PNL-6500 Pt. 1
UC-408

17

Pacific Northwest Laboratory Annual Report for 1987 to the DOE Office of Energy Research

Part 1 Biomedical Sciences
February 1988

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

Pacific Northwest Laboratory
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J. F. Park and Staff

February 1988

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Pacific Northwest Laboratory
Richland, Washington 99352

PREFACE

This 1987 Annual Report from Pacific Northwest Laboratory (PNL) to the U.S. Department of Energy (DOE) describes research in environment, safety and health conducted during fiscal year 1987. The report again consists of five parts, each in a separate volume.

The five parts of the report are oriented to particular segments of the PNL 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 1987 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 — S.G. Weiss, Report Coordinator
G.P. O'Connor, Editor

Part 3: Atmospheric Sciences
Program Manager: C.E. Elderkin — C.E. Elderkin, Report Coordinator
E.L. Owczarski, Editor

Part 4: Physical Sciences
Program Manager: L.H. Toburen — L.H. Toburen, Report Coordinator
P.L. Gurwell, Editor

Part 5: Environment, Safety, Health, and Quality Assurance
Program Managers: L.G. Faust — L.G. Faust and B.L. Steelman, Report Coordinators
B.L. Steelman — S.K. Ennor, M.T. Upton, and J.M. Gephart, Editors
J.M. Selby

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 the many scientists who performed the research and wrote the individual project reports, to the progam 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.

Members of the Scientific Advisory Committee, established in 1985, are:

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Dr. Albert W. Johnson	San Diego State University
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W.J. Bair, Manager
Environment, Health and Safety
Research Program

Previous reports in this series:

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1952	HW-27814, HW-28636
1953	HW-30437, HW-30464
1954	HW-30306, HW-33128, HW-35905, HW-35917
1955	HW-39558, HW-41315, HW-41500
1956	HW-47500
1957	HW-53500
1958	HW-59500
1959	HW-63824, HW-65500
1960	HW-69500, HW-70050
1961	HW-72500, HW-73337
1962	HW-76000, HW-77609
1963	HW-80500, HW-81746
1964	BNWL-122
1965	BNWL-280, BNWL-235, Vol. 1-4; BNWL-361
1966	BNWL-480, Vol. 1; BNWL-481, Vol. 2, Pt. 1-4
1967	BNWL-714, Vol. 1; BNWL-715, Vol. 2, Pt. 1-4
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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
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1979	PNL-3300, Pt. 1-5
1980	PNL-3700, Pt. 1-5
1981	PNL-4100, Pt. 1-5
1982	PNL-4600, Pt. 1-5
1983	PNL-5000, Pt. 1-5
1984	PNL-5500, Pt. 1-5
1985	PNL-5750, Pt. 1-5
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FOREWORD

This report summarizes progress on OHER biomedical and health-effects research conducted at PNL in FY 1987. The research develops the knowledge and scientific principles necessary to identify, understand, and anticipate the long-term health consequences of energy-related radiation and chemicals. Our continuing emphasis is to decrease the uncertainty of health-effects risk estimates from existing and/or developing energy-related technologies through an increased understanding of how radiation and chemicals cause health effects.

The report is arranged to reflect PNL research relative to OHER programmatic structure. The first section, on human health effects, concerns statistical and epidemiological studies for assessing health risks. The next section, which contains reports of health-effects research in biological systems, includes research with radiation and chemicals. The last section is related to medical applications of nuclear technology.

Human Health Effects

The section on human health and risk assessments reports the status of epidemiologic studies, including occupational studies of the Hanford worker population and a molecular study based on Japanese bomb survivor data; of a major database design effort, to assess experimentally derived dose-effect data; and of an evaluation of the benefit versus cost of selected OHER-funded research programs.

In these studies, analyses of causes of mortality in the Hanford worker population were updated; the related lung-cancer study was finalized; the prevalence and case control studies of congenital malformations in infants of occupationally exposed parents were published; and efforts to pool data from worker studies at several DOE facilities were initiated. In Japanese atomic-bomb survivors, data on lung and stomach cancer cases (and appropriate controls) and on prediagnosis levels of serum ferritin and transferrin are being analyzed to study iron stores and risk of cancer. High levels of iron stores are hypothesized to increase cancer risks.

An integrated database of pathological and dosimetric data from five OHER-supported laboratories that conduct lifespan dose-effects studies in beagle dogs was designed. The pathological observation terminology at the five laboratories was standardized so that reporting is consistent.

In a study of the benefit versus cost of OHER-funded research for case studies of three representative projects, investigators concluded that OHER projects have produced results beneficial to DOE, to other agencies, and to industry.

Health Effects Research in Biological Systems

The section on health effects of radiation in biological systems contains results from experimental animal inhalation dose-effect-relationship studies with inhaled radionuclides. Lifespan studies in dogs with inhaled $^{239}PuO_2$, $^{238}PuO_2$, and $^{239}Pu(NO_3)_4$ are summarized to 16, 13, and 10 years after exposure, respectively. The primary plutonium-exposure-related causes of death are lung cancer with inhaled $^{239}PuO_2$ and lung and bone cancer with inhaled $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$. 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. Thus far, the data suggest a threshold dose of about 100 to 200 rad for lung-tumor induction. These lifespan studies are also examining the influence of gender and strain on plutonium-induced pulmonary carcinogenesis. In addition, the pathogenesis and microdosimetry of plutonium-induced lesions are evaluated, using scanning electron microscopy autoradiography. Studies are also in progress in rats with inhaled radon daughters to determine the influence of dose and dose rate on lung-tumor incidence. Ten-working-level (WL) exposure rates show a nonsignificant increase in lung-tumor risk over 100-WL exposure rates for 320-working-level month (WLM) exposures, suggesting a tapering off of the previously observed inverse exposure rate effect at occupational and environmental rates of radon exposure. Mechanistic studies of radon injury are examining the role of oncogenes, epidermal growth factors and their receptors in radon- and/or cigarette-smoke-induced pulmonary carcinogenesis. A radon cellular-exposure system is being used for in vitro studies of DNA damage and repair, and improved animal radon-exposure systems have been developed.

Studies to examine the role of oncogenes in radiation-induced lung cancer are utilizing tumor tissue from the animal studies described above. The DNA from lung tumors of dogs exposed to plutonium and leukemia cells from dogs exposed to external gamma irradiation have undergone changes in known oncogene sequences. Changes consistent with rearrangements, gene amplification, or enhanced transcription have been found for Ki-ras, N-ras, myb fms and sis oncogene-related sequences. The data suggest greater changes in the DNA than those observed with chemical carcinogens.

Studies to understand the mechanisms of tumor initiation for chemicals have shown that the tumor-initiating activity of benzo[a]pyrene (BaP) was decreased by coadministration with complex organic mixtures. Furthermore, binding of ^{3}H-BaP to epidermal DNA, under conditions identical to those used for tumor initiation, resulted in a decrease in amounts of BaP bound to the DNA. High-performance liquid chromatography radioactivity profiles of enzyme-hydrolyzed, adducted DNA demonstrated that, in the presence of the mixtures, the predominant adducts were derived from BaP-diol epoxides; however, the mixtures changed the ratios of the two common isomeric forms of BaP adducts. These data demonstrated that both DNA binding and adducts profiles are important in determining the contribution of a known carcinogen to tumor initiation by mixtures. Efforts to prepare large (µg) quantities of adducts for chemical characterization studies were successful when hepatocytes were incubated with purified DNA and polycyclic aromatic hydrocarbons. The BaP adduct profiles were identical to those obtained from mouse skin under conditions that resulted in the appearance of tumors.

In our developmental studies, injection of neonatal, juvenile, and weanling rats with ^{233}U citrate decreased the growth rate of weanlings relative to that of controls. These ^{233}U exposures did not produce mortality, nor was mortality affected in rats that were subsequently injected with another nephrotoxic agent. Based on previously obtained data, models are being developed to estimate placental transfer and fetal placental distribution of heavy metals. In other studies, we are attempting to determine the morphological changes in the hypoplastic lungs of rat fetuses; the hypoplasia was induced by treatment with complex organic mixtures. The functional impairment observed resulted from early abnormal development of the alveolar region, resulting in less organization in the interstitial tissue and increased alveolar septal thickness at birth; bronchial and bronchiolar regions appeared normal. The effects are related to the influence of the chemicals on lung maturation and differentiation.

Our mutational research is developing a system to study molecular mechanisms that govern genetic hotspots that have unusually high mutation rates. DNA targets in the range of 50 to 100 base pairs have been synthesized and inserted into a target gene of a plasmid. The plasmid is then transformed into a target cell of *Salmonella typhimurium*, which has a genetic background advantageous for mutagenesis experiments.

This health-effects research is an interdisciplinary effort requiring scientific contributions from many research departments at PNL. The personnel in the Biology and Chemistry Department and the Computational Sciences Department are the principal contributors to this report.

Requests for reprints from the list of publications for 1987 will be honored while supplies last.

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Human
Health Effects
Research

• Statistical Health Effects Studies

Principal Investigator: E. S. Gilbert

Other Investigators: J. A. Buchanan and N. A. Holter

The purpose of this project is to provide statistical methodology for evaluating the impact of energy-related activities on health. A major component of this study is the application of these methods to data on the mortality of workers at the Hanford Site. In the past year, statistical methods have been developed to more adequately handle highly skewed exposure distributions, and to account for the dependence of health risks on factors such as age at exposure, sex, and time from exposure. These methods have been applied to the Hanford mortality data. In addition, efforts are underway to conduct analyses of combined data from several facilities involving low-level exposure to radiation. A study of congenital malformations occurring in Tri-Cities hospitals has also been completed.

The most direct approach to assessing human health risks resulting from exposure to low levels of ionizing radiation (and other exposures involved in energy technologies) is the analysis of epidemiological data on human populations that have been exposed at the levels of interest. The objectives of this project are to develop appropriate statistical methods for analyzing such data, and to apply these methods to health effects data on workers at the Hanford site.

Hanford Worker Mortality Data

Updated analyses of the Hanford worker mortality data have been completed and submitted for journal publication. These results were described in the 1986 Annual Report. Two refinements in the analysis of these data have been recently implemented. The first made use of a computer simulation method, while the second provided an approach to account for factors such as time from exposure.

Because of the highly skewed exposure distribution in the Hanford worker study, the usual statistical approximations used to calculate significance levels for tests of the null hypothesis and confidence limits for risks estimates may be inadequate for types of cancer with only a small number of deaths. For this reason, a computer simulation method was developed to provide a more accurate assessment of significance levels for diseases showing suggestive associations, and to provide more accurate confidence limits for rarer diseases, including multiple myeloma and leukemia. The application of this simulation method to the Hanford data indicated that Hanford multiple myeloma risks were clearly inconsistent with those observed in the Japanese atomic bomb survivors. Although the Hanford-based estimate for leukemia risks was negative, the upper confidence limit was about two or three times the linear-quadratic estimate provided by the BEIR III Committee. This result can be interpreted as indicating that the Hanford data have provided direct confirmation, at the dose levels of interest, that extreme departures from current leukemia risk estimates can be excluded.

A precise comparison of Hanford-based and atomic bomb survivor-based estimates requires careful attention to factors such as age at exposure, time from exposure, and sex, since risks have been shown to depend on all these factors. Although the role of these factors cannot be assessed using Hanford data alone, the consistency of the data with patterns of risk that have been observed at high levels of exposure can be examined, and these patterns can be taken into account in calculating risk estimates. For example, leukemia risks have been shown to increase, then decrease, with time from exposure, reaching a peak at 5 to 10 years after exposure. Thus, it may be appropriate to weight doses received within a few years of the time at risk more heavily than doses received many years earlier.

Analyses accounting for the factors noted above were conducted for leukemia, with the objective of comparing Hanford-based estimates with those based on the model provided in the Report of the National Institutes of Health (NIH) Ad Hoc Working Group to Develop Radioepidemiological Tables. These analyses indicated that the Hanford-based upper confidence limit was about three times the estimate provided by the NIH Report and about the same as the factor obtained from the BEIR III comparison, given earlier. However, because of the more careful attention to time from exposure and other factors, a stronger case can be made for the appropriateness of the latter comparison.

Pooling Department of Energy (DOE) Facilities Data

Efforts to implement the pooling of data from studies of populations at different DOE facilities have been initiated. These efforts have included meetings of investigators conducting these studies and a preliminary decision regarding who will conduct analyses for various aspects of the pooling. PNL will be responsible for the analysis of

external exposure data, with the first analyses including pooled data from Hanford, Oak Ridge National Laboratory, and Rocky Flats. Other facilities to be added in the future are Mound Laboratory, the Savannah River Plant, and Los Alamos National Laboratory. These pooled analyses will apply comparable methodology to all study populations, and are expected to provide greater power for detecting effects and a better understanding of differences in the groups studied. The possibility of pooling on an international basis has also been discussed at meetings of investigators who conduct studies of workers in the U.S., Canada, and Great Britain. International pooling is expected to received further attention in the future.

Congenital Malformation Studies

Two papers describing the results of a study of congenital malformations will be published in the *American Journal of Epidemiology* in February 1988. The data for these papers included information on cases of congenital malformations among infants born during the period 1957-1980 (case-control study) and 1968-1980 (prevalence study) in the three hospitals in Richland, Kennewick, and Pasco, WA. The first paper describes case-control analyses and addresses the question of whether parental occupational exposure to low-level ionizing radiation is associated with an increased risk of congenital malformations in their offspring. The second paper describes prevalence-at-birth analyses and compares rates to appropriate comparison populations.

The case-control analyses were based on 672 malformation cases and 977 matched controls. Twelve specific malformation types were analyzed for evidence of association with occupational exposure to ionizing radiation. Neural tube defects (including anencephaly and spina bifida) showed a statistically significant association with parental preconception exposure, but the association was based on a small number of cases. Eleven other defects, including Down's syndrome, for which an association with radiation was considered most likely, did not show evidence of such association. When all malformations were analyzed as a group, the relationship of parental exposure to radiation before conception was in the positive direction, but was not statistically significant ($0.05 < P < 0.10$). In view of strong contradictory evidence, based on the lack of demonstrated effects in genetic studies of atomic bomb survivors in Hiroshima and Nagasaki, the observed correlations are unlikely to have resulted from a cause-and-effect association with parental radiation exposure.

In prevalence-at-birth analyses, 454 malformation cases were identified among 23,319 births, yielding a malformation rate of about 20 per 1000 births. This rate is similar to that reported in other studies. Rates of specific malformations that were ascertained during the first year of life were compared with the combined rates from the states of Washington, Oregon, and Idaho, obtained from the Birth Defects Monitoring Program (BDMP). Among defects that would be expected to be comparably ascertained, neural tube defects were found to be significantly elevated; 40 cases were observed, compared with 23 cases expected. The cleft lip rate was found to be significantly lower than the BDMP rate; 12 cases were observed compared with 23 cases expected. Comparisons for other defects, including Down's syndrome, did not provide evidence that rates were either significantly high or low for the Tri-Cities area.

The excess of 17 cases of neural tube defects cannot possibly be explained by employment of the parents at Hanford, since in only 7 of the total of 40 cases were parents so employed. Estimated releases of radiation to the general public from Hanford operations have been far too low to explain the excess. Rates for neural tube defects show wide geographic variation and, although rates for this study were higher than rates usually observed in the western U.S., the rates are comparable to those observed in the eastern U.S. The etiology of neural tube defects is poorly understood, and excesses have been identified in other geographical areas, without an explanation.

Overall, there are no findings in the congenital malformation studies that can be appropriately interpreted as indicating that adverse effects result from either employment at Hanford or releases from Hanford operations. The papers describing these studies have been reviewed by the Hanford Health and Mortality Study Advisory Committee and many other scientists with relevant expertise, including those selected by the *American Journal of Epidemiology*.

• Iron Stores and Risk of Cancer

Principal Investigator: R. G. Stevens

Other Investigators: K. Neriishi and M. Kabuto, Radiation Effects Research Foundation, Hiroshima, Japan; W. Blot and C. Land, National Cancer Institute, Bethesda, MD

A case-control study of 200 stomach cancer and 85 lung cancer cases occurring between 1973 and 1985 in the Japanese atomic bomb survivor population has been undertaken. Serum samples saved since 1970-1972 from cases and an equal number of controls have been tested for ferritin and transferrin to test the hypothesis that high levels of iron stores increase cancer risk. The data are currently being analyzed.

Subject characteristics may play an important part in modifying susceptibility to radiation carcinogenesis. For this reason, an active research effort at this and other laboratories is examining nutritional antioxidants as possible radioprotectors. As a complement to this research, this project is based on the hypothesis that elevated iron stores may act as a radiosensitizer. Such an epidemiological study of iron-binding proteins and cancer risk in Japanese atomic bomb survivors is based on the following biological rationale.

Under conditions of low iron, transferrin saturation is low. Less ferric iron (Fe^{+++}) gets into the cell, and the amount of intracellular ferritin is low, as is the amount of iron inside each ferritin molecule. Exposure to ionizing radiation results in production of oxygen radicals. Superoxide and hydroxyl radicals that are produced can be reduced to hydrogen peroxide by enzymes such as superoxide dismutase. Hydrogen peroxide can be reduced to water by catalase and glutathione peroxidase.

However, under conditions of high iron, transferrin saturation is high. More ferric iron gets into the cell, and intracellular ferritin increases. In addition, the concentration of nonspecific iron chelates with adenosine diphosphate, for example, increases. Thus, after ionizing radiation exposure, the concentration of the resulting radicals can be further diffused because the iron chelates have depleted the cellular reducing equivalents. Furthermore, hydrogen peroxide can be re-oxidized to reform hydroxyl and superoxide radicals by iron catalysis of these reactions. The result may be increased damage to cellular structures such as DNA.

Based on this rationale, a study was designed using data from the Japanese atomic bomb survivors. Serum samples from approximately 7,000 Japanese bomb survivors have been saved since 1971-1972. Two hundred cases of stomach cancer and 85 cases of lung cancer that have occurred since 1973 have been matched to 285 controls with regard to age, city of residence (Hiroshima or Nagasaki), and sex. The saved serum samples have been tested for nine constituents, including the iron-binding proteins ferritin and transferrin. The data are currently being analyzed in collaboration with researchers from the Radiation Effects Research Foundation (RERF) in Hiroshima and the National Cancer Institute in Bethesda, MD.

Two additional studies have also been started in collaboration with researchers at RERF. The purpose of these studies is to examine possible confounding effects of smoking on the main study, and also to examine the hypothesis in other ways.

The relationship between cigarette smoking and serum chemistries is being examined in the cycle 7 and 11 data bases, which have been compiled from information obtained during clinic visits by Japanese atomic bomb survivors that occurred between 1968 and 1970 and between 1976 and 1978, respectively. Preliminary results show that smokers had lower serum albumin, total protein, and globulin. Relationships between smoking and levels of uric acid, glucose, and cholesterol are also being examined. These results are important because studies of serum markers and cancer can be seriously confounded by an effect of smoking.

Another study has been designed to examine serum albumin and hemoglobin in relation to cancer. Since these determinations were made on all subjects examined, the sample size for the study is approximately 9,000, thus giving greater power to detect real associations (should they exist) than the smaller case-control studies.

• Interlaboratory Toxicology Data Base

Principal Investigator: C. R. Watson

Technical Assistance: J. D. Kaschmitter, J. S. Littlefield, and R. B. White

The goal of this project is to provide investigators with the capability to assess experimentally derived dose-effect data from many laboratories for evaluating potential insults to human health. Initial efforts, reported here, concentrate on the beagle dog lifespan health-effects studies supported by DOE at five laboratories. Significant steps include standardization of the medical observation glossary, development of an independent offsite data tape archive, and preliminary design of a registry to contain common-format dosimetric estimates and histopathologic observations for each major tissue in the more than 5000 dogs under study.

Our goal is to provide investigators with the capability to combine experimentally derived dose-effect data from many laboratories for evaluating potential insults to human health. A manageable subset of this large problem is to integrate information from the five DOE-supported laboratories that conduct lifespan studies of beagle dogs exposed to various radiotoxic insults. These laboratories, shown in Table 1 with their experimental protocols, are: Pacific Northwest Laboratory (PNL); Inhalation Toxicology Research Institute (ITRI); University of California (UC), Davis; University of Utah (Utah); and Argonne National Laboratory (ANL). These studies, which were designed to complement one another, are nearing completion.

This project focuses on three steps leading toward eventual synthesis of the results:

1. integration of diverse medical terminology glossaries into Systematized Nomenclature of Dogs (SNODOG),

2. development of procedures for archiving information from each institution, and

3. design of a database that includes dosimetric and histopathologic observations of each major tissue of animals on study.

TABLE 1. Summary of Lifespan Experiments in Beagle Dogs Exposed to Radiotoxic Insults at DOE-Supported Laboratories.

Laboratory	Route	Agent	Number of Dogs
PNL	Inhalation	PuO_2, $Pu(NO_3)_4$	479
ITRI	Inhalation	Alpha Emitters	599
	Inhalation	Beta Emitters	916
UC, Davis	Injection	^{90}Sr, ^{226}Ra	379
	Ingestion	^{90}Sr	479
	External	X Ray	360
Utah	Injection	Alpha Emitters	1148
	Injection	^{90}Sr	100
ANL	External	X or Gamma Rays	710
	Injection	Beta Emitters	268
Total			5438

SNODOG

Major products of the DOE long-term studies of beagle dogs are pathologists' observations regarding tumor identification and classification, and clinicians' findings on morbidity and tumor development. Eventually, it will be useful to analyze these observations by combining the results of the various studies conducted at the five laboratories. To this end, each institution has made a commitment to encode their observations, using the American Medical Association's hierarchical coding scheme, the Systematized Nomenclature of Medicine (SNOMED), as augmented by the American Veterinary Medical Association in the Systematized Nomenclature of Veterinary Medicine (SNOVET). However, the published SNOMED/SNOVET glossaries are deficient in some areas. For example, topography codes for specific mammary glands or for detailed dissection of the canine lung are lacking. Therefore, each laboratory developed variants of the published glossaries that fit their investigative philosophy. Since this was done without coordination among laboratories, the resulting coded observations were incompatible.

To overcome this difficulty, this project has supplied the coordinating function by:

- providing a unified, 5000-item glossary called SNODOG,

- acting as clearinghouse for additions to SNODOG, and

- providing data-entry software.

The canine-specific medical glossary, SNODOG, derived from SNOMED and SNOVET, has been compiled and installed on the computer at each of the five laboratories. SNODOG resolves the various conflicting supplemental codes assigned by each laboratory. To allow interlaboratory comparison, some modifications in the codes used in previous records were necessary.

Three of the laboratories (ANL, PNL, and UC, Davis) had developed glossaries by manually

entering codes extracted from SNOMED or SNOVET publications as requested by investigators. SNODOG represents the logical union of these three glossaries. (The other two laboratories, ITRI and Utah, provided investigators with access to the entire SNODOG glossary as received on computer tape.) Table 2 shows the inconsistencies among laboratories in choices of codes, as well as the results after standardization in SNODOG. With the concurrence of investigators, infrequently used codes were combined, and the texts of the translations were standardized.

SNODOG is inclusive and permissive; codes in Table 3 are available for optional use. The center column indicates which laboratories used the codes before the introduction of SNODOG. Future updates of the SNODOG glossary will incorporate suggestions made by pathologists in the various laboratories.

TABLE 2. Characterization of SNOMED/SNOVET Glossaries, Showing Total Number of Entries by Laboratory.

Entry Purpose	PNL	UC, Davis	ANL	SNODOG
Disease	127	114	25	169
Etiology	235	177	8	304
Function	514	558	102	746
Morphology	674	623	273	772
Procedure	196	425	9	496
Topography	1291	1469	641	1820
Total	3145	3366	1058	4307

TABLE 3. Examples of SNODOG Codes and Translations.

Code	Laboratories that Previously Used these Codes	Translation
M040000	ANL; PNL; UC, Davis; Utah	Color, Abnormal
M040100	UC, Davis; Utah	Green Color, Abnormal
M040200	ANL; PNL; UC, Davis; Utah	Blue Color, Abnormal (Cyanosis)
M040300	UC, Davis; Utah	Bluish Color, Abnormal
M040400	UC, Davis; Utah	Red Color, Abnormal
M040500	UC, Davis; Utah	Yellow Color, Abnormal
M040900	PNL; UC, Davis; Utah	Loss of Color, Abnormal (Pallor)
T080000	ANL; PNL; UC, Davis; Utah	Lymph Node, NOS
T080001	PNL; UC, Davis	Medulla of Lymph Node
T080200	PNL; UC, Davis; Utah	Sinusoid of Lymph Node
T081000	ANL; Utah	Lymph Node of Head
T081400	ANL; Utah	Parotid Lymph Node
T081600	ANL; PNL; UC, Davis; Utah	Submandibular Lymph Node
T081601	PNL; UC, Davis	Left Submandibular Lymph Node
T081602	PNL; UC, Davis	Right Submandibular Lymph Node
T081603	PNL; UC, Davis	Both Submandibular Lymph Nodes

Archive of Information

Computer-tape copies of the beagle-related information at each institution were obtained and are now stored at DOE headquarters. Each laboratory has developed techniques for translating information from its proprietary data-management systems to machine-independent, American Standard Code Information Interchange format flat files. Extensive documentation of the beagle information management system and tape back-up process at each laboratory provides a basis for projected annual updates of the archive. Offsite storage of tapes and documentation provides additional security for this extensive information set.

Tissue Registry

The planned tissue registry will be a database containing dose information and histopathology observations for each significant tissue from the 5438 animals under long-term study. Meetings have been conducted at each laboratory to refine this concept. A five-level hierarchy (Table 4), which will probably be maintained on a microcomputer, is envisioned for the registry. The projected number of records, based on 10 tissues per animal, is manageable.

TABLE 4. Hierarchy for Tissue Registry Database.

Level	1 Item Per	Number Items	Source of Information
1	Laboratory	5	Annual Reports
2	Study	48	Annual Reports
3	Group	357	Annual Reports
4	Dog	5438	Colony Master File in Each Laboratory
5	Tissue	54380	SNODOG File and/or Keyboard in Each Laboratory
Total		60228	

• Benefit–Cost Analysis of OHER Research

Principal Investigator: R. J. Nesse

Other Investigators: J. M. Callaway, J. E. Englin, M. S. Klan, A. K. Nicholls, and D. E. Serot

This research was undertaken to estimate societal benefits and costs of selected past research performed for OHER. Three case studies of representative OHER and DOE research were performed. One of these, the acid rain case study, included research conducted in another office in DOE. The other two cases were the OHER marine research program and the OHER project that developed high-purity germanium used in radiation detectors. The acid rain case study looked at research benefits and costs of furnace sorbent injection and duct injection, technologies that might reduce acid deposition precursors. Both appeared to show benefits in excess of costs. We examined in detail one of the marine research program's accomplishments, the increase in environmental information used by the Outer Continental Shelf leasing program to manage bidding for off-shore oil drilling. The results of an econometric model showed that, environmentally, marine research supported by OHER is unequivocally linked to government and industry leasing decisions. Finally, the germanium case study indicated that benefits of germanium radiation detectors were significant.

The specific objectives of the research were to: 1) estimate economic and societal benefits of three representative, past research projects supported by OHER; 2) test the usefulness of economic techniques for estimating societal benefits; and 3) document problems and uncertainties in applying the techniques to OHER programs and recommend ways of overcoming these problems.

We deliberately avoided two topics: first, evaluating the scientific quality of the original research, and second, evaluating whether OHER properly funded or managed these programs. Our goal was only to estimate societal benefits resulting from the programs.

Since previous broad assessments of OHER research were available as starting points, we selected three case studies representative of OHER research programs. One of these, the acid rain case study, also included research conducted by another office in DOE and by other federal agencies. The other two case studies comprised the development of high-purity germanium that is used in radiation detectors, and the OHER marine research program.

It became apparent in the initial phases of our research that resources and time were insufficient to exhaustively assess each of the case-study programs. After accomplishments of each research program were reviewed, we focused on estimating benefits of a few accomplishments from each program.

Acid Rain Case Study

The acid rain case study looked at the benefits and research cost of two technologies that might reduce acid deposition precursors: furnace sorbent injection and duct injection. At least three broad conclusions were drawn, based on results of the acid rain case study:

- Both technologies showed benefits in excess of research costs over a wide range of emission reductions and regulatory conditions.
- Net research benefits of duct injection were substantially greater than those for furnace sorbent injection. This conclusion was valid for nearly all sensitivity analyses.
- The pattern of positive net benefits for both technologies is consistent with a primary objective of the National Acid Precipitation Assessment Program to develop lower-cost alternatives for meeting requirements of acid-rain-oriented emission reduction bills.

These conclusions should be interpreted with appropriate regard for the uncertainties associated with forecasting commercial performance of these two technologies and their future R&D costs.

OHER Marine Research Program

Our research indicated that the OHER marine research has improved society's knowledge of ocean currents and its ability to predict the movement of energy-related pollutants in the ocean. We examined in detail one of the contributions of OHER research: the environmental information used by the Outer Continental Shelf (OCS) leasing program, which manages bidding for off-shore oil drilling. In particular, we examined the contribution that OHER made to the leasing of the Georges Bank, off the northeastern United States. Our specific conclusions are:

- Marine environmental research of the type conducted by OHER has been unequivocally linked to governmental decisions about which OCS areas to

offer for lease, and to industrial decisions on whether to bid. For example, we found statistical evidence that a 1% change in the probability that oil will not reach the shore has more effect on leasing decisions by the U.S. Department of Interior than does determining that the site has $1 million worth of oil.

- The societal monetary benefit of OHER research in the Georges Bank was estimated to be $2.75 million.

- The societal monetary benefit of OHER research to the entire OCS leasing program was estimated to be $165 million. However, there is considerable uncertainty in this estimate.

- On the basis of our estimates for Georges Bank and for the entire OCS leasing program, and based on the qualitative information on other achievements of the OHER marine research program, the benefits of this OHER research are regarded as significantly greater than the research costs.

Germanium Research Case Study

Based on our discussions with the users of high-purity germanium detectors, OHER's research has supported development of an improved radiation detector that has lead to a number of new applications. However, because of the lack of necessary data and the proprietary nature of production information, the societal benefits for the new applications could not be estimated. These benefits are, nonetheless, real and appear to be large.

More specific conclusions of this research are as follows:

- High-purity germanium detectors overcame significant difficulties associated with their predecessors, the lithium-drifted detectors. In particular, the portability of the high-purity detector and the reduced need to constantly cool it were cited as significant advantages.

- Germanium detectors, both high-purity and lithium-drifted, represented significant cost savings over the use of laboratory analysis. Costs were approximately $100 for analysis with a germanium detector versus $1,000 to $4,000 for laboratory analysis. We were able to verify previous estimates that cost savings for one application of germanium detectors (that in nuclear power plants), were approximately $200 million.

- Advantages of the high-purity germanium detector resulted from the improved quality of the germanium crystal. OHER's research was the principal basis for these improvements; thus, the benefits of the detector were directly attributable to OHER.

General Conclusions

On the basis of results from these three case studies, retrospective assessments of the societal benefits of basic and applied OHER research determined that the research was cost-effective and useful. Benefits of our research on cost/benefit analysis included providing insights and estimating the impact of several of OHER's major accomplishments. This conclusion was tempered by the fact that lack of available data restricted our ability to exhaustively assess benefits of complete programs. However, tracing and describing accomplishments was an important by-product of our research. Also, cuantitative estimates of even a few of the research accomplishments indicated the substantial value of OHER research.

While the economic techniques were useful for measuring the accomplishments of past OHER research, we believe they would not be especially helpful for evaluating which OHER research project to fund or the appropriate level of OHER funding.

Health Effects Research In Biological Systems

• Inhaled Plutonium Oxide in Dogs

Principal Investigator: J. F. Park

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This project is concerned with long-term experiments to determine the lifespan dose-effect relationships of inhaled $^{239}PuO_2$ or $^{238}PuO_2$ 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 16-year postexposure period. During the 13 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; 14 were sacrificed to obtain plutonium distribution and pathology data; 116 were assigned to lifespan dose-effect studies (Table 1). One hundred sixteen dogs exposed to $^{238}PuO_2$ in 1973 and 1974 were selected for lifespan dose-effect studies (Table 2). Twenty-one additional dogs were exposed for periodic sacrifice. The Appendix (following the entire Annual Report) shows the status of the dogs on these experiments.

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

Dose Level Group	Number of Dogs		Initial Lung Deposition[b]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Control	10	10	0	0
1	12	12	3.5 ± 1.3	0.029 ± 0.011
2	10	11	22 ± 4	0.18 ± 0.04
3	10	10	79 ± 14	0.66 ± 0.13
4	11	11	300 ± 62	2.4 ± 0.4
5	10	11	1100 ± 170	9.3 ± 1.4
6	3	5	5800 ± 3300	50 ± 22
	66	70		

[a] Exposed in 1970 and 1971.

[b] Estimated from external thorax counts at 14 and 30 days post-exposure and estimated lung weights (0.011 x body weight).

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

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

Dose Level Group	Number of Dog		Initial Lung Deposition[b]	
	Male	Female	nCi[c]	nCi/g Lung[c]
Control	10	10	0	0
1	10	10	2.3 ± 0.8	0.016 ± 0.007
2	11	10	18 ± 3	0.15 ± 0.03
3	12	10	77 ± 11	0.56 ± 0.07
4	10	10	350 ± 81	2.6 ± 0.5
5	10	10	1300 ± 270	10 ± 1.9
6	7	6	5200 ± 1400	43 ± 12
	70	66		

[a] Exposed in 1973 and 1974.

[b] Estimated from external thorax counts at 14 and 30 days post-exposure and estimated lung weights (0.011 x body weight).

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

Table 3 summarizes, by dose-level group, the mortality and lesions associated with deaths through 16 years after exposure to $^{239}PuO_2$. During this period, all of the dogs except one in Dose-Level Group 3 and one in the control group were euthanized when death was imminent.

TABLE 3. Summary of Lesions in Dogs Euthanized During the 16 yr Period After Inhalation of $^{239}PuO_2$.

