PNL-5750 Pt. 1
UC-48

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# Pacific Northwest Laboratory Annual Report for 1985 to the DOE Office of Energy Research

## Part 1 Biomedical Sciences
February 1986

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

Pacific Northwest Laboratory
Operated for the U.S. Department of Energy
by Battelle Memorial Institute

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Printed in the United States of America
Available from
National Technical Information Service
United States Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22161

NTIS Price Codes
Microfiche A01

Printed Copy

| Pages | Price Codes |
|---|---|
| 001-025 | A02 |
| 026-050 | A03 |
| 051-075 | A04 |
| 076-100 | A05 |
| 101-125 | A06 |
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# Pacific Northwest Laboratory Annual Report for 1985 to the DOE Office of Energy Research

## Part 1 Biomedical Sciences

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

February 1986

Prepared for
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under Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
Richland, Washington 99352

# PREFACE

This 1985 annual report from Pacific Northwest Laboratory (PNL) to the Department of Energy (DOE) describes research in environment, health, and safety conducted during fiscal year 1985. 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 Environment, Safety and Health. 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 1985 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 - R. E. Wildung | R. E. Wildung, Report Coordinator<br>C. M. Novich, Editor |
| Part 3: Atmospheric Sciences | | |
| | Program Manager - C. E. Elderkin | C. E. Elderkin, Report Coordinator<br>E. L. Owczarski, Editor |
| Part 4: Physical Sciences | | |
| | Program Manager - L. H. Toburen | L. H. Toburen, Report Coordinator<br>J. E. Danko, Editor |
| Part 5: Overview and Assessment | | |
| | Program Manager - L. G. Faust | L. G. Faust, Report Coordinator<br>R. W. Baalman, Editor |

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

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

A highlight this past year was the appointment of a Scientific Advisory Committee. Honoring us by accepting our invitation to serve on the committee are:

| | |
|---|---|
| Dr. Franklin I. Badgley | University of Washington |
| Dr. Leo K. Bustad | Washington State University |
| Dr. Franklin Hutchinson | Yale University |
| Dr. Albert W. Johnson | San Diego State University |
| Dr. J. Newell Stannard | University of Rochester |
| | University of California, San Diego |

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

Previous reports in this series:

**Annual Report for**

| | |
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| 1951 | W-25021, HW-25709 |
| 1952 | HW-27814, HW-28636 |
| 1953 | HW-30437, HW-30464 |
| 1954 | HW-30306, HW-33128, HW-35905, HW-35917 |
| 1955 | HW-39558, HW-41315, HW-41500 |
| 1956 | HW-47500 |
| 1957 | HW-53500 |
| 1958 | HW-59500 |
| 1959 | HW-63824, HW-65500 |
| 1960 | HW-69500, HW-70050 |
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| 1962 | HW-76000, HW-77609 |
| 1963 | HW-80500, HW-81746 |
| 1964 | BNWL-122 |
| 1965 | BNWL-280; BNWL-235, Vol. 1-4; BNWL-361 |
| 1966 | BNWL-480, Vol. 1; BNWL-481, Vol. 2, Pt. 1-4 |
| 1967 | BNWL-714, Vol. 1; BNWL-715, Vol. 2, Pt. 1-4 |
| 1968 | BNWL-1050, Vol. 1, Pt. 1-2; BNWL-1051, Vol. 2, Pt. 1-3 |
| 1969 | BNWL-1306, Vol. 1, Pt. 1-2; BNWL-1307, Vol. 2, Pt. 1-3 |
| 1970 | BNWL-1550, Vol. 1, Pt. 1-2; BNWL-1551, Vol. 2, Pt. 1-2 |
| 1971 | BNWL-1650, Vol. 1, Pt. 1-2; BNWL-1651, Vol. 2, Pt. 1-2 |
| 1972 | BNWL-1750, Vol. 1, Pt. 1-2; BNWL-1751, Vol. 2, Pt. 1-2 |
| 1973 | BNWL-1850, Pt. 1-4 |
| 1974 | BNWL-1950, Pt. 1-4 |
| 1975 | BNWL-2000, Pt. 1-4 |
| 1976 | BNWL-2100, Pt. 1-5 |
| 1977 | PNL-2500, Pt. 1-5 |
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| 1984 | PNL-5500, Pt. 1-5 |

# FOREWORD

This report summarizes progress on OHER biomedical and health-effects research conducted at PNL in FY1985 to develop information for a comprehensive understanding of the interaction of energy-related radiation and chemicals with man. Our continuing emphasis on decreasing the uncertainty of health-effects risk estimates 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 research relative to OHER programmatic needs. The first section concerns evaluation of possible health effects among nuclear workers. The next two sections, which contain reports of health-effects research in biological systems, include health effects of radiation and health effects of chemical mixtures. The last section is related to medical applications of nuclear technology.

The section on human health effects reports progress on the analyses of data on the health of Hanford workers as reflected in their cancer mortality and in congenital malformations that may occur in their offspring.

The section on health effects of radiation contains results from inhalation dose-effect relationship studies with radionuclides. Studies in dogs with inhaled $^{239}PuO_2$, $^{238}PuO_2$, and $^{239}Pu(NO_3)_4$ are summarized to 14, 11, and 8 years after exposure, respectively. Tissues from these dogs are being used to investigate the implications of long-term retention of plutonium particles in bronchial epithelium and to examine the role of oncogenes in radiation carcinogenesis. Dose-effect relationship studies with inhaled $^{239}PuO_2$ in rats are in progress to obtain lung tumor incidence data at lifetime doses of 5 to 1500 rad. Studies are in progress in rats with inhaled radon daughters to determine the influence of dose and dose rate on lung tumor incidence. As radon-daughter exposure is extended to lower levels, the data are becoming increasingly relevant to current exposure levels for uranium miners and to exposures of the general population. The lung tumor dose-effect relationship in rats that inhaled $^{232}U$ nitrate was similar to that for other inhaled actinide nitrates when adjusted for the $^{232}U$ daughter-products dose contribution. This section also reports new methods of aerosol generation for inhalation studies. It also includes results from laboratory animal dose-effect relationship studies with fetally absorbed plutonium, americium, and uranium and from studies concerning gastrointestinal absorption of radionuclides.

The section on health effects of chemical mixtures reports a 20-fold enhancement of mutagenicity of 6-aminochrysene (a known mutagen) in **Salmonella typhimurium** when mixed with aromatic fractions of high-boiling coal liquid. Little or no enhancement was induced by the aliphatic fraction of the coal liquid. In contrast, mouse-skin tumor initiation/promotion studies showed that high-boiling coal liquid distillates decreased the initiating activity of a known carcinogen, benzo[a]pyrene (BaP), compared to that of lower-boiling distillates. Subsequent studies showed that binding of BaP to mouse skin DNA was decreased by the aromatic fraction of these distillates but not by the aliphatic fraction. The decrease in BaP binding was not due to altered BaP metabolism pathways, suggesting that components of the mixture may compete for active metabolic sites and that decreased binding of BaP to DNA is the result. Skin-tumor latency was increased in mice exposed to high-boiling coal liquid that had been nitrosated to destroy primary aromatic amines, compared with that for

mice exposed to non-nitrosated material. In other studies examining the noncarcinogenic effects of complex mixtures, cardiovascular function was adversely affected in rats by a high-boiling coal liquid after inhalation or dermal exposure but not after oral exposure. Dose-related effects on survival and body weight are reported for lifespan studies with rats and mice that inhaled high-boiling coal liquid. Analyses of data obtained from the study of teratologic effects of coal liquids have shown that no direct causal relationship exists between the observed maternal toxicity and specific fetal abnormalities. Studies in rats administered aromatic hydrocarbons suggest that breath analyses may be useful to estimate exposure to compounds containing 1-2 rings.

The research on medical applications reports progress on development of a portable blood irradiator for clinical trials.

The biomedical and health-effects research at PNL is an interdisciplinary effort requiring scientific contributions from many research departments at PNL. The personnel in the Biology and Chemistry Department are the principal contributors to this report. Requests for reprints from the list of publications for 1985 will be honored while supplies last.

# CONTENTS


Human
Health
Effects

## • Statistical Health Effects Study

Principal Investigator: E. S. Gilbert

Other Investigators: J. A. Buchanan, S. Marks, and R. G. Stevens

The objective of this study is to provide data and statistical methodology for assessing health risks from chronic exposures to radiation and other potentially harmful agents or substances. The analysis of data from an ongoing study of the mortality of Hanford workers is a major component of this study. Recently, data have been collected and analyzed for a case-control study of congenital malformations that have occurred in Benton and Franklin counties.

The purpose of this project is to provide an analysis for directly evaluating human health risks resulting from energy-related activities. This is accomplished by developing and applying appropriate statistical methods for analyzing data on human populations that have received low-level exposures to radiation or other agents or substances. An important component of this program is the analysis of data on the health of Hanford workers, as reflected in their mortality and in congenital malformations that may occur in their offspring.

Efforts related to the Hanford mortality study include updating mortality and dosimetry data, distributing the computer program used to analyze these data, researching methods of quantifying risks, performing a lung cancer case-control study, and assessing dose measurement error.

Mortality data, which are collected by the Hanford Environmental Health Foundation (HEHF), are obtained through the Social Security Administration, the National Death Index and, recently, through linkage with death files in the states of Washington and California. An improved data management system at HEHF has facilitated this process; it has entailed the implementation of new procedures for PNL-HEHF communication in order to take full advantage of the new system. Dosimetry data obtained from PNL are also being updated.

Mortality data will soon be reasonably complete up to January 1, 1982. Preliminary analyses indicate that results will not be greatly different from those reported earlier. That is, there is no indication of an association of radiation exposure with overall cancer mortality or leukemia mortality. Of 17 specific cancer types analyzed, only multiple myeloma shows evidence of a statistically significant association with radiation exposure.

We have explored several methodological issues related to quantifying risks based on low-level exposures (such as those received by Hanford workers). These include the adequacy of normal approximations for calculating confidence limits, various ways of incorporating vital statistics into such calculations, the comparison of relative and absolute risk models, and the comparison of linear and log-linear models. This research indicates that confidence limits based on the likelihood-ratio statistic are more accurate than those based on the asymptotic variance of the estimated parameter. For risk estimates that are based on small numbers of deaths (leukemia, for example), even the likelihood-ratio statistic may not provide accurate limits; exact methods for calculating such limits are being explored. This research also indicates that the use of vital statistics does not substantially increase the reliability of estimates and may bias results if the underlying assumptions, upon which their use is based, are violated. Results of earlier research in this area have been published in The Statistician, and more recent results were presented at a symposium on epidemiology and risk assessment in Columbia, Maryland and at the Joint Statistical Meetings in Las Vegas, Nevada.

Data on smoking histories have been extracted from HEHF files for use in the lung cancer case-control study. These data have also been edited and coded to provide a file suitable for analysis. Because several questionnaires have been used at HEHF to collect smoking data in various years, it was necessary to develop comparable codes to deal with these varying formats. The objectives of this study are to examine the association of lung cancer and radiation exposure with control for smoking, and also to examine the association of smoking with variables such as radiation exposure and job category.

A project designed to assess the measurement errors associated with the radiation doses used in the Hanford mortality study has been initiated. This project is being conducted with the cooperation of PNL sci-

entists who have been extensively involved in the dosimetry program at Hanford. The project will include documenting various random and systematic errors in the dose estimation process and determining how such errors affect analyses of the mortality data. A paper on the general issue of dose measurement error in epidemiological studies was presented at the 1985 Coolfont Conference on Statistics and Radiation.

Data from the natality study have been collected and analyzed. These data include information on congenital malformations, as well as on matched controls, of infants born during the period 1957-1980 in the three hospitals in Richland, Kennewick and Pasco. The case-control analyses address the question of whether parental occupational exposure to low-level ionizing radiation is associated with an increased risk of congenital malformations of their offspring. In the prevalence-at-birth analyses of births occurring between 1968 and 1980, rates for several specific defects are compared with rates from the Birth Defects Monitoring Program conducted by the Birth Defects Branch of the U.S. Public Health Service Centers for Disease Control. Rates from several other studies are also considered for comparative purposes.

# Health Effects of Radiation

## • Inhaled Plutonium Oxide in Dogs

Principal Investigator: J. F. Park

Other Investigators: G. A. Apley, R. L. Buschbom, G. E. Dagle, D. R. Fisher, K. M. Gideon, E. S. Gilbert, J. D. Kashmitter, G. J. Powers, H. A. Ragan, R. E. Weller, and E. L. Wierman

Technical Assistance: J. C. Chapman, K. H. Debban, R. F. Flores, B. G. Moore, C. O. Romsos, R. P. Schumacher, and D. H. Willard

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 (ILB) are being observed for lifespan dose-effect relationships. Mortality due to radiation pneumonitis and lung tumor increased in the four highest dose-level groups exposed to $^{239}PuO_2$ during the 14-year postexposure period. During the 11½ years 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 years 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 ILB of ≥80 nCi. Other plutonium-exposure-related effects include sclerosis of the tracheobronchial lymph nodes, focal radiation pneumonitis, adenomatous hyperplasia of the liver, and dystrophic osteolytic lesions in the skeleton.

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 3 summarizes, by dose-level group, the mortality and lesions associated with deaths through 14 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, 14 in Group 3, 15 in Group 2, 17 in Dose-Level Group 1 and 16 in the control group were euthanized when death was imminent.

**Table 1.** Lifespan Dose Effect Studies with Inhaled $^{239}PuO_2$ in Beagles.[a]

| Dose Level Group | Number of Dogs | | Initial Lung Deposition[b] | |
|---|---|---|---|---|
| | Male | Female | nCi[c] | nCi/g Lung[c] |
| Control | 20 | 10 | 0 | 0 |
| 1 | 10 | 10 | 3.5 ± 1.1 | 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 ± 3800 | 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,b]

| Dose Level Group | Number of Dogs | | Initial Lung Deposition[c,d] | |
|---|---|---|---|---|
| | Male | Female | nCi[e] | nCi/g Lung[e,f] |
| 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 ± 13 | 0.56 ± 0.07 |
| 4 | 10 | 10 | 350 ± 83 | 2.6 ± 0.5 |
| 5 | 20 | 10 | 1300 ± 270 | 10 ± 2.9 |
| 6 | 7 | 6 | 7200 ± 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.** Summary of Lesions in Dogs Euthanized During the 14 yr Period After Inhalation of $^{239}PuO_2$.

| | Dose Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Control |
| Number of Dogs/Group | 8 | 22 | 22 | 20 | 21 | 24 | 20 |
| Number of Dead Dogs/Group | 8 | 21 | 20 | 14 | 15 | 17 | 16 |
| Mean Survival Postexposure, yr | 2 | 6 | 10 | 12 | 13 | 12 | 12 |
| Condition[a] | | | | | | | |
| Radiation Pneumonitis | 7 | 1 | | | | | |
| Radiation Pneumonitis and Lung Tumor | 1 | | | | | | |
| Lung Tumor | | 20 | 14 | 5 | 1 | | 4 |
| Malignant Lymphoma and Lung Tumor | | | | 2 | | | |
| Bone Tumor | | | | | 2 | 2 | |
| Hemangiosarcoma (Heart, Spleen, Liver) | | | | | | 3 | 2 |
| Malignant Lymphoma | | | | 1 | | 1 | 3 |
| Pituitary Tumor, Cushing's | | | 2 | | | 1 | |
| Reticulum Cell Sarcoma | | | 2 | | | | |
| Ovarian Tumor | | | | | 1 | | |
| Oral Tumor | | | | | | | 1 |
| Round Cell Sarcoma | | | | | | 1 | |
| Hemangioma (Spleen) | | | | | 1 | | |
| Malignant Melanoma | | | | | 1 | | 1 |
| Pheochromocytoma | | | | | 1 | | |
| Urinary Bladder Tumor | | | | 1 | 1 | | |
| Neurofibrosarcoma | | | | 1 | | | |
| Meningioma | | | | | | 1 | |
| Pneumonia | | | 2 | 1 | 3 | 2 | |
| Epilepsy | | | | | 1 | 1 | 1 |
| Thromboembolism | | | | 1 | | | 1 |
| Pyometra | | | 1 | 1 | | | |
| Unknown | | | | | 1 | 1 | |
| Liver Cirrhosis | | | 1 | | | | |
| Septicemia | | | | | | 1 | |
| Cardiac Insufficiency | | | | 1 | | | |
| Peritonitis | | | | | 1 | | |
| Adrenalitis | | | | | | | 1 |
| Kidney Failure | | | | | | 1 | |
| Nephrosclerosis | | | | | | | 1 |
| Chronic Nephropathy | | | | | 1 | 1 | 1 |
| Glomerulosclerosis | | | | | | 1 | |

[a]Number of dogs with lesion associated with death

Mean survival time was decreased in the three highest dose-level groups compared to that in the other groups. Fourteen dogs were sacrificed for comparison of plutonium tissue distribution. Table 4 shows the primary causes of death and the distribution of $^{239}Pu$ in the tissues of these animals as percent of final body burden. Figure 1 shows the plutonium tissue distribution as percent of initial lung burden.

Table 4 indicates that, as survival time increased, the fraction of plutonium in the lung decreased to ~18% of the final body burden by 13 to 14 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 ~67% of the final body burden at 13 to 14 years after exposure; the abdominal lymph nodes, principally the hepatic nodes, contained ~4%. The fraction of plutonium in liver increased, accounting for ~27% of the final body burden at 13 to 14 years after exposure in the higher (≥75 nCi final body burden) dose-level groups. The organ distribution of plutonium in the periodically sacrificed dogs was generally similar to that of the high-dose-level dogs euthanized when death was imminent during the first 2 years after exposure. The lower-dose-level (≤75 nCi final body burden) dogs sacrificed or

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

| Dog Number | Time After Exposure, mo | Final Body Burden, μCi | Percent of Final Body Burden | | | | | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| | | | Lungs | Thoracic Lymph Nodes[a] | Abdominal Lymph Nodes[b] | Liver | Skeleton | |
| 478M | 0.25 | 0.293 | 98 | 0.15 | 0.02 | 0.24 | 0.18 | Sacrifice |
| 435F | 0.25 | 3.841 | 99 | 0.11 | 0.01 | 0.00 | 0.03 | Sacrifice |
| 816M | 0.50 | 0.399 | 99 | 0.12 | 0.01 | 0.00 | 0.03 | Sacrifice |
| 918M | 1 | 0.074 | 99 | 0.82 | 0.02 | 0.11 | 0.08 | Sacrifice |
| 920F | 1 | 0.011 | 94 | 0.47 | 0.03 | 0.08 | 0.61 | Sacrifice |
| 913M | 1 | 4.849 | 98 | 1.1 | 0.00 | 0.03 | 0.05 | Sacrifice |
| 702F | 5 | 1.682 | 94 | 5.7 | 0.00 | 0.01 | 0.09 | Sacrifice |
| 709M | 5 | 1.726 | 97 | 2.2 | 0.00 | 0.00 | 0.05 | Sacrifice |
| 734M | 5 | 0.914 | 96 | 3.4 | 0.00 | 0.01 | 0.05 | Sacrifice |
| 739F | 5 | 1.511 | 95 | 4.7 | 0.03 | 0.00 | 0.00 | Sacrifice |
| 910M | 11 | 12.229 | 84 | 15 | 0.01 | 0.06 | 0.05 | Radiation Pneumonitis |
| 747F | 12 | 5.434 | 71 | 29 | 0.03 | 0.07 | 0.07 | Radiation Pneumonitis |
| 906F | 12 | 6.154 | 88 | 12 | 0.00 | 0.03 | 0.05 | Radiation Pneumonitis |
| 849F | 13 | 0.0007 | 80 | 15 | 0.20 | 0.04 | 1.6 | Sacrifice |
| 896F | 15 | 4.115 | 81 | 15 | 0.92 | 0.23 | 0.12 | Radiation Pneumonitis |
| 817M | 21 | 3.794 | 64 | 34 | 0.13 | 1.4 | 0.19 | Radiation Pneumonitis |
| 815M | 25 | 0.074 | 64 | 32 | -- | 0.08 | 0.10 | Sacrifice |
| 829M | 26 | 3.198 | 75 | 19 | 0.79 | 4.2 | 0.45 | Radiation Pneumonitis |
| 760M | 31 | 0.978 | 71 | 23 | 0.57 | 3.7 | 0.28 | Radiation Pneumonitis |
| 890F | 31 | 2.012 | 55 | 28 | 2.2 | 13 | 0.26 | Radiation Pneumonitis |
| 804M | 37 | 1.101 | 62 | 29 | 0.19 | 7.9 | 0.36 | Radiation Pneumonitis, Lung Tumor |
| 798F | 43 | 0.0056 | 55 | 44 | 0.02 | 0.17 | 0.43 | Sacrifice |
| 772M | 53 | 1.821 | 42 | 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 |

[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 | |
| 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 | 0.00093 | 19 | 75 | 0.52 | 0.81 | 1.6 | 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 | 43 | 9.3 | 34 | 0.20 | Lung Tumor |
| 823M | 157 | 0.072 | 7.3 | 83 | 1.8 | 6.0 | 1.5 | Urinary Bladder Tumor |
| 838M | 157 | 0.044 | 18.0 | 73 | 0.77 | 5.4 | 1.4 | Malignant Lymphoma, Lung Tumor |
| 788M | 158 | 0.0022 | 22 | 70 | 2.6 | 1.8 | 0.17 | Chronic Nephropathy |
| 845F | 158 | 0.012 | 28 | 69 | 0.25 | 1.5 | 0.64 | Urinary Bladder Tumor |
| 853M | 158 | 0.0081 | 13 | 77 | 2.2 | 5.4 | 0.54 | Bronchopneumonia |
| 750M | 161 | 0.071 | 20 | 51 | 13.0 | 9.5 | 2.4 | Lung Tumor, Malignant Lymphoma |
| 847M | 163 | | | -----Processing----- | | | | Kidney Failure |
| 776M | 163 | 0.0020 | 29 | 67 | 0.11 | 1.2 | 1.1 | Bronchopneumonia |
| 802M | 164 | | | -----Processing----- | | | | Pneumonia |
| 827F | 164 | 0.075 | 4.5 | 49 | 17 | 27 | 1.5 | Acute Pneumonia |
| 874M | 165 | | | -----Processing----- | | | | Chronic Nephropathy |
| 842M | 166 | | | Processing----- | | | | Lung Tumor, Chronic Nephropathy |
| 770F | 166 | | | -----Processing----- | | | | Glomerulosclerosis |

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

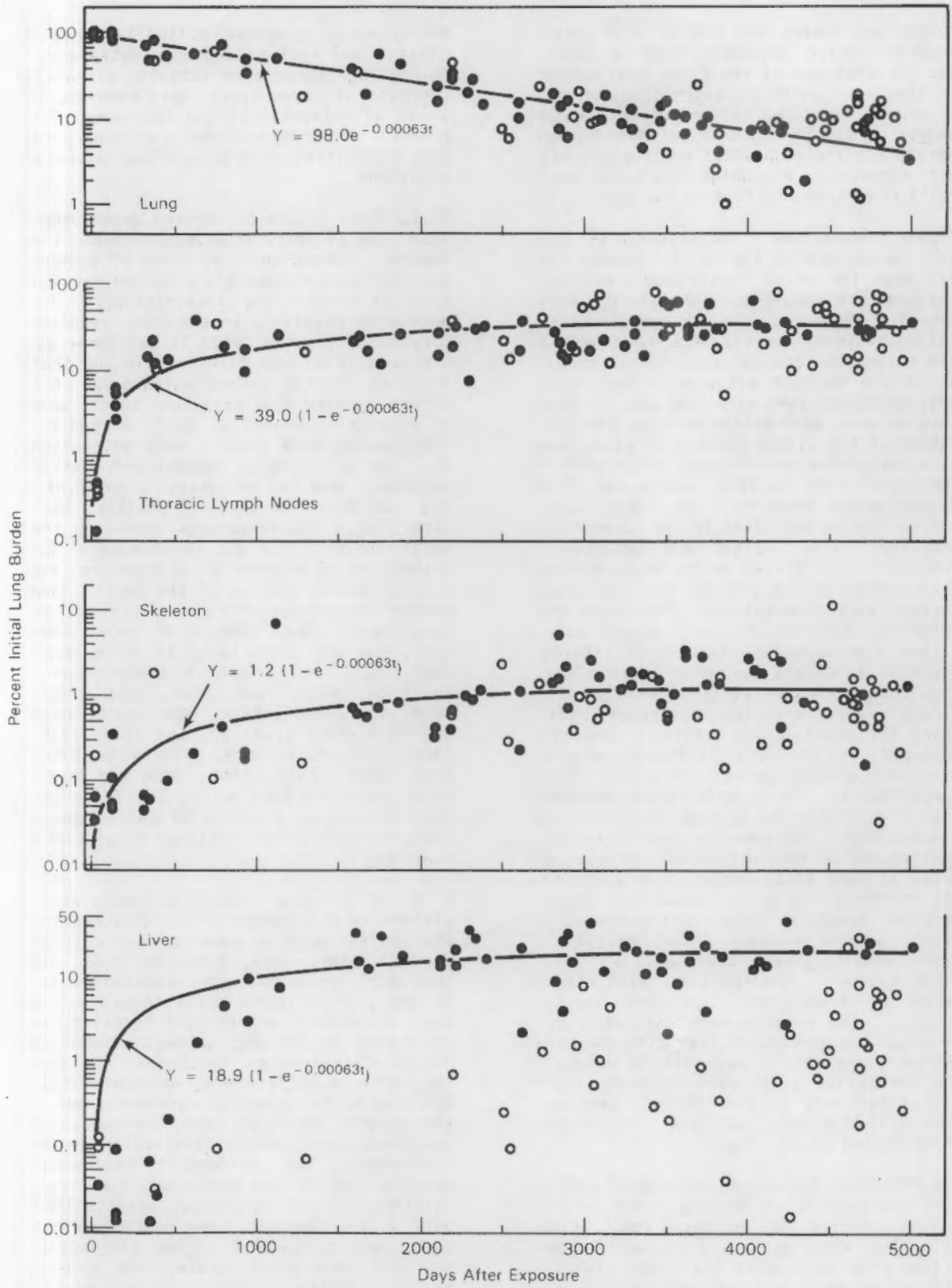


**Figure 1.** Plutonium in Tissues of Dogs After Inhalation of $^{239}PuO_2$. Points represent data from individual dogs (● = ≧ 75 nCi, ○ = ≦ 75 nCi final body burden). The uptake and retention curves and function were based on dogs in which initial lung burdens were estimated from external thorax counts at 14 and 30 days after exposure. The curves for liver were based on dogs with final body burdens ≧ 75 nCi.

euthanized during the 4th to 14th 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 1% of the final body burden was in the skeleton at 13 to 14 years after exposure. Plutonium analyses are still in progress on five of the dogs.

Figure 1 shows the $^{239}Pu$ tissue distribution as percent of the initial burden for all dogs for which tissue radiochemical analyses are complete. Initial lung burdens for those dogs for which radiochemical analysis of excreta were not complete was estimated from external thorax counts at 14 and 30 days after exposure. For dogs whose analyses were complete, initial lung burdens were estimated from the summation of the tissue burdens of plutonium, plus the plutonium excreted, minus plutonium excreted in the feces during the first 3 days after exposure. The latter was assumed to be deposited in the upper respiratory tract. Uptake and retention functions were fitted to the organ burden data. Based on the premise that the organ burdens were interrelated, the uptake and retention function for all organs were fitted simultaneously instead of fitting isolated functions for each organ. The organs were treated as compartments of a single system, with transfer rates specifying the total amount leaving a compartment per unit time and the fractional distribution of that amount among the other compartments. The transfer rates assumed that plutonium moved through the body in a single pass. The material initially deposited in the lung was either excreted or moved to some other organ, from which it was excreted. It was assumed that there were no feedback loops in the system. Organ systems included lung, thoracic lymph nodes, liver, skeleton, and all other tissues. The functions were estimated using weighted, nonlinear least squares. The weights were estimated by bi-weighting procedures that give the more extreme data values very little weight. The curves for liver were based on dogs with final body burdens $\geq$75 nCi because dogs with <75 nCi had less plutonium translocated to the liver.

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-three of the 87 exposed dogs euthanized 3 to 14 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 2, 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. Four control dogs were euthanized because of lung tumors. Dogs 794M, 803M, 809F, 824F, 833F, and 835F (Dose Level 4), 697M, 778M, 782M, 823M, 827F, 834F and 905F (Dose Level 3), 748F, 754M, 769F, 776M, 780F, 802M, 806F, 826F, 831F, 845F, 859M, 862M and 874M (Dose Level 2), and 756M, 770F, 788M, 807F, 825F, 847M, 853M, 870M, 875M, 879M, 886F, 891M, 899F, 900M and 908M (Dose Level 1) died during the 7- to 14-year postexposure period of causes presently thought to be unrelated to plutonium exposure.

In 19 of the dogs, the lung tumors were classified as bronchiolar-alveolar carcinoma; in six dogs as adenosquamous carcinoma; in eight 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 in two dogs with metastases to thoracic and abdominal lymph nodes, trachea, esophagus and mediastinum; adenocarcinoma with metastases to the diaphragm and abdominal lymph nodes in one dog; and combined epidermoid and adenocarcinoma with metastases to the thoracic lymph nodes, diaphragm, liver and kidney in another.

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 2, 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 lymphopenia. 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 lung depositions of 79 nCi or more (Figure 2). Through 123 months after exposure, mean lymphocyte values were significantly lower ($P < 0.05$) for Dose-Level Groups 3 and 4 than for the control group. At 127 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 lung 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 11½ years after exposure to $^{238}PuO_2$. During this period, all of the dogs in the highest-level dose group and in Dose-Level Group 5, nine dogs in Group 4, eight dogs in Group 3, six dogs in Group 2, and six dogs in Dose-Level Group 1 were euthanized when death was imminent. Seven control dogs were euthanized during the 11½-year postexposure period. Mean survival time was decreased in the two highest dose-level groups compared to the other groups. Twenty-one dogs were sacrificed for comparison of plutonium tissue distribution. Table 6 shows the primary causes of death and the distribution of $^{238}Pu$ in the tissues of these animals as percent of final body burden. Figure 3 shows the plutonium tissue distribution as percent initial lung burden.

At 10½ to 11½ years after exposure, the fraction of the final body burden in the lungs of the $^{238}Pu$-exposed dogs was about 2%, compared to 12% in the $^{239}Pu$-exposed dogs (Table 6). At that time, ~9% of the $^{238}Pu$ was in the thoracic lymph nodes, compared to ~60% of the $^{239}Pu$. Livers of the $^{238}Pu$-exposed dogs contained ~45% of the plutonium burden, compared to 10% in the livers of the $^{239}Pu$-exposed dogs. About 45% of the final body burden was in the skeletons of the $^{238}Pu$-exposed dogs, at that time, compared to ~2% in the $^{239}Pu$-exposed dogs. Tissue distribution of $^{238}Pu$ in low-dose-level dogs did not differ from that in high-dose-level dogs. Plutonium analyses are still in progress on one dog. Figure 3 shows the $^{238}Pu$ tissue distribution as percent of initial lung burden for all dogs for which tissue radiochemical analyses are complete. The initial lung burdens and uptake and retention curves were estimated as described previously for $^{239}Pu$. The uptake and retention curves were based on dogs in which initial lung burdens were estimated from the final plutonium body burden, plus the plutonium excreted, minus that excreted in the feces during the first 3 days after exposure.

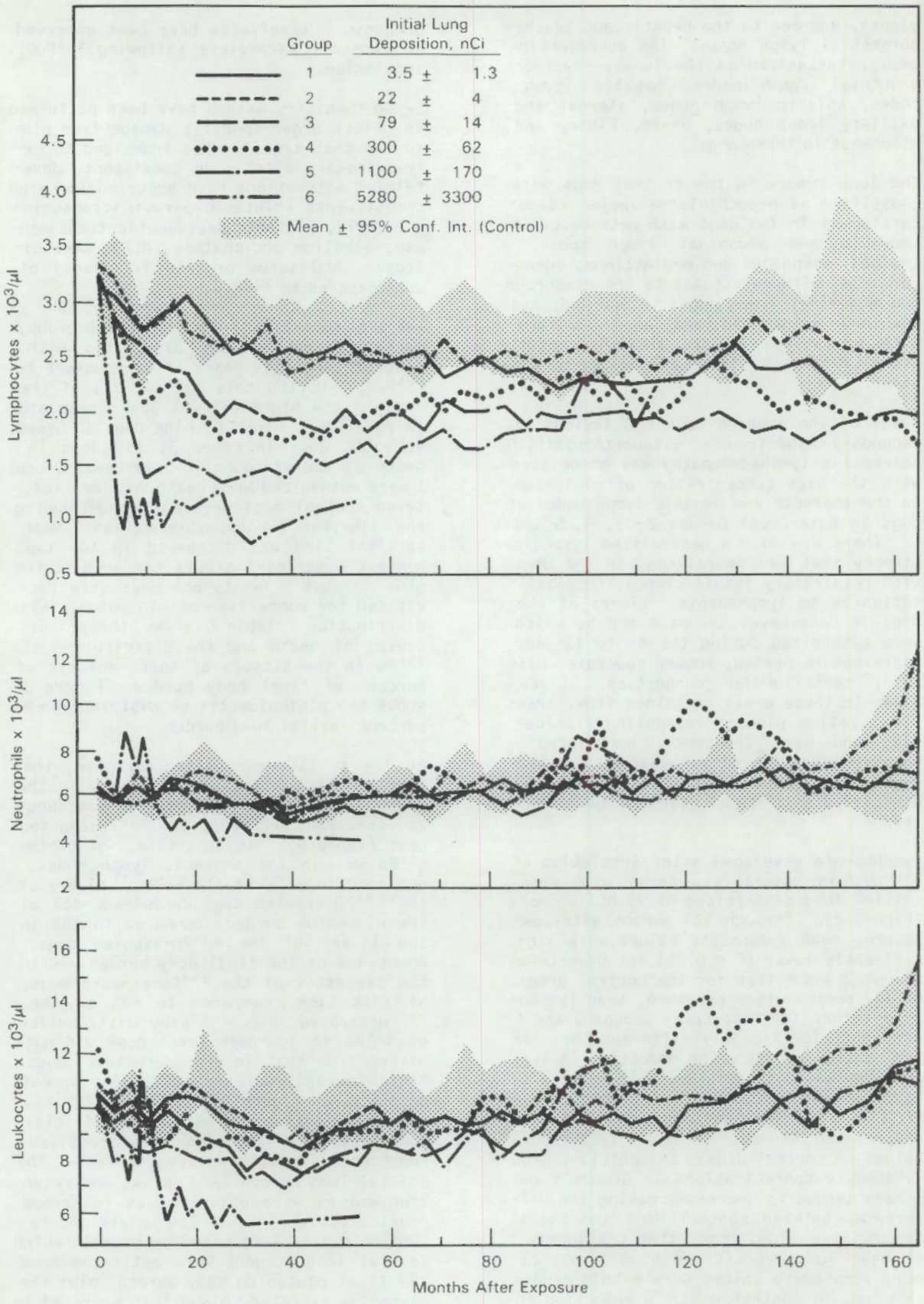


**Figure 2.** Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}PuO_2$.

**Table 5.** Summary of Lesions in Dogs Euthanized During the 11½-yr Period After Inhalation of $^{238}PuO_2$.

| | Dose Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Control |
| Number of Dogs/Group | 13 | 20 | 20 | 22 | 21 | 20 | 20 |
| Number of Dead Dogs/Group | 13 | 20 | 9 | 8 | 6 | 6 | 7 |
| Mean Survival Postexposure, yr | 5 | 7 | 11 | 11 | 11 | 11 | 11 |
| Condition[a] | | | | | | | |
| Bone Tumor | 2 | 11 | 2 | | | 1 | |
| Lung Tumor | 3 | | | 1 | | | |
| Bone and Lung Tumor | 6 | 4 | 2 | | | | |
| Bone Tumor and Addison's Disease | 1 | | | | | | |
| Bone and Lung Tumor and Addison's Disease | | 1 | | | | | |
| Addison's Disease | 1 | 2 | | | | | |
| Malignant Lymphoma | | | 1 | 3 | | 1 | 3 |
| Hemangiosarcoma; Heart and Spleen | | | 1 | | 1 | | |
| Pituitary Tumor, Cushing's | | | | 1 | | | 1 |
| Urinary Bladder Tumor | | | 1 | | | | 2 |
| Brain and Heart Tumor | | | | | | 1 | |
| Brain Tumor | | | | | 1 | | |
| Parathyroid Adenoma | | | | 1 | | | |
| Adrenal Carcinoma | | | | | | 1 | |
| Round Cell Sarcoma; Kidney | | | | | 1 | | |
| Adrenal and Pituitary Tumor | | | 1 | | | | |
| Lung Tumor, Metastatic | | | | | 1 | | |
| Pneumonia | | 1 | 1 | 1 | 1 | | |
| Radiation Pnemonitis | | | | 1 | | | |
| Spinal Cord Degeneration | | | | | 1 | | |
| Pyometra | | | | | | | 1 |
| Herniated Vertebral Disk | | 1 | | | | | |
| Anesthesia | | | | | | 1 | |
| Liver Abscess | | | | | | 1 | |

[a]Number of dogs with lesion associated with death

Of the 62 exposed dogs euthanized, 30 were killed because of bone tumors, 4 because of lung tumors, and 1 because of radiation pneumonitis. Thirteen of the dogs that had bone tumors also had lung tumors. Twenty-eight of the 30 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/or lung tumors were in Dose-Level Groups 3, 4, 5, and 6. Twelve of the 28 osteosarcomas were in vertebrae; two in femora; four in ribs; two in the scapulae; four in the pelvis; one in the tibia; one in the sternum; one in the sacrum; and one in the humerus. Dog 994F (Dose Level 6); dogs 1047M, 1079M, 1096M, and 1191F (Dose Level 5); 983M, 991F, 1030F, 1081M, and 1166M (Dose Level 4); 960M, 1031F, 1040M, 1043F, 1059F, and 1066M (Dose Level 3); 971F, 1070M, 1078F, 1082M, 1188M, and 1229M (Dose Level 2); and 951M, 959M, 1063M, 1069F, and 1106F (Dose Level 1) died during the 11½-year postexposure period of causes presently thought to be unrelated to plutonium exposure.

