were evaluated. In these studies, 10 µCi/kg of ^{239}Pu was administered at 9, 15, or 28 dg; some does were killed 24 hours later, and others at 29 dg.

Concentrations of plutonium in maternal blood and in the skeletal elements (e.g., calvarium, vertebrae, and femur) at 24 hours after administration were significantly higher in does exposed at 28 dg than in those exposed at 9 or 15 dg (Figure 3). The concentrations in the skeletons of does injected at the two earlier

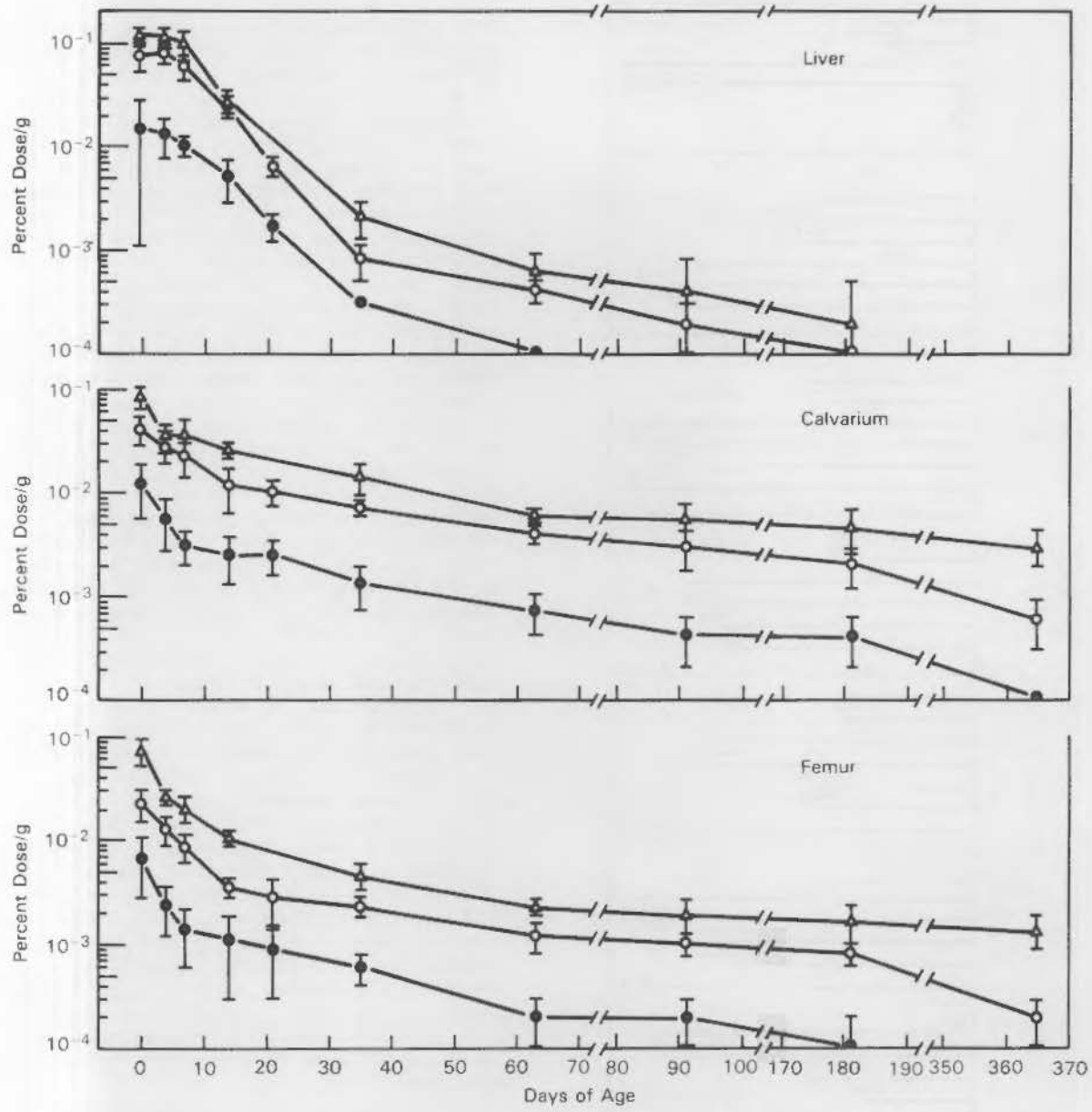

FIGURE 2. Initial Postnatal Concentration and Retention (Percent Dose Per Gram Tissue) in Representative Tissues of Offspring of Rats Injected with ^{239}Pu at 9 (●), 15 (○), or 19 (Δ) Days of Gestations. Vertical bars display standard deviations.

times and killed at 29 dg were similar to those of animals injected at 28 dg and killed at the same gestational stage. Liver concentrations at 24 hours after administration were substantially less in animals injected at 28 dg than in those injected at 9 or 15 dg. The concentration in the liver increased by the end of gestation in those injected at 9 or 15 dg. This pattern of a progressive increase in liver concentrations is similar to that reported for nonpregnant rabbits but differs from that in rats and mice, and suggests a species difference in the disposition of monomeric plutonium. The concentrations of plutonium in the placentas and extrafetal membranes were not nearly so high as those reported in the rat and mouse, and the ratio of concentrations between the two structures was not as dramatic as in rodent studies. However, this disparity may reflect species differences in total mass of membranes relative to mass of villous yolk sac, the placental structure in which most of the plutonium is deposited.

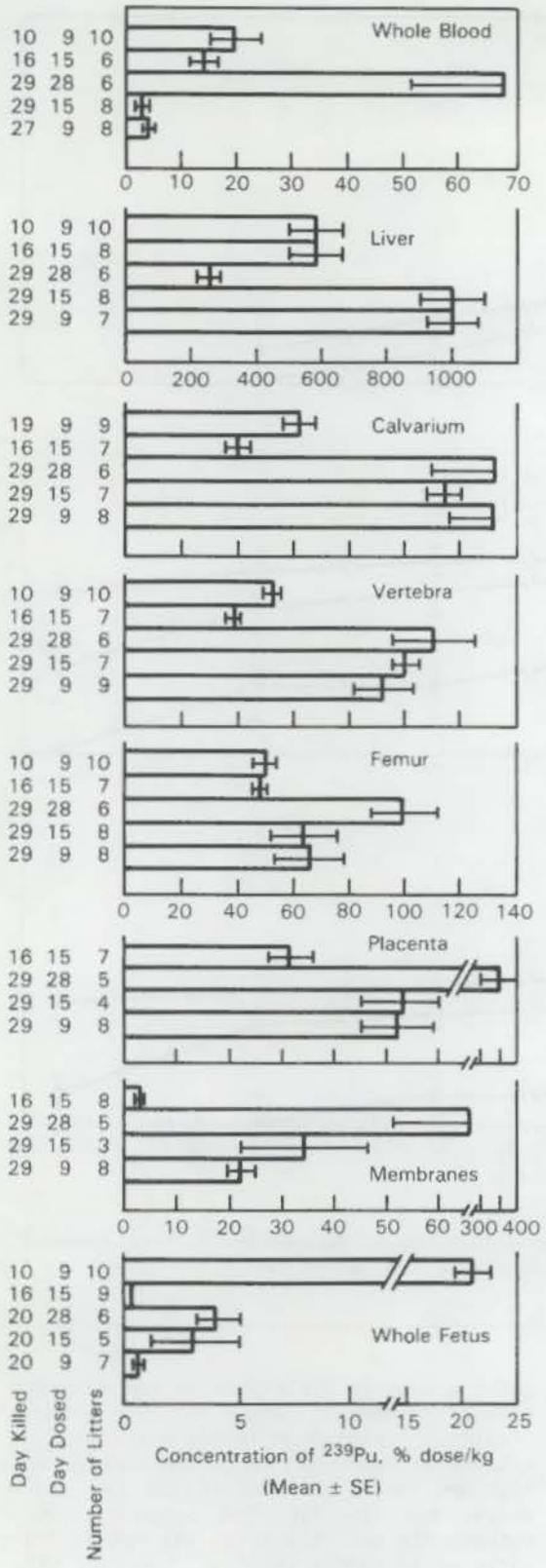

FIGURE 3. Concentration of ^{239}Pu in Maternal and Fetoplacental Tissues of Rabbits Injected at 9, 15, or 28 Days of Gestation.

The design and preliminary data from an experiment to obtain contemporaneous comparisons of dosimetry and toxicity of ^{241}Am and ^{239}Pu in embryos was presented in last year's Annual Report. The developmental toxicology portion of the study has been completed, and increased group sizes were obtained; radioanalysis of additional tissues obtained for dosimetry is still incomplete. The effects relative to administered dose are essentially as previously reported. As an extension of this study, we obtained preliminary data on the embryotoxicity of ^{233}U, using controls from the latter portion of the americium-plutonium study for comparisons. Pregnant animals were injected intravenously with ^{233}U solutions prepared in the same manner as for the other transuranics, so that a constant amount of citrate was injected throughout. Doses were selected to extend the incomplete matrix design employed for the plutonium and americium: the high radiological doses of uranium corresponded to the low dose of plutonium, and the low dose was one-third of the high dose. This dose range extended into the chemically toxic range for adult animals, as confirmed by the death of three of six animals injected at the higher dose level. In the two pregnant rats available at the lower dose, results were indistinguishable from those in controls. At the higher dose, however, prenatal mortality was increased, and both fetal and placental weights were lower than those of controls (Table 1). Despite the small sample size in this pilot study, it may be important that cleft palate was detected in fetuses from all three litters and bent limbs in fetuses from two of the three litters, whereas these lesions were not seen elsewhere in the study. Further evaluations will provide a quantitative assessment of the dose-response relationships and more detailed dosimetry.

The affinity of the maternal liver for americium and plutonium may be involved in the distribution, and thus the toxicity, of these radionuclides. Observed differences between subsequent redistribution patterns may be due to differences in binding properties in tissues. We speculated that metallothionein, a low-molecular-weight, cytoplasmic protein with a high affinity for many metals, may regulate the metabolism and/or storage of actinides in the body. Its role may be age-related, since endogenous concentrations are 20-fold greater in the late fetus or neonate than in the adult rat. Accordingly, liver samples were obtained from adult and fetal rats killed 24 hours or 5 days after exposure to 30 μCi/kg of ^{241}Am or ^{239}Pu. Heat-treated cytosol prepara-

TABLE 1. Effect of Exposure of Rats at 9 Days of Gestation (dg) to ^{233}U on Size and Morphology of Fetuses at 20 dg.

	^{233}U Dose, μCi/kg Body Weight		
	0	3.33	10.0
Number of Litters Evaluated	13	2	3
Implants/Litter[a]	13.5 ± 3.0	16.5 ± 2.1	13.7 ± 5.0
Deaths/Litter[a]	0.5 ± 0.7	0.5 ± 0.7	3.3 ± 5.8
Fetal Weight, g[b]	3.2 ± 0.3	3.3 ± 0.0	1.8 ± 0.7
Placental Weight, g[b]	0.43 ± 0.06	0.41 ± 0.05	0.28 ± 0.03
Number of Skeletons Examined	167	30	28
Cleft Palate[c]	0	0	9/3
Bent Limbs[c]	0	0	17/2
Wavy, Bent or Knobby Ribs[c]	1/1	0	26/3

[a] Mean ± SD
[b] Mean of litter means ± SD
[c] Expressed as number fetuses/number litters affected

tions were chromatographed on G-75 Sephadex and analyzed by scintillation spectrophotometry for ^{241}Am or ^{239}Pu content in the metallothionein fraction. A typical gel filtration profile of maternal liver cytosol is shown is Figure 4. The small amounts of both nuclides associated with a metallothionein-like fraction (molecular weight, approximately 10,000) may represent nonspecific binding; americium appears to have a greater affinity for this material than does plutonium. Unlike the binding of many heavy metals, most of the actinide activity was in a peak corresponding to high-molecular-weight molecules. Because of low placental transfer, we were unable to determine the presence of ^{241}Am or ^{239}Pu in the metallothionein fraction of fetal liver; in vitro labeling studies are planned to determine whether fetal metallothionein has an affinity for the actinides.

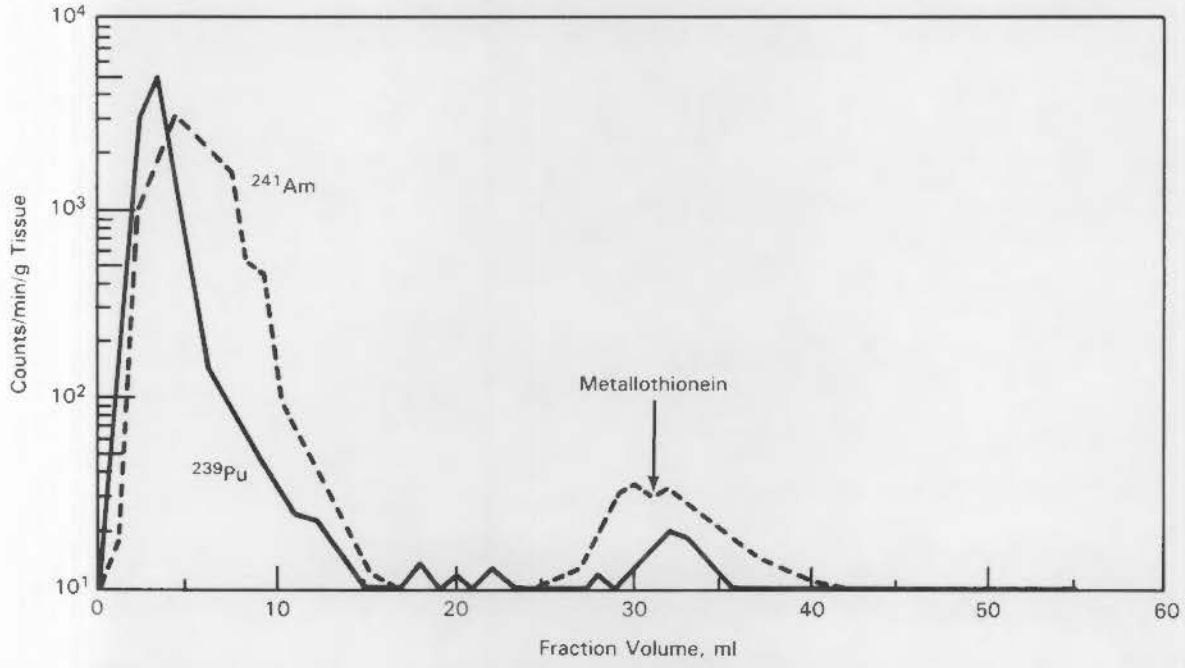

FIGURE 4. Gel Filtration Elution Profile of Heat-Treated Liver Cytosol Obtained from Adult Rats Injected with ^{241}Am or ^{239}Pu.

Mutagenesis

• Mutagenicity of Complex Mixtures

Principal Investigator: R. A. Pelroy

Other Investigators: D. L. Stewart

The effect of coal-derived complex chemical mixtures on the mutagenicity of 6-aminochrysene (6-AC) was determined with *Salmonella typhimurium* TA98. Previous results suggested that the mutagenic potency of 6-AC for TA98 in the standard microsomal activation (Ames) assay increased if it was presented to the cells mixed with high-boiling coal liquids (CL) from the solvent refined coal (SRC) process. In this year's work, the apparent mutational synergism of CL and 6-AC was independently verified in a fluctuation bioassay which allowed quantitation of mutational frequencies and cell viability. The results of this assay system were similar to those in the Ames assay. Moreover, the fluctation assay revealed that mutagenesis and cellular toxicity induced by 6-AC were both strongly enhanced if 6-AC was presented to the cells mixed in a high-boiling CL.

The fluctation mutagenicity bioassay system, which allows direct measurements of both mutagenesis and viability, was used to determine the effect of a CL on the genetic potency of 6-AC for S. typhimurium TA98. As shown in Figure 1, the mutational frequencies for 6-AC plus an EDS 850+°F boiling-point coal distillate (designated 040) were from 10 to >100 times greater than those for 6-AC alone. These measurements were based on the number of revertants of TA98/viable cell, and they are independent, over at least several orders of magnitude, of cell killing. These data strongly support our interpretation of the standard Ames assay data that synergistic effects between 6-AC and CL enhance the potency of 6-AC.

Additional support is given to this theory by the fact that the mixture of 6-AC plus 040 appeared to induce extensive killing of TA98 (Figure 2), ranging from ~50% (at 0.005 μg 6-AC/ml exposure medium) to >95% (0.01 to 0.02 μg 6-AC/ml exposure medium). This is the effect anticipated, since enhanced DNA damage leading to mutation (Figure 3) would likely cause cell death, especially at higher levels of 6-AC.

In contrast to results for 6-AC, the mutagenic potency of benzo[a]pyrene or 1-nitropyrene plus 040 did not appear significantly greater than for these chemical mutagens alone (Figure 4).

Finally, the enhanced mutagenesis of 6-AC plus 040 versus that of 6-AC alone was strongly dependent, in the fluctuation assay, on metabolic activation by S9. However, these data do not show whether the effects leading to enhanced mutagenesis are at the level of the activating enzymes or at the target cell (TA98) level, or both. Future work will be directed to investigating possible mechanisms by which CL enhances the mutagenic potency of 6-AC and other amino polycyclic aromatic hydrocarbons.

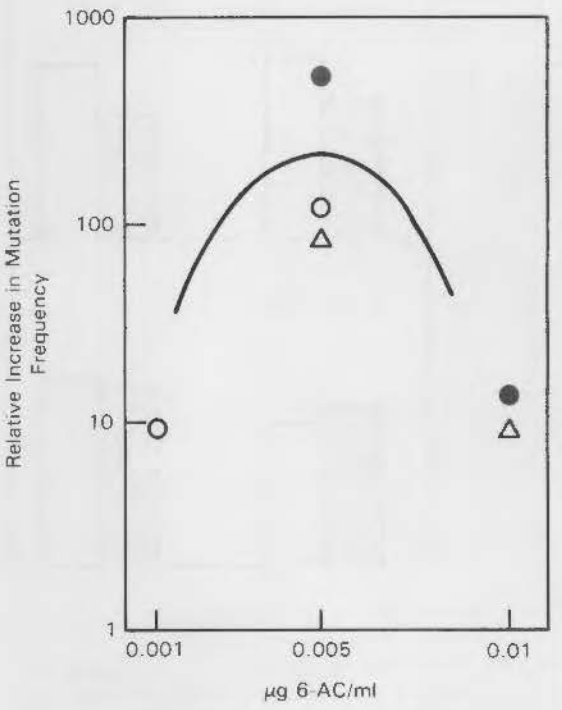

FIGURE 1. Relative Increase in Mutation Frequency in Cells of *S. typhimurium* TA98 Exposed to 6-AC Plus the EDS 850°+F (040) Coal Distillate Versus that for Cells Exposed to 6-AC Alone. Concentrations of 6-AC are as indicated; concentration of EDS 850°+F (040), when present, was 5 μg/ml exposure medium. Relative mutation frequencies are expressed as the ratio of revertants TA98/viable cell for cells exposed to 6-AC plus 040 to revertants TA98/viable cell for 6-AC alone. All assays were carried out in the presence of Aroclor-induced rat liver microsomes (S9). All responses were significant at $P < 10^{-3}$, based on chi-square statistical tests. Symbols identify three different experiments.

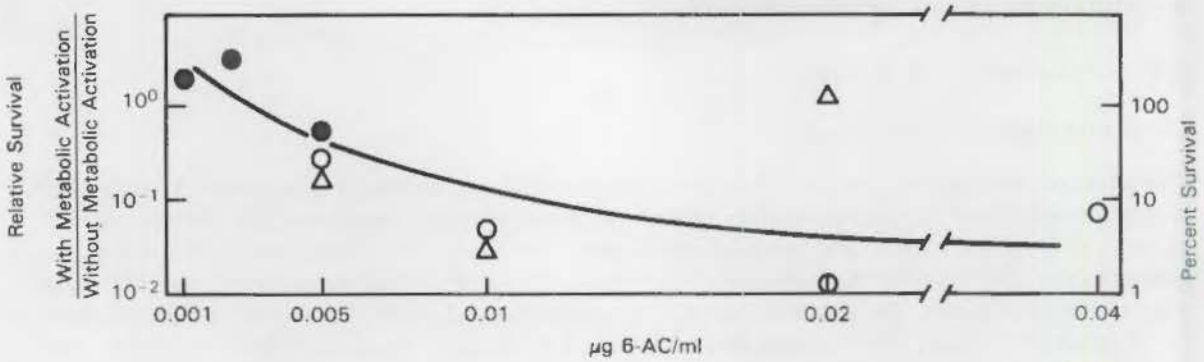

FIGURE 2. Relative Survival of *S. typhimurium* TA98 Exposed to 6-AC Plus EDS 850°+F Coal Distillate (040) Versus that of Cells Exposed to 6-AC Alone. Survival is expressed as the ratio of viable cells TA98 exposed to 6-AC plus 040 to viable cells TA98 exposed to 6-AC alone. Levels of 6-AC are as indicated; concentration of 040 (when present) was 5 μg/ml. All assays were carried out in the presence of Aroclor-induced rat liver microsomes (S9). Symbols identify three different experiments.