	Dose Group						
	6	5	4	3	2	1	Control
Number of Dogs/Group	8	21	22	20	21	24	20
Number of Dead Dogs/Group	8	21	22	19	21	24	19
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		19	13	6	2		4
Lung Tumor and Bile Duct Carcinoma			1				
Urinary Bladder Tumor, Lung Tumor		1					
Leiomyosarcoma, Lung Tumor			1		1		
Adrenal Cortical Carcinoma, Lung Tumor				1			
Kidney Tumor, Lung Tumor				1			
Nephropathy and Lung Tumor			1	1	1		
Malignant Lymphoma and Lung Tumor				1			
Pneumonia, Lung Tumor						1	
Bone Tumor					1	2	
Malignant Lymphoma				1		4	2
Malignant Lymphoma and Bile Duct Carcinoma							1
Lymphocytic Leukemia						1	
Hemangiosarcoma (Heart, Spleen, Liver)						3	2
Pituitary Tumor, Cushing's			1			1	
Cushing's Intestinal Carcinoma							1
Thyroid Carcinoma				1			
Reticulum Cell Sarcoma			1				
Ovarian Tumor					1		
Oral Tumor							1
Round Cell Sarcoma and Bile Duct Adenoma						1	
Hemangioma (Spleen)					1		
Malignant Melanoma					2		1
Pheochromocytoma					1		1
Urinary Bladder Tumor				1	2		
Neurofibrosarcoma				1			
Meningioma						1	
Pneumonia			2	2	4	4	
Epilepsy					1	1	1
Thromboembolism				1			1
Pyometra			1	1			
Unknown					1	1	
Liver Cirrhosis			1				
Septicemia						1	
Cardiac Insufficiency				1	1		
Peritonitis					1		
Adrenalitis							1
Kidney Failure						1	
Nephrosclerosis							1
Chronic Nephropathy					1	1	2
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 cause 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 (ILB).

Table 4 indicates that, as survival time increased, the fraction of plutonium in the lung decreased to 16% of the final body burden by 15 to 16 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 71% of the final body burden at 15 to 16 years after exposure; the abdominal lymph nodes, principally the hepatic nodes, contained ~3%. The fraction of plutonium in liver in-

creased, accounting for 25% of the final body burden 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 higher-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 euthanized during the 4th to 16th postexposure 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. The fraction of plutonium in these dogs was ~7% of the final body burden 15 to 16 years after exposure; about 1% was in the skeleton.

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

[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	
814F	104	0.054	49	33	4.1	10	1.6	Lung Tumor
840F	107	0.389	17	35	5.8	37	2.0	Lung Tumor
777M	109	0.392	11	52	7.8	24	1.7	Lung Tumor
857M	109	0.333	20	39	9.4	27	2.4	Lung Tumor
898F	111	0.333	10	34	28	21	3.4	Urinary Bladder Tumor, 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	Kidney Tumor, Lung 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 and Bile Duct Adenoma
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	Neurolibrosarcoma
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	0.0034	8.0	88	0.38	0.92	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	41	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	2.0	1.8	0.11	Chronic Nephropathy
845F	158	0.012	28	69	0.23	1.5	0.63	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	0.00061	22	75	0.15	0.60	1.2	Kidney Failure
776M	163	0.0020	29	67	0.11	1.2	1.1	Bronchopneumonia
802M	164	0.019	13	45	33	6.7	1.3	Pneumonia
827F	164	0.075	4.5	49	17	27	1.5	Acute Pneumonia
874M	165	0.0048	5.6	90	0.54	1.4	0.56	Chronic Nephropathy
842M	166	0.0054	4.7	90	0.76	3.2	0.75	Lung Tumor, Chronic Nephropathy
770F	166	0.0023	17	80	0.15	0.69	0.52	Glomerulosclerosis
844F	170	0.097	19	50	8.9	19	1.3	Nephropathy, Lung Tumor
819F	170	0.085	18	42	4.2	30	3.0	Nephropathy, Lung Tumor
907F	174	0.00097	7.4	89	1.2	0.78	0.61	Pneumonia
876F	175	0.0080	10	80	1.8	6.1	0.88	Nephropathy, 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	
877F	175	0.011	13	79	2.2	3.8	0.70	Lung Tumor
867M	175	0.0027	23	52	5.8	16	1.6	Malignant Lymphoma
893M	177	0.0021	10	87	0.19	0.63	1.0	Pneumonia
839F	177	0.105	6.4	53	11	27	2.0	Lung Tumor, Bile Duct Carcinoma
841F	178	0.0028	6.8	89	0.13	2.1	0.84	Malignant Lymphoma
832F	178	0.0020	8.3	87	0.17	1.5	0.88	Malignant Lymphoma
767M	180	0.0088	33	64	0.22	1.1	0.96	Valvular Endocardiopathy
848F	180	0.047	9.8	80	4.9	3.7	0.80	Acute Pneumonia
871M	181	0.0028	10	86	0.59	1.6	1.0	Malignant Melanoma, Oral
851F	182	0.025	15	77	1.7	4.8	1.2	Thyroid Carcinoma, Hypothyroidism
865F	182	0.00062	7.0	89	0.23	0.92	1.5	Acute Pneumonia, Lung Tumor
797F	182	0.036	11	43	11	31	1.7	Lung Tumor
881F	182	0.0066	13	85	0.27	0.33	0.75	Acute Pneumonia
786M	183	0.047	11	60	6.5	10	1.4	Adrenocortical Carcinoma, Lung Tumor
858M	183	0.00042	5.4	88	2.2	1.6	0.60	Lymphocytic Leukemia
757M	191	0.018	58	30	2.8	6.4	1.6	Leiomyosarcoma, Kidney and Lung Tumor

[a] Includes tracheobronchial, mediastinal and sternal lymph nodes.

[b] Includes hepatic, splenic and mesenteric lymph nodes.

Figure 1 shows the ^{239}Pu tissue distribution as percent of the ILB for all dogs for which tissue radiochemical analyses are complete. The ILB for those dogs for which radiochemical analysis of excreta were not complete were estimated from external thorax counts at 14 and 30 days after exposure. For dogs whose analyses were complete, ILB 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 was 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 ≥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 postexposure period had increased respiration rates, and hypercapnia and hypoxemia associated with lesions in the lungs. Intermittent anorexia and body weight loss accompanied the respiratory insufficiency. Histopathologic examination of the lungs showed radiation pneumonitis, characterized by focal interstitial and subpleural fibrosis, increased numbers of alveolar macrophages, alveolar epithelial hyperplasia, and foci of squamous metaplasia. Autoradiographs showed activity primarily composed of large stars, more numerous in areas of interstitial and subpleural fibrosis. Dog 804M also had a pulmonary tumor, classified as a bronchiolar-alveolar carcinoma.

Fifty-two of the 115 exposed dogs euthanized 3 to 16 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. Eleven of the dogs with lung tumors were euthanized due to other causes. 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, 809M, 824F, 833F, and 835F (Dose Level 4), 697M, 778M, 782M, 823M, 827F, 834F, 848F, 851F, and 905F (Dose Level 3), 748F, 754M, 769F, 767M, 776M, 780F, 802M, 806F, 826F, 831F, 845F, 859M, 862M, 871M, 874M, and 881F (Dose Level 2), and 756M, 770F, 788M, 807F, 825F, 832F, 841F, 847M, 853M, 858M, 867M, 870M, 875M, 879M, 886F, 891M, 893M, 899F, 900M, 907F, and 908M (Dose Level 1) died during the 7- to 16-year postexposure period of causes presently thought to be unrelated to plutonium exposure.

In 23 of the dogs, the lung tumors were classified as bronchiolar-alveolar carcinoma; in six dogs as adenosquamous carcinoma; in nine dogs, adenocarcinoma; in four dogs, epidermoid and adenocarcinoma; in four dogs, epidermoid carcinoma; in one dog, epidermoid and bronchiolar-alveolar carcinoma; in three dogs, 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 carcinomas metastasized to the lungs, skeletons, brains, intestines and thoracic lymph nodes; the bronchiolar-alveolar carcinomas metastasized only to the thoracic lymph nodes in eight dogs, and to several organs (including mediastinum; kidney; thyroid; skeleton; heart; adrenal gland; aorta; and axillary, prescapular, cervical, splenic, thoracic, 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, hepatic, splenic, sternal and axillary lymph nodes; heart, kidney, and esophagus in five 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.

Bile-duct tumors have been reported by other laboratories in beagles exposed to plutonium. In our $^{239}PuO_2$ study, one Dose-Level 4 dog and one control dog had a bile-duct carcinoma as an incidental lesion not related to the death of the dog. One Dose-Level 1 dog had an incidental bile-duct adenoma. In the $^{238}PuO_2$ study, one Dose-Level 4 dog also had a bile-duct carcinoma as an incidental observation. These four are the total number of bile-duct tumors observed thus far in these studies. One control and two exposed dogs had hepatomas unrelated to their deaths.

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 from those of 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. By 176 months after exposure, too few dogs were alive for meaningful dose-group comparison.

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 $^{239}PuO_2$.

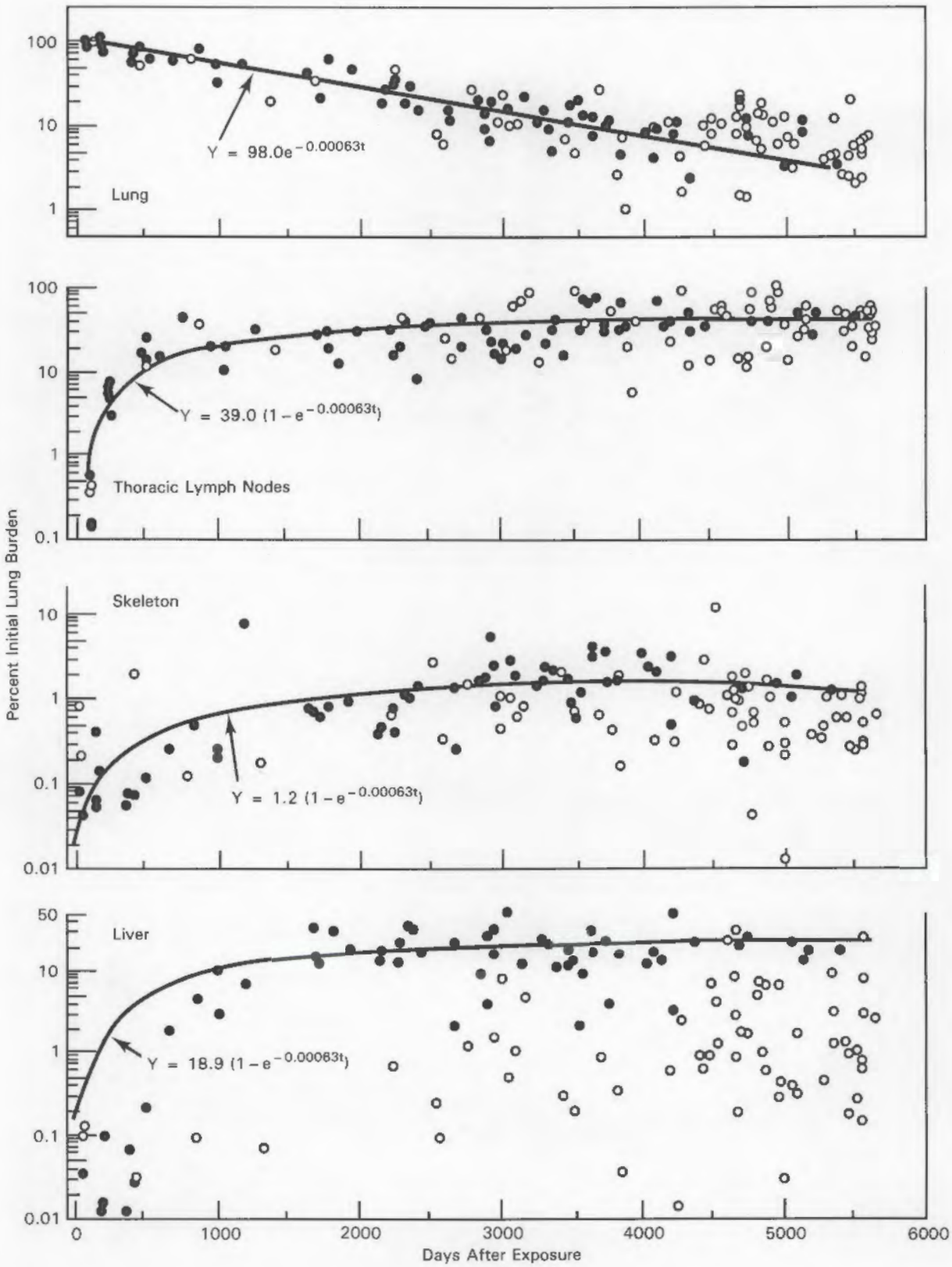

FIGURE 1. Plutonium in Tissues of Dogs After Inhalation of $^{239}PuO_2$. Points represent data from individual dogs (● = ≥ 75 nCi, ○ = ≤ 75 nCi final body burden). The uptake and retention curves and function were based on dogs in which initial lung burdens were estimated from external thorax counts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

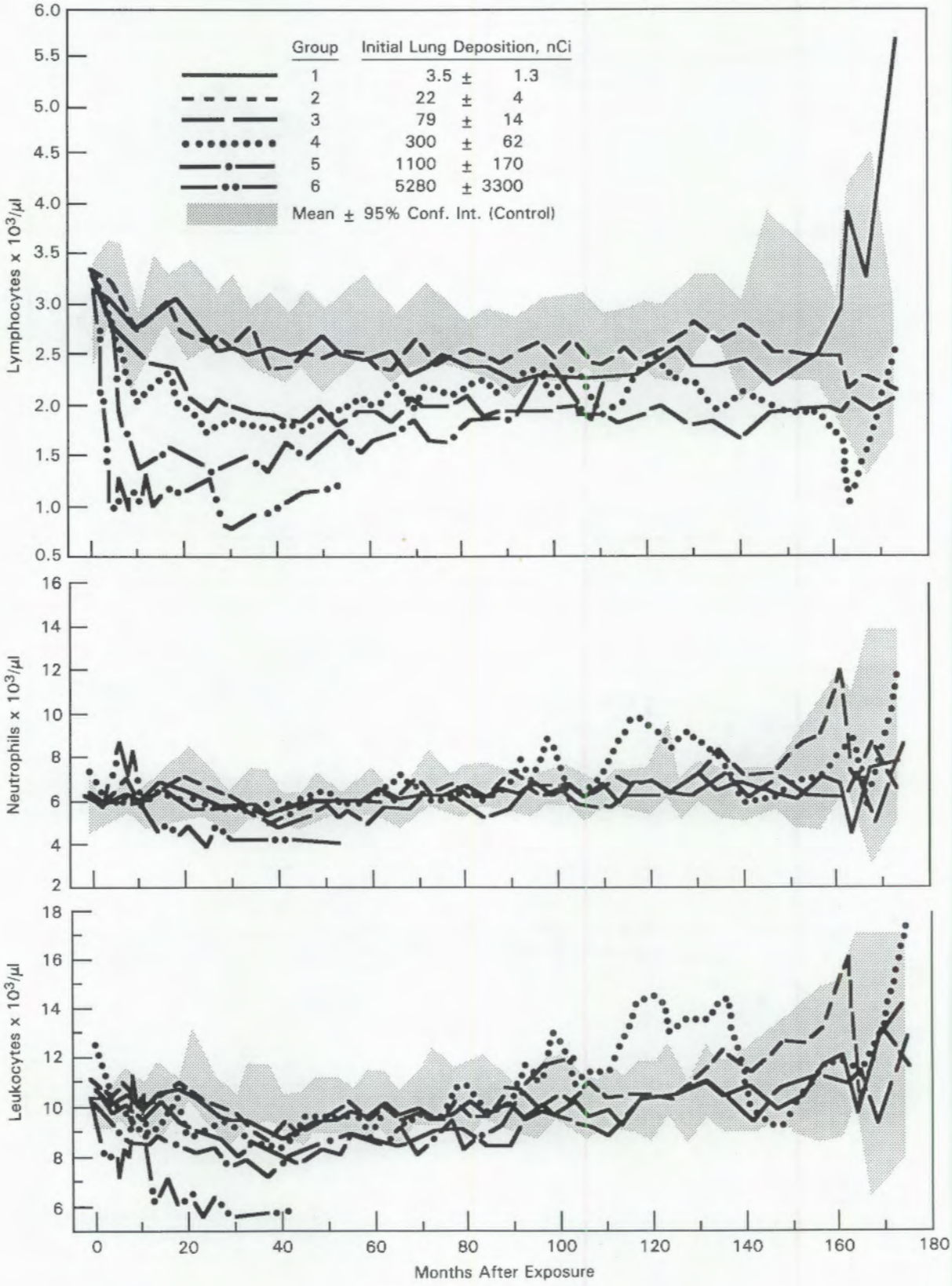

FIGURE 2. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}PuO_2$.

Table 5 summarizes, by dose-level group, mortality and lesions associated with death through 13 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, sixteen dogs in Group 4, twelve dogs in Group 3, eleven dogs in Group 2, and eleven dogs in Dose-Level Group 1 were euthanized when death was imminent. Seven control dogs were euthanized during the 13-year postexposure period. Mean survival time was decreased in the three 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 ILB.

At 12 to 13 years after exposure, the fraction of the final body burden in the lungs of the ^{238}Pu-exposed dogs was about 1%, compared to 15% in the ^{239}Pu-exposed dogs (Table 6). At that time, ~7% of the ^{238}Pu was in the thoracic lymph nodes, compared to 59% of the ^{239}Pu. Livers of the ^{238}Pu-exposed dogs contained 41% of the plutonium burden, compared to 13% in the livers of the ^{239}Pu-exposed dogs. About 46% of the final body burden was in the skeletons of the ^{238}Pu-exposed dogs, at that time, compared to ~3% in the ^{239}Pu-exposed dogs. Tissue distribution of ^{238}Pu in low-dose-level dogs did not differ from that in high-dose-level dogs. Figure 3 shows the ^{238}Pu tissue distribution as percent of ILB for all dogs for which tissue radiochemical analyses are complete. The ILB and uptake and retention curves were estimated as described previously for ^{239}Pu. The uptake and retention curves were based on dogs in which ILB 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.

Of the 83 exposed dogs euthanized, 33 were killed because of bone tumors, 5 because of lung tumors, and 1 because of radiation pneumonitis. Thirteen of the dogs that had bone tumors also had lung tumors. Two dogs with lung tumors were euthanized for other causes. Thirty-one of the 33 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 2, 3, 4, 5, and 6. Thirteen of the 31 osteosarcomas were in vertebrae; two in femora; four in ribs; three in the scapulae; five 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, 1053F, 1081M, 1166M, 1176M and 1220F (Dose Level 4); 960M, 1026M, 1031F, 1040M, 1043M, 1059F, 1165M, 1066M, 1219F and 1309M (Dose Level 3); 971F, 1060F, 1070M, 1078F, 1082M, 1188M, 1216M, 1222M and 1229M (Dose Level 2); and 951M, 959M, 1008M, 1063M, 1069F, 1105F, 1106F, 1193F, 1194F and 1230M (Dose Level 1) died during the 13-year postexposure period of causes presently thought to be unrelated to plutonium exposure.

The lung tumors were classified as bronchiolar-alveolar carcinomas in 13 dogs, bronchiolar-alveolar adenoma in one dog, adenocarcinoma in three dogs, and adenosquamous carcinoma in two dogs. In one dog, three lung-tumor types were observed: bronchiolar-alveolar, adenocarcinoma and fibrosarcoma. Metastases were observed in the lungs; thoracic, hepatic and splenic lymph nodes; trachea; esophagus; mediastinum; thyroid; diaphragm; and hearts of two dogs 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 six dogs with Addison's disease, which were in Dose-Level Groups 4, 5 and 6, 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 Dose-Level Groups 3, 4, 5 and 6 dogs.

TABLE 5. Summary of Lesions in Dogs Euthanized During the 13-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	16	12	11	11	7
Mean Survival Postexposure, yr	5	7	11	12	12	12	12
Condition[a]							
Bone Tumor	2	11	4			1	
Lung Tumor	3			1	1		
Bone and Lung Tumor	6	4	2				
Bone Tumor and Bile Duct Carcinoma			1				
Bone Tumor and Addison's Disease	1						
Bone and Lung Tumor and Addison's Disease		1					
Pneumonia, Lung Tumor			1				
Addison's Disease	1	2					
Malignant Lymphoma, Lung Tumor					1		
Malignant Mesothelioma					1		
Malignant Lymphoma			1	3	1	2	3
Malignant Lymphoma, Addison's			1				
Hemangioma; Spleen			1				
Hemangiosarcoma; Heart, Spleen, liver			1	1	1	1	
Fibrosarcoma, Spleen						1	
Pituitary Tumor, Cushing's			1	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	2	2		
Radiation Pnemonitis				1			
Chronic Nephropathy				1			
Immune Hemolytic Anemia						1	
Spinal Cord Degeneration					1		
Pyometra							1
Herniated Vertebral Disk		1					
Anesthesia						1	
Liver Abscess						1	
Hepatic Dysplasia				1			

[a]Number of dogs with lesion associated with death.

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

Dog Number	Time After Exposure, mo	Final Body Burden, μCi	Percent of Final Body Burden					Cause of Death
			Lungs	Thoracic Lymph Nodes[a]	Abdominal Lymph Nodes[b]	Liver	Skeleton	
1032M	0.25	0.150	97	0.34	0.20	1.7	0.16	Sacrifice
921F	1	0.0044	93	0.65	0.04	0.38	2.1	Sacrifice
930F	1	0.052	99	0.63	0.01	0.07	0.35	Sacrifice
931F	1	0.347	96	1.9	0.01	0.05	0.36	Sacrifice
929F	2	0.017	91	7.5	0.002	0.26	0.58	Sacrifice
932F	2	0.382	96	2.5	0.01	0.18	0.39	Sacrifice
923F	2	0.0023	88	9.4	0.03	0.09	0.44	Sacrifice
925M	3	0.0064	91	4.1	0.04	0.04	1.2	Sacrifice
926M	3	0.078	87	11	0.23	0.65	1.1	Sacrifice
934M	3	0.902	92	4.8	1.7	0.45	0.95	Sacrifice
1318M	12	0.030	45	27	0.08	10	15	Sacrifice
1319M	12	0.077	41	26	0.03	11	20	Sacrifice
1214M	13	0.014	52	9.2	0.32	6.2	16	Sacrifice
1310M	25	0.026	19	36	0.08	15	28	Sacrifice
1317M	25	0.041	20	33	0.16	17	26	Sacrifice
1315M	25	0.047	22	31	0.04	17	28	Sacrifice
1191F	35	0.658	26	32	0.13	18	22	Pneumonia
1215M	36	0.011	21	43	0.17	13	21	Sacrifice
1311M	37	0.036	13	31	0.22	21	32	Sacrifice
994F	42	5.024	17	45	0.50	18	18	Addison's Disease
970F	48	0.0022	20	34	0.36	16	24	Sacrifice
1312M	49	0.035	6.8	29	0.26	25	35	Sacrifice
1143M	49	6.331	11	43	2.0	15	22	Bone Tumor, Lung Tumor
1025M	50	10.033	16	27	7.1	24	23	Lung Tumor
1064M	51	8.427	13	48	1.9	15	20	Bone Tumor, Lung Tumor
1175F	52	3.641	14	31	0.08	25	26	Lung Tumor
1079M	56	2.182	9.8	40	4.3	13	25	Addison's Disease
1096F	59	1.204	4.3	22	2.7	36	24	Addison's Disease
1189M	60	0.044	8.9	25	0.16	37	25	Sacrifice
1115F	61	1.534	5.0	32	2.3	26	33	Bone Tumor
1162F	61	3.663	12	32	5.9	21	25	Bone Tumor, Addison's Disease
1009M	62	4.360	15	25	2.4	31	23	Lung Tumor
974F	64	1.465	5.1	24	5.9	33	29	Bone Tumor
1092M	65	1.515	2.1	26	9.1	29	30	Bone Tumor
975F	66	3.749	11	30	2.1	28	25	Bone Tumor, Lung Tumor
1042F	69	1.494	4.7	25	2.9	32	33	Bone Tumor, Lung Tumor
1037M	69	2.417	7.1	27	7.8	28	27	Bone Tumor
1027M	70	2.546	3.8	15	7.0	40	31	Bone Tumor, Lung Tumor
1006F	72	2.826	7.5	30	3.4	29	26	Bone Tumor, Lung Tumor
1057M	72	1.748	3.0	35	2.2	33	24	Bone Tumor
1082M	78	0.0083	2.4	20	0.31	40	34	Paralysis
1081M	80	0.361	4.6	15	0.48	47	29	Hemangiosarcoma, Heart
1058F	80	1.000	2.0	18	4.4	31	41	Bone Tumor, Adrenal Tumor
1002M	84	1.786	2.9	31	2.0	31	28	Bone Tumor, Lung Tumor
1109F	86	0.885	0.93	23	4.0	34	35	Bone Tumor, Addison's Disease, Lung Tumor
1218F	86	0.678	2.7	23	4.1	42	25	Bone Tumor
1071M	91	1.088	5.4	28	3.4	27	33	Bone Tumor, Lung Tumor
1063M	94	0.00060	3.4	15	1.3	22	43	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

[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	
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	9.1	2.1	1.6	51	34	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	0.142	0.77	5.0	0.89	36	53	Bone Tumor
959M	138	0.0025	3.4	14	0.62	33	48	Liver Abscess
992F	139	0.264	0.73	8.0	2.7	42	42	Bone Tumor
1194F	140	0.0014	0.67	10	9.0	20	56	Malignant Lyphoma
1105F	140	0.00074	0.62	5.6	0.70	44	45	Malignant Lymphoma
1193F	141	0.0037	0.58	9.2	1.0	37	48	Immune Hemolytic Anemia
973F	142	0.127	3.7	7.0	1.8	44	39	Bone Tumor
1060F	142	0.011	0.61	10	0.68	39	47	Pneumonia
1114M	143	0.272	0.51	7.4	2.9	39	47	Bone Tumor, Bile Duct Carcinoma
1222M	143	0.0051	8.5	4.0	0.82	36	47	Malignant Mesothelioma (mediastinal)
1053F	143	0.061	1.9	5.0	0.83	45	41	Cushing's Disease
1176M	145	0.051	0.39	5.9	0.90	52	38	Hemangioma, Spleen
1309M	146	0.019	1.4	4.8	0.96	46	44	Hemangiosarcoma, Liver
1230M	150	0.0027	0.34	12	1.2	41	41	Hemangiosrcoma, Liver
1198M	151	0.156	0.52	2.4	4.5	59	30	Acute Pneumonia, Lung Tumor
1219F	152	0.020	0.76	8.4	0.97	34	50	Chronic Nephropathy
1220F	152	0.136	0.74	7.7	1.1	38	48	Malignant Lymphoma, Addison's
1165M	152	0.042	0.66	7.8	1.6	47	39	Acute Pneumonia
1008M	153	0.00049	1.4	13	0.57	34	47	Fibrosarcoma, Spleen
1033M	154	0.0042	0.93	5.3	0.84	19	70	Lung Tumor
1026M	154	0.072	0.99	4.2	0.46	51	40	Hepatic Dysplasia
1065F	154	0.0035	0.72	8.9	0.69	27	60	Malignant Lymphoma, Lung Tumor
1216M	156	0.0096	2.5	6.9	1.4	49	37	Malignant Lymphoma

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

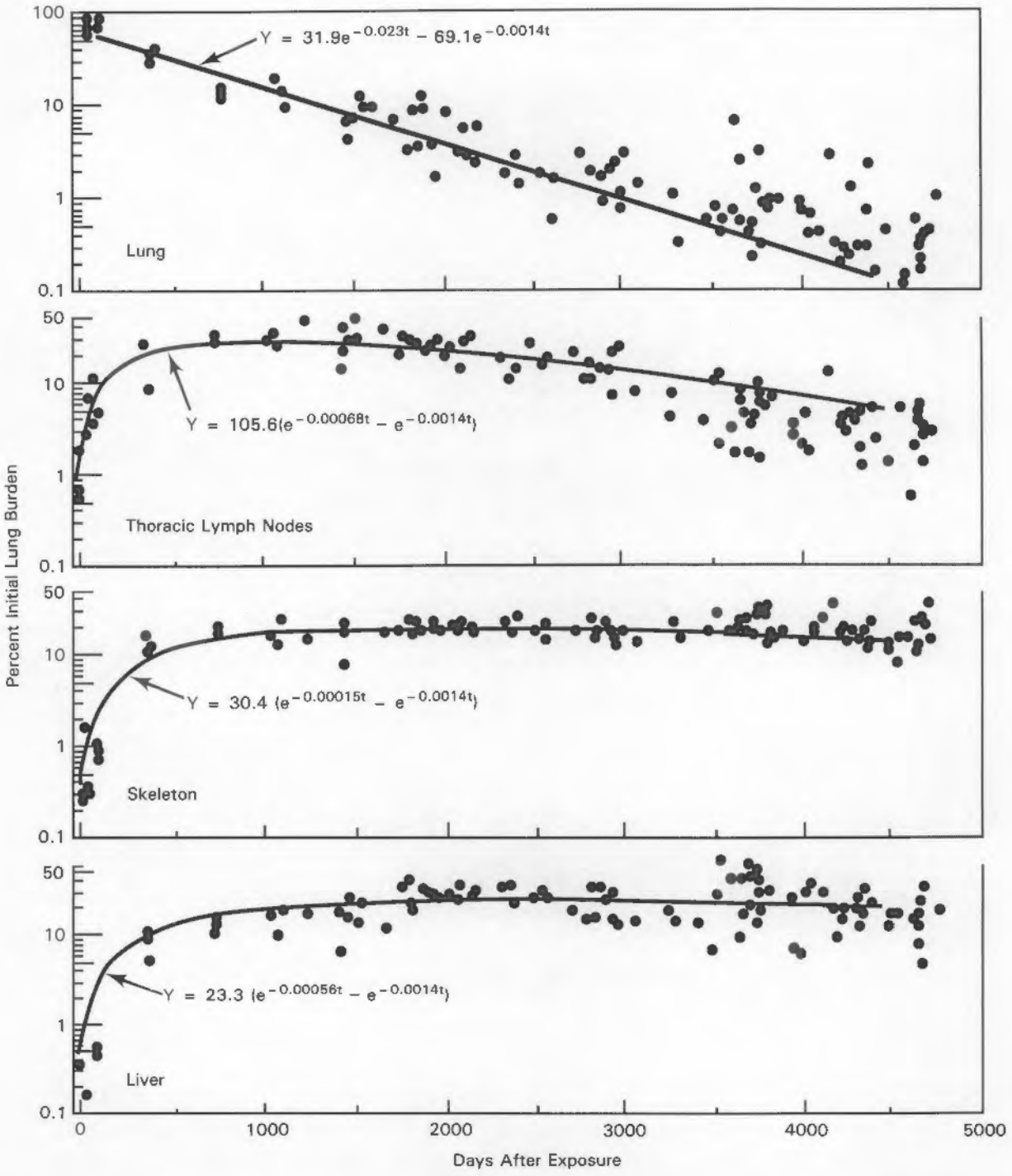

FIGURE 3. Plutonium in Tissues of Dogs After Inhalation of $^{238}PuO_2$. Points represent data from individual dogs. The uptake and retention curves and functions were based on dogs in which initial lung burdens were estimated from the final plutonium body burden, plus the plutonium excreted, minus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

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 sig-

nificantly 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.

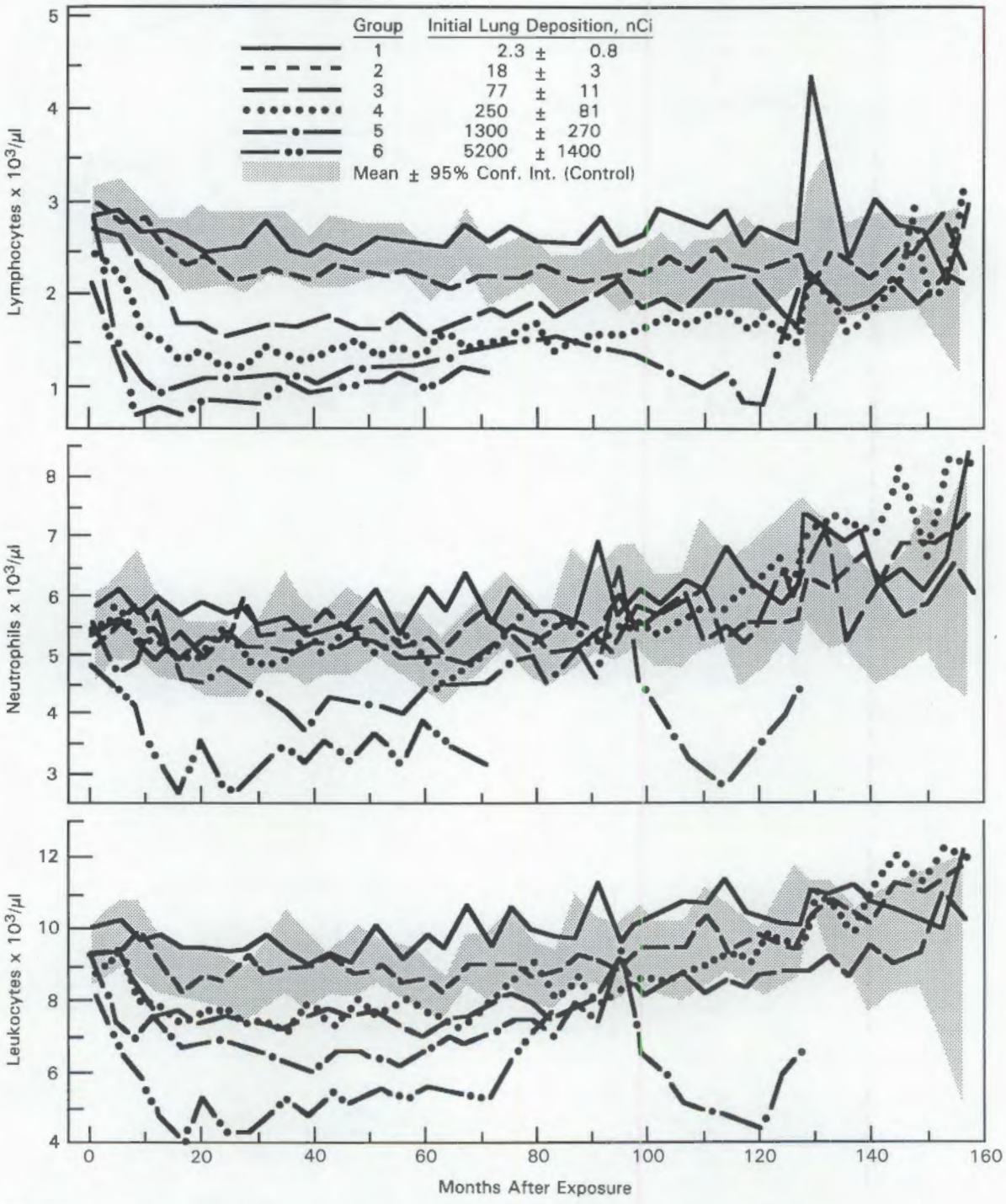

FIGURE 4. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{238}PuO_2$.