The lung tumors were classified as bronchiolar-alveolar carcinomas in 12 dogs, bronchiolar-alveolar adenoma in one dog, adenocarcinoma in one dog, and adenosquamous carcinoma in two dogs. In one dog,

**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 |

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

**Table 6.** 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 | |
| 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 | Brain 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 |
| 1047M | 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 |
| 971F | 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 |
| 1070M | 126 | 0.011 | 1.9 | 9.5 | 0.70 | 51 | 34 | Round Cell Sarcoma, Kidney |
| 1166M | 128 | 0.354 | 1.8 | 11 | 1.6 | 47 | 35 | Malignant Lymphoma |
| 983M | 132 | 0.274 | 1.5 | 5.9 | 2.9 | 47 | 37 | Adrenal Tumor, Pituitary Tumor |
| 1035F | 132 | 0.172 | 2.8 | 10 | 1.9 | 19 | 53 | Bone Tumor, Cushing's |
| 1031F | 134 | 0.025 | 1.9 | 13 | 0.97 | 17 | 65 | Pneumonia |
| 1190F | 134 | 0.033 | 0.84 | 4.4 | 1.2 | 49 | 41 | Lung Tumor |
| 1062M | 135 | 0.270 | 0.63 | 2.6 | 3.9 | 46 | 44 | Bone Tumor, Lung Tumor |
| 1177M | 136 | | | | -----Processing----- | | | Bone Tumor |
| 959M | 138 | 0.0025 | 3.4 | 14 | 0.62 | 33 | 48 | Liver Abscess |

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

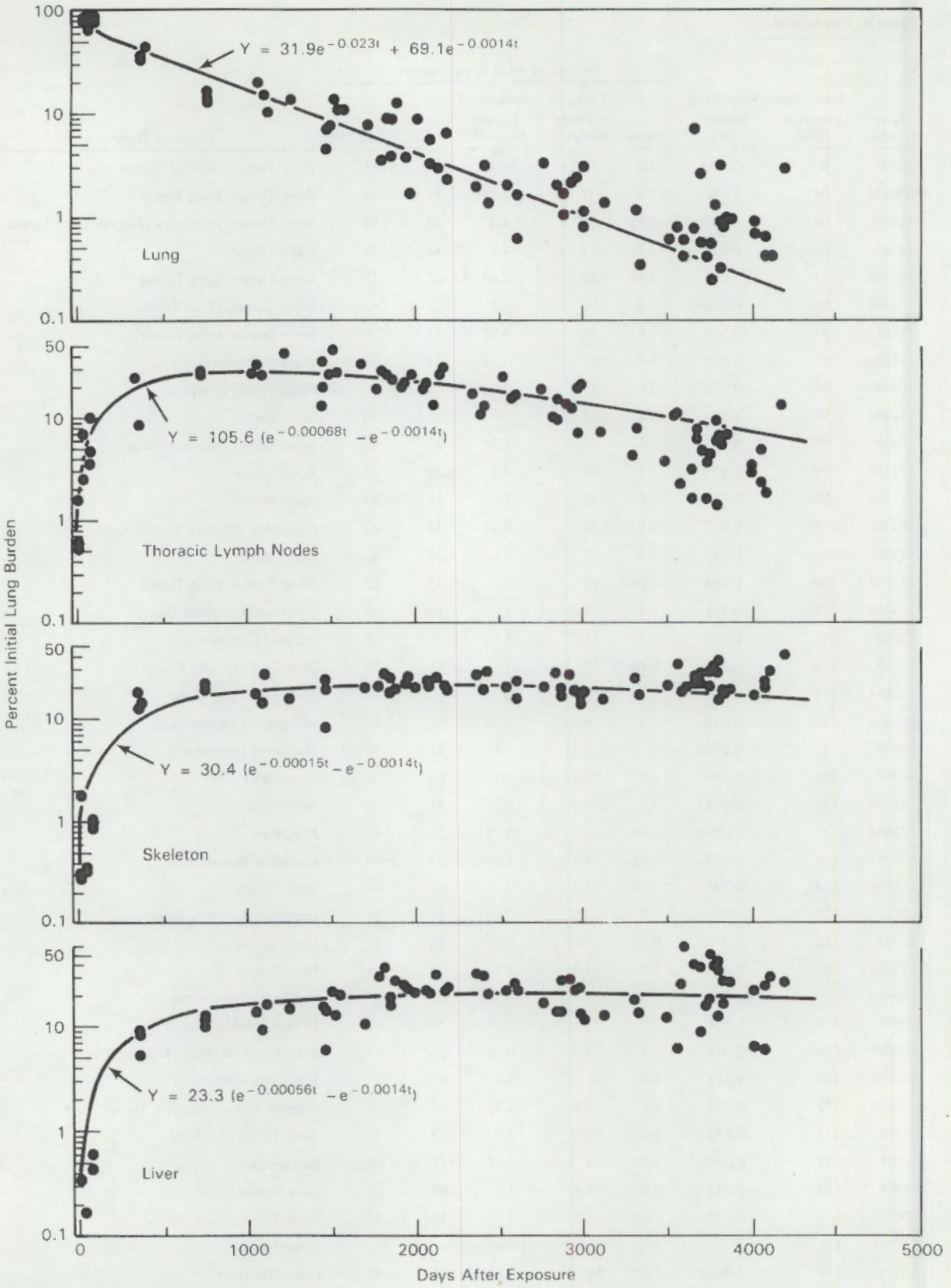


**Figure 3.** Plutonium in Tissues of Dogs After Inhalation of $^{238}PuO_2$. Points represent data from individual dogs. The uptake and retention curves and functions were based on dogs in which initial lung burdens were estimated from the final plutonium body burden, plus the plutonium excreted, minus that excreted in the feces during the first 3 days after exposure.

three lung-tumor types were observed: bronchiolar-alveolar, adenocarcinoma and fibrosarcoma. Metastases were observed in the lungs, thoracic lymph nodes, trachea, mediastinum, and heart of the dog with pulmonary adenocarcinoma. 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 4, 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. Sclerosing lymphadenopathy in the tracheobronchial and mediastinal lymph nodes was associated with high concentrations of plutonium observed as alpha stars in Dose-Level Groups 3, 4, 5 and 6. Similar but less severe lesions were seen in the hepatic lymph nodes. In Dose-Level Groups 5 and 6 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 in Dose-Level Groups 3, 4, 5, and 6. Elevated serum GPT levels, suggestive of liver damage, were observed in the Dose-Level Groups 3, 4, 5 and 6 dogs.

Dose-related lymphopenia was observed in groups with mean lung $^{238}PuO_2$ deposition of 77 nCi or more (Figure 4). 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.

Using the uptake and retention curves shown in Figures 1 and 3, cumulative radiation doses to death were estimated for the lungs of the $^{239}Pu$ dogs and the lungs (Table 7). For the dose calculations, mean plutonium concentration in the entire lung and skeleton was used.

Lung-tumor risk estimates based on data to 11 years after exposure suggested that $^{239}PuO_2$ was more effective than $^{238}PuO_2$ in causing lung tumors, especially at high cumulative lung doses (Figure 5). The influence of deaths due to bone tumors in the $^{238}PuO_2$-exposed dogs and/or other competing causes of death and survival time after exposure were not evaluated in these current risk estimates. Future risk estimates will consider these factors.

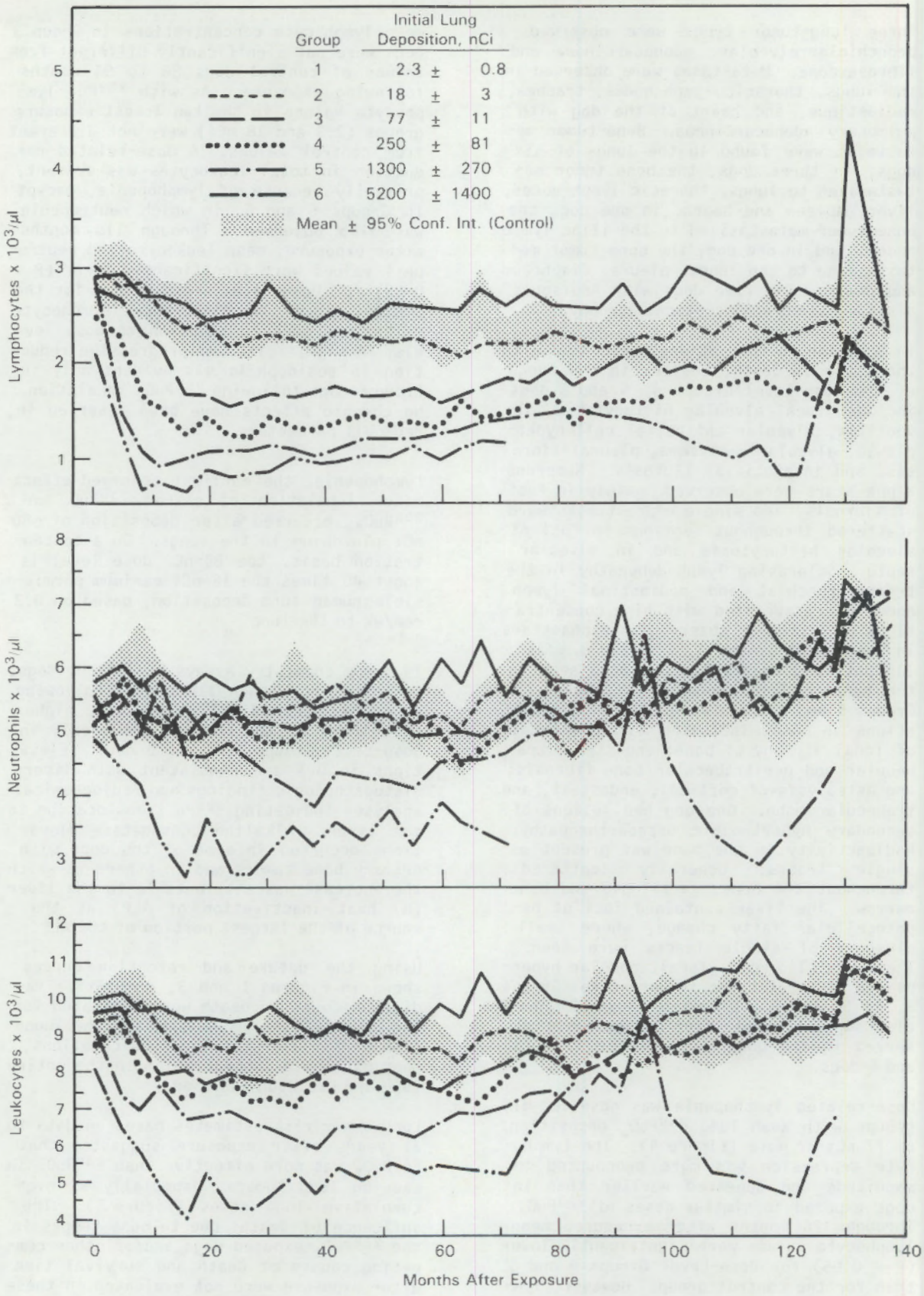


**Figure 4.** Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{238}PuO_2$.

**Table 7.** Estimates of Cumulative Radiation Doses to Lungs ($^{239}Pu$-Exposed) or Lungs and Skeletons ($^{238}Pu$-Exposed) of Dogs with Lung and/or Bone Tumors After Inhalation Exposure.

| | Dose Level Group | Number of Dogs with Tumors | Survival Time Postexposure, mo | Cumulative Dose to Organ, rad |
|---|---|---|---|---|
| $^{239}PuO_2$- Lung Tumors | 6 | 1 | 69 | 7400[a] |
| | 5 | 20 | 37 - 115 | 1700 - 4000 |
| | 4 | 14 | 93 - 156 | 550 - 1500 |
| | 3 | 7 | 98 - 161 | 150 - 550 |
| | 2 | 1 | 166 | 30 |
| | 1 | 0 | --- | --- |
| $^{238}PuO_2$- Lung Tumors | 6 | 9 | 49 - 84 | 2300 - 9800[a] |
| | 5 | 5 | 70 - 110 | 1350 - 2900 |
| | 4 | 2 | 118 - 135 | 400 - 450 |
| | 3 | 1 | 134 | 100 |
| | 2 | 0 | --- | --- |
| | 1 | 0 | --- | --- |
| $^{238}PuO_2$- Bone Tumors | 6 | 9 | 49 - 84 | 180 - 480[b] |
| | 5 | 16 | 61 - 132 | 80 - 230 |
| | 4 | 4 | 118 - 136 | 50 - 60 |
| | 3 | 0 | 0 | --- |
| | 2 | 0 | 0 | --- |
| | 1 | 1 | 99 | <1 |

[a]Dose to lungs
[b]Dose to skeleton

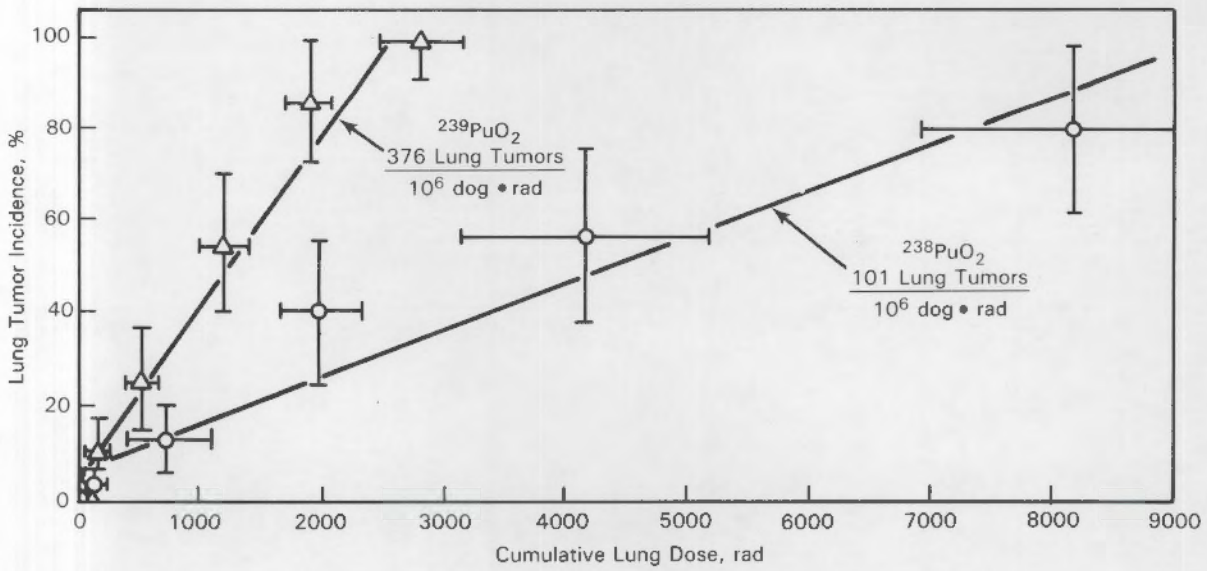


**Figure 5.** Comparison of Lung Tumor Risk Estimates in Dogs at 11 Years After Inhalation of $^{239}PuO_2$ or $^{238}PuO_2$ (Mean ± SD).

## • 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; lymphopenia and neutropenia occurred at the two highest dose levels. We have also observed radiation pneumonitis, lung cancer, and bone cancer at the three 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 being studied with intravenously injected radionuclides at the University of Utah; inhalation studies with beta-, gamma- and alpha-emitting radionuclides at the Inhalation Toxicology Research Institute (Lovelace); and external irradiation at the University of California (Davis) and Argonne National Laboratory.

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 Appendix (following the entire Annual Report) shows the current status of each dog on these experiments.

The average amount of plutonium in the lung decreased to approximately 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 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 1 year after exposure.

**Table 1.** Lifespan Dose-Effect Studies with Inhaled $^{239}Pu(NO_3)_4$ in Beagles.

| Dose Level Group | Number of Dogs | | Initial Lung 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 | |
| 1359M | 0.1 | 0.080 | 90.50 | 0.15 | 0.06 | 2.46 | 3.20 | Sacrifice |
| 1375F | 0.1 | 0.073 | 89.61 | 0.14 | 0.01 | 0.97 | 4.68 | Sacrifice |
| 1407F | 0.1 | 0.092 | 51.87 | 0.41 | 0.13 | 10.99 | 16.70 | Sacrifice |
| 1389M | 0.5 | 0.053 | 24.07 | 0.38 | 0.08 | 41.28 | 26.21 | Sacrifice |
| 1390M | 0.5 | 0.051 | 24.62 | 0.32 | 0.11 | 20.05 | 44.45 | Sacrifice |
| 1445F | 0.5 | 0.057 | 26.42 | 0.32 | 0.11 | 21.28 | 44.73 | Sacrifice |
| 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 |
| 1485F | 54 | 1.052 | 0.82 | 0.35 | 0.07 | 31.13 | 63.94 | Bone Tumor |
| 1502F | 55 | 3.113 | 0.80 | 0.39 | 0.09 | 33.33 | 62.51 | Bone Tumor, Lung 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 |
| 1598F | 60 | 0.058 | 0.90 | 0.14 | 0.17 | 24.44 | 31.62 | Sacrifice |
| 1576M | 60 | 0.065 | 1.54 | 0.36 | 0.13 | 46.23 | 39.15 | Sacrifice |
| 1605F | 60 | 0.025 | 1.87 | 0.11 | 0.12 | 52.32 | 39.37 | Sacrifice |
| 1646F | 60 | 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 |
| 1589F | 63 | 0.029 | 0.68 | 0.04 | 0.13 | 46.43 | 50.32 | Sacrifice |
| 1636M | 66 | 0.634 | 1.21 | 0.27 | 0.52 | 53.97 | 39.09 | Bone Tumor |
| 1652F | 68 | 0.658 | 1.46 | 0.23 | 0.29 | 50.47 | 44.32 | Bone Tumor, Lung Tumor |
| 1498F | 69 | 0.845 | 0.59 | 0.32 | 0.13 | 26.63 | 53.37 | Bone Tumor, Lung Tumor |
| 1659F | 69 | 0.736 | 1.14 | 0.34 | 0.40 | 38.30 | 55.89 | Bone Tumor |
| 1640M | 76 | 0.177 | 4.01 | 0.64 | 0.63 | 54.41 | 36.59 | Lung Tumor |
| 1419M | 76 | 0.873 | 0.69 | 0.28 | 0.39 | 44.06 | 50.70 | Bone Tumor, Lung Tumor |
| 1660M | 82 | | | -----Processing----- | | | | Bone Tumor, Lung Tumor |
| 1621M | 84 | | | -----Processing----- | | | | Bone Tumor, Lung Tumor |
| 1655M | 88 | | | -----Processing----- | | | | Lung Tumor, Bone Tumor |
| 1501M | 92 | 0.002 | 1.62 | 0.50 | 0.79 | 38.05 | 48.41 | Thyroid Tumor |
| 1648M | 92 | | | -----Processing----- | | | | Bone Tumor, Lung Tumor |
| 1641M | 92 | | | -----Processing----- | | | | Lung Tumor |
| 1408F | 93 | 0.181 | 0.60 | 0.19 | 0.37 | 49.47 | 45.52 | Bone Tumor |
| 1404M | 93 | 0.217 | 0.82 | 0.28 | 0.72 | 46.24 | 48.62 | Pleuritis |
| 1470F | 95 | 0.001 | 1.11 | 0.48 | 0.34 | 43.21 | 50.23 | Meningioma |

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

The distribution of plutonium as percent of initial lung burden (ILB) was calculated, using nonparametric statistical techniques, in groups of three dogs from Dosage Level 3, sacrificed at 3 days, 1 month, 3 months, 1 year, or 5 years (Table 3). A compartment model was developed, and we calculated the total amount leaving organ compartments per unit time and the fractional distribution of that amount among the other compartments. The three lung compartments had fractions of 0.30, 0.52, and 0.18, with half-times of, respectively, 5.3 days, 100 days, and 422 days.

**Table 3.** Nonparametrically Polished Organ Burdens as a Percent of Initial Lung Burden at Indicated Times After Exposure.

| Time After Exposure | Percent Initial Lung Burden | | | |
|---|---|---|---|---|
| | Lung | Liver | Bone | Total Tissue |
| 3 Days | 88 | 3 | 5 | >99 |
| 1 Month | 61 | 11 | 17 | 93 |
| 3 Months | 43 | 15 | 22 | 85 |
| 1 Year | 13 | 24 | 31 | 72 |
| 5 Years | 1 | 29 | 25 | 58 |

Radiation doses were estimated by integrating the clearance curves, then multiplying by an appropriate constant to convert to rad dose. Some representative dose estimates (for a 10-kg dog with a 100-nCi ILB) at 5 years after exposure are: lung, 45 rad; liver, 25 rad; skeleton, 14 rad, and tracheobronchial lymph nodes, 2300 rad.

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 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 lung deposition, ~1700 nCi), and Group 6 (~5500 nCi). The reduction in white cells in Groups 5 and 6 is due to the effect of plutonium 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 ILBs of ~80 nCi or more. The lymphocytopenia at lower dose levels of plutonium oxides may be related to the more-extensive translocation of plutonium oxide to the tracheobronchial lymph nodes and subsequent higher dosage levels to lymphocytes circulating through those lymph nodes.

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 8 years following exposure), GPT and ALP values in Dose-Level Groups 3, 4 and 5 are significantly ($P < 0.05$) higher than those for the control group.

Table 4 summarizes, by dose-level group, the mortality and lesions associated with deaths through 8 years after exposure to $^{239}Pu(NO_3)_4$. All five dogs at the highest dose level and two of 20 dogs in Dose-Level Group 5 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.

Osteosarcomas were the principal reason for euthanizing dogs more than 51 months after plutonium exposure. Osteosarcomas were present in 19 dogs euthanized 42 to 92 month after exposure: 17 dogs from the Group 5 dose level and two dogs at the Group 4 dose level. The sites of osteosarcomas, with several dogs having more than one site, were lumbar vertebrae (five dogs), thoracic vertebrae (two dogs), cervical vertebrae (four dogs), humerus (four dogs), sacrum (one dog), pelvis (three dogs), facial bones (two dogs), ribs (two dogs), femur (one dog), and nasal turbinates (one dog). Metastases to distal sites occurred in eight dogs. These dogs also had radiation osteosis, generally characterized by peritrabecular fibrosis.

Large lung tumors were the cause of death in one dog in Dose-Level Group 4, and in two dogs in Dose-Level Group 5. The lung tumors were of multiple histologic types, including bronchioalveolar carcinoma, papillary adenocarcinoma, and combined epidermoid and adenocarcinomas. Systemic metastases occurred in two dogs, and one dog had a bone tumor.

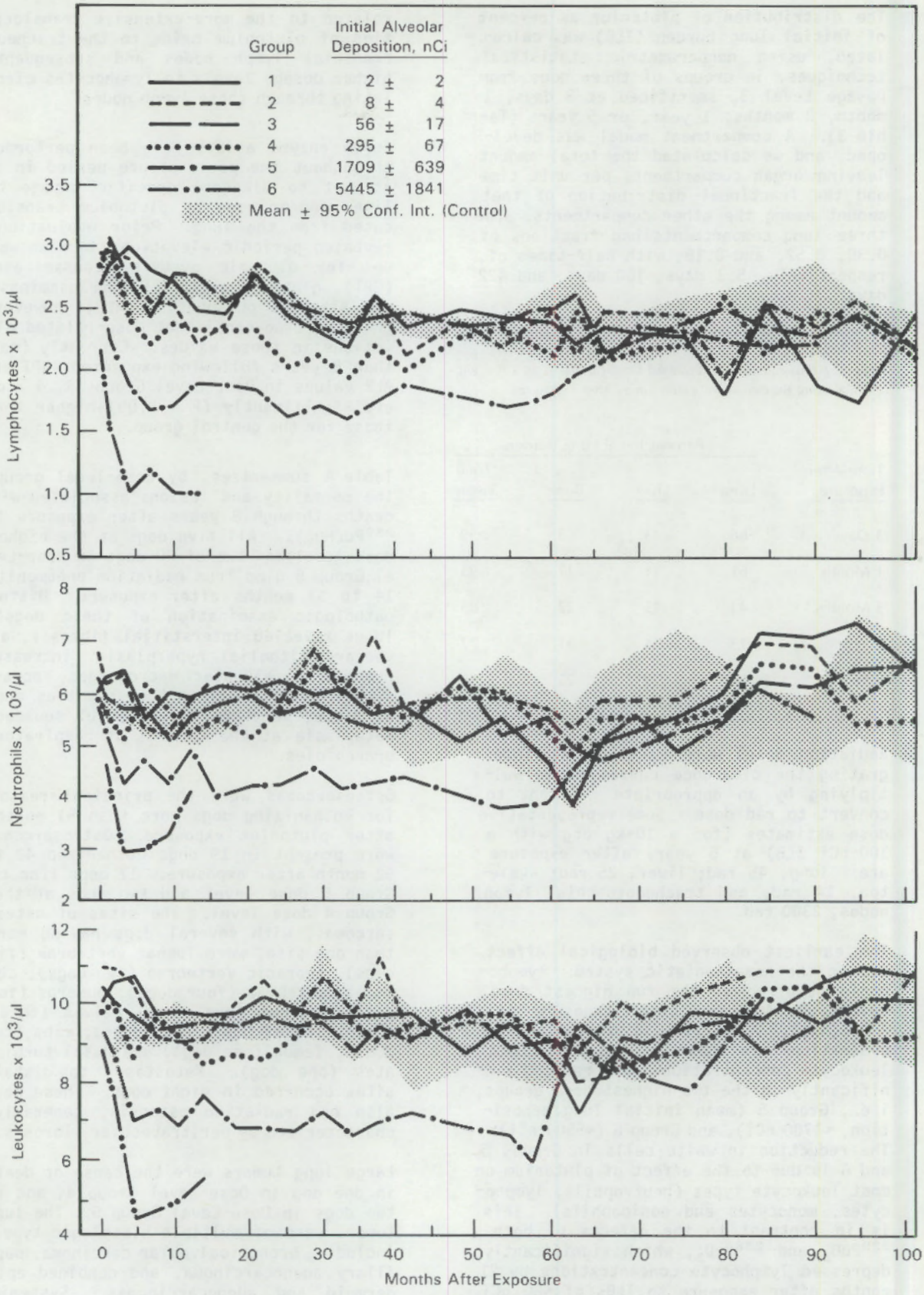


**Figure 1.** Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}Pu(NO_3)_4$.

Table 4. Lesions in Beagle Dogs 8 Years After Inhalation of $^{239}Pu(NO_3)_4$.

| | Dose Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Vehicle | Control |
| Number of Dogs/Group | 5 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Number of Dead Dogs/Group | 5 | 20 | 4 | 0 | 0 | 2 | 1 | 2 |
| Condition[a] | | | | | | | | |
| Radiation Pneumonitis | 4 | 1 | | | | | | |
| Radiation Pneumonitis and Lung Tumor | 1 | 1 | | | | | | |
| Bone Tumor | | 8 | 2 | | | | | |
| Bone and Lung Tumor | | 9 | | | | | | |
| Lung Tumor | | 1 | 1 | | | | | |
| Pneumonia or Pleuritis | | | 1 | | | | | 1 |
| Lymphoma | | | | | | | 1 | |
| Thyroid Tumor | | | | | | 1 | | |
| Meningeal Tumor | | | | | | 1 | | |
| Status Epilepticus | | | | | | | | 1 |

[a]Number of dogs with lesions associated with death

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

## • Oncogenes in Radiation Carcinogenesis

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This research examines the role of known oncogenes in lung tumors induced in beagles by the internally deposited radionuclides $^{238}Pu$ and $^{239}Pu$. We have detected dominant-acting transforming genes in seven of seven plutonium-induced lung tumors. In addition, when DNA from tumor and "normal" tissues from the same dogs was cut with the restriction endonucleases *Bam H1, Hind III,* or *Eco R1* and probed with viral oncogenes, novel (tumor-specific) restriction fragments were detected in some plutonium-induced tumors. These findings are consistent with mutational changes which alter restriction cleavage sites as well as amplification and/or rearrangement of the affected genes.

The object of this research is to examine the role of oncogenes in lung tumors induced in beagle dogs by the internally deposited radionuclides $^{238}Pu$ and $^{239}Pu$. The current research emphasizes three areas: 1) detection, isolation and characterization of dominant-acting oncogenes present in the plutonium-induced lung tumors from beagle dogs and comparison with the proto-oncogene present in normal canine DNA; 2) examination of DNA from radiation-induced tumors and accompanying cohort cells to detect novel restriction fragments present in plutonium-induced tumors; and 3) analyzing RNA from tumor and cohort cells for evidence of altered or enhanced oncogene transcription.

Cellular DNA can be efficiently taken up and integrated into the chromosomal DNA of certain cultured cell lines in a process called transfection. If the DNA contains an active oncogene, the recipient cells will convert to neoplastic phenotypes. Between 10 and 20% of naturally occurring human tumors have been found to contain an active oncogene by this assay.

We have used high-molecular-weight (HMW) DNA in the NIH 3T3 cell transfection assay to detect dominant-acting tranforming genes. The assay consists of exposing cells to 20 µg/well of either purified tumor or cohort DNA. Sixteen wells were assayed for each dog in an experiment, and the DNA was precipitated into the cells by the presence of calcium (0.125 M). The cultures were incubated at 37°C for 4 hours, treated with 7.5% glycerol for 5 minutes, washed, fed, and re-incubated for ~15 days until foci developed.

In our initial studies, using HMW DNA in the NIH 3T3 transfection assay, we detected dominant-acting tranforming genes in seven out of seven plutonium-induced lung tumors (Table 1). None of the cohort or control DNA caused tranformation. A secondary transfection with one of the cloned transformants gave an enhanced transformation frequency. In an analysis of four transformed clones, three of the four contained intense bands of Ki-ras in their DNA, as indicated by the banding in Southern (DNA hybridization) analysis. These hybridizations were conducted under conditions that detect dog Ki-ras DNA sequence but not murine Ki-ras. Experiments are underway to isolate and characterize these tranforming genes.

**Table 1.** Transforming Activity of High-Molecular-Weight DNA from Plutonium-Exposed Beagle Dogs.

| DNA Source | ffu/µg[a] | Positive Assays/ Total Assays |
|---|---|---|
| Dog No. | | |
| 772 LT[b] | 0.025 | 1/1 |
| 880 LT-1 | 0.075 | 4/4 |
| 880 LT-1° Transformant | 0.25 | 1/1 |
| 880 LT-2 | 0.05 | 3/3 |
| 880 Spleen-Normal | <0.003 | 1/6 |
| 889 LT-1 | 0.07 | 2/2 |
| 889 LT-2 | 0.041 | 2/2 |
| 889 Spleen-Normal | <0.003 | 0/2 |
| 1640-LT | 0.12 | 3/3 |
| 1640 Rhabdosarcoma | 0.09 | 3/3 |
| 1640-NL[c] | <0.003 | 0/3 |
| 1655-LT | 0.075 | 1/1 |
| 1655-NL | <0.003 | 0/1 |
| 1831-NL | <0.003 | 0/3 |
| Controls | | |
| NIH3T3 Cellular DNA | <0.003 | 2/14 |
| PT24 Cloned Oncogene | ~700 | 14/14 |
| LLC[d] | 0.06 | 4/6 |
| pNRSac Cloned Oncogene | 12 | 6/6 |

[a]Foci-forming units/microgram of DNA
[b]LT = Lung tumor
[c]NL = Normal lung
[d]LLC = Lewis lung carcinoma cellular DNA

In a second aspect of our study, we are examining the DNA from these radiation-induced tumors and accompanying cohort cells to see if tumor-specific lesions (detected as novel restriction fragments) can be seen in plutonium-induced tumors. This technique involves isolation of HMW DNA from tumor tissues and cohort tissues as well as control tissues. The DNA is then completely digested with specific restriction endonucleases, separately electrophoresed on agarose gels, then examined by Southern hybridization analyses, using various oncogenes as molecular probes. The restriction enzymes used in this study were Bam H1, Eco R1, and Hind III, all of which have recognition sequences that are six nucleotides in length.

Proto-oncogenes have been detected in normal canine DNA with >85% homology to viral probes against Ha-ras, Ki-ras, N-ras, myc, src, erb B and sis. A number of the beagle proto-oncogenes were found to be heterozygous and, as a result, restriction-fragment-length polymorphisms (RFLP) were observed in them. These studies pointed out the need for comparisons between cohort (or normal) DNA and tumor DNA from the same animals in order to detect tumor-specific changes in oncogenes. When DNA from tumor and "normal" tissues from the same dog were cut with the restriction endonucleases Bam H1, Hind III, or Eco R1 and probed with viral oncogene probes, a number of novel restriction fragments were detected in plutonium-induced lung tumors. When src was used as the probe there was very little gene heterozygosity, and only one tumor-specific RFLP was observed (Table 2). Similar studies with Ha-ras detected lung-tumor-specific RFLP in one of seven dogs, and with myc, in one of nine dogs (data not shown).

