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IITRI NO. LO6139

# RESEARCH AND DEVELOPMENT ON INHALATION TOXICOLOGIC EVALUATION OF RED PHOSPHORUS/BUTYL RUBBER COMBUSTION PRODUCTS

PHASE III REPORT

Prepared by

CATHERINE ARANYI

DECEMBER 1984

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IIT RESEARCH INSTITUTE, LIFE SCIENCES RESEARCH DEPARTMENT
10 WEST 35th STREET, CHICAGO, ILLINOIS 60616

Contracting Officer's Technical Representative

ROBERT FINCH, PH.D.

HEALTH EFFECTS RESEARCH DIVISION
U.S. ARMY MEDICAL BIOENGINEERING RESEARCH
AND DEVELOPMENT LABORATORY
FORT DETRICK, FREDERICK, MARYLAND 21701-5010

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Combinations of exposure concentrations, durations and frequencies were tested in four-week inhalation exposures followed by two weeks of recovery to define the interactive effects of these variables on biologic responses and to select the most sensitive biologic response parameters for the subsequent subchronic studies. Response surface modeling was used for the experimental design and statistical analysis of the data. Results of preliminary testing suggested that exposure duration and frequency did not have major effects. Subsequently male and female Sprague-Dawley rats were exposed in separate studies to RP/BR aerosols ranging from 0.40 to 1.20 mg/l or to filtered air for 2.25 hr/day on four days/week for four weeks. Test atmosphere monitoring data demonstrated that aerosol concentrations were consistently within 4% of the target values and mean particle size ranged from 0.44-0.64 µm with mean σ g' of 1.66-1.97. During the exposure period, wheezing and labored breathing were obse. in male rats exposed to the high dose. Decreased body weights, body weight gains and reduced food consumption seen in male rats only at all

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|---|---|---|
| Cellular protein | Inhalation toxicology | Pulmonary free cells |
| Clinical chemistry | Lavage fluid protein | Pulmonary lavage |
| Combustion products | Locomotor activity | Radiolabeled bacteria |
| Ectoenzymes | Micronucleus test | Red Phosphorus/Butyl Rubber |
| Exposure duration | Necropsy | Response surface modeling |
| Exposure Frequency | Neurobehavioral activity | Smoke |
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| Hematology | Phagocytosis | Statistical evaluation |
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Block 19. ABSTRACT (continued).

concentration levels during the exposures returned to normal after the recovery period.

Various biological endpoints were examined within 1-hr after the last exposure, and for selected treatment groups after a 14-day recovery period. Although some statistically significant effects were found for clinical pathology, most of these were biologically non-significant due to their absolute value being within or close to the published normal ranges. The most consistent changes were decreases for BUN and cholesterol levels in rats of both sexes and in triglicerides for female rats only, with the latter two parameters showing partial recovery. No treatment-related histopathological changes were found in any tissue outside the respiratory tract however.

Examination of the pulmonary free cells collected by lung lavage (97-99% were alveolar macrophages) showed an increase or an increasing trend in total numbers, increased cellular ATP levels and decreased ectoenzyme activity for 5'nucleotidase after most of the RP/BR exposures of both sexes, suggesting increased energy levels and potential activation for the macrophages. Protein levels in the lavage fluid were elevated after the high doses. Pulmonary bactericidal activity to inhaled $^{35}$-K. pneumoniae was not affected by the exposures in either of the sexes. Mild to moderate terminal broncheolar fibrosis was found in the lungs of rats of both sexes exposed to the medium and high doses. Except for the fibrosis and the 5'nucleotidase activity most of these changes were reversible.

Of the neurobehavioral parameters examined, only locomotor activity was significantly affected by treatment with RP/BR aerosols. Male rats showed increased motor activity at all concentrations and incomplete recovery after two weeks at some concentrations. In females there was a trend toward increased activity but no evidence of effects after the recovery period. None of the other behavioral endpoints were altered by the exposures.

Micronecleus analysis was performed on bone marrow polychromatic erythrocytes and normachromatic erythrocytes and on circulating red blood cells of female rats exposed for two of four weeks and after a two-week recovery following four weeks of exposures. The results showed a significant clastogenic response in both bone marrow and RBC of rats that were exposed for two weeks to the RP/BR aerosol. No effects were found after four weeks of exposures or after a two-week recovery period following the four weeks of exposures suggesting that the rats recruit biochemical pathways to detoxify and clear the genotoxic fractions and an adaptation is in effect.

# EXECUTIVE SUMMARY

The Phase III studies were designed to evaluate the interactive effects of inhalation exposure concentration, duration and frequency to select the most sensitive biologic responses for the subsequent subchronic studies of Phase IV. Response surface modeling, a statistical approach that allowed us to examine multiple response parameters under a large number of experimental conditions and to select the most appropriate combinations of these factors was used for the experimental design. The experimental conditions included various combinations of exposure concentrations, durations and frequencies used over a four-week period. The biological endpoints tested immediately after the last exposure and after a two-week recovery period included pulmonary cellular responses, neurobehavioral activity, genetic toxicology, clinical and morphological pathology, and standard toxicologic observations.