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/week 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 and skeletons of the ^{238}Pu dogs (Table 7). For the dose calculations, mean plutonium concentration in the entire lung and skeleton was used.

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	16	93 - 177	550 - 1500
	3	10	98 - 183	150 - 550
	2	4	166 - 191	30 - 120
	1	1	182	4
$^{238}PuO_2$- Lung Tumors	6	9	49 - 84	2300 - 9800[a]
	5	5	70 - 110	1350 - 2900
	4	3	118 - 151	400 - 480
	3	1	134	100
	2	2	154	8 - 20
	1	0	—	---
$^{238}PuO_2$- Bone Tumors	6	9	49 - 84	180 - 480[b]
	5	16	61 - 132	80 - 230
	4	7	118 - 143	50 - 100
	3	0	0	---
	2	0	0	---
	1	1	99	<1

[a] Dose to lungs.

[b] Dose to skeleton.

• 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, or bone cancer in the four highest dose levels.

The skeleton is generally considered the critical tissue after inhalation of "soluble" plutonium (e.g., plutonium nitrate), on the assumption that the plutonium will be rapidly translocated from the respiratory system to skeleton. In several rodent studies, however, inhalation of "soluble" plutonium has resulted primarily in lung tumors. Skeletal tumors were seen less often, perhaps because they were not expressed within the short lifespan of the rodents. Therefore, beagle dogs were chosen for this study, to compare relative risks with those from intravenously injected radionuclides in beagles 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. More specifically, this study can be compared with inhaled $^{239}PuO_2$ studies in beagle dogs at PNL (see Park et al., this report).

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 obtain plutonium distribution and pathogenesis data in 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.

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	18.70	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	38.90	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	0.854	0.76	0.53	0.53	37.51	56.17	Bone Tumor, Lung Tumor
1621M	84	0.840	0.94	0.56	0.29	40.87	54.55	Bone Tumor, Lung Tumor
1655M	88	0.505	1.05	0.22	0.93	41.83	52.14	Lung Tumor, Bone Tumor
1501M	92	0.002	1.62	0.50	0.79	38.05	48.41	Thyroid Tumor
1648M	92	0.639	1.12	0.25	0.73	42.83	50.61	Bone Tumor, Lung Tumor
1641M	92	0.869	0.78	0.	0.48	45.72	48.89	Lung Tumor
1408F	93	0.181	0.60	0.19	0.37	49.47	45.52	Bone Tumor

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

TABLE 2. 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	
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
1489F	98			-----Processing-----				Esophageal Tumor
1565F	101			-----Processing-----				Hemangiosarcoma
1385M	101			-----Processing-----				Bone Tumor, Lung Tumor
1364M	102			-----Processing-----				Lung Tumor
1503F	103			-----Processing-----				Thyroid Tumor
1645F	105			-----Processing-----				Lung Tumor
1587M	106			-----Processing-----				Hemangiosarcoma, Lung Tumor
1534M	106			-----Processing-----				Congestive Heart Failure
1521F	106			-----Processing-----				Bone Tumor, Lung Tumor
1599F	107			-----Processing-----				Adrenal Tumor
1413F	109			-----Processing-----				Malignant Lymphoma
1391M	111			-----Processing-----				Thyroid Tumor, Lung Tumor
1581M	111			-----Processing-----				Hemangiosarcoma
1602M	111			-----Processing-----				Epilepsy
1428F	114			-----Processing-----				Bone Tumor, Lung Tumor
1386M	116			-----Processing-----				Hemangiosarcoma
1568M	116			-----Processing-----				Pneumonia
1590F	118			-----Processing-----				Mammary Tumor

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

The earliest observed biological effect was on the hematopoietic system: lymphopenia occurred at the two highest dose levels at 4 weeks after exposure to $^{239}Pu(NO_3)_4$. The results of these continuing evaluations are shown in Figure 1. Total leukocyte concentrations were reduced significantly in the two highest dose groups, i.e., Group 5 (mean initial alveolar deposition, ~1700 nCi), and Group 6 (~5500 nCi). The reduction in white cells in Groups 5 and 6 is due to an effect on most leukocyte types (neutrophils, lymphocytes, monocytes and eosinophils). This is in contrast to the effects of both $^{239}PuO_2$ and $^{238}PuO_2$, which significantly depressed lymphocyte concentrations by 21 months after exposure in groups with initial lung burdens of ~80 nCi or more. The lymphopenia at lower dose levels of plutonium oxides may be related to the more-extensive translocation of plutonium oxide to the tracheobronchial lymph nodes 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 identify specific damage to liver and/or bone by plutonium translocated from the lung. Previous evaluations had 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 10 years following exposure), GPT and ALP values in Dose-Level Groups 3 and 4 are significantly ($P < 0.05$) higher than those for the control group.

Table 3 summarizes, by dose-level group, the mortality and lesions associated with deaths through 10 years after exposure to $^{239}Pu(NO_3)_4$. All five dogs at the highest dose level (Group 6) died from radiation pneumonitis 14 to 41 months after exposure. Histopathologic examination of these dogs' lungs revealed interstitial fibrosis, alveolar epithelial hyperplasia, increased numbers of alveolar macrophages, occasional small emphysematous cavities and, at times, very small nodules of squamous metaplasia at the termini of respiratory bronchioles. One dog at the highest dose level had a small bronchioloalveolar carcinoma as well as radiation pneumonitis.

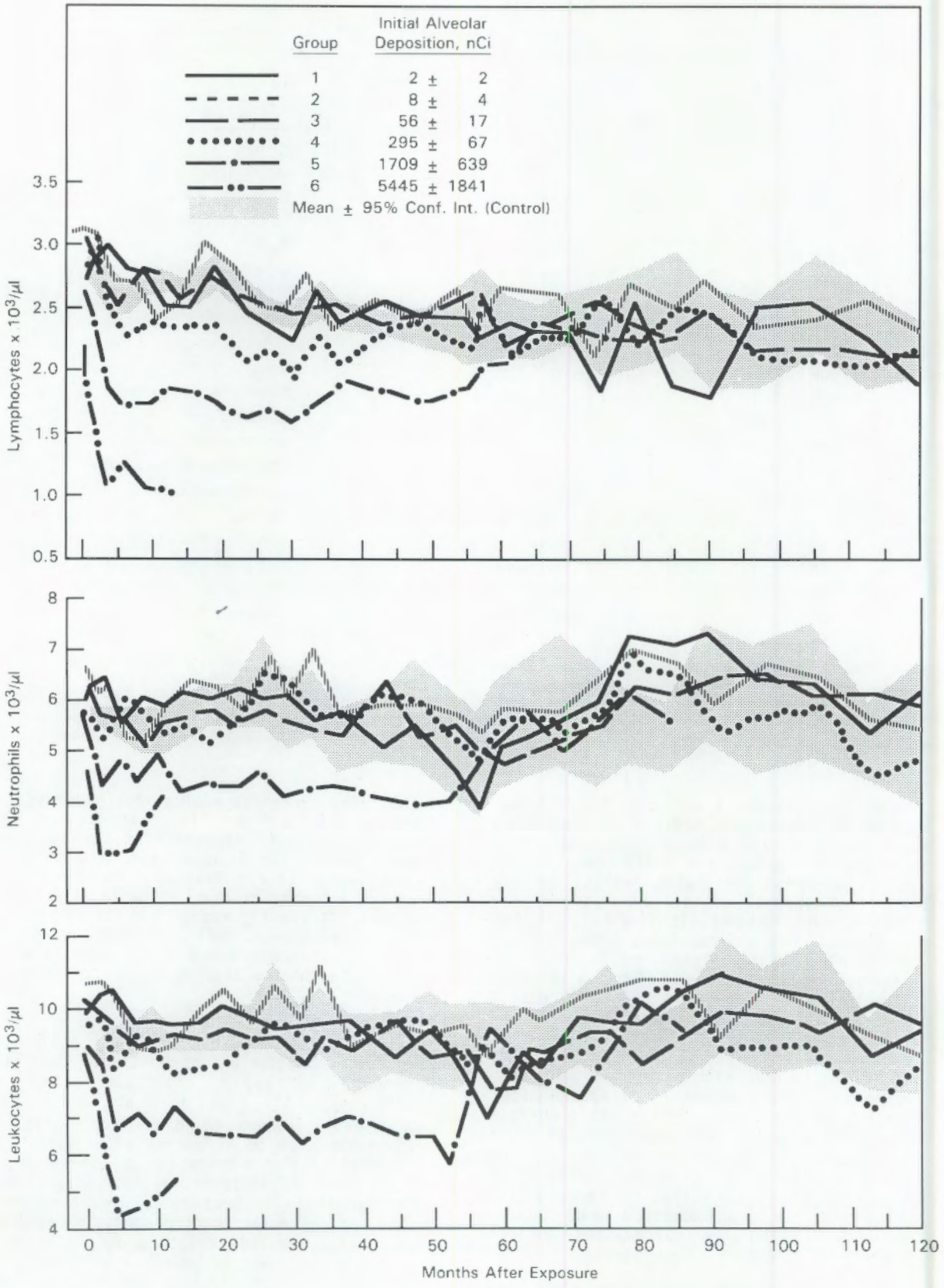

FIGURE 1. Mean Leukocyte, Neutrophil and Lymphocyte Values in Dogs After Inhalation of $^{239}Pu(NO_3)_4$.

TABLE 3. Lesions in Beagle Dogs 10 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	10	5	4	5	2	3
Condition[a]								
Radiation Pneumonitis	4	1						
Radiation Pneumonitis and Lung Tumor	1	1						
Bone Tumor		8	2					
Bone and Lung Tumors		9	3					
Lung Tumor		1	3					
Hemangiosarcoma and Lung Tumor				1				
Thyroid and Lung Tumors				1				
Pneumonia or Pleuritis			1	1				1
Lymphoma				1			1	
Thyroid Tumor					1	1		1
Meningeal Tumor						1		
Status Epilepticus					1			1
Congestive Heart Failure			1					
Hemangiosarcoma				1		2		
Adrenal Tumor					1			
Esophageal Tumor						1		
Intervertebral Disc Protrusion							1	
Mammary Tumor					1			

[a] Number of dogs with lesions associated with death.

All the dogs in Dose-Level Group 5 died or were euthanized 34 to 92 months after plutonium exposures. The principal cause of death at this exposure level was osteosarcoma, which occurred in 17 of 20 dogs; several had more than one site. The sites of the osteosarcomas were lumbar vertebrae (four dogs), cervical vertebrae (three dogs), thoracic vertebrae (two dogs), humerus (five dogs), pelvis (two dogs), facial bones (two dogs), ribs (two dogs), and nasal turbinates (one dog). Metastases to distal sites occurred in six dogs; these dogs also had radiation osteosis, generally characterized by peritrabecular fibrosis.

Other deaths in Dose-Level Group 5 were caused by radiation pneumonitis (two dogs) and multiple lung tumors (one dog). The multiple lung tumors, in different lobes, were papillary adenocarcinomas, combined epidermoid and adenocarcinoma, and bronchioloalveolar carcinoma; metastases were present in the tracheobronchial lymph nodes.

Malignant but nonfatal lung tumors were also present in nine dogs from Dose-Level Group 5 that died from osteosarcomas and in one dog that died from radiation pneumonitis. Typically, these arose subpleurally, proximal to areas of interstitial fibrosis or small cavities communicating with bronchioles. They consisted of bronchioloalveolar carcinomas in four dogs; papillary adenocarcinomas in two dogs; both bronchioloalveolar carcinoma and papillary adenocarcinoma in one dog; both papillary and tubular adenocarcinomas in one dog; a combined epidermoid and adenocarcinoma in one dog; and a bronchioloalveolar carcinoma, papillary adenocarcinoma, and a mixed lung tumor in one dog. No metastases of these lung tumors were observed.

In Dose-Level Group 4, 10 dogs have now died, 54 to 114 months after plutonium exposure. The principal causes of death were bone tumors (five dogs), lung tumors (three dogs), suppurative pleuritis (one dog), and congestive heart failure (one dog). Three dogs that died because of bone tumors also had nonfatal lung tumors.

Mortality in the remaining exposure level groups was similar to that in control groups, and the incidence of fatal lesions was similar among control groups of dogs and the three lower exposure levels. Lung tumors were present in two of the five dogs in Dose-Level 3 that died from miscellaneous other causes. Perhaps the most significant observation in this study thus far is that lung tumors were observed at 9 to 10 years after exposure. This is 5 years after the plutonium content of the lung is less than 1% of the final body burden, and a time when bone and liver contain more than 95% of the final body burden.

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

Principal Investigator: C. L. Sanders

Other Investigators: K. E. Lauhala, J. A. Mahaffey, and K. E. McDonald

A total of 3192 female Wistar rats, 198 male Wistar, 192 female Long-Evans and 200 female Fischer-344 rats were either sham-exposed or given a single inhalation to $^{239}PuO_2$ and are being examined during their lifespan for tumor formation. Histopathological analyses have been completed on 1459 of the 3192 rats in the initial lifespan study. Percentages of animals with lung tumors, and their doses (in parentheses), are: 0.7% (sham-exposed controls); 0.4% (5.9 rad); 0% (11 rad); 0% (23 rad); 3.4% (46 rad); 0% (84 rad); 12% (190 rad), 19% (350 rad); 66% (740 rad); 77% (1500 rad). The dose-response curve continued to be best fitted by a quadratic function and a "practical" threshold of about 100 rad, with maximum incidence at about 800 rad. Plutonium particle aggregation was measured in 303 of the lifespan rats in the initial study with lung doses >35 rad. A mean, focal, chronic dose-rate of only a few rad per day from peribronchiolar $^{239}PuO_2$ aggregates was sufficient to induce lung carcinomas, preceded by a cellular evolution of inflammation, fibrosis and bronchiolar hyperplasia and metaplasia. Bronchiolar alpha-star distribution was determined by quantitative scanning electron microscopy autoradiography. The majority of the bronchiolar dose was delivered by plutonium particles retained for prolonged periods in peribronchiolar alveoli.

Previous lifespan studies in rats exposed to ^{239}Pu aerosols indicated that lung-tumor incidence might be increased at radiation doses to the lung comparable to doses received by humans from the maximum permissible occupational lung deposition of 16 nCi ^{239}Pu. A total of 3192 young-adult, female, SPF, Wistar rats were used in the initial lifespan study: 2134 were exposed to $^{239}PuO_2$ at initial lung burdens (ILB) ranging from 0.25 nCi to about 180 nCi, and 1058 were sham-exposed. Histopathological analyses have been completed on 1459 of the 3192 rats, including 464 sham-exposed controls and 995 exposed animals. Cell kinetic, autoradiographic and morphometric techniques are being used to evaluate the spatial-temporal dose-distribution patterns and the cellular events leading up to lung-tumor formation in 167 serially sacrificed female Wistar rats given a single exposure to $^{239}PuO_2$. In addition, 198 male Wistar rats, 192 female Long-Evans rats and 200 female Fischer-344 rats were exposed to aerosols of $^{239}PuO_2$, in order to compare lung-tumor response at lung doses of about 100 and 1000 rad in other strains and in male rats (Table 1).

Lifespan Tumor Studies

The percentages of all rats with lung tumors (mean dose level) were: 0.7% (sham-exposed controls); 0.4% (5.9 rad); 0% (11 rad); 0% (23 rad); 3.4% (46 rad); 0% (84 rad); 12% (190 rad), 18% (350 rad); 66% (740 rad); and 77% (1500 rad). Only three primary lung tumors, including one adenocarcinoma, were seen in 464 sham-exposed controls. A total of 105 lung tumors were found in 995 exposed rats, including 59 squamous cell carcinomas, 27 adenocarcinomas and 10 hemangiosarcomas. To date, only four lung tumors (two were pulmonary carcinomas) have been found in 769 rats with lung doses of less than 100 rad (incidence of 0.52%); 101 lung tumors (of which 88 were pulmonary carcinomas) have been found in 226 rats with lung doses greater than 100 rad (incidence of 45%). This indicates the possibility of a practical threshold dose of about 100 rad for lung-tumor formation from inhaled $^{239}PuO_2$, below which a tumor is much less likely (Table 2).

TABLE 1. Status of Study Groups as of October 1987.

Strain	Sex	Mean IAD, nCi[a]	Number of Rats Alive	Number of Rats Dead	Completed Histopathology
Wistar	F	0	0	1058	464
Wistar	F	0.44 ± 0.09	0	919	284
Wistar	F	0.79 ± 0.20	0	610	198
Wistar	F	1.7 ± 0.33	0	163	128
Wistar	F	3.5 ± 0.90	0	112	89
Wistar	F	6.1 ± 1.2	0	105	84
Wistar	F	15 ± 3.1	0	36	33
Wistar	F	26 ± 5.7	0	68	61
Wistar	F	58 ± 20	0	46	44
Wistar	F	120 ± 37	0	75	74
Wistar	M	0	54	6	0
Wistar	M	6.8 ± 2.8	67	11	0
Wistar	M	94 ± 21	46	14	0
Long-Evans	F	0	57	3	0
Long-Evans	F	5.1 ± 1.3	65	7	0
Long-Evans	F	77 ± 16	49	11	0
Fischer-344	F	0	60	0	0
Fischer-344	F	5.6 ± 1.1	76	4	0
Fischer-344	F	75 ± 7.9	47	13	0
Wistar[b]	F	0	25	30	
Wistar[b]	F	104 ± 32	37	75	

[a] Initial alveolar deposition + standard deviation

[b] Serially killed at 1, 14, 30, 60, 90, 120, 151, 180, 210, 240, 270, 300, 350, 400, 450, 500, 550 and 600 days after inhalation

TABLE 2. Lung Tumors in Female Wistar Rats Following Inhalation of $^{239}PuO_2$ Particles.

Mean Dose to Lung, rad	Number of Rats	Percentage of Rats with Lung Tumors				
		Squamous Carcinoma	Adenocarcinoma	Hemangiosarcoma	Other	Total
0	464	0	0.22	0	0.43	0.65
6.0 ± 1.3	284	0	0.35	0	0	0.35
11 ± 2.1	198	0	0	0	0	0
23 ± 4.5	128	0	0	0	0	0
47 ± 9.6	89	1.1	0	0	2.3	3.4
83 ± 15	84	0	0	0	0	0
190 ± 38	33	9.1	3.0	0	0	12.1
350 ± 71	61	3.3	11.5	0	3.3	18.0
740 ± 140	44	40.9	13.6	9.1	2.3	65.9
1500 ± 360	74	47.3	16.2	8.1	5.4	77.0

The dose-response relationship continues to be best fitted by a pure quadratic function, with an estimated coefficient of 0.00062 (compared with 0.00074, obtained last year). A quadratic function also continues to provide the best fit for both lung adenocarcinoma and squamous carcinoma types. We continue to propose that the lower dose-range of the quadratic curve (<100 rad) represents primarily initiation (mutation) events, while the much steeper, higher dose portion of the curve (>100 rad) represents mostly promotion events due to plutonium particle aggregation, resulting in the progressive expression of carcinogenesis.

The incidence of nonpulmonary tumors in several organs was higher in exposed rats than in controls. For example, the incidence of brain tumors was 3.2 greater than in controls, while thyroid tumors occurred 2.5 times more often than in controls. Some tumor types were found only in exposed animals; for example, cranial sarcomas (eight), and thyroid carcinomas (10; Table 3).

Scanning Electron Microscopy (SEM) Pathology and Quantitative Autoradiography

An SEM autoradiographic technique has been developed that gives a more three-dimensional view of a comparatively large lung tissue mass than is possible with light or transmission electron microscopy autoradiography. Fifty young-adult Wistar rats were exposed to an aerosol of high-fired, submicron-sized ^{169}Yb, $^{239}PuO_2$ particles (mean initial alveolar deposition, 104 ± 32 nCi) and examined with SEM at time intervals up to 240 days after exposure. The cardiac lobe was prepared for SEM histopathologic and SEM autoradiograph examination. All airways sectioned at an oblique angle, thus exposing a flat epithelial surface, were examined by SEM autoradiography. The total area of this flat surface was measured, and the number of alpha stars were counted. Stars were differentiated according to position on the epithelial surface or radiating through the mucosa from adjacent alveoli (Figures 1 and 2).

Plutonium particle concentration on the surface of bronchioles was about 10 times greater than particle concentration on the surface of the trachea at all time periods. Clearance curves for particles on the surface of bronchioles and trachea were biphasic, like those seen for the whole lung when measured by liquid scintillation counting. The majority of radiation dose delivered to the bronchiolar epithelium was from plutonium particles in peribronchiolar alveoli. Peribronchiolar particles appeared to be preferentially retained, while most other alveolar particles were rapidly cleared from the lung (Figure 3). The prolonged peribronchiolar particle retention may play a prominent role in the development of lung carcinomas.

Primary lung carcinoma formation is preceded by a cellular evolution of focal inflammation, fibrosis, and epithelial hyperplasia and metaplasia associated with plutonium aggregates. Particle aggregation increased with time, resulting in well-defined focal inflammatory lesions after 120 days and fibrotic lesions after 180 days. High alpha-radiation doses were delivered to bronchiolar and subpleural surfaces adjacent to plutonium particle aggregates. Mononuclear inflammatory cells, composed largely of histiocytes, were markedly more numerous in small, focal regions of plutonium particle aggregation (Figure 4). The initial inflammatory cell response was followed by accumulation of necrotic cells, alveolar fibrosis, loss of functional capillaries, loss of inflammatory cells, decrease in alveolar space, alveolar collapse and replacement with scar tissue. Bronchiolar hyperplasia and adenomatous bronchiolization, composed in part of ciliated cells, were first seen at 180 days, increasing in severity by 240 days. Hyperplastic, inflammatory and fibrotic lesions were clearly associated with particle aggregations.

TABLE 3. Distribution of Tumors According to Location and Tumor Type in the Intial $^{239}PuO_2$ Lifespan Study with Female Wistar Rats.

		Control		Exposed		
Location	Tumor Type	Number	Percent	Number	Percent	Exposed/Control
Abdominal Cavity	All Types	0	0	8	0.8	---
Adrenal	All Types	10	2.2	26	2.6	1.2
Auditory	All Types	2	0.43	8	0.81	1.9
Bone	All Types	2	0.43	3	0.30	0.7
Brain	All Types	3	0.65	21	2.1	3.2
	Gliomas	3	0.65	10	1.0	1.5
	Sarcomas	0	0	8	0.81	---
Eye	All Types	0	0	1	0.10	---
G.I. Tract	All Types	2	0.43	8	0.81	1.9
Harderian	All Types	0	0	1	0.10	---
Heart	All Types	3	0.65	3	0.30	0.5
Kidney	All Types	6	1.3	13	1.3	1.0
Liver	All Types	0	0	3	0.31	---
Lung	All Types	3	0.65	105	10.7	16.5
	Squamous Carcinoma	0	0	59	6.0	---
	Adenocarcinoma	1	0.22	27	2.8	12.5
	Hemangiosarcoma	0	0	10	1.0	---
	Others	2	0.43	9	0.9	2.1
Lymph Node	All Types	5	1.1	16	1.6	1.5
Mammary	All Types	172	37.1	298	29.9	0.8
Muscle	All Types	0	0	3	0.31	---
Nasal Cavity	All Types	0	0	2	0.20	---
Oral Cavity	All Types	0	0	1	0.10	---
Ovary	All Types	0	0	5	0.51	---
Pancreas	All Types	5	1.1	3	0.31	0.3
Pituitary	All Types	237	51.1	415	41.7	0.8
Salivary	All Types	0	0	3	0.31	---
Skin	All Types	47	10.1	65	6.5	0.6
Spleen	All Types	3	0.65	5	0.51	0.8
Thymus	All Types	3	0.65	14	1.4	2.2
Thyroid	All Types	6	1.3	32	3.3	2.5
	Adenomas	6	1.3	20	2.0	1.6
	Carcinomas	0	0	10	1.0	---
Urinary Bladder	All Types	0	0	1	0.1	---
Uterus	All Types	132	28.4	226	22.7	0.8

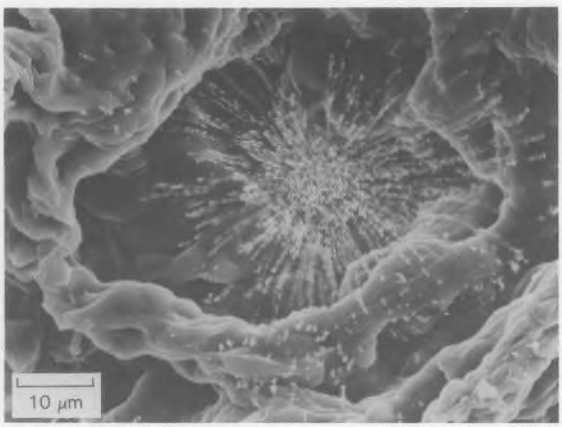

FIGURE 1. Scanning Electron Microscopy Autoradiograph Showing an Alpha-Star in the Alveolar Region at 210 Days after Inhalation of $^{239}PuO_2$.

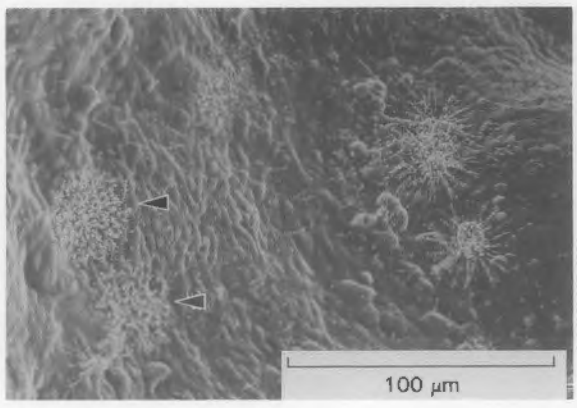

FIGURE 2. Scanning Electron Microscopy Autoradiograph, Showing Distribution of Alpha-Stars Originating from Macrophages on the Surface and from Adjacent Alveoli (Arrows) at 150 Days after Inhalation of $^{239}PuO_2$.

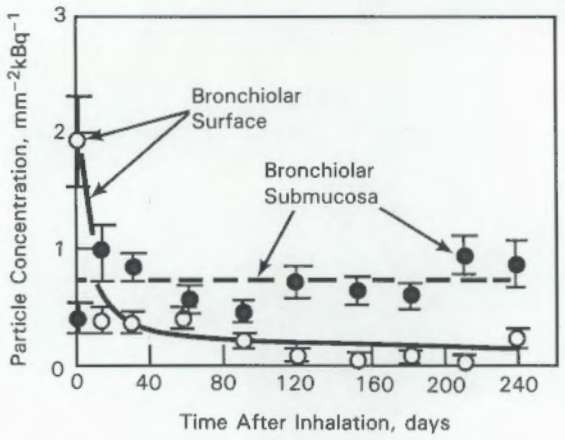

FIGURE 3. Concentration of Inhaled $^{239}PuO_2$ Particles on the Surface of Bronchioles and in Adjacent Submucosal Regions as a Function of Time after Exposure. Points are means with standard error bars (n = 5).

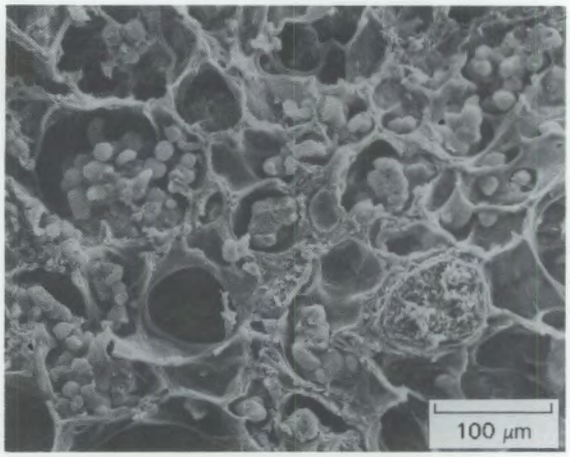

FIGURE 4. Scanning Electron Microscopy View of Inflammatory Cell Accumulation within Hyalinized, Nonfunctional Alveoli, Caused by Focal Aggregration of $^{239}PuO_2$ Particles at 240 Days after Inhalation.

Promotion of Lung-Tumor Formation by Plutonium Particle Aggregation

Promotion of lung tumor formation in rats from inhaled $^{239}PuO_2$ may be associated with aggregation of plutonium particles near bronchioles. The relationship of plutonium particle aggregation in the lung and the development of lung tumors after inhalation of $^{239}PuO_2$ was studied in 664 lifespan rats (from the initial lifespan study), including 361 sham-exposed (control) rats and 303 exposed rats at mean lung doses ranging from 35 to 2000 rad. Plutonium particle concentration and aggregation were determined from autoradiographic sections of the left lung lobe. Both the increase in particles/cm^2 and mean number of particles per aggregate up to 2000 rad and the increase in aggregates/cm^2 up to 800 rad were directly proportional to lung dose. Aggregates with >25 particles increased linearly with dose from 0.2% at 140 rad to 8.2% at 2000 rad (Figure 5) in a pattern similar to increasing severity of pulmonary fibrosis and the incidence of lung tumors. Lung tumor incidence increased from about 6% at 140 rad to 83% at 800 rad; no further increase in lung tumors was seen at doses >800 rad (Figure 6). Maximum lung tumor incidence at 800 rad corresponded to a particle concentration of 130/cm^2 and an aggregate concentration of 25/cm^2, with 4% of aggregates having >25 particles. Aggregation of inhaled plutonium particles in clusters of >25 particles resulted in daily doses of a few rad to focal tissue regions containing clustered particles. These doses appeared sufficient to cause pulmonary fibrosis and promotion of pulmonary carcinogenesis.

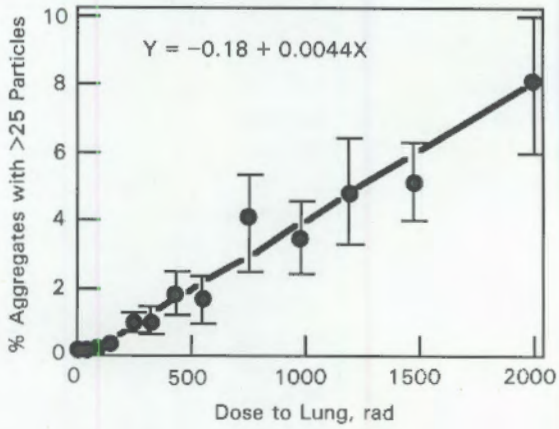

FIGURE 5. Relationship of Percentage of Plutonium Particle Aggregates with >25 Particles to Radiation Dose to the Lung Following Inhalation of $^{239}PuO_2$. Values are means ± standard error.

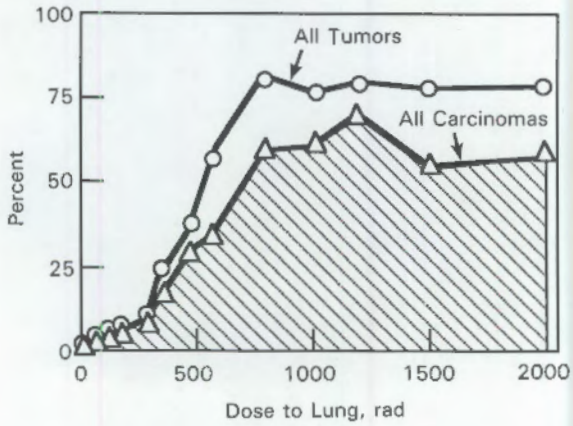

FIGURE 6. Relationship Between Incidence of Lung Tumors and Radiation Dose Following Inhalation of $^{239}PuO_2$.

• Inhalation Hazards to Uranium Miners

Principal Investigator: F. T. Cross

Other Investigators: E. F. Blanton, R. L. Buschbom, G. E. Dagle, R. A. Gies, E. S. Gilbert, H. A. Ragan, and C. O. Romsos

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

Using both large and small experimental animals, the goal is to investigate levels of air contaminants that produce respiratory system disease in radon-exposed populations. Lung cancer incidence and deaths from degenerative lung disease are significantly elevated among uranium miners, but the cause-effect relationships for these diseases are based on inadequate epidemiological data. This project indentifies 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 for 10-working-level (WL) exposure rates show a nonsignificant increase in lung-tumor risk over 100-WL exposure rates for 320 working level months (WLM) exposures suggesting a tapering-off of the inverse exposure rate effect at occupational and environmental rates of radon exposure. More rigorous analyses of the data confirm the presence of an inverse exposure rate effect above 100 WL and 640 WLM, particularly when the tumors are considered incidental to the death of the animal. Exposures of rats to uranium ore dust alone was completed, and renal function data are reported.

Small-Animal Studies

The 6000 (1000-working level; WL) and 7000 (100-WL) 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 (100-WL) 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 exposure level. The exposures of 6000, 7000 and 8000 Series animals are completed. Exposures of 9000 Series animals are temporarily discontinued, ceasing with the 80-WLM and 15-mg/m^3 ore dust exposures. Exposures of rats to uranium ore dust alone (10,000 Series experiments; Table 4) was completed, along with urinalyses. The ore-dust studies address recent experimental data in rats (as well as human epidemiological data) linking silica exposures to lung cancer. Because the silica content of the ore dust in the PNL animal studies exceeds 60%, this potential link in the response to combined ore-dust and radon-daughter exposures needed to be clarified.

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

Number of Animals[a]	Exposure Regimen[b,c]	Total Exposure, WLM[d]
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	10,240
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	5120
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	2560
32	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	1280
64	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	640
128	1000 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	320
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 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration. Previous exposure at 900 WL for 84 hr/wk to 9200 WLM produced an 80% incidence of carcinoma.

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

Number of Animals[a]	Exposure Regimen[b]	Total Exposure, WLM[c]
64	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	640[d]
64	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	320[d]
160	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	160
352	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	80
448	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	40
512	100 WL Radon Daughters 15 mg/m^3 Uranium Ore Dust	20
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 1.3×10^5 MeV of potential α-energy. Working Level Month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

[d] Repeat exposure is for normalization with Table 1 data.

The 7000 (100-WL) Series animals show an increase in lung tumors, compared to the 6000 (1000-WL) Series animals, at all exposure levels except 320 WLM (Figure 1). The ratios of percent lung tumors, uncorrected for life-shortening differences, (7000 Series/6000 Series) progressively increase from 1.6 at 5120 WLM to 2.8 at 640 WLM.