With Ki-ras, there were considerable differences in restriction fragment size from one dog to another (Table 3). In addition, five of seven dogs examined had potential tumor-specific lesions or unique restriction fragments in lung-tumor DNA. These findings are consistent with mutational changes that alter restriction cleavage sites, or with amplification and/or rearrangement of the affected genes. Further studies are underway to characterize each specific mutation.

In the third aspect of this research, we have just begun to measure oncogene messenger-RNA in lung-tumor cells for evidence of altered or enhanced oncogene transcription. These studies will help us to identify those oncogenes that have been altered by radiation and to characterize the lesions (e.g., deletions, translocations, etc.) that are present in oncogenes associated with plutonium-induced cancers of beagles.

**Table 2.** Restriction-Fragment-Length Polymorphisms of the src Oncogene in Plutonium-Induced Lung Tumors from Beagle Dogs.

| | Restriction Endonuclease[a] | | |
|---|---|---|---|
| Dog No. | Bam H1 | EcoR1 | Hind III |
| 727 | 5 | 5.5, 3.6 | 10 |
| 777 | 5 | 5.5, 3.6<br>17, 10, 5.5, 3.6[b] | 10 |
| 796 | 5 | 5.5, 3.6 | 10 |
| 880 | 5 | 5.5, 3.6 | 10 |

[a]Fragment size expressed as kilo base pairs
[b]Lung-tumor-specific pattern

**Table 3.** Restriction-Fragment-Length Polymorphisms of the Ki-ras Oncogene in Plutonium-Induced Lung Tumors from Beagle Dogs.

| | Restriction Endonuclease[a] | | |
|---|---|---|---|
| Dog No. | Bam H1 | EcoR1 | Hind III |
| 783 | 7.1<br>9.2, 7.1, 5.2[b] | 7.1<br>15.5, 13, 7.1[b] | |
| 796 | 4.5 | 4.2 | |
| 880 | 3.8 | 6.2, 3<br>9.4, 8.4, 4.8, 4.3[b] | 5<br>12[b] |
| 889 | 9.4<br>9.5, 6.6[b] | 10, 3 | |
| 1391 | 5.8<br>9.8, 5.8[b] | 10.4, 6.2, 5.8 | 5.7<br>5.5[b] |
| 1640 | | 6.2, 3<br>10.3, 6.2, 3[b] | |
| 1655 | | 6.2, 3 | |

[a]Fragment size expressed as kilo base pairs
[b]Lung-tumor-specific pattern

## • Cigarette Smoke and Plutonium

Principal Investigator: R. E. Filipy

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

Technical Assistance: K. E. Lauhala

Autoradiographic techniques with 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 a plutonium aerosol only. Much more plutonium than expected was detected on the inner surfaces of bronchi of dogs exposed to low levels of plutonium several years ago. Differences were demonstrated in the distribution of plutonium in upper pulmonary airways, depending on the chemical and isotopic form inhaled.

The major objective of this project is to obtain experimental data on whether cigarette smokers are at greater risk than nonsmokers to potential health effects of inhaled plutonium. Track-etch film autoradiography of internal bronchial surfaces, a technique developed as part of this project, showed much more plutonium present in bronchi of beagle dogs 400 days after inhalation of approximately 1 μCi of $^{239}PuO_2$ than was expected (Annual Report, 1984). Because of that discovery, we decided to apply the technique to bronchi of dogs that were exposed to relatively low levels of $^{239}Pu(NO_3)_4$, $^{238}PuO_2$, and $^{239}PuO_2$ as part of other projects at this laboratory. Although this represented a deviation from the original objectives, it was done because information regarding the spatial distribution of plutonium in lungs several years after inhalation exposure might contribute to understanding of the mechanisms of plutonium carcinogenesis.

An exploratory application of the autoradiographic technique was performed with lungs from the six dogs listed in Table 1. The primary objective of the work was to determine if the method was sufficiently sensitive to detect plutonium at low initial lung burdens (ILB) and long postexposure times. A single lung lobe (right apical lobe) was resected at necropsy and fixed by immersion in 10% neutral buffered formalin. The bronchial airways were isolated from the parenchyma to approximately the level of the tertiary bronchi, then split and pressed to a small (approximately 2- x 3-cm) piece of film with the mucosa in contact with the film. Portions of liver and salivary gland were also fixed by immersion in formalin and, after fixation, were recut so that freshly cut surfaces were pressed to the film. After 7 to 9 weeks of exposure, the films were etched in 4N NaOH at 60°C for 2 hours.

Although no attempt was made to collect quantitative data from the initial preparations, several interesting observations were made. These are discussed below according to the chemical form of plutonium inhaled and are illustrated by a series of photomicrographs. The magnification for all the photomicrographs was the same; each represents an area of tissue approximately 1 x 1.5 mm.

### Plutonium-239 Nitrate

Very high concentrations of plutonium were detected in the bronchi of Dog #1655 at 88 months after exposure (Figure 1A). All alpha "tracks" were single tracks as would be expected, since plutonium nitrate is considered the most soluble of the chemical forms listed in Table 1. Frequently, the tracks were arranged in rows rather than randomly distributed. This phenomenon is discussed later in this report. The concentration of tracks was very similar throughout all areas of the bronchial tree.

**Table 1.** Exposure Data from Beagle Dogs from which Selected Tissues were Autoradiographed with Cellulose Nitrate Film.

| | Plutonium | | | | |
|---|---|---|---|---|---|
| Dog Number | Isotope | Chemical Form | Initial Lung Burden, μCi | Time After Exposure, mo | Tissues[a] |
| 1655 | $^{239}Pu$ | Nitrate | 1094 | 88 | Lu |
| 1521 | $^{239}Pu$ | Nitrate | 205 | 107 | Li, SG |
| 1053 | $^{238}Pu$ | Oxide | 148 | 143 | Lu |
| 1177 | $^{238}Pu$ | Oxide | 262 | 136 | Lu |
| 844 | $^{239}Pu$ | Oxide | 135 | 170 | Lu, Li, SG |
| 819 | $^{239}Pu$ | Oxide | 163 | 170 | Lu, Li, SG |

[a]Lu = lung; Li = liver, and SG = salivary gland.

To rule out the possibility that all tissues of the body might contain enough plutonium to produce similar autoradiographs, autoradiographic films were made of slices from the liver and parotid salivary gland of Dog #1521, which was also exposed to $^{239}Pu(NO_3)_4$, but at one-fifth the ILB of Dog #1655. This form of plutonium is known to accumulate in the liver (30% of the ILB after 3 years); very little has been previously noted in salivary glands. As expected, the liver produced a dense concentration of tracks, which were quite randomly distributed (Figure 1B); the salivary gland produced almost none.

Plutonium-238 Oxide

Most of the tracks on autoradiographic films from Dogs #1053 and #1177 were present as individual tracks (Figure 1C) like those for plutonium nitrate; however, occasional alpha "stars" were seen at the rate of 1 to 2 stars/cm$^2$. The arrangement of tracks in rows was also noted in the bronchi of these dogs, although not to the extent seen in Dog #1655 (plutonium nitrate).

In general, the density of tracks in films from Dog #1177 was greater than in films from Dog #1053. The method is, therefore, sensitive enough to detect the expected twofold difference in lung content (based on the ILB value and similar postexposure times). The higher concentration of plutonium was in the larger, main bronchi instead of in secondary and tertiary bronchi, as reported previously (Annual Report, 1984). Probable reasons for this are discussed later in this report.

An extraordinarily dense accumulation of alpha tracks was observed on an autoradiograph of a bronchus from Dog #1177 (Figure 1D) at the approximate location of a bronchial bifurcation. In over 100 autoradiographs examined, this was the first such observation.

Plutonium-239 Oxide

In contrast to the dogs that had inhaled $^{238}PuO_2$, autoradiographs of the bronchi of Dogs #819 and #844 contained primarily alpha stars (Figure 1E). Frequently, however, the stars were arranged in rows (Figure 1F) like the single tracks in the other dogs. The plutonium particles were apparently at varying distances from the film during autoradiographic exposure: alpha penetration from some plutonium particles was very dense, but others only partially penetrated the film (Figures 1E and 1F). Because the film was in contact with the epithelial surface, the distance between the particle and film could only have been greater if the particle was beneath or within the epithelium. Liquid photographic emulsion autoradiographs of bronchial cross sections have been used to show plutonium particles beneath the mucosa (Annual Report, 1984).

In general, plutonium particles were more numerous in the secondary and tertiary bronchi of these dogs compared with observations in dogs with $^{238}PuO_2$ lung burdens, where particles were more numerous in main bronchi. However, dogs from previous studies (Annual Report, 1984), which had inhaled nearly seven times as much $^{239}PuO_2$, also had more numerous particles in secondary and tertiary bronchi.

A considerable amount of $^{239}PuO_2$ was detected in slices of liver; the concentrations of alpha stars were equivalent to those seen in the bronchial preparation (Figure 1F). Only single isolated particles, detected as stars, were present in the salivary glands.

One of the questions raised as a result of these observations concerns the arrangement of plutonium in rows within the bronchi. There are several possible explanations, including: 1) the plutonium was incorporated in mucus, which then "streams" on its way out of the bronchus; 2) folds are formed in the mucosa during preparation of the autoradiographs. The former is unlikely because of the amount of postexposure time involved. The latter is unlikely because preparation involves flattening a concave surface to compress it on to the film, which probably stretches the mucosa rather than causing folds. A more probable explanation for particle arrangement in rows is that the plutonium was initially carried into lymphatic vessels within the lamina propria and remained in association with those vessels, either because lymphatic drainage ceased when lymph nodes became fibrotic or because the plutonium penetrated the vessel wall during the time between initial pulmonary clearance and the death of the animal. In that case, the dense accumulation of particles in the bronchus of Dog #1177 (Figure 1D) might have been because the autoradiograph was of lymphatic tissue associated with the bronchus rather than of bronchial mucosa. The tortuous paths of the lymph vessels could account for the difference in depth of particles with respect to the film, seen in Figures 1E and 1F.

This hypothesis might also explain the distributional differences between $^{238}PuO_2$ and $^{239}PuO_2$. The $^{238}PuO_2$, being slightly more soluble, may have been carried, by lymphatic vessels, farther from its orig-

inal deposition site in the lung before its progress was halted.

Future research effort will involve an electron microscopic search for plutonium particles within bronchial walls. If found, two questions may be answered: 1) Are the particles still contained within macrophages? 2) Are the particles associated with lymphatic vessels?

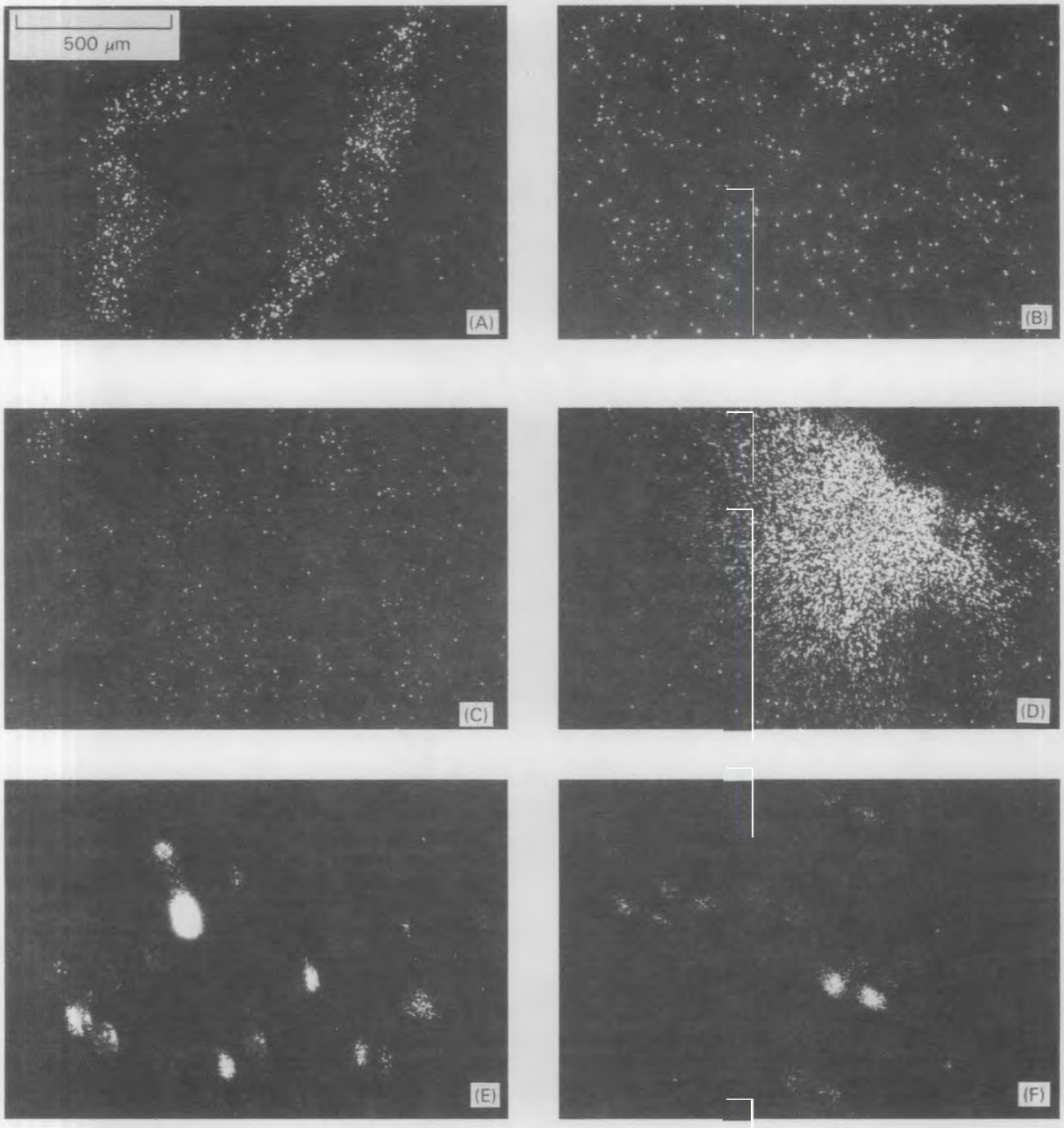


**Figure 1.** Photomicrographs of Cellulose Nitrate Track-Etch Autoradiographs. Magnification is the Same in all Photos. (A) Bronchus of $^{239}Pu(NO_3)_4$-Exposed Dog at 88 mo After Exposure; (B) Liver of $^{239}Pu(NO_3)_4$-Exposed Dog at 107 mo After Exposure; (C) Bronchus of $^{238}PuO_2$-Exposed Dog at 143 mo After Exposure; (D) Bronchus of $^{238}PuO_2$-Exposed Dog at 136 mo After Exposure; (E) Bronchus of $^{239}PuO_2$-Exposed Dog at 170 mo After Exposure; (F) Bronchus of Same Dog as in "E", Showing Particles Arranged in Rows.

A continued effort is underway to determine the quantity of plutonium present in bronchi, based on track-etch autoradiograms. This involves collecting plutonium aerosols on a series of Nuclepore filters, nondestructive analysis of each filter for plutonium content, and preparation of track-etch autoradiographs of each filter. The resulting films would serve as standards with which to compare bronchial autoradiographs. An image-analyzing computer recently obtained will be used to make these comparisons. Information concerning the quantity of plutonium present in airways versus that in the parenchyma of the lung would be useful in determining the proportion of radiation dose delivered to dividing basal cells in airway epithelia. Based on preliminary, nonquantitative data, indications are that doses to those cells are greater than previously thought.

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

Principal Investigator: C. L. Sanders

Other Investigator: K. E. McDonald

This project will produce data to generate a dose-response curve for lung-tumor incidence in rats following inhalation of $^{239}PuO_2$ at levels producing lifetime radiation doses to the lung of <5 rad to >2,000 rad. A total of 1727 of 2134 exposed and 869 of 1058 sham-exposed lifespan rats have died. Histopathological evaluations have been completed on 418 of the exposed and 194 of the sham-exposed rats. The incidence of primary lung tumors (mostly squamous cell carcinoma, adenocarcinoma and hemangiosarcoma, in order of decreasing abundance) was 84% at 1500 rad, 67% at 750 rad, 18% at 350 rad, 15% at 200 rad, 0.0% at 83 rad, 2.3% at 44 rad, 0.0% at 23 and 10 rad, 1.4% at 5.5 rad and 0.0% for sham-exposed rats. Overall, only two primary lung tumors have been found in 2 of 449 rats with lung doses <100 rad, while 84 lung tumors have been found in 66 of 163 rats with lung doses >100 rad, indicating a clear threshold dose for lung-tumor induction from inhaled $^{239}PuO_2$.

This project was designed to provide data for estimating the dose-response relationships of lung-tumor incidence in rats exposed by inhalation to $^{239}PuO_2$. The initial alveolar depositions (IAD) were determined by whole-body counting for $^{169}Yb$ calcined with $^{239}PuO_2$ particles. The number of rats in each exposure group were determined by statistical analysis of previous higher-dose studies and by the historical frequency of primary lung tumors in untreated, female, Wistar rats. Radiation dose calculations to lung are determined to day of death by a formula that incorporates a master lung-clearance curve and IAD determinations, using $^{169}Yb$ whole-body counting data (Annual Reports, 1981-1984). Dead rats were distributed among radiation dose cohort groups in the following dose ranges: >1,000 rad, 500-1,000 rad, 250-500 rad, 125-250 rad, 63-125 rad, 32-63 rad, 16-32 rad, 8-16 rad, <8 rad and 0 rad. Mean ± standard deviation (SD) lung dose groups for this report are: 1500 ± 360, 750 ± 140, 350 ± 73, 200 ± 39, 83 ± 15, 44 ± 8.9, 23 ± 4.1, 10 ± 2.2, 5.5 ± 1.4 and 0 rad.

The status of the lifespan study, as of October 1985, is shown in Table 1. A total of 1,727 of 2,134 exposed rats and 869 of 1,058 sham-exposed rats have died. Histopathological evaluations have been completed on 418 exposed and 194 sham-exposed rats. Only the highest deposition level (150 nCi) exhibited substantially decreased survival due to radiation pneumonitis. This group had a median survival time of 568 days; median survival times in all other groups ranged from 682 to 843 days.

The presence and degree of severity of pulmonary fibrosis was significantly increased only at the two highest dose levels (750 and 1500 rad). Nonsignificant increases in pulmonary fibrosis were also seen at 200 and 350 rad doses. There was a dose-related increase in both squamous cell metaplasia and adenomatous metaplasia and in the severity of metaplastic involvement in the lung with increasing radiation dose, starting at about 100 rad (Table 2).

**Table 1.** Status of the Lifespan Study as of October 1985.

| Mean IAD[a], nCi | Number of Rats | | | |
|---|---|---|---|---|
| | Alive | Dead | Total | Control Cohort |
| 0 | 189 | 869 | 1058 | -- |
| 0.60 | 279 | 720 | 999 | 498 |
| 0.98 | 113 | 425 | 538 | 269 |
| 2.4 | 10 | 195 | 205 | 103 |
| 5.7 | 2 | 94 | 96 | 44 |
| 7.5 | 1 | 59 | 60 | 29 |
| 17 | 1 | 58 | 59 | 29 |
| 32 | 0 | 60 | 60 | 28 |
| 82 | 1 | 58 | 59 | 29 |
| 150 | 0 | 58 | 58 | 29 |
| Totals | 596 | 2596 | 3192 | 1058 |

[a] Initial alveolar deposition

The incidence of primary lung tumors at the highest dose levels continue to be similar to what has previously been reported for inhaled high-fired $^{239}PuO_2$ in female, Wistar rats (C. L. Sanders et al., 1976, Radiat. Res. 68: 349-360; C. L. Sanders and J. A. Mahaffey, 1981, Health Phys. 41: 629-644). However, fewer than expected adenocarcinomas were seen at moderate to low radiation doses. The total incidences of lung tumors were 84% at 1500 rad, 67% at 750 rad, 18% at 350 rad, 15% at 200 rad, 0.0% at 83 rad, 2.3% at 44

**Table 2.** Incidences and Grade of Pulmonary Fibrosis and Epithelial Metaplasias in the Lung as a Function of Radiation Dose (N = Number of Animals).

| Dose to Lung, rad | N | Mean Grade[a] | | Percent With Metaplasia | |
|---|---|---|---|---|---|
| | | Pulmonary Fibrosis | Epithelial Metaplasia | Squamous | Adenomatous |
| 0 | 194 | 02.1 | 0.03 | 1.5 | 2.1 |
| 5.5 | 72 | 0.25 | 0.05 | 2.8 | 2.8 |
| 10 | 58 | 0.10 | 0.0 | 0.0 | 0.0 |
| 23 | 61 | 0.18 | 0.0 | 0.0 | 0.0 |
| 44 | 43 | 0.21 | 0.0 | 0.0 | 0.0 |
| 83 | 31 | 0.26 | 0.05 | 0.0 | 6.5 |
| 200 | 20 | 0.70 | 0.12 | 5.0 | 10 |
| 350 | 38 | 0.87 | 0.12 | 2.6 | 13 |
| 750 | 33 | 2.15 | 0.74 | 24 | 58 |
| 1500 | 62 | 2.89 | 1.75 | 68 | 82 |

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

rad, 0.0% at 23 and 10 rad, 1.4% at 5.5 rad and 0.0% at 0 rad (Table 3). No primary lung tumors have been seen in 194 sham-exposed control rats. A total of 86 primary lung tumors have been found in 68 rats; 16 rats had two different primary tumors, and 1 rat had three different primary tumors.

**Table 3.** Incidences of Primary Lung Tumors as a Function of Radiation Dose (N = Number of Animals).

| Dose To Lung, rad | N | Percent of Lung Tumors | | | |
|---|---|---|---|---|---|
| | | Squamous Cell Carcinoma | Adeno-carcinoma | Hemangio-sarcoma | Total |
| 0 | 194 | 0.0 | 0.0 | 0.0 | 0.0 |
| 5.5 | 72 | 0.0 | 1.4 | 0.0 | 1.4 |
| 10 | 58 | 0.0 | 0.0 | 0.0 | 0.0 |
| 23 | 61 | 0.0 | 0.0 | 0.0 | 0.0 |
| 44 | 43 | 0.0 | 0.0 | 0.0 | 2.3 |
| 83 | 31 | 0.0 | 0.0 | 0.0 | 0.0 |
| 200 | 20 | 10 | 5 | 0.0 | 15 |
| 350 | 38 | 2.6 | 11 | 0.0 | 18 |
| 750 | 33 | 42 | 15 | 6.1 | 67 |
| 1500 | 62 | 52 | 18 | 9.7 | 84 |

Only one pulmonary adenocarcinoma has been seen in 449 rats with lung doses <100 rad; 78 primary lung tumors (squamous cell carcinoma, adenocarcinoma, hemangiosarcoma) have been seen in 163 rats with lung doses >100 rad (Figure 1). An additional seven primary fibrosarcomas, mesotheliomas and carcinomas were seen in the lung; six were in animals that received doses >100 rad. To date, our data on primary lung tumors indicate that a clear threshold exists for induction of lung tumors by inhaled $^{239}PuO_2$. This dose, about 100 rad, appears to be a threshold level not only for primary lung tumors but also for pulmonary fibrosis and for epithelial metaplasias in the lung. Future pulmonary autoradiographic studies should indicate whether 100 rad is also the threshold dose for subpleural and peribronchiolar aggregations of inhaled $^{239}PuO_2$ particles.

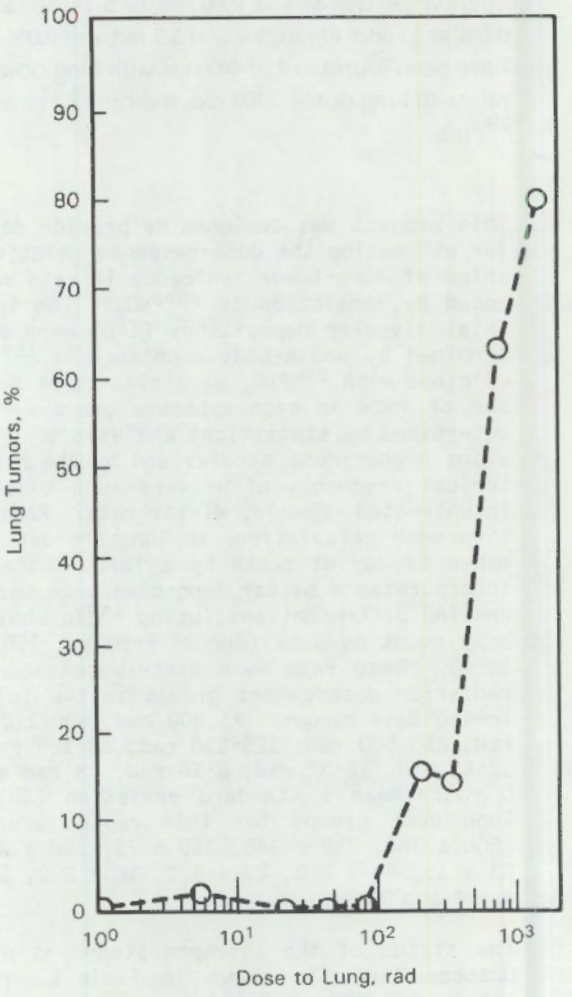


**Figure 1.** Cumulative Percent and Incidence of Primary Lung Tumors (Adenocarcinoma, Squamous Cell Carcinoma, Hemangiosarcoma) as a Function of Radiation Dose. Data are from 612 rats with completed histopathology, 61 of which had 79 lung tumors of types indicated.

Primary lung tumors were mostly invasive in the thoracic cavity and often multicentric and metastatic in thoracic lymph nodes. Several pulmonary squamous cell carcinomas were metastatic to the kidney; otherwise, none of the pulmonary carcin-

omas or hemangiosarcomas metastasized to other organs. Lung tumors were the cause of death in most rats with these tumors.

Other than the lung tumors in the 750- and 1500-rad groups, the most prevalent tumor sites in all groups are uterus, and pituitary and mammary glands; both uterine and pituitary tumors are common probable causes of death. Although the incidences of these tumors do not appear to be related to lung dose (Table 4); several other extrapulmonary tumor types may be. Two fibrosarcomas of thoracic lymph nodes were seen at 762 and 1309 rad, and a single hepatocellular carcinoma was seen at 313 rad. Thyroid tumors were more prevalent in high-dose groups: 5 adenomas, 2 carcinomas and 1 hemangiosarcoma were found in 163 rats with lung doses >100 rad; only 2 adenomas were found in 449 rats with lung doses <100 rad.

**Table 4.** Incidences of Extrapulmonary Tumors as a Function of Radiation Dose to the Lung (N = Number of Animals).

| Dose To Lung, rad | N | Percent Extrapulmonary Tumors In: Uterus[a] | Pituitary Gland[b] | Mammary Gland[c] |
|---|---|---|---|---|
| 0 | 194 | 37 | 46 | 31 |
| 5.5 | 72 | 22 | 35 | 17 |
| 10 | 58 | 16 | 36 | 21 |
| 23 | 61 | 23 | 49 | 33 |
| 44 | 43 | 26 | 26 | 28 |
| 83 | 31 | 58 | 48 | 26 |
| 200 | 20 | 25 | 30 | 35 |
| 350 | 38 | 24 | 47 | 13 |
| 750 | 33 | 3.0 | 24 | 39 |
| 1500 | 62 | 13 | 24 | 18 |

[a] Leiomyoma, leiomyosarcoma, stromal sarcoma, squamous cell carcinoma, adenocarcinoma, hemangiosarcoma, carcinosarcoma
[b] Adenoma, adenocarcinoma
[c] Fibroadenoma, adenocarcinoma

## • Inhalation Hazards to Uranium Miners

Principal Investigator: F. T. Cross

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

Technical Assistance: R. M. Briones and C. R. Petty

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 uranium mine air 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 serially sacrificed rats are reported for approximately 20- to 640- working-level-month (WLM) radon-daughter exposures delivered at one-tenth the rate of previous 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 700 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 working-level-month (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 radiation 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 non-neoplastic lesions of the respiratory tract. Histopathologic data for these lesions in serially sacrificed animals (six animals from each group at 6, 12 and 18 months following completion of exposures) 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.

**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<br>15 mg/m$^3$ Uranium Ore Dust | 10,240 |
| 32 | 1000 WL Radon Daughters<br>15 mg/m$^3$ Uranium Ore Dust | 5120 |
| 32 | 1000 WL Radon Daughters<br>15 mg/m$^3$ Uranium Ore Dust | 2560 |
| 32 | 1000 WL Radon Daughters<br>15 mg/m$^3$ Uranium Ore Dust | 1280 |
| 64 | 1000 WL Radon Daughters<br>15 mg/m$^3$ Uranium Ore Dust | 640 |
| 128 | 1000 WL Radon Daughters<br>15 mg/m$^3$ Uranium Ore Dust | 320 |
| 64 | Controls | |

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

(b) Exposure rate, 90 hr/wk; planned periodic sacrifice.

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

(d) Working level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of $1.3 \times 10^5$ MeV of potential $\alpha$-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 |
| 192 | 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.
[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 $1.3 \times 10^5$ MeV of potential $\alpha$-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 1 data.

In the 1984 Annual Report, we summarized the incidence of tumors primary to the lung in the remaining rats in the 6000 Series experiments. Histopathological data for the 7000 Series experiments have not yet been developed for comparison with the 10-fold higher exposure rate data of the 6000 Series experiments.

Similar serial sacrifice data for the 8000 Series experiments revealed no malignant lung tumors in the 20- to 640-WLM exposure range, 6 to 18 months following completion of exposures. Because the ore dust was used as the carrier aerosol for the radon daughters, a change in WLM exposure also produced a proportional change in cumulative ore-dust exposures. A descriptive summary follows of the lesions for animals sacrificed in each exposure level in the 8000 Series.

The lungs from rats at all exposure levels had focal aggregates of alveolar macrophages containing uranium ore dust, with the average severity increasing with increased time and exposure level. Averages of exposure-group focal interstitial reaction were somewhat increased over those of control rats in the two highest exposure groups (320 and 640 WLM). The focal interstitial reaction was generally associated with aggregates of alveolar macrophages and included thickened alveolar septa, prominent alveolar epithelial cells and, occasionally, evidence of early interstitial fibrosis. Bronchiolarization, composed of very few or few columnar epithelial cells, apparently extending from terminal bronchioles into adjacent alveolar ducts, also occurred in the two highest exposure groups. A low incidence of vesicular emphysema, possibly related to exposure, occurred at 640-WLM exposures. Additional changes in lungs did not appear to be related to exposure level. They included peribronchiolar lymphocytic cellular infiltration, increased numbers of alveolar macrophages that did not contain uranium ore dust, focal cellular infiltration, very few granulomas, adenomatosis, a very small papillary adenoma, focal calcification, osseous metaplasia, and nodular fibrosis.

**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 |
| 192 | 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.
[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 $1.3 \times 10^5$ MeV of potential $\alpha$-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

Mediastinal lymph nodes in rats from each exposure group had aggregrates of macrophages laden with uranium ore dust. The average severity was progressively higher with increase in exposure level. Reactive hyperplasia, associated with the dust deposition, was increased over levels found in control rats at all exposure levels except the very lowest. At the higher exposure levels, the mediastinal lymph nodes became quite large. Nodular fibrosis was present in several rats at the 320- and 640-WLM exposure levels. Cystic degeneration occurred occasionally without relationship to exposure level.

There were no changes clearly related to exposure in the larynx, trachea, nose, or other organs.

Large-Animal Studies

Fifteen (seven exposed and eight controls) of 35 beagle dogs remain on study to determine the pathogenic role of carnotite uranium ore dust in inhalation exposure.

The animals, to date, have received 8½ years of exposure (20 hours/week) to 15 $mg/m^3$ uranium ore dust concentrations.

## • 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 $^{233}UO_2(NO_3)_2$ and $^{232}UO_2(NO_3)_2$ aerosols (0.6 to 53 nCi initial lung burden) have been observed for their life span. Retention kinetics in major tissues and metabolic data have been presented in previous Annual Reports (1975-1984). Dose-response relationships for malignant lung-tumor and bone-tumor induction after $^{232}UO_2(NO_3)_2$ inhalation are discussed below.

Cumulative radiation dose to lung and skeleton, the tissues most affected by $^{232}U$ inhalation, was calculated from the quantity of $^{232}U$ and $^{228}Th$ measured in the lung and skeleton at death. Generalized retention curves (Figures 1 and 2) were constructed for the two radionuclides, using the pooled data for the three graded-dose groups. Retention curves were derived by fitting multiexponential functions to data for individual rats that died and were analyzed during the lifespan study. Estimated lung and skeleton doses were divided into dose ranges (Table 1), arbitrarily selected for the purpose of plotting the data.

When the data are adjusted for the $^{232}U$ daughter-product dose contributions, the lung-tumor response to inhaled $^{232}U$ nitrate is in close agreement to results we have observed in similar studies with other inhaled actinide nitrates. Peak lung tumor incidence (70%) for $^{232}U$ was observed in the seven rats that sustained a cumulative lung radiation dose of >1000 rad; pulmonary adenocarcinoma was the primary malignant lesion induced by the $^{232}U$ decay-chain nuclides.

Malignant bone-tumor incidence, also shown in Table 1, was of minor significance compared to the incidence of lung tumors. However, this is not necessarily the case in a species that lives longer than the rat. Uranium-232 daughter-product accretion and the corresponding increase in cumulative radiation dose to skeleton appeared to be an ongoing process throughout

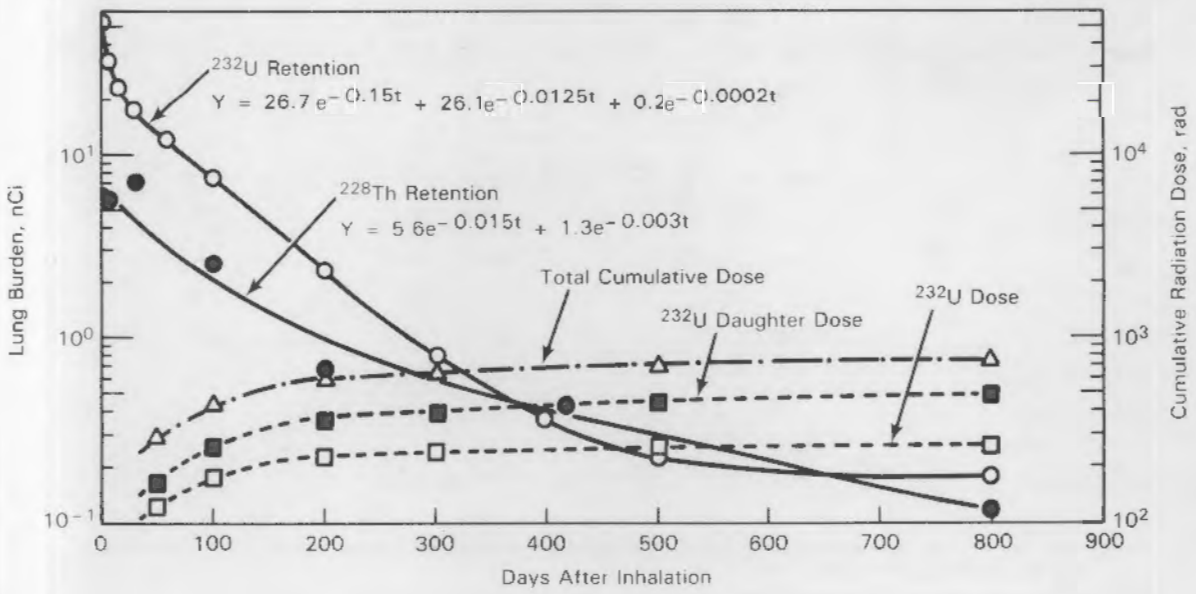


**Figure 1.** Retention of $^{232}U$ and $^{228}Th$ in Rat Lung and Corresponding Cumulative Radiation Dose Estimates.

the rats' life span (Figure 2). The radiation dose to lung, on the other hand, was essentially constant after about 1 year (Figure 1).