The investigation was divided into three main four-week studies. The first defined the combinations of exposure concentrations, durations and frequencies that produced maximal effects in the response parameters. Our statistical approach made it possible to work with a low subject number (n=4) in this initial study, as necesitated by the complex experimental design, which consisted of four concentrations (0, 0.40, 0.75 and 1.00 mg/l), two durations (1 and 3.5 hr) and three frequencies (number of exposures per week). The frequencies examined were exposures on two consecutive days (F1), four consecutive days (F2), or two days separated by two days of rest (F3). Maximally stressed controls inhaling filtered air for 3.5 hr/day on four consecutive days/week were used with all exposure combinations. The endpoint assays were conducted immediately after the last exposure and for high dose and control, one frequency (F2) and one duration (3.5 hr) also after a two-week recovery period. Thus animals exposed to the most stressful conditions were used in the recovery study.

The sample size of four is adequate for tests of main effects and two-way (but not four-way) interactions and the study yields more than adequate statistical power for an initial characterization of the response surface. The results of this first study showed relatively few compound-related-effects and those that were observed generally also exhibited complete recovery. In general, when statistically significant interactions did occur, main effects were absent, and strong main effects only occurred for parameters which did not have interactions indicating that these observations were spurious. Thus it could be concluded that duration and frequency did not produce major changes in the effects of exposure concentration.

Based on these results more specific conditions with increased

sample size were selected for the subsequent studies. In the second and third extended studies with male and female rats respectively more detailed examination of dose response relations were made for a single duration and frequency combination. Since the outcome of the first study showed that frequency and duration did not affect results significantly, exposure on four consecutive days per week (F2) was selected to explore the "worst case" situation and 2.25 hr, the logarithmic mean between the previously tested 1 and 3.5 hr was chosen as the single duration. The RP/BR exposure concentrations of 0.75, 1.00 and 1.20 mg/l were used in the study with male rats and this range was lowered to 0.40, 0.75 and 1.0 mg/l for the study with female rats. The sample size was increased to n=15 allowing direct estimates of the recovery effect (i.e. concentration by recovery interaction) and also to obtain multivariate, in addition to the previously reported univariate, test statistics.

Aerosol exposure monitoring data demonstrate that the target concentrations were well maintained at each exposure level throughout the three studies. Mean RP/BR mass concentrations were consistently within 4% of the target values with standard deviations of the daily means below ± 8%. The mean particle size data ranging from 0.44 to 0.64 um with $\sigma$gs from 1.66 to 1.97 indicate excellent aerosol stability throughout the exposures. Total phosphorous acid levels ranged from 61 to 74%.

Wheezing and labored breathing observed in male rats exposed to the high doses, decreased body weights, body weight gains and reduced food consumption seen in male rats at all concentration returned to normal after the recovery period. Although an overall mortality of 12.1% was observed in male rats exposed to the high dose, this was due to a concentration overrun in one of the chambers on the first day. The 5.2% value observed in a second chamber reflects the effect of the exposure more realistically. In female rats only a single death was observed during the entire study and this 0.8% mortality occurred in the medium (0.75 mg/l) dose.

While some statistically significant effects were found for individual response parameters in clinical pathology, most of these were judged to be biologically nonsignificant due to their absolute value being within or close to the published normal range for the particular parameter measured. The most consistent changes were decreases for BUN and cholesterol levels in rats of both sexes and in triglycerides for female rats only, with the latter two parameters showing partial recovery. No treatment-related histopathological changes were found in any tissue outside the respiratory tract however.

Of the neurobehavioral parameters, locomotor activity was significantly affected. Male rats showed increased motor activity at all concentrations and incomplete recovery after two weeks at

some concentrations. In females there was a trend toward increased activity but no evidence of effects after the recovery period. None of the other behavioral endpoints were altered by the exposures in a consistent fashion.

A micronucleus analysis performed on bone marrow polychromatic erythrocytes and normachromatic erythrocytes and on circulating red blood cells of female rats exposed for two or four weeks to 1.0 mg/l of RP/BR showed significant clastogenic responses in both bone marrow and RBC's of rats after two but not after four weeks of exposures or after a two-week recovery period following the four-week exposures. These results suggest that RP/BR aerosol is a weak clastogen for female Sprague-Dawley rats and, furthermore, that the animals recruit biochemical pathways to detoxify and clear the genotoxic fractions and that under the exposure regimen used, an adaptation is in effect.

Evaluation of the pulmonary response data showed that *in vivo* bactericidal activity of alveolar macrophages (AM) to inhaled [35]S-*K. pneumoniae* and the percentage of macrophages in the cellular lavage were not affected by the exposures in either of the sexes and *in vitro* phagocytosis was unchanged in AM of female rats. Total cell counts were significantly increased in the pulmonary lavage from female rats immediately after exposure to 0.75 or 1.0 mg/l. Since differential counts remained unchanged and 97 to 99% of the cells were macrophages, this indicates an increased number of AM in the lungs following exposures. After the recovery period the counts were no longer different from controls.

Only part of the significant increases in cellular ATP levels of male and female rats found after the last exposure remained elevated after recovery. The general increase in cellular ATP levels indicates an increased energy supply that may have been responsible for the unimpaired phagocytic and bactericidal activity observed. The most consistent finding in AM from all treatment groups was decreased activity of the plasma membrane-associated ectoenzyme 5'-nucleotidase (5'-ND).

A significant increase in the protein level of the pulmonary lavage fluid of rats of both sexes after exposures to the high doses, indicating pulmonary capillary fragility, exhibited complete recovery in males.