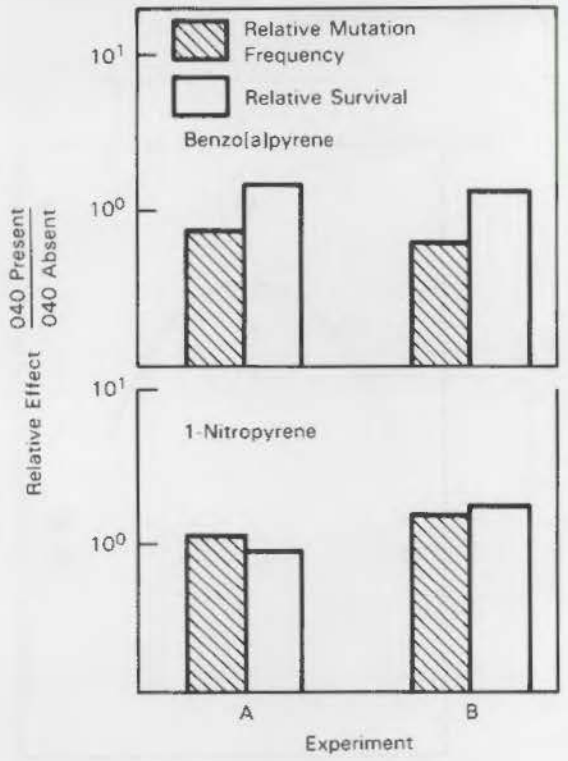

FIGURE 3. Relative Changes in Mutation Frequency and Survival for Cells of *S. typhimurium* TA98 Exposed to Benzo[a]-pyrene Plus or Minus EDS 850°+F Distillate (040) and 1-Nitro-pyrene Plus or Minus 040. Relative mutation frequency is expressed as the ratio of revertants TA98/viable cell plus 040 to revertants TA98/viable cell minus 040. Similarly, relative survival is expressed as the ratio of viable cells TA98 exposed to 040 (plus chemical) to viable cells TA98 exposed to chemical alone. Benzo[a]pyrene was present in the exposure medium at 10 μg/ml; 1-nitropyrene at 0.2 μg/ml and 040 at 5 μg/ml. All assays were carried out in the presence of Aroclor-induced rat liver microsomes (S9). All mutational responses (plus or minus 040) were significant at $P < 10^{-3}$, based on chi-square statistical tests. Viable count for cells exposed to benzo[a]-pyrene was not significantly different ($P > 0.05$) from that of solvent controls.

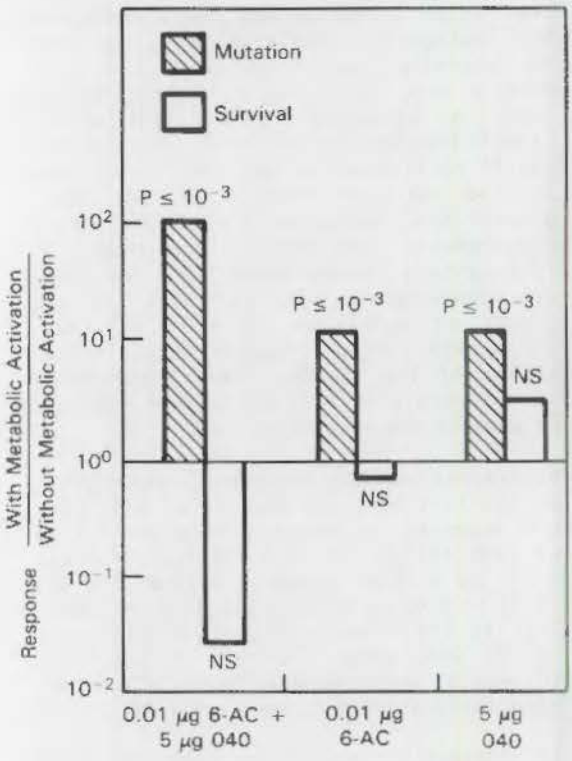

FIGURE 4. Dependency of Mutagenesis and Cell Survival on Metabolic Activation. Metabolic activation supplied by Aroclor-induced rat liver microsomes (S9). P-value followed by a number indicates the level of significance, based on chi-square test, or NS (not significant) if $P > 0.05$.

Systems
Damage

• Gut-Related Studies of Radionuclide Toxicity

Principal Investigator: M. F. Sullivan

Other Investigators: R. L. Buschbom, 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.

Earlier experiments demonstrated that the transfer factor, f_1, for neptunium decreased as the gavaged dose decreased. By restricting food consumption or by supplementing gavaged doses of $^{237}Np(V)$ or $^{233}U(VI)$ with oxidizing chemicals we showed that this decrease was related to the reducing effect of the intestinal contents. However, more recent studies have shown that the intestinal contents and/or oxidizing and reducing chemicals have similar effects on the f_1 factors for ^{238}Pu, ^{241}Am, ^{244}Cm, ^{147}Pm and ^{109}Cd; some of these radionuclides have only a single stable oxidation state. Both oxidizing agents and withholding food stimulated absorption; food in the gut and reducing agents depressed absorption. This suggested that the increased absorption must be the result of something other than a change in the oxidation state of the element gavaged.

We have also demonstrated that both oxidizing and reducing forms of iron lower the high intestinal absorption of plutonium and lead in neonates by at least an order of magnitude. Therefore, it appears that, in the neonate, plutonium is primarily absorbed by the iron uptake system and that iron reduces absorption by competing with plutonium and lead for a common carrier system. Furthermore, the data suggest that plutonium absorption by neonates is not merely passive or the result of the neonatal intestine's high permeability to large molecules, as previously thought.

Influence of Fasting and/or Oxidizing or Reducing Agents on ^{238}Pu Absorption

Results reported earlier (Annual Report, 1983) demonstrated that absorption of both uranium and neptunium was increased by fasting and by the administration of Fe^{3+} and decreased by food consumption and by Fe^{2+}. Since both neptunium and uranium are polyvalent and are absorbed in higher amounts when administered in the higher oxidation states, it seemed plausible that oxidation of those actinide metals by Fe^{3+} occurred *in vivo*. It also seemed reasonable that reduction by Fe^{2+} to lower oxidation states, which are absorbed at lower rates, was an explanation for the effects observed.

To determine whether the GI contents were also responsible for altering plutonium transport, groups of rats were fasted 24 hours before and 4 hours after ^{238}Pu nitrate gavage. Other groups of rats were fed *ad libitum*, or fasted and gavaged with plutonium supplemented with either a suspension of iron powder or a solution of ferric nitrate. Some rats were injected intramuscularly with iron dextran (Fe-Dex) to satisfy iron requirements for hematopoiesis. The results obtained when the animals were killed, a week after ^{238}Pu gavage, are shown in Table 1. The data indicate that fasting increased absorption about threefold and that absorption by fasted rats that received Fe-Dex was even higher.

Iron powder, Fe^{0}, decreased the effect of fasting. Ferric iron (Fe^{3+}) increased ^{238}Pu absorption by fasted rats to 18 times the value due to fasting alone or to 50 times the value in fed rats. Fe-Dex decreased the effect of ferric iron. Ascorbic acid, a reducing agent that also chelates metals such as iron, increased ^{238}Pu absorption much more than Fe^{3+} but also caused diarrhea, which contaminated urine collections, making accurate calculations of radioactivity in excreta impossible.

Influence of Fasting and/or Oxidizing or Reducing Agents on the GI Absorption of Americium

The effect of fasting and oxidizing or reducing chemicals on ^{237}Np, ^{233}U and ^{238}Pu in adults may be explained by the changes in their oxidation states that makes them more or less absorbable from

TABLE 1. Effect of Fasting and Oxidizing or Reducing Agents on Absorption of Gavaged ^{238}Pu, ^{241}Am, ^{244}Cm, or ^{210}Pb Nitrates and ^{147}Pm or ^{109}Cd Chloride by Rats Killed 7 Days After Gavage[a]

	Percent of Gavaged Dose ± SEM × 100															
	Control															
Radionuclide	Fed	N	Fasted	N	Fe-Dex[a]	N	Fe^{2+}[a]	N	Fe^{3+}[a]	N	Quinhydrone[a]	N	Fe^{0}[a]	N	Ascorbic Acid	N
^{238}Pu	1.5 ± 0.3	7	4.4 ± 1.0	6	8.6 ± 1.3	6	2.3 ± 0.3	6					77 ± 12	6	214 ± 87[b]	6
^{241}Am	1.7 ± 0.2	12	12.4 ± 1.4	10			1.9 ± 0.3[b]	4	3.1 ± 0.6[b]	4	6.1 ± 1.6[b]	4	119 ± 25		173 ± 94[b]	6
^{244}Cm	3.3 ± 0.3	4	10.4 ± 0.6	5			6.0 ± 0.4	6					61 ± 12	6		
^{147}Pm	1.1 ± 0.2	8	7.0 ± 1.5	6									118 ± 18	6		
^{109}Cd	1.3 ± 0.1	9	1.8 ± 0.1	5									20.8 ± 4.2	5		
^{210}Pb	3.5 ± 0.5	5	19.3 ± 1.9	5							3.8 ± 0.3	5	2.7 ± 0.5	5		

[a]All rats in groups given chemical supplements were fasted

[b]Total retention values shown for some Am- and ascorbic acid-treated rats because of urine contamination by fecal radioactivity. All other values are percent absorbed.

the GI tract. Americium, however, is trivalent in solution and is converted to other states only with difficulty. We therefore expected that administration of ^{241}Am in combination with oxidation or reducing agents would not alter its absorption coefficient. Table 1 also shows results of experiments testing the effects of fasting and the effect of the oxidizing chemicals, Fe^{3+} and quinhydrone, and the reducing agents, Fe^{2+}, Fe^{0} and ascorbic acid. Fasting increased absorption by an order of magnitude, and Fe^{3+} increased absorption by fasted rats by another order of magnitude. Retention values are shown only for effects of the oxidizing chemical, quinhydrone, and the reducing agents because the urine collections were contaminated by fecal radioactivity during collection. The retention values show effects similar to those observed with ^{238}Pu, ^{233}U and ^{237}Np. This suggests that their influence on actinide absorption may be by some mechanism other than the altered oxidation state of the actinide.

Effect of Fasting and/or Oxidizing and Reducing Agents on GI Absorption of Curium

Curium is another polyvalent actinide metal that is trivalent in solution and is converted to other valences only by arduous procedures. To corroborate the data on americium, which has that same property, we performed a similar experiment with curium. We also hoped that the results might provide further information on the mechanisms responsible for the changes seen in plutonium, uranium, neptunium, and americium transport. The results, shown in Table 1 for curium, demonstrate that the effect of fasting and oxidizing or reducing chemicals on absorption is similar to that on the other actinides studied but of lesser magnitude.

Effect of Fasting and an Oxidizing Agent on GI Absorption of Promethium, Lead, and Cadmium

To determine whether the effects of fasting and oxidizing chemicals also influenced absorption of elements that are divalent or trivalent in solution, we performed an experiment similar to those previously described. The results in (Table 1) demonstrate that fasting and Fe^{3+} both had a greater effect on ^{147}Pm than on ^{241}Am, indicating that the metal need not be polyvalent to be affected. The data in Table 1 show that cadmium absorption was increased by fasting and further increased by administering Fe^{3+}. Lead absorption was increased by fasting but, in constrast to the effect of oxidants on the absorption of other metals in this study, adding Fe^{3+} or quinhydrone to the gavage solution decreased ^{210}Pb absorption by fasted rats to the value obtained for lead absorption by rats fed *ad libitum*.

Influence of Ferrous or Ferric Iron on Plutonium, Cadmium and Lead Retention by Neonatal Rats

Supplements of ferric iron also increased ^{237}Np absorption by neonatal rats and Fe^{2+} decreased it, as in adult rats (Annual Report, 1983). To determine whether these chemicals influenced ^{238}Pu, ^{109}Cd, or ^{210}Pb absorption similarly, groups of 8-day-old rats were gavaged with mixtures of ^{238}Pu and ferric nitrate or ferric sulfate; some rats were also injected with Fe-Dex. Other groups were gavaged with either ^{210}Pb or ^{109}Cd and Fe^{3+} ^{109}Cd or ^{210}Pb and Fe^{3+}. The results, shown in Table 2, indicate that both ferric and ferrous iron decreased ^{238}Pu retention. Injected Fe-Dex decreased retention in all age groups but not to the same extent as

TABLE 2. Effect of Iron Supplements on Retention of ^{238}Pu, ^{109}Cd or ^{210}Pb by Neonatal Rats Gavaged with Solutions of the Radionuclides When They Were 8 Days Old. Rats were killed a week later.

	Percent of Gavaged Dose ± SEM Retained											
			Supplement Administered[a]									
Radionuclide	Control	N	Fe-Dex[b]	N	Fe-Dex + Fe^{2+}	N	Fe-Dex + Fe^{3+}	N	Fe^{2+}	N	Fe^{3+}	N
^{238}Pu	1.5 ± 0.2	13	0.8 ± 0.1	15	0.05 ± 0.004	8	0.08 ± 0.004	10	0.07 ± 0.01	10	0.1 ± 0.01	8
^{109}Cd	1.3 ± 0.2	7							2.5 ± 0.2	13	2.8 ± 0.3	9
^{210}Pb	55 ± 2	7									3.4 ± 0.2	7

[a] Iron Dextran (Fe-Dex) was injected intramuscularly at 24 hours and 1 hour before ^{238}Pu gavage.
[b] Ferrous and ferric iron were gavaged simultaneously with ^{238}Pu, ^{109}Cd or ^{210}Pb.

the gavaged solution. These results differ from those in adult rats, suggesting that plutonium is absorbed by different mechanisms in adult and neonatal rats.

Cadmium-109 retention in neonates was doubled by administering Fe^{3+}; as in adult rats, the effect on absorption also increased, but to a lesser degree. In contrast, Fe^{3+} decreased ^{210}Pb absorption by 95% in the neonate. The magnitude of that decrease was about the same in the neonates as in the adults. These results suggest that both cadmium and lead may be absorbed by similar processes in adult and neonatal rats.

The data on actinide absorption in adults and neonates cannot be explained by a single mechanistic hypothesis. However, these results suggest studies with different metals and dietary conditions that will explain these mechanisms in both neonates and adults. Such studies may allow accurate prediction of absorption in a variety of situations.

• Teratology of Complex Mixtures

Principal Investigator: P. L. Hackett

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Technical Assistance: J. Rusin

During the past year, studies were performed to define the dose response, maternal effects and the most sensitive embryonic age following acute administration of Harmarville process solvent (HPS). Maternal weight gains and thymus weights were depressed when HPS was administered on or after 9 dg. Fetal survival was reduced only when exposure occurred on 6 dg. Fetal body weights were lower than normal when the dams were dosed on 9, 11, 12, or 16 dg, and malformations were most common following exposure on 11, 12, 13 or 14 dg. From this study we defined an exposure regimen for determining the developmental toxicity of SRC materials. Most toxic or teratogenic events resulting from exposure to the fractionally distilled material occurred in the fractions that boiled above 750°F. Exposure to a hydrotreated fuel oil blend (FOB-H) did not produce the same significantly lower fetal lung weights as FOB, but effects on maternal thymus weight were similar for both FOB and FOB-H. In a separate, preliminary study of possible mechanisms for the action of SRC material on fetal development, the effects of HPS exposure were compared with those of a known teratogen, a corticosteroid, triamcinolone acetonide (TAC).

Determination of Sensitive Developmental Periods

We extended previous studies of SRC materials to include the effects of acute administration of a high dose level of HPS on development during the peri-implantation period, early embryonic stages or the onset of rapid fetal growth.

Harmarville process solvent, which has a boiling range of 300 to >850°F, was used in these studies. Suspensions of HPS were prepared in milk immediately prior to intragastric intubation of a constant-volume dose. Female rats (Sprague-Dawley, CD, Charles River Laboratories) were mated and randomly assigned to treatment groups to receive 1.85 g of HPS/kg body weight on 6, 9, 11, 12, 13, 14, or 16 dg. 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, then removed and weighed.

Results of the acute administration of a high dose of HPS on specific days of gestation are shown in Tables 1 and 2 and Figure 1. In HPS-dosed rats, maternal body-weight gains during gestation tended to be lower than those of control animals; significant weight depressions occurred following exposure to HPS on or after 9 dg, except in dams dosed on 11 dg. Thymus weights of exposed rats were also lower than those of controls during this time interval. An increase in adrenal weights, previously observed following multiple daily exposures to a high-boiling coal liquid designated heavy distillate, was evident only when dosing was performed on 13 or 14 dg. The disparity between effects in the dam (no toxicity) and in the fetus (decreased survival) may be due to the fact that the long interval after the 6-dg dose allowed the dam to recover, whereas the fetus sustained irreversible damage.

Lung weights of fetuses exposed to HPS on 11 dg or later were significantly lower than those of control fetuses (Table 2). Body weights for these pups were depressed in litters exposed on 9, 11, 12 and 16 dg. Fetal malformations included small lungs, cleft palates and diaphragmatic hernias (Figure 1). Diaphragmatic hernias occurred more frequently following dosing on 12 dg, and cleft palate incidence was higher when dosing was performed on 12 or 13 dg. Major vessel variations, which included retroesophageal or absent aortic arches, ectopic origin of the left carotid artery and missing innominate arteries, were observed, on the average, in 19% of the fetuses of each litter following dosing on 11 dg. The mean value for these variations was 5%/litter in fetuses exposed on 9 dg, but no major vessel anomalies were detected in fetuses of any other treatment group.

TABLE 1. Measures (Mean ± SE) in Pregnant Rats Following Acute Oral Administration of 1.85 g/kg Body Weight of a Harmarville Process Solvent (HPS) on Specific Days of Gestation.

Group	Day of Gestation, dg	Number of Animals	Weight Gain, g[a]	Thymus Weight, mg	Adrenal Weight, mg	Live Fetuses %/Litter
Control		14	51 ± 4	221 ± 17	77 ± 3	96 ± 1
Treated	6	12	42 ± 4	201 ± 20	75 ± 4	49 ± 8[b]
Treated	9	10	33 ± 3[b]	126 ± 17[b]	79 ± 3	86 ± 5
Treated	11	7	38 ± 4	121 ± 18[b]	80 ± 3	86 ± 4
Treated	12	5	30 ± 4[b]	115 ± 42	84 ± 5	67 ± 17
Treated	13	6	25 ± 7[b]	90 ± 12[b]	110 ± 6[b]	90 ± 4
Treated	14	6	15 ± 8[b]	103 ± 17[b]	102 ± 6[b]	87 ± 6
Treated	16	8	30 ± 7[b]	101 ± 18[b]	93 ± 8	87 ± 4

[a] Extragestational weight gain (body weight minus weight of gravid uterus) from 0 to 20 dg
[b] Significantly different ($P < 0.05$) from control value

TABLE 2. Fetal Body and Lung Weights (Mean ± SE) Following Acute Exposure of Pregnant Rats to 1.85 g/kg Body Weight of Harmarville Process Solvent (HPS) During Development.

Group	Day of Gestation, dg	Fetal Body Weight, g	Fetal Lung Weight, mg
Control		3.58 ± 0.08	119 ± 4.1
Treated	6	3.45 ± 0.15	106 ± 4.7
Treated	9	3.02 ± 0.13[a]	104 ± 2.5
Treated	11	2.98 ± 0.05[a]	72 ± 4.7[a]
Treated	12	3.00 ± 0.09[a]	65 ± 6.6[a]
Treated	13	3.40 ± 0.09	77 ± 4.9[a]
Treated	14	3.13 ± 0.13	81 ± 5.2[a]
Treated	16	2.98 ± 0.05[a]	80 ± 3.4[a]

[a] Significantly different ($P < 0.05$) from control values

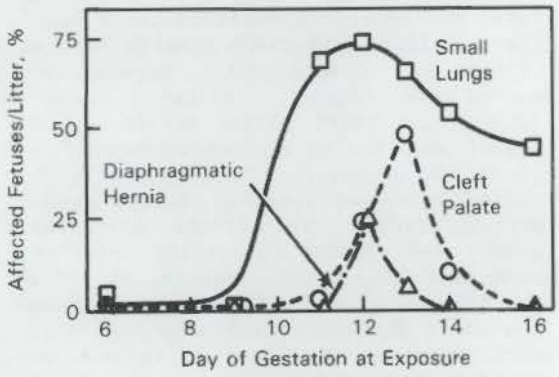

FIGURE 1. Fetal Malformations Following Acute Oral Administration to Pregnant Rats of Harmarville Process Solvent (HPS).

Effects of Modified SRC Materials

Process strategies such as fractional distillation and hydrotreatment have been developed to eliminate undesirable components from SRC materials. In current studies, we have determined the developmental toxicity of these modified materials.

For studies of the effects of exposure to the SRC materials modified by fractional distillation, boiling-range cuts of HPS were sequentially reconstituted by serial addition of successively higher-boiling-range material. These mixtures were administered to rats by intragastric intubation on 13 dg at a dose level equivalent to 1.85 g/kg of crude HPS (Table 1). Analyses of the relative chemical composition of these boiling-range cuts revealed that aliphatic hydrocarbons decreased and the more polar, nitrogen-containing polycyclic aromatic hydrocarbons increased in the higher boiling ranges; the content of polycyclic aromatic hydrocarbons remained relatively constant.