The 9000 (10-WL) Series animals, exposed to 15 mg/m^3 uranium ore-dust concentrations, continued to show an increase in lung tumors at 320 WLM (Figure 1). However, these data, uncorrected for life-shortening differences, are not significantly different from the similar 100-WL and 1000-WL exposure-rate data. This would suggest, in the absence of more detailed analyses, a tapering-off of the inverse exposure rate effect at occupational and environmental rates of radon exposure. However, data from other animals in the 8000 and 9000 Series experiments have not yet been analyzed. Preliminary data regarding the 320-WLM exposures at 3 mg/m^3 dust concentration do not alter these conclusions.

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 1.3×10^5 MeV of potential α-energy. Working level month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

TABLE 4. Control Study for Uranium Ore Dust Carcinogenesis in Rats (10,000 Series Experiments).

Number of Animals	Exposure Regimen[a]
96	15 mg/m^3 Uranium Ore Dust
64	Sham-Exposed Controls

[a] Exposures, 12-18 mo at 72 hr/wk; planned periodic sacrifice.

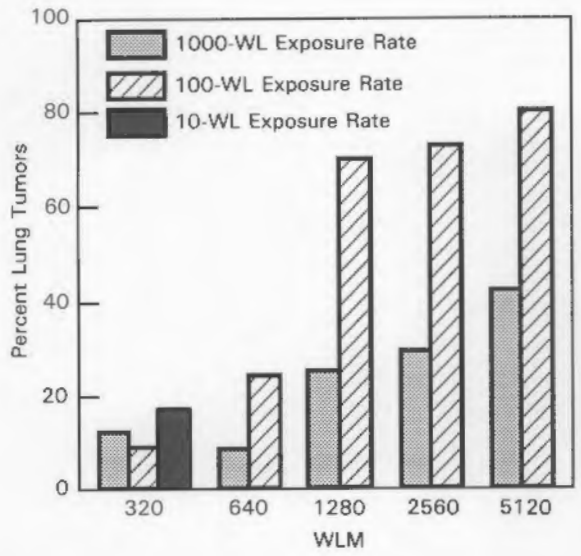

FIGURE 1. Percent of Lung Tumors in Rats Versus Radon-Daughter Exposure Rate and Level. WLM = Working Level Months (see Text).

Age-specific lung cancer risks in rats exposed at 100-WL concentrations (7000 Series experiments) were compared with those in rats exposed at 1000 WL (6000 Series experiments), based on alternative assumptions: 1) that all malignant tumors are fatal, or 2) that all tumors are incidental to the death of the animal. Preliminary analyses yield evidence for higher risks above 640 WLM for low-dose rates, with higher significance when the tumors are considered incidental.

Renal function was evaluated on 15 uranium-ore-dust exposed and 15 control rats in the 10,000 Series experiments following 67 weeks of sham exposure or exposure to 15-mg/m^3 ore dust concentrations (1.6 µm mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] of 2.8). The ore dust contained about 2% U_3O_8 by weight. Tests conducted on 16-hour urine samples collected over ice included: specific gravity, pH, glucose, protein, creatinine, electrolytes (Na, K, Cl), glutamic oxaloacetic transaminase, gamma glutamyl transpeptidase, alkaline phosphatase, and a microscopic examination of sediment. There were no statistically significant differences in water consumption, urine volume voided, specific gravity, pH or urinary sediment for the exposed rats compared with their controls. When corrected for urine volume, there were no significant differences in urine chemistry between exposed and control animals.

Large-Animal Studies

Beagle dogs on study to determine the pathogenic role of carnotite uranium ore dust in inhalation exposures were killed in FY 1986 following a total of 9.1 years of exposure (20 hours/week) to 15 mg/m^3 uranium ore-dust concentrations; the uranium content ranged from 2 to 4%. The tissues await histopathological examinations.

• Mechanisms of Radon Injury

Principal Investigator: F. T. Cross

Other Investigators: R. L. Buschbom, W. C. Cannon, G. E. Dagle, H. S. DeFord, M. E. Frazier, R. A. Gies, R. F. Jostes, F. C. Leung, S. Marks, J. A. Reese, L. L. Scott, G. L. Stiegler, and R. B. Westerberg

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

In this new project, we conduct molecular, cellular and whole-animal research relevant to understanding the inhalation toxicology of radon and radon-daughter exposures. The work specifically addresses the exposure-rate effect in radon-daughter carcinogenesis; the induction-promotion relationships associated with exposure to radon and cigarette-smoke mixtures; the role of oncogenes in radon-induced cancers; the effects of radon on DNA as well as on DNA repair processes; and the involvement of growth factors and their receptors in radon-induced carcinogenesis. Preliminary experiments showed that oncogenes are activated in radon-induced lung tumors. We have therefore begun further exposures pertinent to the oncogene and growth-factor studies. An in vitro radon cellular-exposure system was designed, and cell exposures were initiated. Initiation-promotion-initiation studies with radon and cigarette-smoke mixtures have also begun; and we are compiling a radon health-effects bibliography.

Oncogene Studies

Preliminary experiments revealed that oncogenes were activated in radon-induced lung tumors. High-molecular-weight DNA from three radon-exposed rats caused transformation frequencies 10 times more often than DNA from normal lung. Experiments to identify and isolate the transforming genes will be initiated.

Exposures of male SPF Wistar rats to mixtures of radon, uranium ore dust and cigarette smoke were begun for eventual determination of oncogene and growth factor/receptor involvement. Cumulative radon-daughter levels were 320 working level months (WLM); uranium ore-dust concentrations ranged from 4 to 6 mg/m^3. Cigarette smoke, in exposures of 1 hour/day 5 days/week, for 17 weeks, contained total particulate mass concentrations of about 0.5 mg/L and carbon monoxide concentrations between 600 and 700 ppm.

Growth Factor/Receptor Studies

We are using immunocytochemistry to examine the involvement of growth factors and receptors in radiation-induced lung tumors that have been preserved in paraffin block sections. Dog lung squamous-cell tumors demonstrated elevated epidermal growth factor receptors (EGF-R) in a radioreceptor binding assay. This capability for measuring molecular markers in paraffin block sections will be employed to examine EGF-R involvement in lung tumors (both radon-induced and spontaneously occurring) collected from dogs and rodents in previous experimental radon studies.

In Vitro Radon Cellular-Exposure System and Cellular Studies

An in vitro, noncirculating radon exposure system containing 0.7 Ci ^{226}Ra, which generates approximately 88 µCi ^{222}Rn per minute, was designed for cell-culture irradiation. Unused radon is trapped in a charcoal-filtered radon-holdup-system. Exposure parameters are determined by controlling radon, room air and vacuum flows. The cell-culture environment utilizes CO_2 for pH control, sterile filters, a water bath for temperature control, and a magnetic stirrer. Mechanisms for sample injection and removal are included. We have conducted dosimetric calibration of the system, and radon cellular studies have begun. They include radon exposures of cycling peripheral human lymphocytes in suspension culture, to determine the level and spectrum of chromosomal aberrations.

Initiation-Promotion-Initiation Studies

Initiation-promotion-initiation experiments are in progress in male SPF Wistar rats with radon and cigarette-smoke mixtures. Our objective is to determine: 1) the respective roles of radon and cigarette smoke in lung tumorigenesis, and 2) to see if these lung tumors are consistent with the two-stage model of carcinogenesis developed elsewhere in mouse-skin studies. The exposure protocols are shown in Table 1.

TABLE 1. Initiation-Promotion-Initiation Protocol for Radon (R), Dust (D) and Cigarette Smoke (S) Inhalation Exposure of Rats[a].

	Duration of Exposure, wk					
Group	0	4	8	17	21	25
1	R + D ---------- →					
2	R + D ---------- →				R + D ---------- →	
3	R + D ---------- → S ----------				R + D ---------- →	
4	R + D ----------		→ S ----------			→
5	S ----------			→ R + D ----------		→
6	D ----------		→ S ----------			→

[a] Moderately low concentrations of uranium ore dust (D)accompany radon exposures as the carrier aerosol for the daughters; sham-exposed control animals (not shown) are included in each pair of exposure groups. Animals from each group are killed at 25 or 52 weeks to evaluate developing lesions. Protocol may be repeated for different radon-daughter exposure rates and levels.

Initial exposures are at 100-WL concentrations with cumulative levels up to 320 WLM; ore-dust concentrations are approximately 4 to 6 mg/m^3. Cigarette-smoke exposures are given for 1 hour/day, 5 days/week for 17 weeks. Total particulate mass and CO concentrations are about 0.5 mg/L and 600 to 700 ppm, respectively. Exposures of Group 1 and portions of Groups 3 and 4 animals to radon and dust were completed.

Radon Health-Effects Bibliography

We are compiling a bibliography on the health effects of radon inhalation exposures. Topics currently included are experimental animal studies and human epidemiology studies.

• Aerosol Technology Development

Principal Investigator: W. C. Cannon

Other Investigators: E. F. Blanton, B. J. Greenspan, and O. R. Moss

Under this project we have developed methods and apparatus for employing aerosols in studying the biological effects of energy-related pollutants in animals. This year we have completed the exposure-chamber-development phase of the project, and we report here on improvements in both nose-only and whole-body exposure equipment.

Performance of a Whole-Body Exposure Chamber at Low Flow Rates

The Battelle-designed Hazleton-1000 whole-body exposure chamber was designed to be operated at 10 cfm flow through the chamber, but operation at higher flow rates has also proven quite satisfactory. Thorough mixing of chamber air is achieved by a set of baffles in the chamber, which also perform the function of excreta catch pans.

Recently, the need arose to operate Hazleton-1000 chambers at low flow rates so that exposure concentrations of radon gas could be increased. (The output of the radon gas source was fixed.) Since the performance of these chambers had not been assessed at flows below 10 cfm, we performed experiments to evaluate chamber performance at 2 cfm by studying water flow patterns in a transparent, 1/6th-scale model of the chamber. The flow rates in the model were chosen so that the Reynolds numbers of water flow in the model would equal those of a 2-cfm air flow in the actual chamber. Under these conditions, flow patterns in the model are the same as scale models of flow patterns in the chamber. The criterion for acceptable operation was that the time, t_u (determined visually), required for a bolus of colored dye to be uniformly distributed throughout the chamber should be no more than one-quarter of a "change time," t_c (numerically equal to the chamber volume divided by the flow rate). In the model, t_c is 20.6 min; in the full-scale chamber, at 2 cfm t_c is 39.3 min.

The model test set-up is shown schematically in Figure 1. In the first test, with the unmodified chamber, t_u was nearly 0.5 t_c, with a flow rate equivalent to 2 cfm.

We then modified the original (full-scale) chamber inlet (an annular slit, 1 in. wide x 3 in. diameter). The modified inlet has four holes, 7/16 in. diameter, arranged so that the jets coming through the holes impinge on the four walls of the chamber top transition piece. This modification increased flow velocity at the inlet and promoted better mixing: t_u was reduced to about 0.2 t_c.

Animal loading must also be considered when operating these chambers at reduced flow rates. If animal loading is too high, other problems may arise, including increased humidity and ammonia levels (from urine) in the chamber, as well as high CO_2 levels and even oxygen depletion. These problems may exist even though mixing is improved with the modified inlet. They must be considered when undertaking exposures at reduced flow rates.

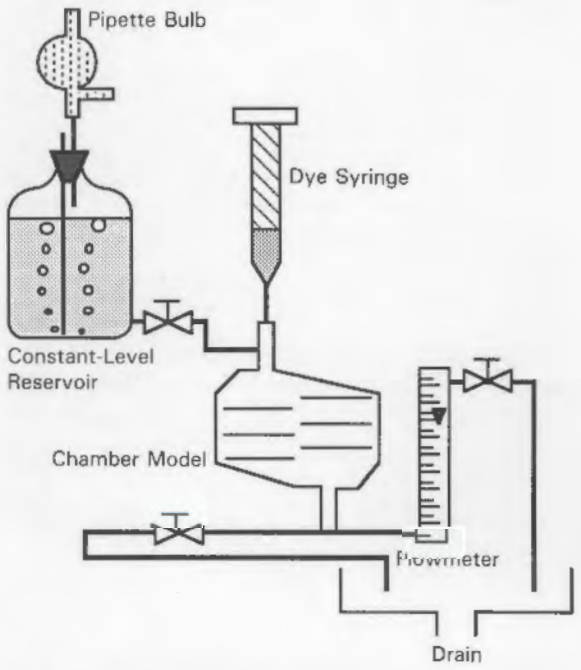

FIGURE 1. Schematic Diagram of the Set-Up Used to Assess the Performance of a Whole-Body Animal Exposure Chamber at Low Flow Rates.

Evaluating a New Nose-Only Exposure Chamber

An improved, nose-only, rat exposure chamber was described in the Annual Report for FY 1986. Because of its modular design, that chamber could be cleaned easily, and its size could be adjusted to the number of animals in an exposure group. However, a drawback of that design was that making leak-

tight seals between the modules required extra machine work in manufacturing the chamber.

Last year, when several chambers were needed for a non-DOE project, it was decided to change the design to reduce manufacturing costs. (This redesign was funded by Battelle as a natural part of our technology transfer process, rather than by DOE.) The resulting chamber has a fixed number of exposure ports (48) arranged in 12 tiers of 4 ports each and costs between one-half and one-third as much to manufacture as the original. Adjustments can be made for small exposure groups by blocking off unused ports to avoid wasting aerosol.

The new chamber has another advantage. The overall diameter of the chamber (without rat containment tubes) was reduced from 9 to 6.5 in., allowing the chamber to be inserted in a glove-box through a standard 8-in. glove port. A plastic bag is fitted over the port to permit even a contaminated chamber to be safely inserted in or removed from the glove box. Several chambers, each dedicated to a different aerosol, can be used in a single glove box.

These newest chambers have not yet been used for radioactive aerosol exposures, therefore we have no aerosol deposition data to demonstrate their performance. However, to evaluate these chambers for future DOE use we conducted tests to demonstrate that they will provide the same high-quality exposures as those of the previous design, but at lower cost. In a uniformity test, we compared concentration measurements at a single reference port to that at the other 47 ports. The mean concentration ratio was 0.996, and the standard deviation was 0.032; the maximum deviation was 0.072. We determined that less than 0.2% of the aerosol in the exhaust manifold of the chamber reached exposure ports. The measured total leak rate into a sealed chamber was less than 35 cc/min, which is only 14% of the minimum recommended aerosol flow rate to each exposure port.

A Chamber for Nose-Only Exposure of Dogs

The success of the flow-past configuration in nose-only exposure chambers for rats led to consideration of this scheme for nose-only chambers for dogs. Previous chambers accommodated only one dog. However, we recognized that in cases where containment requirements would not preclude multiple exposures, there would be an advantage to exposing more than one dog at a time. The cylindrical arrangement of the rat chambers appeared ideal for a chamber that would accommodate up to four dogs at a time.

A schematic diagram of this chamber is shown in Figure 2. Aerosol first enters the inlet manifold [1]. Short side arms [2], extending radially out from the inlet manifold, conduct aerosol to the inlet end of a venturi [3], through which aerosol is drawn when the dog inspires. This venturi is the sensing element of an instrument that measures the volume of each breath. On inspiration, aerosol passes through a passive valve system [4] into a special mask [5], which fits around the dog's muzzle. On expiration, exhaled air is diverted to an exhaled aerosol sampler (filter) [6], then into the exhaust system downstream from the chamber exhaust manifold [7]. Excess aerosol from each side arm flows into the exhaust manifold, which is concentric with the inlet manifold.

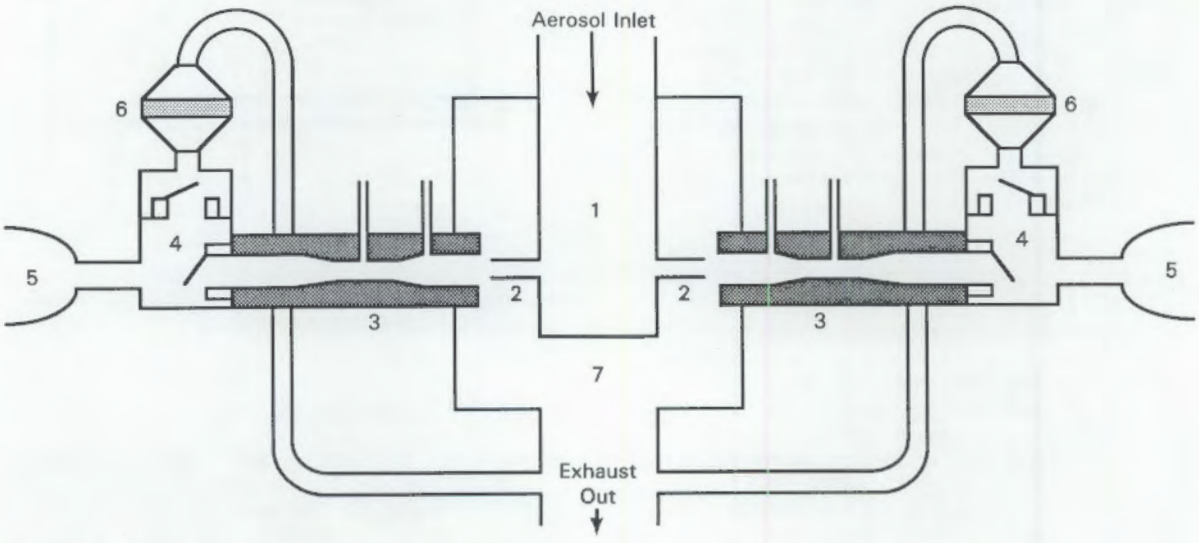

FIGURE 2. Sketch of the Nose-Only Exposure Chamber for Dogs, Showing a Side View. Number labels are referred to in text. Two Other Exposure Ports (not shown) are in the Front and Rear of the Chamber.

In the old-style chambers, a single venturi was inserted through the wall of a cylindrical aerosol chamber. Aerosol was drawn into the port during inspiration and exhaled air was either returned to the chamber or drawn off by aerosol samplers.

In addition to allowing multiple exposures, the new chamber differs from the old in the interval between the time aerosol is introduced into the chamber and the time when the dog receives the full concentration. If, at time t = 0, an aerosol of concentration C is introduced, with a flow F, into a well-mixed chamber of volume V, the time, t_{99}, for the concentration in the chamber to reach 0.99 x C is 4.605 x (V/F). The value of V for the old chamber is 18.29 L; for the new chamber it is 0.38 L (the volume of the inlet manifold plus that of the side arms). At a flow of 10 L/min, t_{99} would be 8.4 min for the old chamber but only 10.5 sec for the new chamber. In actual operation, the minimum flow through each side arm should equal the peak flow into the venturi during inspiration, so that only fresh aerosol is drawn in. This would require 10 L/min (or more) per dog, and t_{99} should then be even less than 10.5 sec when more than one dog is exposed at a time. To minimize stress, dog exposures at PNL usually last 30 min or less. For accurate exposure control, therefore, it is important to have the chamber fill rapidly at the beginning of an exposure and clear rapidly at the end, because the amount of aerosol inhaled during the filling and clearing times is hard to predict and measure.

When fewer than four dogs are exposed at once, unused ports can be blocked off by plugging the side arms and replacing the venturi with a plug, avoiding waste of aerosol. Aerosol characterization samples are collected either directly from the inlet manifold or at an unused exposure port.

A prototype chamber has been built, and preliminary tests predict that it will perform well in dog exposures.

• Oncogenes in Radiation Carcinogenesis

Principal Investigator: M. E. Frazier

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Technical Assistance: B. Miller, S. R. Peterson, and R. J. Rausch

Lung tumors and leukemic cells obtained from studies of lifespan, dose-effect relationships in beagles exposed either to plutonium by inhalation or to external whole-body gamma-irradiation are being used to examine the role of oncogenes in radiation-induced carcinogenesis. We are in the process of determining whether radiation causes distinctive patterns of genetic change in the activated oncogenes that we have detected. These studies are a necessary first step for determining whether oncogene activation is a cause or an effect of radiation-induced cancers.

To examine the role of oncogenes in radiation-induced cancers, we are examining lung tumors obtained from studies of lifespan dose-effect relationships in beagles exposed to plutonium by inhalation at PNL. We are comparing cells from these tumors with leukemia cells obtained from studies of lifespan, dose-effect relationships in beagles exposed to external whole-body gamma-irradiation at Argonne National Laboratory (ANL).

Initial studies have provided several lines of evidence that oncogenes are activated in radiation-induced malignancies. 1) DNA from radiation-induced cancers (both in lung tumors and leukemias) can transform NIH 3T3 cells. 2) The gene responsible (both in lung tumors and leukemias) is a ras-related oncogene. 3) DNA from plutonium-induced lung tumors contains tumor-specific alterations in the Ki-ras gene, while gamma-radiation-induced myeloproliferative disorders have an activated N-ras. 4) Steady-state levels of ras gene transcripts are higher in plutonium-induced lung cancer tissue than in normal cohort tissue from the same animal. 5) Preliminary observations indicate enhanced expression of myb, fms, and N-ras as well as decreased expression of sis transcripts in spleens from dogs with gamma-radiation-induced myeloproliferative disorders (Table 1).

In summary, data from both the plutonium-induced lung tumors and the gamma-radiation-induced myelogenous leukemias suggest that oncogene sequences of tumor cell DNA are altered following these radiation exposures. In some instances, these changes are more extensive than the single-base changes which have generally been observed in chemically induced or spontaneous tumors in other studies. These findings are consistent with amplification and/or rearrangement of the affected genes.

Examination of bone-marrow cells from beagles exposed to gamma-irradiation revealed a number of cytogenic alterations, including a high incidence of first-chromosomal changes in animals which either have or are developing myeloproliferative disorders. The most frequent observation was a translocation that results in the elongation of the q-arm of the first chromosome (T. Seed, ANL).

TABLE 1. Expressing of Oncogenes in Spleens from Dogs with Gamma-Radiation-Induced Myeloproliferative Disorders.

Dog Number	Leukemia Type[a]	Expression of Oncogene[b]					
		ras	sis	myb	abl	fms	src
1688	Lymphocytic	±	o	±	o	o	o
2331	Myelomonocytic	+	–	+	+	+	o
2385	Myelomonocytic	+	–	+	±	+	o
3863	Myelomonocytic	+	–	+	+	+	o

[a] Only the myelomonocytic leukemias were radiation-induced.

[b] Key:
- o = No detectable change in expression relative to normal spleen
- – = Decreased expression relative to normal spleen
- + = Increased expression relative to normal spleen (>10-fold)
- ± = Slight increase in expression relative to normal spleen

All of the data discussed above suggest that the radiation causes chromosome breaks and rearrangements that activate oncogenes in close proximity to these breaks. This is consistent with the observed relationship (in humans) between chromosome abnormalities in cancer cells and proto-oncogene activation. In human cancers, fragile breakpoints occur in regions that are joined together by translocation and often lie adjacent to or within known proto-oncogene sequences.

Evidence in the literature supports a certain specificity in oncogene activation by cancer-causing agents. In other words, certain chemical agents cause characteristic point mutations in specific oncogenes, and these mutations are consistent with the known mutagenic activity of the chemical agent. Data presented in our portion of last year's Annual Report suggest that the activating mutations are the direct consequence of the agent's specific mutagenic activity. If this is true, it is important to fully characterize the activating lesions in the oncogenes from these radiation-induced tumors. In order to study the molecular events in radiation-induced carcinogenesis, it is necessary to have a detailed knowledge of the molecular damage to these oncogenes. However, the lesion cannot be fully characterized unless the molecular structure of the normal gene is known. Toward this end, we have established a lambda EMBL 3 clone bank of canine genomic DNA sequences. Using characterized mammalian oncogene sequences as molecular probes, we are identifying canine proto-oncogene sequences from our canine DNA fragment library, and determining the exact molecular structure of these specific sequences. This detailed information will be used to design synthetic DNA probes for detecting specific base mutations.

Our first approach is designed to detect specific base-pair changes in a known gene sequence. This procedure has been used extensively to examine changes in the 12th and 61st codons of c-Ki-ras gene. After the sequence of normal Ki-ras gene is determined from the canine library, we will synthesize oligonucleotide probes (15-21 nucleotides in length), which can be used to distinguish between normal and altered canine Ki-ras genes. This will allow us to screen all our lung-tumor DNA samples for a mutational event in or near the 12th or 61st codons of the Ki-ras proto-oncogene. The same technique will be used to examine the N-ras oncogene in the DNA from gamma-radiation-induced myeloproliferative disorders.

Our second approach results in the enzymatic amplification of specific DNA sequences. When the DNA sequences of the normal gene are known, oligonucleotide primers (>21 nucleotides in length) are constructed which correspond to the two ends of the fragments to be amplified (Figure 1). The source of DNA is denatured and allowed to hybridize to the oligonucleotide primers (which are present in excess concentrations). A DNA polymerase and the four deoxynucleoside triphosphates are added, and the primers are extended. This is followed by a series of cycles of denaturation, hybridization and polymerase extension of primers, resulting in an exponential increase in the desired DNA fragment (Figure 2). In this synthesis, the DNA sequences being amplified include the primer regions as well as all the sequences between those two primers. An example of the results of this amplification process is shown in Figure 3. A very small quantity (0.5 ng) of DNA was used to generate the specific DNA fragment observed in the Southern blot. This procedure allows us to extract a specific sequence and produce a 10^6-fold increase in the number of target sequences. Specific enzymatic amplification allows us to conduct detailed sequence analysis of amplified gene sequences that are representative of a population of naturally occurring or activated oncogene sequences (Figure 4).

The advantages of these techniques are clear when compared with the current methods of analysis, which involve molecular cloning and nucleotide sequence determination that can examine only one molecule of an entire population of molecules—a severe limitation when analyzing mutational spectra such as those that may be produced by radiation. For example, using traditional procedures, analysis of the oncogenes from each dog would require library construction, screening, mapping, subcloning, and sequencing of each oncogene. Using the polymerase chain-reaction method described, entire sequences of interest can be amplified and directly sequenced.

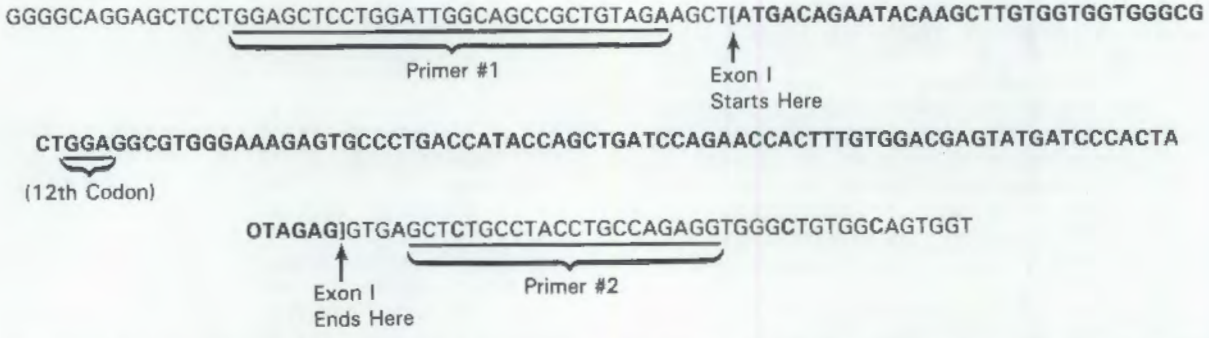

FIGURE 1. Sequence Showing Exon 1 of a c-Ha-ras Gene. The use of these primers in the polymerase chain-reaction method could produce sufficient DNA to allow sequencing of the first exon.

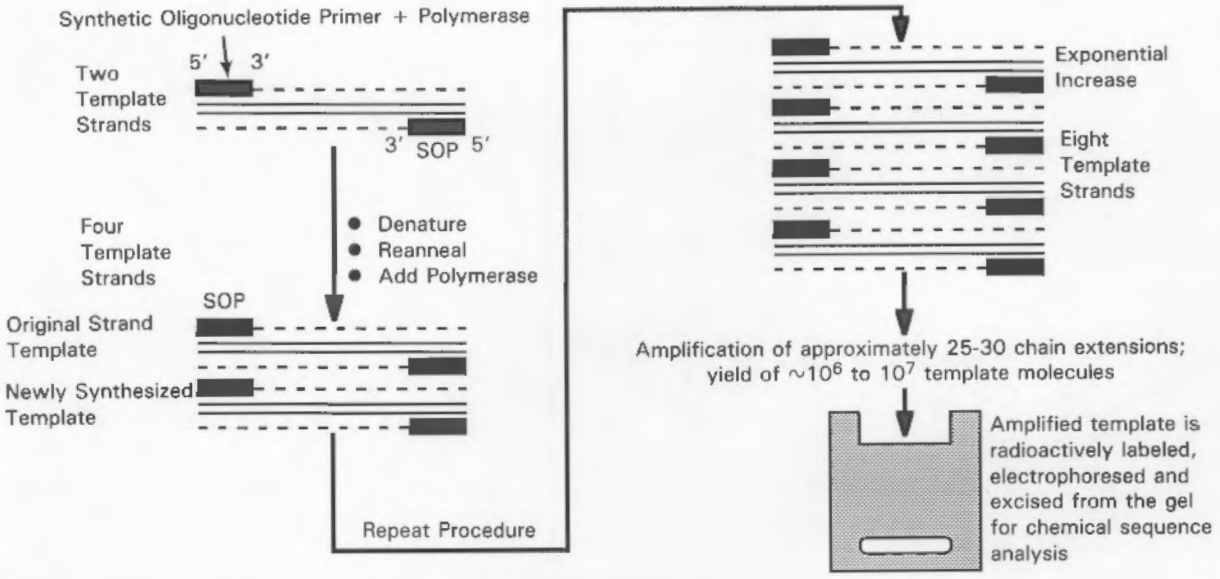

FIGURE 2. Polymerase Chain-Reaction Method for Amplifying Specific DNA Sequences.

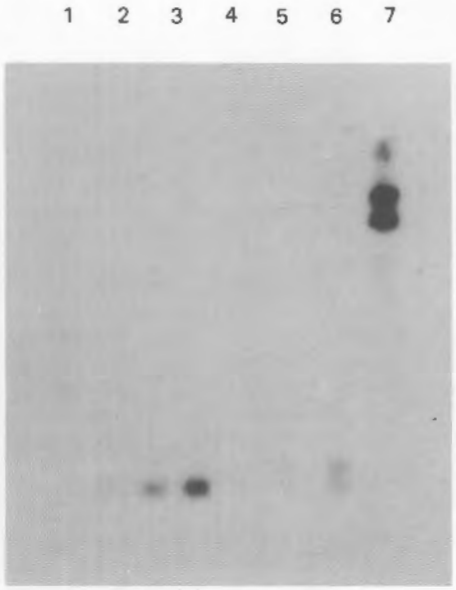

FIGURE 3. Amplified DNA, Produced by a Polymerase Chain Reaction, is Shown by the Arrow. Lanes 1 through 3 contain 1 μl, 2 μl, and 3, μl, respectively, of the completed reaction mixture, which contained only 0.5 ng DNA at the start of the procedure. The final volume of the reaction mixture was 30 μl. Lanes 4 through 6 contain 1 μl, 2 μl, and 3 μl of the exon 1 product, which has been cut with the restriction endonuclease Bam H1. This digestion produces two fragments.

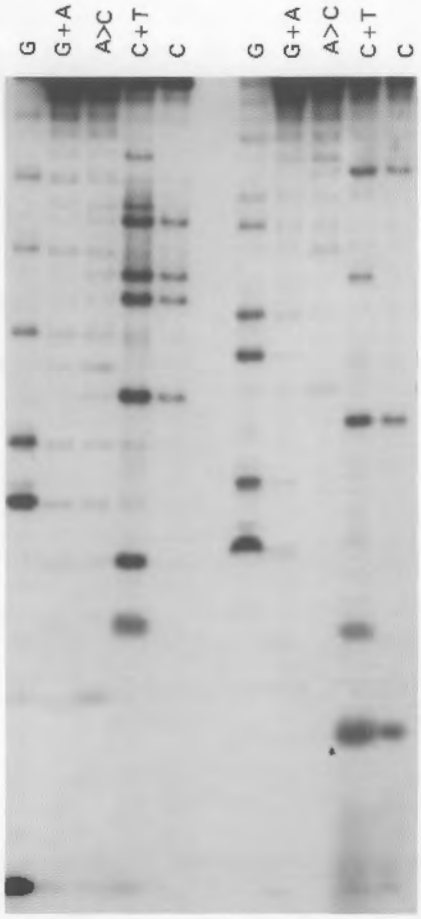

FIGURE 4. Sequence Determinations of a Portion of the c-Ha-ras Gene as determined using DNA Prepared by the Polymerase Chain-Reaction Method. DNA sequences were determined using the Maxam-Gilbert method.

• Molecular Events During Tumor Initiation

Principal Investigator: D. L. Springer

Other Investigators: R. M. Bean, J. A. Cushing, D. A. Dankovic, D. D. Mahlum, D. B. Mann, B. L. Thomas, and R. C. Zangar

The purpose of the project is to extend our understanding of the mechanism of tumor initiation by individual chemical carcinogens and to determine the influences of complex organic mixtures (COM) on this mechanism. Previously, we demonstrated that co-incubation of benzo[a]pyrene (BaP) and COM decreased the metabolism and mutagenic activity of BaP. Because of these influences, five mixtures and BaP were co-administered dermally to mice to initiate tumor development. Results from these studies demonstrated that BaP tumor-initiating activity was decreased substantially by four of the five mixtures. When one of the mixtures was fractionated into chemical class fractions, the polycyclic aromatic hydrocarbon (PAH) and nitrogen-containing polycyclic aromatic compounds (NPAC) fractions were the most effective, and the aliphatic and hydroxy-PAH fractions were the least effective as inhibitors of tumor initiation. Binding of ^{3}H-BaP to epidermal DNA under conditions identical to those used for tumor initiation, were decreased by co-administration of all five mixtures. High-performance liquid chromatography (HPLC) radioactivity profiles of enzyme hydrolyzed adducted DNA indicated that, in the presence of the mixtures, the predominant adducts were derived from BaP-diol epoxide (BPDE); however, the mixtures decreased the ratios of the anti-BPDE-deoxyguanosine (dGuo) to syn-BPDE-dGuo adducts. Dermal absorption studies using radiolabeled BaP as the marker compound indicated that the residence time for BaP increased and the concentration of BaP metabolites at the site of treatment decreased when BaP was co-administered with the COM. These data indicate that the prevailing influences of the mixtures (i.e., decreased DNA binding and adducts shifts) were similar to those observed with other bioassays following co-administration of binary mixtures. These data also demonstrate that both DNA binding and adducts profiles are important in determining the contribution of a known carcinogen to tumor initiation by COM.