No treatment-related histopathologic changes were seen in tissue outside the respiratory tract in any of the studies. The primary lesion in the lung, was terminal bronchiolar fibrosis. When male rats were exposed to 0.75, 1.0 or $\geq$1.2 mg/l and female rats inhaled 0.4, 0.75, or 1.0 mg/l of RP/BR aerosols for 2.25 hr per day, on four consecutive days per week for four weeks, all except those exposed to 0.4 mg/ had terminal bronchiolar fibrosis. The lesion increased in incidence and severity with increased concentrations

and length of exposure and did not exhibit recovery. The use of Masson's trichrome stain confirmed that part, but not all, of the changes was due to fibrosis - the formation of new collagen fibers in excess of what would normally be present.

In order to choose the most appropriate animals for the upcoming subchronic exposures, a comparison study was conducted between rats from the Madison, WI and Indianapolis, IN breeding colonies of Harlan-Sprague-Dawley, Inc. Based on the observations made in this study and the advisability of working with PVM-free animals in inhalation exposures the rats from the Indianapolis breeding colony were selected for the subchronic exposures.

# FOREWORD

This report, IITRI No. L06139, Phase III Report describes studies conducted by the Life Sciences Department, IIT Research Institute for the Health Effects Research Division, U.S. Army Medical Bioengineering Research and Development Laboratory during the period of August 1983 through July 1984. The studies were carried out under Contract No. DAMD17-82-C-2121.

Catherine Aranyi served as Principal Investigator and Study Director and James Fenters was Co-Investigator in charge of administrative matters. Stanley Vana was responsible for the inhalation exposure facilities and the aerosol generation and monitoring throughout the studies. Jeannie Bradof and Marianna Furedi respectively, were in charge of the experiments for the pulmonary and standard toxicology endpoints and for general toxicologic observations. Necropsy procedures, tissue collection and preparation for histopathologic evaluation were under the supervision of Vladislava Rac and Carol Thompson. Barry Levine was in charge of clinical pathology. The experiments for the neurobehavioral and genetic toxicology endpoints were designed and conducted by Maurlene Preache and Robert Guerrero, respectively. Robert Gibbons, Consultant Biostatistician was responsible for statistical analysis of the experimental data. Histopathologic evaluation of the collected tissue samples was performed by W. D. Iverson, Consultant Pathologist from Experimental Pathology Laboratories, Inc., Herndon, VA.

Animal experiments were conducted according to the "Guide for the Care and Use of Laboratory Animals" (1978), DHEW Publiction No. (NIH) 78-23 prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council; regulations and standards of the Department of Agriculture and Public Law 91-579, "Laboratory Animal Welfare Act" (1970).

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James D. Fenters

James D. Fenters
Head, Microbiology and Toxicology
Life Sciences Research

Catherine Aranyi

Catherine Aranyi
Scientific Advisor
Princial Investigator/Study Director
Life Sciences Research

## QUALITY ASSURANCE STATEMENT

Between July 14, 1983 and May 18, 1984 approximately 35 laboratory inspections were conducted by Josephine M. Reed and Kirit Parikh observing the critical phases of Study Nos. 79, 79S, 79SF and 79SC. These included exposure procedures, chemical analyses, in-life toxicologic observations and all final end-point assay procedures. Data audits and pathologic specimen inspections were performed on September 20, 1983 and January 20, February 2, March 23, April 11 through 25, August 8, 1984 and October 30 to November 30, 1984 by Josephine M. Reed, Kirit Parikh and Julie McPhillips. The studies were conducted in accordance with IITRI Life Sciences Quality Assurance criteria. Raw data and specimens generated during the course of these studies will be retained in the IITRI Life Sciences Archives as described in Standard Operating Procedures.

Josephine M. Reed
Supervisor, Quality Assurance
Life Sciences Department

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# 1. INTRODUCTION

As part of an overall concern for personnel health and safety, the U.S. Army Medical Research and Development Command is seeking to evaluate the effects produced by inhalation of combustion products from red phosphorus/butyl rubber used as an obscurant smoke for troops and vehicles in tactical and training environments. Laboratory rats, exposed in chambers, are being used to provide a comprehensive definition of the biologic effects of red phosphorus smoke to mammalian systems under conditions which approximate the potential troop exposure. The approach to this research includes range finding acute studies to determine lethal concentrations and influence of exposure duration on mortality; repeated exposure studies to define time-concentration relationships as well as threshold levels, healing, and adaptation in biologic reactions; and a subchronic exposure study with a recovery and observation period after the experimental exposure. The principal biologic response criteria to be monitored include overt toxic signs, clinical and morphological pathology, pulmonary bactericidal activity, examination of pulmonary free cells, lavage content and alveolar macrophage function, neurobehavioral activity and genetic toxicology. The Phase III intermediate term exposure studies have been designed to define the interactive effects of the exposure concentration, duration and frequency conditions and to select the most sensitive biologic response parameters for the subsequent subchronic studies of Phase IV.

# 2. MATERIALS AND METHODS

## 2.1. ANIMALS

Male and female Sprague-Dawley rats, 3 to 4 weeks-old were obtained from Harlan/Sprague-Dawley, Inc., Madison, WI for all studies. In addition, male rats used for comparison studies SN79-SC and SN79-SC-2 were also obtained from the supplier's Indianapolis, IN breeding facility.