Maternal weight gains tended to be lower in all animals dosed with the reconstituted boiling-range cuts of HPS and were significantly lower in the rats that received the lowest-boiling-range material (Table 3). Mortality was observed only in the group that received the cut boiling at 300 to 800°F. Thymus weights were lower than those of controls following exposure to the higher-boiling-range cuts (800°F and above), but adrenal weights were

higher only for animals dosed with crude HPS. Intrauterine mortality tended to be higher when dams were exposed to cuts with boiling-range maxima above 800° (Table 4). Fetal body weights (Figure 2) were lowest in litters exposed to the material boiling at 300 to 800° and 300 to 850°; lung weights in these fetuses progressively declined as the boiling range of the dosing material increased. Increased incidences of small lungs and cleft palates were observed in litters dosed with HPS cuts boiling above 750° and 850°, respectively.

Most toxic or teratogenic events occurred following exposure to materials boiling above 750°, most commonly at 800° or higher. Certain toxic signs, such as maternal mortality and depressed maternal and fetal weights, were apparently elicited by materials in a narrow boiling range. We speculate that these effects may have been induced by the sequential addition of certain classes of chemicals contained in the mixtures. On the other hand, certain effects (e.g., lower fetal body weights) were mitigated by the addition of high-boiling complex mixtures.

TABLE 3. Maternal Measures (Mean ± SE) Following Exposure to Reconstituted Boiling Range Cuts of Harmarville Process Solvent (HPS).

Treatment	Number of Animals	Mortality, %	Weight Gain, g[b]	Thymus Weight, mg	Adrenal Weight, mg
Vehicle	12	0	41 ± 5[c]	184 ± 16[c]	73 ± 4[c]
HPS Cut					
300-700[a]	7	0	19 ± 3[d]	111 ± 16[c,d,e]	84 ± 7[c,d]
300-750	8	0	36 ± 4[c]	131 ± 11[c,d]	74 ± 4[c]
300-800	11	36	37 ± 7[c,d]	160 ± 25[c,d]	76 ± 4[c]
300-850	10	0	37 ± 4[c]	98 ± 10[d,e]	69 ± 2[c]
300->850	8	0	25 ± 3[c,d]	64 ± 9[e]	76 ± 5[c]
Crude HPS					
300->850	6	0	25 ± 6[c,d]	90 ± 12[d,e]	110 ± 6[d]

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

TABLE 4. Fetal Measures (Mean ± SE) Following Exposure to Reconstituted Boiling Range Cuts of Harmarville Process Solvent (HPS).

		Incidence[b]		
Treatment	Intrauterine Mortality, %	Small Lungs	Cleft Palate	Diaphragmatic Hernia
Vehicle	1.6 ± 1.6	1.7 ± 0.4[c]	0[c]	0
HPS Cut				
300-700[a]	5.5 ± 2.9	3.5 ± 2.5[c,d]	0[c]	0
300-750	0	8.1 ± 4.9[c,d]	0[c]	0
300-800	3.2 ± 3.2	38.1 ± 12.4[d,e]	1.1 ± 1.1[c]	1.3 ± 1.3
300-850	13.9 ± 8.4	41.3 ± 7.8[e]	7.3 ± 4.0[c,d]	1.4 ± 1.4
300->850	14.5 ± 10.8	54.7 ± 17.2[d,e]	11.2 ± 4.5[d]	0
Crude HPS				
300->850	12.2 ± 7.9	65.3 ± 17.0[e]	48.2 ± 6.5[e]	6.3 ± 6.3

(a) Boiling range (°F)
(b) Percent/litter
(c-e) Values that do not share a common superscript letter are significantly different ($P < 0.05$).

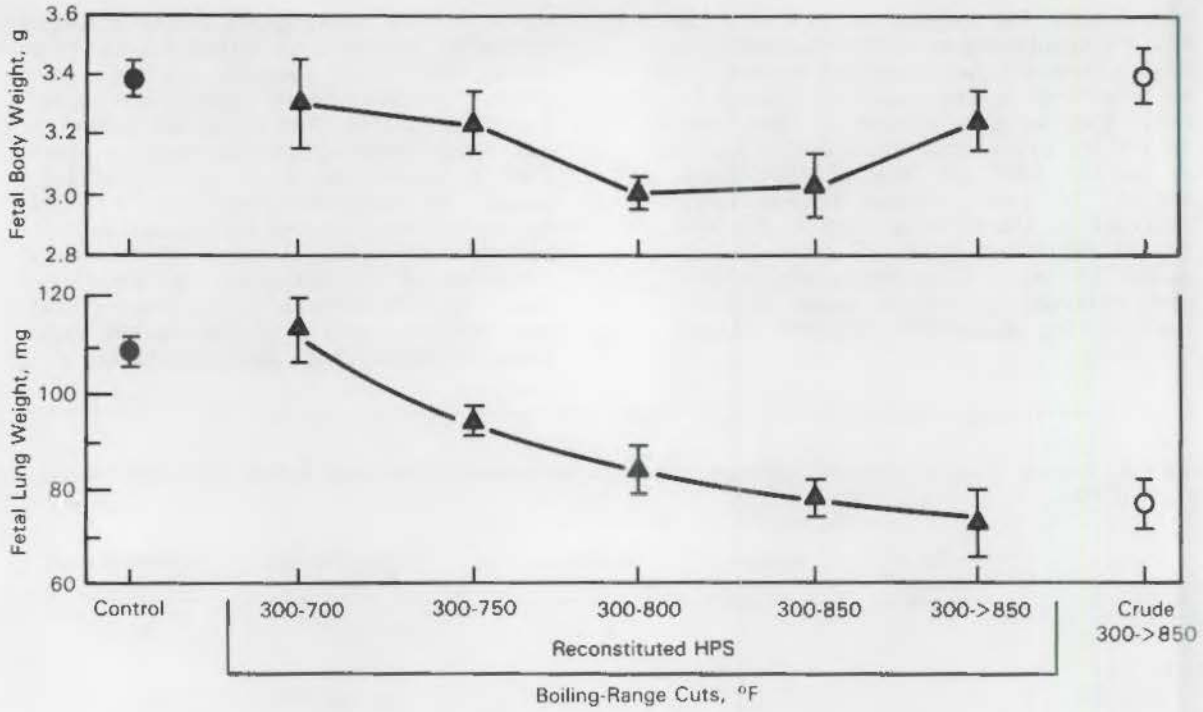

FIGURE 2. Fetal Body and Lung Weights Following Exposure to Reconstituted Boiling-Range Cuts of Harmarville Process Solvent (HPS).

To ascertain whether the biological effects of SRC materials could be modified by hydrotreatment, FOB or FOB-H was administered to rats on 13 dg at a dose level of 1.85 g/kg. The FOB (2.9 parts of material boiling at 350 to 550° to 1 part boiling at 550 to 850°) contained two- and three-ring aromatic and heteroatomic species, and phenolic and polynuclear aromatic components. The FOB-H contained a lower-molecular-weight hydroaromatic species and lower concentrations of the heteratomic species and nitrogen-containing compounds than the FOB.

Exposure to FOB induced effects that were qualitatively similar (Table 5) to those observed following exposure to the same dose level of crude HPS (Tables 3 and 4). The less severe repression of maternal thymus weights and fetal lung weights by FOB may be attributable to the fact that it contains materials with lower boiling points than does HPS. Exposure to FOB-H

TABLE 5. Maternal and Fetal Effects of Exposure to Fuel Oil Blend (FOB) or Hydrotreated Fuel Oil Blend (FOB-H).

Observations	Treatment		
	Vehicle	FOB	FOB-H
Maternal			
Weight Gain, g	51 ± 3.7	40 ± 3.0	33 ± 5.7
Thymus Weight, mg	221 ± 17[a]	139 ± 18[b]	141 ± 12[b]
Fetal			
Survival, %/litter	96 ± 0.9	94 ± 1.5	89 ± 5.1
Body Weight, g	3.58 ± 0.08	3.25 ± 0.07	3.20 ± 0.08
Lung Weight, mg	119 ± 4[a]	96 ± 5[b]	104 ± 3[a,b]
Small Lungs, %/litter	1.6 ± 1.6	19 ± 8.4	1.0 ± 1.0

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

did not produce significantly lower fetal lung weights, but maternal thymus weights were low in animals exposed to either FOB and FOB-H.

Comparison of Effects of HPS with a Known Teratogen

Reports in the literature (Rowland and Hendrickx, Teratology 27: 13, 1983) have indicated that depressed maternal thymus weights and increased incidences of cleft palate were induced by the administration of corticosteroids to pregnant rats. These results are consistent with our observations of the effects of HPS exposures, with the exception of the HPS-induced fetal morphologic lesion, small lungs. In a separate study, we administered a corticosteroid (0.25 mg TAC/kg, intramuscularly) or 0.74 g HPS/kg (intragastrically) during the same period of development (12-14 dg) to obtain a direct, qualitative comparison of their action.

Results are shown in Table 6: Extragestational weight gains were severely depressed in rats that received TAC, and thymus weights were low in both HPS- and TAC-treated animals. Maternal adrenal weights tended to be lower than those of controls only in the TAC group, but the difference was not significant. This trend in the TAC animals is in contrast to the high adrenal weights observed following exposure to high doses of HPS on 13 or 14 dg.

Fetal body weights, which were significantly lower than those of controls following treatment with HPS, were even lower in the TAC-treated rats, and lung weights were lower than control values in both treatment groups. Incidences of small lungs and cleft palate were similar for both agents. No diaphragmatic hernias were observed in fetuses exposed to HPS, but 36% of the TAC fetuses exhibited this lesion. Previous studies using this dosing regimen for HPS showed a very low incidence of diaphragmatic hernia.

Although TAC and HPS may initiate toxic and teratogenic events along entirely separate metabolic or physiologic pathways, the maternal and fetal observations at necropsy are very similar. The suggestion that TAC may induce both localized and generalized growth retardation, as evidenced by the high incidence of cleft palate and the lower fetal body weights, may also be appropriate for HPS. Since both agents produced overt signs of maternal toxicity, we speculate that they may exert an indirect, rather than a direct, effect on fetal development.

TABLE 6. Comparison of Effects (Mean ± SE) in Pregnant Rats Dosed with Harmerville Process Solvent (HPS) or Triamcinolone Acetonide (TAC) from 12 Through 14 Days of Gestation.

	Treatment		
Observations	Control	HPS 0.74 g/kg Body Weight	TAC 0.25 mg/kg Body Weight
Maternal Measures			
Body Weight Gain, g	49 ± 11[a]	38 ± 8[a,b]	6 ± 6[b]
Thymus Weight, mg	226 ± 10[a]	77 ± 10[b]	53 ± 10[b]
Adrenal Weight, mg	78 ± 7	80 ± 5	56 ± 5
Fetal Measures			
Survival, %	88 ± 6	80 ± 8	81 ± 6
Body Weight, g	3.79 ± 0.1[a]	3.10 ± 0.1[b]	2.32 ± 0.2[c]
Lung Weight, mg	128 ± 5[a]	67 ± 11[b]	59 ± 7[b]
Incidence of			
Small Lungs	0	65 ± 17	56 ± 14
Cleft Palate	0	36 ± 12	48 ± 13
Diaphragmatic Hernia	0	0	36 ± 14

[a,b,c]Values that do not share a common superscript letter are significantly different ($P \leq 0.05$).

• Perinatal Effects of Complex Mixtures

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Other Investigators: R. L. Buschbom, P. L. Hackett, and D. D. Mahlum

Technical Assistance: D. G. Jones, D. C. Snyder, and R. C. Zangar

This report describes results of a study to determine whether exposure to high-boiling coal liquids results in adverse effects on female reproductive performance. For this study, female rats were exposed by whole-body inhalation to SRC-II heavy distillate (HD) for 6 weeks. These animals were repeatedly bred after exposure and evaluated for their ability to become pregnant. Evaluation was also made for dam growth during gestation, litter size, offspring survival and growth, and grossly observable malformations. Preliminary interpretation of these data indicates that reproductive capability and offspring parameters measured were not significantly altered by exposure.

During the past year, we conducted a study to determine the effect of SRC-II HD on female reproductive capability. The rationale for conducting this study was based on previously obtained data that showed a substantial reduction in ovary weights for animals exposed for 13 weeks to HD. Futhermore, single doses of polyaromatic hydrocarbons such as benzo[a]pyrene, which is present in HD, are known to result in smaller than normal numbers of primordial oocytes in rodent ovaries. These observations suggested that the high-boiling coal liquids could reduce the reproductive capabilities of rats and that occupationally exposed workers might be at risk.

For this study, 10-week-old, female, CD rats (Charles River) were exposed by whole-body inhalation to an aerosol of HD at concentrations of 0.68 ± 0.03 (high), 0.19 ± 0.003 (middle), 0.049 ± 0.0008 (low) and 0.0 (control) mg/L of air for 6 hours /day, 5 days/week for 6 weeks. Particle sizes ranged from 1.7 to 1.8 μm mass median aerodynamic diameter, with geometric standard deviations of 2.0 to 2.2. Prior to exposure, animals were randomly assigned by weight to one of the treatment groups, each of which had 96 animals. Immediately after exposure, males were placed with females (one male per female), and copulation was detected the next morning by the presence of sperm in vaginal lavage fluid. The day on which sperm were detected was designated 0 day of gestation (dg). Dams were repeatedly placed with males for 12 consecutive days (approximately three estrous cycles), or until sperm were detected. Dams were weighed at 0, 9, 15 and 20 dg.

Eighteen to 20 dams from each treatment group were sacrificed at 20 dg, and data were collected for resorptions, corpora lutea and mean litter size. Fetuses were examined for gross abnormalities, and pup weight was recorded. The other pregnant animals (approximately 28 dams) were allowed to deliver, and their pups were also examined. Body weights were obtained at 1, 3, 7 and 21 days of age. After weaning the pups at 21 days after birth, females were again bred, and information on breeding performance and offspring survival, growth and gross fetal abnormalities was recorded. This procedure was repeated through three complete breeding cycles.

Body-weight data before, during and after exposure to HD are shown in Figure 1. They indicate that high-dose animals grew more slowly than controls during the last 2 weeks of exposure, and that body weight rapidly increased to control levels after the end of exposure. Three animals from the high-dose group died during exposure, during weeks 3, 5, and 6, respectively.

Table 1 shows data for pregnant dams exposed to HD and sacrificed at 20 dg. These data indicate that the number of pregnant dams, the number of corpora lutea, the number of implantation sites, the number of resorptions, and the mean litter size were not altered by exposure. The apparent increase in the number of resorptions for the middle exposure group was due to one dam, whose litter (11 implants) was totally resorbed. Since this effect was not observed for animals in the high-dose group, it is probably not attributable to exposure. Weight data indicate that total weight gain during gestation for high-dose animals was significantly lower than for controls; however, gravid uterus weight, extragestational weight gain and fetal weights were not altered by HD exposure (Table 2). No major malformations were observed from gross examination of offspring.

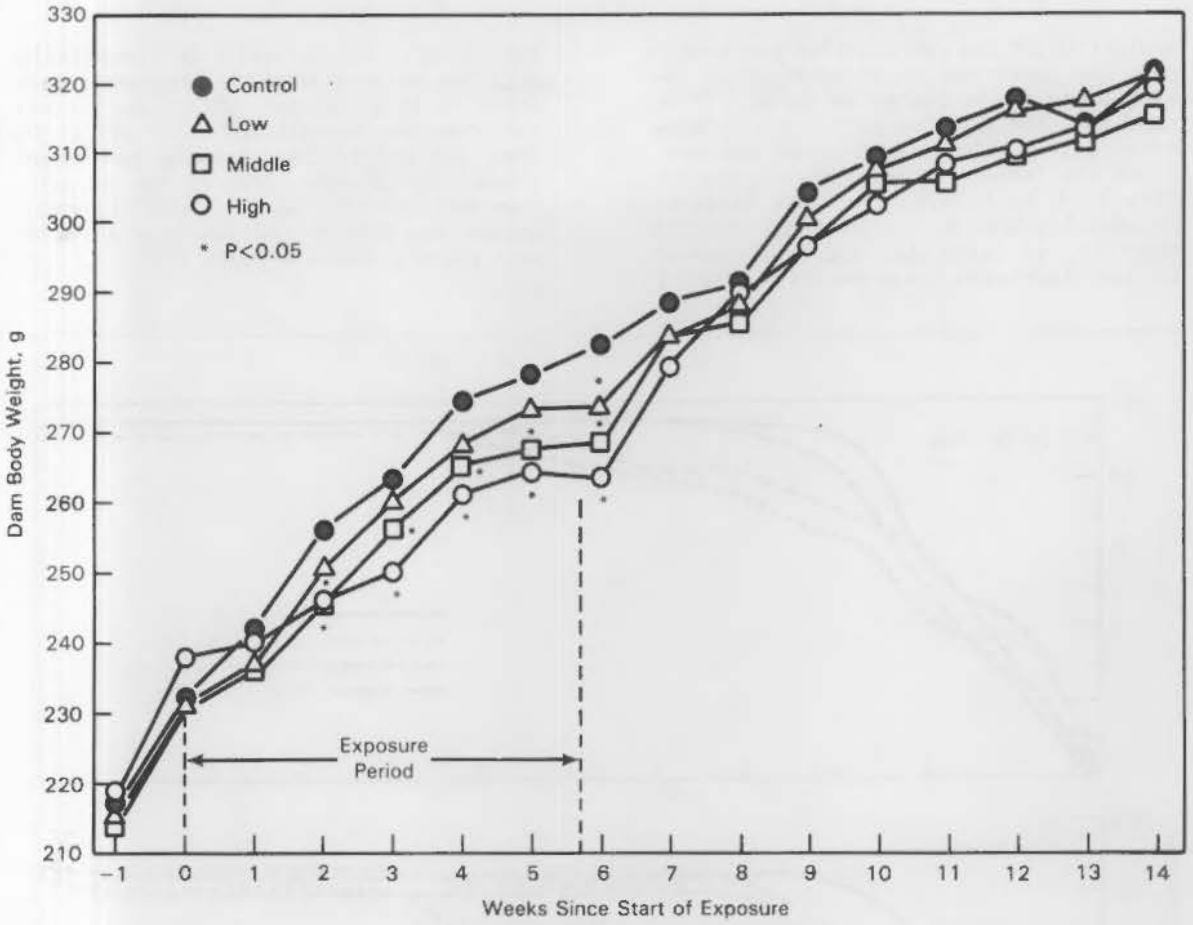

FIGURE 1. Body Weights for Female Rats Before, During and After Exposure to Heavy Distillate (Significantly Different from Control Group, $P < 0.05$).

TABLE 1. Breeding Data for Pregnant Rats Exposed to Heavy Distillate and Sacrificed at 20 Days of Gestation.

	Control	Low	Middle	High
No. Dams at Start	20	20	20	20
No. Dams Sperm-Positive	19	18	20	20
No. Dams that Delivered	19	19	20	20
No. Corpora lutea ($\bar{x}$ ± SEM)	16.4 ± 0.30	16.9 ± 0.68	16.7 ± 0.40	17.2 ± 1.4
No. Implantations ($\bar{x}$ ± SEM)	15.8 ± 0.38	14.1 ± 0.87	15.6 ± 0.44	14.2 ± 1.0
No. Resorptions (Total)	14	15	25	14
No. Live Pups ($\bar{x}$ ± SEM)	15.1 ± 0.49	13.3 ± 1.0	14.3 ± 0.70	13.4 ± 1.0

TABLE 2. Weight Data at 20 Days of Gestation for Pregnant Rats and Fetuses Exposed to Heavy Distillate ($\bar{x}$ ± SEM).

	Control	Low	Middle	High
Gestational Weight Gain (g)	155 ± 4.3	145 ± 8.3	149 ± 4.1	134 ± 7.5[a]
Gravid Uterus Weight (g)	80.7 ± 2.3	71.7 ± 5.3	80.0 ± 3.2	72.4 ± 5.5
Extragestational Weight Gain (g)	74.0 ± 3.0	73.4 ± 5.6	69.0 ± 2.9	65.2 ± 2.6
Fetal Weight (g)	3.38 ± 0.06	3.47 ± 0.15	3.47 ± 0.07	3.43 ± 0.09

[a] $P < 0.05$

Evaluation of the reproductive performance data for dams from the first breeding indicated that the number of animals that copulated and the time to copulation were not significantly altered by HD exposure. Since the length of the estrous cycle for rats is 4 to 5 days, and since animals grouped together have a tendency to cycle together, we calculated the total number of dams that were sperm-positive after 5 and 10 days, respectively, of cohabitation with the males. When the data were evaluated in this manner, 95% of the control and high-dose animals and about 80% of the low- and middle-dose animals had copulated. By 10 days, 95% of the animals from the control, middle- and high-dose groups and 92% of the low-dose animals were sperm-positive (Figure 2).