The dose contribution from $^{232}U$ decay products (Figures 1 and 2) was estimated from the amount of $^{228}Th$ found in tissues when the rat died. The dose calculation assumed that all $^{232}U$ decay-chain nuclides were in equilibrium with $^{228}Th$. This assumption was required since our analytical capabilities were limited to $^{232}U$ and $^{228}Th$ analyses, and no measurements were available for subsequent decay products.

Results now available from other ongoing studies, in which $^{232}U$, $^{228}Th$, $^{224}Ra$, $^{212}Pb$, $^{212}Bi$ and $^{208}Tl$ are measured, suggest that dose estimates assuming daughter equilibrium with $^{228}Th$ tend to overestimate the cumulative dose because no allowance has been made for loss of $^{220}Rn$ and subsequent decay products. The effect of $^{220}Rn$ loss on lung dose would be the greatest, since up to 10% of the $^{220}Rn$ formed in lung may be lost through respiration. The dose to bone is probably less affected because of the low diffusion rate and resulting greater retention of $^{220}Rn$ in compact bone.

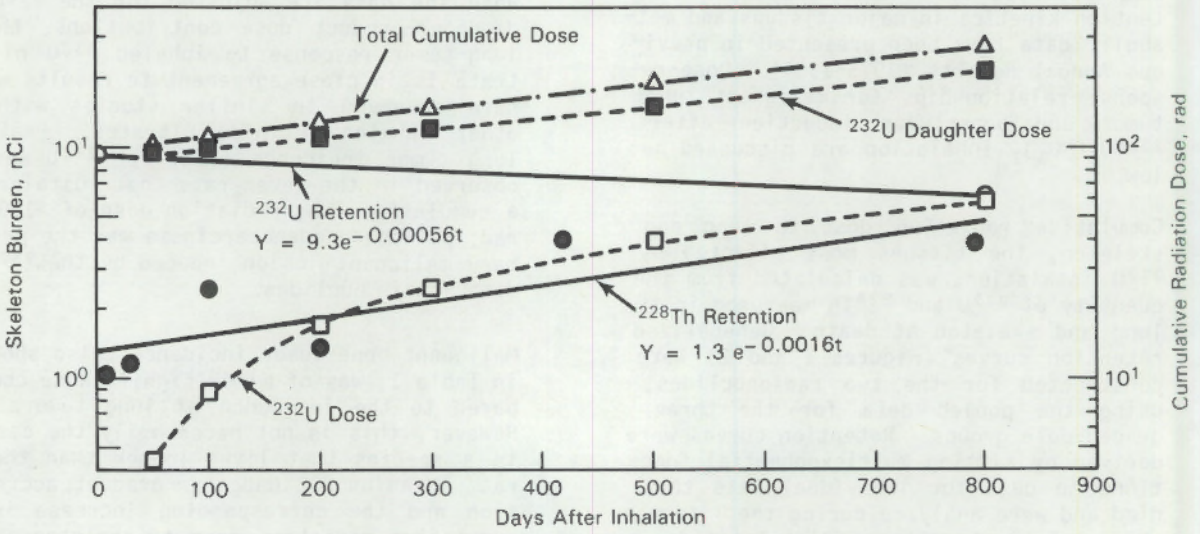


**Figure 2.** Retention of $^{232}U$ and $^{228}Th$ in Rat Skeleton and Corresponding Cumulative Radiation Dose Estimates.

**Table 1.** Cumulative Radiation Dose and Incidence of Malignant Lung and Bone Tumors in Rats Exposed to Inhaled $^{232}UO_2(NO_3)_2$ Aerosols.

| | Number of Malignant Tumors/Number of Rats | | | | Incidence, % | |
|---|---|---|---|---|---|---|
| Dose Range, rad[a] | Lung | | Skeleton | | Lung | Skeleton |
| <10 | 1/39 | (767)[b] | 0/65 | (719) | 2.6 | 0 |
| 10-100 | 2/57 | (674) | 1/60 | (676) | 3.5 | 1.7 |
| 100-500 | 25/59 | (654) | 2/56 | (643) | 42.4 | 3.6 |
| 500-1000 | 13/20 | (699) | 0/4 | (814) | 65 | 0 |
| 1000-5000 | 7/10 | (729) | --- | | 70 | --- |
| Treated Control | 0/63 | (746) | 0 | | 0 | 0 |
| Shelf Control | 2/44 | (663)[c] | 0 | | 4.5 | 0 |

[a] The dose due to $^{232}U$ was multiplied by 2.8 for lung and by 5 for skeleton to compensate for the ingrowth of daughter products (see Figures 1 and 2.)

[b] Mean survival time (days) in parentheses

[c] Lung tumors: a squamous cell carcinoma and an osteosarcoma

## • Aerosol Technology Development

Principal Investigator: W. C. Cannon

Technical Assistance: M. L. Clark, B. J. Greenspan, B. W. Killand, and O. R. Moss

In this project we have developed apparatus for aerosol generation, characterization and delivery of aerosols for studies of biological effects of inhaled air pollutants. In this report we discuss development of a special electrical aerosol generator and improvements on a standard compressed-air aerosol generator.

### Development of an Electric Field Nebulizer

A liquid nebulizer is being developed that disperses the liquid into fine droplets by means of an electric field rather than by using the high-speed air jets in the standard nebulizer. This new type of nebulizer can produce submicron-size droplets that are all the same size (monodisperse). Since the nebulizer output is independent of air flow, it can produce a denser aerosol than most compressed-air types. The droplets have a very high electric charge, which may be useful in controlling the transport of aerosols that may have to be neutralized before use. We will use the nebulizer to generate monodisperse aerosols for instrument and filter testing as well as for inhalation toxicology experiments.

The electric-field nebulizer has a liquid reservoir connected to a small capillary, from which the particles are ejected (Figure 1). The positive terminal of a high-voltage power supply is connected either to the capillary, if it is made of electrically conductive material, or to an electrode in contact with the liquid in the reservoir. In these experiments, the negative terminal is usually connected to a collecting cup or to a metal grid to attract the charged particles. We found that we could achieve some charge neutralization by means of the corona discharge from a sharp-pointed, negatively charged probe located 1 or 2 cm from the capillary.

To generate the desired submicron-size monodisperse aerosol, we found that the

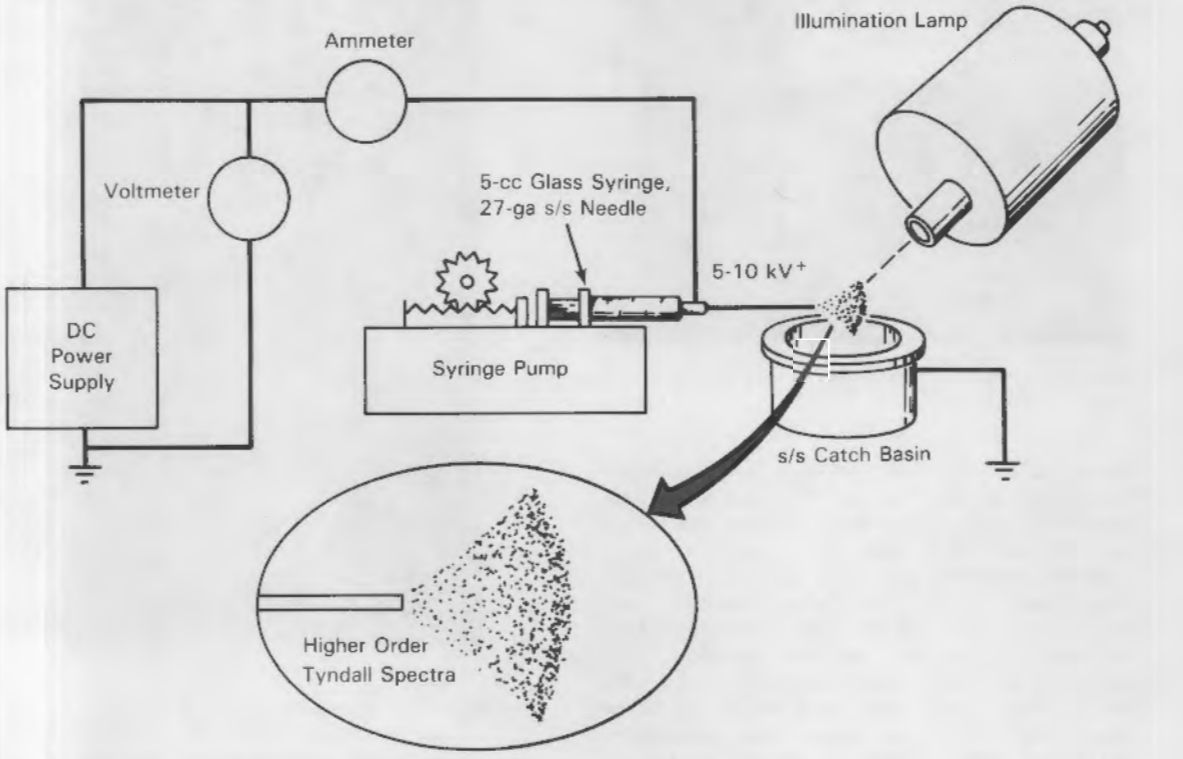


**Figure 1.** Schematic Diagram of Electric Field Nebulizer.

charging voltage must be between 5 and 10 kV. At voltages outside this range, the nebulizer produced polydisperse aerosols with large particles. We also determined the upper and lower limits on the liquid feed rate to the capillary that were required to produce the monodisperse aerosols. For example, a 0.203-mm-i.d. capillary produced monodisperse water droplets at feed rates from 9 to 13 µl/min, using a syringe pump to control the flow. Outside this range the generation became unstable, and the aerosols were polydisperse. In these experiments the monodispersity of the aerosols was inferred from observing higher-order Tyndall spectra (HOTS) when white light was used to illuminate a cloud of droplets (Figure 1). A special nebulizer with nine capillaries, fed by a single syringe pump, increased the output approximately ninefold (Figure 2).

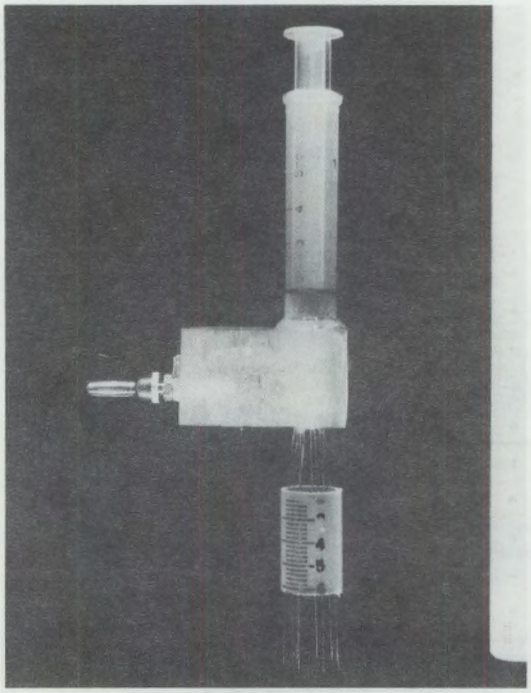

**Figure 2.** Syringe with Nine Capillaries for Increasing Output of the Electric Field Nebulizer.

Water, alcohols and ketones are generally the liquids best suited for use with the electric-field nebulizer. Other materials can be generated when dissolved in these liquids provided that the solution properties remain in the following ranges: conductivity, $10^{-5}$ to $10^{-9}$/ohm-cm; dielectric constant, 6 to 80; surface tension, 73 dynes/cm or less; and viscosity, 2 to 1000 millipoise. Only very pure water could be generated. We also found that dimethylsulfoxide (DMSO) aerosols could easily be generated by the electric-field nebulizer.

Since DMSO can act as a vehicle for transport of dissolved materials through cell membranes, aerosolized DMSO solutions may have interesting applications in inhalation toxicology.

Solid-particle aerosols were produced when solutions of materials such as NaCl and polystyrene were nebulized, and the solvents were evaporated. Figure 3 is a scanning electron micrograph of polystyrene particles (filter pore size, 0.2 µm) formed after evaporation of the methyl-ethyl ketone solvent from electric-field-nebulized droplets.

To develop a generator capable of delivering very small clouds or puffs of dense aerosol, an additional positively charged electrode was used to focus the normally fan-shaped spray emitted from the nebulizer capillary into a narrow stream. This electrode could also be used to switch the generator on and off by increasing the voltage variations.

In future studies, we will seek a broader range of generator materials, methods for pulsed operation of the nebulizer, electric control of charged particles and more effective neutralization of particle charge.

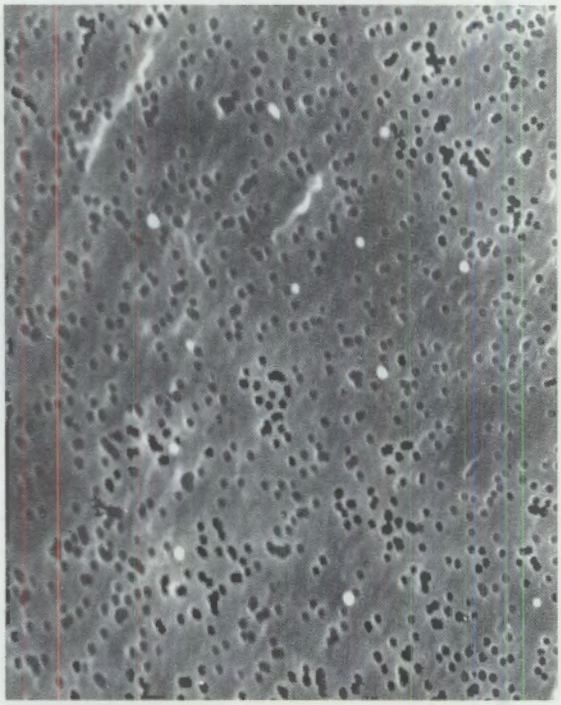

**Figure 3.** Electron Micrograph of Polystyrene Particles on 0.2- µm-Pore Filter. Methyl Ethyl Ketone Solvent was Evaporated from Electric-Field-Nebulized Droplets to Produce the Solid-Particle Aerosol.

Stable Compressed-Air Aerosol Generator Development

Stable operation of compressed-air nebulizers has been achieved for soluble materials over periods of several hours by using a special reservoir that maintains a constant generator solution concentration. This stability has been hard to achieve with insoluble materials because, even with constant stirring, generator suspensions tend to lose particles that attach to reservoir walls. We used the theory of a rotating drum, which usually applies to the case of an aerosol in a large rotating cylinder, and modified it to apply to a liquid suspension of particles in a small rotating cylinder. This analysis showed that stable generator suspensions could be maintained for up to 5 days in a 1-in.-diameter tube. A preliminary design was developed for a horizontal rotating syringe that would slowly feed a particle suspension to a nebulizer at a replacement rate. Several rotating syringe design concepts have been studied, including the one shown in Figure 4, which uses pressurized air to compress the syringe plunger and rotates the pressure vessel containing the syringe on a set of powered rollers.

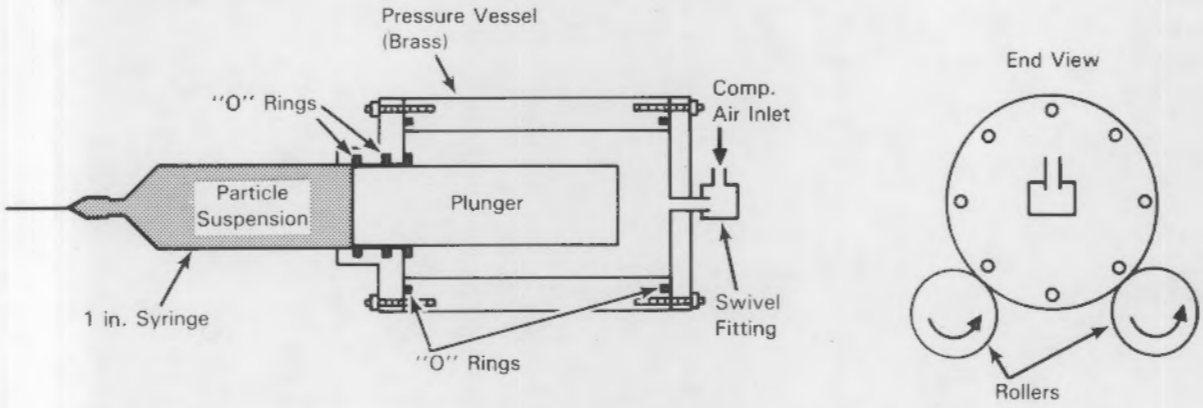


**Figure 4.** Conceptual Design of Rotating Syringe to Achieve Stable Generator Suspensions for Up To 5 Days.

## • Fetal and Juvenile Radiotoxicity

Principal Investigator: M. R. Sikov

Other Investigators: R. L. Buschbom, 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: M. O. Carey, J. A. Cushing, J. J. Evanoff, R. L. Rommereim, and T. T. Sherer

This project is directed at obtaining detailed comparative information on the deposition, distribution, retention, and toxicity of radionuclides in prenatal and juvenile mammals. 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. It has been confirmed that prenatal exposure to $^{239}Pu$ increases the incidence of bone tumors in the offspring of treated rats. The overall incidence was not markedly affected by foster-rearing by an unexposed dam, even though the offspring received a lower radiation dose to the skeleton. Comparative studies in rats and guinea pigs demonstrated that the placental transfer of $^{241}Am$ was lower than that of $^{239}Pu$, and the selective incorporation in the fetal membranes was not as pronounced. Further studies with prenatal exposure to $^{233}U$ have confirmed its embryotoxicity and have shown dose-dependent effects on malformation incidence as well as on prenatal mortality, fetal weight, and placental weight.

In previous Annual Reports (1981, 1982), we presented the rationale and protocol for an experiment to study the influence of foster-rearing on bone-tumor incidence and other postnatal effects produced by prenatal $^{239}Pu$ exposure in rats.

Some results relating to postnatal growth and longevity and the radionuclide distribution patterns associated with the various combinations of prenatal and postnatal exposure to plutonium have also been described (Annual Reports, 1983, 1984). In these studies, pregnant rats at 19 days of gestation (dg) were injected intravenously with 60 nCi/g of a citrated (70-fold molar excess) $^{239}Pu$ solution or with a citrate solution. The offspring from some litters were fostered to other dams at 1 day of age to form the six experimental groups indicated in Table 1. Tentative radiation doses to skeletal components have now been calculated; these results are consistent with the patterns we reported previously and were similar in all prenatally exposed groups. Radiation doses to the liver of exposed offspring fostered to control mothers was less than those of pups nursed by exposed animals. In all cases, rats that were exposed only postnatally received extremely low radiation doses relative to those exposed prenatally.

In contrast to the results of our earlier studies that led to this experiment, the incidence of bone tumors was elevated in all three groups that were exposed to plutonium prenatally, but the incidence was

**Table 1.** Interactions Between Prenatal $^{239}Pu$ Exposure and Neonatal Fostering on Radiation Doses and Tumor Incidences.

| Prenatal Exposure of Offspring: | Exposed | Exposed | Control | Exposed | Control | Control |
|---|---|---|---|---|---|---|
| Exposure of Foster Mother: | NF[a] | Exposed | Exposed | Control | Control | NF |
| Cumulative Doses, rad, During First Year After Exposure | | | | | | |
| Femur | 45 | 45 | 1 | 43 | --- | --- |
| Mandible | 89 | 99 | 5 | 92 | --- | --- |
| Liver | 84 | 82 | 1 | 71 | --- | --- |
| Percent of Animals Developing Tumors[b] | | | | | | |
| Bone | 19 | 14 | 0 | 15 | 0 | 3 |
| Mammary, Females | 62 | 50 | 64 | 70 | 65 | 85 |
| Mammary, Males | 0 | 8 | 5 | 3 | 0 | 5 |

[a] Not fostered

[b] Calculated on basis of number of rats at 6 mo of age

not influenced by exposure of the animals that reared the offspring. However, these data have not yet been adjusted for the observed among-group differences in longevity, and there will be small adjustments in values. Mammary tumor incidences were unaffected by prenatal exposure to plutonium, or by the postnatal rearing of the animals.

In previous Annual Reports (1983, 1984), we described the design and presented embryotoxicity results from an experiment that contemporaneously compared the dosimetry and toxicity of $^{241}Am$ and $^{239}Pu$ administered to pregnant animals.

The effects of $^{239}Pu$ were substantially greater than those of $^{241}Am$ relative to administered dose. The partition of the two nuclides among the components of the fetoplacental unit was markedly different (Figure 1), confirming preliminary results from previous experiments. The concentrations are expressed as percent dose/kg to allow for combining and comparing the different exposure-dose groups; absolute values cannot be compared directly across gestational stages because of the differing weight of the pregnant animals and the components of the fetoplacental unit. There were quantitative differences between stages at exposure and an effect of the interval between injection and evaluation. However, the concentration of $^{239}Pu$ was consistently higher in the placenta than in the embryo or fetus, and was still higher in the fetal membranes. A similar pattern was found after injection with $^{241}Am$ at 9 dg, although there was a smaller difference between the concentrations in the placenta and membranes. When $^{241}Am$ was injected later in gestation, the concentration in the placenta was higher than that in the membranes.

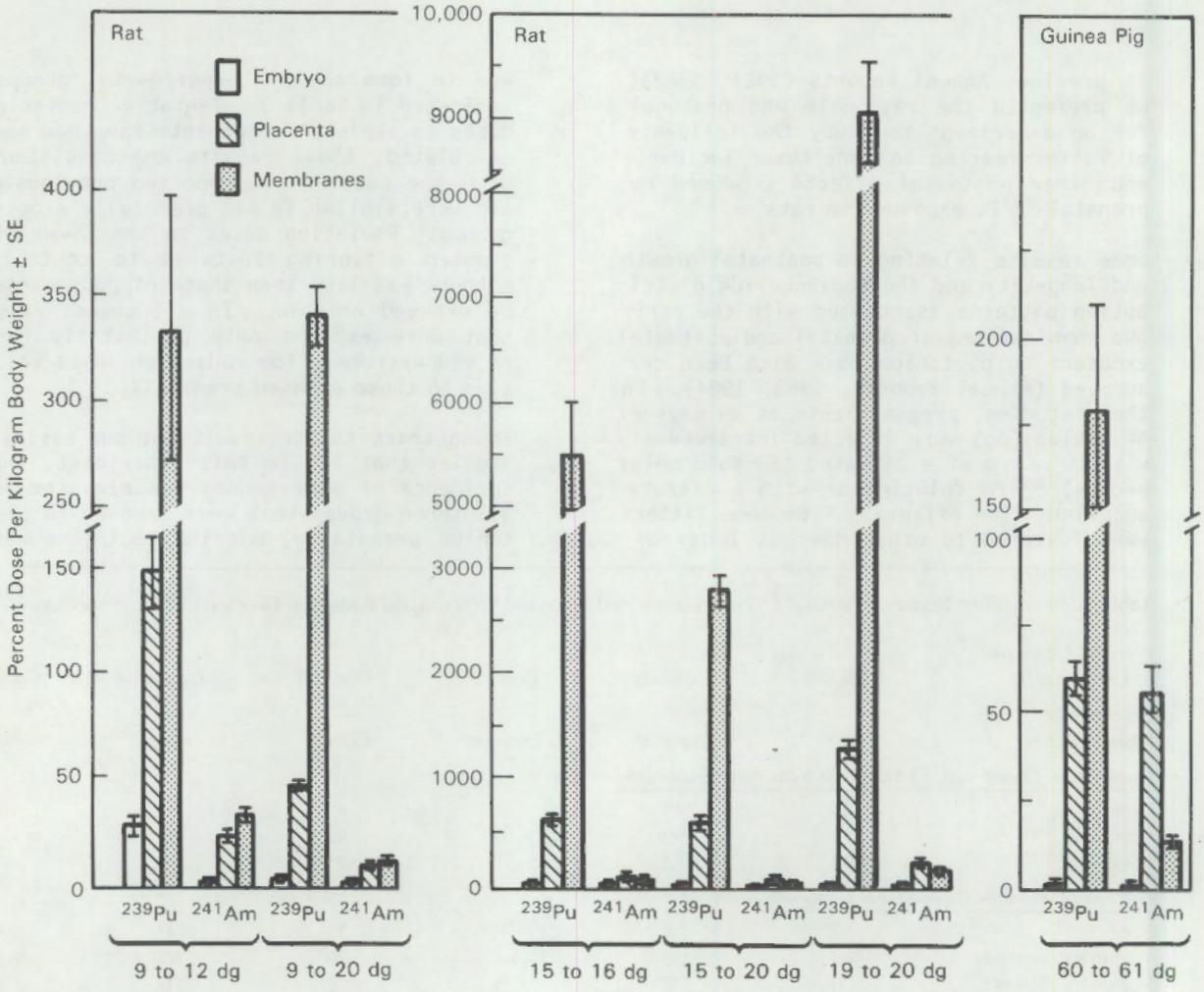


**Figure 1.** Placental Transfer and Fetoplacental Distribution of Americium and Plutonium in Rats and Guinea Pigs at Representative Stages of Gestation.

As part of our continuing effort to obtain comparative data on relative actinide distribution in the fetoplacental unit, pregnant guinea pigs were injected with $^{239}Pu$ or $^{241}Am$ at 60 dg and killed 24 hours later (61 dg). This is the stage used for measurements of clearance in our in situ placental perfusion studies (Annual Reports, 1982, 1983) and is generally comparable to 19 to 20 dg in rats, although the guinea pigs are at a more advanced stage of gestation. In agreement with the clearance values, the fetal concentration of $^{241}Am$ was less than that of $^{239}Pu$. Moreover, $^{239}Pu$ concentration in the embryo, placenta, and membranes progressively increased while the concentration of $^{241}Am$ in the fetal membranes was less than in the placenta.

Because of the marked stage dependence in maternal distribution of $^{239}Pu$ relative to stage of gestation in rabbits (Annual Report, 1984), we examined partition of plutonium and americium at 1 day after exposure in rats and guinea pigs at comparable stages of gestation (Table 2). No detectable effect of injected dose or gestational stage was seen in the concentration of plutonium in the maternal rat femur at 24 hours after administration. The concentration of $^{239}Pu$ in the femur was about twice that of $^{241}Am$ after injection at 15 dg, and 1.5 times at 19 dg. As previously reported in the literature, the $^{241}Am$ concentration in maternal liver was more than twofold higher than with plutonium at both stages of gestation. Again, there was no significant dose effect with either radionuclide, although hepatic concentration was slightly greater after injection at 15 than at 19 dg with both nuclides. This is generally consistent with the difference in body mass at injection and does not suggest a marked stage-dependent difference such as that seen in the rabbit.

In the guinea pig, however, the concentrations of $^{241}Am$ and $^{239}Pu$ in the liver were essentially identical. In the pregnant guinea pig, on the other hand, the concentration of americium in the femur was about six times that of plutonium. This surprising result is not completely in accord with the general literature, but group sizes were so small that this may be a spurious result, although it certainly warrants further examination.

As indicated in last year's Annual Report (1984), a pilot experiment with $^{233}U$ was conducted concurrently with the embryotoxicity and distribution studies performed with $^{241}Am$ and $^{239}Pu$. Although group sizes were small, embryotoxicity was clear. A similar experiment has been completed using a wider range of intravenously administered doses, including a dose intermediate between the two used previously and one that was about half of the lower dose (Table 3). The highest dose was clearly toxic to the adult animals. There was a statistically significant trend toward increased prenatal mortality with dose at both gestational stages studied, but the incidence was significantly different from that in the control group only at the highest dose. When injected at 9 dg, there was a significant decrease in fetal weight only at the highest dose. A more marked effect was produced by injection at 15 dg. Placenta weights showed a significant trend toward decreasing with dose at 9 dg, and all weights at higher doses were significantly different from those of controls; exposure at 15 dg produced an irregular, although significant, effect. Cleft palate was found only in the highest dose group at 9 dg. Exposure at 9 (but not at 15 dg) affected rib morphology; incidence increased with dose. The two higher dose levels resulted in edema when animals were injected at 15 dg.

**Table 2.** Effect of Dose and Stage of Gestation on Concentrations (Percent Dose per kg ± SE) in Femurs and Livers of Pregnant Rats and Guinea Pigs at 1 Day after Intravenous Injection with $^{241}Am$ or $^{239}Pu$.

| | | Days of Gestation, dg, Species and Injected Dose, μCi/kg | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 15- to 16-dg Rat | | | 19- to 20-dg Rat | | | 60- to 61-dg Guinea Pig |
| Dose, μCi: | | 10 | 30 | 90 | 10 | 30 | 90 | 30 |
| Femur | $^{239}Pu$ | 1.94 ± 0.09 | 1.60 ± 0.28 | | 1.65 ± 0.24 | 1.42 ± 0.11 | | 0.14 ± 0.04 |
| | $^{241}Am$ | | 0.96 ± 0.05 | 0.76 ± 0.04 | | 1.14 ± 0.16 | 0.99 ± 0.06 | 0.83 ± 0.31 |
| Liver | $^{239}Pu$ | 1.80 ± 0.10 | 2.53 ± 0.29 | | 0.92 ± 0.13 | 1.43 ± 0.22 | | 3.38 ± 0.33 |
| | $^{241}Am$ | | 4.80 ± 0.10 | 4.50 ± 0.25 | | 3.81 ± 0.02 | 3.33 ± 0.31 | 3.02 ± 0.18 |

**Table 3.** Maternal Toxicity in Rats Exposed to $^{233}U$ at 9 or 15 Days of Gestation (dg) and Effects on Developmental Measures Evaluated at 20 dg.

| | 9-dg Exposures | | | | |
|---|---|---|---|---|---|
| Dose, μCi/kg Body Weight: | 0 | 1.8 | 3.33 | 5.75 | 10.0 |
| Number of Pregnant Rats Exposed | 19 | 20 | 20 | 20 | 23 |
| Number Dead at 20 dg | 0 | 0 | 2 | 6 | 12 |
| Number Aborted at 20 dg | 0 | 0 | 0 | 0 | 1 |
| Number of Litters Evaluated | 19 | 20 | 18 | 14 | 10 |
| Implants/Litter | 14.1 ± 1.5 | 13.3 ± 1.6 | 13.7 ± 2.5 | 14.4 ± 1.7 | 14.0 ± 2.6 |
| Deaths/Litter | 0.6 ± 0.8 | 1.3 ± 1.2 | 1.2 ± 1.2 | 1.3 ± 1.4 | 2.7 ± 3.9 |
| Fetal Weight, g | 2.9 ± 0.2 | 2.9 ± 0.2 | 2.9 ± 0.4 | 2.7 ± 0.5 | 2.1 ± 0.7 |
| Placental Weight, g | 0.45 ± 0.06 | 0.42 ± 0.05 | 0.41 ± 0.04 | 0.36 ± 0.05 | 0.30 ± 0.05 |
| Number of Skeletons Examined | 254 | 263 | 206 | 172 | 103 |
| Cleft Palate[a] | 0 | 0 | 0 | 0 | 9/3 |
| Edema[a] | 0 | 0 | 0 | 0 | 0 |
| Wavy, Bent, Knobby Ribs[a] | 7/2 | 20/6 | 6/4 | 30/7 | 50/6 |

| | 15-dg Exposures | | | | |
|---|---|---|---|---|---|
| Dose, μCi/kg Body Weight: | 0 | 1.8 | 3.33 | 5.75 | 10.0 |
| Number of Pregnant Rats Exposed | 15 | 13 | 11 | 12 | 13 |
| Number Dead at 20 dg | 0 | 0 | 1 | 0 | 0 |
| Number Aborted at 20 dg | 0 | 0 | 0 | 0 | 0 |
| Number of Litters Evaluated | 15 | 13 | 10 | 12 | 13 |
| Implants/Litter | 14.8 ± 1.4 | 15.2 ± 2.6 | 13.0 ± 3.9 | 13.6 ± 2.6 | 15.0 ± 1.9 |
| Deaths/Litter | 1.3 ± 1.2 | 1.5 ± 1.1 | 1.1 ± 1.0 | 1.2 ± 1.2 | 2.8 ± 3.7 |
| Fetal Weight, g | 3.0 ± 0.2 | 2.8 ± 0.4 | 2.5 ± 0.7 | 2.3 ± 0.7 | 1.9 ± 0.7 |
| Placental Weight, g | 0.42 ± 0.04 | 0.38 ± 0.05 | 0.40 ± 0.06 | 0.38 ± 0.05 | 0.34 ± 0.05 |
| Number of Skeletons Examined | 201 | 164 | 110 | 137 | 148 |
| Cleft Palate[a] | 0 | 0 | 0 | 0 | 0 |
| Edema[a] | 0 | 0 | 0 | 8/2 | 5/2 |
| Wavy, Bent, Knobby Ribs[a] | 6/4 | 1/1 | 0 | 2/1 | 2/2 |

[a] Number of fetuses/number of litters affected

## • Gut-Related Studies of Radionuclide Toxicity

Principal Investigator: M. F. Sullivan

Other Investigators: P. S. Ruemmler, J. L. Ryan, R. P. Schneider, and R. C. Thompson

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 tract after clearance from the lungs.

Research in this field has been conducted, during the past 5 years, in a few laboratories in the U.S., and in laboratories in England, France, Japan, and Germany. To evaluate the current state of knowledge, avoid duplication of effort, identify research needs, and to coordinate future efforts, we conducted an international workshop, "Gastrointestinal Absorption of Actinides and Other Metals," at the Battelle Seattle Research Center in June 1985. Arrangements for the meeting, development of the agenda, invitation of participants and publication of the proceedings were funded by this project. Metals included in the agenda were those similar to the actinides in their behavior in the intestine or those that influence actinide absorption from the gastrointestinal tract. Topics discussed included: mechanism studies with in vitro preparations; animal experiments with rodents or baboons; and with humans; radiation dosimetry; radiological protection; and the long-range purposes of the research.

At the conclusion of the workshop an effort was made to identify critical areas in which further research is needed to protect workers in the nuclear industry or the general public. Areas identified included: human data; basic studies that provide an understanding of mechanisms of absorption; and animal experiments that can be related to human studies. The proceedings of the workshop will be published in 1986.

Considering these recommendations, studies in this project at the Pacific Northwest Laboratory should address fundamental mechanisms of absorption. In vitro or in situ preparations of small-animal intestines will be used to elucidate mechanisms of uptake in order to provide a better understanding of the effect of such factors as redox chemicals, iron deficiency, calcium, vitamin D, fat, chelating agents or fasting on actinide transport.