This study was conducted to extend our understanding of the mechanism of tumor initiation by complex organic mixtures (COM). The tumor-initiating activity and other metabolic processes associated with tumor development were determined for a marker carcinogen (benzo[a]pyrene; BaP) when it was co-administered with COM. We systematically evaluated five distillates with limited boiling ranges and determined whether the constituents responsible for inhibition of BaP tumor-initiating activity were segregated into certain boiling ranges or were associated with specific chemical classes. In addition, the influence of these mixtures on BaP-DNA binding, DNA adducts profiles, rate of absorption from the site of application, and extent of epidermal conversion of BaP to metabolites were determined for mouse skin under conditions identical to those used in tumor-initiation studies.

The COM used in this study were obtained from the solvent refined coal (SRC)-II process; all five distillates were obtained from distillation of a full-boiling-range (300 to >850°F) blend of atmospheric flash bottoms and recycle process solvent. In addition, the 750 to 800°F distillate was separated by alumina adsorption column chromatography to isolate the following chemical classes: aliphatic hydrocarbons (AH); neutral polycyclic aromatic hydrocarbons (PAH); nitrogen-containing polycyclic aromatic compounds (NPAC); and hydroxy-functional polycyclic aromatic hydrocarbons (HPAH). These chemical classes were the primary constituents of the five COM. With the exception of the 300 to 700°F fraction, PAH were the predominant chemical class fraction in these mixtures.

Charles River CD-1 female mice (groups of 30) were used to determine initiating activity. They were housed five/cage and given food and water ad libitum. At the beginning of the experiment, they were individually ear-tagged, and their backs were shaved. Test materials were applied to their backs in 50 µl of methylene chloride; controls received 50 µl of methylene chloride only. The effect of COM on the initiating activity of BaP was determined by applying 25 µg of BaP in the presence of 5 mg of the COM. Other groups were initiated with 25 µg of BaP alone, or with 5 mg of COM. Beginning 2 weeks after initiation, the mice were promoted with twice-weekly applications of 5 µg of 12-O-tetradecanoylphorbol-13-acetate (TPA) in 50 µl of acetone for 24 weeks. The time of tumor appearance and the number of tumors were recorded as measures of response.

The group initiated with 25 µg of BaP alone showed the greatest tumor response, producing 7.07 ± 0.67 tumors per mouse (Table 1). Applying 25 µg of BaP in 5 mg of a COM that boiled between 300 and 700°F did not significantly affect the tumor response. (It should be noted that this COM did not have significant tumor-initiating activity.) Although the other COM had significant

initiating activities by themselves, they appeared to inhibit the tumorigenicity of BaP when co-administered with the individual carcinogen. This inhibitory effect was particularly noticeable when the mean number of tumors per mouse was used as the measure. For example, co-administering 5 mg of 750 to 800°F COM with the BaP reduced the number of tumors per mouse to 2.9 ± 0.33. It thus appears that the initiating activity of BaP was reduced in the presence of this COM to about 41% of the activity found when BaP was administered alone. This was true for the 800 to 850°F and >850°F distillates, even though the distillates themselves have substantial initiating activity.

TABLE 1. Effect of Coal Distillates with Varying Boiling Ranges on Benzo[a]pyrene (BaP) Tumor-Initiating Activity.

Initiation[a]	No. of Mice per Group	Tumors per Mouse
Solvent	30	0.17 ± 0
BaP	30	7.07 ± 0.67
300-700°F + BaP	30	6.63 ± 0.50
700-750°F + BaP	29	4.14 ± 0.49
750-800°F + BaP	29	2.93 ± 0.33
800-850°F + BaP	30	3.00 ± 0.36
>850°F + BaP	30	6.33 ± 0.75
300-700°F Distillate	30	0.37 ± 0.13
700-750°F	30	0.57 ± 0.14
750-800°F	30	0.60 ± 0.18
800-850°F	30	1.23 ± 0.43
>850°F	29	4.52 ± 0.43

[a] Initiators were applied topically, followed 2 wk later by twice-weekly applications of 5 µg of 12-0-tetradecanoylphorbol-13-acetate. Twenty-five-µg doses of BaP and 5-mg doses of the distillates were used; thus, when BaP was coadministered with a distillate, the ratio of distillate to BaP was 200.

Because the 750 to 800°F distillate exhibited substantial inhibition of BaP-initiating activity with little initiating activity of its own at the dose used (5 mg), we fractionated it into its chemical classes (Table 2) and tested the fractions for their effect on BaP tumor-initiating activity. Each of the chemical fractions was used in amounts equivalent to their content in the 750 to 800°F distillate from which they were derived. For example, the PAH fraction constituted approximately 50% of the distillate; therefore, since 5 mg of the distillate had been tested for its effect on the initiating activity of 25 µg of BaP, 2.5 mg of the PAH fraction was used in this experiment. The effect of the chemical classes on BaP-initiating activity is shown in Table 2 (tumors/mouse). The AH and HPAH fractions had little effect on the tumor-initiating activity of BaP. However, both the PAH and the NPAC fractions inhibited BaP tumorigenicity to about the same extent as did a 5-mg dose of the parent distillate.

TABLE 2. Effect of Chemical Class Fractions[a] Derived from a Coal Distillate with a Boiling Range of 750 to 800°F on the Expression of Benzo[a]pyrene (BaP) Tumor-Initiating Activity.

Initiation[b]	No. of Mice per Group	Tumors per Mouse
Solvent	29	0.24 ± 0.07[c]
BaP	29	7.21 ± 0.65
Crude Distillate	29	0.69 ± 0.09
AH	30	0.13 ± 0
PAH	30	0.67 ± 0.08
NPAC	30	0.27 ± 0.06
HPAH	30	0.23 ± 0.07
Crude Distillate + BaP	30	2.23 ± 0.29
AH + BaP	30	5.73 ± 0.78
PAH + Bap	30	2.50 ± 0.32
NPAC + BaP	27	2.81 ± 0.51
HPAH + Bap	27	6.44 ± 0.53

[a] The 750-800°F coal distillate was fractionated to produce chemical class fractions: aromatic hydrocarbon (AH), aliphatics and olefins; neutral polycyclic aromatic hydrocarbon (PAH); nitrogen-containing polycyclic aromatic compounds (NPAH); hydroxy polycyclic aromatic hydrocarbon (HPAH). Fractions were used in the same proportion that they were found in the parent material (see Table 1).

[b] Test materials were applied topically, followed 2 wk later by twice-weekly applications of 5 µg of 12-0-tetradecanoylphorbol-13-acetate. The BaP was administered at a dose of 25 µg/mouse, applied with 5 mg of distillates or with an amount of chemical class fraction proportional to their content in distillate.

[c] Mean ± SEM.

TREATMENT OF ANIMALS FOR DNA BINDING AND ADDUCTS

The backs of female CD-1 mice (Charles River, Portage, MI) 10 to 20 weeks of age, were shaved 2 days before dosing and only animals in the resting phase of the hair-growth cycle were used. A 25-µg dose of ^{3}H-BaP (375 µCi) was applied to the shaved backs of mice in 50 µl of methylene chloride. The five distillates spiked with tritiated BaP (25 µg, 375 µCi/mouse) were applied in 50 µl of methylene chloride at a dose of 5.0 mg per mouse. Twenty-four hours after dosing, the mice were killed by cervical dislocation, and the treated area of the skin was identified under ultraviolet light and removed. The DNA was extracted and purified, and the amount of co-purifying radioactivity was determined. Purified DNA was enzymatically digested with DNAse-I, phosphodiesterase and alkaline phosphatase to yield adducted and nonadducted nucleo-

sides. The DNA adducts were purified by high-performance liquid chromatography (HPLC), and radiochromatograms were prepared.

The amounts of radiolabeled BaP bound to mouse-skin DNA in the presence and absence of the five COM are shown in Table 3. Typically, about 500 µg of purified DNA were obtained from the skin of each mouse. Binding of BaP alone at a dose of 25 µg resulted in approximately 6.0 pmol BaP bound per mg DNA. When a similar amount of BaP was co-administered with 5 mg of the lowest-boiling mixture, binding was decreased by approximately 50% relative to that for BaP administered alone. Co-administration of BaP with the other four mixtures resulted in decreases of 75 to 85% in binding, with the two highest-boiling mixtures producing the greatest effect.

TABLE 3. In Vivo Binding of ^{3}H-Benzo[a]pyrene (BaP) to Mouse-Skin DNA in the Presence of Five Complex Organic Mixtures (COM); Three to Four Mice per Treatment Group (See text for Methods).

	Dose		Binding
Test Material	COM, mg	BaP, µg	pmole/mg DNA
BaP	5.0	25	6.30 ± 0.63
300-700°F + BaP	5.0	25	2.94 ± 0.59
700-750°F + BaP	5.0	25	1.28 ± 0.10
750-800°F + BaP	5.0	25	1.31 ± 0.13
800-850°F + BaP	5.0	25	0.87 ± 0.06
>850°F + BaP	5.0	25	0.90 ± 0.12

Radiochromatograms of BaP adducts in the presence of the five COM are shown in Figure 1. The general appearance of the radiochromatograms indicated that there were no major changes in the adduct profiles attributable to co-administration with the COM. In all cases, the predominant adduct (peak I) was located in the region of the chromatogram where the anti-BaP diol epoxide (BPDE) isomer is known to elute. The adducts also co-chromatographed with a standard prepared from anti-BPDE and calf-thymus DNA (CT-DNA; chromatogram not shown). Similarly, another radioactive compound (peak II), which eluted shortly after the anti-BPDE adducts, was present in all chromatograms; this adduct was shown to be syn-BPDE-deoxyguanosine (dGuo).

Further analysis of the radiochromatographic data indicated that, relative to the amount observed for BaP alone, the major influence of the COM was to decrease the total amount of radiolabel eluting from the HPLC column as either anti-BPDE-dGuo or syn-BPDE-dGuo (Table 4). The magnitude of these decreases was approximately equal to that for BaP-DNA binding prior to enzymatic digestion. The most effective inhibitors were the two highest-boiling COM, and the least effective was the lowest-boiling fraction (i.e., 300 to 700°F). Further data analysis indicated that the ratio of anti-BPDE to syn-BPDE was decreased by about 50% relative to that for BaP administered alone, and that all five COM were about equally effective in producing this change.

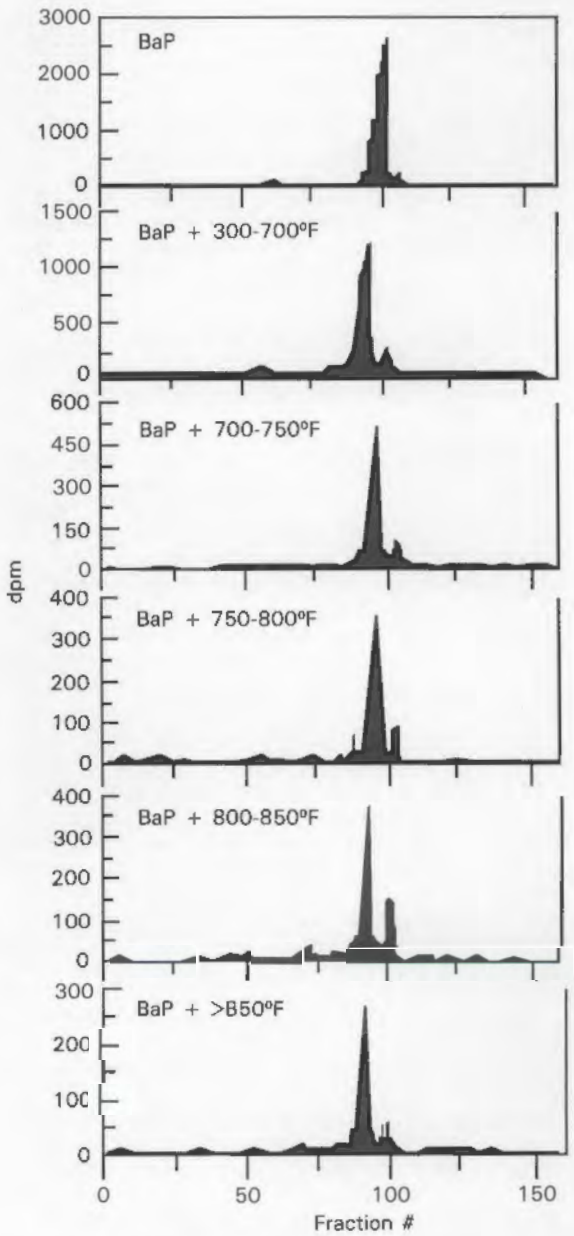

FIGURE 1. Radiochromatograms after High-Performance Liquid Chromatography (HPLC) Separation into Individual Benzo[a]pyrene (BaP) Adducts. The DNA was isolated from mouse skin 24 hr after treatment with either radiolabeled BaP or radiolabeled BaP coadministered with complex organic mixtures (COM). After extensive purification, the DNA was enzymatically hydrolyzed to nucleosides, and adducted radiolabeled nucleosides were purified by HPLC procedures.

TABLE 4. Influence of Complex Organic Mixtures (COM) on Benzo[a]pyrene Diolepoxide (BPDE)-DNA Adducts for Mouse-Skin DNA 24 hr after Carcinogen Exposure.[a]

Test Material	pmoles bound/mg DNA		
	Anti-BPDE-dGuo	Syn-BPDE-dGuo	Anti/Syn Ratio
BaP	1.47	0.120	12.2
300-700°F + BaP	0.44	0.061	7.2
700-750°F + BaP	0.31	0.049	6.4
750-800°F + BaP	0.27	0.042	6.4
800-850°F + BaP	0.12	0.022	5.4
>850°F + BaP	0.17	0.031	5.4

[a] Mice were treated with ^{3}H-BaP and complex mixtures as described in the legend in Table 3. Binding and ratios for BPDE-dGuo adducts were calculated from total dpm for each peak after high-performance liquid chromatography separations. Values are representative of data for 2 to 3 mice per treatment group.

Several modifier compounds have been shown to alter the activity of carcinogenic PAH. For example, it was demonstrated that dermal administration of benzo[e]pyrene (BeP) 5 minutes prior to application of an initiating dose of several PAH carcinogens resulted in decreased mouse-skin tumor-initiating activity for some carcinogenic PAH and a modest increase in initiating activity for BaP. Corresponding changes were also observed for carcinogen binding to epidermal DNA. It was also shown that the antioxidant butylated hydroxyanisole, an inhibitor of BaP carcinogenesis, caused decreases in the amount of BaP bound to DNA and reduced the target organ concentration of anti-BPDE-dGuo by 55 to 75%. Studies with Syrian hamster embryo cells in culture have shown that co-administration of BeP with BaP decreased the amount of BaP bound to DNA and also decreased the ratio of anti-BPDE to syn-BPDE adducts, suggesting that the modifying PAH produced shifts in the pathways involved in BaP metabolic activation. Thus, the major influences that have been demonstrated for compounds that modify PAH carcinogenesis are decreases in the amount of binding of carcinogen to DNA and alterations in the profile of PAH-DNA adducts that are produced.

Although a number of studies describe the influences of modifier compounds on PAH carcinogenesis and DNA adduct formation, the effect of COM as modifiers has not been reported. Our results indicate that co-administration of five COM with BaP decreased the tumor-initiating activity of the BaP to varying degrees. Moreover, the mixtures caused decreased total binding of carcinogen to DNA. Chromatographic data of enzyme-digested DNA demonstrated that adducts were derived from BPDE metabolites, and that the mixtures produced shifts in the amounts of anti-BPDE- and syn-BPDE-derived adducts. Results from our study indicate that the change associated with co-administration of COM were similar to those reported for binary mixtures.

Comparison of the data for the tumor-initiating activity with the amount of BaP bound to DNA on a relative weight basis are shown in Figure 2. Co-administration of the COM with BaP decreased, in all cases, the number of tumors initiated as well as the amount of BaP bound to epidermal DNA; however, binding to DNA was decreased to a greater extent than was tumor-initiating activity. This disparity between initiating activity and the amount of BaP bound to DNA consistently differed, by approximately a factor of 2, for co-administration of all five COM.

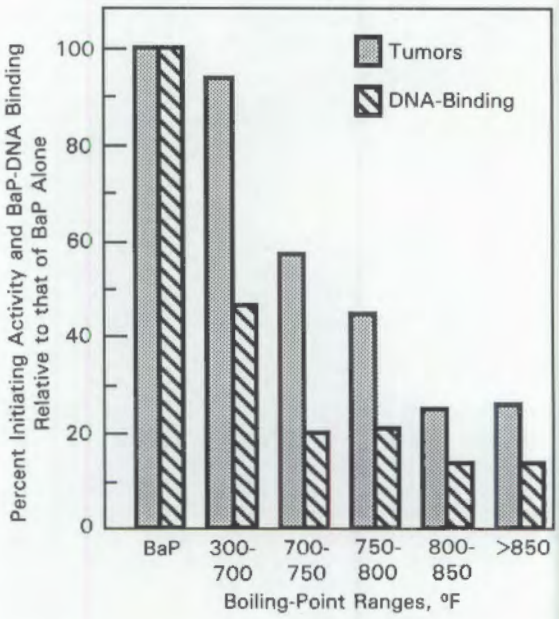

FIGURE 2. Comparison of Tumor-Initiating Activity and DNA Binding. Data indicate that in the presence of a complex organic mixture (COM), the bound benzo[a]pyrene (BaP) was more effective in initiating tumors.

EFFECTS OF COM ON DERMAL ABSORPTION OF BaP FROM SKIN

Groups of 20 mice were dosed with 25 µg of BaP, either alone or mixed with 5 mg of one of five COM. The BaP included approximately 0.1 µCi ^{14}C-labeled BaP. Four mice from each group were sacrificed at intervals of 0, 3, 6, 12, and 24 hours after dosing. The dosed area of skin was removed and digested with proteinase K, and the digestate was made basic by the addition of 80% ethanol/0.5 N

NaOH. The sample was then extracted twice with n-hexane, and both the hexane and aqueous phases were sampled and counted. The effects of the COM on the dermal residence time of BaP are summarized in Table 5. While all of the COM tested prolonged the residence time of BaP on mouse skin, the high-boiling COM were clearly more effective than the lower-boiling COM, increasing the biological half-life of BaP to more than 24 hours.

TABLE 5. Effects of Complex Orgaic Mixtures (COM) on the Dermal Half-Life of Benzo[a]pyrene (BaP).

COM[a]	Dose, mg	BaP, μg	BaP Half-Life, hr[b]
None	—	25	4.3 ± 0.35
300-700°F + BaP	5	25	7.8 ± 0.52
700-750°F + BaP	5	25	12.9 ± 1.36
750-800°F + BaP	5	25	14.8 ± 2.02
800-850°F + BaP	5	25	25.7 ± 3.34
>850°F + BaP	5	25	29.7 ± 4.26

[a] Designated according to boiling-point range.
[b] At site of application on mouse skin.

The effects of the COM on the formation of BaP metabolites at the site of application on mouse skin are shown in Figure 3. A maximum of 10.5% of the total dose of BaP was recovered from the application site as BaP metabolites at 6 hours after dosing. This percentage was greatly reduced by the COM, particularly the high-boiling COM; no more than 0.6% of the dose was recovered as BaP metabolites at any time interval, after dosing with BaP plus the 800 to 850°F COM, and no more than 0.2% after dosing with BaP plus the >850°F COM.

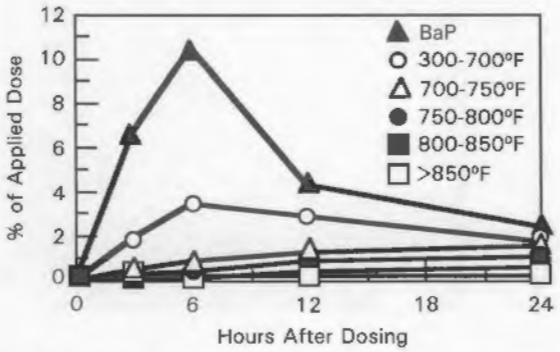

FIGURE 3. Percent of a Total Dose (25 μg) of Benzo[a]pyrene (BaP) Applied to Mouse Skin that was Isolated from the Application Site as BaP Metabolites. The treated skin patch was removed, digested, and extracted as described in the text. The BaP metabolites were determined by liquid scintillation counting of the aqueous phase of the sample, following hexane extraction. All mice received 25 μg of BaP; all but the "BaP only" group also received 5 mg of a complex organic mixture (COM), designated in the key by its boiling-point range (°F).

Both the increase in the residence time of BaP on skin and the decrease in the percent of BaP recovered as metabolites (at the site of application) may partially explain the inhibition of BaP-induced tumor initiation previously observed with these COM. The biochemical mechanisms responsible for these differences in inhibition of metabolism and binding to DNA as well as the differences in the carcinogenic activities of the COM are unclear. Since the mixtures are composed primarily of PAH and heteroatomic PAH, the reduced binding of BaP to DNA may be the result of altered rates and/or routes of metabolism because of competition for the active site(s) on the mixed-function oxidase enzymes. Presumably, many of these PAH are noncarcinogenic, yet most (if not all) are metabolized by the mixed-function oxidase enzymes. This interpretation is consistent in that suppressed mutagenic activity in the Salmonella/microsome assay was caused by inhibition of metabolic activation, probably due to binding of an unidentified component(s) to cytochrome P-450. Although decreases in both metabolism and DNA binding accounted for a portion of the decrease in tumor-initiating activity, the data also indicated that there was an additional influence since, in the presence of COM, the BaP that was bound was more effective (by a factor of approximately 2) in producing tumors.

INHIBITION OF BaP METABOLISM IN VITRO BY COM

We have examined the effects of five COM, with boiling points of 300 to 700°F, 700 to 750°F, 750 to 800°F, 800 to 850°F, and >850°F on both the rate and the route of BaP metabolism by rat liver homogenates in vitro. The five COM were mixed with ^{14}C-labeled BaP, and added to a metabolizing system consisting of rat liver homogenate (S9) from an Aroclor-1254-induced rat, NADPH, and the appropriate co-factors. The incubations were terminated at intervals ranging from 1 to 60 minutes, and the percent of BaP metabolized was determined using a simple extraction technique. The effects of the five COM on the rate of BaP metabolism in vitro are shown in Figure 4. When co-metabolized in 40:1 excess with BaP, all of the COM inhibit BaP metabolism. The 300 to 700°F COM reduced the initial rate of BaP metabolism to 34% of the rate for BaP alone, while the four higher-boiling COM reduced it to 6.3% to 9.3% of the rate for BaP alone.

In addition, the effects of the five COM on the metabolite profile of BaP in vitro was examined, using HPLC analysis of the metabolites produced. As shown in Figure 5, the two highest-boiling COM (800 to 850°F and >850°F boiling points) were found to reduce the formation of BaP-7,8-diol (the essential precursor to formation of the carcinogenic BPDE) to 81 and 49% of that observed using BaP alone. None of the lower-boiling COM

(Figure 6) inhibited BaP-7,8-diol formation, whereas the 300 to 700°F COM appeared to increase it.

In general, these results agree with the results of tumor initiation studies with the same COM plus BaP: all of the COM with boiling points >700°F inhibited BaP metabolism in vitro, just as they inhibited tumor formation in vivo. In addition, the two highest-boiling COM appear to specifically inhibit the formation of BPDE, which are considered the ultimate carcinogenic metabolites of BaP. Both the competitive inhibition of BaP metabolism (by all of the COM) and the apparent specific inhibition of BaP-7,8-diol formation (by the 800 to 850° and >850° COM) may play a role in inhibiting formation of BaP-induced skin tumors by these COM.

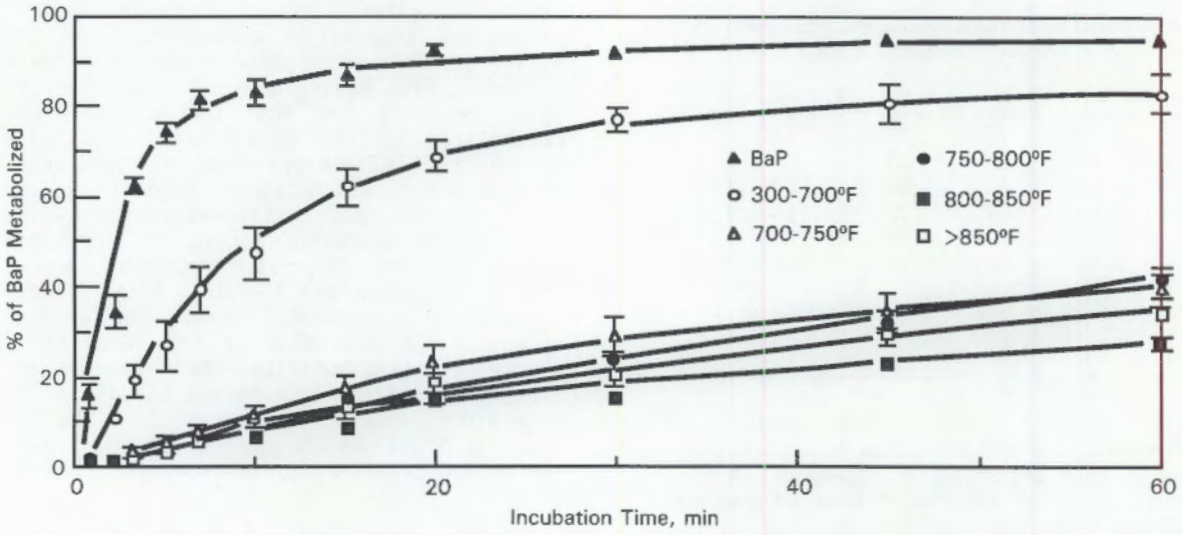

FIGURE 4. The In Vitro Effects of Five Complex Organic Mixtures (COM) on the Rate of Metabolism of Benzo[a]pyrene (BaP) by Rat Liver Homogenate (S9). Incubations included 5 μg/ml BaP, and all but the "BaP only" group received 200 μg/ml of a COM, designated in the key by its boiling-point range (°F).

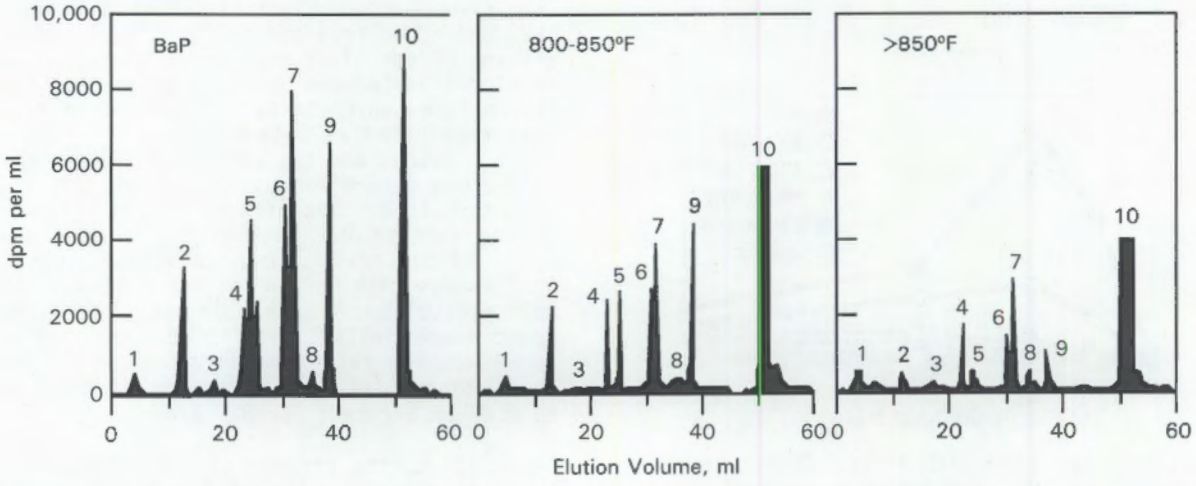

FIGURE 5. In Vitro Effects of Five High-Boiling Complex Organic Mixtures (COM) on the High-Performance Liquid Chromatography (HPLC) Profile of Benzo[a]pyrene (BaP) Metabolites Formed by Rat Liver Homogenate (S9). Incubations included 5 μg/ml BaP, and 200 μg/ml of the COM, designated in the key by its boiling-point ranges (°F). Incubation times used and percent of total BaP metabolized are as follows: BaP alone, 1.5 min incubation time and 67% of BaP metabolized; 800 to 850°F, 60 min incubation, and 67% of the BaP metabolized; and >850°F, 45 min incubation time, and 65% of the BaP metabolized. Tentative peak identifications, based on comparison of retention times with known standards, are as follows: Peak 1, polar fraction; peak 2, BaP-9,10-dihydrodiol; peak 3, unknown (probably BaP-triols); peak 4, BaP-4,5-dihydrodiol; peak 5, BaP-7,8-dihydrodiol; peak 6, BaP-1,6-dione; peak 7, BaP-3,6-dione; peak 8, 9-hydroxy-BaP; peak 9, 3-hydroxy-BaP; and peak 10, BaP.

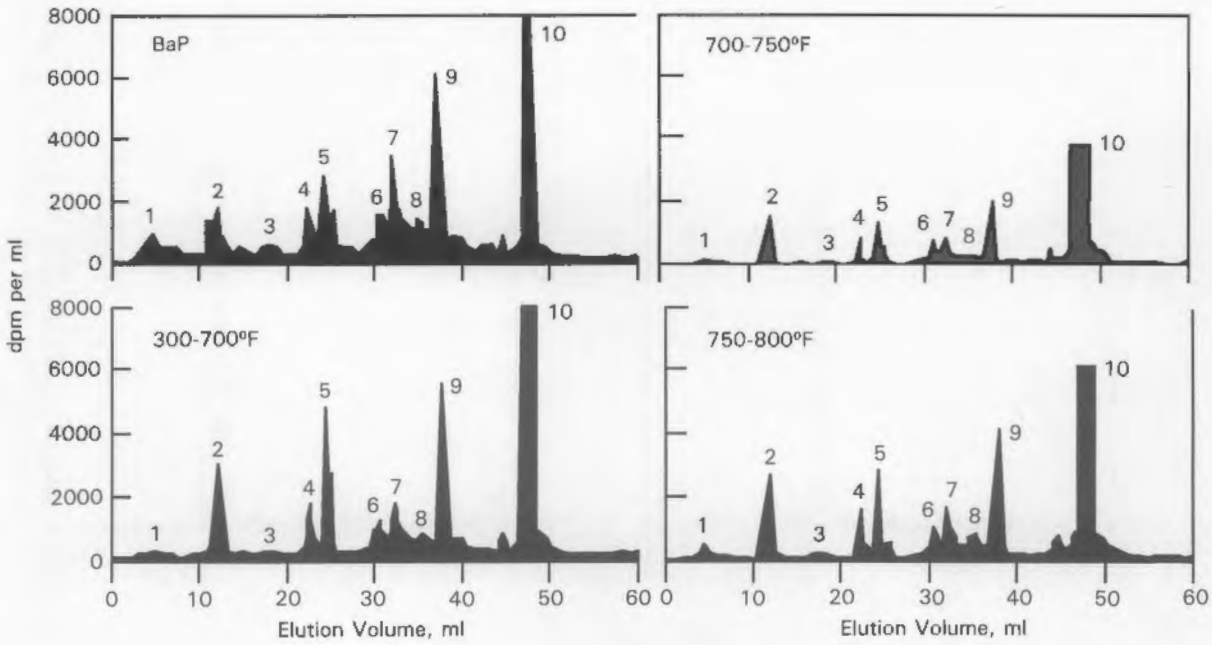

FIGURE 6. Effects of Three Complex Organic Mixtures (COM) on the HPLC Profile of Benzo[a]pyrene (BaP) Metabolites Formed by Rat Liver Homogenate (S9) In Vitro. Incubations included 5 μg/ml BaP, and 200 μg/ml of each COM, which are designated by boiling-point range and are described in text. Incubation times and percent of total BaP metabolized are: BaP alone, 1.5 min incubation time, and 67% metabolized; 300-700°F, 5 min incubation time, and 44% metabolized; 700-750°F, 30 min incubation time, and 18% metabolized; and 750-800°F, 45 min incubation time, and 32% metabolized. Tentative peak identifications, based on comparison of retention times with known standards.

PREPARATION OF BaP-DNA ADDUCT, USING ISOLATED RAT HEPATOCYTES

The preparation of DNA adduct standards in quantities sufficient for chemical characterization is often difficult. Although chemically reactive metabolites of carcinogens (such as diol epoxides) are available for BaP and a few other PAH, thus facilitating in vitro chemical synthesis of adduct standards, the appropriate reactive metabolites are not available for the vast majority of carcinogenic PAH. Numerous investigators have therefore used biosynthetic methods of adduct preparation, often using either rat liver homogenates (S9) or microsomes plus CT-DNA.

Unfortunately, the HPLC profile of BaP adducts obtained using microsomes plus CT-DNA has been shown to differ substantially from that observed in mouse skin. In contrast, the major adducts formed with the endogenous hepatocellular DNA by isolated rat hepatocytes in vitro are essentially identical to those observed in mouse skin in vivo. Other data in the literature suggested that the formation of DNA adducts by isolated rat hepatocytes in vitro could be effectively amplified by the addition of exogenous CT-DNA. We have found that this system (hepatocytes + CT-DNA) can be utilized effectively for the preparation of relatively large (i.e., microgram) quantities of DNA adducts, and that the adducts produced from BaP are the same as those formed by mouse skin in vivo.

Viable rat hepatocytes were prepared by collagenase perfusion and incubated with 1 mg/ml CT-DNA. The DNA was isolated by a series of phenol extractions, and RNA and protein were digested enzymatically and removed by solvent extraction. The DNA was enzymatically digested into deoxyribonucleosides, and the BaP-DNA adducts were analyzed by HPLC, as shown in Figure 7. The HPLC profile of the BaP-DNA adducts obtained using hepatocytes plus CT-DNA was compared to that of BaP-DNA adducts isolated from the skins of mice treated with BaP in vivo. In both mouse skin and hepatocytes plus CT-DNA, the predominant peak is the (+)-anti-BPDE-dGuo.