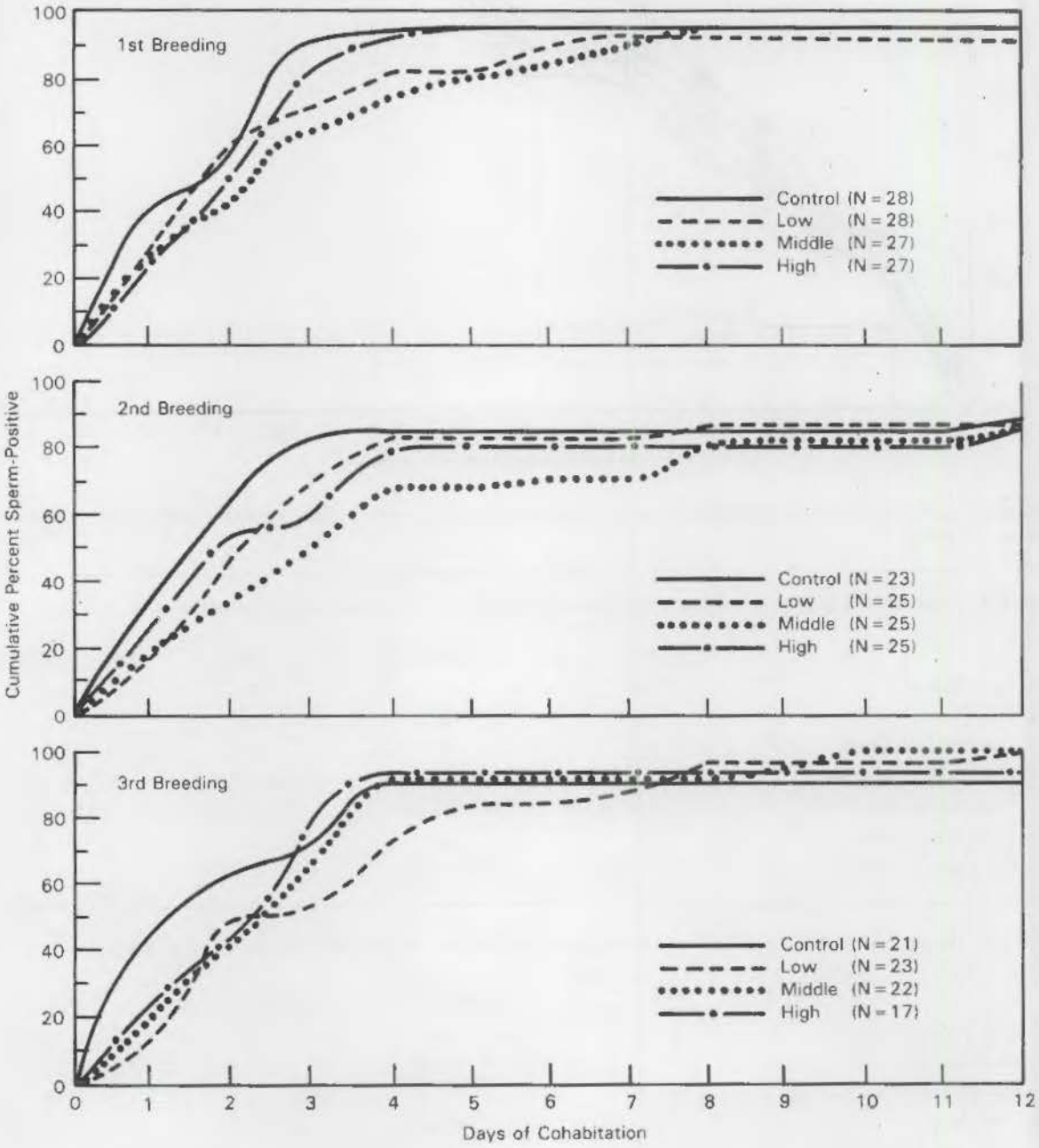

FIGURE 2. Time to Copulation for Three Consecutive Breedings of Rats Exposed to Heavy Distillate.

For exposed dams, there were no significant differences, relative to controls, in the number that delivered, gestational body-weight gain, litter size, or number of pups that died between birth and 21 days of age (Table 3). No malformations of offspring were observed.

TABLE 3. Reproduction Performance Data for Three Consecutive Breedings of Rats Exposed to Heavy Distillate.

Breeding No. 1	Control	Low	Middle	High
No. Dams at Start	28	28	27	27
No. Dams Sperm-Positive	27	26	26	26
No. Dams that Delivered	23	24	26	24
Gestational Weight Gain (g: $\bar{x}$ ± SEM)	146 ± 6.4	146 ± 5.8	140 ± 4.0	149 ± 5.2
Litter Size ($\bar{x}$ ± SEM)	13.5 ± 0.54	13.8 ± 0.55	13.5 ± 0.60	13.0 ± 0.61
No. Pups Dead or Missing/No. of Litters	9/8	5/5	7/6	10/6
Breeding No. 2				
No. Dams at Start	23	24	25	24
No. Dams Sperm-Positive	21	21	22	21
No. Dams that Delivered	21	22	23	17
Gestational Weight Gain (g: $\bar{x}$ ± SEM)	159 ± 6.3	149 ± 6.0	146 ± 4.5	143 ± 7.6
Litter Size ($\bar{x}$ ± SEM)	15.9 ± 0.67	14.9 ± 0.72	14.6 ± 0.55	15.7 ± 0.63
No. Pups Dead or Missing/No. of Litters	8/8	8/8	17/8	6/6
Breeding No. 3				
No. Dams at Start	21	22	22	17
No. Dams Sperm-Positive	19	22	22	16
No. Dams that Delivered	17	18	21	16
Gestational Weight Gain (g: $\bar{x}$ ± SEM)	136 ± 5.7	144 ± 3.2	137 ± 4.2	147 ± 3.9
Litter Size ($\bar{x}$ ± SEM)	13.2 ± 1.1	15.9 ± 0.41	13.4 ± 0.84	16.1 ± 0.55
No. Pups Dead or Missing/No. of Litters	10/8	4/4	27/9	9/6

After the second breeding, between 82 and 91% of the animals copulated. Animals from the middle-dose group tended to take longer than the other groups to copulate; however, there were no other significant differences between treatment and control groups.

Data for animals from the third breeding group indicated that 90, 100, 100 and 94% of the control, low-, middle- and high-dose groups, respectively, had copulated by 12 days of cohabitation with the males. The cohabitation period before copulation tended to be longer for the low-dose group than for the other groups. Other measures indicated that reproductive performance and offspring survival and growth were not influenced by exposure (Table 4).

This study was partially funded by the project "Biostudies of Complex Mixtures."

TABLE 4. Weights of Offspring Delivered After the First Breeding of Rats Previously Exposed to Heavy Distillate.

Age, days	Control	Low	Middle	High
1	6.8 ± 0.1	7.0 ± 0.1	6.8 ± 0.1	6.8 ± 0.1
3	8.4 ± 0.2	8.8 ± 0.2	8.5 ± 0.2	8.4 ± 0.2
7	15.9 ± 0.3	16.6 ± 0.3	15.8 ± 0.3	15.1 ± 0.3
21	52.1 ± 1.1	57.3 ± 0.9	51.9 ± 1.2	51.0 ± 1.0

• Health Effects of Complex Mixtures

Principal Investigator: R. A. Renne

Other Investigators: R. L. Buschbom and M. E. Frazier

Technical Assistance: S. M. Baze, P. T. Hackett, V. L. Madden, and C. White

The purpose of this project is to study the potential human health hazards associated with exposure to complex hydrocarbon mixtures. Studies in progress are investigating the carcinogenic potential of cutaneous exposure to various chemical class fractions of materials and products from the solvent refined coal technology. An in vitro assay system using cultured mouse skin is being developed in an attempt to correlate primary DNA damage induced by complex hydrocarbon mixtures in vitro to carcinogenic effects observed in vivo.

Epidermal carcinogensis studies were completed on distillates of Harmarville process solvent (HPS) from the solvent refined coal (SRC) Process Demonstration Unit at Harmarville, PA (Annual Report, 1983). Recently completed studies of a nitrosated sample of the 750-800°F distillate indicate that destruction of primary aromatic amines (PAA) by nitrosation does not decrease the carcinogenicity of this sample (Figure 1). This may be explained by the potency of polycyclic aromatic hydrocarbon (PAH) carcinogens, which mask any decrease in carcinogenicity due to loss of PAA. An alternative explanation is that PAA are not as potent carcinogens as the higher-molecular-weight carbazoles and azaarenes, both of which are present in high-boiling coal liquids.

Studies are in progress on neutral PAH and nitrogen-containing polycyclic aromatic compound (NPAC) fractions of the 750-800°F distillate; these fractions were obtained by adsorption-column chromatography, using neutral alumina as an adsorbent. Skin-tumor incidence and latency data, based on gross observations of these mice (Figure 1), indicate that both the PAH and NPAC fractions possess significant carcinogenicity for mouse skin. The carcinogenicity of the NPAC fraction appears to be independent of the presence of significant amounts of PAH. However, the response to these NPAC may be masked by a concurrent response to PAH when both groups of compounds are present in a complex hydrocarbon mixture. Planned future studies will examine the roles of various components (PAA, carbazoles, and azaarenes) in the carcinogencity of the NPAC fraction.

An in vitro assay system using cultured mouse epidermis is being developed in an attempt to correlate primary DNA damage induced by complex hydrocarbon mixtures in vitro to carcinogenic effects observed in mouse skin in vivo. Epidermal tumors from mice chronically exposed to coal liquids are being cultured to develop continuous

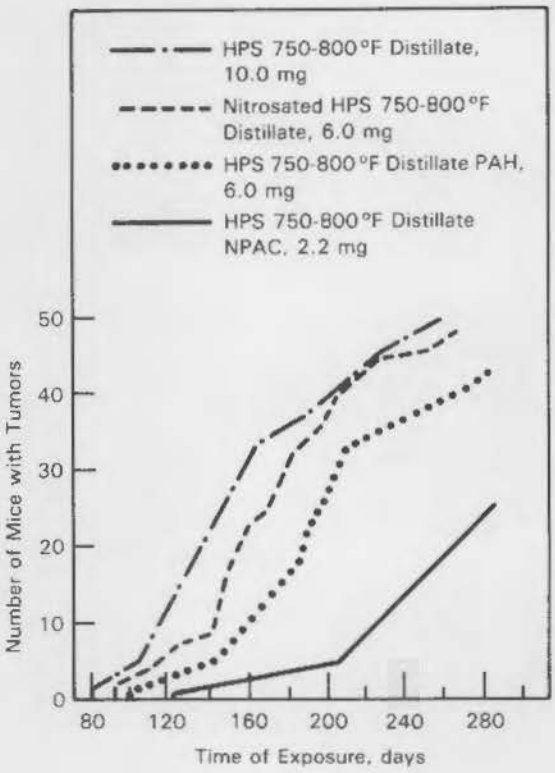

FIGURE 1. Skin Tumor Response in Mice Exposed Repeatedly to the 750-800°F Distillate of HPS, to a Nitrosated Sample of that Distillate, or to Selected Chemical-Class Fractions of that Distillate.

cell lines. The five candidate cell lines currently growing will be used to determine whether mouse epidermal cells are more sensitive than Chinese hamster ovary (CHO) cells in detecting the frequency of sister chromatid exchange (SCE) resulting from exposure to coal liquids.

In the first phase of this work, SCE frequencies of CHO cells exposed to coal liquids were examined. The background rates in the CHO cells were between 10 and 15

SCE per spread (between 0.5 and 0.7 SCE/chromosome). The exposure of cells to 30 µg/ml of either HPS or SRC-II heavy distillate in the presence of activated rat liver homogenates and an NADP generating system resulted in statistically significant increases in SCE frequencies. No increases in SCE frequencies were observed in the absence of exogenous activating enzymes.

• Tissue Dose in Fossil Fuel Exposure

Principal Investigator: R. E. Schirmer

Other Investigators: L. J. Felice, D. D. Mahlum, D. L. Springer, W. C. Weimer, and R. B. Westerberg

Technical Assistance: J. A. Cushing, B. K. Hayden, D. L. Lundstrom, and C. Veverka

In studies designed to develop a method of analyzing absorption and disposition of aromatic amine components of complex mixtures in mammals, the 6-AC levels in the skin from skin-painted mice and rats were measured using high-performance liquid chromatography (HPLC) with an electrochemical detector. The 6-aminochrysene (6-AC) was cleared from mouse skin more rapidly than from rat skin. In the mouse, the clearance rate was similar to that measured previously for benzo[a]pyrene (BaP). Continuing studies on BaP have shown that the presence of coal liquids reduces the rate of metabolism in vitro. For the two boiling-point (bp) cuts tested, the reductions in rate of BaP metabolism corresponded to the reduction in tumor initiation in vivo.

Further work has been done on the analytical procedure for analyses of 6-AC and other polynuclear aromatic amines (PAA) in tissue samples, using HPLC with electrochemical detection. The objective is to develop a simple method of analysis that can be used for studies of the absorption and disposition of these compounds in mammals. Chromatographic separation of the PAA was accomplished using a C-8 or a C-18 reverse-phase column with an acetonitrile/0.1 M citrate buffer mobile phase. This system allows the separation to be controlled by adjusting the percentage of acetonitrile and the pH of the citrate buffer. Amines eluting from the column were detected using a Bioanalytical Systems LC-4A electrochemical detector with a glassy-carbon, thin-layer electrode referenced to an Ag/AgCl electrode. Voltammetric detection allows the PAA to be detected without interference from N-heterocyclic compounds (Table 1) or polynuclear aromatic hydrocarbons present in coal liquids. Additional selectivity can be achieved by adjusting the working electrode potential, since compounds oxidizing at potentials above that of the working electrode are not detected. The large differences in oxidation potentials among several PAA typical of coal liquids are shown in the hydrodynamic voltammograms in Figure 1. Quantities as small as 1 picomole of PAA are easily determined using this procedure, and a minimum detection limit on the order of 0.1 picomole may be achievable for the more easily oxidized amines.

This method was used to evaluate the procedure for extracting PAA from rat and mouse skin in skin-painting experiments and to determine the rate of absorption of 6-AC painted on the skin of rats (Sprague-Dawley CD, Charles River) and mice (CD-1, Charles River). For recovery studies, animals were shaved, killed with carbon dioxide, and the skin was harvested and placed on ice immediately following death. Two-cm pieces of mouse skin and 4-cm pieces of rat skin were then spiked with either 1.0 µg or 10 µg of an aromatic amine applied in an acetone solution (40 µg/ml). The PAA were recovered by extracting the skin with acetonitrile, and extracts were analyzed without further treatment. Complete recovery was achieved for all four PAA tested.

TABLE 1. Electrochemical Detector Response to Aromatic Nitrogen Compounds.

Compound	Nanomoles Injected	Peak Area / Nanomole $\times 10^{-4}$
Quinoline	3.11	ND[b]
4-Azafluorene	1.26	ND
Benzo[c]cinnoline	1.27	ND
5,6-Benzoquinoline	1.18	ND
Carbazole	0.392	0.0745
4-Aminobiphenyl	0.0437	4.41
1-Aminonaphthalene	0.0552	6.20
1-Aminoanthracene	0.0823	4.01
6-Aminochrysene	0.168	3.28

[a] HPLC Conditions: C-18 column with 1 ml/min 45% acetonitrile/55% 0.1 M citrate and glassy-carbon electrode at +0.9 V versus an Ag/AgCl reference electrode

[b] ND = None Detected

The percutaneous absorption of 6-AC in vivo in rats was studied following application of 40 nmoles of 6-AC in 25 µl of acetone to the shaved backs of eight ani-

mals. Pairs of rats were killed at 0, 1, 4 and 24 hours, and the skin at the site of application was removed and analyzed using the HPLC procedure. The percutaneous absorption of 6-AC in mice was studied using the same protocol, except that the dose was 37 nmoles/animal, and mice were also killed at 0.25 and 0.50 hours to better define the early part of the clearance curve. Results (Figure 2) show that 6-AC was removed from mouse skin much more rapidly than from rat skin: 16% remained at the site of application at 4 hours in the mouse, compared with 56% in the rat.

The clearance rate of 6-AC observed in the mice in this study was similar to that of BaP under similar conditions. In the case of BaP, there is evidence that metabolism makes a significant contribution to clearance from the skin; it remains to be determined whether metabolism is also important in 6-AC clearance.

Earlier work in our laboratory has shown that BaP is cleared from the skin of mice more rapidly when it is applied in a mixture with solvent refined coal (SRC) heavy distillate (HD). It has also been shown that initiation of skin tumors in mice by BaP is suppressed when the BaP is applied in combination with a complex coal liquid. Since both clearance and tumor initiation are affected by metabolism, an in vitro experiment was conducted to determine the effect of a complex matrix on the metabolism of BaP. Rat liver S9 from Aroclor-treated rats was used to oxidize tritiated BaP (4 nmoles, 1.8 µCi) either alone, in the presence of 11 or 110 µg of an 800-850°F bp cut from SRC-II HD, or in the presence of 13 or 130 µg of a >850°F bp cut from HD. The components of the S9 activation system were mixed and allowed to equilibrate at 37°C for 2 minutes; the reaction was then initiated by the addition of the BaP or BaP/coal liquid mixture. The reaction was terminated by the addition of 0.5 N sodium hydroxide in 80%

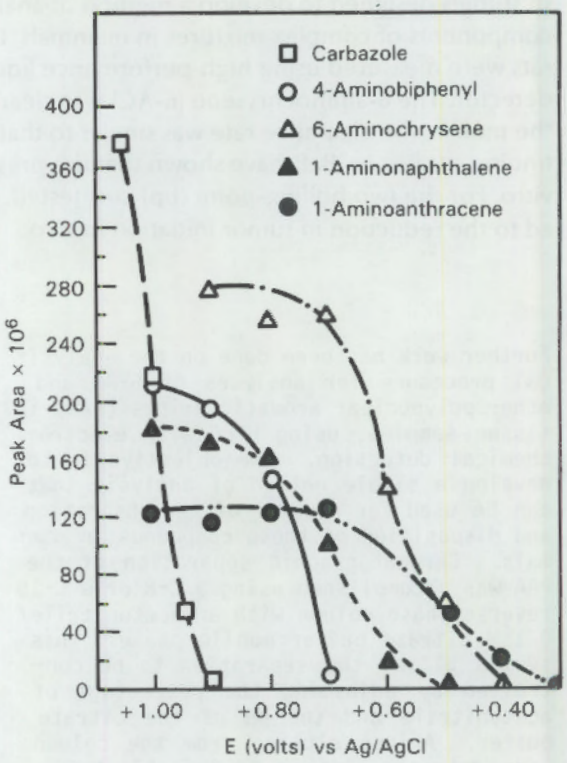

FIGURE 1. Hydrodynamic Voltammetry of Polynuclear Aromatic Amines.

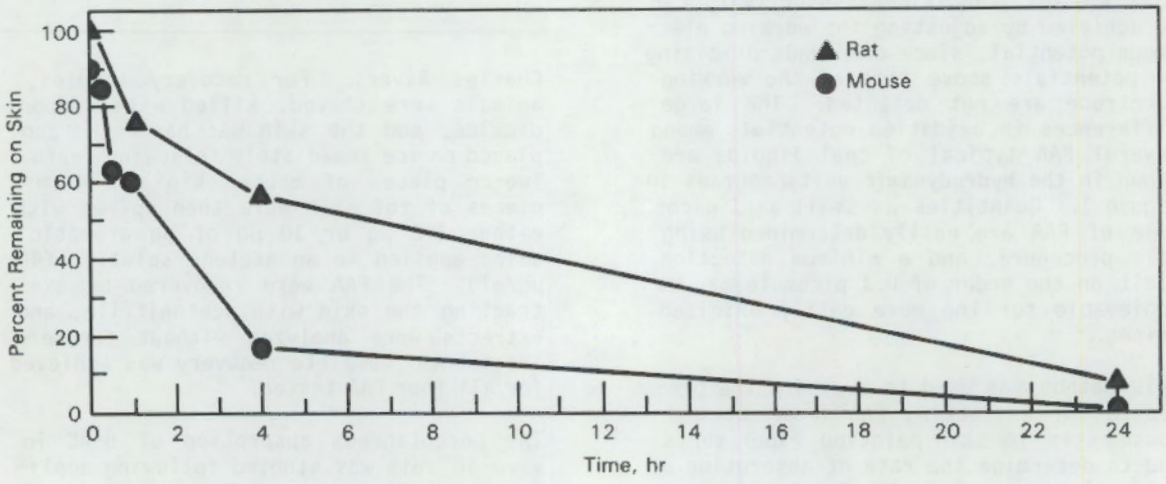

FIGURE 2. Comparison of Clearance Rates for 6-Aminochrysene Painted on Skins of Rats and Mice.

ethanol. The extent of metabolism was estimated by extracting unreacted BaP from each mixture with hexane, centrifuging to precipitate solids, measuring the radioactivity remaining in the aqueous layer, then calculating the fraction of initial radioactivity recovered in the aqueous phase. The results are shown in Figure 3. Both bp cuts reduced the rate of metabolism of BaP, but the 800-850°F cut caused a greater reduction per microgram added than the >850°F. Thus, the rank order of metabolic rates in this system corresponds with tumorigenic activity in vivo, with a higher rate of metabolism corresponding to greater tumorigenicity. Assuming that the suppression of metabolism observed in vitro also occurs in vivo, both the decreased metabolism and the enhanced clearance of BaP would contribute to the decrease in tumorigenicity observed in the presence of complex oils in mice.