# Health Effects of Chemical Mixtures

## • Mutagenicity of Complex Mixtures

Principal Investigator: R. A. Pelroy

Other Investigators: D. L. Stewart and E. L. Sass

The aromatic fractions of high-boiling complex chemical mixtures from a coal liquid (CL) enhanced the mutagenicity of 6-aminochrysene (6AC) for inducing both frameshift and point mutations in both adenine/thymine (A/T) and guaninecytosine (G/C) DNA targets in *Salmonella typhimurium*. The strongest effects were observed for the tester strains that detect frameshift mutagens and point mutagens active at G/C DNA targets. Little or no enhancement of genetic activity was induced by the aliphatic fractions of the CL.

Previous work demonstrated that the apparent microbial mutagenicity of amino polycyclic aromatic hydrocarbons (amino-PAH), notably 6-aminochrysene (6-AC) and 2-aminoanthracene (2-AA), was enhanced by mixing the amines into chemically complex coal liquids (CL) prior to exposure of target organisms of Salmonella typhimurium. In the present work, high-boiling CL, known to strongly enhance the mutagenicity of amino PAH, were fractionated by alumina column chromatography into four major chemical classes, i.e., aliphatic ($A_1$), neutral PAH ($A_2$), nitrogen-containing PAH ($A_3$) and hydroxy-PAH ($A_4$). The resulting fractions, representing the major chemical classes in CL, were then tested for their ability to enhance the mutagenicity of amino PAH. In all cases, only the aromatic fractions enhanced the mutagenicity of the amino PAH; the $A_1$ components were of marginal or no effectiveness in altering the potency of the amino PAH.

Four S. typhimurium mutagen tester strains, representing both guanine/cytosine (G/C) and adenine/thymine (A/T) targets and frameshift and point mutations, were used to measure the mutagenicity of amino-PAH alone, of the A fractions (or crude CL) alone, and of mixtures of amino-PAH and A fractions (or crude CL).

As shown by the data in Figures 1 and 2, the A fractions and the unfractionated CL were without activity, or showed marginal genetic activity, in the Salmonella/microsomal bioassay system. At the levels of 6-AC used in these experiments (0.02 µg/plate), little or no frameshift mutation (TA98 and TA97) was induced. Slightly higher rates of mutagenic response appeared to be induced in the point mutants (TA100 and TA102). However, only in the case of TA102 (an excision-repair-competent mutagen tester strain carrying an A/T point mutation in the his G gene) was a significant level of mutagenicity induced by 6-AC.

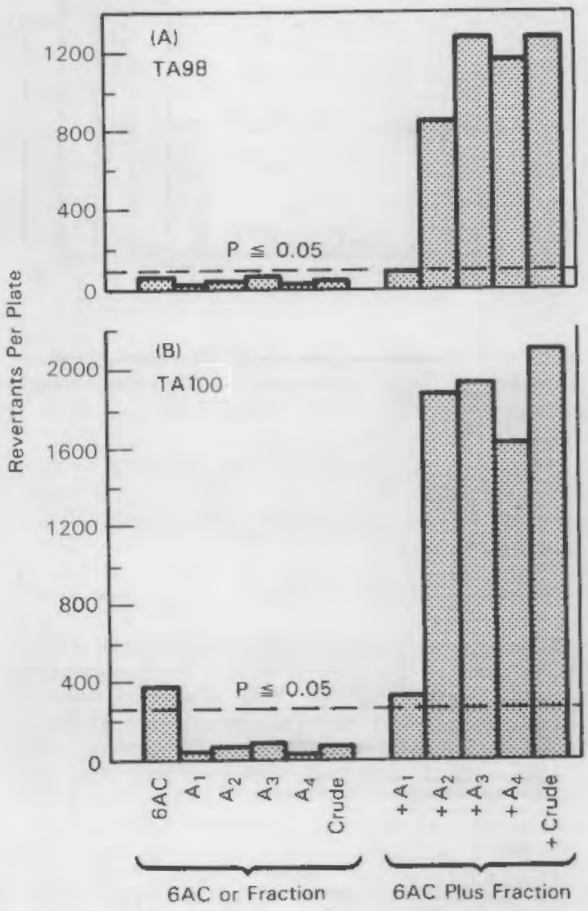


**Figure 1.** Mutagenicity of 6-Aminochrysene (6AC) for Salmonella typhimurium TA98 (A) and TA100 (B), in the Presence and Absence of Chemical Class Fractions from a High-Boiling Coal Liquid (CL). Aliphatic fraction ($A_1$), neutral polycyclic aromatic hydrocarbon (PAH) fraction ($A_2$), nitrogen-containing PAH fraction ($A_3$), hydroxy PAH fraction ($A_4$), unfractionated CL (crude). Response values on ordinate are in revertant colonies per plate obtained at 0.02 µg 6AC and/or 5 µg fraction (or crude CL) per plate. $P \leq 0.05$ response indicated on the ordinates is based on twofold increase in response over background, from historical control data.

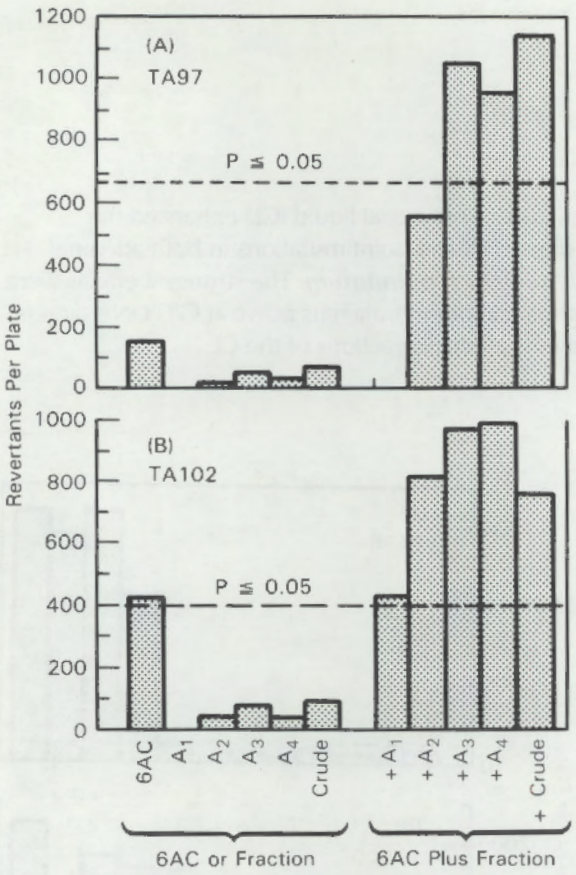


**Figure 2.** Mutagenicity of 6-Aminochrysene (6AC) for Salmonella typhimurium TA97 (A) and TA102 (B), in the Presence and Absence of Chemical Class Fractions from a High-Boiling Coal Liquid. Symbols and response values same as for Figure 1.

Mixtures of 6-AC plus $A_1$ had essentially the same mutagenicity as the corresponding level of 6-AC alone. The aromatic chemical class fractions ($A_2$, $A_3$, and $A_4$), however, induced increases in mutagenic response that were much greater than the sum of responses for 6-AC alone and for the fraction alone. In relative terms, the effect was particularly strong for the frameshift mutant TA98, showing increases of around 20-fold in response. The other three tester strains all showed approximately similar responses to the mixture of 6-AC and A fractions, with apparent increases of two- to fourfold. Therefore, it appears that only the aromatic fractions of the CL increase the mutagenicity of 6-AC.

Similar studies have shown that other amino-PAH are similarly affected by the aromatic A fractions, although these effects were most pronounced on the amino PAH with the amino group beta (i.e., one carbon removed) from a fused ring or nonsubstitutable carbon atom. This suggests that amino-PAH that demonstrate a strong "para" effect, or increased mutagenicity due to resonance stabilization of the positively charged metabolite formed from P450 metabolism, are particularly susceptible to synergistic interactions with components in the aromatic A fractions.

Data bearing on this point (Figure 3) show that the A fractions and crude CL had little or no effect on the apparent mutagenicity of 2-aminofluorene (2-AF), a compound which should demonstrate much less resonance stabilization (i.e., para effect) after metabolic activation than 6-AC. For all four tester strains, the mutagenicities of 2-AF alone and 2-AF plus an A fraction were approximately equal.

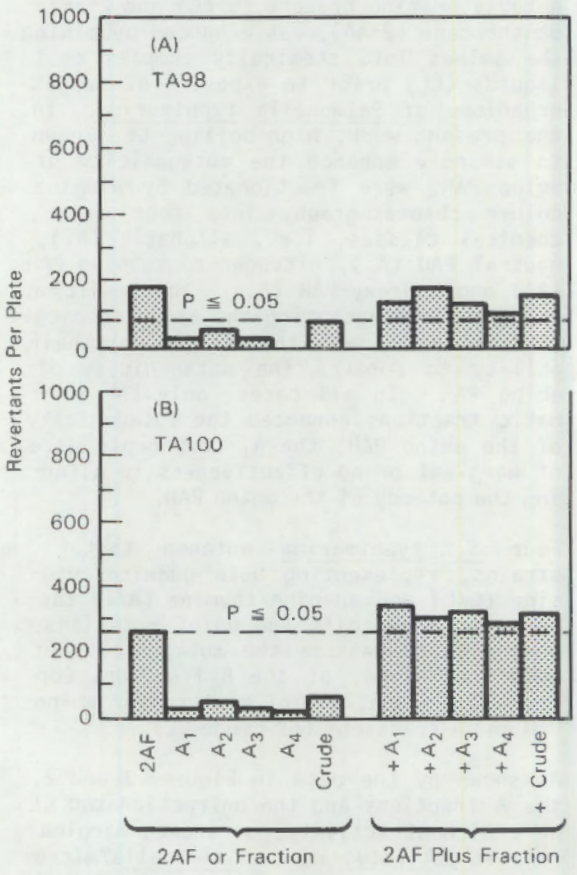


**Figure 3.** Mutagenicity of 2-Aminofluorene (2AF) for TA98 (A) and TA100 (B), in the Presence and Absence of Chemical Class Fractions from a High-Boiling Coal Liquid. Response values on ordinate for TA98 are in revertant colonies per plate obtained at 0.2 μg 2AF and/or 5 μg fraction (or crude CL) per plate. Response values on ordinate for TA100 are in revertant colonies per plate obtained at 1.0 μg 2AF and/or 5 μg fraction (or crude CL) per plate. P ≤ 0.05 response indicated on the ordinates is based on twofold increase in response over background from historical data.

## • Complex Mixtures Biostudies

Principal Investigator: D. L. Springer

Other Investigators: R. M. Bean, R. L. Buschbom, D. A. Dankovic, M. E. Frazier, K. M. Gideon, P. L. Hackett, D. D. Mahlum, R. A. Miller, L. B. Sasser, and B. L. Thomas

Technical Assistance: T. A. Breier, R. A. Clark, J. A. Cushing, J. J. Evanoff, K. L. Hopkins, and R. C. Zanger

The objective of this project is to identify toxic responses associated with potential human exposures to complex organic mixtures derived from energy-related industries. Mouse-skin initiation/promotion data showed that although distillates boiling from 300 to 700°F did not alter the initiating activity of benzo[a]pyrene (BaP), distillates boiling above 700°F effectively decreased activity. Subsequent studies have shown that binding of radiolabeled BaP to mouse skin DNA decreased as the dose of complex mixtures increased; at the initiating dose, binding was very low. In addition, binding decreased substantially when BaP was coadministered with classes of compounds containing fused aromatic rings. Since similar effects on BaP binding to DNA were observed in an in vitro assay system, metabolism studies were conducted under similar conditions. Even though the quantity of metabolites produced decreased significantly, the metabolite profiles were similar, indicating that in the presence of the mixture, BaP was metabolized by the same pathway. These data suggest that the components of the mixtures compete for active sites on mixed-function oxidase enzymes and that decreased binding of the marker compound to DNA is the result. Studies to confirm previous results demonstrated that inhalation exposure to a high-boiling complex mixture resulted in a transient elevation of blood pressure and heart rate and changes in other cardiovascular parameters. These effects were also observed after dermal treatment but were absent following oral exposure to the test material. The inhalation study, in which rats and mice were exposed to solvent refined coal (SRC)-II heavy distillate (HD) for either 1, 4 or 12 weeks, has been completed except for evaluation of tissues. Results from this study demonstrated a dose-time relationship for body weight gain and survival for both rats and mice.

### Initiation/Promotion (I/P) Studies

Past experiments have shown that mouse-skin tumor-initiating activity of known carcinogens is not fully expressed when the carcinogen is present in a complex mixture derived from coal. Direct evidence for inhibition of benzo[a]pyrene (BaP) initiating activity by a broad-boiling-range coal liquid was obtained by initiating mouse skin with BaP in acetone or in a 300 to >850°F coal liquid. The activity of BaP applied in acetone was substantially higher than that administered in the coal liquid. We are interested in identifying the components responsible for this inhibition. As a first step in this process, we tested the effect of distillates with discrete boiling ranges on BaP initiating activity.

Twenty-five-µg doses of BaP in methylene chloride or in methylene chloride containing 5 mg of coal liquid distillates were applied to the dorsal surface of female CD-1 mice. The distillates had boiling ranges (°F) of: a) 300 to 700; b) 700 to 800; c) 750 to 800; d) 800 to 850; and e) >850. Beginning 2 weeks after initiation, mice were promoted twice weekly with 5 µg of 12-O-tetradecanoylphorbol-13-acetate for 24 weeks.

Table 1 shows that applying BaP in the presence of 5 mg of the 300 to 700°F distillate did not affect tumor response, whether measured by incidence or the number of tumors per group of 30 mice. The response was, however, decreased by all the other distillates. These data confirm and extend our observations with other coal-derived liquids. We will next examine the effect of chemical class fractions prepared from one of the distillates on BaP expression in an attempt to determine which components are responsible for suppressing initiating activity.

Several studies have shown that the carcinogenicity of coal liquids lies primarily in materials boiling above 700°F, and that the neutral polycyclic aromatic hydrocarbons (PAH) are the primary contributors to mouse-skin tumorigenicity. Less is known about the carcinogenic components of shale oil; therefore, we decided to determine if the carcinogenicity of shale oil can be segregated into the higher-boiling components. Paraho shale oil was distilled into components having boiling ranges of 0 to 650, 650 to 700, 700 to 750, and >750°F. These distillates were tested for tumor-initiating activity by applying 25-mg doses to female CD-1 mice,

and then promoting as described above. The results (Table 2) indicate that none of the distillates had as much activity as the crude shale oil. However, the >750°F distillate was slightly more active than lower-boiling ones.

**Table 1.** Effect of Solvent Refined Coal-II Distillates on Benzo[a]pyrene (BaP) Mouse-Skin Tumor-Initiating Activity.

| Initiator | Percent Incidence | Number of Tumors/30 Mice |
|---|---|---|
| BaP (25 μg) | 100 | 215 |
| 330-700°F Distillate (5 mg) | 27 | 16 |
| 700-750°F Distillate (5 mg) | 33 | 17 |
| 750-800°F Distillate (5 mg) | 43 | 19 |
| 800-850°F Distillate (5 mg) | 76 | 45 |
| >850°F Distillate (5 mg) | 97 | 146 |
| BaP (25 μg) + 300-700°F Distillate (5 mg) | 100 | 214 |
| BaP (25 μg) + 700-750°F Distillate (5mg) | 97 | 128 |
| BaP (25 μg) + 750-800°F Distillate (5 mg) | 90 | 97 |
| BaP (25 μg) + 800-850°F Distillate (5 mg) | 90 | 96 |
| BaP (25 μg) + >850°F Distillate (5 mg) | 97 | 207 |

**Table 2.** Skin-Tumor-Initiating Activity of Shale Oil Distillates Relative to Temperature of Distillation.

| Treatment | Percent Incidence | Number of Tumors/30 Mice |
|---|---|---|
| Methylene Chloride | 13 | 4 |
| Crude Shale Oil | 43 | 22 |
| 0-650°F | 20 | 8 |
| 650-700°F | 20 | 6 |
| 700-750°F | 23 | 8 |
| >750°F | 30 | 13 |

We then fractionated Paraho shale oil, using high-performance liquid chromatography (HPLC), into four fractions: 1) primarily aliphatic hydrocarbons and one- to two-ring aromatics; 2) three- to six-ring aromatics and alkylated species; 3) moderately polar (nitrogen compounds); and 4) polar compounds (phenols and cresols). We evaluated these fractions for skin-tumor-initiating activity by applying them to mouse skin in the amounts that were present in 25 mg of the crude. We compared the response to the fractions to that obtained with a 25-mg dose of the crude. Since we had previously found that fractionation of a dose of coal liquid resulted in a higher response, we also tested the response when a 25-mg dose was applied in five increments of 5 mg each to determine if a similar effect occurred with a very different material. The results from this experiment showed that Fraction 2 had the highest activity, even greater than on the group initiated with the crude shale oil (Table 3). We also found that fractionating the dose resulted in about three times as many tumors as when a single dose of 25 mg was used. These results indicate that the neutral PAH are the most active carcinogens in shale oil as well as in coal liquids. We are presently attempting to better define the components responsible for the carcinogenic activity. We are also attempting to define the factors involved in the enhanced activity seen when the dose is divided into several smaller doses.

**Table 3.** Skin-Tumor-Initiating Activity of Shale Oil and High-Performance Liquid Chromatography (HPLC) Fractions.

| Initiator | Percent Incidence | Number of Tumors/30 Mice |
|---|---|---|
| Vehicle Control | 10 | 3 |
| BaP (25 μg) | 100 | 199 |
| Crude Shale Oil (1 x 25 mg) | 43 | 15 |
| Crude Shale Oil (5 x 5 mg) | 70 | 50 |
| HPLC #1 | 23 | 9 |
| HPLC #2 | 50 | 22 |
| HPLC #3 | 23 | 10 |
| HPLC #4 | 17 | 7 |

## Metabolism and DNA Binding

As shown above, the skin-tumor-initiating activity of individual carcinogens of BaP was suppressed when it was coadministered with a complex organic mixture. A previous study showed that mice treated with the >850°F distillate developed 2.5 times as many tumors as those initiated with the 800 to 850°F distillate, even though both mixtures contained equal amounts of BaP. These data demonstrate that the initiating activity of BaP was suppressed when it was presented to the animal 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 in the presence of complex organic mixtures.

Results from studies conducted in FY 1984 demonstrated that, relative to the binding of BaP alone, BaP binding decreased by approximately 98% when it was coadministered with initiating doses (25 mg) of either the 800 to 850 or >850°F distil-

late. In addition, when BaP was coadministered with smaller doses of the distillates (500 µg/mouse), binding decreased by approximately 50% relative to that of BaP alone. These data demonstrated that the binding of a marker carcinogen (BaP) increased as the dose of complex mixture decreased, and that the binding of a known carcinogen was low relative to the amount bound for the individual compound.

In subsequent studies, we determined the effect of chemical class fractions on the binding of $^3$H-BaP to DNA. For these studies, the >850°F distillate was fractionated by alumina column chromatography into aliphatics, neutral PAH, nitrogen-containing polycylic aromatic compounds (NPAC) and hydroxylated PAH. The BaP (50 µg) was coadministered with each of these chemical class fractions to determine which fractions were responsible for the observed inhibition of BaP binding to DNA. For these studies, $^3$H-BaP, $^3$H-BaP coadministered with 500 µg of the >850°F distillate, or $^3$H-BaP coadministered with chemical class fractions derived from >850°F distillate, were applied in dichloromethane to the shaved backs of CD-1 mice. In all cases, $^3$H-BaP (375 µCi/mouse) was applied at 50 µg/dose; chemical class fractions were applied at doses proportional to their concentration in the starting material. Twenty-four hours after dosing, the treated area of the skin was removed, and the tissue was digested with proteinase K. The DNA was extracted once with phenol-chloroform-isoamyl alcohol and twice with chloroform-isoamyl alcohol. After precipitation with ethanol, the DNA was resuspended 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 as an estimate of purity. After this purification, background levels were 1 to 2 dpm/µg DNA, and the ratios of absorbance at 260 to 280 nm were 1.8 to 1.9.

Data for binding of $^3$H-BaP in the presence of these fractions are shown in Table 4. When BaP (50 µg) was coadministered with the >850°F distillate (500 µg; 1:10, BaP to distillate), BaP binding decreased by approximately 67%. Coadministration of the same amount of BaP with the aliphatic fraction did not result in a significant effect on binding. In the presence of the other three chromatographic fractions, binding decreased to 47, 55 and 66% of that for BaP alone for the PAH, NPAC and hydroxy-PAH fractions, respectively. These data indicate that the most effective inhibitors of binding were the fractions with aromatic nuclei. Furthermore, the degree of inhibition increased as the mass of the fractions increased, suggesting that the major effect was mass action.

**Table 4.** In Vivo Binding of $^3$H-Benzo[a]pyrene (BaP) to Mouse Skin DNA in the Presence of the >850°F Coal Liquid Distillate and its Chemical Class Fractions.

| | Dose, µg | | |
|---|---|---|---|
| Test Material | BaP | Class Fraction | pmol BaP Bound/mg DNA |
| BaP | 50 | ---- | 21.8 ± 2.91 |
| BaP + 850°F | 50 | 500 | 7.1 ± 0.93 |
| BaP + Aliphatic | 50 | 8 | 18.9 ± 3.16 |
| BaP + PAH[a] | 50 | 215 | 10.2 ± 2.01 |
| BaP + NPAC[b] | 50 | 171 | 12.0 ± 2.49 |
| BaP + HPAH[c] | 50 | 104 | 14.4 ± 2.06 |

[a]Polycyclic aromatic hydrocarbon
[b]Nitrogen-containing polycyclic aromatic compound
[c]Hydroxylated PAH

Because of these results, another study was conducted to determine whether this influence of complex mixtures also occurred in vitro. For this study, $^3$H-BaP (1.6 µg) or $^3$H-BaP coadministered with a complex mixture (100 µg) were incubated together with rat liver S9, calf thymus DNA and appropriate cofactors. After 30 minutes of incubation, the DNA was isolated, purified, and radioactivity associated with the DNA was determined. In the presence of either mixture (ratio 1:62, BaP to distillate), binding decreased by 90%, indicating that inhibition of binding can be produced in vitro and that, under these conditions, the magnitude of inhibition was similar to that for mouse-skin DNA.

Since metabolism studies are readily conducted in an in vitro system, an experiment was performed to determine the influence of the complex mixtures on BaP metabolism. Reaction conditions were similar to those used for binding studies except that the reaction was run at optimal conditions (i.e., 80 µM BaP). The reaction was initiated with $^3$H-BaP or $^3$H-BaP plus 850°F distillate, terminated by addition of 0.5N NaOH/80% ethanol, and extracted with ethyl acetate to remove unmetabolized BaP and metabolites. The solvent was then evaporated under a stream of nitrogen, the metabolite redissolved into methanol, and applied to a C-18 reverse-phase HPLC column. Metabolites were eluted with a methanol-water gradient, and fractions were collected at 30-sec inter-

vals. Metabolite standards, obtained from the National Cancer Institute repository, were used as reference materials, and radioactivity eluting in regions of the chromatogram associated with the classes of metabolites was summed to give an estimate of the extent and metabolism pathway of the marker compound.

Results suggested that the general pathway for the metabolism of BaP was unaltered by the complex mixture (Figure 1), but that the metabolism of the marker compound was decreased by about 65% relative to that of BaP alone (Table 5). These results tend to confirm the hypothesis that the primary mode of action of the mixture was to decrease the overall rates of conversion of BaP to metabolites, and that reduced binding to DNA is the result of these changes in the conversion of BaP to reactive intermediates.

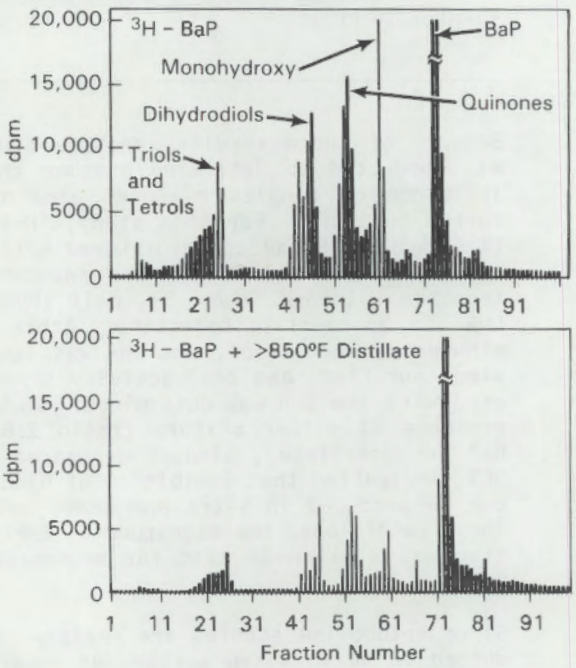


**Figure 1.** Radioactivity Associated with Radiolabeled Benzo[a]-pyrene (BaP) Metabolites Produced by In Vitro Incubation of Rat Liver S9 and $^3$H-BaP or $^3$H-BaP Coadministered with a Complex Organic Mixture. Separation by High Pressure Liquid Chromatography.

## Cardiovascular Studies

We have previously observed elevated blood pressures in rats after exposure to high concentrations of a high-boiling coal liquid (solvent refined coal [SRC]-II heavy distillate [HD]). The number of animals used in that study was small, only a single high concentration of HD was used (0.68 mg/L), and the recovery period between exposure and cardiovascular evaluation was short. Therefore, a second study was conducted to investigate the dose-response relationship for this effect and to determine whether HD causes permanent or reversible changes in cardiovascular function.

Nine-week-old, male Fischer rats were exposed to 0, 0.24, or 0.70 mg/L HD via inhalation for 6 weeks (6 hours/day, 5 days/week). Half the groups were evaluated 10 to 15 days after completion of exposure, whereas the remainder were evaluated after a 6-week recovery period. Direct arterial blood pressure was measured through a cannula surgically implanted in the femoral artery following sodium pentobarbital anesthesia. Heart rate and electrocardiogram readings were simultaneously recorded, and blood was collected for determining plasma electrolytes, aldosterone and angiotensin concentrations. Plasma volume was measured by dye dilution, and blood pH and partial pressures of $O_2$ and $CO_2$ were determined.

Blood pressure and heart rate of rats from both the low and high exposure groups were significantly elevated compared to those of controls (Figure 2), confirming and extending the results of the previous study. Plasma and blood volumes were also elevated in a dose-related fashion. After a 6-week recovery period, neither the blood pressure nor the heart rate of either exposure group was different from control values.

Plasma angiotensin levels were significantly ($P < 0.01$) depressed in a dose-related manner, but aldosterone levels were not affected (Figure 3). The reason for this unexpected decline in angiotensin is unclear; correlations between angiotensin and blood pressure are usually positive. These data suggest that the elevation in blood pressure was not induced by angiotensin; rather, that elevated blood pressure was responsible for the depressed angiotensin concentrations.

Two weeks after the end of exposure, blood $PO_2$ was slightly decreased in the high dose group only; otherwise, blood gases were not altered by HD exposure. Blood pH was slighly depressed in the high dose group 2 weeks after exposure. Potassium, the only plasma cation altered by exposure, was also significanly elevated in the plasma of the high dose group at that time, but not after the 6-week recovery period. Plasma $Na^+$ and $Mg^{2+}$, cations known to be involved in the elevation of blood pressure, were not affected.

**Table 5.** Ratio (%) of Classes of Metabolites to the Total Quantity of Metabolites for Radiolabeled Benzo[a]pyrene (BaP) in the Presence of Two Complex Organic Mixtures.

| Substrate | Time, min | Triols + Tetrols | Dihydrodiols | Quinones | Mono-Hydroxy | % BaP Metabolized |
|---|---|---|---|---|---|---|
| BaP | 5 | 17 | 23 | 22 | 22 | 25 |
| BaP | 30 | 13 | 21 | 25 | 24 | 37 |
| BaP + 800-850°F | 5 | 16 | 23 | 28 | 16 | 9 |
| BaP + 800-850°F | 30 | 16 | 21 | 37 | 8 | 12 |
| BaP + >850°F | 5 | 15 | 23 | 33 | 12 | 9 |
| BaP + >850°F | 30 | 14 | 21 | 29 | 20 | 12 |

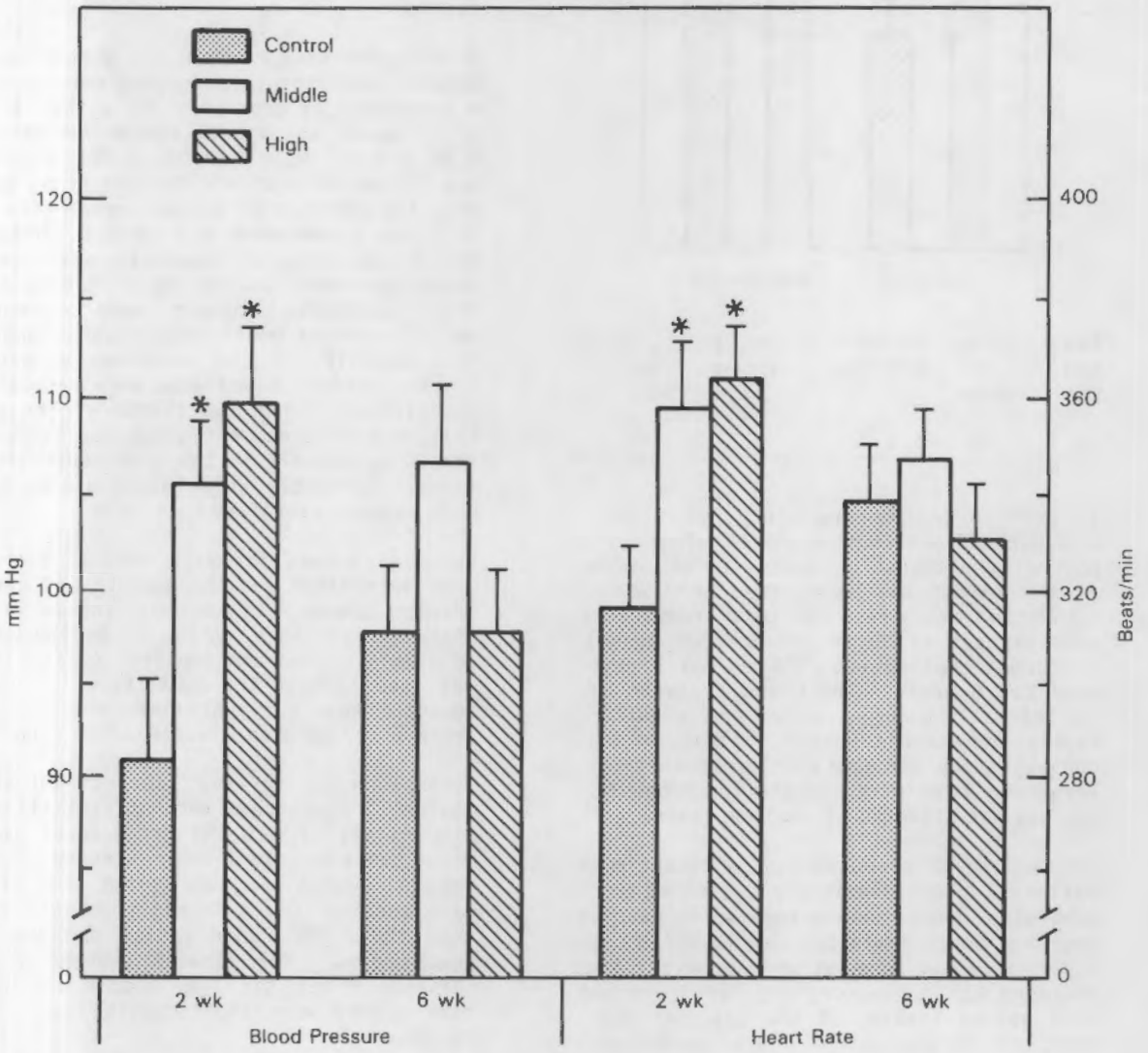


**Figure 2.** Blood Pressure and Heart Rates of Rats, Measured Approximately 2 or 6 Wk After a 6-Wk Inhalation Exposure to Solvent Refined Coal-II Heavy Distillate.

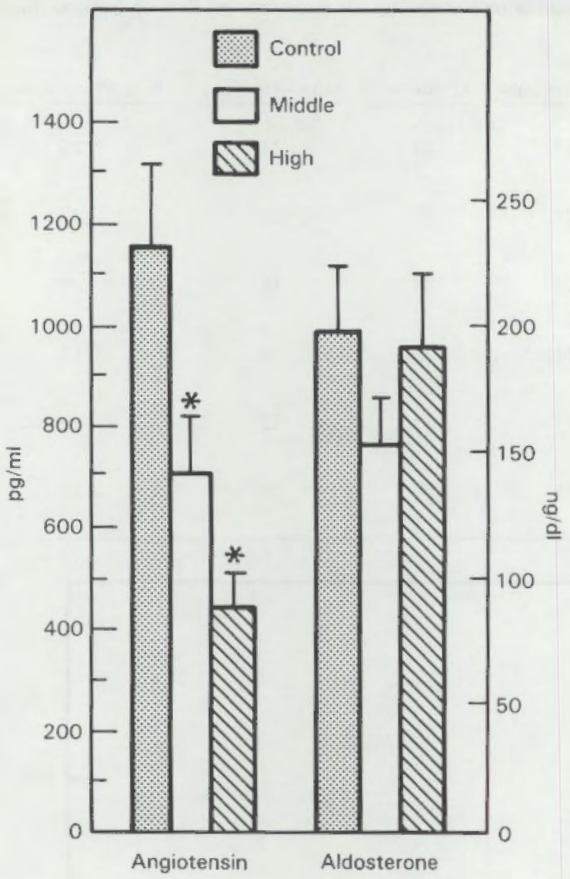


**Figure 3.** Plasma Angiotensin and Aldosterone Levels of Rats 2 Wk After a 6-Wk Inhalation Exposure to SRC-II Heavy Distillate.

In another preliminary study, we determined blood-pressure response after exposure by alternative routes to determine if the effect was associated only with inhalation exposure. For this study, rats were exposed to HD by gavage (300 mg/kg) or dermal application (500 mg/kg) 5 days week for 6 weeks. The blood pressure of the dermally exposed group was significantly increased compared to that of the control group and was similar to that observed in rats after inhalation exposure, but was not affected by oral exposure.

In summary, HD produced a significant elevation in blood pressure and altered several other measurements related to cardiovascular function in the rat 10 to 15 days after a 6-week inhalation exposure. The elevated blood pressure may have resulted from volume loading of the vascular system, but further studies are needed to identify the mechanisms and chemical components involved in producing this effect. These changes in cardiovascular function appear to be transient because most parameters measured were normal after a 6-week recovery period. Dermal application of HD was also effective in elevating the blood pressure of rats, providing evidence that HD does not act directly on the pulmonary system in producing this effect. These data suggest that the cardiovascular system may be at risk from long-term exposure to high-boiling complex mixtures due directly to high blood pressure or to cardiovascular diseases associated with prolonged high blood pressure.

Inhalation Studies

Animals on lifespan studies after exposure to SRC-II HD have died or were sacrificed. These studies were conducted to determine whether short- to moderate-term exposure to a high-boiling coal liquid resulted in shorter than normal lifespans, tumor development and/or other undesirable effects.

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, 4, or 12 weeks 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, 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. When two-thirds of the animals in each treatment group had died, the remaining animals in the group were sacrificed. Currently, all rats and mice have died or were sacrificed.