Preliminary experiments have also been carried out to establish conditions for the preparation of 7,12-dimethylbenzanthracene (DMBA) adducts, using isolated rat hepatocytes plus CT-DNA. Although optimal conditions have not yet been established, the covalent binding of 42 to 72 pmol DMBA per mg DNA has been observed. We hope that this method of DNA adduct preparation will prove useful for DMBA as well as other PAH.

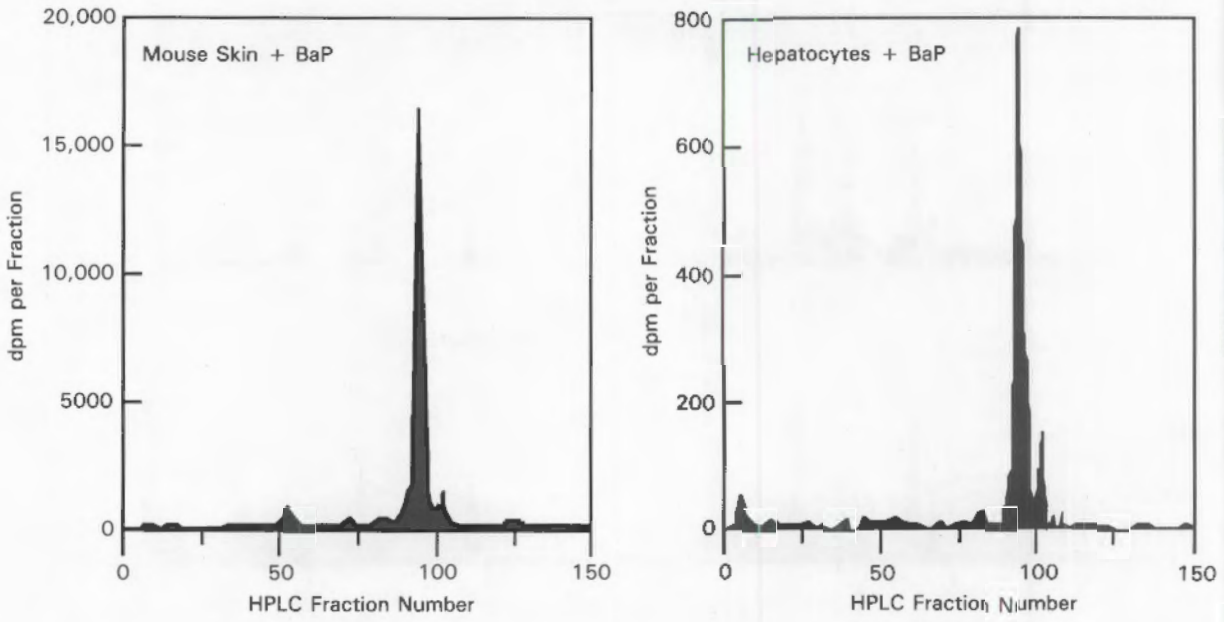

FIGURE 7. Radiochromatograms of Benzo[a]pyrene (BaP)-DNA Adducts Isolated from: (a) Mouse Skin, 24 hr after Application of a 100-μg Dose of BaP, and (b) from Calf-Thymus DNA Incubated for 2 hr with 180 μM BaP and Isolated Rat Hepatocytes. Adducts were chromatographed using reverse-phase high-performance liquid chromatography, with a methanol-water gradient.

• Fetal and Juvenile Radiotoxicity

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Other Investigators: R. L. Buschbom, G. E. Dagle, D. R. Kalkwarf, B. J. Kelman, and D. N. Rommereim

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In this project we have obtained comparative information on the deposition, distribution, retention, and toxicity of several radionuclides in prenatal and juvenile mammals. The primary approach is quantitative, even though the specific values cannot necessarily be directly extrapolated to man. Accordingly, efforts are directed at identifying patterns, determining phenomenologic interactions, and investigating mechanisms. The resulting relationships are being used by standards-setting groups for developing meaningful radiological protection practices for rapidly growing infants or children and for pregnant women.

Injection of neonatal, juvenile and weanling rats with ^{233}U citrate did not affect the growth of neonates, but growth of juveniles relative to controls was equivocally suppressed, and weanlings had significant growth depression. These ^{233}U exposures produced little mortality in any age group and did not affect mortality in rats subsequently injected with $HgCl_2$.

Analyses are in progress to identify patterns associated with placental transfer and fetoplacental deposition values for radionuclides and to help us understand their differences and similarities. Initially, analytical models of these relationships were used to make quantitative and qualitative comparisons between kinetic and organ depositional approaches to examining metabolic differences between exposures to plutonium and americium.

There is a potential for human exposure associated with the mining, processing, and fabrication of uranium, which is extensively used in the nuclear industry, and from disposal of its waste- and end-products. Despite the associated occupational and environmental interest, only limited toxicology data were available for the prenatal or neonatal periods. We have therefore performed a series of experiments with ^{233}U to evaluate its fetoplacental dosimetry and neonatal distribution, to determine the potential for producing prenatal effects such as embryotoxicity and teratogenicity after injection of pregnant rats, and to study toxicity in the postnatal period. As noted previously, observed teratologic effects included an increased incidence of fetuses with skeletal anomalies, cleft palate, or edema (Annual Report, 1985). Radiation doses calculated from parallel radioanalytical data suggested that observed early maternal and developmental effects were attributable to chemical toxicity rather than to radiation (Annual Report, 1986). Other results indicated that some effects on the conceptus may be mediated through altered maternal fluid balance, which is consistent with the known nephrotoxic effect of uranium. This raised the possibility that exposure during late gestation might affect neonatal kidney development. A pilot study to address this question (Annual Report, 1986) suggested that exposures to either uranium or colchicine (a positive control material) increased excretion of an orally administered water load at 1 day of age but did not have a significant effect at older ages. Both materials also produced transient decreases in intrinsic urine volumes in rats assayed at 5 or 12 days of age, but only colchicine significantly affected osmolarity.

During the past year we performed an additional study to examine uranium toxicity relative to age. Neonatal, juvenile, or weanling rats (1, 12, or 21 days of age, respectively) were intraperitoneally injected with ^{233}U citrate at doses of 0, 2, 5, or 10 μCi/kg body weight. Groups of 10 to 14 rats of each sex from each age and dose group were held for studies of effects. The lowest dose had no effect, the intermediate dose tended to decrease growth of both male and female weanlings, and the highest exposure level produced a statistically significant decrease (Figure 1). Only at the highest dose level did uranium have a statistically significant depressive effect on the growth of juvenile females, and even this dose did not significantly affect males. Exposure had no effect on the growth of rats injected at 1 day of age.

This pattern of effect on growth is consistent with the literature on other chemical nephrotoxins, whose potential for producing effects appears to increase with the progressive maturation of the kidney. In our study, neither the partition of uranium among the various tissues, nor its retention, was dependent on age at exposure (Table 1). There was a tendency toward increased fractional deposition in the kidney at the highest dose administered, especially at 30 days after exposure and in the two older groups of rats. There was sub-

stantial within-group variability and, because groups of only three or four rats were used at each time point in the dosimetry portion of the study, none of these differences were statistically significant.

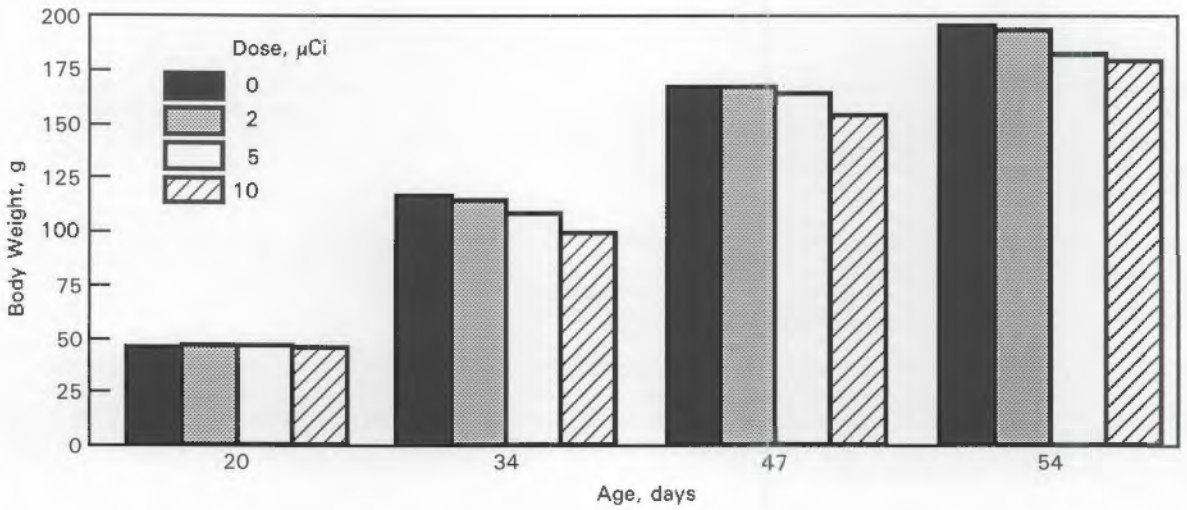

FIGURE 1. Mean Weights of Female Rats Before Exposure and at Selected Times After Exposure to ^{233}U Citrate at 21 Days of Age.

TABLE 1. Distribution and Retention of Uranium-233 Citrate in Tissues after Intraperitoneal Injection of Newborn, Juvenile or Weanling Rats (Fraction of Dose per Gram Tissue Weight).

	Newborn, 1 day[a]			Juvenile, 12 days[a]			Weanling, 21 days[a]		
Time After Injection	2[b]	5[b]	10[b]	2[b]	5[b]	10[b]	2[b]	5[b]	10[b]
Blood									
2 hr	0.119	0.0449	0.0166	---	---	---	---	---	---
4 hr	0.0083	0.0110	0.0134	---	---	---	---	---	---
1 d	0.0019	0.0009	0.0010	0.0002	0.0002	0.0002	0.0002	0.0001	NM[c]
7 d	0.0002	0.0002	0.0020	0.0001	0.0001	0.0001	NM[c]	NM[c]	NM[c]
30 d	NM[c]	NM[c]	NM[c]	NM[c]	NM[c]	NM[c]	NM[c]	NM[c]	NM[c]
Femur									
2 hr	0.635	0.451	0.404	---	---	---	---	---	---
4 hr	0.732	0.402	0.688	---	---	---	---	---	---
1 d	0.690	0.545	0.417	0.108	0.114	0.109	0.056	0.082	0.068
7 d	0.115	0.132	0.113	0.068	0.064	0.049	0.024	0.039	0.022
30 d	0.015	0.008	0.018	0.010	0.011	0.014	0.009	0.008	0.014
Kidney									
2 hr	0.354	0.612	0.591	---	---	---	---	---	---
4 hr	0.337	0.683	0.761	---	---	---	---	---	---
1 d	0.227	0.277	0.392	0.079	0.085	0.161	0.034	0.014	0.075
7 d	0.107	0.109	0.131	0.036	0.030	0.085	0.015	0.013	0.034
30 d	0.009	0.011	0.017	0.003	0.006	0.020	0.001	0.006	0.015

[a] Age at indection

[b] Dose injected, μCi/kg body weight

[c] NM indicates activities below measurable level.

Injection with uranium produced little mortality in any of the age groups, and there were no statistically significant increases in mortality with increasing exposure level. We attempted to detect latent derangements of the kidney by determining whether uranium exposure had altered the animals' sensitivity to $HgCl_2$, another nephrotoxic agent. Surviving animals of each uranium-dose and age group were randomly divided into three subgroups when they reached 7 weeks of age. They were intraperitoneally injected with 5, 10, or 15 mg/kg of $HgCl_2$, and numbers of deaths that occurred at ½-day intervals thereafter were noted. In all age groups, survival times decreased with increasing doses of $HgCl_2$ (Table 2), but previous uranium exposure had no effect. Further mathematical and morphological analyses of data and tissue samples from this study are being performed in an attempt to identify undetected subtle interactions and mechanisms.

TABLE 2. Mean Survival Time (Days) of Rats Injected with $HgCl_2$ at 7 Weeks of Age Subsequent to Injection with Various Doses of ^{233}U at 1, 12, or 21 Days of Age.

^{233}U Dose, μCi/kg Body Weight	1[a]			12[a]			21[a]		
	5[b]	10[b]	15[b]	5[b]	10[b]	15[b]	5[b]	10[b]	21[b]
0	4.1 ± 1.3	2.6 ± 0.2	2.0 ± 0.1	3.7 ± 0.3	2.8 ± 0.4	2.1 ± 0.2	3.6 ± 0.4	2.5 ± 0.2	1.9 ± 0
2	4.4 ± 0.8	2.8 ± 0.1	3.2 ± 0.2	3.2 ± 0.2	3.1 ± 0.2	2.3 ± 0.1	3.9 ± 0.3	2.8 ± 0.1	2.0 ± 0
5	4.3 ± 0.3	2.3 ± 0.1	2.1 ± 0.2	3.9 ± 0.9	2.9 ± 0.2	2.6 ± 0.2	4.7 ± 1.4	2.8 ± 0.3	2.3 ± 0
10	3.0 ± 0.0	2.7 ± 0.2	2.1 ± 0.2	4.4 ± 0.8	2.1 ± 0.1	2.0 ± 0.2	3.7 ± 0.6	2.5 ± 0.3	2.0 ± 0

[a] Age at injection, days

[b] $HgCl_2$ dose, mg/kg body weight

We have begun comparisons of the placental transfer and fetoplacental distribution of the heaviest metals, using data from our past experiments and reports by other laboratories. The initial graphic patterns (Figure 2) illustrate marked differences in placental transfer and fetal deposition among individual nuclides. Differences between the ratios of concentrations in placental and in fetal membrane compartments to those in the fetus are also notable. Placental transfer of heavier elements is less than that of lead, which serves as a benchmark. Within this heavier range, fetal concentrations of uranium, neptunium, and plutonium are higher than those of other elements, but there is no obvious correlation with placental or membrane concentration ratios. Factors such as valence, effective radii, and binding to serum proteins are being examined but have not yet yielded clear patterns. Further information is currently being assembled for use as a basis for additional comparisons, analyses, and modeling.

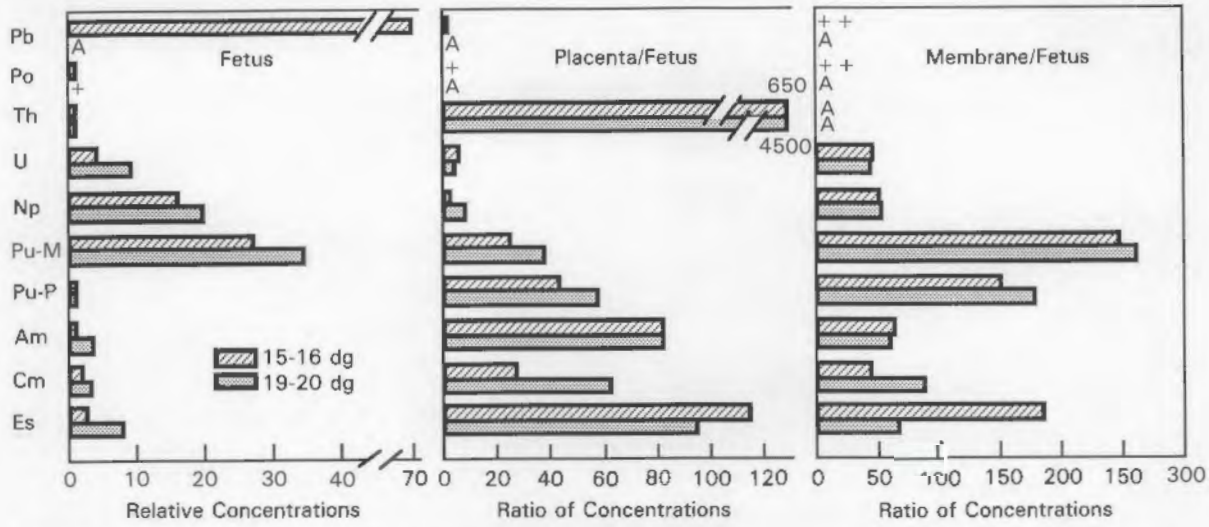

FIGURE 2. Relative Fetal Concentrations Following Injection of Rats with Heavy Elements During the Early or Late Fetal Period. Also shown are corresponding ratios of average concentrations in placentas or fetal membranes to fetal concentration. The symbol A is used to indicate an absence of reported data and + or ++ roughly indicates substantial but incompletely quantified values. Pu - M and Pu - P signify the monomeric and polymeric forms, respectively.

As reported previously (see Annual Reports, 1984 and 1985), we have performed experiments to investigate, in rats, observed differences between the placental transfer and effects of plutonium with those of americium at various gestation stages. These differences were also evident in guinea pig tissues at 24 hours after injection of the two nuclides (Annual Report, 1985); analyses of fetoplacental tissues have been obtained for comparative calculations (Table 3). The concentration of plutonium in the fetuses was greater than that of americium. Concentrations of both nuclides were higher in fetal femurs than in calvaria; this relationship is opposite to that observed in comparable studies using rats, and is probably attributable to the more advanced degree of development of the guinea pig at term. Concentrations of both nuclides were higher in the fetal placenta than in the maternal placenta. The concentration of ^{239}Pu in the yolk sac was markedly elevated relative to that in the amnion as well as to that in most other fetoplacental tissues, but fetal concentration ratios were substantially less with ^{241}Am, and the yolk sac:placenta ratios were reversed. These quantitative patterns confirm autoradiographic and less definitive counting results from experiments with rats and mice.

TABLE 3. Concentration (Mean nCi/g ± SD) of ^{239}Pu and ^{241}Am in Selected Fetoplacental Structures at 24 Hours after Intravenous Injection of Near-Term (~60 Days of Gestation) Pregnant Guinea Pigs with 30 μCi/kg Body Weight.

Structure	Plutonium	Americium
Fetus	0.54 ± 0.261	0.13 ± 0.045
Calvarium	1.49 ± 0.55	0.66 ± 0.299
Femur	3.76 ± 1.59	1.27 ± 0.529
Liver	0.63 ± 0.21	0.29 ± 0.032
Fetal Placenta	16.31 ± 2.49	16.14 ± 6.093
Maternal Placenta	11.11 ± 3.168	8.49 ± 5.22
Amnion	0.17 ± 0.191	0.07 ± 0.076
Yolk Sac	47.45 ± 20.728	3.82 ± 1.018

The limited amount of information currently available for many nuclides requires relatively simple calculational models. A multiple-compartment model (Figure 3), which includes major maternal and fetoplacental components and corresponding transfer coefficients, is the minimum that would be appropriate for analyses of kinetics or for interpretive dosimetry of radionuclides, metabolites, and chemical agents. Plutonium and americium were used for initial examination of the applicability of this model because of their marked differences and the availability of equivalent kinetic and fetoplacental concentration data sets for the two nuclides in guinea pigs from perfusion experiments (Annual Reports, 1981, 1983) and from the radioanalytic values presented above. Extensive data in the literature on time-dependent concentrations in pregnant and nonpregnant adults allow calculation and intercomparison of coefficients 1 and 2 for several species, independent of embryo/fetal data. Furthermore, because intravenous injections were used in both types of study, the values for these coefficients were ignored for the calculations, the results of which are summarized in Table 4. Coefficients 3 and 4 were estimated from the perfusion data and from fetoplacental concentrations at 24 hours; however coefficient 4 was considered negligible. The perfusion experiments provided direct measures of the sum of coefficients 3 and 5 and, when combined with concentration changes, provided reasonable estimates of net accumulation resulting from coefficients 7 and 8. Independent estimates of steady-state maternal plasma concentrations were obtained from the blood clearance curves of the perfusion experiments and measurements of values at 24 hours. The calculated transfer per day agreed well with the measured fetal content of both radionuclides in fetuses at 1 day after injection (Table 4).

FIGURE 3. Simple Form of Multiple-Compartment Model for Placental Transfer, Including Maternal, Placental, or Fetal Compartments and Bidirectional Transfer Coefficients.

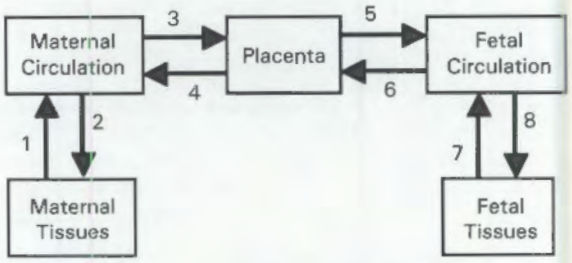

TABLE 4. Parameters and Results of Calculations of Placental Transfer and Fetal Concentrations of ^{239}Pu or ^{241}Am During In Situ Perfusion Experiments or at 24 Hours after Intravenous Injection of 30 μCi/kg to Pregnant Guinea Pigs (at 50 days Gestation).

Paramter or Value	^{239}Pu	^{241}Am
Maternal Plasma, nCi/ml		
Steady State[a]	6.5	2.5
Measured in 24-hr Necropsy Samples	5.2	1.5
Clearance, μl/min, mother to fetus	2.3	3.5
Corrected[b]	16	---
Calculated Transfer to Fetus, nCi/fetus/day	22	12.6
Corrected[a]	150	---
Measured Fetal Content at 24 hr, nCi/fetus	29	7.3

[a] Concetration estimated from plutonium and americium plasma clearance curves of perfusion experiments.

[b] Value that would have been obtained if correction were made for decreased blood flow detected during perfusion study.

We had observed that these high dose levels of ^{239}Pu (but not that of ^{241}Am) reduced maternal blood flow to the placenta, which resulted in an additional decrease in the clearance value (Annual Reports, 1982, 1983). The impact of this effect was examined in the model by considering the corrected value for ^{239}Pu clearance, i.e., that which would have been obtained in the absence of its effect on blood flow. Agreement between calculated and measured fetal content was poor when this was done, suggesting that the blood flow effect was real. This blood flow effect may not pertain to all species, however; for example, fetal concentration ratios of plutonium to americium were smaller in guinea pigs than in rats.

More complete biological models of greater complexity are needed to scale the data and patterns derived from studies in experimental animals to human pregnancies. Such a model might take the form of the example shown in Figure 4, which contains the major compartments, with their anatomical and physiological relationships generalized to encompass most gestation stages. Moreover, the existence, relative importance, and actual values of the compartmental concentrations and transfer coefficients cannot yet be defined. At a minimum, however, reasonable extrapolations will require the indicated degree of sophistication. Moreover, they must include provisions for the perturbations associated with the normal functional changes that occur during gestation and those that are produced by the various factors that have been shown to affect metabolism. Such a model is more complex than would be necessary for radiological protection calculations in operational situations. However, our efforts are being extended further because even more comprehensive models are needed to derive the several dosimetric factors that must be incorporated into useful operational paradigms and for understanding and defining fetal nutrition and pharmacodynamics.

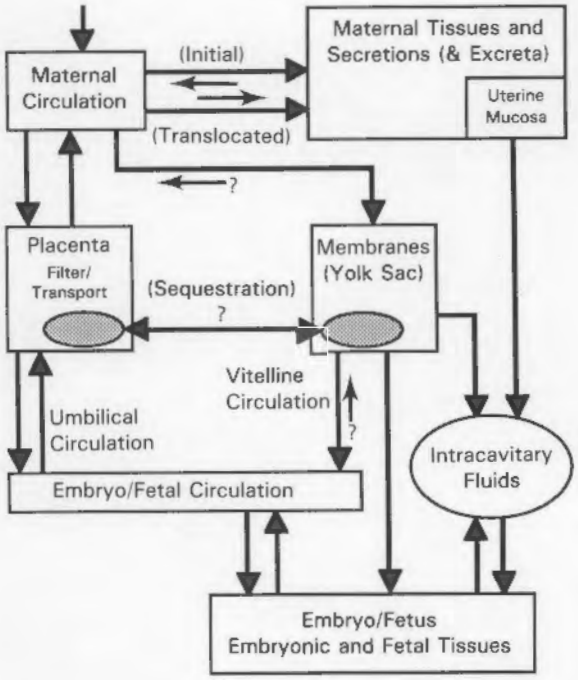

FIGURE 4. Model of the Pregnant Organism as Morphologically and Physiologically Related to the Components of the Fetoplacental Unit.

• Molecular Markers During Development

Principal Investigator: D. L. Springer

Other Investigators: D. A. Haugen, D. D. Mahlum, C. Peraino, C. A. Reilly Jr., and R. C. Zangar

The initiating activity of two high-boiling, coal-derived complex organic mixtures were compared, using the rat hepatic gamma-glutamyl transpeptidase and mouse-skin models. One-day-old rat pups were treated by intraperitoneal injection to initiate the development of neoplastic changes in their livers. These animals were placed on a synthetic diet containing phenobarbital at 3 weeks of age and were maintained on the diet for 10 weeks. Mice were treated at 10 weeks of age by dermal application of the test materials and tumor development was promoted by twice-weekly applications of tetradecanoylphorbol acetate. Results indicated that the complex organic mixtures were poor initiators of preneoplastic changes in the liver but were very active as initiators of mouse skin tumors. Co-administration of the complex mixtures with the known carcinogens benzo[a]pyrene or dimethylnitrosamine resulted in significantly fewer tumors, in both the hepatic and dermal models, compared to the number of preneoplastic changes observed with the known carcinogens administered alone. These data suggest that tumor-initiating activity is, to a large degree, determined by the matrix in which it is administered.

In the last several years, a large database has been established relative to the mutagenic and carcinogenic activity of complex mixtures derived from coal. This database clearly demonstrates that mixtures boiling below about 650 to 700°F lack carcinogenic activity; however, above 700°F, carcinogenicity increases with increasing boiling point. Experiments with chemical class fractions derived from the crude distillates indicate that most of the carcinogenic activity is associated with the neutral polycyclic aromatic hydrocarbon (PAH) and nitrogen-containing polycyclic aromatic compound (NPAC) fractions. These experiments also indicated that the biological activity of the fractions is higher than for the parent material. Evidence obtained by Reilly and coworkers is consistent with this observation. Our findings suggested that the carcinogenic components of complex mixtures are not being fully expressed. In a direct test of this hypothesis, benzo[a]pyrene (BaP) was tested for mouse skin-tumor-initiating activity in the presence of a wide-boiling-range coal liquid. The coal liquid substantially reduced the activity of BaP.

Most of the carcinogenicity data for the tumor initiating activity of coal liquids, as well as the data showing that complex mixtures inhibit expression of initiating activity of known carcinogens, have been obtained in mouse-skin studies. Because we wanted to determine whether other tissues responded in a similar way, we used the neonatal liver model to determine whether tumor development could be initiated in nondermal systems with complex mixtures known to be carcinogenic to mouse skin. We also wanted to determine if the coal liquids interfered with the initiating activity of BaP and diethylnitrosamine (DEN), two compounds that show substantial initiating activity in the neonatal rat liver system. In this report, the response of the rat liver is compared with that obtained with the mouse-skin model.

Liver Studies

One-day-old female Sprague-Dawley rats (Charles River Laboratories., Portage, MI) were injected intraperitoneally with the initiator dissolved in sesame seed oil; controls received only the sesame seed oil. At weaning (21 days of age), all rats were given a semi-synthetic diet containing 0.05% phenobarbital. In Part A of the experiment, heavy distillate (HD) and two high-boiling distillates (800-850°F and >850°F) from the solvent refined coal-II process, the NPAC and neutral PAH fractions from the >850° distillate, and a gasifier tar were used as initiators; BaP and DEN were used as positive controls. In Part B, BaP and DEN were tested for initiating activity in the presence of either HD or gasifier tar. The doses used are shown in Table 1.

TABLE 1. Dosing Information for Treatment of Neonatal Rats with the Known Carcinogen Benzo[a]pyrene (BaP) and Diethylnitrosamine (DEN) or Known Carcinogen Coadministered with Complex Organic Mixture. Treated animals were evaluated as adults for hepatic changes in foci of gamma glutamyl transpeptidase activity.

Initiator	Dose, μg/g body wt	BaP[a], μg/g body wt
BaP[b]	150	---
DEN[b]	15	---
800-850°F Distillate[b]	450	0.8
PAH Fraction[b]	450	1.6
NPAC Fraction[b]	450	—
>850°F Distillate	450	0.8
PAH Fraction[c]	450	1.6
NPAC Fraction[c]	450	0
Gasifier Tar[c]	450	0.3

[a] Benzo[a]pyrene (BaP) contributed by the complex organic mixture.
[b] Vehicle was sesame seed oil.
[c] Vehicle was sesame seed oil:dichloromethane (9:1 v/v).

All rats were killed at 11 weeks of age, and their livers were analyzed histochemically for the presence of altered hepatocyte foci that exhibited elevated levels of gamma-glutamyl transpeptidase activity. The data are expressed as the number of such foci per square centimeter of liver.

Skin Studies

Female Charles River CD-1 mice, 6-8 weeks of age, were housed five per cage and given food and water ad libitum. Their backs were shaved, and the initiator was applied in a total volume of 50 µl. Two weeks after initiation, all animals (30/group) received twice-weekly applications of 5 µg of 12-O-tetradecanoylphorbol acetate (TPA) in 50 µl of acetone for 24 weeks. The number of mice with tumors and the total number of tumors were determined biweekly.

In the first experiment, the >850°F distillate was fractionated to obtain four chemical class fractions identified as aliphatic, PAH, NPAC and hydroxy-PAH (HPAH). Mice received an initiating dose of 17 mg of the parent distillate or an amount of the chemical class fraction proportional to its concentration in the distillate. In the second experiment, several distillates (boiling ranges: 300-700, 700-750, 750-800, and 800-850°F) were examined for their influence on the initiating activity of BaP. Mice were initiated with 25 µg of BaP in acetone:methylene chloride alone or in acetone:methylene chloride containing 5 mg of the test distillate. Other mice received 5 mg of the distillate in acetone:methylene chloride and were promoted with TPA, as described above.

Figure 1 shows the skin tumor-initiating activity of the >850°F distillate and its chemical class fractions. Most striking is the finding that the neutral PAH fraction had as much activity as the parent material, even though it represented only about 50% of the mass in the distillate. The NPAC fraction also contained substantial activity, but the aliphatic fraction was inactive. There was only a hint of activity in the HPAH fraction.

The 300-700°F distillate had very little activity of its own (Figure 2) and had little effect on the initiating activity of BaP, with a tumor yield almost identical to that for BaP alone. The other distillates, however, substantially decreased the initiating activity of BaP; only about half as many tumors were found when BaP was applied in the presence of the 700-750, 750-800, or 800-850°F distillates as when BaP was applied alone.

Benzo[a]pyrene and DEN were both effective initiators in rat liver, resulting in 15-20 foci/cm^2 of liver (Figure 3). In contrast, the complex mixtures that showed substantial initiating activity in the mouse skin model had only minimal initiating activity for the liver. Less than 1.0 focus/cm^2 was produced by the 800-850 and >850°F distillates or their neutral PAH and NPAC fractions.

When BaP and DEN were tested for initiating activity in the presence of the 800-850 and >850°F distillates or gasifier tar, their activities were greatly reduced (Figure 4). The BaP activity was reduced by 40-60%, with the 800-850° distillate being the most effective. The degree of suppression of DEN activity was less, ranging from 20 to 50%, with the >850°F distillate the most effective.

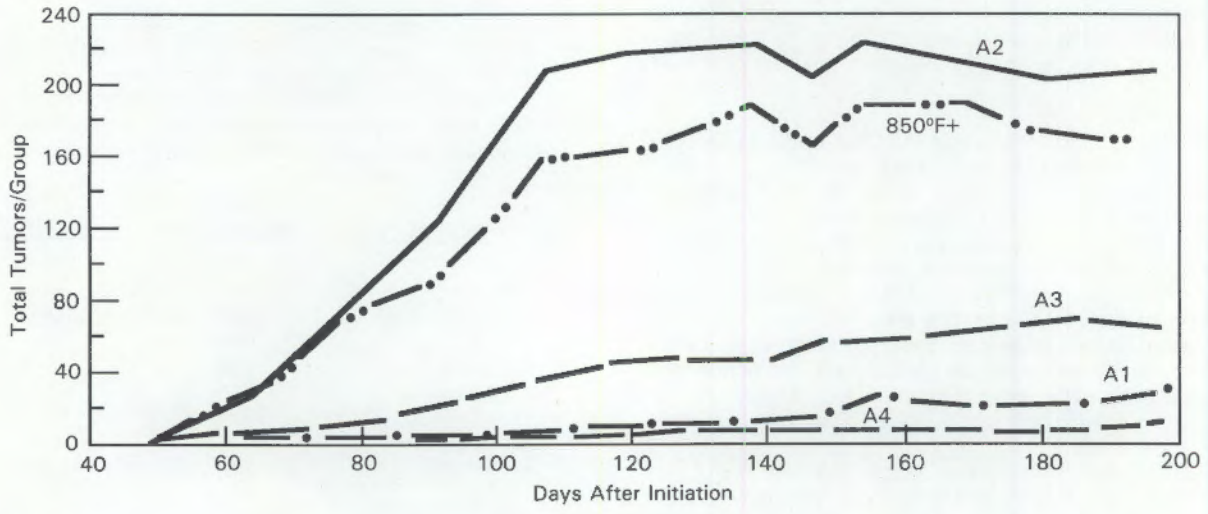

FIGURE 1. Mouse Skin-Tumor-Initiating Activity for the >850°F Boiling-Point Distillate of a Complex Organic Mixture and Its Chemical Class Fractions.