The animals were observed daily during a 14-day quarantine period. Prior to assignment to treatment groups all rats were subjected to physical examination. Nasal swabs, tracheal aspirates, lung homogenates and intestinal tract materials were examined for pathogenic bacteria, molds, yeasts, Mycoplasma and endoparasites. Serum samples from ten rats were sent to Microbiological Associates, Bethesda, MD, to assay for virologic antibody titers for Kilham rat virus (KRV), Toolan H-1, Pneumonia virus of mice (PVM), Sendai, Rat coronavirus (RCV) and Sialodacryoadenitis virus (SDA). All findings were negative except for positive antibody titers to PVM for the rats from the Madison, WI breeding colony.

The rats were housed individually in stainless steel inhalation

cage compartments measuring 18.4 x 16.5 x 15.9 cm. Twenty four cage units each containing four compartments, were attached to each rack housing a total of 96 rats. When attached to the racks the cages were equipped with an automatic drinking water distribution system and were suspended over excrement pans. For exposure the cages were removed from the racks and the rats were moved in their cages into the inhalation chambers. The animals were transferred weekly to clean cages and deotized absorbing cage boards placed on the excrement pans were changed three times per week.

The animal rooms were maintained on 12 hr-light/dark cycle. Temperature and percent relative humidity (RH) were regulated in such a manner that extreme fluctuations between the animal room and exposure chamber conditions would be avoided. Purina Certified Rodent Chow 5002 and water was available to the rats *ad libitum* except during the exposures.

Animals were randomized to treatment groups using a constrained random process, stratified by weight, such that all groups were comparable in pretest body weight, but assignment of individual animals to groups was random. Each test animal was identified with a unique number by an ear tag.

## 2.2. GENERATION AND MONITORING OF THE INHALATION CHAMBER ATMOSPHERE

### 2.2.1. Red Phosphorus/Butyl Rubber (RP/BR)

The test article RP/BR softened with hexane and prepackaged in 0.75 in-diameter and 4.5 in-long stainless steel feed cylinders (billets) with end caps was supplied by the Sponsor through Oak Ridge National Laboratories (ORNL) and was stored at ambient temperature. A record of the test article was maintained which included date of receipt with identification numbers of each cylinder and the date and study number for which it was used.

### 2.2.2. Inhalation Exposure Facility

The facility consisted of inhalation exposure chambers equipped with air flow and differential pressure controls; conditioned air supply and chamber air exhaust systems; red phosphorus/butyl rubber extrusion-combustion generators and various aerosol monitoring systems.

Supply air to the inhalation exposure laboratory was preconditioned by passing through prefilters, charcoal filters and an air conditioning unit. Automatically controlled heating and humidifying units built into the supply air system maintained the air temperature and RH at the specified ranges of 24 to 27°C and

40 to 60 percent respectively. Prior to entering the exposure chambers the conditioned air was further filtered through a fiberglass coarse filter, a charcoal bed and HEPA filter.

The combined exhaust air from the exposure chambers was filtered through a single-housing, 30-element coalescent filter and exhausted above the roof of the building. To prevent acid corrosion the filter housing was built of polyvinyl chloride. The control chamber exhaust was independent from that of the experimental test chambers to avoid potential contamination from the RP/BR aerosol. The negative pressure and airflow rate in the chambers and exhaust filter loading were monitored by differential pressure gauges.

The aerosol was generated by specially designed hydraulic extrustion-combustion generators provided by the Sponsor through ORNL. The generator operates by exerting hydraulic pressure on the RP/BR forcing it to extrude from an orifice into a burn chamber where it is ignited. The aerosol generated from the combustion products is transported directly into the exposure chamber inlet port. At a constant chamber airflow rate the concentration of the aerosol is a function of the extrusion rate of the RP/BR which is controlled by a precision hydraulic metering pump.

The rats were exposed to the test atmosphere in seven identical 1-$m^3$-sized stainless steel inhalation chambers operating at an airflow rate of 500 l/min. Five RP/BR aerosol exposure chambers and two filtered air control chambers were located in separate rooms. (The inhalation exposure facilities and aerosol monitoring methods have been described in detail in the Phase I Report of these studies).

### 2.2.3. Aerosol Monitoring

The RP/BR aerosol was monitored within each exposure chamber for mass concentration by gravimetric filter collection twice during the 1-hr and three times during the 2.25- and 3.5-hr exposure durations. In addition, mass concentration was monitored with light scattering photosensors and amplifier signal output continuously recorded. An integrated average of the photosensor reading was recorded simultaneously with the gravimetric filter sample collection. Aerosol particle size was determined with a Quartz Crystal Microbalance-based cascade impactor. The particle size was monitored in each chamber once on each exposure day. Determination of total phosphorus was conducted by spectrophotometric analysis of the solubilized filter-collected samples on one filter sample per chamber per exposure week. All collected filters were recorded and stored in sealed containers until submitted for chemical analysis. Oxygen levels in the chambers were checked daily during each experiment and were

consistently 21 percent.

## 2.3. BIOLOGICAL ENDPOINT ASSAYS

In the following sections the experimental methodology is described for all assays. Information on the number of rats used for each assay is provided in the subsequent section on "Experimental Design".