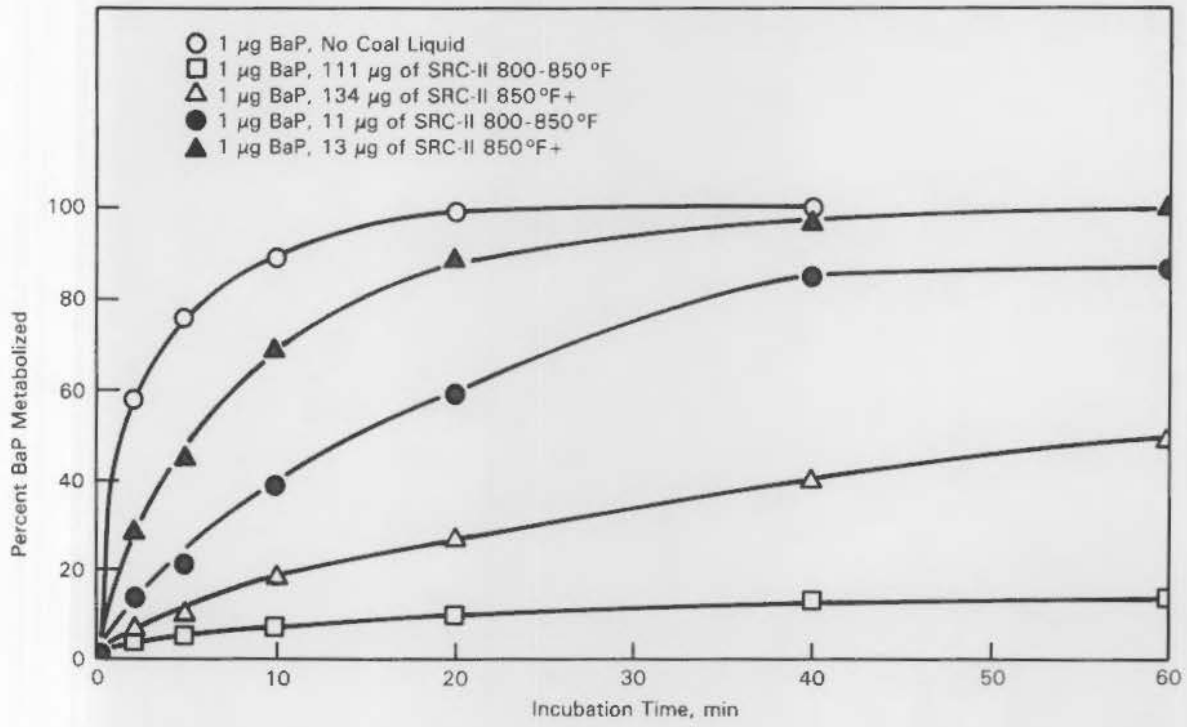

FIGURE 3. In Vitro metabolism of Benzo[a]pyrene (BaP): Percent BaP Metabolized Versus Time.

• Aerosol Technology Development

Principal Investigator: W. C. Cannon

Other Investigators: E. F. Blanton, M. L. Clark, and O. R. Moss

This project develops apparatus and techniques to improve the quality of animal aerosol exposures for inhalation toxicology studies of airborne pollutants. In this report, we discuss work involving real-time instrumentation for use in exposure control.

Testing a Quartz Crystal Microbalance (QCM) Cascade Impactor

The deposition of inhaled particles in the lung depends on the aerodynamic diameter of the particles. Real-time measurement of the concentration of exposure aerosols in several particle-size ranges would improve our ability to deliver a prescribed initial lung burden (ILB) in nose-only exposures. A specially instrumented cascade impactor that can make such measurements should help to predict the amount of aerosol deposited during exposure so that we can end the exposure in time to attain the target ILB. In these cascade impactors, each impaction plate is the sensing crystal of a QCM. The natural frequency of the QCM sensing crystal decreases as mass is attached to the crystal. The change of frequency is directly proportional to the added mass up to some saturation value, above which the sensitivity progressively decreases. The QCM are reported to be able to detect about 10 ng of mass; 10 ng of pure $^{239}PuO_2$ contain about 0.54 nCi of activity, which is near the limit of detection with our radioactive counting methods for this material.

In operation, both sides of the QCM sensing crystals are coated with a viscous grease to help attach the aerosol particles to the plate (a standard practice in cascade impactor sampling). The particles are first collected on one side of the crystal; then, before the saturation mass is exceeded, the crystals are rotated, and collection continues on the opposite side. The instrument can be operated either in a continuous mode, with periodic measurement of the crystal frequencies, or in a mode where grab samples are taken and the frequency change of each crystal for each sample is measured. The second mode would be used for higher aerosol concentrations to avoid saturating the sensing crystal too soon.

In the course of evaluating the QCM cascade impactor as an exposure aerosol monitor, we made some interesting observations. In our experiments we used both sodium chloride and ammonium fluorescein aerosols, which we monitored with a real-time aerosol monitor (RAM-1, a product of GCA Environmental Instruments). We observed the frequency changes of a series of grab samples; then, after a short pause to rotate the sensing crystals, we continued the measurements using the opposite side of the sensing crystals. Figure 1 is a plot of frequency change per second of sample time against the cumulative sample time for Stage 6 with sodium chloride aerosol; Figure 2 shows the same kind of plot for ammonium fluorescein. Figure 3 is a plot of the RAM-1 readings against sample time during both experiments; it shows that the aerosol concentrations were stable. All samples were of approximately 10 sec duration. Assuming the aerosols were stable, the frequency changes per second of sample should have been constant, at least for several samples. Instead, they decreased with cumulative sample time until the crystals were rotated, then the relative sensitivity returned to a high value and decreased as before. The data represented are typical of the highest impactor stages. These apparent changes in sensitivity may result from changes in the collection efficiency of the impactor or from actual changes in sensitivity of the QCM.

By gravimetric measurement we determined that the ammonium fluorescein aerosol concentration was 74 mg/m^3. The average mass per hertz for all impactor stages on the first sample was 49 ng. Later, when the sensitivity had apparently decreased, the average mass per hertz rose to 69 ng. The sensitivity of these QCM is reported to be between 10 and 14 ng/Hz. To determine whether the observed behavior was due to changes in QCM sensitivity or to changes in stage collection efficiencies, we will measure stage mass directly by spectrofluorimetry and examine the relationship between mass and frequency change.

Aerosol Dose Monitoring

We have improved our real-time concentration monitor for radioactive aerosols. The original instrument employed a zinc-sulfide-coated photomultiplier tube as a

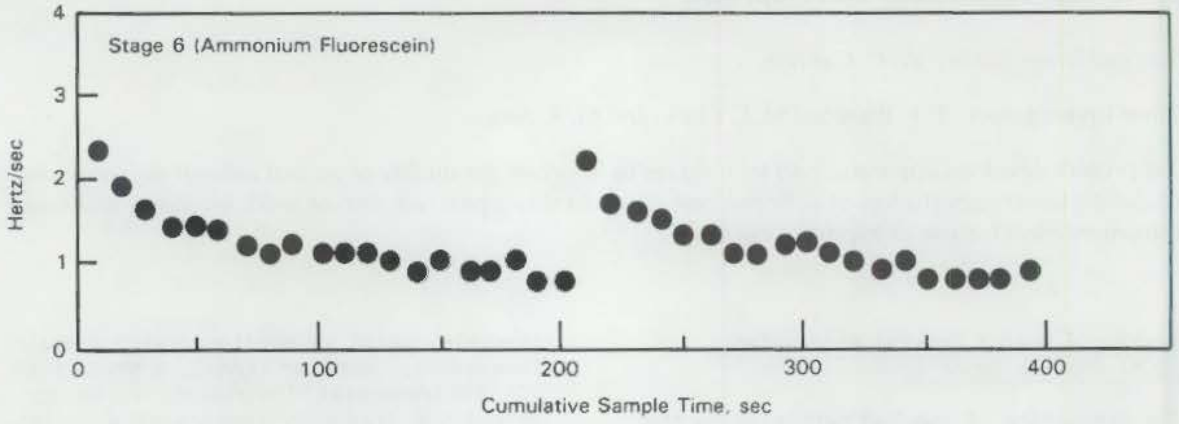

FIGURE 1. Frequency Change Per Second of Sample Versus Cumulative Sample Time with NaCl on Stage 6.

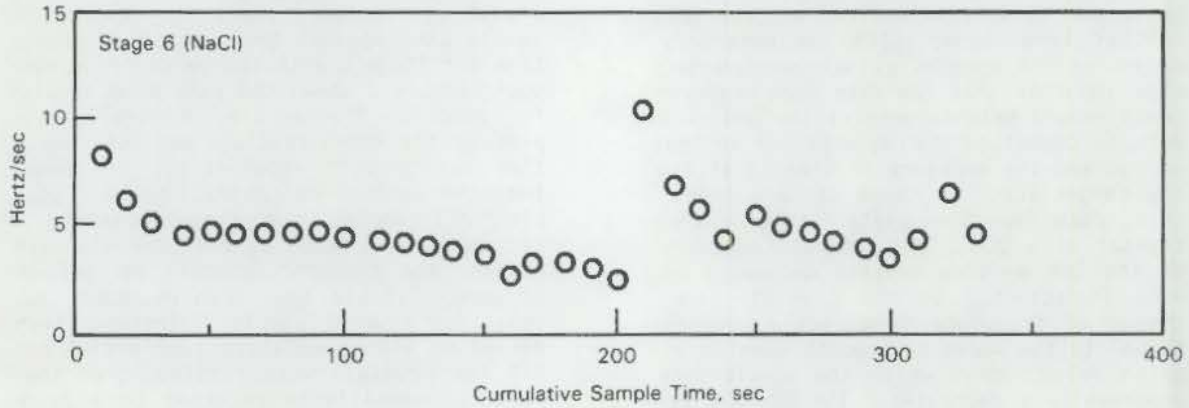

FIGURE 2. Frequency Change Per Second of Sample Versus Cumulative Sample Time with Ammonium Fluorescein on Stage 6.

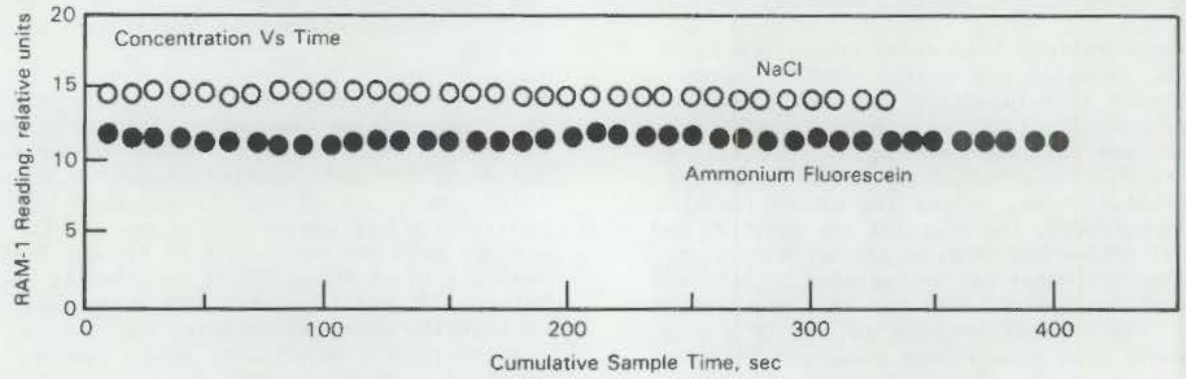

FIGURE 3. Plots of RAM-1 Readings when QCM Cascade Impactor Samples of Figures 1 and 2 were Taken.

sensing element for alpha-emitting aerosols. We have removed the zinc sulfide coating from the tube and installed interchangeable alpha or beta phosphor plastic disks so that the instrument can now be used to monitor either beta- or alpha-emitting aerosols. Figure 4 shows the counting efficiency of the monitor versus sample activity for three isotopes. The aluminized Mylar® light shield for the photomultiplier tube probably makes the instrument less efficient in counting the 225-keV beta of ^{147}Pu than the 526-keV beta of ^{90}Sr.

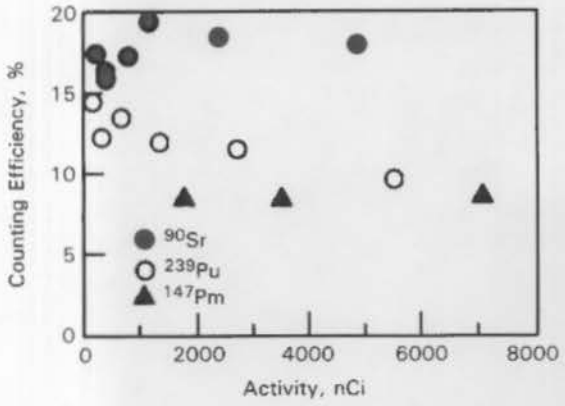

FIGURE 4. Counting Efficiency Versus Sample Activity for ^{239}Pu, ^{90}Sr and ^{147}Pm.

We have also devised a better way of monitoring aerosols during nose-only exposures. For rodents, where the ILB or the initial alveolar deposition is usually prescribed, the amount of most alpha- and beta-emitting aerosols (or nonradioactive aerosol) deposited in the animal cannot be monitored in real time. One can, however, monitor a sampler that collects aerosol similarly to the animals and relate this to the ILB of the animals. If the flow rate of a sampler equals the effective minute volume of the animals being exposed, the aerosol in the sampler at any time equals the ILB if the exposure were stopped at that time.

Originally, we collected grab samples of a known volume with our real-time monitor. The resulting change in count rate yielded the activity of the sample which, divided by the volume, equals the aerosol concentration. We now sample continuously, using the fact that the net count rate at any time is proportional to the activity in the lungs of the exposed animals.

• Biological Effects of Magnetic Fields

Principal Investigator: B. J. Kelman

Other Investigators: J. R. Decker, Jr., E. G. Kuffel, D. D. Mahlum, and R. L. Rommereim

Technical Assistance: M. Carey

The scope of this project is best understood within the historical context of previously completed work. The objective 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. The first controlled life-time study of mice exposed to a strong magnetic field (1 tesla) concluded this year. The study was carried out in a unique facility which permitted exposure and sham-exposure of animals under nearly identical conditions. No pattern of changes related to exposure was clearly identified in this study; several individual measurements were statistically significant and will require some further analysis to determine whether they are related to exposure.

Facilities

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

A 1200-ft^2 metal building was 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 that 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 housing units.

Lifetime Exposure to Magnetic Fields

Lifetime exposures of female CD-1 mice to 1-T homogeneous and 2-T/m gradient fields were concluded on May 3, 1984. The study was begun on April 13, 1982, when mice were 5 months of age. At that time, 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 were transferred from the energized magnet to the nonenergized magnet. The previously energized magnet was then degaussed, and the nonenergized magnet was energized. This procedure was designed to control for any slight differences that might have been present between the two magnets. At the termination of the experiment, data were obtained on mortality, body and organ weights, gross pathology, physiology, clinical chemistry, and histopathology.

Figure 1 shows the mean weights 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. Mice exposed or sham-exposed to the gradient fields grew more slowly during the first 40 days of exposure. The origin of the difference is not readily apparent, although we strongly suspect it is directly related to a condition that was initially undetected in the gradient animals and was corrected at about 40 days of exposure. This aspect of the study has been described in detail in a previous Annual Report (1983).

Table 1 shows the number of animals with lesions observed at necropsy, regardless of when the necropsies were performed.

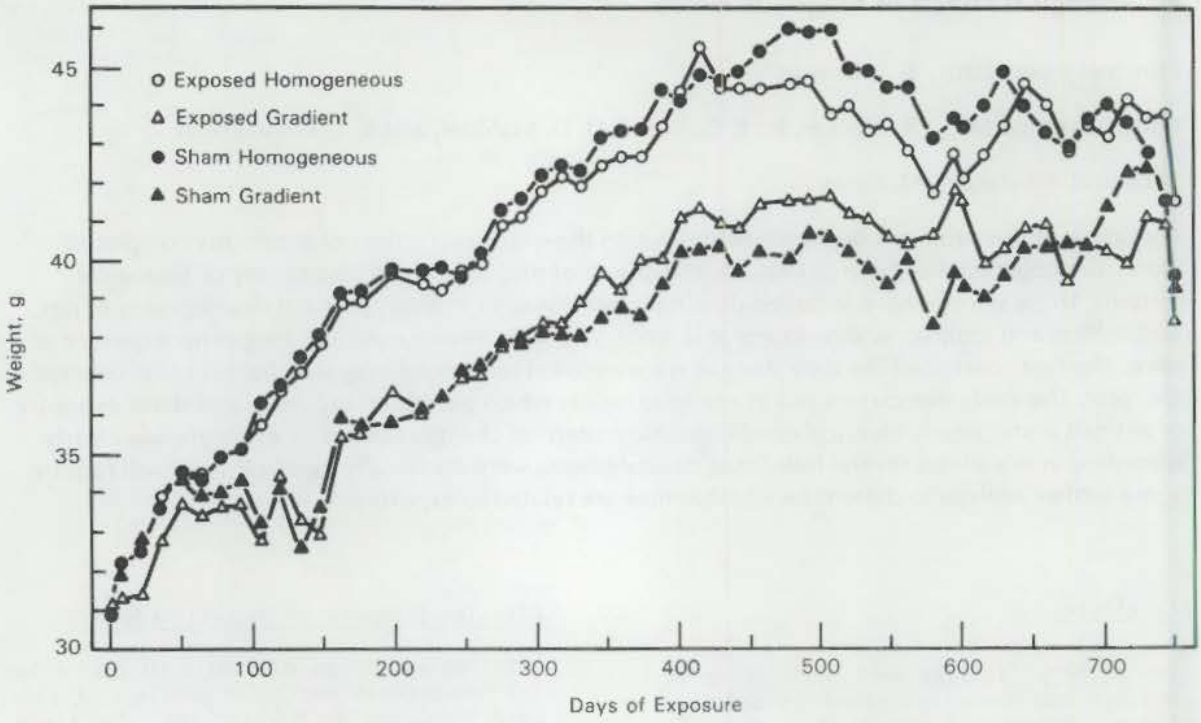

FIGURE 1. Mean Body Weights of Mice Exposed or Sham-Exposed to Magnetic Fields.

TABLE 1. Lesions Observed at Necropsy in All Mice Exposed to Magnetic Fields.

	Homogeneous		Gradient	
Organ	Sham	Exposed	Sham	Exposed
Lung	24	26	36	32
Liver	10	8	32	20
Kidney	10	14	4	0
Ovary	34	32	48	44
Uterus	40	28	48	36
Lymph	48	40	36	32
Spleen	24	18	12[a]	28[a]
Thymus	18	16	16	16
GI Tract	12	16	4[b]	20[b]
Mammary	8	2	0[b]	12[b]
Eyes	18	8	8	16
Pituitary	6	6	2	0
Subcutaneous	12	18	8	16
Heart	8	4	0	4
Number Examined	50	50	25	25

[a] $p < 0.025$
[b] $p < 0.01$

Significant increases were observed in splenic, gastrointestinal (GI), and mammary tissue lesions in gradient-exposed mice. Splenic and GI lesions were variable, but all mammary tissue lesions were carcinomas.

Table 2 shows the numbers of animals that survived 745 days of exposure and had lesions at necropsy. The number with liver and eye lesions was significantly higher in those exposed to the gradient field than for controls. The eye lesions were not confirmed by histopathological examination.

TABLE 2. Lesions Observed at Necropsy in Mice Surviving 750 Days of Exposure to Magnetic Fields

	Homogeneous		Gradient	
Organ	Sham	Exposed	Sham	Exposed
Lung	15	31	33	30
Liver	0	6	56[a]	20[a]
Kidney	0	13	0	0
Ovary	46	38	33	60
Uterus	69	56	67	80
Lymph	15	38	33	20
Spleen	0	13	11	20
Thymus	0	19	0	10
GI Tract	0	0	0	10
Mammary	0	6	0	0
Eyes	15	6	0[b]	30[b]
Pituitary	8	4	11	0
Subcutaneous	15	19	0	0
Heart	0	0	0	0
Number Surviving at 740 Days	13	16	9	10

[a] $p < 0.025$
[b] $p < 0.01$

Table 3 shows the number of animals with abnormal cardiac events. Heart rate was significantly higher in animals exposed to gradient fields than in sham-exposed animals. However, the number of animals with abnormal electrocardiograms did not differ significantly among groups. The hematology and clinical chemistry measurements listed in Table 4 were also completed for both exposed and sham-exposed groups. No significant changes were observed in any of these measurements. Histopathological examinations showed no consistent exposure-related effect in exposed animals.

TABLE 3. Cardiac Events in Mice Exposed to Magnetic Fields.