Survival curves for each treatment group were determined and the equality of curves between groups was tested. The survival distributions were estimated by the product-limit method and the Breslow statistic was used to test the equality of survival curves. Mean survival times are given in Table 6 for each species/sex/dose group.

Comparison of survival curves for mice indicates that there were no statistically significant ($P < 0.05$) differences among dose levels for the 1-week exposure group. For the 4-week exposure group, the high-dose survival curve is significantly lower than those for control, low and middle dose groups. For 12-week exposed mice, survival rates for low, middle and high dose groups were signficantly lower than for controls.

For rats, survival curves show no significant differences for 1- or 4-week expo-

**Table 6.** Mean Survival Time from Start of Exposure, Days ($\bar{x}$ ± SEM) of Mice Exposed by Inhalation to Solvent Refined Coal-II Heavy Distillate.

| Group | Length of Exposure, wk | Control | Low | Middle | High |
|---|---|---|---|---|---|
| Mice (Females) | 1 | 645 ± 28 | 641 ± 29 | 595 ± 24 | 551 ± 26 |
| Mice (Females) | 4 | 623 ± 30 | 652 ± 15 | 593 ± 20 | 471 ± 33[a] |
| Mice (Females) | 12 | 682 ± 27 | 540 ± 26[a] | 576 ± 20[a] | 437 ± 28[a] |
| Rats (Males) | 1 | 730 ± 29 | 769 ± 14 | 777 ± 18 | 751 ± 22 |
| Rats (Males) | 4 | 753 ± 24 | 758 ± 24 | 746 ± 22 | 741 ± 28 |
| Rats (Males) | 12 | 735 ± 18 | 813 ± 21 | 776 ± 32 | 585 ± 46[b] |
| Rats (Females) | 1 | 792 ± 24 | 704 ± 38 | 758 ± 30 | 752 ± 34 |
| Rats (Females) | 4 | 811 ± 33 | 846 ± 20 | 860 ± 21 | 810 ± 35 |
| Rats (Females) | 12 | 772 ± 19 | 839 ± 24 | 788 ± 22 | 621 ± 43[b,c] |

[a]Statistically different from control group ($P < 0.05$)
[b]Statistically different from low dose group ($P < 0.05$)
[c]Statistically different from middle dose group ($P < 0.05$)

sures for either sex. However, for 12-week-exposed rats, the survival rate for the high dose group was significantly lower than that of the low dose group for both males and females. Also, the high-dose survival rate was significantly lower than that of the middle dose group for females. Results indicate differences between survival curves for the high dose groups and controls for males and females, and a difference between high and middle dose groups for females; probabilities were 0.086, 0.12 and 0.11, respectively.

Body-weight data were analyzed by a randomization test to determine the equality of growth curves between dose groups for a given species/sex/dose-group combination. Growth curves for rats and mice after 12 weeks of exposure are shown in Figure 4. Comparison of these curves for female mice exposed for 1 week indicate that growth curves for control, middle and high dose groups were not significantly different, but that the low dose group curve was significantly ($P < 0.05$) lower than that of the other three groups. For female mice exposed for 4 weeks, growth curves were not significantly different from each other. Female mice exposed for 12 weeks showed an unusual growth pattern: the growth curve for the high dose group was significantly different from that of the low and middle dose groups but not different from that of the control group. Growth curves for female rats exposed for 1 week were not significantly different from each other. Similar curves for 4-week-exposed female rats indicated that high-dose animals lost weight during the first week of the exposure, failed to gain weight during the exposure and, even though they never returned to control levels, gained weight at a rate similar to that for controls. Similar results were observed for female rats exposed for 12 weeks, although the magnitude of the effect was greater than for 4-week-exposed animals.

Results for male rats were similar to those for female rats: growth curves for the high dose groups were significantly lower than those of controls for 4- and 12-week exposure groups. In addition, the magnitude of the difference for males tended to be greater than for females because of the more rapid growth of males.

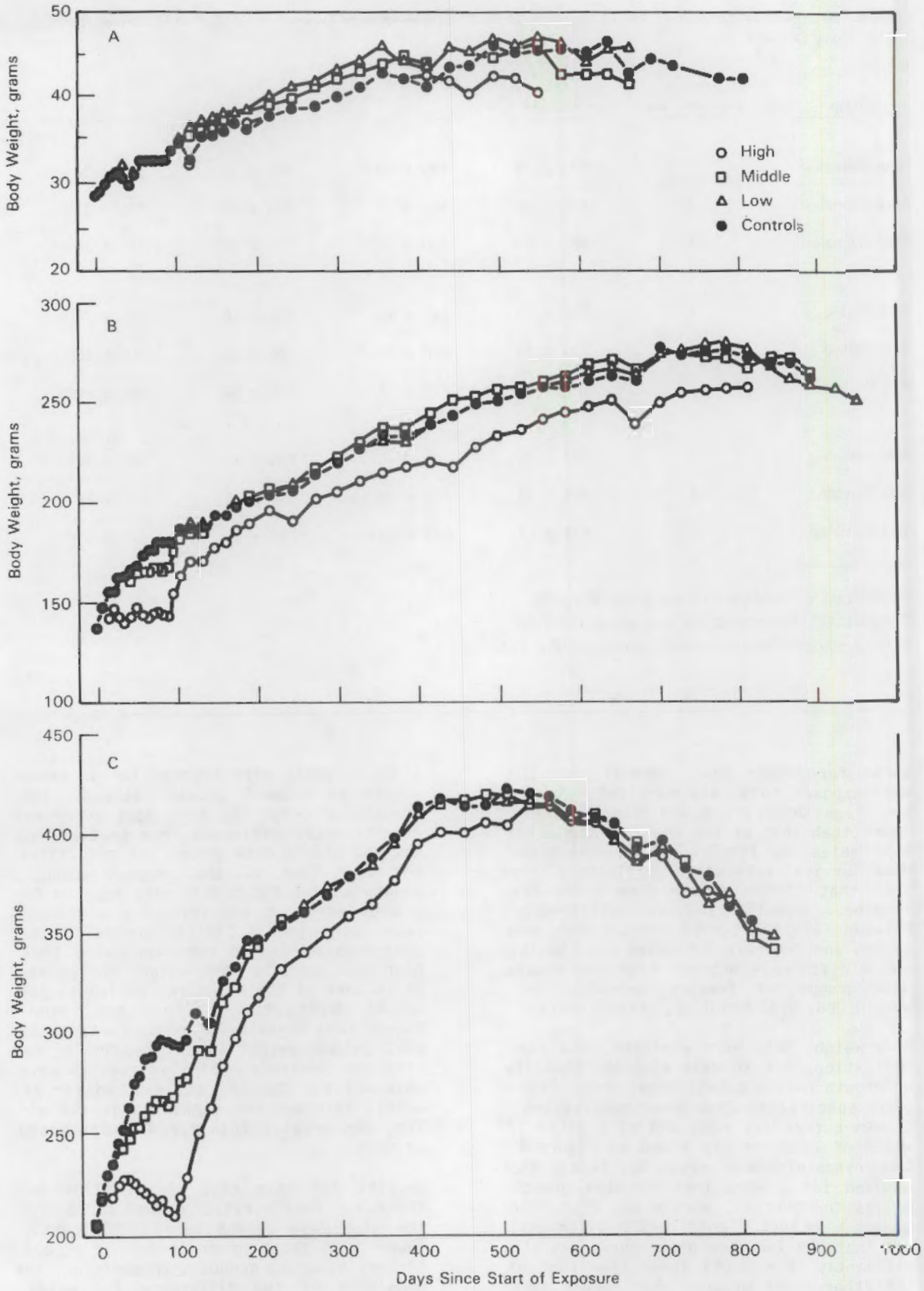


**Figure 4.** Body Weights for Female Mice (A), Female Rats (B), and Male Rats (C), Exposed for 12 Wk to Solvent Refined Coal-II Heavy Distillate.

## • Teratology of Complex Mixtures

Principal Investigator: P. L. Hackett

Other Investigator: R. L. Rommereim

Correlations between maternal indices of toxic effects and fetal indicators of retarded development and teratogenicity in rats exposed to Harmarville process solvent (HPS) during gestation suggest that no direct causal relationship exists between the observed maternal toxicity and specific fetal abnormalities.

Previous studies to define the effects of intrauterine exposure to complex mixtures in rats have indicated that certain maternal and fetal indices are consistently altered. Maternal toxicity, observed following exposure to complex mixtures such as Harmarville process solvent (HPS), is manifested as depressed body weight gains and decreased thymus weights. In litters of these dams, decreased fetal body and lung weights, reduced skeletal ossification and increased incidences of anomalies are observed. These changes in fetal parameters are often attributed to maternal toxicity or related to maternal stress, altered metabolism or organ dysfunction. In an initial study to examine the hypothesis that the observed fetal effects may be mediated by alteration of maternal organ systems, we reported that administration of a corticosteroid, triamcinolone acetate, to rats during gestation produced fetal effects consistent with those observed following exposure to HPS. Subsequently, data from a number of studies in which HPS was administered to pregnant rats were examined to determine if changes in maternal and fetal indices of effects were directly related to one another.

Suspensions of HPS (boiling range: 300 to >850°F) were prepared in milk immediately prior to an intragastric (IG) intubation of a constant-volume dose. Female rats (Sprague-Dawley CD; Charles River Laboratories) received either the diluent or 1.85 g/kg of HPS on 11, 12, 13, or 14 days of gestation (dg). Maternal animals were weighed at intervals and sacrificed on 20 dg to evaluate external, visceral and skeletal effects.

Frequency distributions for consistent indices of maternal toxicity (extragestational gain and thymus weights) are shown in Figures 1A and 1B. Median values for each of these parameters were lower than those of control dams. Frequency distributions for fetal parameters utilized as indicators of retarded development or teratogenicity are shown in Figures 2A through 2D. Fetal indices of effect (decreased fetal body and lung weights and increased incidence of fetal anomalies and

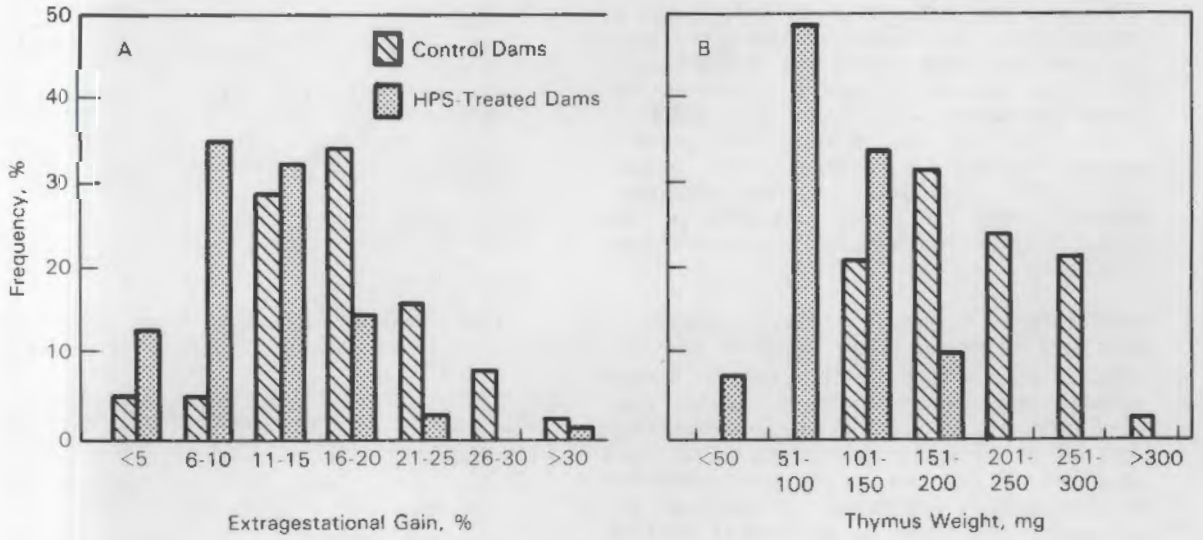


**Figure 1.** Frequency Distribution of Maternal Indices of Rats Dosed with Harmarville Process Solvent (HPS): (A) Extragestational Gain; (B) Thymus Weight.

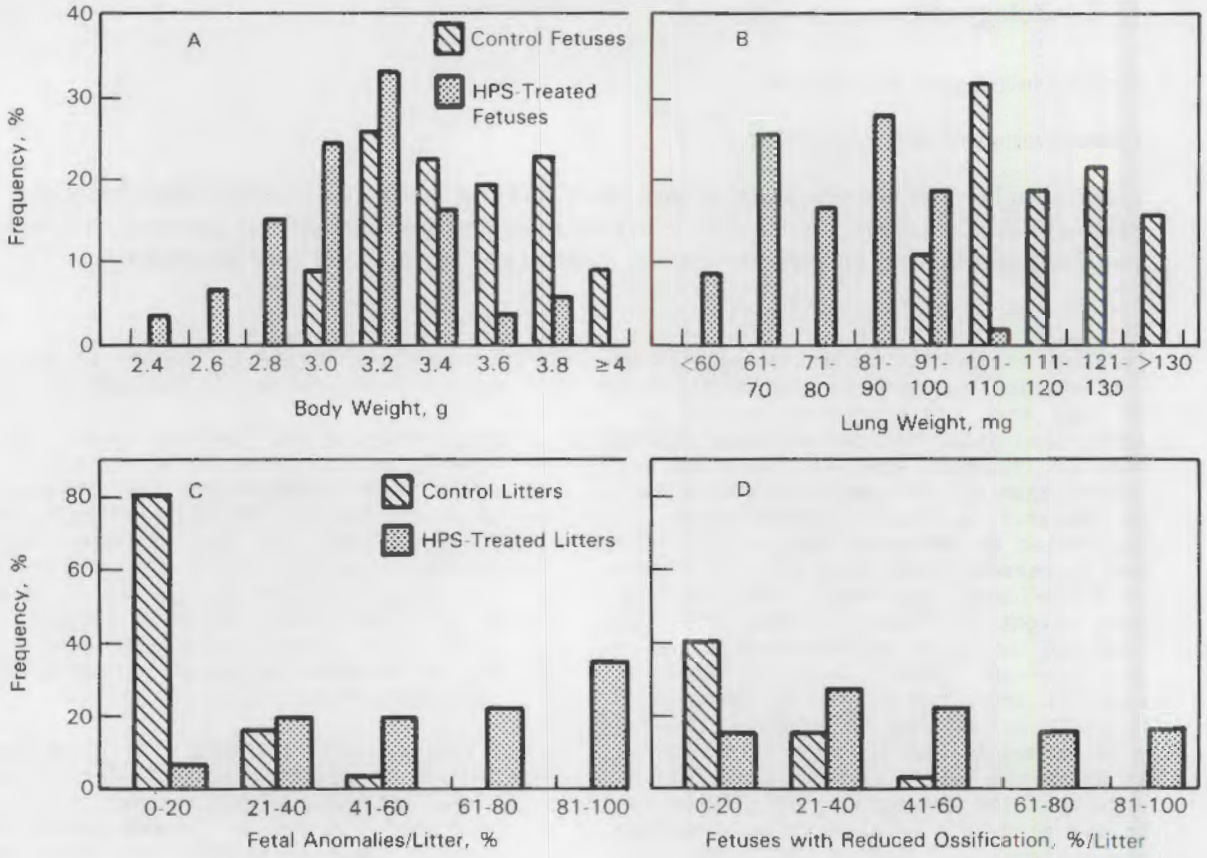


**Figure 2.** Frequency Distribution of Fetal Indices in Litters of Pregnant Rats Dosed with Harmarville Process Solvent (HPS): (A) Body Weight; (B) Lung Weight; (C) Fetal Anomalies; (D) Reduced Skeletal Ossification.

reduced skeletal ossification) were encountered more frequently in HPS-treated litters than in control litters.

When data for maternal body weight gains during gestation were compared with fetal body weight, lung weight and reduced ossification, no significant differences in these parameters were found in litters of control or HPS-treated dams that showed either minimal or maximal weight gains (Table 1). Similarly, no correlations were observed for fetal lung weights and anomalies, or for maternal thymus weights (Table 2).

Furthermore, values for fetuses exposed to HPS were different from those of control fetuses even when maternal gains or thymus weights were similar. These results suggest that these overt fetal abnormalities may not be directly related to toxic signs observed in the dam at necropsy and that more sensitive indicators of abnormal development should be determined at earlier stages of gestation.

**Table 1.** Relationship Between Fetal Parameters and Maternal Weight Gain of Rats Dosed with Harmarville Process Solvent (HPS).

| Fetal Parameter | Treatment | Extragestational Weight Gain, %[a] 0-10 | 11-20 | >20 |
|---|---|---|---|---|
| Body Weight, g | Control | 3.56 ± 0.17 | 3.58 ± 0.06 | 3.53 ± 0.09 |
| | HPS | 3.17 ± 0.05 | 3.22 ± 0.07 | 3.33 ± 0.03 |
| Lung Weight, mg | Control | 118 ± 4.6 | 116 ± 2.8 | 116 ± 5.4 |
| | HPS | 75 ± 2.5 | 79 ± 2.6 | 87 ± 6.2 |
| Reduced Skeletal Ossification, %/Litter | Control | 24 ± 7.4 | 25 ± 4.4 | 20 ± 5.9 |
| | HPS | 47 ± 4.9 | 49 ± 6.3 | 58 ± 12.5 |

[a] Mean ± SE

**Table 2.** Relationship Between Fetal Parameters and Maternal Thymus Weight of Rats Dosed with Harmarville Process Solvent (HPS).

| Fetal Parameter | Treatment | Maternal Thymus Weight, mg[a] <100 | 101-200 | >200 |
|---|---|---|---|---|
| Lung Weight, mg | Control | --- | 113 ± 2.5 | 121 ± 3.5 |
| | HPS | 76 ± 2.2 | 79 ± 2.8 | --- |
| Anomalies, %/Litter | Control | --- | 8 ± 2.0 | 9 ± 3.3 |
| | HPS | 63 ± 5.3 | 62 ± 5.4 | --- |

[a] Mean ± SE

## • Perinatal Effects of Complex Mixtures

Principal Investigator: D. L. Springer

Other Investigators: R. L. Buschbom, D. A. Haugen*, D. D. Mahlum, C. Peraino*, and C. A. Reilly, Jr.*

Technical Assistance: T. A. Breier, R. A. Clark, D. G. Jones, and R. C. Zanger

This report describes the results of a study to determine whether the tumor-initiating activities of individual carcinogens are decreased when they are applied simultaneously with complex coal-derived organic mixtures. In the present study, the number of altered hepatocyte foci which stained for gamma glutamyl transpeptidase were determined in rats that were initiated neonatally and promoted with dietary phenobarbital for 8 wk after weaning. The initiating activities of the complex coal-derived mixtures were evaluated relative to either benzo[a]pyrene (BaP) or diethylnitrosamine (DEN). Although the complex organic mixtures contained known carcinogens, their initiating activities were low at the doses used. Coadministration of complex, coal-derived mixtures with BaP or DEN decreased the response to both carcinogens. Promotion of preneoplastic hepatic foci was also observed in rats neonatally initiated with a single intraperitoneal injection of BaP or DEN and exposed after weaning to repeated dermal applications of complex organic mixtures. Like the data from previous studies with the skin initiation/promotion (I/P) model, the results suggest that inhibition of initiating activity of known carcinogens in complex mixtures is a general phenomenon. This was a cooperative study between PNL and Argonne National Laboratory.

Several reports have indicated that the dermal carcinogenic activities of benzo-[a]pyrene (BaP) and other pure carcinogens are altered when they are simultaneously administered with a complex mixture. For example, it has been shown that the skin-tumor-initiating activities of coal liquids and their polycyclic aromatic hydrocarbon (PAH) fractions were less than predicted from the carcinogenic PAH content of these mixtures. Liver tumors have been induced in rats by the intraperitoneal administration of an initiating dose of BaP or diethylnitrosamine (DEN) to neonatal animals, followed by promotion with dietary phenobarbital upon weaning. Furthermore, it has been demonstrated that the appearance of tumors is preceded by the presence of altered foci, which can be detected by a variety of histochemical assays, including a stain for gamma glutamyl transpeptidase (GGT) activity. The invariable appearance of such foci prior to tumor formation in carcinogen-treated rats suggests that the foci are useful early indicators of incipient neoplasia. We used the hepatic initiation/promotion (I/P) system to determine: 1) the initiating activities of complex organic mixtures containing known carcinogens; 2) whether the presence of the complex mixtures decreased the initiating activities of individual carcinogens (BaP or DEN); and 3) whether dermal application of these complex mixtures promoted preneoplastic changes in initiated liver cells.

The two complex mixtures used in this study were obtained from the solvent-refined-coal (SRC)-II process. These distillates, with boiling-point cuts of 800-850°F and >850°F, were fractionated by alumina column chromatography to obtain PAH and nitrogen-containing polycyclic aromatic compound (NPAC) fractions. The coal gasification tar was a by-product formed during gasification of lignite coal in a slagging fixed-bed gasifier. The chemical composition of the gasifier tar was qualitatively similar to that of the coal liquids except that components of the gasifier tar tended to be less alkylated than were those from the SRC materials.

Solutions of BaP (15 mg/ml), DEN (1.5 mg/ml), 800-850°F distillate (45 mg/ml), and PAH and NPAC fractions (45 mg/ml) were prepared in sesame seed oil. Solutions (45 mg/ml) of gasifier tar and the >850°F distillate were prepared in sesame seed oil:dichloromethane (9:1 v/v) because they were not completely soluble in sesame seed oil.

One-day old female pups (approximately 20/treatment group) were injected intraperitoneally with 0.01 ml/g body weight. Pups were weaned at 21 days of age, ear-tagged, segregated into treatment groups, and placed on a 30% casein diet containing 0.05% phenobarbital. Other animals, fed

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the same diet without phenobarbital, were treated topically twice weekly with either SRC-II heavy distillate (HD; 550-850°F) or gasifer tar at doses of 0.8 mg/g body weight. Animals were housed in solid-bottom cages (six/cage) and had water and food available ad libitum.

Animals were observed daily for mortality and weighed at 1, 3, and 11 weeks of age. Data for body weights, incidence of foci, foci per section and foci per $cm^3$ of liver were statistically analyzed using Duncan's multiple range test. Data for mortality were evaluated by chi-square comparison to appropriate control groups.

After 8 weeks of promotion, animals were sacrificed and their livers were removed. A cylindrical plug, 1.6 cm in diameter, was removed from the left lobe of the liver, frozen on dry ice, placed in air-tight plastic bags and stored at -80°C. The GGT activity was assayed on 15-μm frozen sections from each plug. The number of foci per section was determined by direct microscopic examination, and the number of foci per $cm^3$ of liver was estimated by quantitative stereology.

Results from this study indicated that initiation with BaP resulted in the appearance of numerous foci, and that 16 of 18 animals injected exhibited a positive response for GGT activity (Table 1). Although 100% of the animals initiated with DEN developed foci, the mean number of foci per section was slightly lower than for the BaP-initiated group.

The initiating activity of the distillates, PAH fractions and NPAC fractions was evident from the observation that the incidence of rats with foci in these groups ranged from 24 to 50%. However, the small number of foci per liver in the responding rats indicated that the initiating potency of these mixtures was weak relative to that of BaP or DEN (ranging from 2.2 to 6.1% of the number initiated by BaP). Although the concentrations of carcinogens were greater in the chromatographic fractions than in the distillates, none of the fractions was significantly more active than the distillate from which they were derived. Administration of gasifier tar did not result in an increase, relative to controls, in the incidence of animals with foci.

The effects of coadministration of complex mixtures containing known carcinogens on the initiating potential of the pure carcinogens, BaP and DEN, are illustrated in Table 2. The responses to both BaP and DEN were significantly decreased ($P < 0.05$) when coadministered with each of the three complex organic mixtures relative to the responses for the individual carcinogens. In addition, when the data were evaluated as foci/$cm^3$, the response for the group coadministered BaP and the 800-850°F distillate was significantly less than for those coadministered BaP and either the >850°F distillate or gasifier tar ($P > 0.05$). Conversely, responses after coadministration of the distillates with DEN suggested ($P > 0.078$) that the >850°F distillate was the most effective inhibitor.

**Table 1.** Initiating Potential of Complex Coal-Derived Organic Mixtures and Their Chromatographic Fractions ($\bar{x}$ ± SEM).

| Initiator | Dose, μg/g Body Weight | Incidence[a] | No. Foci/Section | No. Foci/$cm^3$ Liver |
|---|---|---|---|---|
| Sesame Seed Oil | | 0/20 | 0 | 0 |
| Sesame Seed Oil: Dichloromethane (9:1) | | 0/21 | 0 | 0 |
| BaP | 150 | 16/18[b] | 17.6 ± 2.9 | 230 ± 37 |
| DEN | 15 | 17/17[b] | 14.8 ± 2.1 | 186 ± 23 |
| 800-850°F Distillate | 450 | 6/19[b] | 0.6 ± 0.2 | 9 ± 4 |
| PAH Fraction | 450 | 7/16[b] | 0.6 ± 0.3 | 12 ± 5 |
| NPAC Fraction | 450 | 8/19[b] | 0.8 ± 0.2 | 14 ± 4 |
| >850°F Distillate | 450 | 6/17[b] | 0.4 ± 0.2 | 5 ± 2 |
| PAH Fraction | 450 | 7/14[b] | 0.9 ± 0.4 | 14 ± 8 |
| NPAC Fraction | 450 | 4/17[b] | 0.4 ± 0.2 | 5 ± 3 |
| Gasifier Tar | 450 | 1/21 | 0.05 ± 0.05 | 1 ± 1 |

[a]Number of animals with foci/number of animals in group
[b]Statistically different from control group ($P < 0.05$)

**Table 2.** Effect of Coadministration of Complex Coal-Derived Organic Mixtures on the Initiation of Gamma Glutamyl Transpeptidase (GGT) Foci by Benzo[a]pyrene (BaP) and Diethylnitrosamine (DEN; $\bar{x}$ ± SEM).

| Group | Initiator | No. of Animals | No. Foci/ Section | Response, % of BaP or DEN | No. Foci/ $cm^3$ Liver | Response, % of BaP or DEN |
|---|---|---|---|---|---|---|
| 1 | Sesame Seed Oil | 20 | 0 | --- | 0 | --- |
| 2 | Sesame Seed Oil: Dichloromethane (9:1) | 21 | 0 | --- | 0 | --- |
| 3 | BaP | 18 | 17.6 ± 2.9 | 100 | 230 ± 37 | 100 |
| 4 | BaP + 800-850°F Distillate | 14 | 7.1 ± 1.3[a] | 40 | 86 ± 13[a,b] | 37 |
| 5 | BaP + >850°F Distillate | 13 | 10.3 ± 2.4[a] | 59 | 145 ± 17[a] | 63 |
| 6 | BaP + Gasifier Tar | 21 | 10.0 ± 1.3[a] | 57 | 143 ± 17[a] | 62 |
| 7 | DEN | 17 | 14.8 ± 2.1 | 100 | 186 ± 23 | 100 |
| 8 | DEN + 800-850°F Distillate | 18 | 10.4 ± 1.4[a] | 70 | 120 ± 16[a] | 65 |
| 9 | DEN + >850°F Distillate | 14 | 6.5 ± 1.4[a] | 44 | 80 ± 15[a,c] | 43 |
| 10 | DEN + Gasifier Tar | 20 | 9.4 ± 1.0[a] | 64 | 117 ± 15[a] | 63 |

[a]In all cases the responses for the coadministration groups (groups 4-6 and 8-10) were significantly less than for the respective groups receiving individual carcinogens (groups 3 and 7; $P < 0.05$)
[b]The response for group 4 was significantly less than that for groups 5 and 6 ($P < 0.05$)
[c]$P = 0.078$ when groups 8 and 9 were statistically compared

The coal-derived materials, when applied to the skin of BaP- or DEN-initiated rats, also promoted the appearance of hepatic foci, although to a smaller degree than did dietary phenobarbital (Table 3). In all cases, promotion involved increases in both the numbers and sizes of the foci. The observation that promotion was obtained with all the I/P combinations used in this study indicates the general re-

**Table 3.** Effect of Dermal Treatment with Complex Coal-Derived Organic Mixtures on the Appearance of Hepatic Foci ($\bar{x}$ ± SEM).

| Group | Initiator | Promoter | No. Rats | No. Foci Per Section | No. Foci per $cm^3$ Liver |
|---|---|---|---|---|---|
| 1 | Vehicle | Vehicle | 18 | 0 | 0 |
| 2 | Vehicle | Phenobarbital | 20 | 0 | 0 |
| 3 | Vehicle | Gasifier Tar | 18 | 0.05 ± 0.05 | 1 ± 1 |
| 4 | Vehicle | Heavy Distillate | 14 | 0 | 0 |
| 5 | BaP | Vehicle | 16 | 0.7 ± 0.2 | 14 ± 5 |
| 6 | BaP | Phenobarbital | 16 | 19.8 ± 2.8 | 259 ± 36 |
| 7 | BaP | Gasifier Tar | 16 | 5.4 ± 0.9 | 84 ± 15 |
| 8 | BaP | Heavy Distillate | 15 | 10.1 ± 1.8 | 155 ± 25 |
| 9 | DEN | Vehicle | 17 | 0.8 ± 0.4 | 14 ± 6 |
| 10 | DEN | Phenobarbital | 17 | 14.8 ± 2.1 | 186 ± 23 |
| 11 | DEN | Gasifier Tar | 17 | 8.2 ± 1.2 | 123 ± 18 |
| 12 | DEN | Heavy Distillate | 14 | 7.3 ± 1.4 | 103 ± 16 |

sponsivness of this experimental system to I/P stimuli, regardless of their structural and metabolic diversity.

With regard to the mechanism by which the topically applied mixtures promoted hepatocyte foci, we suggest that the hepatic response was produced by components that were absorbed and subsequently transported to the liver. This interpretation is supported by studies documenting the percutaneous absorption of topically applied coal tar and its constituents, and the subsequent rapid induction of hepatic enzymes, including microsomal mono-oxygenases and ornithine decarboxylase.

Analysis of the complex mixtures used in these studies shows that a number of carcinogenic and cocarcinogenic components are present in the mixtures. Moreover, other studies have shown that these mixtures were effective initiators of skin tumorigenesis. However, the data in this report indicate that, relative to BaP and DEN, the complex organic mixtures were only minimally effective as initiators of GGT-positive foci.

## • Health Effects of Complex Mixtures

Principal Investigator: R. A. Renne

Other Investigators: R. L. Buschbom, M. E. Frazier, and C. W. Wright

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

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 complex hydrocarbon materials and products from the solvent-refined-coal technology. An in vitro system using cultured mouse skin is being developed in an attempt to correlate primary DNA damage induced in vitro by complex hydrocarbon mixtures with carcinogenic effects observed in vivo.

Epidermal carcinogenesis studies in mice were completed on selected complex organic hydrocarbon mixtures from the solvent-refined-coal (SRC) technology. Samples of the 750 to 800°F distillate cut of Harmarville process solvent (HPS) were nitrosated to destroy primary aromatic amines (PAA); additional samples of this distillate cut were fractionated by adsorption column chromatography to obtain discrete polycyclic aromatic hydrocarbon (PAH) and nitrogen-containing polycyclic aromatic compound (NPAC) chemical class fractions (Annual Report, 1984). Skin-tumor incidence and latency data from these studies were analyzed statistically using the nonparametric product-limit method of Kaplan and Meier to estimate cumulative skin-tumor-free survival (Figures 1 and 2). An adaptation of the Weibull analysis was utilized to compare epidermal carcinogenic potency of the test materials to that of benzo[a]pyrene (BaP; Table 1).

Skin-tumor latency was significantly ($P = 0.01$) increased in mice exposed to the nitrostated 750 to 800°F boiling-point (bp) cut compared with that for animals exposed to the non-nitrosated bp cut (Figure 1). This statistical difference was due to a decrease in tumor latency in female mice exposed to the non-nitrosated material. Weibull analysis (Table 1) indicated that the non-nitrosated material was slightly more potent than the nitrosated bp cut when data from both sexes were pooled. Skin-tumor incidence and latency data from studies of the alumina-derived fractions of the 750 800°F bp cut (Figure 2) indicated that both PAH and NPAC fractions were carcinogenic for mouse skin; Weibull analysis (Table 1) of these data indicated that both fractions were comparable in potency to the crude bp cut.

Data from the nitrosation study suggest that PAA, which are destroyed by nitrosation, do not play a major role in the dermal carcinogenicity of these complex organic mixtures. However, results from the studies of the alumina-derived fractions of the 750 to 800°F bp cut indicate that the NPAC fraction, which contains the PAA, is as potent a dermal carcinogen as the PAH fraction, when the data are compared using the Weibull analysis. This suggests that the majority of the dermal carcinogenicity of the NPAC alumina fraction is due not to PAA but to some other component of the fraction. The other major chemical groups present in alumina-derived NPAC fractions of SRC-II materials are carbazoles and aza-arenes; certain members of both these chemical groups have been shown to be carcinogenic for mouse skin.

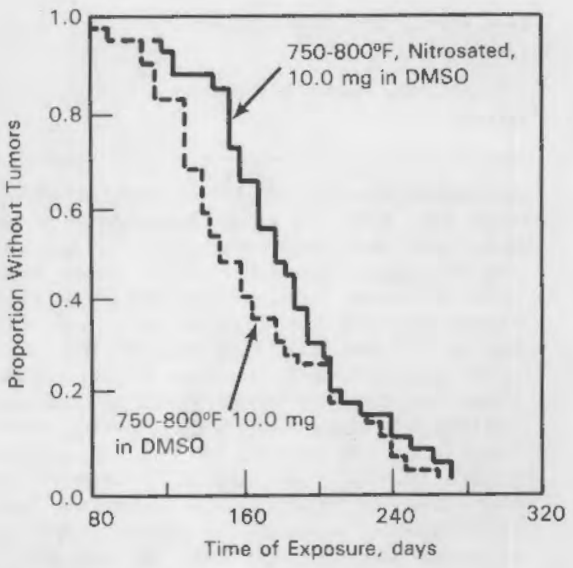


**Figure 1.** Proportion of Group Surviving Without a Skin Tumor in Mice Exposed Three Times Weekly to the 750-800°F Boiling-Point Distillate Cut of SRC-II HPS, or to a Nitrosated Sample of this Boiling-Point Cut. Pooled data from both sexes; Kaplan-Meier estimates.

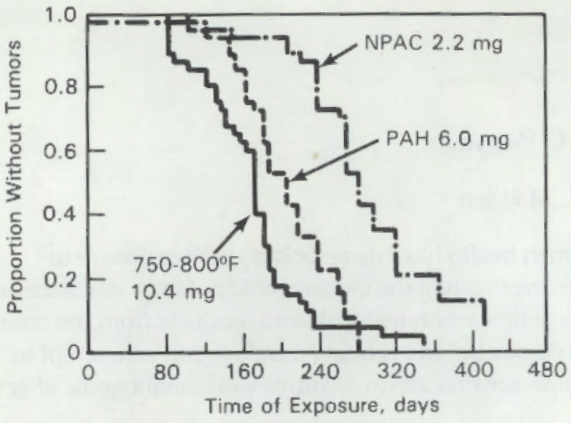


**Figure 2.** Proportion of Group Surviving Without a Skin Tumor in Mice Exposed Three Times Weekly to the 750-800°F Boiling-Point Distillate Cut of SRC-II HPS, or to Alumina-Derived Fractions of this Distillate Cut. Kaplan-Meier estimates.