### 2.3.1. Pulmonary Response Parameters

#### 2.3.1.1. Pulmonary Bactericidal Activity to [35]S-*K. pneumoniae*

Aerosols of [35]S-*K. pneumoniae* disseminated with a Retec X-70 disposable nebulizer were used for the bactericidal activity assay, using a method previously described for mice (Aranyi et al., J. Toxicol. and Environ. Health 12, 55, 1983) and adapted for rats. Radiolabeled *K. pneumoniae* were grown in a medium in which the sulfate requirement of the bacteria was provided by [$^{35}$S]sodium sulfate. Before aerosolization, the bacteria were washed repeatedly and centrifuged for removal of unattached radiolabel. Bacterial counts were determined in a Petroff-Hausser counting chamber by dark-field microscopy and by the culture plate technique. Radioactive counts were measured in a Mark III Liquid Scintillation System (Tracor Inc.).

The radioactive bacterial aerosol exposure chamber installed in a glove box consisted of an 87-liter main compartment (adequate for exposure of 30 rats) that was accessible through appropriate airlocks through which the animals were moved. An additional small airlock provided entry into the glove box for the nebulizers and impingers. To prevent radioactive and pathogenic exposure hazard to laboratory personnel, all air exhausted from the chamber was passed first through an absolute filter placed within the glove box and subsequently through a HEPA filter located on the outside.

Pulmonary bactericidal activity was determined in the lungs of the individual animals from both exposed and control groups that simultaneously inhaled aerosols of the viable radiolabeled bacteria. The ratio of the viable bacterial counts to the radioactive counts in each animal's lungs provided the rate at which bacteria were destroyed 3 hr after infection. Thus,

$$\% \text{ Bactericidal activity} = \left(1 - \frac{R_3}{K_o}\right) 100$$

where $R_3$ is the ratio of bacterial to radioactive counts in the lungs of individual rats at 3 hr, and $K_o$ is an average

determined from the same ratios in the lungs of rats killed immediately after inhaling the bacteria.

2.3.1.2. Pulmonary Free Cells and Lavage Fluid

Within 4 hr or 14 days after the last exposure, alveolar macrophages (AM) were obtained by tracheobronchial lavage. The rats were weighed, killed with an overdose of sodium pentobarbital by intraperitoneal injection, and the lungs were lavaged through a blunted 18 g needle inserted into an incision in the trachea with nine consecutive 6-ml infusions of warm saline. The AM were collected from the lavage fluids by centrifugation and resuspended in Hanks' balanced salt solution (HBSS). The supernantant was saved for lavage fluid-protein determination.

Cell Counts. Total cell counts were made in a hemocytometer. For determination of the cellular distribution (i.e., percent of AM, polymorphonuclear leukocytes and lymphocytes), differential counts were made on cytocentrifuge preparations of cells fixed in methanol and stained with Wright's stain.

Cellular adenosine triphosphate (ATP) levels were determined as previously described (Aranyi et al, ASTM STP 732, D. D. Dunnom, ed., Am. Soc. for Testing and Materials, 1981, pp. 48-61), using a DuPont 760 Luminescence Biometer with the procedure recommended for the instrument. The assay is based on the principle that when a microsample containing ATP is injected into a suitably buffered reaction mixture of luciferase and luciferin, the peak intensity of the resulting light flash is directly proportional to the concentration of ATP. ATP was extracted from aliquots of the cell suspension cells by dimethyl sulfoxide (DMSO). The DMSO extracts were diluted with a specially prepared 0.01 M morpholinopropane sulfonic acid (MOPS) buffer to overcome the quench effect of the high concentration of DMSO in the aqueous extract for the luciferase-luciferin reaction.

Phagocytosis. An in vitro phagocytosis assay which measures the ability of rat AM to engulf $^{51}$Cr-labeled chicken red blood cells ($^{51}$CR-CRBC) was used (Smialowitz et al, Environ. Res. 33, 413, 1984). AM lavaged from the lungs of exposed or control rats were adjusted to

$1 \times 10^6$ AM/ml in media containing the maximum subagglutinating dilution of anti-CRBC antiserum and three 0.5 ml samples were placed in 12x75 mm sterile polypropylene tubes. $^{51}$Cr-CRBC at a 10:1 of CRBC to AM ratio are added in 50 µl volumes to each tube. The assay tubes were placed in carrier tubes to guard against possible radioactive leakage and incubated for 1 hr on a tube rotator in a 37°C $CO_2$ incubator. After incubation, the tubes were centrifuged and spontaneous release counts were made on the collected supernatants. The pellets were then resuspended in lysing buffer to lyse any nonengulfed $^{51}$Cr-CRBC. The cell suspensions were centrifuged one more time, the supernatants discarded, and the AM-associated $^{51}$Cr-CRBC were counted in the pellets in a gamma counter.

Total cellular protein. For determination of total cellular protein content, aliquots of the cell suspensions were treated with 1 percent sodium deoxycholate (SDC) and assayed by the Lowry method (Lowry et al, J. Biol. Chem. 193, 265, 1951).

Lavage fluid proteins. Lavage fluids were assayed for protein with the Lowry method without SDC treatment.

Ectoenzyme Activity. Alveolar macrophage plasma membrane ectoenzyme activities were determined on aliquots of AM lysates. Approximately $2.5 \times 10^6$ AM per rat were lysed in 0.05 percent Triton X-100 and frozen until use.