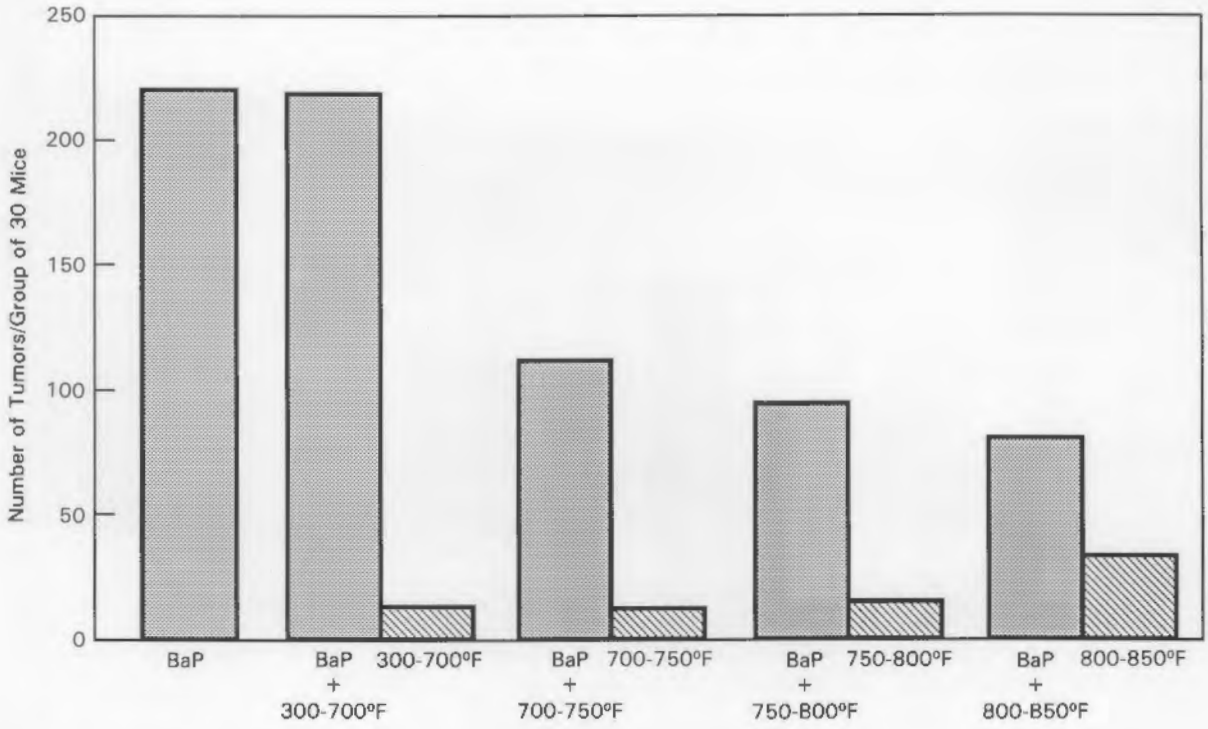

FIGURE 2. Effect of Complex Organic Mixtures with Differing Boiling-Point Ranges on the Skin-Tumor-Initiating Activity of Benzo[a]pyrene (BaP).

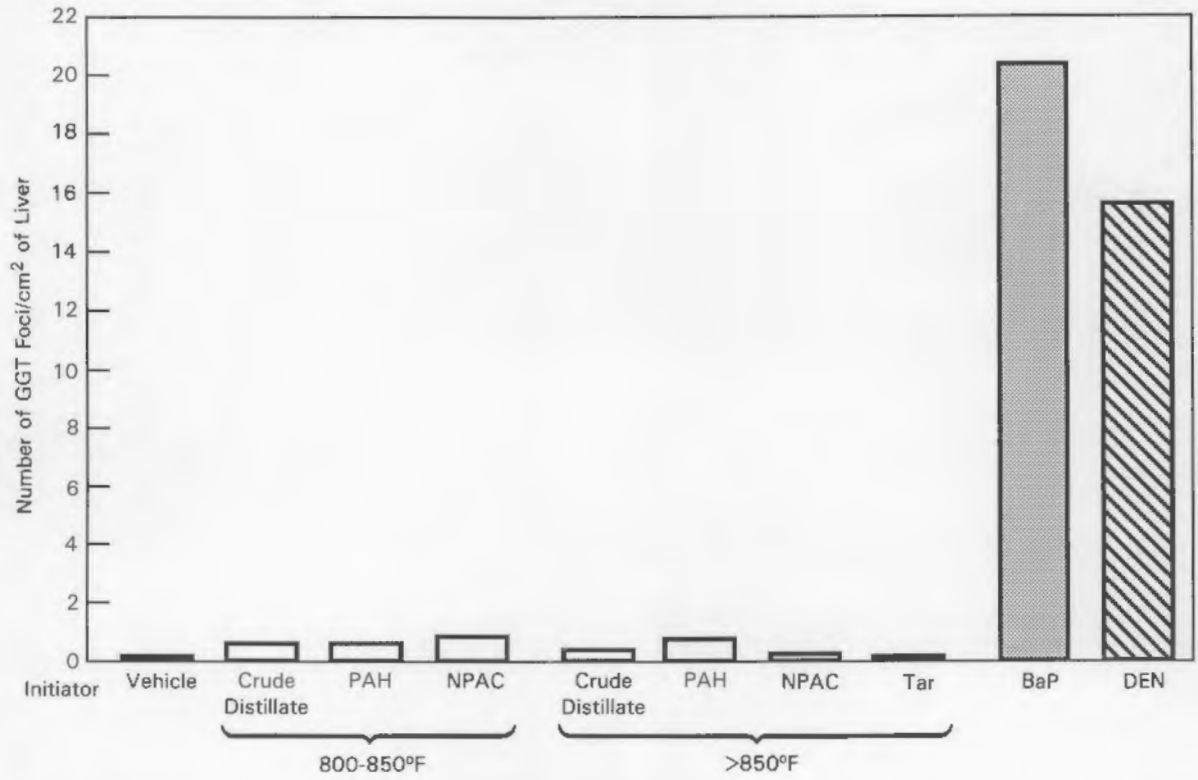

FIGURE 3. Initiating Activity for Two Known Carcinogens, Benzo[a]pyrene (BaP) and Diethylnitrosamine (DEN), and Complex Organic Mixtures, Using the Hepatic Gamma-Glutamyl Transpeptidase (GGT) Model. PAH = Polycyclic Aromatic Hydrocarbons; NPAC = Nitrogen-Containing Polycyclic Aromatic Compounds.

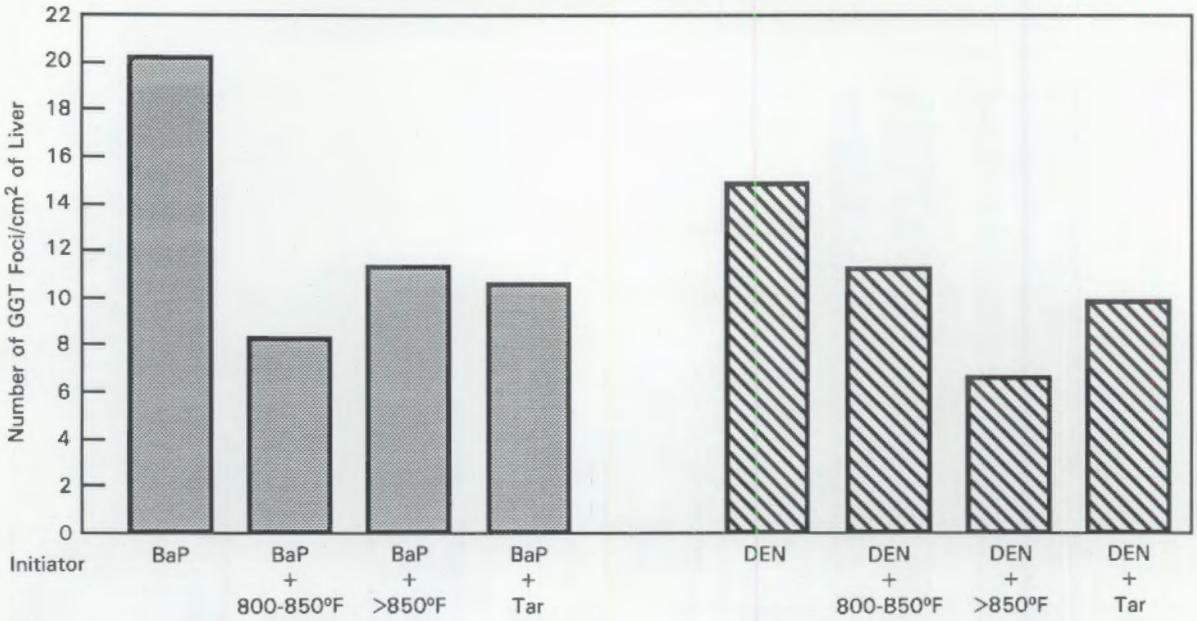

FIGURE 4. Influence of Co-Administering Two Complex Organic Mixtures on the Hepatic Initiating Activity of the Known Carcinogens Benzo[a]pyrene (BaP) and Diethylnitrosamine (DEN).

The results obtained in these experiments demonstrate that several of the complex mixtures derived from coal were active skin tumor initiators. A dose of 17 mg of the >850°F distillate was as active as a 50-µg dose of BaP, while the 800-850°F distillate was substantially lower in activity. The neutral PAH component of the mixtures was particularly effective; the NPAC fraction was also active. In contrast, these mixtures had only minimal initiating activity when tested in the neonatal liver. Since the neonatal liver responds well to the pure carcinogens BaP and DEN, it is not clear why the response to the complex mixtures was so low. We speculate that the complex mixtures are somewhat toxic to neonatal liver, thereby preventing the components in the mixture from being activated to their ultimate carcinogenic form. The toxicity of the mixtures is evidenced by the death of several animals in the groups that received complex mixtures. However, since most of the animals survived in each group, other mechanisms are likely involved as well. We intend to determine the capability of the neonatal liver to bioactivate some of the known carcinogens in the mixtures and compare the metabolic capability of neonatal rat liver to that of adult mouse skin.

Skin-tumor-initiating activities of the distillates and their neutral PAH and NPAC fractions relative to the parent material certainly suggested that simplifying the mixture actually increased the biological activity. This suggests that some of the components in the mixture inhibited the activity of carcinogenic components. Suppression of the initiating activity of BaP by the different distillates provided direct evidence that this is indeed the case. Interestingly, a similar situation was found in the neonatal rat hepatic model. The activities of both BaP and DEN were inhibited when they were administered with a mixture. We suspect that this inhibition of carcinogenic activity is due to inhibition of bioactivation precarcinogens in the mixtures, probably as a result of competition for the mixed-function oxidase system. Haugen and Springer have presented evidence that the metabolism of BaP is inhibited in the presence of complex mixtures, which supports this hypothesis. Springer has also shown that the binding of labeled BaP to DNA is likewise decreased in the presence of a complex mixture.

• Molecular Control of Lung Development

Principal Investigator: T. J. Mast

Other Investigators: R. L. Rommereim and J. S. Young

Coal-derived liquids have previously been shown to be teratogenic when pregnant rats or mice were exposed to these complex mixtures (CM) by either inhalation, oral, or dermal routes. Pulmonary hypoplasia is a major abnormality induced in the offspring of pregnant rats exposed to this CM. In order to provide a framework for further research into the molecular mechanisms regulating pulmonary maturation, this study on the temporal development of fetal lungs in control and CM-treated fetuses was undertaken. When compared to those of controls, hypoplastic lungs were not only much smaller but had less organization in the interstitial tissue and also had increased septal thickness. Although bronchial and bronchiolar regions of the hypoplastic lungs appeared normal, these data indicate that functional impairment may result from abnormal development of the alveolar region. The similarity between the overall effects of the glucocorticoid treatment and those noted as a result of treatment with CM may imply a common mechanism. Results of this study will be used as a basis for future work intended to elucidate the molecular mechanisms regulating lung maturation and differentiation.

Coal-derived liquids have previously been shown to be teratogenic when pregnant rats or mice were exposed to these complex mixtures (CM) by either inhalation, oral, or dermal routes (Hackett, Annual Report for 1985, pp. 61-62). Subsequent studies on the chemical class fractions of this mixture, obtained by liquid chromatography, showed that the teratogenic activity resided almost entirely in the polynuclear aromatic hydrocarbon (PAH) fraction (Mast, Annual Report for 1987, pp. 65-69). The major abnormalities induced in the offspring of pregnant rats exposed to the PAH fraction were the same as those caused by exposure to the original mixture and included: pulmonary hypoplasia, cleft palate, generalized edema, cutaneous syndactyly, and hemorrhages in the sagittal suture area.

The pulmonary hypoplasia, defined in fetuses whose lung to body weight ratios were at least two standard deviations below the mean lung to body weight ratio of the controls, is of particular interest in that it may serve as a model to elucidate molecular mechanisms regulating pulmonary differentiation and maturation (Figure 1). Electron micrographs of 20-days-of-gestation (dg) hypoplastic fetal rat lungs have shown them to be abnormal with respect to alveolar and interstitial tissues; however, the temporal sequence of the abnormal development was not known. In order to provide a framework for further research into the molecular mechanisms regulating pulmonary maturation, this study on the temporal development of fetal lungs in control and CM-treated fetuses was undertaken.

Timed-pregnant (2-hour matings) Sprague-Dawley rats were dermally exposed to coal-derived CM or to a vehicle control (acetone). The CM, 500 mg/kg body weight in acetone, or vehicle (acetone) was applied to the shaved backs of dams in a constant dosing volume of 1.0 ml/kg, on 11 to 15 dg. Groups of dams (number = 5) were serially sacrificed between 16 and 22 dg.

FIGURE 1. Fetal Rat Lungs at 20 Days of Gestation. Left: control fetus; right: fetal lung following *in utero* exposure to coal-derived complex mixture.

For comparative purposes, another group of dams was given the synthetic glucocorticoid, triamcinolone (TAC). Administration of synthetic glucocorticoids during certain stages of pregnancy in the rat has previously been shown to cause defects similar to those resulting from exposure to CM. The TAC was administered (0.25 mg/kg/day) as a subcutaneous injection on 11 to 14 dg. This group was sacrificed on 20 dg.

In preparation for electron microscopy, fetal lungs were inflated in situ with

McDowell-Trumps (glutaraldehyde-cacodylate) buffer, excised, then refrigerated in the buffer. In preparation for scanning electron microscopy (SEM), the fixed lungs were dehydrated, then cryofractured in a brass cup cooled with liquid nitrogen. Fractured pieces were critical-point dried, mounted with the fractured side up, and sputter-coated with gold/palladium. Transmission electron microscopy (TEM) samples were post-fixed in osmium tetroxide, dehydrated and embedded in resin. Thin sections, ~700 Å, were mounted on copper grids and stained with uranyl acetate and lead citrate.

Differences in fetal lung to body weight ratios between vehicle control and treated fetuses were evident as early as 17 dg (Figure 2). Examination of electron micrographs

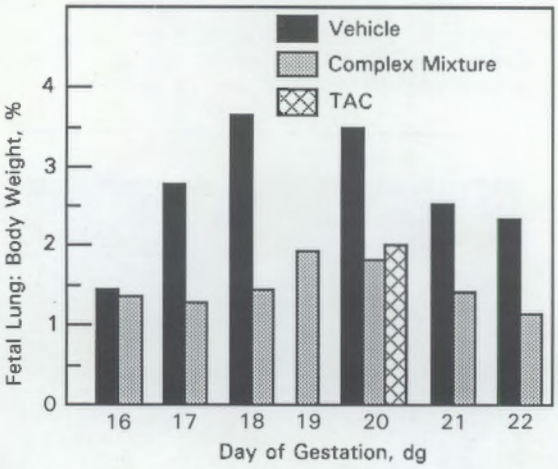

FIGURE 2. Percent Fetal Lung to Body Weight for Control and Treated Fetuses by Gestational Age. TAC = triamcinolone.

of the serially sacrificed lungs revealed that differences in alveolar epithelial cell (AEC) development between the treated and control lungs were also evident as early as 17 dg (Figure 3). There was evidence of accelerated maturation in the treated lungs, shown by a premature transition of AEC from a columnar to a flattened, cuboidal form; this process does not normally occur until 19 to 20 dg in the rat. Transmission electron micrographs (not shown) showed that the AEC in treated lungs were also slightly vacuolated and, compared to controls, had some evidence of disorganization as well. By 19 dg, the AEC of the treated lungs (Figure 4) were in an advanced stage of differentiation into Type I and Type II alveolar cells, a stage not achieved by the controls until 21 dg. Transmission electron micrographs (not shown) also showed a nearly complete loss of

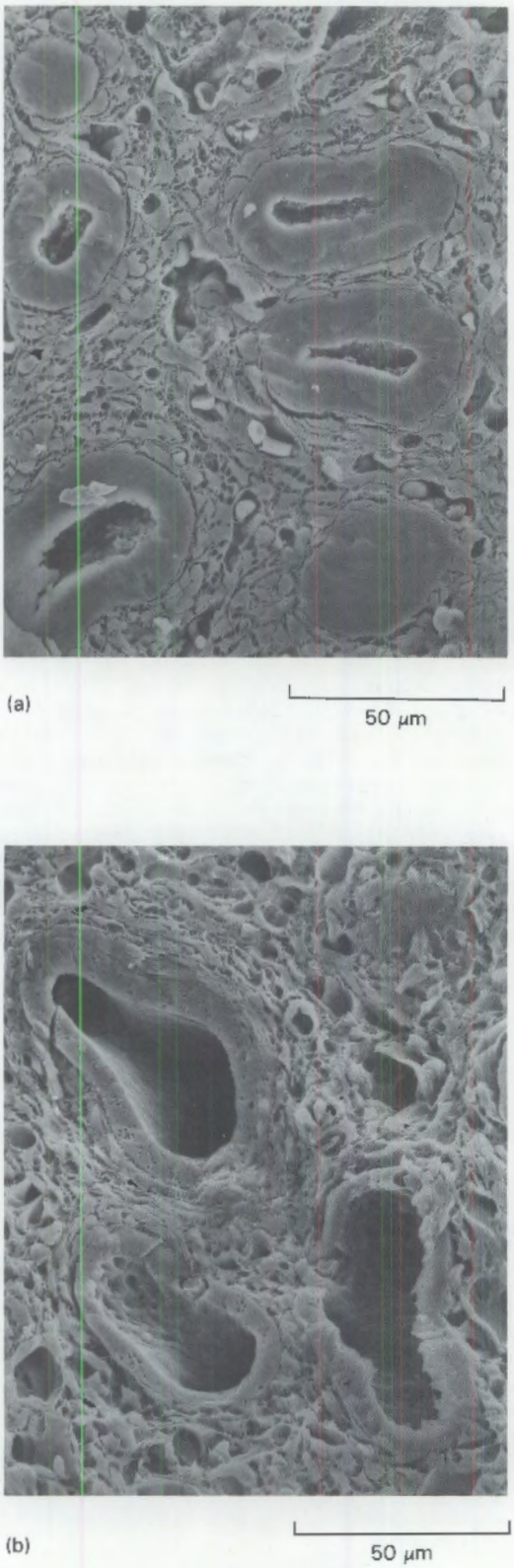

FIGURE 3. Fetal Rat Lungs at 17 Days of Gestation; (a) Control, (b) Treated. See text for details.

"early type" microvilli in the treated lung AEC. The difference between treated and control lung tissue was not as readily apparent in micrographs of 20-dg lung tissue (Figure 5) as it was in earlier and later gestational ages. However, a thickening of

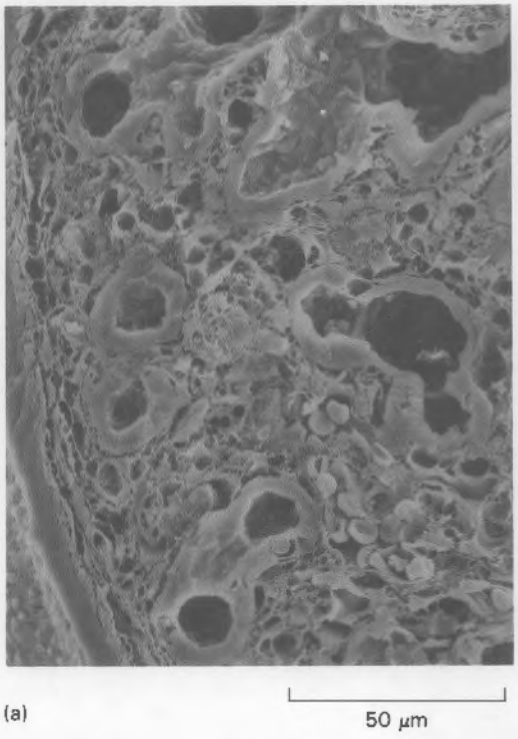

FIGURE 4. Fetal Rat Lung at 19 Days of Gestation; (a) Control, (b) Treated. See text for details.

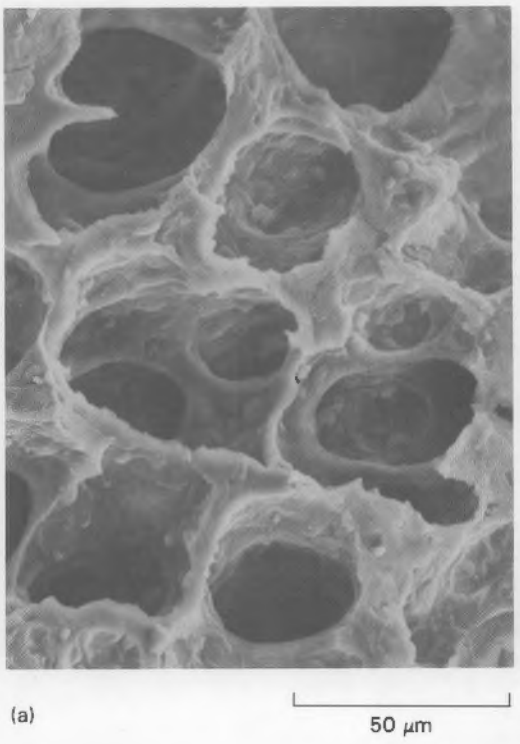

FIGURE 5. Fetal Rat Lungs at 20 Days of Gestation; (a) Control, (b) Treated. See text for details.

septal walls in the treated tissue, compared to control tissue, began to be apparent at this stage, and became very pronounced by 22 dg (Figure 6). By 22 dg (full-term in the rat), the CM-treated lungs showed abnormal AEC and very thick septal walls, while the control lungs had thin septal walls, with AEC differentiated into Type I and Type II cells. At this stage the treated lungs were severely hypoplastic. Electron micrographs of 20-dg TAC-treated lungs showed very disorganized alveolar and interstitial tissue, with precocious surfactant production (Figure 7). A strong similarity was noted between 22-dg CM-treated lungs and the 20-dg TAC-treated lungs.

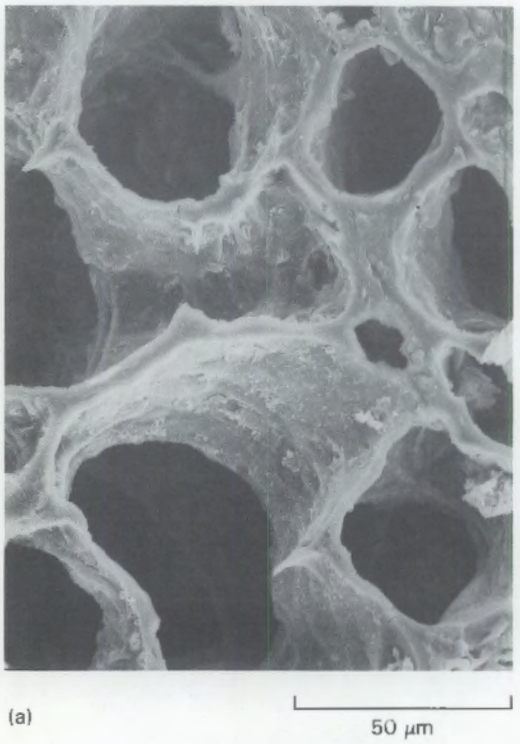

FIGURE 6. Fetal Rat Lungs at 22 Days of Gestation; (a) Control, (b) Treated. See text for details.

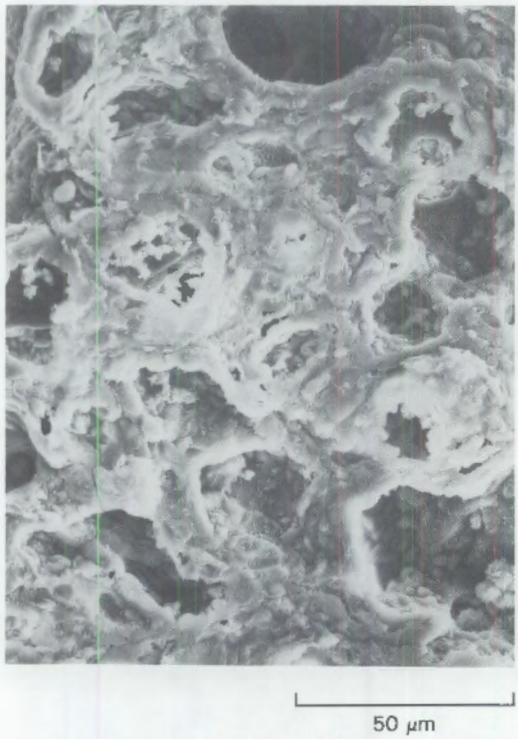

FIGURE 7. Fetal Rat Lungs at 20 Days of Gestation; *in utero* Exposure to Triamcinolone.

In summary, when compared to controls, hypoplastic lungs were not only much smaller but had less organization in the interstitial tissue and increased septal thickness. Interestingly, bronchial and bronchiolar regions of the hypoplastic lungs appeared normal. These data indicate that functional impairment may result from abnormal development of the alveolar region. The similarity between the overall effects of the glucocorticoid treatment and those noted as a result of treatment with CM may imply a common mechanism. Results of this study will be used as a basis for future work intended to elucidate the molecular mechanisms regulating lung maturation and differentiation.

• Mutational Studies in DNA Targets

Principal Investigators: R. A. Pelroy and L. K. Fritz

We have synthesized DNA targets, based on the primary sequences of known naturally occurring genetic hotspots, and placed them in the N-terminal region of the *lac* Z gene of the lactose operon of *Escherichia coli*. (The lactose operon was inserted into plasmid PDM, which was then introduced into *Salmonella typhimurium*.) The construction of the synthetic DNA targets prevents translation of the lac Z gene into β-galactosidase because of frameshift mutations that disrupt the reading frame for this structural gene. Mutations that reverse the synthetic mutations in the synthetic DNA targets and restore functionality to the *lac* Z gene can be scored by growth of *S. typhimurium* on lactose as the sole carbon source. Using this system, it is possible to detect mutational events within the DNA targets with great sensitivity, because a large number of bacteria can be exposed to a given mutagenic insult and because of the low background (spontaneous mutation rates) of these plasmid constructs.

Genetic hotspots are defined as regions of DNA, generally comprising less than 100 base pairs (bp), that show unusually high rates of induced or spontaneous mutation. Mutagenesis by chemical agents is localized to genetic hotspots, usually of no more than 20 bp in length and many have similar sequences. For example, nearly all known hotspots have repeated runs of guanine (G), adenine (A), or alternating runs of G and cytosine (C) or A and thymine (T) within or near DNA sequences where frameshift mutations most frequently occur. Mechanisms for genetic hotspot activity at the molecular level are poorly understood. One general hypothesis assumes that mutations within a hotspot sequence are specified by the hotspot sequences alone, independently of surrounding DNA. It is also possible that certain hotspots are active as a result of synergistic interactions with flanking sequences. There is fragmentary evidence for each of those hypotheses. However, without the ability to vary the composition of genetic hotspots and/or their location in DNA, it is difficult to test the various hypotheses adequately.

We are developing a system to study molecular mechanisms that govern genetic hotspots. To do this, DNA targets in the range of 50 to 100 bp have been synthesized and inserted into a target gene of a plasmid PDM. Plasmid PDM, with or without synthetic DNA-targets, is then transformed into a target cell of Salmonella typhimurium with a genetic background advantageous for mutagenesis experiments. The sequences of the DNA targets are similar to known genetic hotspots. The main advantage of this approach is that the experimenter controls the DNA composition of each DNA-target, and each one can be varied and/or sequenced after mutagenesis to determine critical domains that control activity.

The main outlines of the system are shown in Figures 1 and 2. Schematically, DNA targets synthesized de novo, are inserted into the N-terminal region of the lac operon in a Bam HI cloning site engineered several bp downstream (3-prime) from the start codon. The inserted DNA targets are intended to inactivate lac Z, thus preventing β-galactosidase synthesis. This is a selectable biochemical trait because mutations (i.e., changes in DNA sequences) that restore the reading frame allow S. typhimurium to grow on lactose as a sole carbon and energy source. The lac Z gene, along with the other structural genes of the Escherichia coli lac operon are contained in plasmid PDM. The three structural genes (lac Z, y and a) were placed under the control of a high-expression synthetic promoter inserted 5-prime to the operator for the lac Z structural gene. Plasmid PDM was then introduced into strains of S. typhimurium.

Without plasmid PDM, the S. typhimurium strains in this study are incapable of using lactose as a carbon source because they lack the entire lac operon, or equivalent genes, for lactose hydrolysis. When the lactose operon in PDM is functional, strains of S. typhimurium that carry PDM acquire the ability to hydrolyze lactose into glucose and galactose. Both 6-carbon sugars are readily utilized for growth by S. typhimurium. Therefore acquisition of PDM with a functional lac Z gene allows growth of S. typhimurium on a lactose minimal agar medium. Insertion of DNA-targets into lac are intended to prevent β-galactosidase synthesis and cause the strains to lose their ability to grow on lactose.

If it is possible to inactivate lac Z in PDM by insertion of DNA-targets, it should be possible to genetically select for the reverse mutation to lac Z function (β-galactosidase synthesis), scoring for the ability to grow on lactose. As will be shown, we are able to inactivate lac Z in PDM by insertion of synthetic DNA targets. We are also able to force reverse mutations to occur within the inserted DNA target (see below). This general approach is powerful because very large numbers of bacteria (e.g., more than 1 x 10^8/ml) can be plated on lactose agar. Therefore, reverse mutational frequencies as low as 10^{-7} should be detectable with the synthetic DNA-targets/PDM-Salmonella system.

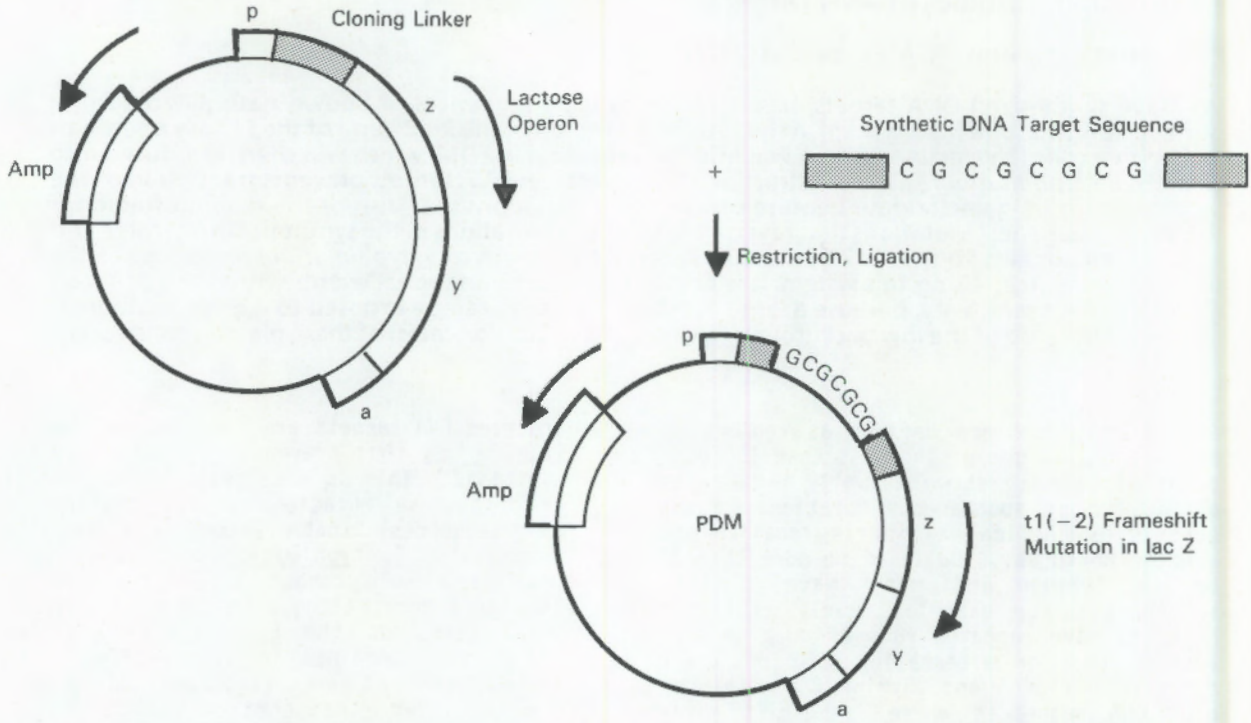

FIGURE 1. Essential Features of Plasmid PDM and the Synthetic DNA Targets are Illustrated by the Lactose Operon (Genes z, y, a); the Synthetic Promoter (P); a Cloning Linker for DNA Targets (▨); and the DNA Target (e.g., CgCgCg). Introduction of the DNA target into the cloning site by enzymatic ligation interrupts the reading frame of the lac operon, abolishing the activity of the lac Z gene. Arrows indicate the direction of transcription.

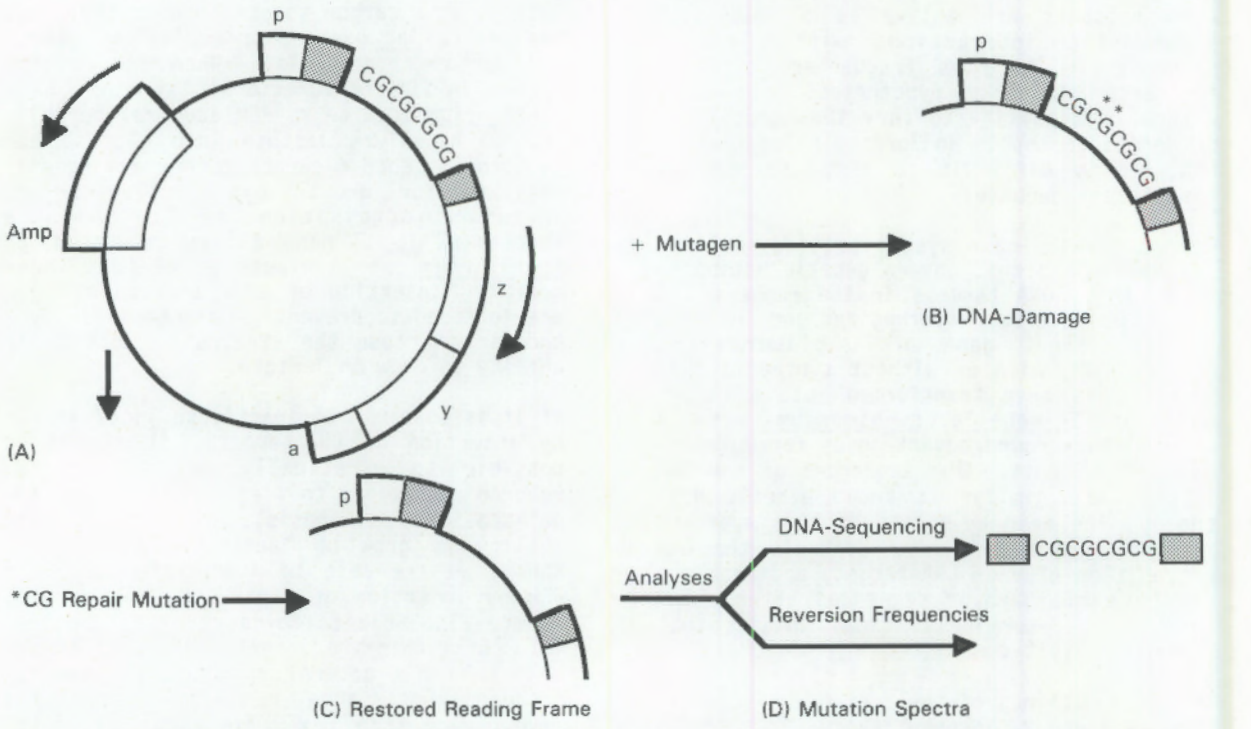

FIGURE 2. Strategy for Mutagenesis of a DNA Target in PDM, Illustrated by: (A) Exposure to a Mutagen; (B) Mutagen-Induced Primary DNA Damage (*) to bp in the Target; (C) Cell-Mediated Error-Prone Repair, Resulting in Mutation, Leading to Restoration of Reading Frame; (D) Analysis of the Mutagenesis Event by Reverse Mutation and by Direct Sequencing of DNA Targets from Reverted Clones.