**Table 1.** Carcinogenic Potency of 750-800°F bp Cut of Harmarville Process Solvent (HPS) and its Alumina Fractions, Relative to Benzo[a]pyrene.

| | Potency Versus BaP | |
|---|---|---|
| | % | Ratio |
| BaP | 100.00 | 1/1.0 |
| SRC-II 750-800°F bp Cut | 0.32 | 1/312 |
| SRC-II 750-800°F bp Cut in DMSO | 0.23 | 1/435 |
| Nitrosated SRC-II 750-800°F bp Cut in DMSO | 0.20 | 1/500 |
| PAH Alumina Fraction of 750-800°F bp Cut | 0.27 | 1/370 |
| NPAC Alumina Fraction of 750-800°F bp Cut | 0.29 | 1/345 |

Although present in lower concentration than PAH, NPAC are major components of SRC materials and are responsible for most of the microbial mutagenicity of these complex mixtures. Data from dermal initiation/promotion studies, in mice, of the 800 to 850 and 850°F+ bp cuts of HPS indicate that the NPAC alumina fractions of these bp cuts, although less active as initiators than the corresponding PAH fractions, are capable of initiating skin tumors in mice. Skin-painting studies are currently in progress to determine the carcinogenic response in mouse skin to repeated exposure to the PAH and NPAC alumina fractions of the 800 to 850°F bp cut of HPS.

In an attempt to devise an in vitro assay that was predictive of skin-painting studies, we investigated the induction of sister chromatid exchange (SCE), using cultures of embryonic mouse skin. Cultures of primary embryonic mouse-skin cells were prepared and, after two or three passages, were subcultured with 10 µg/ml of bromodeoxyuridine for 24 hours before challenge with test chemicals. No exogenous microsomal preparations were added. For comparison, similar studies were performed using Chinese hamster ovary (CHO) cells and activating enzymes, consisting of Aroclor-induced rat liver S9 preparations in the presence of an NADPH regenerating system.

Our initial results are shown in Table 2. The data indicate that mouse-skin cells are capable of metabolically activating carcinogens (e.g., BaP). However, culturing embryonic mouse-skin cells is difficult and time-consuming, and they do not appear to be significantly more sensitive to SCE than CHO cells with added activating enzymes. Even CHO cells do not appear to be very useful as a quantitative assay for screening these complex mixtures. Good dose-response relationships were not observed with the mixtures, nor did we see high levels of activity relative to our positive controls. Based on these data, SCE does not appear to be a good in vitro screening assay for these complex organic mixtures.

**Table 2.** Sister Chromatid Exchanges Induced in Chinese Hamster Ovary (CHO) and Embryonic Mouse Skin Cells by Known Carcinogens and Complex Organic Mixtures in the Presence of Activating Enzymes.

| | | Sister Chromatid Exchanges/Chromosome | |
|---|---|---|---|
| Test Material | Dose, µg/ml | CHO Cells | Mouse Skin Cells |
| Ethylmethylsulfonate | 100 | 0.85[a] | NT[b] |
| Mitomycin C | 2 | 1.68 | 1.02[a] |
| | 0.6 | 0.87[a] | |
| Benzo[a]pyrene | 3 | 0.7 [a] | 0.69[a] |
| | 10 | 0.67[a] | NT[b] |
| 6-Aminochrysene | 60 | 0.40 | NT[b] |
| 2-Aminoanthracene | 20 | 0.49 | NT[b] |
| | 50 | 0.62[a] | NT[b] |
| SRC-II Heavy Distillate | 3 | 0.41 | NT[b] |
| | 10 | 0.60[a] | 0.50 |
| | 30 | 0.54 | NT[b] |
| Harmarville Process Solvent | 3 | 0.51 | NT[b] |
| | 10 | 0.65[a] | 0.61[a] |
| | 30 | 0.54 | NT[b] |
| Control (DMSO Solvent) | -- | 0.38 | 0.44 |

[a] Significantly different from control at P = 0.05
[b] Not tested

## • Tissue Dose in Complex Mixture Exposures

Principal Investigator: W. C. Weimer

Other Investigator: D. L. Springer

Technical Assistance: E. M. Crow, B. K. Hayden, D. L. Widrig, and R. C. Zanger

In studies designed to examine the disposition of complex-mixture components in experimental animals as a function of several variables, the elimination of several individual marker compounds by exhalation was examined. One-, two-, and three-ring aromatic hydrocarbons and substituted hydrocarbons were evaluated during 24-hr experiments to examine the time course of blood and breath concentrations. Breath exhalation was a major clearance route for the nonpolar, one-ring compounds, benzene and toluene; up to 40% of the total dose was eliminated by exhalation. For the polar compound, phenol, and the two- and three- ring compounds, naphthalene and phenanthrene, less than 2% of the total amount administered was eliminated by exhalation.

The disposition of complex-mixture components administered to rats (female, Sprague-Dawley CD, Charles River) is being investigated as a function of individual compound, time after exposure, presence or absence in a complex-mixture carrier matrix, route of exposure, and the temporal pattern of dosing. The time course of blood and breath levels of specific marker compounds (benzene, toluene, phenol, naphthalene, and phenanthrene) was followed during the 24-hour time period after dosing. The purpose of this work is to develop a predictive capability to estimate levels of complex-mixture components in target organs as they relate to varying exposure regimes and, ultimately, to link these pharmacokinetic data with toxicologic data from other programs in order to model toxicity resulting from particular levels and patterns of exposure.

Components of complex mixtures were tagged with $^{14}C$ and doses (10 μCi) were administered to rats by intraperitoneal injection. Individual rats were placed in a glass metabolism cage, and all exhaled vapors were collected and passed over Tenax to trap the parent compound and through solutions of phenethylamine to collect carbon dioxide. Ten concurrent samples of blood and exhaled vapors were collected during the 24-hour period following dosing. The concentrations of radiotracer were determined in each of these samples, and the breath/blood partition coefficient (exhaled air concentration/ blood concentration) was calculated for each set of breath and blood samples. Each marker compound was evaluated individually in four to seven animals.

Figure 1 displays the time course of the radiotracer blood levels for each of the compounds tested. Each time point is the mean value of data for all animals tested with a specific compound. For all compounds except toluene the maximum blood concentration was reached within 1 to 2 hours after injection. Blood concentrations for toluene reached maximum immediately and decreased steadily with time, as did all of the other materials. Since these data represent the total radiotracer concentrations in the blood, some metabolic products may be included as well as parent compounds. The breath/blood partition coefficients calculated for these time points (Figure 2) were constant for approximately 10 hours except that for benzene, which showed a continual decrease throughout the 24 hours. This apparent decrease is likely due to the rapid build-up of radiolabeled metabolic products in the blood during this time and the method of calculating the partition coefficient.

The values for the average partition coefficients for each of these marker compounds are given in Table 1. For these representative complex mixture components, the partition coefficients range from $1.4 \times 10^{-1}$ for benzene to approximately $10^{-6}$ for phenanthrene. Also listed in this table are the vapor pressures calculated at 20°C for these compounds. A simple linear regression plot of the breath/blood partition coefficient versus the vapor pressure demonstrates a very strong correlation between these two variables. The ability of a compound to be transferred from the blood across the alveolar capillary membranes into the exhaled air is directly related to the vapor pressure of the material.

The relationship between the breath/blood partition coefficients and the clearance of these compounds from the animal is shown by the data presented in Table 2. The fraction of the total dose that was collected from the exhaled air ranged from

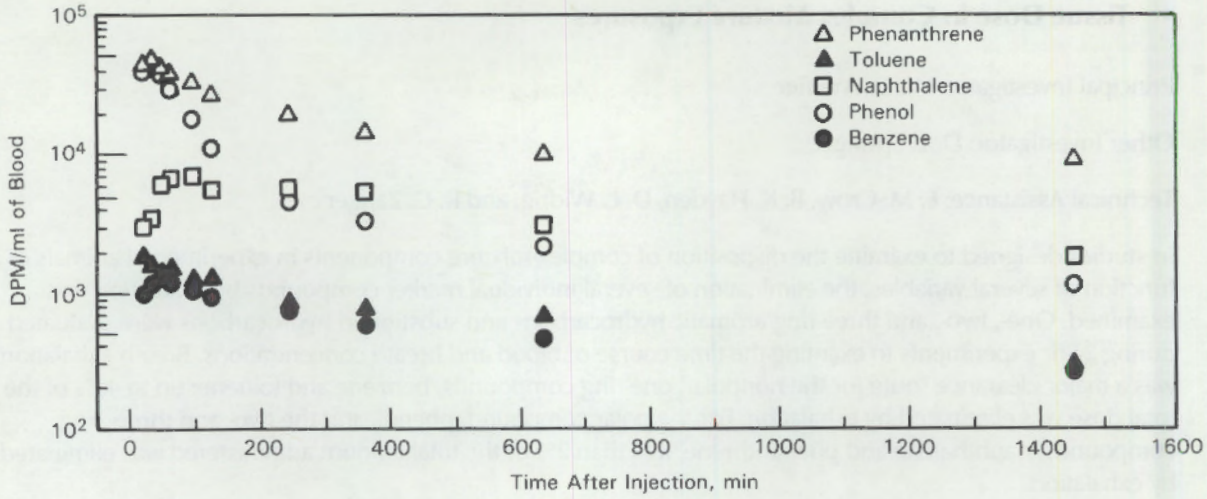


**Figure 1.** Time Course of Radiotracer Concentrations in Blood of Rats Adminstered Complex-Mixture Compounds.

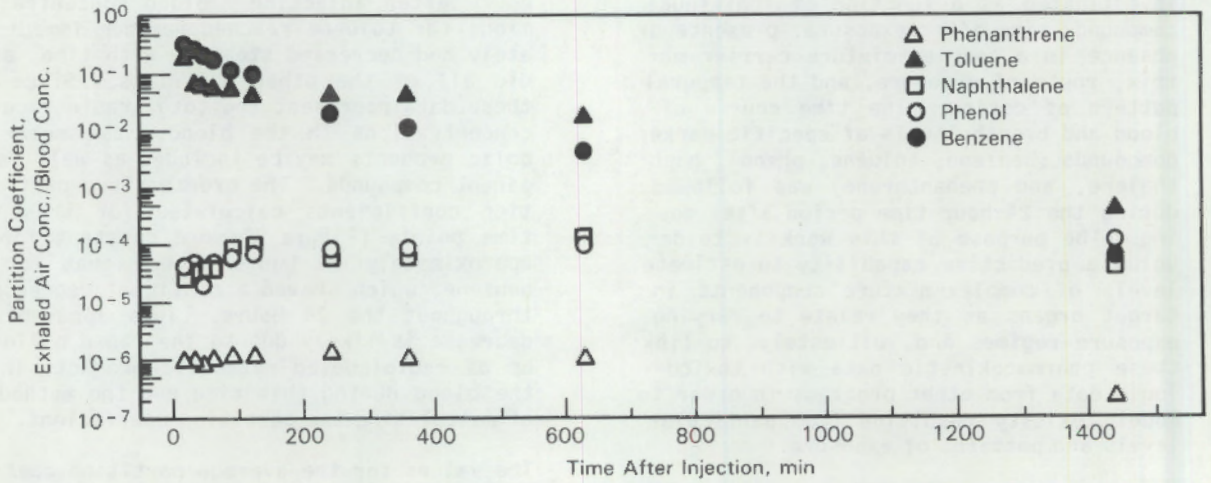


**Figure 2.** Partition Coefficient Versus Time After Injection. Time course of partition coefficient (exhaled air concentration/blood concentration) in rats administered complex-mixture components.

0.2% to greater than 40%. Exhalation appears to be a major route of clearance for the one-ring nonpolar compounds, benzene and toluene, with 41% and 22%, respectively, of the total dose being cleared in the breath. For phenol, the more-polar one-ring compound evaluated, approximately 0.2% of the total dose was cleared in the breath. For the somewhat larger (two and three aromatic rings) neutral compounds, naphthalene and phenanthrene, exhalation clearance was 1.2% and 0.4%, respectively, of the dose administered. These data demonstrate that nonpolar compounds with few rings are cleared very adequately from the blood by transfer across the alveolar capillary membranes into the exhaled breath.

These data have potential application in the development of effective dosimetric techniques, using breath analysis to measure integrated exposure of an individual to these complex-mixture components from all routes of entry to the body. Because of the chemical equilibrium that is established between the concentrations of compounds in the total blood reservoir and in expired air, analysis of breath can provide a rapid and convenient indicator of the blood concentrations of compounds and an estimate of total exposure. The results of these experiments indicate that breath analysis can be used for evaluating exposure to light, nonpolar hydrocarbons having up to three rings.

**Table 1.** Relationship of Partition Coefficient and Vapor Pressure of Complex-Mixture Compounds Administered to Rats.[a] Exhaled vapors were collected and breath/blood partition coefficient was calculated for each set of samples.

| Compound | Average Partition Coefficient | Vapor Pressure Calculated for 20°C, Torr |
|---|---|---|
| Benzene | $1.44 \times 10^{-1}$ | 57.7975 |
| Toluene | $5.35 \times 10^{-2}$ | 21.0919 |
| Phenol | $6.22 \times 10^{-5}$ | 0.4475 |
| Naphthalene | $6.25 \times 10^{-5}$ | 0.1726 |
| Phenanthrene | $1.04 \times 10^{-6}$ | 0.0023 |

[a] Linear Regression of Partition Coefficient vs Vapor Pressure $r^2 = 0.99989$

**Table 2.** Percent of Dose Collected from Air Exhaled by Rats Administered Complex-Mixture Components.

| Compound | Percent of Dose Collected | |
|---|---|---|
| | On Tenax | As $Co_2$ |
| Benzene | 33 | 8.1 |
| Toluene | 21 | 0.72 |
| Phenol | 0.15 | 0.02 |
| Naphthalene | 1.2 | 0.01 |
| Phenanthrene | 0.39 | <0.01 |

# Medical Applications of Nuclear Technology

## • Blood Irradiator Development

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

Other Investigators: L. R. Bunnell, W. F. Riemath, and P. Roberson

The fully portable blood irradiator developed to provide continuous intracorporeal irradiation of circulating blood has been evaluated for external radiation doses in anticipation of clinical trials. A computer code was developed to describe the external radiation field, and a design for an irradiator to be used for humans was prepared that provided for suitable shielding. Using this design, a lead working model was constructed and used to measure the isodose distribution. These data have been submitted for evaluation by the University of Washington Radiation Safety Committee in preparation for clinical trials. Despite concerted efforts to locate dogs with blood diseases so that we might evaluate their response to blood irradiator treatment, no animals have been obtained during the year.

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 guidance from the computer code, which provided isodose curves for the irradiator, a shield design was developed (Figure 1) and a 960-g lead shield piece was constructed. Ultimately, shields will be made of tungsten (or hevimet) for improved shielding efficiency and greater durability; this initial model was made of lead because it is easily machined. In this model, no attempt was made to restrict radiation streaming at the juncture of the two halves of the shield.

Confirmatory dosimetry with the initial model was achieved using a hyper-pure intrinsic germanium detector with a beryllium window, two thicknesses of LiF thermoluminescent dosimeters and an ionization chamber. Exposure rates measured by the ionization chamber were used to relate the thermoluminescent dosimeter measurements to the dose in air. Figure 2 gives the observed isodose distribution curves.

Although not shown in the figure, a rapid increase in dose rate occurs at the surface of the shield. We therefore plan to provide for a 2.5-cm separation between the shield and the skin of the limb on which the device will be worn. With this separation, the ratio of dose to limb relative to dose to blood would be $8.3 \times 10^{-4}$, i.e., a dose of 90,000 rad to blood would give a maximum dose to the limb of 75 rad (the annual occupational exposure limit for a limb).

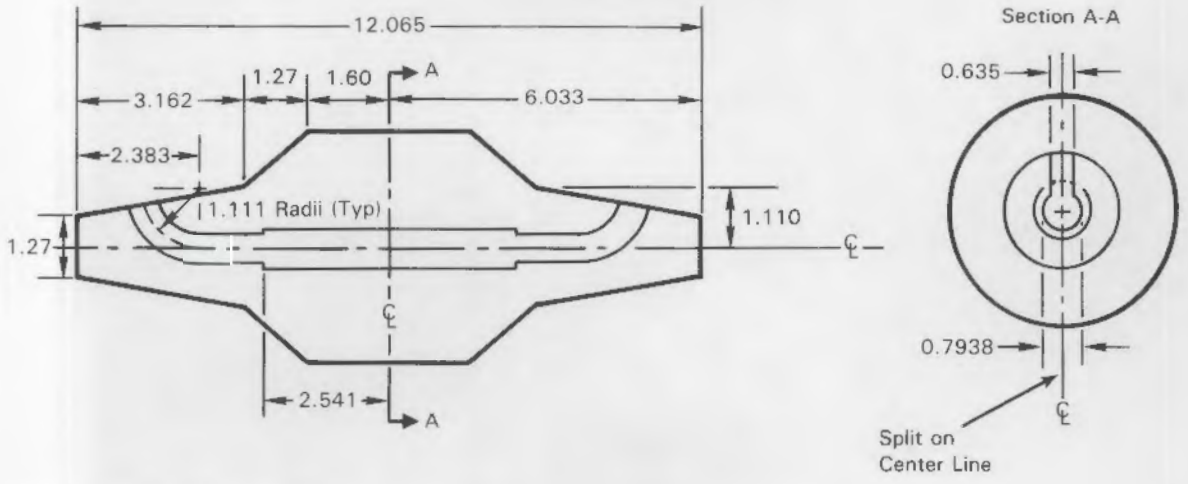


**Figure 1.** Blood Irradiator Shielding.

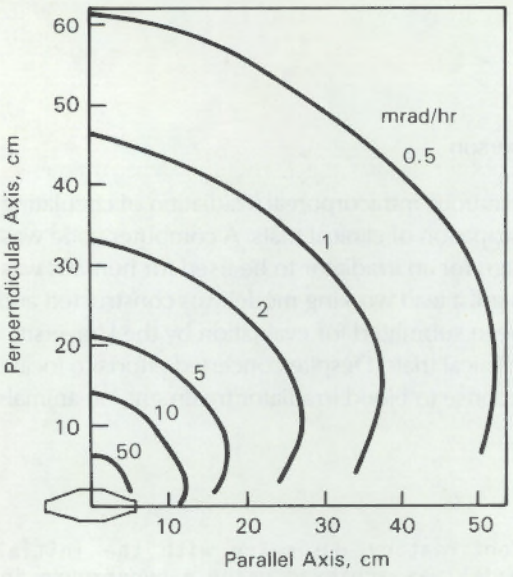


**Figure 2.** Isodose Distribution Near the Blood Irradiator. Values are in units of mrad/hr for an irradiator with an average transit dose rate to blood of 140 rad (assuming a flow rate of 100 ml/min).

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Two follow-on steps are in progress. First, a new shield piece, to be made of tungsten (hevimet), is being designed. This unit will have the same physical dimensions as the lead shield and will have approximately three times the shielding capability of the lead model because of its increased density. Thus, the ratio of the maximum dose to the limb relative to the dose to blood will be $2.8 \times 10^{-4}$. Second, we have approached the Radiation Safety Committee at the University of Washington to determine if the data now available are sufficient for them to accept this device for clinical trials. (We expect an answer in 1986.) If the response is favorable, we will be able to approach the institutional review committees for permission to conduct clinical trials when that becomes appropriate.

We have anticipated testing the efficacy of the blood irradiator on dogs affected by blood diseases, such as chronic lymphocytic leukemia. Thus far, we have been unable to obtain such dogs despite the assistance of the Fred Hutchinson Cancer Center in Seattle, contacts with several dog oncology reference centers and published memoranda in several professional newsletters. Animals from the Pacific Northwest Laboratories beagle colony may occasionally be available for treatment when such treatment does not interfere with the protocol of other ongoing experiments.

Additional design modifications for the tubing connectors are in progress to shorten the overall length of the irradiator and thus minimize shield weight. The new connector will be tested for possible thrombus formation when prototype units are available.

We have recently acquired several monoclonal cell lines and test sera that will permit identification of subpopulations of T-cell lymphocytes. This will permit a more complete description of precisely which T-cells are most affected by blood irradiation. We may then be able to extrapolate results obtained with dogs to those expected in clinical applications.

- **List of DOE Radioisotope Customers with Summary of Radioisotope Shipments, FY 1984**

Principal Investigator: D. A. Baker

The annual list of DOE radioisotope customers (PNL-5492) 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 FY 1984 were $8.2 million, a decrease of 14% 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 lung 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 9/30/85 | 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 | | 169.8* | Malignant Lymphoma |
| CONTROL | 749 F | 0 | 0.00 | 0.00 | | | | 09/14/84 | | 183.4* | Adrenalitis |
| CONTROL | 755 M | 0 | 0.00 | 0.00 | | | | 12/10/82 | | 162.2* | Status Epilepti, Nephrosclero |
| CONTROL | 766 M | 0 | 0.00 | 0.00 | | | | 06/26/84 | | 180.3* | Lung Tumor |
| CONTROL | 775 F | 0 | 0.00 | 0.00 | | | | 10/05/81 | | 147.3* | Pulmonary Thromboembolism |
| CONTROL | 785 M | 0 | 0.00 | 0.00 | | | | | 194.4* | | |
| 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 | | | | | 191.3* | | |
| CONTROL | 801 M | 0 | 0.00 | 0.00 | | | | 02/23/82 | | 148.1* | Lung Tumor |
| CONTROL | 811 F | 0 | 0.00 | 0.00 | | | | 02/24/85 | | 183.1* | Oral cav.: Malignant Melanoma |
| CONTROL | 846 M | 0 | 0.00 | 0.00 | | | | 04/08/83 | | 159.6* | Nephrosclerosis |
| CONTROL | 861 M | 0 | 0.00 | 0.00 | | | | | 189.0* | | |
| CONTROL | 868 F | 0 | 0.00 | 0.00 | | | | | 187.7* | | |
| CONTROL | 872 F | 0 | 0.00 | 0.00 | | | | 11/05/82 | | 152.8* | Lung Tumor |
| CONTROL | 878 M | 0 | 0.00 | 0.00 | | | | 01/22/85 | | 177.4* | Chronic Nephropathy |
| 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 | | | | 01/30/85 | | 174.6* | Malignant Lymphoma |
| 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 | 01/23/85 | | 162.6 | Kidney Failure |
| D-1 LOWEST | 858 M | 0 | 0.00 | 0.00 | 13.5 | 18.2 | 07/06/71 | | 170.8 | | |
| D-1 LOWEST | 865 F | 0 | 0.00 | 0.00 | 9.0 | 17.4 | 07/06/71 | | 170.8 | | |
| 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 | | 166.7 | | |
| 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 | | 173.2 | | |
| 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 | | 170.8 | | |
| D-1 LOWEST | 891 M | 6 | 0.04 | 0.41 | 14.0 | 16.0 | 11/10/71 | 06/26/81 | | 115.5 | Septicemia |
| D-1 LOWEST | 853 M | 8 | 0.05 | 0.51 | 15.0 | 21.3 | 10/07/71 | 12/12/84 | | 158.2 | Bronchopneumonia |
| 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 | 11/29/84 | | 166.3 | Glomerulosclerosis |

* 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 9/30/85 | 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 | Chronic Nephropathy |
| D-1 LOWEST | 850 F | 5 | 0.06 | 0.63 | 8.0 | 21.3 | 10/07/71 | 06/06/83 | | 140.0 | Chronic Nephropathy |
| D-1 LOWEST | 893 M | 9 | 0.06 | 0.61 | 14.0 | 14.9 | 10/07/71 | | 167.8 | | |
| 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 | 6 | 0.07 | 0.75 | 8.0 | 17.7 | 06/08/71 | | 171.8 | | |
| 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 | Bronchopneumonia |
| D-2 LOW | 842 M | 10 | 0.07 | 0.77 | 13.5 | 18.6 | 07/06/71 | 05/01/85 | | 165.8 | Lung Tmr, Chronic Nephropathy |
| D-2 LOW | 767 M | 10 | 0.08 | 0.83 | 12.0 | 18.2 | 12/21/70 | | 177.3 | | |
| D-2 LOW | 920 M | 11 | 0.08 | 0.92 | 12.0 | 16.0 | 06/08/72 | 07/07/72 | | 1.0 | Sacrificed |
| D-2 LOW | 862 M | 13 | 0.09 | 1.00 | 13.0 | 17.3 | 06/08/71 | 06/25/83 | | 144.6 | Peritonitis |
| D-2 LOW | 871 M | 13 | 0.09 | 0.96 | 13.5 | 16.9 | 07/06/71 | | 170.8 | | |
| D-2 LOW | 874 M | 16 | 0.11 | 1.24 | 13.0 | 16.8 | 07/06/71 | 04/09/85 | | 165.1 | Chronic Nephropathy |
| 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 | Urinary Bladder Tumor |
| D-2 LOW | 748 F | 14 | 0.16 | 1.75 | 8.0 | 19.5 | 01/19/71 | 08/19/81 | | 127.0 | Unknown Cause |
| D-2 LOW | 798 F | 16 | 0.16 | 1.78 | 9.0 | 15.6 | 02/09/71 | 08/29/74 | | 42.6 | Sacrificed |
| D-2 LOW | 826 F | 19 | 0.17 | 1.90 | 10.0 | 19.1 | 07/06/71 | 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 | | 167.8 | | |
| 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 | | 177.3 | | |
| D-2 LOW | 876 F | 19 | 0.24 | 2.69 | 7.0 | 17.9 | 10/07/71 | | 167.8 | | |
| 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 | | 167.8 | | |
| 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 | 12/28/84 | | 164.1 | Pneumonia |
| 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 | | 174.9 | | |
| 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 | Urinary Bladder Tumor |
| D-3 MED-LOW | 883 M | 63 | 0.44 | 4.85 | 13.0 | 17.7 | 10/07/71 | | 167.8 | | |
| 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 | Malignant Lymphoma, Lung Tmr |
| 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 | | 167.8 | | |
| 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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-3 MED-LOW | 797 F | 85 | 0.70 | 7.73 | 11.0 | 16.4 | 03/04/71 | | 174.9 | | |
| D-3 MED-LOW | 848 F | 75 | 0.72 | 7.94 | 9.5 | 21.3 | 10/07/71 | | 167.8 | | |
| D-3 MED-LOW | 827 F | 89 | 0.74 | 8.09 | 11.0 | 16.7 | 04/26/71 | 01/06/85 | | 164.4 | Acute Pneumonitis |
| 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 | Lung Tmr, Malignant Lymphoma |
| 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 | 08/08/85 | | 170.0 | Processing |
| D-3 MED-LOW | 905 F | 127 | 1.36 | 14.94 | 8.5 | 15.9 | 11/10/71 | 02/07/83 | | 134.9 | Malignant Lymphoma |
| D-4 MEDIUM | 866 M | 200 | 1.35 | 14.81 | 13.5 | 17.4 | 07/06/71 | 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 | | 173.2 | | |
| 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 | 256 | 1.66 | 18.29 | 14.0 | 17.8 | 06/08/71 | 03/16/81 | | 117.3 | Lung Tumor |
| D-4 MEDIUM | 819 F | 163 | 1.74 | 19.18 | 8.5 | 18.2 | 06/08/71 | 08/20/85 | | 170.4 | Processing |
| 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 | 2.71 | 29.80 | 10.0 | 64.0 | 10/09/70 | 10/16/70 | | 0.2 | Sacrificed |
| D-4 MEDIUM | 808 F | 270 | 2.89 | 31.76 | 8.5 | 14.6 | 02/10/71 | 09/09/82 | | 138.9 | Lung Tumor |
| D-4 MEDIUM | 805 F | 257 | 3.12 | 34.27 | 7.5 | 18.5 | 06/08/71 | 07/22/82 | | 133.5 | Esophageal & Lung Tumor |
| D-4 MEDIUM | 812 M | 438 | 3.19 | 35.04 | 12.5 | 17.1 | 04/26/71 | 11/12/79 | | 102.6 | Lung Tumor |
| D-4 MEDIUM | 857 M | 486 | 3.40 | 37.38 | 13.0 | 17.3 | 06/08/71 | 07/01/80 | | 108.8 | Lung Tumor |
| D-4 MEDIUM | 892 M | 494 | 3.59 | 39.52 | 12.5 | 16.0 | 11/10/71 | 10/26/81 | | 119.5 | Lung Tumor |
| D-4 MEDIUM | 816 M | 398 | 3.62 | 39.80 | 10.0 | 16.8 | 04/25/71 | 05/11/71 | | 0.5 | Sacrificed |
| D-4 MEDIUM | 777 M | 546 | 3.97 | 43.68 | 12.5 | 20.2 | 03/04/71 | 03/26/80 | | 108.7 | Lung Tumor |
| D-4 MEDIUM | 803 M | 547 | 4.32 | 47.57 | 11.5 | 18.1 | 04/26/71 | 11/10/77 | | 78.5 | Interstitial Pneumonitis |
| D-5 MED-HIGH | 787 M | 651 | 4.73 | 52.08 | 12.5 | 19.5 | 03/04/71 | 02/08/79 | | 95.2 | Lung 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 | 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 | 837 M | 1283 | 8.04 | 88.48 | 14.5 | 18.8 | 07/07/71 | 07/21/77 | | 72.5 | Lung Tumor |
| D-5 MED-HIGH | 863 F | 980 | 8.48 | 93.33 | 10.5 | 17.4 | 07/07/71 | 10/21/77 | | 75.5 | Lung Tumor |

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

| DOSE GROUP | DOG IDENT | INITIAL ALVEOLAR DEPOSITION NCI | NCI/G LUNG | NCI/ KG | INHALATION EXPOSURE WEIGHT (KG) | AGE* (MO) | DATE | DATE OF DEATH | MONTHS SINCE INHALATION 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-5 MED-HIGH | 820 F | 847 | 8.56 | 94.11 | 9.0 | 18.2 | 06/08/71 | 06/01/79 | | 95.8 | Lung Tumor |
| D-5 MED-HIGH | 852 F | 1187 | 9.38 | 103.22 | 11.5 | 21.3 | 10/08/71 | 02/22/78 | | 76.5 | Lung Tumor |
| D-5 MED-HIGH | 880 F | 840 | 9.55 | 105.00 | 8.0 | 17.8 | 10/08/71 | 12/04/78 | | 85.9 | Lung Tumor |
| D-5 MED-HIGH | 889 F | 1089 | 9.90 | 108.90 | 10.0 | 16.0 | 11/10/71 | 09/20/79 | | 94.3 | Lung Tumor, Osteoarthropathy |
| D-5 MED-HIGH | 783 M | 1394 | 10.14 | 111.52 | 12.5 | 18.9 | 02/09/71 | 12/03/75 | | 57.8 | Lung Tumor |
| D-5 MED-HIGH | 804 M | 1344 | 10.18 | 112.00 | 12.0 | 20.5 | 07/07/71 | 08/18/74 | | 37.4 | Lung Tumor, Rad. 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 | 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 |
| D-5 MED-HIGH | 739 F | 1511 | 17.17 | 188.88 | 8.0 | 18.5 | 11/10/70 | 04/01/71 | | 4.7 | Sacrificed |
| D-6 HIGH | 753 F | 2448 | 23.43 | 257.68 | 9.5 | 18.5 | 12/21/70 | 10/02/76 | | 69.4 | Lung Tumor |
| D-6 HIGH | 817 M | 3164 | 23.97 | 263.67 | 12.0 | 19.2 | 07/07/71 | 03/26/73 | | 20.6 | Radiation Pneumonitis |
| D-6 HIGH | 829 M | 3515 | 24.58 | 270.38 | 13.0 | 19.1 | 07/07/71 | 09/13/73 | | 26.3 | Radiation Pneumonitis |
| D-6 HIGH | 890 F | 3101 | 31.32 | 344.56 | 9.0 | 16.0 | 11/10/71 | 06/13/74 | | 31.1 | Radiation Pneumonitis |
| D-6 HIGH | 435 F | 3840 | 33.25 | 365.71 | 10.5 | 75.5 | 11/05/70 | 11/12/70 | | 0.2 | Sacrificed |
| D-6 HIGH | 913 M | 4900 | 35.64 | 392.00 | 12.5 | 17.4 | 07/19/72 | 08/18/72 | | 1.0 | Sacrificed |
| D-6 HIGH | 906 F | 6632 | 63.46 | 698.11 | 9.5 | 15.9 | 11/09/71 | 11/22/72 | | 12.5 | Radiation Pneumonitis |
| D-6 HIGH | 896 F | 5515 | 66.85 | 735.33 | 7.5 | 16.0 | 11/10/71 | 02/12/73 | | 15.1 | Radiation Pneumonitis |
| D-6 HIGH | 747 F | 7476 | 97.09 | 1068.00 | 7.0 | 19.6 | 01/20/71 | 01/13/72 | | 11.8 | Radiation Pneumonitis |
| D-6 HIGH | 910 M | 14267 | 103.76 | 1141.36 | 12.5 | 15.9 | 11/10/71 | 10/12/72 | | 11.1 | Radiation Pneumonitis |

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

| DOSE GROUP | DOG IDENT | INITIAL ALVEOLAR DEPOSITION NCI | NCI/G LUNG | NCI/ KG | INHALATION EXPOSURE WEIGHT (KG) | AGE* (MO) | DATE | DATE OF DEATH | MONTHS SINCE INHALATION 9/30/85 | 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 | | | | 10/30/84 | | 161.7* | Malignant Lymphoma |
| CONTROL | 978 M | 0 | 0.00 | 0.00 | | | | | 172.6* | | |
| 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* | Malignant Lymphoma |
| CONTROL | 1005 M | 0 | 0.00 | 0.00 | | | | | 172.0* | | |
| CONTROL | 1007 F | 0 | 0.00 | 0.00 | | | | | 172.0* | | |
| CONTROL | 1024 M | 0 | 0.00 | 0.00 | | | | | 171.5* | | |
| CONTROL | 1038 M | 0 | 0.00 | 0.00 | | | | | 169.4* | | |
| CONTROL | 1045 M | 0 | 0.00 | 0.00 | | | | | 169.4* | | |
| CONTROL | 1054 F | 0 | 0.00 | 0.00 | | | | | 169.1* | | |
| CONTROL | 1061 F | 0 | 0.00 | 0.00 | | | | 07/07/81 | | 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 | | | | | 164.6* | | |
| CONTROL | 1112 M | 0 | 0.00 | 0.00 | | | | | 164.4* | | |
| CONTROL | 1116 F | 0 | 0.00 | 0.00 | | | | | 164.1* | | |
| CONTROL | 1186 F | 0 | 0.00 | 0.00 | | | | 07/26/85 | | 155.3* | Urinary Bladder Tumor |
| CONTROL | 1197 M | 0 | 0.00 | 0.00 | | | | | 157.0* | | |
| CONTROL | 1209 M | 0 | 0.00 | 0.00 | | | | | 156.7* | | |
| CONTROL | 1225 F | 0 | 0.00 | 0.00 | | | | | 155.9* | | |
| 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 | | 152.4 | | |
| D-1 LOWEST | 1003 M | 0 | 0.00 | 0.00 | 14.0 | 19.6 | 01/18/73 | | 152.4 | | |
| D-1 LOWEST | 1023 F | 0 | 0.00 | 0.00 | 12.5 | 19.2 | 01/18/73 | | 152.4 | | |
| D-1 LOWEST | 1039 M | 0 | 0.00 | 0.00 | 11.0 | 17.0 | 01/18/73 | | 152.4 | | |
| D-1 LOWEST | 1044 F | 0 | 0.00 | 0.00 | 11.5 | 17.0 | 01/18/73 | | 152.4 | | |
| D-1 LOWEST | 1055 M | 0 | 0.00 | 0.00 | 13.0 | 16.8 | 01/18/73 | | 152.4 | | |
| 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 | 02/08/85 | | 140.3 | Processing |
| D-1 LOWEST | 1194 F | 0 | 0.00 | 0.00 | 10.5 | 19.8 | 04/18/74 | | 137.4 | | |
| 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 | | 137.4 | | |
| 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 | | 152.4 | | |
| D-1 LOWEST | 1193 F | 2 | 0.01 | 0.16 | 12.5 | 19.8 | 04/18/74 | | 137.4 | | |
| D-1 LOWEST | 959 M | 3 | 0.02 | 0.22 | 13.5 | 19.2 | 12/19/72 | 06/22/84 | | 138.1 | Liver Abcess |