	Homogeneous		Gradient	
Measurement	Sham	Exposed	Sham	Exposed
ECG (% Abnormal)	58	73	43	71
Rate (BPM ± SD)	612 ± 31	617 ± 39	609 ± 31[a]	648 ± 33[a]
Number Measured	12	11	7	7

[a] $p < 0.01$

Figure 2 shows the cumulative mortality in all four groups as a function of exposure duration. Mortality curves are not significantly different for animals exposed or sham-exposed to the homogeneous field or sham-exposed to the gradient field. However, animals exposed to the gradient field showed a significantly lower mortality rate, which is not consistent with the greater number of lesions identified in those animals. We have therefore concluded that the lower mortality rate, combined with a lack of patterns in abnormalities, indicates that exposure to homogeneous or gradient fields did not adversely affect the animals in the study. Sufficient numbers of abnormal lesions were observed to make further investigation of their pathogenesis important. Accordingly, a second lifetime study is in the process of initiation.

TABLE 4. Hematological and Clinical Chemistry Measurements Performed on Mice Exposed to Magnetic Fields.

- Erythrocytes
  - Red Blood Cell Count (RBC)
  - Hemoglobin (g Hg/100 g)
  - Volume of Packed Red Cells (VPRC, ml/100 ml)
  - Mean Corpuscular Volume (MCV, μ^3)
  - Mean Corpuscular Hemoglobin (MCH, $\mu\mu g$)
  - Mean Corpuscular Hemoglobin Concentration (MCHC, %)
- Leukocytes (Cells x 10^3 mm^3)
  - White Blood Cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
- Bone Marrow
- Blood Urea Nitrogen (BUN, mg/100 ml)
- Protein (mg/100 ml)
- Albumin (mg/100 ml)
- Serum Glutamic-Oxaloacetic Transaminase (SGOT, IU/L)
- Serum Glutamic-Pyruvic Transaminase (SGPT, IU/L)

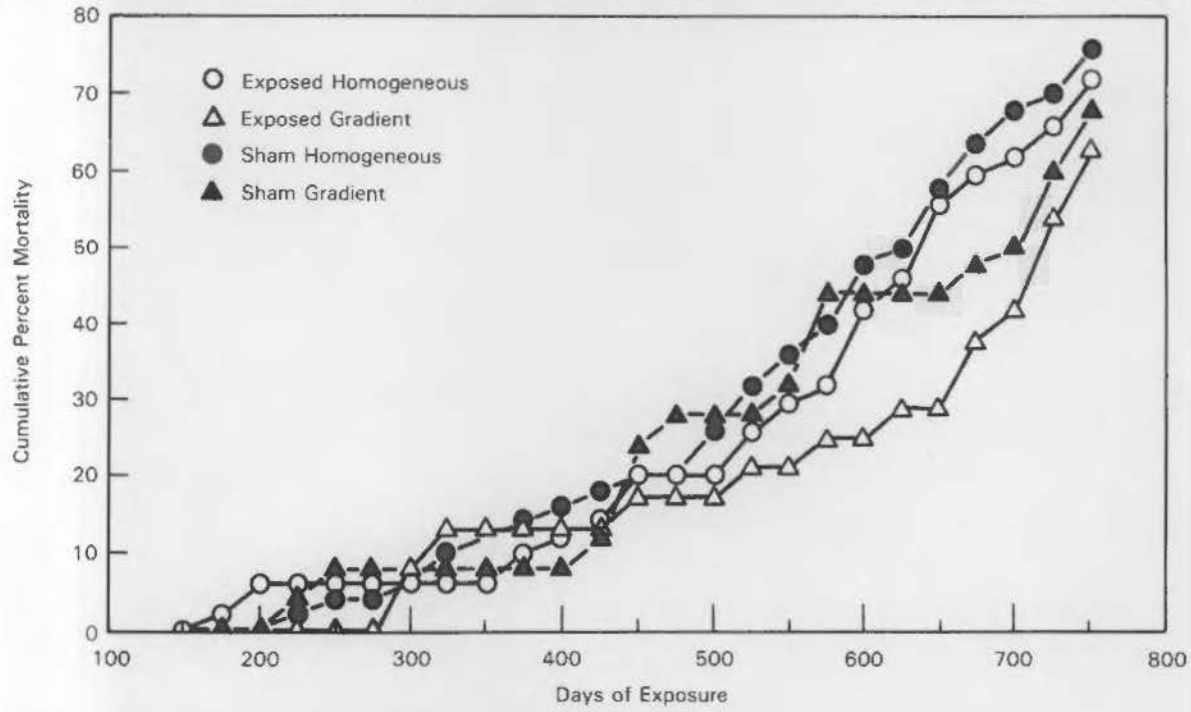

FIGURE 2. Cumulative Mortality Rate of Mice Exposed or Sham-Exposed to Magnetic Fields.

General Life
Sciences

• Metal-Membrane Interactions

Principal Investigator: R. P. Schneider

Other Investigators: R. A. Lindberg

Technical Assistance: L. E. Daughtry, and K. A. Kafton

Using zinc uptake system of *Neurospora crassa* as a model system, we have investigated the kinetics and regulation of heavy metal uptake by eukaryotic microorganisms. We performed experiments designed to show whether free Zn^{2+} or the zinc-citrate complex is the form recognized by the zinc-membrane receptor. These experiments showed that the affinity of the uptake system is the same for free zinc or the citrate chelate, indicating that the receptor is indifferent to the form of the metal. The system is highly specific; i.e., zinc uptake is not affected by 100-fold higher concentrations of Co, Pb, U, Ni, Ca, Mg or Fe. Uptake of Zn is inhibited by Hg and Cd, but these two metals are not taken up by the system at measurable rates.

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

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. We have also shown that zinc is taken up by the cells from solutions in which 99.9% of the metal is chelated by citrate. Further, we showed that citrate is not taken up in amounts sufficient to account for zinc uptake (Annual Report, 1982). Thus, either the transport system strips zinc from the zinc-citrate complex, or the small amount (0.1%) of free Zn^{2+} is the form recognized and transported.

Last year we examined the kinetics of zinc uptake by zinc-starved Neurospora in the presence or absence of citrate. The dependence of uptake rate on zinc concentration was about the same in the presence or absence of 8 mM citrate (Figure 1). These data strongly suggest that the transport receptor (or carrier) has the same affinity for free zinc or for zinc citrate, because only 0.1% of the zinc is free when citrate is present. If free zinc were the substrate, one would expect the affinity of the system in the absence of citrate to be 1000-fold higher than in its presence. The citrate complex is probably the normal substrate because Neurospora excretes large quantities of citrate during normal growth, and Zn^{2+} is an uncommon form of the metal in nature. Through some unknown mechanism, the receptor is able to recognize zinc, whether free or chelated, with the same affinity--a highly unusual property.

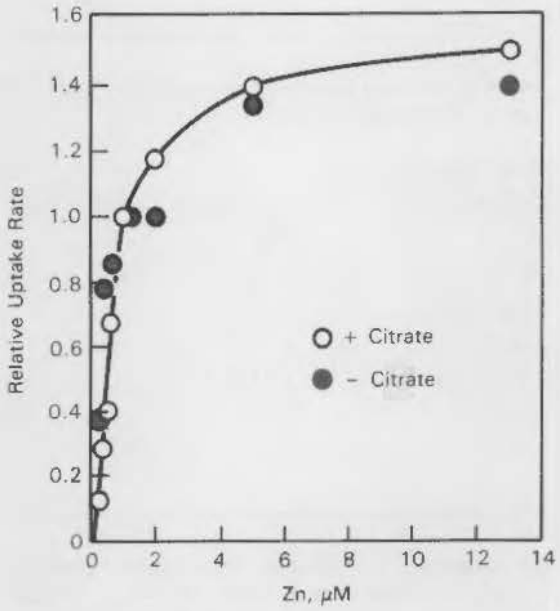

FIGURE 1. Dependence of Zinc Uptake Rate on Zinc Concentration by Zinc-Starved *Neurospora crassa* in the Presence or Absence of 8 mM Citrate. Data (means of three experiments) are normalized by expressing them as a proportion of the rates at a concentration of 1 μM zinc.

Toxic trace metals are probably accumulated by microorganisms via uptake systems for nutrient metals. For this reason, cells were starved for zinc in order to

depress synthesis of the zinc uptake system, then used to investigate the effects of several other metals on zinc uptake (Table 1). Our hypothesis was that metals taken up by the zinc system would inhibit uptake by competition. Of the metals studied, only cadmium and mercury inhibited uptake of zinc; however, subsequent experiments with radioisotopes of cadmium and mercury showed that they were not taken up by zinc-starved Neurospora (Figure 2). The system is highly specific because most enzyme systems discriminate poorly between cadmium and zinc. Although the presence of cadmium in the environment may interfere with accumulation of zinc by Neurospora, the specifity of the uptake system protects against accumulation of toxic concentrations of cadmium even when Neurospora is starved for zinc.

TABLE 1. Effect of Other Metals on Uptake of 1 μM Zinc by Zinc-Starved *Neurospora crassa*.

Metal Concentration, μM:	1	10	100
Metal Added	Percent Control Uptake		
Cd^{2+}	39	6	0
Co^{2+}	99	103	133
Hg^{2+}	126	52	0
Ni^{2+}	117	90	97
UO_2^{2+}	109	95	112
Pb^{2+}	--	--	103
Fe^{2+}	--	85	87

In summary, our studies have shown that N. crassa synthesizes a high-affinity uptake system for zinc when growing in a zinc-deficient environment. Uptake is dependent on metabolic energy. The system is also negatively regulated; when sufficient quantities of zinc are accumulated, the system is inactivated, with a half-time of about 10 minutes. The affinity for Zn^{2+}

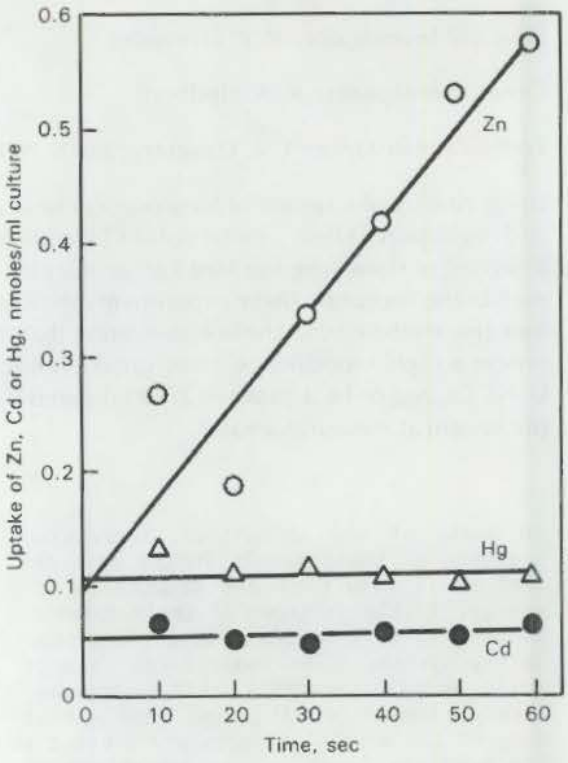

FIGURE 2. Uptake of Zinc, Cd and Hg by Zinc-Starved *Neurospora crassa*.

and zinc citrate is about the same, K_m = 1.5 μM. The system is highly specific; of the divalent metal ions examined, only cadmium and mercury inhibit zinc uptake, and even they are not taken up by zinc-starved cells.

When these kinds of data are available for other microorganisms and nutrient transport systems (e.g., iron, copper and magnesium), we will be able to predict bioaccumulation of toxic metals based on their amounts relative to nutrient metals, in a given environment.

Health and Environmental Risk Analysis

• Complex Mixtures — Relative Potency Matrix

Principal Investigator: P. J. Mellinger

Other Investigators: R. O. Gilbert and B. W. Wilson

The purpose of this program was to provide a relative potency matrix to relate potential human health risks from one hydrocarbon industry to another.

A relative potency matrix was generated to test how nonhuman biological data may be used to predict potential human-health risks from a variety of hydrocarbon-based industries. Ames assay (mutagenicity), mammalian cell transformation (carcinogenicity), and mouse skin-painting (carcinogenicity) data were gathered for coal-gasification tar, coal-liquefaction heavy distillate, shale oil cigarette-smoke condensate, and the emissions from roofing tar, petroleum and the combustion of diesel and gasoline engines. The range of relative potencies suggests a decrease with increasing biological complexity of the test.

After chemistry data were added to the matrix, biological test data were compared statistically, based on eight "predictors": molecular weight, the presence of aliphatic hydrocarbons, polycyclic aromatic hydrocarbons (PAH), hydroxy PAH, nitrogen-containing polycyclic aromatic compounds, hydroaromatics, amino-PAH, and the degree of alkylation.

Preliminary findings suggest the following: 1) for mutation, amino-PAH is always highly significant no matter what other "predictor" occurs in the regression equation. 2) For initiation/promotion, molecular weight is always significant in the regression equation, no matter what other predictor also occurs. 3) No conclusions can be reached about chronic data at this time because of the small sample size.

Medical Applications of Nuclear Technology

• Blood Irradiator Development

Principal Investigators: F. P. Hungate and R. E. Weller

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

A fully portable blood irradiator has been developed to provide continuous extracorporeal irradiation of circulating blood. The beta irradiation used typically reduces the numbers of circulating lymphocytes to less than 10% of the pretreatment level within 1-2 weeks. It is anticipated that the device will be useful in suppressing early rejection of transplanted tissues or organs and in treating certain blood diseases. In FY 1984 we developed a computer model to predict external radiation doses. We also demonstrated that the functioning of transplanted kidneys was protected from the early rejection process in dogs that received treatment with the irradiator.

In anticipation of using the blood irradiator in clinical trials, radiation doses to the patient and to attending personnel must be evaluated. On the basis of measured doses escaping from the units with their existing shielding, a computer code was developed to establish isodose curves and to optimize the disposition of shielding. With the computer model as a guide, construction drawings are being prepared on the assumption that tungsten will provide the major shielding. We have also assumed that components will be formed using sintering technology. When the design is approved, a complete shield unit will be fabricated and tested to verify the computer code used to predict external doses.

Initially, it was assumed that the dose rate to blood for humans would need to be greater than that used for dogs by the ratio of human blood volume/dog blood volume (i.e., about six- to eightfold). To achieve this, we had planned to elongate each unit and to place two units in parallel so that blood would circulate through both as it passed from the artery through the irradiator and back to the vein. However, the computer model showed that lengthening the unit and using two units in parallel would increase shielding weight to an objectionable degree. Our research with goats, however, showed that it might not be necessary to increase the dose to blood as much as previously thought. In goats weighing 30 to 40 kg, the decline in numbers of circulating lymphocytes was almost equal to that observed in dogs that weighed 10 to 15 kg. In both cases, the transit doses were in the range of 20 to 35 rad. Thus, transit doses of 40 to 50 rad are now planned for initial human clinical trials, and it will not be necessary to use two units to use the longer design.

Studies of the efficacy of the irradiators in controlling early rejection of kidney transplants were continued, using mongrels as donors and beagles from our own colony as hosts. The genetic difference between the breeds causes more severe rejection than could be attained with the beagle-beagle transplants performed earlier. Treatment regimens included installing a carotid-jugular shunt and immediately inserting an irradiator in the shunt flow. Each irradiator was left in place for 2 to 3 weeks prior to the kidney transplant. The animals were maintained with 5 g of aspirin and 25 mg Persantine (Geigy Pharmaceutical), twice a day, until blood flow through the shunt and irradiator could no longer be maintained. The dog's own two kidneys were removed, so that survival was dependent on the success of the transplanted organ.

The four successfully treated animals survived 26, 28, 30 and 41 days, respectively. In another animal, which succumbed 16 days after the transplant, the shunt and irradiator were removed the day following surgery. This early demise without irradiation emphasizes the importance of maintaining continuous irradiation until the transplant is functioning well. Typically, animals that received kidney transplants without irradiation therapy survive for only 10 to 12 days.

This year we are beginning new studies with leukemic dogs as part of a collaborative effort with Dr. E. D. Thomas and Dr. F. Appelbaum (Fred Hutchinson Cancer Center, Seattle, WA) to evaluate the use of the irradiator for treatment of blood diseases. In order to use the irradiator with dogs of various sizes, we have designed a new whole-body harness of nylon netting for attaching the irradiator to the dogs.

In addition, we plan to finalize irradiator design for use in human clinical trials.

*Department of Surgery, University of Washington, Seattle, WA

- **List of DOE Radioisotope Customers with Summary of Radioisotope Shipments, FY 1983**

Principal Investigator: D. A. Baker

The annual list of DOE radioisotope customers was published in August. The document contains the various radioisotopes sold by the DOE laboratories to domestic, foreign, and other DOE facilities. A list of suppliers is given along with the isotopes sold or transferred. Lists of customers are given, with their addresses and the isotopes purchased. Customers are also cross-referenced by isotope and state, or country for foreign sales. A table of isotope sales by number of shipments, quantity, and dollar value is given for each customer type (domestic, DOE, and foreign). Total value of sales of DOE radioisotopes for FY83 were $9.5 million, a decrease of 13% from last year.

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 IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
CONTROL	738 F	0	0.00	0.00				08/11/83		171.5*	Hemangiosarcoma, Heart
CONTROL	740 F	0	0.00	0.00				06/18/83		169.6*	Malignant Lymphoma
CONTROL	749 F	0	0.00	0.00				09/14/84		181.4*	Processing
CONTROL	755 M	0	0.00	0.00				12/10/82		162.2*	Status Epilept, Nephrosclero
CONTROL	766 M	0	0.00	0.00				06/26/84		180.3*	Processing
CONTROL	775 F	0	0.00	0.00				10/05/81		147.3*	Pulmonary Thromboembolism
CONTROL	785 M	0	0.00	0.00					182.4*		
CONTROL	789 M	0	0.00	0.00				07/25/83		167.9*	Malignant Lymphoma
CONTROL	792 M	0	0.00	0.00				04/28/76		79.5*	Oral Tumor
CONTROL	800 F	0	0.00	0.00					179.3*		
CONTROL	801 M	0	0.00	0.00				02/23/82		148.1*	Lung Tumor
CONTROL	811 F	0	0.00	0.00					178.2*		
CONTROL	846 M	0	0.00	0.00				04/08/83		159.6*	Nephrosclerosis
CONTROL	861 M	0	0.00	0.00					177.1*		
CONTROL	868 F	0	0.00	0.00					175.7*		
CONTROL	872 F	0	0.00	0.00				11/05/82		152.8*	Lung Tumor
CONTROL	878 M	0	0.00	0.00					173.7*		
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					170.6*		
CONTROL SACRIFICE	701 F	0	0.00	0.00				04/18/79		121.0*	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	Epilepsy
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		158.9		
D-1 LOWEST	858 M	0	0.00	0.00	13.5	18.2	07/06/71		158.9		
D-1 LOWEST	865 F	0	0.00	0.00	9.0	17.4	07/06/71		158.9		
D-1 LOWEST	879 M	0	0.00	0.00	14.5	17.9	10/07/71	07/27/84		153.7	Hemangiosarcoma, Liver,Spleen
D-1 LOWEST	886 F	0	0.00	0.00	10.5	18.2	11/10/71	04/04/84		148.8	Meningioma, malignant
D-1 LOWEST	907 F	0	0.00	0.00	11.5	15.9	11/10/71		154.7		
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	12/19/83		145.3	Chondrosarcoma, Nasal
D-1 LOWEST	832 F	2	0.02	0.22	9.0	16.5	04/26/71		161.2		
D-1 LOWEST	900 M	3	0.02	0.22	13.0	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	05/04/84		154.0	Pneumonia
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		158.9		
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		155.8		
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	6	0.06	0.63	9.5	19.1	01/19/71		164.4		

* 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 IDENT		INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-1 LOWEST	788	M	8	0.06	0.62	13.0	18.7	02/09/71	04/13/84		158.1	Processing
D-1 LOWEST	850	F	5	0.06	0.53	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		155.8		
D-1 LOWEST	807	F	8	0.07	0.73	11.0	14.6	02/09/71	07/24/81		125.4	Pituitary Tumor, Cushing's
D-1 LOWEST	841	F	5	0.07	0.75	8.0	17.7	06/08/71		159.8		
D-1 LOWEST	908	M	9	0.07	0.77	11.0	15.9	11/10/71	04/01/80		100.7	Unknown, Pulmon. Hyalinosis
D-2 LOW	776	M	10	0.07	0.74	13.5	20.2	03/04/71	09/19/84		162.6	Processing
D-2 LOW	842	M	10	0.07	0.77	13.5	18.6	07/06/71		158.9		
D-2 LOW	767	M	10	0.08	0.83	12.0	18.2	12/21/70		165.3		
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	662	M	13	0.09	1.00	13.0	17.3	06/08/71	06/25/83		144.6	Peritonitis
D-2 LOW	871	M	13	0.09	0.96	13.5	16.9	07/06/71		158.9		
D-2 LOW	874	M	16	0.11	1.24	13.0	16.8	07/06/71		158.9		
D-2 LOW	754	M	22	0.15	1.69	13.0	19.5	01/19/71	01/10/78		83.7	Epilepsy
D-2 LOW	845	F	19	0.15	1.63	11.5	17.6	06/08/71	08/09/84		158.1	Processing
D-2 LOW	748	F	14	0.16	1.75	8.0	19.8	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	04/17/84		153.4	Hemangioma, Spleen
D-2 LOW	831	F	21	0.18	2.00	10.5	17.9	06/08/71	05/14/84		155.2	Pneumonia
D-2 LOW	881	F	19	0.19	2.09	9.0	17.7	10/07/71		155.8		
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	04/22/84		153.6	Urinary Bladder Tumor
D-2 LOW	757	M	36	0.23	2.57	14.0	18.5	12/21/70		165.3		
D-2 LOW	876	F	19	0.24	2.69	7.0	17.9	10/07/71		155.8		
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	12/15/83		153.4	Multilobular Sarcoma, Skull
D-2 LOW	877	F	34	0.29	3.24	10.5	17.9	10/07/71		155.8		
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		161.2		
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	19.2	01/20/71	11/02/83		153.4	Lung Tumor
D-3 MED-LOW	782	M	62	0.42	4.59	13.5	19.0	02/10/71	05/27/83		147.5	Neurofibrosarcoma, Brachial P
D-3 MED-LOW	786	M	62	0.42	4.59	13.5	19.5	03/04/71		162.9		
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	05/24/84		156.9	Processing
D-3 MED-LOW	883	M	63	0.44	4.85	13.0	17.7	10/07/71		155.8		
D-3 MED-LOW	778	M	74	0.46	5.10	14.5	20.2	03/04/71	08/26/79		101.7	Pulmonary Thromboembolism
D-3 MED-LOW	838	M	56	0.46	5.09	11.0	17.8	06/08/71	07/20/84		157.4	Processing
D-3 MED-LOW	795	F	54	0.49	5.40	10.0	15.0	01/20/71	09/06/83		151.5	Lung Tumor
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		155.8		
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