The DNA targets shown in Figure 3 represent a series of minus 1/plus 2 frameshift mutations. All have been synthesized, and the first three that contain core sequences of G_6 $[GC]_3$ and $[AT]_3$ have been inserted into PDM and transformed into appropriate S. typhimurium strains.

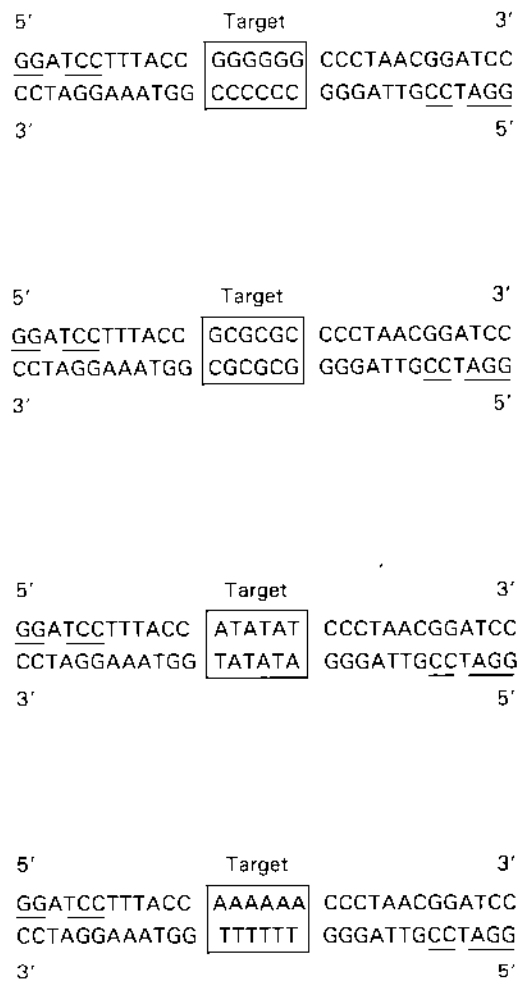

FIGURE 3. Primary Sequences of Four DNA Targets in the Plus 1 (Minus 2) Reading Frame Relative to the lac Z Gene.

Reverse mutations that restore the reading frame in lac Z can be scored directly by growth of S. typhimurium strains on lactose. DNA targets that specify minus 1/plus 2 frameshift mutations in lac Z (F-3) will be reversed only by deletions of DNA resulting in a net loss of 1 bp (or gain of 2 bp) relative to the reading frame of lac Z. Comparable DNA-targets are being constructed for plus 1/minus 2 frameshift mutations. Core sequences like those in F-3 are common in genetic hotspots for bulky polycyclic hydrocarbons that intercalate into DNA or that form covalent adducts with DNA during the mutagenesis process. For the synthetic DNA targets shown in Figure 3, we have chosen a standard core length of 6 bp.

We needed a way of excluding second-site mutations falling outside of the DNA-targets but capable of correcting the reading frame of lac Z. Because the DNA-targets are located in the extreme N-terminal region of lac Z, we can exclude second-site mutations on the left of (5-prime to) the DNA-targets. In order to confine mutational events to the target sequence on the 3-prime side, we have placed a translational-step codon 3-prime to the core sequence and an inverted-stop codon 5-prime to the left of the core sequence. The 3-prime stop codon will erase the effect of any second-site frameshift mutation to the right of the DNA-target sequences. Moreover, the inverted-stop codon will be read as a stop codon if the DNA-target is inserted in the opposite orientation to that shown in Figure 2. Therefore, for all DNA targets in Figure 2, in both possible orientations, a translational stop codon is 3-prime to the core sequence and therefore bounded to the right. As stated, the N-terminal location of the DNA-target bounds the target (i.e., confines mutational event) to the left.

The DNA targets in Figure 3 represent a net insertion of 25 bp into the lac Z gene. Since the reading frame for the genetic code is 3 bp, the 25-bp length represents an addition of 1-bp to the natural reading frame for lac Z. Accordingly, the frameshift mutations in the DNA-targets of F-3 can be reversed by deletion of a single bp or addition of 2 bp (or any multiple of 3N-1 bp of DNA where N is an integer). Each of the DNA targets in Figure 3 is therefore functionally equivalent to a plus 1/minus 2 frameshift mutation in lac Z without an inserted DNA-target. Similar DNA targets for a minus 1/plus 2 frameshift will be synthesized and inserted into lac Z in PDM.

The data in Table 1 were obtained from 20 clones of S. typhimurium SL 4213 transformed with plasmid PDM containing DNA target (corresponding to plus 1/minus 2 frameshift mutations). Most transformants formed white colonies on agar plates containing a chemical indicator for lac Z formation. White colony formation is presumptive indication of the loss of the lac Z gene function. Spontaneous reversion frequencies ranged from less than 10^{-8} to 2×10^{-6}, comparable to a range of spontaneous mutation rates in bacterial and mammalian chromosome systems. All white (lac Z) minus clones were incapable of growth when subcultured on lactose minimal agar medium, showing low levels of β-galactosidase activity that were correlated with loss of lactose utilization as a carbon source. All clones probing positive for DNA targets were lac-negative, showing that incorporation of DNA targets resulted in loss of the lactose operon.

TABLE 1. Characteristics of Salmonella typhimurium TA98 and TA1535 Transformed with Plasmid PDM-Carrying DNA Targets.

Clone	Input DNA-Target Core Sequence	Colony Hybridization Probe[a]	X-gal[b]	Growth on Lactose[c]	Mutation Frequency
1-38	[gcgcgc]	(+)	−	−	$\sim 10^{-8}$
2-38	[gcgcgc]	+	+	−	1.3×10^{-6}
3-38	[gcgcgc]	(+)	(+)	−	$<10^{-8}$
4-38	[gcgcgc]	+	+		5×10^{-7}
5-38	[gcgcgc]	−	−	−	$<10^{-8}$
6-38	[gcgcgc]	+	−	−	$<10^{-8}$
8-35	[gcgcgc]	(+)	−	−	$<10^{-8}$
9-35	[gcgcgc]	−	−	−	$<10^{-8}$
10-35	[gcgcgc]	+	+	−	1.4×10^{-6}
11-38	[atatat]	(+)	−	−	2×10^{-6}
12-38	[atatat]	+	−	−	$<10^{-8}$
12-35	[atatat]	+	(+)	−	2.1×10^{-6}
13-38	[atatat]	−	−	−	$<10^{-8}$
14-38	[atatat]	+	+	−	7.5×10^{-7}
15-35	[atatat]	+	−	−	$<10^{-8}$
16-35	[atatat]	+	−	−	$<10^{-8}$
17-35	[atatat]	−	−	−	$<10^{-8}$
18-35	[atatat]	(+)	(+)	−	$<10^{-8}$
19-35	[atatat]	+	−	−	$<10^{-8}$
20-35	[atatat]	+	−	−	$<10^{-8}$

[a] Colony hybridization carried out with ^{32}P-labeled DNA probes to the 25-bp DNA-target. There was no cross-reaction with the plasmid PDM sequences under conditions used for the hybridizations. − indicates strong probing, (+) weak probing, and −, nonprobing.

[b] β-galactosidase formation detected by hydrolysis of the chromagenic dye X-gal on tryptose/yeast extract/sodium chloride (LB) agar medium. +, (+), −, symbols as in (a).

[c] Agar minimal medium, 0.2% w/v β-lactose.

[d] Revertant (lactose positive) clones per viable cell on lactose minimal medium.

There were indications that individual lac- negative clones were heterogeneous at the molecular level. First, 4/20 lactose-negative clones failed to probe for DNA-target sequences, indicating that lac Z mutations were being introduced into PDM as a consequence of the DNA-target insertion procedure without introduction of all or most of the DNA target. Another 5/20 clones probed weakly positive for DNA targets and weakly positive for residual Xgal hydrolysis (see below), indicating DNA target sequences with some alterations, or single, possibly "copy," DNA targets. The remaining 11/20 lactose-negative clones probed strongly positive for DNA target sequences, indicating incorporation of single copies of DNA targets without alteration or multiple insertions of DNA target (multiple copies).

Alterations in bp sequences within DNA targets could include partial deletions or rearrangements of bp or multiple inserts of DNA targets in the clones that probed positive for the parental DNA targets. In order to provide single-copy insertions of DNA targets into PDM, it will be necessary to distinguish single-copy from multiple-copy inserts and to verify by direct sequence analysis that inserted DNA targets of the correct molecular weight have not been rearranged.

Multiple inserts have been detected in several clones by restriction enzyme analysis with Bam HI. Three clones from the alternating GC set of DNA targets have produced convincing evidence for single inserts of the DNA targets. This evidence consists of showing a Bam HI restriction fragment from clones of 130 bp, which is the size of the synthetic promoter plus a single copy of the DNA target (25 bp). It also consists of a restriction fragment pattern otherwise identical to plasmid PDM without the DNA target. Finally, the three clones probe positive for the DNA target and are lactose-negative, as discussed. These clones are being subcultured and will be sequenced directly to verify that they have the required DNA targets, i.e., the alternating GC target shown in Figure 3. Comparable synthesis is beginning on DNA-targets with the core sequences alternating, as shown in Figure 3. The immediate emphasis is on obtaining well-defined single-copy inserts of the DNA tar-

gets shown in Figure 3 into PDM. We may eventually screen some strains of S. typhimurium that contain multiple inserts of the DNA targets. Generating an array of DNA sequences via insertion reactions may prove to be a simple way to generate a variety of DNA targets from a single parental target.

We have three major objectives in the near term: 1) to determine the effect of lengthening (or shortening) the core sequences and/or altering the flanking sequences on the genetic activity of hotspots. 2) The second objective is to study mutagenesis at the molecular level by direct analysis of bp changes that are responsible for reverse mutations in the DNA targets. The use of computer modeling will be investigated for studying mechanisms of mutagenesis with these targets. 3) We will attempt to determine if DNA targets are differentially sensitive to individual mutagens and if they can be used to detect such mutagens in environmental mixtures through the construction of mutational spectra.

Medical Applications Of Nuclear Technology

- **List of DOE Radioisotope Customers with Summary of Radioisotope Shipments, FY 1986**

Principal Investigator: D. A. Lamar

Data were collected and compiled on radioisotopes produced and sold by Department of Energy (DOE) facilities, and on services rendered by DOE facilities. Compiled data were published and distributed in the document *List of DOE Radioisotope Customers with Summary of Radioisotope Shipments, FY 1986*, PNL-6361, October 1987. The DOE facilities that supplied information for the compilation were Argonne National Laboratory, Brookhaven National Laboratory, Hanford Engineering Development Laboratory, Idaho National Engineering Laboratory, Los Alamos National Laboratory, Oak Ridge National Laboratory, Pacific Northwest Laboratory, Savannah River Plant, and UNC Nuclear Industries, Inc. (Hanford).

The data provided were reported in several different ways: 1) a list of radioisotopes and services provided by each facility; 2) a list of radioisotope customers, the supplying DOE facility, and the radioisotope or service provided to each customer; and 3) a list of the quantity and value of each radioisotope or service sold by each DOE facility. The sales information covered foreign customers, domestic private customers, and domestic DOE customers.

Appendix

APPENDIX

• Dose-Effect Studies with Inhaled Plutonium in Beagles

On the following pages data are presented for all dogs assigned to 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 9/30/87	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				12/10/87		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				09/02/87		217.5*	Processing
CONTROL	789 M	0	0.00	0.00				07/25/83		167.9*	Malignant Lymphoma
CONTROL	792 M	0	0.00	0.00				04/28/78		79.5*	Oral Tumor
CONTROL	800 F	0	0.00	0.00				11/17/88		204.9*	Malignant Pheochromocytoma
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	848 M	0	0.00	0.00				04/08/83		159.6*	Nephrosclerosis
CONTROL	861 M	0	0.00	0.00				11/18/86		202.6*	Cushing's, Intestinal Carc
CONTROL	868 F	0	0.00	0.00				03/24/87		205.4*	Chronic Nephropathy
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		98.2*	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		162.8	Kidney Failure
D-1 LOWEST	858 M	0	0.00	0.00	13.5	18.2	07/06/71	10/01/88		182.9	Lymphocytic Leukemia
D-1 LOWEST	865 F	0	0.00	0.00	9.0	17.4	07/06/71	09/16/86		182.4	Acute Pneumonia, Lung Tumor
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	05/10/86		174.0	Pneumonia
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	03/03/86		178.2	Malignant Lymphoma
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	02/07/88		175.1	Malignant Lymphoma
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	8	0.06	0.63	9.5	19.1	01/19/71	11/29/84		168.3	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 9/30/87	DEATH	COMMENTS ON DEAD DOGS
D-1 LOWEST	788 M	8	0.08	0.62	13.0	18.8	02/10/71	04/13/84		158.1	Chronic Nephropathy
D-1 LOWEST	850 F	5	0.06	0.83	8.0	21.3	10/07/71	08/06/83		140.0	Bone Tmr, Chronic Nephropathy
D-1 LOWEST	893 M	9	0.06	0.61	14.0	14.9	10/07/71	07/01/86		176.8	Pneumonia
D-1 LOWEST	807 F	8	0.07	0.73	11.0	14.6	02/10/71	07/24/81		125.4	Pituitary Tumor, Cushing's
D-1 LOWEST	841 F	8	0.07	0.75	8.0	17.7	06/08/71	04/01/86		177.8	Malignant Lymphoma
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	778 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	12/09/85		179.6	Valvular Endocardiopathy
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	882 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	0.98	13.5	16.9	07/08/71	07/24/86		180.6	Malignant Melanoma, Oral
D-2 LOW	874 M	16	0.11	1.24	13.0	16.8	07/08/71	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	15.7	02/10/71	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	12/20/86		182.4	Acute Pneumonia
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	11/26/86		191.2	Leiomyosarcoma,Kidney,Lung Tm
D-2 LOW	876 F	19	0.24	2.69	7.0	17.9	10/07/71	05/05/86		174.9	Nephropathy,Lung Tumor
D-2 LOW	808 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	05/06/86		174.9	Lung Tumor
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	Kidney Tumor, Lung 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	05/29/86		182.8	Adrenocortical Carc, Lung Tmr
D-3 MED-LOW	752 M	62	0.43	4.77	13.0	18.8	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		191.8		
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	12/07/86		182.0	Thyroid Carc, Hypothyroidism
D-3 MED-LOW	918 M	74	0.58	8.43	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 9/30/87 DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	797 F	85	0.70	7.73	11.0	16.4	03/04/71	05/16/86	182.4	Lung Tumor
D-3 MED-LOW	848 F	75	0.72	7.94	9.5	21.3	10/07/71	10/02/86	179.8	Acute Pneumonia
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	684 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	Nephropathy,Lung Tumor
D-3 MED-LOW	905 F	127	1.38	14.94	8.5	15.9	11/10/71	02/07/83	134.9	Malignant Lymphoma
D-4 MEDIUM	868 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	02/03/86	177.3	Lung Tumor,Bile Duct Carcinom
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	03/18/81	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	Nephropathy,Lung Tumor
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	14.8	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	108.7	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	110.9	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 9/30/87	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	19.0	02/10/71	12/03/75		57.7	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	798 F	1318	11.41	125.52	10.5	15.7	02/10/71	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	02/10/71	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	908 F	6632	63.46	698.11	9.5	15.9	11/09/71	11/22/72		12.5	Radiation Pneumonitis
D-6 HIGH	898 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	7478	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 9/30/87	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					196.5*		
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				02/24/87		188.8*	Processing
CONTROL	1007 F	0	0.00	0.00					195.9*		
CONTROL	1024 M	0	0.00	0.00				07/13/87		192.9*	Processing
CONTROL	1038 M	0	0.00	0.00				12/16/86		183.9*	Processing
CONTROL	1045 M	0	0.00	0.00				06/08/86		177.6*	Processing
CONTROL	1054 F	0	0.00	0.00					193.1*		
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					188.6*		
CONTROL	1112 M	0	0.00	0.00				12/02/86		178.4*	Processing
CONTROL	1116 F	0	0.00	0.00					188.1*		
CONTROL	1186 F	0	0.00	0.00				07/26/85		155.3*	Urinary Bladder Tumor
CONTROL	1197 M	0	0.00	0.00					181.0*		
CONTROL	1209 M	0	0.00	0.00					180.7*		
CONTROL	1225 F	0	0.00	0.00					179.8*		
CONTROL SACRIFICE	986 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	04/11/86		158.7	Processing
D-1 LOWEST	1003 M	0	0.00	0.00	14.0	19.6	01/18/73	04/01/87		170.4	Processing
D-1 LOWEST	1023 F	0	0.00	0.00	12.5	19.2	01/18/73		176.4		
D-1 LOWEST	1039 M	0	0.00	0.00	11.0	17.0	01/18/73	07/04/86		161.5	Processing
D-1 LOWEST	1044 F	0	0.00	0.00	11.5	17.0	01/18/73		176.4		
D-1 LOWEST	1055 M	0	0.00	0.00	13.0	16.8	01/18/73	06/04/87		172.5	Processing
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	Malignant Lymphoma
D-1 LOWEST	1194 F	0	0.00	0.00	10.5	19.8	04/18/74	12/03/85		139.5	Malignant Lymphoma
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	09/30/86		149.4	Hemangiosarcoma, Liver
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	10/24/85		153.2	Fibrosarcoma, Spleen
D-1 LOWEST	1193 F	2	0.01	0.16	12.5	19.8	04/18/74	01/22/86		141.2	Immune Hemolytic Anemia
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 9/30/87	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	08/12/87		170.4	Processing
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		163.1		
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	07/01/86		162.4	Processing
D-1 LOWEST	1106 F	5	0.05	0.50	10.0	16.4	05/31/73	03/14/83		117.4	Adrenal Tmr,Osteoarthropathy
D-2 LOW	1065 F	6	0.05	0.60	10.0	18.3	05/31/73	04/10/86		154.3	Malignant Lymphoma, Lung Tmr
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		172.0		
D-2 LOW	1090 F	10	0.08	0.83	12.0	17.3	05/31/73	05/10/87		167.3	Processing
D-2 LOW	1222 M	15	0.10	1.07	14.0	19.0	04/18/74	03/19/86		143.0	Malig (mediast) Mesothelioma
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	01/31/88		157.4	Processing
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	01/27/87		169.3	Processing
D-2 LOW	1033 M	17	0.14	1.55	11.0	19.1	02/22/73	12/17/85		154.8	Lung Tumor
D-2 LOW	1036 F	16	0.14	1.52	10.5	18.2	02/22/73	05/06/87		170.4	Processing
D-2 LOW	1216 M	23	0.16	1.77	13.0	19.3	04/18/74	04/22/87		156.1	Malignant Lymphoma
D-2 LOW	1060 F	22	0.18	2.00	11.0	17.8	02/22/73	12/21/84		141.9	Pneumonia
D-2 LOW	981 M	30	0.21	2.31	13.0	19.0	12/19/72		177.3		
D-2 LOW	1046 M	27	0.22	2.45	11.0	18.1	02/22/73		175.2		
D-2 LOW	1050 F	22	0.22	2.44	9.0	18.1	02/22/73	05/14/86		158.7	Processing
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		163.1		
D-2 LOW	1196 F	28	0.25	2.80	10.0	17.9	02/26/74		163.1		
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	03/04/86		158.5	Processing
D-3 MED-LOW	1089 F	41	0.34	3.73	11.0	17.3	05/31/73		172.0		
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	12/05/86		151.6	Chronic Nephropathy
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		166.8		

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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 9/30/87	DEATH	COMMENTS ON DEAD DOGS
D-3 MED-LOW	1185 M	76	0.43	4.75	16.0	17.3	11/06/73	07/21/86		152.4	Acute Pneumonia
D-3 MED-LOW	1309 M	60	0.44	4.80	12.5	18.5	03/04/75	04/22/87		145.6	Hemangiosarcoma, Liver
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		150.9		
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	78	0.58	6.33	12.0	19.0	12/19/72	01/29/86		157.3	Processing
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	18.4	05/31/73	01/14/87		163.5	Processing
D-3 MED-LOW	1000 F	70	0.71	7.78	9.0	18.7	12/19/72		177.3		
D-3 MED-LOW	1056 M	97	0.71	7.78	12.5	17.9	02/22/73	06/17/86		159.8	Processing
D-3 MED-LOW	1004 M	116	0.73	8.00	14.5	19.8	01/18/73	04/30/87		171.3	Processing
D-3 MED-LOW	1028 M	116	0.78	8.59	13.5	19.2	01/18/73	11/13/85		153.8	Hepatic Displasia
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	1.12	12.33	9.0	17.8	02/26/74		163.1		
D-4 MEDIUM	1178 M	129	0.87	9.56	13.5	16.8	11/06/73	12/12/85		145.2	Hemangioma, Spleen
D-4 MEDIUM	1221 F	124	1.13	12.40	10.0	19.0	04/18/74		161.4		
D-4 MEDIUM	1195 M	228	1.38	15.20	15.0	18.1	02/26/74	07/29/87		161.0	Processing
D-4 MEDIUM	1032 M	162	1.40	15.43	10.5	16.3	11/30/72	12/08/72		0.3	Sacrificed
D-4 MEDIUM	1053 F	148	1.42	15.58	9.5	17.9	02/22/73	02/02/85		143.3	Cushing's Disease
D-4 MEDIUM	997 M	203	1.60	17.65	11.5	19.8	01/18/73	05/08/86		159.8	Processing
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		141.8	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	11/10/86		161.3	Processing
D-4 MEDIUM	1114 M	430	2.70	29.66	14.5	16.4	05/31/73	04/23/85		142.8	Bone Tumor,Bile Duct Carcinom
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		79.8	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	09/14/88		150.6	Acute Pneumonia, Lung Tumor
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	1188 M	673	4.08	44.87	15.0	17.3	11/06/73	06/23/84		127.5	Malignant Lymphoma

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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 9/30/87 DEATH	COMMENTS ON DEAD DOGS
D-4 MEDIUM	1220 F	518	4.28	47.09	11.0	19.0	04/18/74	12/09/86	151.7	Malignant Lymphoma, Addison's
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
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	11/08/73	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	11/08/73	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	18.4	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	11/08/73	09/22/81	94.5	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1211 M	1764	11.08	121.66	14.5	17.6	02/26/74	05/17/82	98.6	Bone Tumor
D-5 MED-HIGH	1096 F	1478	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	348.38	11.0	19.6	01/18/73	01/18/79	72.0	Bone Tumor, Lung Tumor
D-6 HIGH	975 F	3988	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	18.7	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	8201	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 9/30/87	DEATH	COMMENTS ON DEAD DOGS
CONTROL	1356 M	0	0.00	0.00				04/07/87		154.9*	Processing
CONTROL	1365 M	0	0.00	0.00					160.8*		
CONTROL	1378 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				06/19/87		155.9*	Processing
CONTROL	1405 M	0	0.00	0.00				08/13/84		121.3*	Sacrificed, Heart Base Tumor
CONTROL	1409 M	0	0.00	0.00					158.8*		
CONTROL	1418 M	0	0.00	0.00					158.5*		
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				08/20/87		156.5*	Processing
CONTROL	1483 F	0	0.00	0.00					156.9*		
CONTROL	1509 M	0	0.00	0.00				10/30/86		145.1*	Processing
CONTROL	1516 F	0	0.00	0.00					155.8*		
CONTROL	1525 M	0	0.00	0.00					155.6*		
CONTROL	1526 M	0	0.00	0.00					155.6*		
CONTROL	1528 F	0	0.00	0.00				04/06/87		149.2*	Processing
CONTROL	1543 M	0	0.00	0.00				08/12/86		141.3*	Processing
CONTROL	1563 F	0	0.00	0.00					144.8*		
CONTROL	1572 F	0	0.00	0.00					144.7*		
CONTROL	1577 M	0	0.00	0.00					144.7*		
CONTROL	1584 F	0	0.00	0.00					144.6*		
CONTROL	1594 F	0	0.00	0.00					144.6*		
CONTROL	1608 M	0	0.00	0.00					144.3*		
CONTROL	1633 F	0	0.00	0.00				11/10/86		126.9*	Thyroid Tumor
CONTROL	1638 F	0	0.00	0.00				09/08/87		136.5*	Processing
VEHICLE	1361 M	0	0.00	0.00	8.5	21.0	02/13/76		139.5		
VEHICLE	1381 F	0	0.00	0.00	8.5	19.8	02/13/76		139.5		
VEHICLE	1392 M	0	0.00	0.00	13.0	22.0	04/22/76		137.3		
VEHICLE	1406 M	0	0.00	0.00	13.5	21.8	04/22/76		137.3		
VEHICLE	1412 F	0	0.00	0.00	9.0	19.0	02/13/76		139.5		
VEHICLE	1421 M	0	0.00	0.00	13.0	23.3	06/23/76		135.2		
VEHICLE	1457 F	0	0.00	0.00	12.0	20.8	04/22/76		137.3		
VEHICLE	1491 F	0	0.00	0.00	8.0	21.8	06/23/76		135.2		
VEHICLE	1504 F	0	0.00	0.00	10.0	20.9	06/23/76		135.2		
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		134.1		
VEHICLE	1531 F	0	0.00	0.00	9.0	20.9	07/27/76		134.1		
VEHICLE	1542 M	0	0.00	0.00	12.0	20.8	07/27/76		134.1		
VEHICLE	1566 M	0	0.00	0.00	14.0	18.3	03/15/77		126.5		
VEHICLE	1578 M	0	0.00	0.00	10.5	18.2	03/15/77		126.5		
VEHICLE	1593 F	0	0.00	0.00	11.0	18.0	03/15/77		126.5		
VEHICLE	1601 F	0	0.00	0.00	8.5	18.0	03/15/77		126.5		

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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 9/30/87	DEATH	COMMENTS ON DEAD DOGS
VEHICLE	1620 M	0	0.00	0.00	11.0	21.1	12/01/77	01/06/87		109.2	Vertebral Disc
VEHICLE	1634 F	0	0.00	0.00	10.5	19.6	12/01/77		117.9		
VEHICLE	1651 F	0	0.00	0.00	11.0	19.2	12/01/77		117.9		
D-1 LOWEST	1418 M	0	0.00	0.00	12.0	22.1	05/20/76		136.3		
D-1 LOWEST	1458 F	0	0.00	0.00	10.5	21.5	05/20/76		136.3		
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		136.3		
D-1 LOWEST	1573 M	0	0.00	0.00	11.5	19.4	04/19/77		125.4		
D-1 LOWEST	1581 M	0	0.00	0.00	16.5	19.3	04/19/77	07/31/88		111.4	Hemangiosarcoma
D-1 LOWEST	1598 M	0	0.00	0.00	14.0	19.2	04/19/77		125.4		
D-1 LOWEST	1600 F	1	0.01	0.11	11.0	19.2	04/19/77		125.4		
D-1 LOWEST	1603 M	2	0.01	0.12	14.0	19.2	04/19/77		125.4		
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		136.3		
D-1 LOWEST	1570 F	2	0.02	0.18	10.0	19.4	04/19/77	06/19/87		122.0	Processing
D-1 LOWEST	1465 F	4	0.03	0.35	12.0	21.0	05/20/76		136.3		
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		136.3		
D-1 LOWEST	1592 F	4	0.03	0.29	13.5	19.2	04/19/77		125.4		
D-1 LOWEST	1607 M	5	0.03	0.35	13.0	19.0	04/19/77		125.4		
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		136.3		
D-1 LOWEST	1583 F	4	0.04	0.40	9.5	19.2	04/19/77		125.4		
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	0.08	0.67	11.5	19.4	04/19/77	09/28/85		101.3	Hemangiosarcoma
D-2 LOW	1513 M	0	0.00	0.00	11.5	19.8	05/20/76		136.3		
D-2 LOW	1520 M	1	0.01	0.12	10.5	19.5	05/20/76		136.3		
D-2 LOW	1415 M	2	0.02	0.20	11.5	22.2	05/20/76		136.3		
D-2 LOW	1575 M	3	0.02	0.19	14.0	19.4	04/19/77		125.4		
D-2 LOW	1466 F	5	0.03	0.37	14.0	21.0	05/20/76		136.3		
D-2 LOW	1606 F	5	0.04	0.42	12.5	19.0	04/19/77		125.4		
D-2 LOW	1579 M	8	0.05	0.59	14.0	19.3	04/19/77		125.4		
D-2 LOW	1590 F	8	0.05	0.51	12.0	19.2	04/19/77	03/18/87		118.9	Mammary Tumor
D-2 LOW	1585 F	8	0.08	0.68	12.0	19.2	04/19/77		125.4		
D-2 LOW	1580 F	9	0.07	0.82	11.0	19.3	04/19/77		125.4		
D-2 LOW	1591 M	11	0.07	0.78	15.0	19.2	04/19/77		125.4		
D-2 LOW	1417 M	11	0.08	0.89	12.0	22.1	05/20/76		136.3		
D-2 LOW	1423 M	10	0.08	0.87	11.0	22.1	05/20/76		136.3		
D-2 LOW	1567 M	10	0.08	0.83	12.0	19.4	04/19/77		125.4		
D-2 LOW	1472 F	10	0.09	1.01	10.0	21.0	05/20/76		136.3		
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	08/10/86		111.7	Epilepsy

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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 9/30/87	DEATH	COMMENTS ON DEAD DOGS
D-2 LOW	1484 F	11	0.10	1.08	10.0	20.5	05/20/76		136.3		
D-2 LOW	1599 F	10	0.10	1.14	9.0	19.2	04/19/77	03/12/88		108.7	Adrenal Tumor
D-2 LOW	1490 F	16	0.15	1.65	9.5	20.5	05/20/76		136.3		
D-3 MED-LOW	1336 M	21	0.14	1.52	13.5	18.0	10/16/75	11/13/75		0.9	Sacrificed
D-3 MED-LOW	1341 F	19	0.16	1.78	10.5	17.2	10/16/75	11/13/75		0.9	Sacrificed
D-3 MED-LOW	1605 F	25	0.20	2.19	11.5	17.8	03/15/77	03/24/82		60.3	Sacrificed
D-3 MED-LOW	1386 M	34	0.21	2.38	14.5	22.0	04/20/76	01/04/86		116.5	Hemangiosarcoma
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	12/02/86		116.6	Pneumonia
D-3 MED-LOW	1595 M	50	0.29	3.23	15.5	18.0	03/15/77		126.5		
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	Thyroid Tumor, Lung Tumor
D-3 MED-LOW	1587 M	53	0.31	3.40	15.5	18.1	03/15/77	01/14/86		106.0	Hemangiosarcoma, Lung Tumor
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	11/25/86		124.1	Processing
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		126.5		
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	1584 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		137.3		
D-3 MED-LOW	1439 F	53	0.42	4.61	11.5	21.0	04/20/76		137.3		
D-3 MED-LOW	1523 F	55	0.42	4.60	12.0	21.3	07/22/76		134.3		
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	5.08	12.5	19.1	01/20/76	05/24/87		136.1	
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	09/27/87		126.4	Processing
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		126.5		
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		137.3		
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	1383 M	85	0.74	8.09	10.5	20.2	01/20/76	05/12/87		135.7	
D-3 MED-LOW	1604 M	85	0.74	8.10	10.5	18.0	03/15/77		126.5		
D-3 MED-LOW	1530 F	72	0.76	8.41	8.5	20.8	07/22/76	09/17/86		121.9	Processing
D-3 MED-LOW	1456 F	61	0.79	8.68	7.0	20.5	04/20/76	04/21/87		132.0	
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		140.3		
D-4 MEDIUM	1637 M	192	1.45	15.99	12.0	18.9	11/07/77		118.7		

* 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 9/30/87	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		118.7		
D-4 MEDIUM	1379 M	278	1.74	19.16	14.5	19.1	01/20/76		140.3		
D-4 MEDIUM	1382 M	267	1.87	20.54	13.0	20.2	01/20/76		140.3		
D-4 MEDIUM	1639 F	248	2.05	22.57	11.0	18.5	11/07/77		118.7		
D-4 MEDIUM	1647 M	294	2.05	22.58	13.0	18.5	11/07/77		118.7		
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	08/07/86		105.0	Lung Tumor
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	08/14/86		126.8	Processing
D-4 MEDIUM	1618 F	277	2.40	26.36	10.5	20.3	11/07/77		118.7		
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	10/28/85		114.3	Bone Tumor, Lung Tumor
D-4 MEDIUM	1635 F	345	3.13	34.48	10.0	20.7	07/22/76	10/06/86		122.5	Processing
D-4 MEDIUM	1446 F	354	3.22	35.40	10.0	21.0	04/20/76	08/10/86		123.7	Processing
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	38.27	10.0	18.0	10/16/75	11/14/75		1.0	Sacrificed
D-5 MED-HIGH	1348 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	Bone Tumor, Lung Tumor
D-5 MED-HIGH	1347 F	686	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	108.24	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	21.8	06/23/76	10/16/80		51.8	Bone Tumor
D-5 MED-HIGH	1459 F	2645	26.72	293.89	9.0	22.8	06/23/76	09/25/80		51.1	Rad. Pneumonitis, Lung Tumor
D-6 HIGH	1518 M	3565	29.46	324.09	11.0	20.8	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 9/30/87	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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