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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 9/30/85 | 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 | | 148.0 | | |
| 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 | | 139.1 | | |
| 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 | | 153.4 | | |
| D-1 LOWEST | 1106 F | 5 | 0.05 | 0.50 | 10.0 | 16.4 | 05/31/73 | 03/14/83 | | 117.4 | Osteoarthropathy |
| D-2 LOW | 1065 F | 6 | 0.05 | 0.60 | 10.0 | 18.3 | 05/31/73 | | 148.0 | | |
| 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 | | 148.0 | | |
| D-2 LOW | 1090 F | 10 | 0.08 | 0.83 | 12.0 | 17.3 | 05/31/73 | | 148.0 | | |
| D-2 LOW | 1222 M | 15 | 0.10 | 1.07 | 14.0 | 19.0 | 04/18/74 | | 137.4 | | |
| 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 | | 153.4 | | |
| 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 | 12/13/83 | | 126.4 | Round Cell Sarcoma: Kidney |
| 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 | | 153.4 | | |
| D-2 LOW | 1033 M | 17 | 0.14 | 1.55 | 11.0 | 19.1 | 02/22/73 | | 151.2 | | |
| D-2 LOW | 1036 F | 16 | 0.14 | 1.52 | 10.5 | 18.2 | 02/22/73 | | 151.2 | | |
| D-2 LOW | 1216 M | 23 | 0.16 | 1.77 | 13.0 | 19.3 | 04/18/74 | | 137.4 | | |
| D-2 LOW | 1060 F | 22 | 0.18 | 2.00 | 11.0 | 17.8 | 02/22/73 | 12/21/84 | | 141.9 | Processing |
| D-2 LOW | 981 M | 30 | 0.21 | 2.31 | 13.0 | 19.0 | 12/19/72 | | 153.4 | | |
| D-2 LOW | 1046 M | 27 | 0.22 | 2.45 | 11.0 | 18.1 | 02/22/73 | | 151.2 | | |
| D-2 LOW | 1050 F | 22 | 0.22 | 2.44 | 9.0 | 18.1 | 02/22/73 | | 151.2 | | |
| 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 | | 139.1 | | |
| D-2 LOW | 1196 F | 28 | 0.25 | 2.80 | 10.0 | 17.9 | 02/26/74 | | 139.1 | | |
| 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 | 972 F | 40 | 0.33 | 3.64 | 11.0 | 19.2 | 12/19/72 | | 153.4 | | |
| D-3 MED-LOW | 1089 F | 41 | 0.34 | 3.73 | 11.0 | 17.3 | 05/31/73 | | 148.0 | | |
| 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 | | 137.4 | | |
| 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 | | 142.8 | | |

* 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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-3 MED-LOW | 1165 M | 76 | 0.43 | 4.75 | 16.0 | 17.3 | 11/06/73 | | 142.8 | | |
| D-3 MED-LOW | 1309 M | 60 | 0.44 | 4.80 | 12.5 | 18.5 | 03/04/75 | | 126.9 | | |
| 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 | | 126.9 | | |
| 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 | 05/09/85 | | 134.4 | Lung Tumor |
| 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 | | 153.4 | | |
| 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 | | 148.0 | | |
| D-3 MED-LOW | 1000 F | 70 | 0.71 | 7.78 | 9.0 | 18.7 | 12/19/72 | | 153.4 | | |
| D-3 MED-LOW | 1056 M | 97 | 0.71 | 7.76 | 12.5 | 17.9 | 02/22/73 | | 151.2 | | |
| D-3 MED-LOW | 1004 M | 116 | 0.73 | 8.00 | 14.5 | 19.6 | 01/18/73 | | 152.4 | | |
| D-3 MED-LOW | 1026 M | 116 | 0.78 | 8.59 | 13.5 | 19.2 | 01/18/73 | | 152.4 | | |
| D-3 MED-LOW | 1043 F | 98 | 0.89 | 9.80 | 10.0 | 18.1 | 02/22/73 | 09/21/81 | | 102.9 | Empyema, Pituit.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 | Pneumonia |
| D-3 MED-LOW | 1212 F | 111 | 1.19 | 13.06 | 9.0 | 17.6 | 02/26/74 | | 139.1 | | |
| D-4 MEDIUM | 1176 M | 129 | 0.87 | 9.56 | 13.5 | 15.5 | 10/06/73 | | 143.8 | | |
| D-4 MEDIUM | 1221 F | 124 | 1.13 | 12.40 | 10.0 | 19.0 | 04/18/74 | | 137.4 | | |
| D-4 MEDIUM | 1195 M | 228 | 1.38 | 15.20 | 15.0 | 18.1 | 02/26/74 | | 139.1 | | |
| D-4 MEDIUM | 1032 M | 161 | 1.40 | 15.43 | 10.5 | 16.3 | 11/30/72 | 12/08/72 | | 0.3 | Sacrificed |
| D-4 MEDIUM | 1053 F | 148 | 1.42 | 15.58 | 9.5 | 17.9 | 02/22/73 | 02/02/85 | | 143.3 | Processing |
| D-4 MEDIUM | 997 M | 203 | 1.60 | 17.65 | 11.5 | 19.6 | 01/18/73 | | 152.4 | | |
| 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 | 03/12/85 | | 136.1 | Bone Tumor |
| 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 | 10/08/84 | | 141.6 | Bone Tumor |
| 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 | | 148.0 | | |
| D-4 MEDIUM | 1114 M | 430 | 2.70 | 29.66 | 14.5 | 16.4 | 05/31/73 | 04/23/85 | | 142.8 | Processing |
| D-4 MEDIUM | 1062 M | 435 | 2.93 | 32.22 | 13.5 | 17.8 | 02/22/73 | 05/30/84 | | 135.2 | Bone Tumor, Lung Tumor |
| D-4 MEDIUM | 934 M | 454 | 3.06 | 33.63 | 13.5 | 19.1 | 11/30/72 | 03/01/73 | | 3.0 | Sacrificed |
| D-4 MEDIUM | 1081 M | 541 | 3.07 | 33.81 | 16.0 | 18.0 | 05/31/73 | 01/18/80 | | 79.6 | Hemangiosarcoma, Heart |
| D-4 MEDIUM | 1030 F | 340 | 3.25 | 35.79 | 9.5 | 19.1 | 02/22/73 | 04/14/83 | | 121.7 | Pneumonia, Rad. Pneumonitis |
| D-4 MEDIUM | 1198 M | 539 | 3.50 | 38.50 | 14.0 | 17.9 | 02/26/74 | | 139.1 | | |
| D-4 MEDIUM | 952 F | 365 | 3.69 | 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 | Malignant Lymphoma |

* 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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-4 MEDIUM | 1220 F | 518 | 4.28 | 47.09 | 11.0 | 19.0 | 04/18/74 | | 137.4 | | |
| D-4 MEDIUM | 992 F | 555 | 4.39 | 48.26 | 11.5 | 18.8 | 12/19/72 | 07/26/84 | | 139.2 | Bone Tumor |
| D-4 MEDIUM | 983 M | 617 | 4.67 | 51.42 | 12.0 | 19.0 | 12/19/72 | 12/29/83 | | 132.3 | Adrenal & Pituitary Tumor B |
| 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 | 1035 F | 571 | 5.46 | 60.11 | 9.5 | 18.2 | 02/22/73 | 03/04/84 | | 132.3 | Bone Tumor, Cushing's Disease |
| 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-5 MED-HIGH | 1160 F | 1344 | 10.18 | 112.00 | 12.0 | 17.3 | 11/06/73 | 09/22/81 | | 94.5 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 1211 M | 1764 | 11.06 | 121.66 | 14.5 | 17.6 | 02/26/74 | 05/17/82 | | 98.6 | Bone Tumor |
| D-5 MED-HIGH | 1096 F | 1476 | 12.20 | 134.18 | 11.0 | 16.6 | 05/31/73 | 05/08/78 | | 59.2 | Addison's Disease |
| D-5 MED-HIGH | 1218 F | 1710 | 12.95 | 142.50 | 12.0 | 17.3 | 02/26/74 | 04/24/81 | | 85.9 | Bone Tumor |
| D-5 MED-HIGH | 1092 M | 1848 | 13.44 | 147.84 | 12.5 | 17.3 | 05/31/73 | 10/23/78 | | 64.8 | Bone Tumor |
| D-5 MED-HIGH | 1027 M | 2148 | 13.95 | 153.43 | 14.0 | 19.2 | 01/18/73 | 12/01/78 | | 70.4 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 1115 F | 1885 | 14.90 | 163.91 | 11.5 | 16.1 | 05/31/73 | 07/11/78 | | 61.3 | Bone Tumor |
| D-5 MED-HIGH | 974 F | 1718 | 15.62 | 171.80 | 10.0 | 20.2 | 01/18/73 | 05/24/78 | | 64.1 | Bone Tumor |
| D-5 MED-HIGH | 1079 M | 2620 | 15.88 | 174.67 | 15.0 | 18.0 | 05/31/73 | 02/12/78 | | 56.4 | Addison's Disease, G.I. Tumor |
| D-5 MED-HIGH | 1058 F | 1907 | 16.51 | 181.62 | 10.5 | 17.8 | 02/22/73 | 11/01/79 | | 80.3 | Bone Tumor, Adrenal Tumor |
| D-6 HIGH | 1002 M | 2907 | 18.88 | 207.64 | 14.0 | 19.6 | 01/18/73 | 01/21/80 | | 84.1 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 1057 M | 3116 | 20.98 | 230.81 | 13.5 | 17.9 | 02/22/73 | 03/07/79 | | 72.4 | Bone Tumor |
| D-6 HIGH | 1009 M | 3630 | 26.40 | 290.40 | 12.5 | 19.6 | 01/18/73 | 04/01/78 | | 62.4 | Lung Tumor, Osteoarthropathy |
| D-6 HIGH | 1042 F | 2959 | 28.32 | 311.47 | 9.5 | 18.1 | 02/22/73 | 11/10/78 | | 68.6 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 994 F | 3453 | 31.39 | 345.30 | 10.0 | 19.6 | 01/18/73 | 07/04/76 | | 41.5 | Addison's Disease |
| D-6 HIGH | 1006 F | 3810 | 31.49 | 346.36 | 11.0 | 19.6 | 01/18/73 | 01/18/79 | | 72.0 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 975 F | 3968 | 36.07 | 396.80 | 10.0 | 20.2 | 01/18/73 | 07/25/78 | | 66.2 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 1037 M | 4854 | 44.13 | 485.40 | 10.0 | 18.2 | 02/22/73 | 11/21/78 | | 68.9 | Bone Tumor |
| D-6 HIGH | 1143 M | 7691 | 53.78 | 591.62 | 13.0 | 18.2 | 11/06/73 | 12/05/77 | | 49.0 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 1025 M | 8479 | 57.10 | 628.07 | 13.5 | 19.2 | 01/18/73 | 03/17/77 | | 49.9 | Lung Tumor |
| D-6 HIGH | 1064 M | 9453 | 63.66 | 700.22 | 13.5 | 16.7 | 01/18/73 | 04/14/77 | | 50.8 | Bone Tumor, Lung Tumor |
| D-6 HIGH | 1162 F | 6959 | 70.29 | 773.22 | 9.0 | 17.3 | 11/06/73 | 12/19/78 | | 61.4 | Bone Tumor, Addison's Disease |
| D-6 HIGH | 1175 F | 6201 | 75.16 | 826.80 | 7.5 | 16.6 | 11/06/73 | 02/24/78 | | 51.6 | Lung Tumor |

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INHALED PLUTONIUM NITRATE IN DOGS

| DOSE GROUP | DOG IDENT | INITIAL ALVEOLAR DEPOSITION NCI | NCI/G LUNG | NCI/ KG | INHALATION EXPOSURE WEIGHT (KG) | AGE* (MO) | DATE | DATE OF DEATH | MONTHS SINCE INHALATION 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 1356 M | 0 | 0.00 | 0.00 | | | | | 136.7* | | |
| CONTROL | 1365 M | 0 | 0.00 | 0.00 | | | | | 136.6* | | |
| 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 | | | | | 135.3* | | |
| CONTROL | 1405 M | 0 | 0.00 | 0.00 | | | | 08/13/84 | | 121.3* | Heart Base Tumor |
| CONTROL | 1409 M | 0 | 0.00 | 0.00 | | | | | 134.8* | | |
| CONTROL | 1418 M | 0 | 0.00 | 0.00 | | | | | 134.5* | | |
| 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 | | | | | 133.8* | | |
| CONTROL | 1483 F | 0 | 0.00 | 0.00 | | | | | 132.9* | | |
| CONTROL | 1509 M | 0 | 0.00 | 0.00 | | | | | 132.1* | | |
| CONTROL | 1516 F | 0 | 0.00 | 0.00 | | | | | 131.8* | | |
| CONTROL | 1525 M | 0 | 0.00 | 0.00 | | | | | 131.6* | | |
| CONTROL | 1526 M | 0 | 0.00 | 0.00 | | | | | 131.6* | | |
| CONTROL | 1528 F | 0 | 0.00 | 0.00 | | | | | 131.1* | | |
| CONTROL | 1543 M | 0 | 0.00 | 0.00 | | | | | 130.9* | | |
| CONTROL | 1563 F | 0 | 0.00 | 0.00 | | | | | 120.8* | | |
| CONTROL | 1572 F | 0 | 0.00 | 0.00 | | | | | 120.7* | | |
| CONTROL | 1577 M | 0 | 0.00 | 0.00 | | | | | 120.7* | | |
| CONTROL | 1584 F | 0 | 0.00 | 0.00 | | | | | 120.6* | | |
| CONTROL | 1594 F | 0 | 0.00 | 0.00 | | | | | 120.6* | | |
| CONTROL | 1608 M | 0 | 0.00 | 0.00 | | | | | 120.3* | | |
| CONTROL | 1633 F | 0 | 0.00 | 0.00 | | | | | 113.6* | | |
| CONTROL | 1638 F | 0 | 0.00 | 0.00 | | | | | 113.3* | | |
| VEHICLE | 1361 M | 0 | 0.00 | 0.00 | 8.5 | 21.0 | 02/13/76 | | 115.5 | | |
| VEHICLE | 1381 F | 0 | 0.00 | 0.00 | 8.5 | 19.8 | 02/13/76 | | 115.5 | | |
| VEHICLE | 1392 M | 0 | 0.00 | 0.00 | 13.0 | 22.0 | 04/22/76 | | 113.3 | | |
| VEHICLE | 1406 M | 0 | 0.00 | 0.00 | 13.5 | 21.6 | 04/22/76 | | 113.3 | | |
| VEHICLE | 1412 F | 0 | 0.00 | 0.00 | 9.0 | 19.0 | 02/13/76 | | 115.5 | | |
| VEHICLE | 1421 M | 0 | 0.00 | 0.00 | 13.0 | 23.3 | 06/23/76 | | 111.2 | | |
| VEHICLE | 1457 F | 0 | 0.00 | 0.00 | 12.0 | 20.6 | 04/22/76 | | 113.3 | | |
| VEHICLE | 1491 F | 0 | 0.00 | 0.00 | 8.0 | 21.6 | 06/23/76 | | 111.2 | | |
| VEHICLE | 1504 F | 0 | 0.00 | 0.00 | 10.0 | 20.9 | 06/23/76 | | 111.2 | | |
| VEHICLE | 1514 M | 0 | 0.00 | 0.00 | 14.0 | 20.9 | 06/23/76 | 08/06/82 | | 73.4 | Malignant Lymphoma |
| VEHICLE | 1524 M | 0 | 0.00 | 0.00 | 12.0 | 21.5 | 07/27/76 | | 110.1 | | |
| VEHICLE | 1531 F | 0 | 0.00 | 0.00 | 9.0 | 20.9 | 07/27/76 | | 110.1 | | |
| VEHICLE | 1542 M | 0 | 0.00 | 0.00 | 12.0 | 20.8 | 07/27/76 | | 110.1 | | |
| VEHICLE | 1566 M | 0 | 0.00 | 0.00 | 14.0 | 18.3 | 03/15/77 | | 102.5 | | |
| VEHICLE | 1578 M | 0 | 0.00 | 0.00 | 10.5 | 18.2 | 03/15/77 | | 102.5 | | |
| VEHICLE | 1593 F | 0 | 0.00 | 0.00 | 11.0 | 18.0 | 03/15/77 | | 102.5 | | |
| VEHICLE | 1601 F | 0 | 0.00 | 0.00 | 8.5 | 18.0 | 03/15/77 | | 102.5 | | |

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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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VEHICLE | 1620 M | 0 | 0.00 | 0.00 | 11.0 | 21.1 | 12/01/77 | | 94.0 | | |
| VEHICLE | 1634 F | 0 | 0.00 | 0.00 | 10.5 | 19.6 | 12/01/77 | | 94.0 | | |
| VEHICLE | 1651 F | 0 | 0.00 | 0.00 | 11.0 | 19.2 | 12/01/77 | | 94.0 | | |
| D-1 LOWEST | 1416 M | 0 | 0.00 | 0.00 | 12.0 | 22.1 | 05/20/76 | | 112.4 | | |
| D-1 LOWEST | 1458 F | 0 | 0.00 | 0.00 | 10.5 | 21.5 | 05/20/76 | | 112.4 | | |
| D-1 LOWEST | 1489 F | 0 | 0.00 | 0.00 | 8.0 | 20.5 | 05/20/76 | 08/04/84 | | 98.5 | Esophageal Tumor |
| 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 | | 112.4 | | |
| D-1 LOWEST | 1573 M | 0 | 0.00 | 0.00 | 11.5 | 19.4 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1581 M | 0 | 0.00 | 0.00 | 16.5 | 19.3 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1596 M | 0 | 0.00 | 0.00 | 14.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1600 F | 1 | 0.01 | 0.11 | 11.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1603 M | 2 | 0.01 | 0.12 | 14.0 | 19.2 | 04/19/77 | | 101.4 | | |
| 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 | | 112.4 | | |
| D-1 LOWEST | 1570 F | 2 | 0.02 | 0.18 | 10.0 | 19.4 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1465 F | 4 | 0.03 | 0.35 | 12.0 | 21.0 | 05/20/76 | | 112.4 | | |
| 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 | | 112.4 | | |
| D-1 LOWEST | 1592 F | 4 | 0.03 | 0.29 | 13.5 | 19.2 | 04/19/77 | | 101.4 | | |
| D-1 LOWEST | 1607 M | 5 | 0.03 | 0.35 | 13.0 | 19.0 | 04/19/77 | | 101.4 | | |
| 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 | | 112.4 | | |
| D-1 LOWEST | 1583 F | 4 | 0.04 | 0.40 | 9.5 | 19.2 | 04/19/77 | | 101.4 | | |
| 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 | 09/28/85 | | 101.3 | Processing |
| D-2 LOW | 1513 M | 0 | 0.00 | 0.00 | 11.5 | 19.8 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1520 M | 1 | 0.01 | 0.12 | 10.5 | 19.5 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1415 M | 2 | 0.02 | 0.20 | 11.5 | 22.2 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1575 M | 3 | 0.02 | 0.19 | 14.0 | 19.4 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1466 F | 5 | 0.03 | 0.37 | 14.0 | 21.0 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1606 F | 5 | 0.04 | 0.42 | 12.5 | 19.0 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1579 M | 8 | 0.05 | 0.59 | 14.0 | 19.3 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1590 F | 6 | 0.05 | 0.51 | 12.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1585 F | 8 | 0.06 | 0.68 | 12.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1567 M | 10 | 0.07 | 0.77 | 12.0 | 19.4 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1580 F | 9 | 0.07 | 0.82 | 11.0 | 19.3 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1591 M | 11 | 0.07 | 0.76 | 15.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1417 M | 11 | 0.08 | 0.89 | 12.0 | 22.1 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1423 M | 10 | 0.08 | 0.87 | 11.0 | 22.1 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1472 F | 10 | 0.09 | 1.01 | 10.0 | 21.0 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1503 F | 9 | 0.09 | 1.03 | 8.5 | 19.8 | 05/20/76 | 12/13/84 | | 102.8 | Thyroid Tumor |
| D-2 LOW | 1602 M | 15 | 0.09 | 1.03 | 14.5 | 19.2 | 04/19/77 | | 101.4 | | |

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

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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-2 LOW | 1484 F | 11 | 0.10 | 1.08 | 10.0 | 20.5 | 05/20/76 | | 112.4 | | |
| D-2 LOW | 1599 F | 10 | 0.10 | 1.14 | 9.0 | 19.2 | 04/19/77 | | 101.4 | | |
| D-2 LOW | 1490 F | 16 | 0.15 | 1.65 | 9.5 | 20.5 | 05/20/76 | | 112.4 | | |
| 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 | 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 | | 113.3 | | |
| D-3 MED-LOW | 1389 M | 27 | 0.23 | 2.54 | 10.5 | 21.9 | 04/20/76 | 05/04/76 | | 0.5 | Sacrificed |
| D-3 MED-LOW | 1413 F | 29 | 0.24 | 2.68 | 11.0 | 18.2 | 01/20/76 | 03/01/85 | | 109.3 | Malignant Lymphoma |
| 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 | | 102.5 | | |
| D-3 MED-LOW | 1595 M | 50 | 0.29 | 3.23 | 15.5 | 18.0 | 03/15/77 | | 102.5 | | |
| 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 | 07/22/85 | | 111.0 | Processing |
| D-3 MED-LOW | 1587 M | 53 | 0.31 | 3.40 | 15.5 | 18.1 | 03/15/77 | | 102.5 | | |
| 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 | | 110.3 | | |
| 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 | | 102.5 | | |
| 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 | | 113.3 | | |
| D-3 MED-LOW | 1439 F | 53 | 0.42 | 4.61 | 11.5 | 21.0 | 04/20/76 | | 113.3 | | |
| D-3 MED-LOW | 1523 F | 55 | 0.42 | 4.60 | 12.0 | 21.3 | 07/22/76 | | 110.3 | | |
| 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 | | 116.3 | | |
| 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 | | 102.5 | | |
| 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 | | 102.5 | | |
| 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 | | 113.3 | | |
| D-3 MED-LOW | 1522 F | 78 | 0.71 | 7.78 | 10.0 | 21.3 | 07/22/76 | 10/18/76 | | 2.9 | Sacrificed |
| D-3 MED-LOW | 1363 M | 85 | 0.74 | 8.09 | 10.5 | 20.2 | 01/20/76 | | 116.3 | | |
| D-3 MED-LOW | 1604 M | 85 | 0.74 | 8.10 | 10.5 | 18.0 | 03/15/77 | | 102.5 | | |
| D-3 MED-LOW | 1530 F | 72 | 0.76 | 8.41 | 8.5 | 20.8 | 07/22/76 | | 110.3 | | |
| D-3 MED-LOW | 1456 F | 61 | 0.79 | 8.68 | 7.0 | 20.5 | 04/20/76 | | 113.3 | | |
| D-3 MED-LOW | 1598 F | 93 | 1.06 | 11.65 | 8.0 | 18.0 | 03/15/77 | 03/10/82 | | 59.8 | Sacrificed |
| D-3 MED-LOW | 1422 F | 99 | 1.12 | 12.35 | 8.0 | 18.1 | 01/20/76 | | 116.3 | | |
| D-4 MEDIUM | 1637 M | 192 | 1.45 | 15.99 | 12.0 | 18.9 | 11/07/77 | | 94.8 | | |

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

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 9/30/85 | 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 | 06/07/85 | | 106.5 | Bone Tumor, Lung Tumor |
| D-4 MEDIUM | 1656 M | 211 | 1.54 | 16.90 | 12.5 | 18.4 | 11/07/77 | | 94.8 | | |
| D-4 MEDIUM | 1379 M | 278 | 1.74 | 19.16 | 14.5 | 19.1 | 01/20/76 | | 116.3 | | |
| D-4 MEDIUM | 1362 M | 267 | 1.87 | 20.54 | 13.0 | 20.2 | 01/20/76 | | 116.3 | | |
| D-4 MEDIUM | 1639 F | 248 | 2.05 | 22.57 | 11.0 | 18.5 | 11/07/77 | | 94.8 | | |
| D-4 MEDIUM | 1647 M | 294 | 2.05 | 22.58 | 13.0 | 18.5 | 11/07/77 | | 94.8 | | |
| 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 | | 94.8 | | |
| D-4 MEDIUM | 1534 M | 295 | 2.14 | 23.57 | 12.5 | 20.8 | 07/22/76 | 05/26/85 | | 106.1 | Congestive Heart Failure |
| D-4 MEDIUM | 1414 F | 233 | 2.35 | 25.86 | 9.0 | 18.2 | 01/20/76 | | 116.3 | | |
| D-4 MEDIUM | 1618 F | 277 | 2.40 | 26.36 | 10.5 | 20.3 | 11/07/77 | | 94.8 | | |
| 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 | | 113.3 | | |
| D-4 MEDIUM | 1535 F | 345 | 3.13 | 34.48 | 10.0 | 20.7 | 07/22/76 | | 110.3 | | |
| D-4 MEDIUM | 1446 F | 354 | 3.22 | 35.40 | 10.0 | 21.0 | 04/20/76 | | 113.3 | | |
| D-4 MEDIUM | 1364 M | 463 | 3.24 | 35.65 | 13.0 | 20.2 | 01/20/76 | 08/02/84 | | 102.4 | Lung Tumor |
| D-4 MEDIUM | 1387 F | 345 | 4.48 | 49.30 | 7.0 | 19.0 | 01/20/76 | 08/13/80 | | 54.8 | Bone Tumor |
| D-5 MED-HIGH | 1329 F | 363 | 3.30 | 36.27 | 10.0 | 18.0 | 10/16/75 | 11/14/75 | | 1.0 | Sacrificed |
| D-5 MED-HIGH | 1346 M | 656 | 4.42 | 48.59 | 13.5 | 17.2 | 10/16/75 | 11/14/75 | | 1.0 | Sacrificed |
| D-5 MED-HIGH | 1648 M | 811 | 5.90 | 64.90 | 12.5 | 18.5 | 11/07/77 | 07/11/85 | | 92.1 | Processing |
| 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 | 11/19/84 | | 84.4 | Bone Tumor, Lung Tumor |
| 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 | 06/28/85 | | 91.7 | Lung Tumor |
| D-5 MED-HIGH | 1660 M | 1518 | 10.22 | 112.41 | 13.5 | 18.3 | 11/07/77 | 09/05/84 | | 81.9 | 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 | 03/18/85 | | 88.3 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 1652 F | 1320 | 12.00 | 131.95 | 10.0 | 18.4 | 11/07/77 | 07/20/83 | | 68.4 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 1619 F | 1490 | 12.32 | 135.50 | 11.0 | 20.3 | 11/07/77 | 01/21/83 | | 62.5 | Bone Tumor |
| D-5 MED-HIGH | 1512 M | 2411 | 14.61 | 160.71 | 15.0 | 20.9 | 06/23/76 | 12/23/79 | | 42.0 | Bone Tumor |
| D-5 MED-HIGH | 1419 M | 1559 | 14.92 | 164.11 | 9.5 | 23.3 | 06/23/76 | 10/22/82 | | 76.0 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 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 | 1502 F | 3008 | 20.25 | 222.80 | 13.5 | 20.9 | 06/23/76 | 01/21/81 | | 55.0 | Bone Tumor, Lung Tumor |
| D-5 MED-HIGH | 1485 F | 2330 | 21.18 | 233.00 | 10.0 | 21.7 | 06/23/76 | 12/30/80 | | 54.2 | Bone Tumor |
| D-5 MED-HIGH | 1471 F | 2508 | 21.71 | 238.82 | 10.5 | 22.1 | 06/23/76 | 05/01/79 | | 34.2 | Radiation Pneumonitis |
| D-5 MED-HIGH | 1492 F | 2473 | 24.98 | 274.82 | 9.0 | 21.6 | 06/23/76 | 10/16/80 | | 51.8 | Bone Tumor |
| D-5 MED-HIGH | 1459 F | 2645 | 26.72 | 293.89 | 9.0 | 22.6 | 06/23/76 | 09/25/80 | | 51.1 | Rad. Pneumonitis, Lung Tumor |
| 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 |

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

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 9/30/85 | DEATH | COMMENTS ON DEAD DOGS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D-6 HIGH | 1420 M | 3840 | 30.36 | 333.91 | 11.5 | 23.3 | 06/23/76 | 07/12/78 | | 24.6 | Radiation Pneumonitis |
| D-6 HIGH | 1517 F | 5185 | 49.62 | 545.79 | 9.5 | 20.6 | 06/23/76 | 11/02/77 | | 16.3 | Radiation Pneumonitis |
| D-6 HIGH | 1510 F | 6969 | 55.09 | 606.02 | 11.5 | 20.9 | 06/23/76 | 11/09/77 | | 16.6 | Radiation Pneumonitis |
| D-6 HIGH | 1424 M | 7681 | 69.83 | 768.12 | 10.0 | 23.2 | 06/23/76 | 08/31/77 | | 14.3 | Radiation Pneumonitis |

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

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# PRESENTATIONS

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Bean, R. M., D. D. Dauble, B. L. Thomas, R. W. Hanf, and E. K. Chess. "Factors Affecting Bioabsorption, Metabolism and Storage of Organic Compounds by Aquatic Biota." Presented at the 24th Hanford Life Sciences Symposium, October 21-24, 1985, Richland, Washington.

Braby, L. A. "A Portable Dose Equivalent Meter Based on Microdosimetry." Presented at the Eighth Conference on the Application of Accelerators in Research and Industry, November 12-14, 1984, Denton, Texas.

Braby, L. A., N. F. Metting, and J. M. Nelson. "Unrepaired Damage in Plateau Phase CHO Cells: Potentially Lethal or Sublethal." Presented at the 34th Annual Meeting of the Radiation Research Society, Radiation Physics, April 13-17, 1985, Las Vegas, Nevada.

Braby, L. A., J. M. Nelson, N. F. Metting, and W. C. Roesch. "Differences in the Repair of Oxygen-Dependent and -Independent Radiation Damage." Presented at the 33rd Annual Meeting of the Radiation Research Society, May 4-9, 1985, Los Angeles, California.

Braby, L. A., C. A. Ratcliffe, and N. F. Metting. "A Portable Microdosimetry System." Presented at the Fifth Symposium on Neutron Dosimetry, September 17-21, 1984, Munich, West Germany.

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Braby, L. A., C. A. Ratcliffe, and N. F. Metting. "Evaluation of a Portable Microdosimetry System." Presented at the Workshop on Practical Implementation of Microdosimetric Counters in Radiation Protection, European Radiation Dosimetry Group, United Kingdom and Universitat Des Saarlandes, West Germany, May 15-17, 1984, Homburg/Saar, West Germany.

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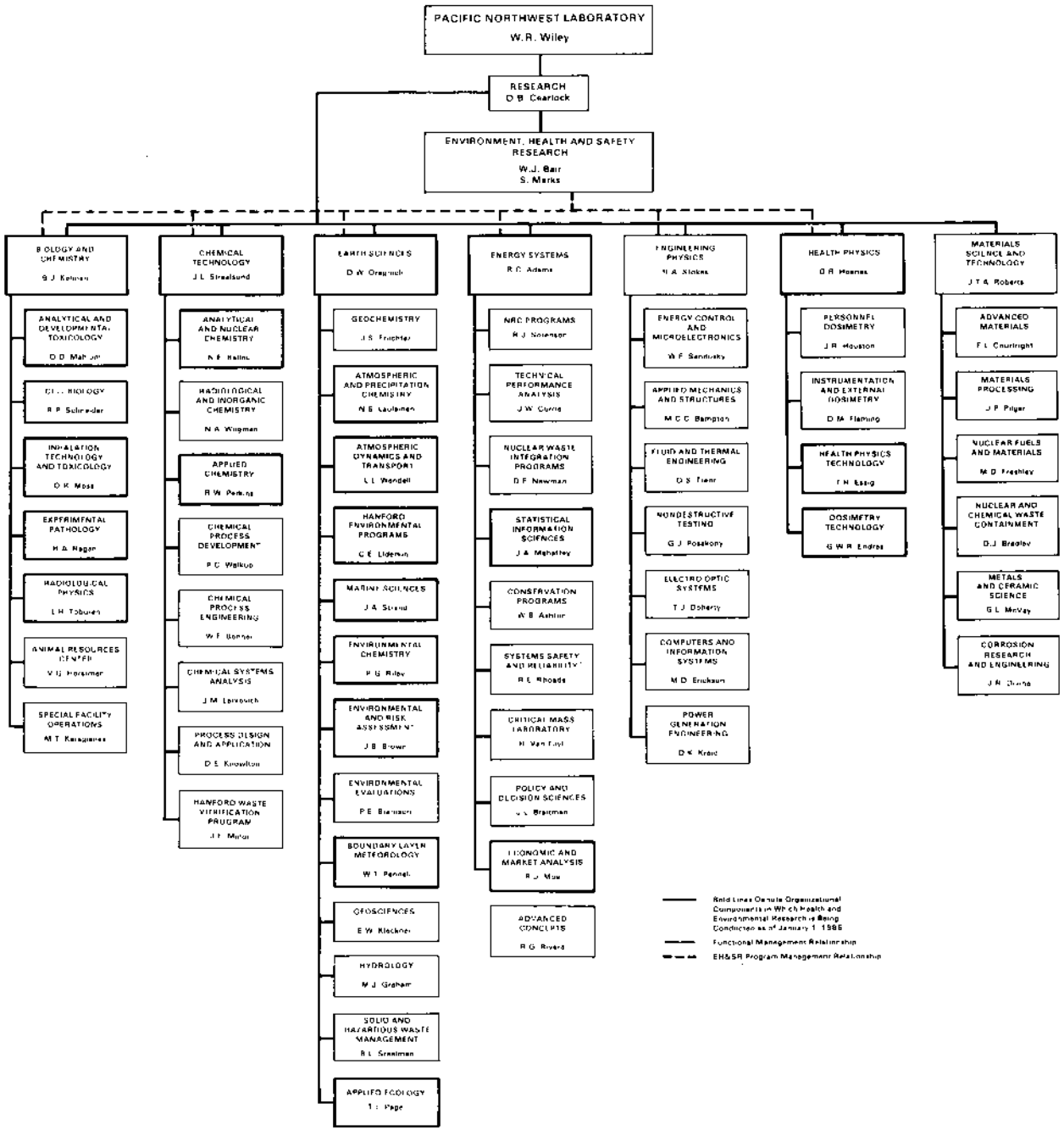

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