* 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 IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	797 F	85	0.70	7.73	11.0	16.4	03/04/71		162.9		
D-3 MED-LOW	848 F	75	0.72	7.94	9.5	21.3	10/07/71		155.8		
D-3 MED-LOW	827 F	89	0.74	8.09	11.0	16.7	04/26/71		161.2		
D-3 MED-LOW	697 M	140	0.85	9.33	15.0	19.5	10/30/70	05/08/80		114.3	Cardiac Valve Insufficiency
D-3 MED-LOW	750 M	118	0.93	10.26	11.5	19.6	01/20/71	06/28/84		161.2	Processing
D-3 MED-LOW	884 M	123	1.12	12.30	10.0	17.8	10/08/71	09/12/84		155.2	Lung Tumor
D-3 MED-LOW	844 F	135	1.17	12.86	10.5	17.6	06/08/71		159.8		
D-3 MED-LOW	905 F	127	1.36	14.94	9.5	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	06/27/84		155.7	Lung Tumor
D-4 MEDIUM	809 F	157	1.36	14.95	10.5	15.3	03/04/71	05/28/81		122.8	Liver Cirr, Thy T., Addison's
D-4 MEDIUM	764 F	158	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		161.2		
D-4 MEDIUM	814 F	140	1.50	16.47	8.5	15.1	03/04/71	10/17/79		103.5	Lung Tumor, Thyroid Adenoma
D-4 MEDIUM	836 M	255	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		159.8		
D-4 MEDIUM	888 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	06/24/82		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, Adrenal & 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 Tumor, 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	2.73	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	438	3.19	35.04	12.5	17.1	04/26/71	11/12/79		102.6	Lung Tumor
D-4 MEDIUM	857 M	496	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	783 M	1394	10.14	111.92	12.5	18.9	02/09/71	12/03/75		57.8	Lung Tumor
D-5 MED-HIGH	884 M	1344	10.18	112.00	12.0	20.5	07/07/71	08/18/74		37.4	Lung Tumor, Rad. Pneumonitis
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	Lung Tumor, 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	787 M	651	4.73	52.08	12.5	19.5	03/04/71	02/08/79		95.2	Lung Tumor, Intestinal Tumor
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	772 M	1896	14.99	164.87	11.5	19.8	02/09/71	06/26/75		52.5	Lung Tumor, 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

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

DOSE GROUP	DOG IDENT		INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
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	Uri Bladr & Lung & Adr Tumor
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	739	F	1511	17.17	188.88	8.0	18.5	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		76.5	Lung Tumor
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	Lung Tumor, Osteoarthropathy
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	753	F	2448	23.43	257.68	9.5	18.5	12/21/70	10/02/76		69.4	Lung Tumor
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	910	M	14267	103.76	1141.36	12.5	15.9	11/10/71	10/12/72		11.1	Radiation Pneumonitis
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	913	M	4900	35.64	392.00	12.5	17.4	07/19/72	08/18/72		1.0	Sacrificed
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

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

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
CONTROL	939 M	0	0.00	0.00				10/01/82		136.9*	Urinary Bladder Tumor
CONTROL	949 F	0	0.00	0.00					160.7*		
CONTROL	978 M	0	0.00	0.00					160.6*		
CONTROL	990 F	0	0.00	0.00				07/08/79		97.4*	Pyometra
CONTROL	996 F	0	0.00	0.00				07/06/84		157.2*	Processing
CONTROL	1005 M	0	0.00	0.00					160.0*		
CONTROL	1007 F	0	0.00	0.00					160.0*		
CONTROL	1024 M	0	0.00	0.00					159.5*		
CONTROL	1038 M	0	0.00	0.00					157.4*		
CONTROL	1045 M	0	0.00	0.00					157.4*		
CONTROL	1054 F	0	0.00	0.00					157.1*		
CONTROL	1061 F	0	0.00	0.00				07/07/01		118.2*	Malignant Lymphoma
CONTROL	1093 M	0	0.00	0.00				11/04/83		142.4*	Pituitary Tumor, Cushing's
CONTROL	1097 F	0	0.00	0.00					152.6*		
CONTROL	1112 M	0	0.00	0.00					152.4*		
CONTROL	1116 F	0	0.00	0.00					152.1*		
CONTROL	1186 F	0	0.00	0.00					145.5*		
CONTROL	1197 M	0	0.00	0.00					145.0*		
CONTROL	1209 M	0	0.00	0.00					144.7*		
CONTROL	1225 F	0	0.00	0.00					143.9*		
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	1118 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		140.4		
D-1 LOWEST	1003 M	0	0.00	0.00	14.0	19.6	01/18/73		140.4		
D-1 LOWEST	1023 F	0	0.00	0.00	12.5	19.2	01/18/73		140.4		
D-1 LOWEST	1039 M	0	0.00	0.00	11.0	17.0	01/18/73		140.4		
D-1 LOWEST	1044 F	0	0.00	0.00	11.5	17.0	01/18/73		140.4		
D-1 LOWEST	1055 M	0	0.00	0.00	13.0	16.8	01/18/73		140.4		
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		136.0		
D-1 LOWEST	1194 F	0	0.00	0.00	10.5	19.8	04/18/74		125.4		
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		125.4		
D-1 LOWEST	951 M	2	0.01	0.14	14.0	19.3	12/19/72	02/14/83		121.9	Anesthetic Death
D-1 LOWEST	1008 M	2	0.01	0.15	13.5	19.6	01/18/73		140.4		
D-1 LOWEST	1193 F	2	0.01	0.16	12.5	19.8	04/18/74		125.4		
D-1 LOWEST	959 M	3	0.02	0.22	13.5	19.2	12/19/72	06/22/84		138.1	Processing

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

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	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	Malignant Lymphoma
D-1 LOWEST	1095 F	2	0.02	0.19	10.5	16.6	05/31/73		136.0		
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		127.1		
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		141.4		
D-1 LOWEST	1106 F	5	0.05	0.50	10.0	16.4	05/31/73	01/14/83		117.4	Adrenal Carcinoma, BPO
D-2 LOW	1065 F	6	0.05	0.60	10.0	18.3	05/31/73		136.0		
D-2 LOW	1082 M	11	0.06	0.69	16.0	18.0	05/31/73	12/04/79		78.1	Paralysis, Spinal Cord Degen.
D-2 LOW	1188 M	11	0.06	0.71	15.5	18.4	02/26/74	01/15/84		118.6	Metastatic Lng Tmr, Prim. Unk
D-2 LOW	1084 M	13	0.07	0.76	17.0	17.5	05/31/73		136.0		
D-2 LOW	1090 F	10	0.08	0.83	12.0	17.3	05/31/73		136.0		
D-2 LOW	1222 M	15	0.10	1.07	14.0	19.0	04/18/74		125.4		
D-2 LOW	971 F	13	0.11	1.24	10.5	19.2	12/19/72	05/04/83		124.5	Hemangiosarcoma, Spleen
D-2 LOW	999 F	11	0.11	1.16	9.5	18.7	12/19/72		141.4		
D-2 LOW	1229 M	16	0.11	1.19	13.5	16.8	02/26/74	05/25/84		122.9	Pneumonia, Thyroid Tumor
D-2 LOW	1070 M	22	0.12	1.33	16.5	18.1	05/31/73	12/13/82		126.4	Processing
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		141.4		
D-2 LOW	1033 M	17	0.14	1.55	11.0	19.1	02/22/73		139.2		
D-2 LOW	1036 F	16	0.14	1.52	10.5	18.2	02/22/73		139.2		
D-2 LOW	1216 M	23	0.16	1.77	13.0	19.3	04/18/74		125.4		
D-2 LOW	1060 F	22	0.18	2.00	11.0	17.8	02/22/73		139.2		
D-2 LOW	981 M	30	0.21	2.31	13.0	19.0	12/19/72		141.4		
D-2 LOW	1046 M	27	0.22	2.45	11.0	18.3	02/22/73		139.2		
D-2 LOW	1050 F	22	0.22	2.44	9.0	18.1	02/22/73		139.2		
D-2 LOW	1078 F	29	0.22	2.42	12.0	18.0	05/31/73	11/09/83		125.3	Meningioma, malignant
D-2 LOW	1207 F	22	0.24	2.59	8.5	17.6	02/26/74		127.3		
D-2 LOW	1196 F	28	0.25	2.80	10.0	17.9	02/26/74		127.1		
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	Malignant Lymphoma
D-3 MED-LOW	1089 F	41	0.31	3.42	12.0	17.3	05/31/73		136.0		
D-3 MED-LOW	972 F	40	0.33	3.64	11.0	19.2	12/19/72		141.4		
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		125.4		
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		130.8		

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

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

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	1165 M	76	0.43	4.75	16.0	17.3	11/06/73		130.8		
D-3 MED-LOW	1309 M	60	0.44	4.80	12.5	18.5	03/04/75		114.9		
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		114.9		
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	Delayed Radiation Pneumonitis
D-3 MED-LOW	1190 F	71	0.54	5.92	12.0	18.1	02/26/74		127.1		
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		141.4		
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	Malignant Lymphoma
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		136.0		
D-3 MED-LOW	1000 F	70	0.71	7.78	9.0	18.7	12/19/72		141.4		
D-3 MED-LOW	1056 M	97	0.71	7.76	12.5	17.9	02/22/73		139.2		
D-3 MED-LOW	1004 M	116	0.73	8.00	14.5	19.6	01/18/73		140.4		
D-3 MED-LOW	1026 M	116	0.78	8.59	13.5	19.2	01/18/73		140.4		
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	05/04/84		134.3	Processing
D-3 MED-LOW	1212 F	111	1.19	13.06	8.5	17.6	02/26/74		127.1		
D-4 MEDIUM	1176 M	129	0.87	9.56	13.5	15.5	10/06/73		131.8		
D-4 MEDIUM	1221 F	124	1.13	12.40	10.0	19.0	04/18/74		125.4		
D-4 MEDIUM	1195 M	228	1.38	15.20	15.0	18.1	02/26/74		127.1		
D-4 MEDIUM	1032 M	162	1.40	15.43	10.5	18.3	11/30/72	12/08/72		0.3	Sacrificed
D-4 MEDIUM	1053 F	149	1.42	15.58	9.5	17.9	02/22/73		139.2		
D-4 MEDIUM	997 M	203	1.60	17.65	11.5	19.6	01/18/73		140.4		
D-4 MEDIUM	991 F	194	1.76	19.40	10.0	18.8	12/19/72	06/20/83		126.0	Urinary Bladder & Ovarian Tmr
D-4 MEDIUM	1177 M	262	1.76	19.41	13.5	16.6	11/06/73		130.8		
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	Bone Tumor, Lung Tumor
D-4 MEDIUM	973 F	271	2.24	24.64	11.0	19.2	12/19/72		141.4		
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		136.0		
D-4 MEDIUM	1114 M	430	2.70	29.66	14.5	16.4	05/31/73		136.0		
D-4 MEDIUM	1062 M	435	2.93	32.22	13.5	17.8	02/22/73	05/30/84		135.2	Processing
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	16.0	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	Pneumonia, Rad. Pneumonitis
D-4 MEDIUM	1198 M	539	3.50	38.50	14.0	17.9	02/26/74		127.1		
D-4 MEDIUM	952 F	365	3.59	40.56	9.0	19.2	12/19/72	06/03/83		125.4	Bone Tumor
D-4 MEDIUM	1166 M	673	4.08	44.87	15.0	17.3	11/06/73	06/23/84		127.5	Processing

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

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION: NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE: WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION: 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-4 MEDIUM	1220 F	518	4.28	47.09	11.0	19.0	04/18/74		125.4		
D-4 MEDIUM	992 F	555	4.39	48.26	11.5	18.8	12/19/72	07/26/84		139.2	Processing
D-4 MEDIUM	983 M	617	4.67	51.42	12.0	19.0	12/19/72	12/29/83		132.3	Processing
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	1191 F	591	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	03/02/84		123.8	Bone 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	1035 F	571	5.46	60.11	9.5	18.2	02/22/73	03/04/84		132.3	Processing
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	18.8	05/31/73	02/12/78		56.4	Addison's, Disease, G.I. Tumo
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-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 & Lung Tumor, Addison's
D-6 HIGH	1162 F	6959	70.29	773.22	9.0	17.3	11/06/73	12/19/78		61.4	Bone Tumor, Addison's Disease
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	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	1064 M	8453	63.66	700.22	13.5	16.7	01/18/73	04/14/77		50.8	Bone Tumor, Lung 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	1037 M	4854	44.13	485.40	10.0	18.2	02/22/73	11/21/78		68.9	Bone Tumor
D-6 HIGH	1175 F	6201	75.16	826.80	7.5	16.6	11/06/73	02/24/78		51.6	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	1009 M	3630	26.40	290.40	12.5	19.6	01/18/73	04/01/78		62.4	Lung Tumor, Osteoarthropathy
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	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	1002 M	2907	18.88	207.64	14.0	19.6	01/18/73	01/21/80		84.1	Bone Tumor, Lung Tumor

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG IDENT		INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
CONTROL	1356	M	0	0.00	0.00					124.7*		
CONTROL	1365	M	0	0.00	0.00					124.6*		
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					123.3*		
CONTROL	1405	M	0	0.00	0.00				08/13/84		121.3*	Processing
CONTROL	1409	M	0	0.00	0.00					122.8*		
CONTROL	1418	M	0	0.00	0.00					122.5*		
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					121.9*		
CONTROL	1483	F	0	0.00	0.00					120.9*		
CONTROL	1509	M	0	0.00	0.00					120.1*		
CONTROL	1516	F	0	0.00	0.00					119.9*		
CONTROL	1525	M	0	0.00	0.00					119.6*		
CONTROL	1526	M	0	0.00	0.00					119.6*		
CONTROL	1528	F	0	0.00	0.00					119.1*		
CONTROL	1543	M	0	0.00	0.00					118.9*		
CONTROL	1563	F	0	0.00	0.00					108.8*		
CONTROL	1572	F	0	0.00	0.00					108.7*		
CONTROL	1577	M	0	0.00	0.00					108.7*		
CONTROL	1584	F	0	0.00	0.00					108.6*		
CONTROL	1594	F	0	0.00	0.00					108.6*		
CONTROL	1608	M	0	0.00	0.00					108.4*		
CONTROL	1633	F	0	0.00	0.00					101.6*		
CONTROL	1638	F	0	0.00	0.00					101.3*		
VEHICLE	1361	M	0	0.00	0.00	8.5	21.0	02/13/76		103.6		
VEHICLE	1381	F	0	0.00	0.00	8.5	19.8	02/13/76		103.6		
VEHICLE	1392	M	0	0.00	0.00	13.0	22.0	04/22/76		101.3		
VEHICLE	1406	M	0	0.00	0.00	13.5	21.6	04/22/76		101.3		
VEHICLE	1412	F	0	0.00	0.00	9.0	19.0	02/13/76		103.6		
VEHICLE	1421	M	0	0.00	0.00	13.0	23.3	06/23/76		99.3		
VEHICLE	1457	F	0	0.00	0.00	12.0	20.6	04/22/76		101.3		
VEHICLE	1491	F	0	0.00	0.00	8.0	21.6	06/23/76		99.3		
VEHICLE	1504	F	0	0.00	0.00	10.0	20.9	06/23/76		99.3		
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		98.1		
VEHICLE	1531	F	0	0.00	0.00	9.0	20.9	07/27/76		98.1		
VEHICLE	1542	M	0	0.00	0.00	12.0	20.8	07/27/76		98.1		
VEHICLE	1566	M	0	0.00	0.00	14.0	18.3	03/15/77		90.5		
VEHICLE	1578	M	0	0.00	0.00	10.5	18.2	03/15/77		90.5		
VEHICLE	1593	F	0	0.00	0.00	11.0	18.0	03/15/77		90.5		
VEHICLE	1601	F	0	0.00	0.00	8.5	18.0	03/15/77		90.5		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
VEHICLE	1620 M	0	0.00	0.00	11.0	21.1	12/01/77		82.0		
VEHICLE	1634 F	0	0.00	0.00	10.5	19.6	12/01/77		82.0		
VEHICLE	1651 F	0	0.00	0.00	11.0	19.2	12/01/77		82.0		
D-1 LOWEST	1416 M	0	0.00	0.00	12.0	22.1	05/20/76		100.4		
D-1 LOWEST	1458 F	0	0.00	0.00	10.5	21.5	05/20/76		100.4		
D-1 LOWEST	1489 F	0	0.00	0.00	8.0	20.5	05/20/76	08/04/84		98.5	Processing
D-1 LOWEST	1501 M	0	0.00	0.00	14.0	20.4	05/20/76	01/03/84		91.5	Thyroid Tumor
D-1 LOWEST	1515 M	0	0.00	0.00	13.5	19.8	05/20/76		100.4		
D-1 LOWEST	1573 M	0	0.00	0.00	11.5	19.4	04/19/77		89.4		
D-1 LOWEST	1581 M	0	0.00	0.00	16.5	19.3	04/19/77		89.4		
D-1 LOWEST	1596 M	0	0.00	0.00	14.0	19.2	04/19/77		89.4		
D-1 LOWEST	1600 F	1	0.01	0.11	11.0	19.2	04/19/77		89.4		
D-1 LOWEST	1603 M	2	0.01	0.12	14.0	19.2	04/19/77		89.4		
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		100.4		
D-1 LOWEST	1570 F	2	0.02	0.18	10.0	19.4	04/19/77		89.4		
D-1 LOWEST	1465 F	4	0.03	0.35	12.0	21.0	05/20/76		100.4		
D-1 LOWEST	1470 F	3	0.03	0.29	10.5	21.0	05/20/76	04/09/84		94.7	Meningioma
D-1 LOWEST	1507 M	4	0.03	0.32	14.0	19.8	05/20/76		100.4		
D-1 LOWEST	1592 F	4	0.03	0.29	13.5	19.2	04/19/77		89.4		
D-1 LOWEST	1607 M	5	0.03	0.35	13.0	19.0	04/19/77		89.4		
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		100.4		
D-1 LOWEST	1583 F	4	0.04	0.40	9.5	19.2	04/19/77		89.4		
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		89.4		
D-2 LOW	1513 M	0	0.00	0.00	11.5	19.8	05/20/76		100.4		
D-2 LOW	1520 M	1	0.01	0.12	10.5	19.5	05/20/76		100.4		
D-2 LOW	1415 M	2	0.02	0.20	11.5	22.2	05/20/76		100.4		
D-2 LOW	1575 M	3	0.02	0.19	14.0	19.4	04/19/77		89.4		
D-2 LOW	1466 F	5	0.03	0.37	14.0	21.0	05/20/76		100.4		
D-2 LOW	1606 F	5	0.04	0.42	12.5	19.0	04/19/77		89.4		
D-2 LOW	1579 M	8	0.05	0.59	14.0	19.3	04/19/77		89.4		
D-2 LOW	1590 F	6	0.05	0.51	12.0	19.2	04/19/77		89.4		
D-2 LOW	1585 F	8	0.06	0.68	12.0	19.2	04/19/77		89.4		
D-2 LOW	1580 F	9	0.07	0.82	11.0	19.3	04/19/77		89.4		
D-2 LOW	1591 M	11	0.07	0.76	15.0	19.2	04/19/77		89.4		
D-2 LOW	1417 M	11	0.08	0.89	12.0	22.1	05/20/76		100.4		
D-2 LOW	1423 M	10	0.08	0.87	11.0	22.1	05/20/76		100.4		
D-2 LOW	1567 M	10	0.08	0.83	12.0	19.4	04/19/77		89.4		
D-2 LOW	1472 F	10	0.09	1.01	10.0	21.0	05/20/76		100.4		
D-2 LOW	1503 F	9	0.09	1.03	8.5	19.8	05/20/76		100.4		
D-2 LOW	1602 M	15	0.09	1.03	14.5	19.2	04/19/77		89.4		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG IDENT	INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-2 LOW	1484 F	11	0.10	1.08	10.0	20.5	05/20/76		100.4		
D-2 LOW	1599 F	10	0.10	1.14	9.0	19.2	04/19/77		89.4		
D-2 LOW	1490 F	16	0.15	1.65	9.5	20.5	05/20/76		100.4		
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[f]	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		101.4		
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		104.3		
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		90.5		
D-3 MED-LOW	1595 M	50	0.29	3.23	15.5	18.0	03/15/77		90.5		
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		101.4		
D-3 MED-LOW	1587 M	53	0.31	3.49	15.5	18.1	03/15/77		90.5		
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		98.3		
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		90.5		
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		101.4		
D-3 MED-LOW	1439 F	53	0.42	4.61	11.5	21.0	04/20/76		101.4		
D-3 MED-LOW	1523 F	55	0.42	4.60	12.0	21.3	07/22/76		98.3		
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		104.3		
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		90.5		
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		90.5		
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		101.4		
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		104.3		
D-3 MED-LOW	1604 M	85	0.74	8.10	10.5	18.0	03/15/77		90.5		
D-3 MED-LOW	1530 F	72	0.76	8.41	8.5	20.8	07/22/76		98.3		
D-3 MED-LOW	1456 F	61	0.79	8.68	7.0	20.5	04/20/76		101.4		
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		104.3		
D-4 MEDIUM	1637 M	192	1.45	15.99	12.0	18.9	11/07/77		82.8		