Leucine aminopeptidase (LAP) activity was determined according to the method of Morahan (Morahan, in Methods for studying mononuclear phagocytes, Academic Press, 1981, pp. 473-476). The AM lysate was placed in pH 7.5 phosphate buffer and incubated for 15 min at 37°C with 10 mM leucine p-nitroanilide substrate. The amount of p-nitroaniline released was measured at 405 nm with a spectrophotometer.

Alkaline phosphodiesterase (APD1). An aliquot of AM lysate was mixed with Sorenson's glycine II Buffer (pH 9.6) and incubated 30 min at 37°C with 1.5 mM thymidine-5'-phosphate-p-nitrophenol to

measure APD1 activity according to the method of Edelson and Gass (Edelson and Gass, In Methods for studying mononuclear phagocytes, Academic Press, 1981, pp. 469-472). The release of p-nitrophenol by APD1 was quantitated by measuring optical density at 400 nm in a spectrophotometer.

5'-Nucleotidase (5'-N) activity was measured according to the procedure of Edelson and Duncan (Edelson and Duncan, In Methods for studying mononuclear phagocytes, Academic Press, 1981, pp. 473-476). The AM lysate was mixed with pH 9.0 Tris-HCl buffer and incubated with 25 nCi 5'[$^3$H]-AMP/ml, 0.15 mM 5'-AMP and 6 mM p-nitrophenylphosphate for 30 minutes at 37°C. The amount of tritiated 5'-AMP hydrolyzed was measured with a liquid scintillation counter.

For calculations of ectoenzyme activities the protein concentration of each AM lysate was determined according to the method of Bradford (Edelson and Duncan, In Methods for studying mononuclear phagocytes, Academic Press, 1981, pp. 339-343). Dilutions of AM lysates were mixed with Bio-Rad Protein Assay Dye Reagent and the optical density read at 595 nm in a spectrophotometer. Protein concentrations of AM lysates were obtained by comparing O.D. values with samples of known protein concentration using reverse linear regression.

Expression of data: Bactericidal activity was expressed as the percent of inhaled [35]S-*K. pneumoniae* killed in the lungs 3 hr after challenge (% BC). Total cells counts were expressed as number of cells x $10^6$ per rat or as total cells x $10^3$ per g body weight (Totcell/g BW). The relative macrophage portion of the differential cell counts was expressed as % macrophages. Cellular protein content was reported as ug protein per $10^5$ cells. Cellular ATP content was expressed as ATPfgx$10^8$ per $10^5$ cells and as ATPfgx$10^6$ per ug protein. Phagocytosis of $^{51}$Cr-CRBC was reported as the mean radioactive count (CPM). Lavage fluid protein was expressed as total g protein recovered per g body weight. The specific activity of each of the ectoenzymes (LAP, APD1 and 5'-N) was expressed as units of specific activity (SA) where SA-nmoles substrate hydrolyzed/min/mg protein. Because of the programming limitations of the computer-generated tables used in the "Results" and "Appendix A" sections the abbreviations used to identify each assay and the mode in which the data are expressed are summarized in Table 1 for the pulmonary response parameters.

Table 1

IDENTIFICATIONS OF ABBREVIATIONS FROM COMPUTER-GENERATED TABLES AND MODE OF EXPRESSING THE DATA FOR PULMONARY DEFENSE PARAMETERS

| ASSAY | Expression of Data |
|---|---|
| % BC | % of inhaled $^{35}$S-*K. pneumoniae* killed in 3 hr |
| TOT CELLS | total cell counts x $10^6$/rat |
| TOTCELL/g BW | total cell counts x $10^3$/g body weight |
| %MACROPHAGES | relative macrophage portion of differential cell count |
| PROT/10⁵CELL | µg protein/$10^5$ cells |
| ATP/10⁵ CELL | ATP fg x $10^8$/$10^5$ cells |
| ATP/ug PROT | ATP fg x $10^6$/µg protein |
| PHAGO [CPM] | phagocytosis of $^{51}$Cr-CRBC[mean radioactive count] |
| LAVPROT/g BW | total lavage fluid protein, µg/g body weight |
| LAP | leucine aminopeptidase, nmoles substrate hydrolyzed/min/mg protein |
| APDI | alkaline phosphodiesterase I, nmoles substrate hydrolyzed/min/mg protein |
| 5'-N | 5'-nucleotidase, nmoles substrate hydrolyzed/min/mg protein |

## 2.3.2. Standard Toxicology

### 2.3.2.1. Mortality, Clinical Observations, Body Weights and Food Consumption

All animals were observed daily in the morning for survival, physical appearance, behavior and any pharmacologic and/or toxicologic signs. All observations were recorded on an individual test animal basis. In addition afternoon survival checks were performed.

Each animal was weighed using a Mettler PE 1600 balance with a special animal weighing mode at the time of test animal selection, at the initiation of the study, weekly thereafter and prior to the last exposure. For the rats designated for recovery the body weights were recorded at the aforementioned time points and continued weekly until termination.

Average food consumption (FC) was measured individualy for a 24 hr period for the rats designated for recovery prior to the last exposure (FC1)and again at the end of recovery (FC2).

### 2.3.2.2. Clinical Pathology

Blood samples were collected from the abdominal aorta prior to necropsy for determination of the hematology and clinical chemistry parameters listed in the following sections. The various methods of analysis are indicated with associated references where appropriate. The mode of expressing the data is shown in parenthesis.