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INHALED PLUTONIUM NITRATE IN DOGS

DOSE GROUP	DOG IDENT		INITIAL ALVEOLAR DEPOSITION NCI	NCI/G LUNG	NCI/ KG	INHALATION EXPOSURE WEIGHT (KG)	AGE* (MO)	DATE	DATE OF DEATH	MONTHS SINCE INHALATION 9/30/84	DEATH	COMMENTS ON DEAD DOGS
D-4 MEDIUM	1404	M	260	1.48	16.25	16.0	21.5	04/20/76	02/03/84		93.5	Pleuritis
D-4 MEDIUM	1521	F	205	1.49	16.37	12.5	21.3	07/22/76		98.3		
D-4 MEDIUM	1656	M	211	1.54	16.90	12.5	18.4	11/07/77		82.8		
D-4 MEDIUM	1379	M	278	1.74	19.16	14.5	19.1	01/20/76		104.3		
D-4 MEDIUM	1362	M	267	1.87	20.54	13.0	20.2	01/20/76		104.3		
D-4 MEDIUM	1639	F	248	2.05	22.57	11.0	18.5	11/07/77		82.8		
D-4 MEDIUM	1647	M	294	2.05	22.58	13.0	18.5	11/07/77		82.8		
D-4 MEDIUM	1640	M	307	2.06	22.71	13.5	18.5	11/07/77	03/20/84		76.4	Lung Tumor
D-4 MEDIUM	1645	F	257	2.13	23.39	11.0	18.5	11/07/77		82.8		
D-4 MEDIUM	1534	M	295	2.14	23.57	12.5	20.8	07/22/76		98.3		
D-4 MEDIUM	1414	F	233	2.35	25.86	9.0	18.2	01/20/76		104.3		
D-4 MEDIUM	1618	F	277	2.40	26.36	10.5	20.3	11/07/77		82.8		
D-4 MEDIUM	1385	M	373	2.42	26.63	14.0	19.0	01/20/76	07/12/84		101.7	Bone Tumor, Lung Tumor
D-4 MEDIUM	1408	F	331	2.62	28.77	11.5	18.5	01/20/76	10/12/83		92.7	Bone Tumor
D-4 MEDIUM	1428	F	378	3.12	34.36	11.0	21.1	04/20/76		101.4		
D-4 MEDIUM	1535	F	345	3.13	34.48	10.0	20.7	07/22/76		98.3		
D-4 MEDIUM	1446	F	354	3.22	35.40	10.0	21.0	04/20/76		101.4		
D-4 MEDIUM	1364	M	463	3.24	35.65	13.0	20.2	01/20/76	08/02/84		102.4	Processing
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	1660	M	1518	10.22	112.41	13.5	18.3	11/07/77	09/05/84		81.9	Processing
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	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		82.8		
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	10.9	22.1	06/23/76	05/01/79		34.2	Radiation Pneumonitis
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	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	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	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	1648	M	811	5.90	64.90	12.5	18.5	11/07/77		82.8		
D-5 MED-HIGH	1498	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	1459	F	2645	26.72	293.89	9.0	22.6	06/23/76	09/25/80		51.1	Rad. Pneumonitis, Lung Tumor
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	7.32	80.51	12.3	18.3	11/07/77	08/19/83		69.4	Bone Tumor
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		82.8		
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		82.8		
D-6 HIGH	1420	M	3840	30.36	333.91	11.5	23.3	06/23/76	07/12/78		24.6	Radiation Pneumonitis

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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	1518 M	3565	29.46	324.09	11.0	20.6	06/23/76	12/18/79		41.8	Rad. Pneumonitis, Lung Tumor
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	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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Anderson, L. E. "Biological Effects of Electric Fields on Experimental Animals." Presented at the Bonneville Power Administration Colloquium, July 13, 1984, Portland, Oregon.

Anderson, L. E. "Neurochemical Effects of 60-Hz Electric Fields." Presented at the DOE/EPRI Contractor's Review, November 5-9, 1984, St. Louis, Missouri.

Anderson, L. E. "The Pineal Gland and Implications in Electric Field Research." Presented at the DOE/EPRI Contractor's Review, November 5-9, 1984, St. Louis, Missouri.

Anderson, L. E., D. I. Hilton, E. K. Chess, and B. W. Wilson. "Neuroendocrine Responses in Rats Exposed to 60-Hz Electric Fields." Presented at the 23rd Annual Hanford Life Sciences Symposium, October 2-4, 1984, Richland, Washington.

Ballou, J. E. and A. C. Case. "Disposition of ^{232}U and Daughter Radionuclides following Intratracheal Instillation of $^{232}UO_2(NO_3)_2$ in Rats." Presented at the Annual Meeting of the Health Physics Society, June 3-8, 1984, New Orleans, Louisiana.

Chess, E. K., D. W. Later, and B. W. Wilson. "Characterization of Components in Mutagenic Organic Extracts of Coal Fly Ash." Presented at the Fourth Symposium on Environmental Analytical Chemistry, EPRI, DOE/OHER, Thermochemical Institute/BYU, June 18-20, 1984, Provo, Utah.

Chess, E. K., D. W. Later, B. W. Wilson, W. R. Harris, and D. J. Okamoto. "Mass Spectral Comparison of Mutagens Extracted from Fluidized-Bed and Pulverized Coal Combustion Fly Ashes." Presented at the 32nd Annual Conference on Mass Spectrometry and Allied Topics, May 27-June 1, 1984, San Antonio, Texas.

Chess, E. K. and R. D. Smith. "Development of Capillary Column Supercritical Fluid Chromatography-High Performance Mass Spectrometry for the Analysis of Polar Materials." Presented at the First Contractors Meeting on AR&TD and Surface Coal Gasification Instrumentation Projects, Morgantown Energy Technology Center, June 13-14, 1984, Morgantown, West Virginia.

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tical Meetings, August 1984, Philadelphia, Pennsylvania.

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Hackett, P. L., R. L. Rommereim, and D. D. Mahlum. "Teratogenic Potential of Boiling Range Cuts of Solvent Refined Coal Materials in Rats." Presented at the Annual Meeting of the Teratology Society, June 3-7, 1984, Boca Raton, Florida.

Hilton, D. I. and L. E. Anderson. "Catecholamine and Indolamine Levels in Various Brain Regions in Rats Exposed to 60-Hz Electric Fields." Presented at the 14th Annual Meeting of the Society for Neurosciences, October 10-15, 1984, Los Angeles, California.

Hopkins, K. L., M. E. Frazier, D. D. Mahlum, and D. L. Springer. "Studies on Benzo[a]pyrene Carcinogenesis and DNA Binding in the Presence of Complex Mixtures." Presented at the Northwest Section Meeting of the Society for Experimental Biology and Medicine, October 13, 1984, Pullman, Washington.

Hungate, F. P. "Irradiating Foods." Presented at the Sunnyside Rotary Meeting, March 12, 1984, Sunnyside, Washington.

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Hungate, F. P. "Irradiating Foods." Presented at the Farm and Land Institute, May 17, 1984, Yakima, Washington.

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Kalkwarf, D. R. "Photolysis Kinetics of Polycyclic Aromatic Amines." Presented at the National Meeting of the American Chemical Society, August 26-31, 1984, Philadelphia, Pennsylvania.

Kaune, W. T. and M. C. Miller. "Comparative Dosimetry for Guinea Pigs Exposed to ELF Electric Fields." Presented at the Bioelectromagnetics Society Meeting, July 14, 1984, Atlanta, Georgia.

Kelman, B. J., R. L. Rommereim, and D. D. Mahlum. "Lifetime Exposure of CD-1 Mice to 1-T Homogeneous and 2-T/Meter Gradient DC Magnetic Fields." Presented at the Sixth Annual Meeting of the Bioelectromagnetics Society, July 15-19, 1984, Atlanta, Georgia.

Later, D. W. "Capillary Column Gas Chromatographic Methods for the Determination of Nitrogen Functional Polycyclic Aromatic Compounds." Presented at Labcon West 84 (Invited Paper), Analytical Chemists Meeting, May 9, 1984, Long Beach, California.

Later, D. W. "Heterocyclic Polycyclic Aromatic Compounds in Coal Liquefaction Process Materials." Presented at the International Conference on Environmental Contamination, Imperial College of London, July 10-13, 1984, London, England.

Later, D. W. "Systematic Nomenclature of the Nitrogen Functional Polycyclic Aromatic Compounds." Presented at the Ninth International Symposium on Polycyclic Aromatic Hydrocarbons, October 29-November 1, 1984, Columbus, Ohio.

Later, D. W., E. K. Chess, C. W. Wright, R. B. Lucke, D. D. Mahlum, and B. W. Wilson. "Mass Spectrometric and Chromatographic Methods Applied to the Isolation and Identification of Tumorigenic Polycyclic Aromatic Hydrocarbons in Coal Liquefaction." Presented at the 32nd Annual Conference on Mass Spectrometry and Allied Topics, May 27-June 1, 1984, San Antonio, Texas.

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Toste, A. P. "Analysis of Organic Chelating Agents in Nuclear Wastes Including Tank 102AZ." Presented at the Seminar for the Waste Management Process Technology Unit of Rockwell International, Hanford Operations, February 14, 1984, Richland, Washington.

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Udseth, H. R. and R. D. Smith. "Studies of Supercritical Fluid Extraction and Fractionation Processes for Polar and Mixed Fluids by OFI-MS." Presented at the 32nd Annual Conference on Mass Spectrometry and Allied Topics, May 27-June 1, 1984, San Antonio, Texas.

Weller, R. F. "Cancer-Associated Hypercalcemia in Domestic Animals." Presented at the Veterinary Cancer Society Forum at the Annual Meeting of the American Animal Hospital Association, April 2, 1984, San Francisco, California.

Weller, R. E., G. A. Apley, R. P. Schumacher, and E. L. Wierman. "Serum Thyroid-Stimulating Hormone (TSH) Concentration in Euthyroid, Hypothyroid and Aged Dogs." Presented at the American College of Veterinary Internal Medicine Symposium, May 17-20, 1984, Washington, DC.

Weller, R. E., G. A. Apley, R. P. Schumacher, and E. L. Wierman. "Thyrotropin (TSH) Concentrations in Euthyroid, Hypothyroid and Aged Colony-Reared Beagle Dogs." Presented at the American Association of Laboratory Animal Science, October 28-November 2, 1984, Cincinnati, Ohio.

Wilson, B. W., R. A. Pelroy, D. W. Later, D. D. Mahlum, and C. W. Wright. "Chemical Basis for Reduced Toxicologic Activity in Advanced Coal Liquefaction Processes." Presented at the Ninth Annual Conference

on Clean Liquid and Solid Fuels, May 8-10, 1984, Palo Alto, California.

Wilson, B. W., R. A. Pelroy, D. O. Mahlum, C. Wright, and D. W. Later. "Chemical Basis for Toxicologic Activity in Coal Liquids: A Comparison of Direct Liquefaction Materials." Presented at the Fossil Based Synfuels Symposium, EPRI, EPA, DOE, University of Georgia, June 11-15, 1984, Atlanta, Georgia.

Wright, B. W. and R. D. Smith. "Capillary Supercritical Fluid Chromatography: Approaches and Applications." Invited speaker at the Labcon West 84 Conference, May 8-10, 1984, Long Beach, California.

Wright, B. W., R. D. Smith, and H. R. Udseth. "Approaches and Applications of Supercritical Fluid Chromatography and Supercritical Fluids Chromatography-Mass Spectrometry Techniques." Invited speaker at the Pittsburgh Conference on Analytical Chemists and Spectroscopists, March 7, 1984, Atlantic City, New Jersey.

Wright, C. W. "Systematic Nomenclature of Sulfur Functional Polycyclic Aromatic Hydrocarbons." Presented at the Ninth International Symposium on Polynuclear Aromatic Hydrocarbons, October 31, 1984, Columbus, Ohio.

Wright, C. W. "Comparative Analysis of Four Quantitative Methods for Coal Liquids Analysis Using Capillary Column Chromatography." Presented at the Pittsburgh Conference, March 5-9, 1984, Atlantic City, New Jersey.

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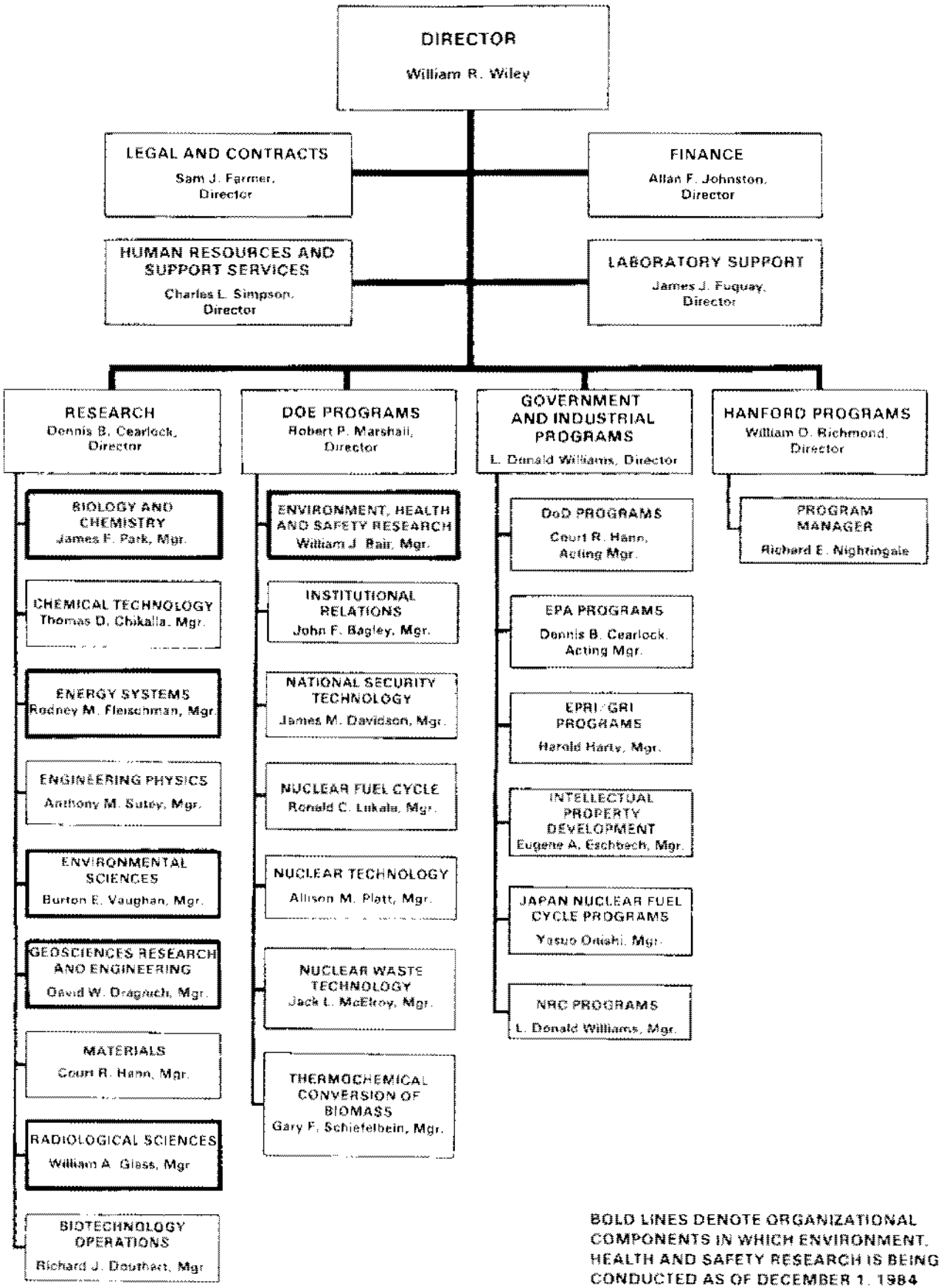

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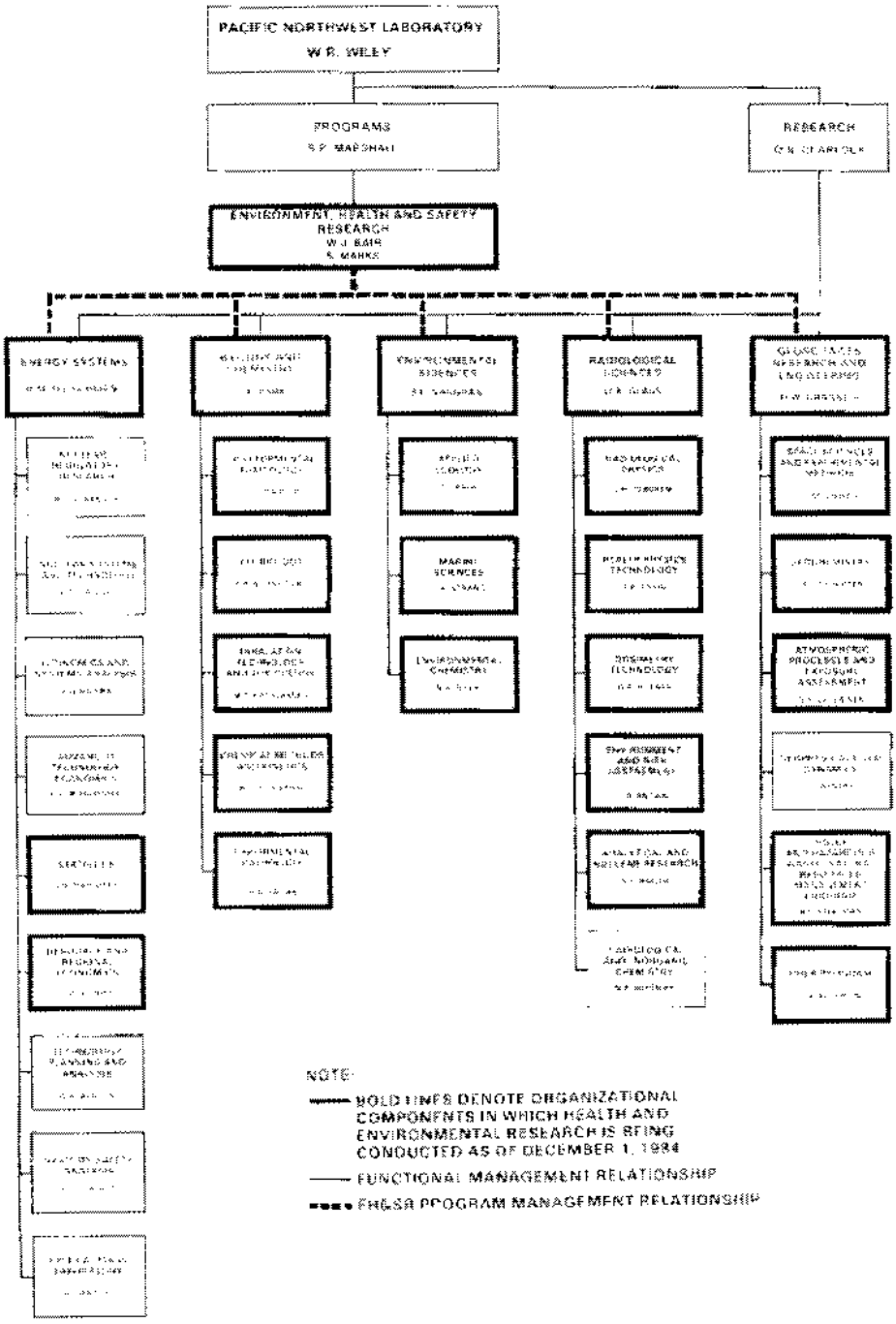

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