#### 2.3.2.2.1. Hematology

Coulter Counter Model S System:

Hematocrit (HCT % rbc) Indirect method; calculated value based on erythrocyte count and mean corpuscular volume
Hemoglobin (HGB g/dl) Cyanmethemoglobin method
Mean Corpuscular Volume (MCV $um^3$), Electronic Sizing Procedure
Mean Corpuscular Hemoglobin: (MCH pg) Indirect method; calculated value based on erythrocyte count and hemoglobin
Mean Corpuscular Hemoglobin Concentration (MCH g/dl) Indirect method; calculated value based on hematocrit and hemoglobin
Erythrocyte Count ($RBCx10^6/mm^3$) Electronic Counting Procedure
Leukocyte Count ($WBCx10^3/mm^3$) Electronic Counting Procedure

Direct Microscopic Count:

Leukocyte Differential Count: Immature Neutrophils (IM NEU %wbc), Mature Neutrophils (M NEU %wbc), Monocytes (MON %wbc), Lymphocytes (LYMPH % wbc), Eosinophils (EOS % wbc). Wright stain procedure: (Schalm et al, Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lea and Febiger, 1975)
Nucleated RBC's (NRBCs/100 WBC) Wright stain procedure: (Schalm et al, Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lea and Febiger, 1975)
Platelet Count (PLTx$10^3$/$mm^3$) Direct Method (Schalm et al, Veterinary Hematology, p. 69, 3rd Edition, Lea and Febiger, 1975)

2.3.2.2.2. Clinical Chemistry

Centrifichem Centrifugal Analyzer System:

Glucose: (GLU mg/dl), Hexokinase method (Neeley, Clin. Chem. 18, 509, 1972.)
Urea Nitrogen: (BUN g/dl) Modified urease technique (Karmen, J. Clin. Chem. 34, 131, 1955.)
Alanine aminotransferase: (ALT IU/l), Modified Wroblewski and LaDue technique (Henry et al, Am. J. Clin. Path. 34, 381, 1960.)
Triglycerides: (TRIG mg/dl) Tetrazolium salt reduction method (Klotzsch et al, Advances in Automated Analysis Vol. 1, Mediad Inc., Tarrytown, N.Y. p. 111, 1973.)
Total Protein: (T PRO g/dl) Biuret technique (Falling et al, Am. J. Clin. Path. 33, 83, 1960.)
Albumin: (ALB g/dl), Bromocresol green method (Rodkey, Clin. Chem. 11, 478, 1965.)
Globulin: (GLOB g/dl) calculated value as T PROT minus ALB.
Albumin/Globulin ratio: (ALB/GLOB) calculated value
Cholesterol: (CHOL mg/dl) Cholesterol esterase cholesterol oxidase method Roeschlau et al, Z. Klin. Chem. u. Klin. Biochem. 12, 226, 1974.)
Bilirubin, direct: (D BIL mg/dl) Modified Walters and Gerarde method (Walters et al, Microchem. J. 15, 231, 1970.)
Bilirubin, total: (T BIL mg/dl) Modified Walters and Gerarde method (Walters et al, Microchem. J. 15, 231, 1970.) Alkaline Phosphatase: (AL PHOS IU/l) Modified Bessey-Lowry technique (Neumann et al, Clin. Chem. Acta. 17, 183, 1967.)
Calcium: (Ca mg/dl), Alizarin method (Connerty et al, Clin. Chem.11, 716, 1965.)
Inorganic Phosphorus: (P mg/dl) Daly and Ertingshausen technique (Daly et al, Clin. Chem. 18, 263, 1972.)
Creatine Phosphokinase: (CPK IU/l) Modified Oliver method(Oliver, Biochem. J. 61, 116, 1955.)

Kline Flame Photometer (Beckman):

Sodium: ($Na^+$ mMol/l) Flame photometry
Potassium: ($K^+$ mMol/l) Flame photometry

Chloride Meter (Corning Medical Co.)

Chloride: ($Cl^-$ Meq/l) Silver chloride precipitation method (Catlove *et al*, J. Lab. Clin. Med. 50, 358, 1958.)

The abbreviations used to identify each assay in the computer generated tables are summarized in Tables 2 and 3 for the hematology and clinical chemistry data, respectively.

2.3.2.3. Necropsy and Histopathology

Rats were killed with sodium pentobarbital and subsequent exsanguination, either following the last exposure or 14 days post-exposure, and necropsied under the supervision of the staff pathologist. The necropsy procedure included a thorough, systemic examination and dissection of the animal viscera and carcass and collection and fixation of all major tissues in 10% neutral buffered formalin (NBF).

All tissues and/or organs were examined *in situ* before dissection from the carcass for individual examination. Tongue, trachea, lungs and pulmonary lymph nodes were removed intact. The lungs and nasal passages were infused with NBF prior to submersion into NBF. All tissues were fixed not less than 24 hours prior to trimming.

Tissue trimming (wet sectioning) was performed at IITRI under the supervision and direction of the staff pathologist. Organs were trimmed to allow the largest surface area possible for examination. Each lung lobe was sectioned along its main bronchus. Both a cross section and a longitudinal section of trachea were made.

For all designated animals the following tissues and/or organs were microscopically examined: the entire trachea, pulmonary lymph nodes, each lobe of the lungs and two transverse sections of the skull through the nasal turbinates. (The first section was the palatal ridge level). In addition, for the control rats and those rats which were exposed to the highest concentration and frequency of RP/BR, adrenals, duodenum, esophagus, eyes, heart, liver, kidneys, stomach and urinary bladder were also examined.

Tissues in paraffin blocks were submitted to Experimental Pathology Laboratories Inc. (EPL), Decatur, IL where hematoxylin and eosin stained sections were prepared and examined. Selected specimens from lung tissue were also examined by Masson's trichrome stain for collagen fiber formation.

Table 2

IDENTIFICATIONS OF ABBREVIATIONS FROM COMPUTER-GENERATED TABLES AND MODE OF EXPRESSING THE DATA FOR HEMATOLOGY PARAMETERS

| HEMATOLOGY VALUES | Key to Abbreviations | |
|---|---|---|
| HCT % | Hematocrit | |
| HGB g/dl | Hemoglobin | |
| MCV $um^3$ | Mean Corpuscular Volume | |
| MCH pg | Mean Corpuscular Hemoglobin | |
| MCHC g/dl | Mean Corpuscular Hemoglobin Concentration | |
| RBCx $10^6/mm^3$ | Erythrocyte Count | |
| WBCx $10^3/mm^3$ | Leukocyte Count - Total | |
| PLTx $10^3/mm^3$ | Platelet Count | |
| IM NEU %WBC | Immature Neutrophils | Differential Leukocyte Count |
| M NEU %WBC | Mature Neutrophils | |
| LYMPH %WBC | Lymphocytes | |
| MON %WBC | Monocytes | |
| EOS %WBC | Eosinophils | |
| NRBC/100 WBC | Nucleated Red Blood Cells | |

Table 3

IDENTIFICATIONS OF ABBREVIATIONS FROM COMPUTER-GENERATED TABLES AND MODE OF EXPRESSING THE DATA FOR CLINICAL CHEMISTRY PARAMETERS

| CLIN. CHEM. VALUES | Key to Abbreviations |
|---|---|
| GLU mg/dl | Glucose |
| BUN mg/dl | Blood Urea Nitrogen |
| ALT IU/l | Alanine Aminotransferase |
| TRIG mg/dl | Triglycerides |
| T PRO g/dl | Total Protein |
| ALB g/dl | Albumin |
| CHOL mg/dl | Cholesterol |
| D BIL mg/dl | Direct Bilirubin |
| T BIL mg/dl | Total Bilirubin |
| AL PHOS IU/l | Alkaline Phosphatase |
| Ca mg/dl | Calcium |
| P mg/dl | Inorganic Phosphorus |
| Na mMol/l | Sodium |
| K mMol/l | Potassium |
| Cl Meq/l | Chloride |
| CPK IU/l | Creatine Phosphokinase |
| GLOB g/dl | Globulin |
| ALB/GLOB | Albumin/Globulin Ratio |

### 2.3.3. Neurobehavioral Activity

Subsets of the rats were tested behaviorally within 48 hr after the last exposure. In the preliminary study (SN 79), the post-exposure tests were administered on the day following the last exposure, whereas, in study Nos. 79-S and 79-SF, the post-exposure behavioral testing was on the same day as the last exposure. In all three studies, separate groups of rats were evaluated for recovery of behavioral indices 14 days after the last exposure. The behavioral indices considered were locomotor activity as measured in a figure 8 maze, fore- and hindlimb grip strength, and one-way active escape-avoidance acquisition and short-term retention. The three tests were administered in the order listed above. The fore- and hindlimb grip strength test was omitted for SN 79-SF.

#### 2.3.3.1. Locomotor Activity

The apparatuses for locomotor activity measurements were two figure-eight mazes (Digiscan Animal Activity Monitors, Omnitech Electronics, Columbus, OH) with an eight-channel printout counter (Datalogger 8000, Omnitech). In the figure-eight maze, activity is measured as photobeam interruptions for 8 sets of photobeam-sensor combinations spaced through the arms of the maze. Each animal was placed individually in the figure-eight maze for a period of 20 min and an interim count was printed after the first 10 min. Thus, the three activity counts analyzed were expressed as: activity for the first 10 min, activity for the second 10 min and activity for the total 20 min.

#### 2.3.3.2. Fore- and Hindlimb Grip Strength

The apparatus and procedures for fore- and hindlimb grip strength were as described by Meyer et al (Neurobehav. Toxicol. 1, 233, 1979). Briefly, this test employed pull-push strain gauges (Chatillon, Models DPP-1.0 kg and DPP-2.5 kg, J. A. King, Greensboro, NC) to measure the grip force of the fore- and hindlimbs. The animal was placed in a trough and allowed to grip with its forepaws a triangular grasping ring which was attached to the forward-mounted strain gauge. The animal was steadily pulled by the tail away from the ring until the grip was broken. Pulling was continued until the hindlimbs grasped a T-bar mounted on a second strain gauge behind the trough, and further continued until the grip of the hindpaws on the T-bar was broken. The animal received three consecutive trials and fore- and hindlimb grip strength (grams force) was recorded from the forward and rear strain gauges. The fore- and hindlimb grip strength scores for each animal were derived by averaging the results of the three trials.

### 2.3.3.3. One-Way Active Escape-Avoidance

The apparatus for this test was comprised of two plexiglass compartments with a connecting guillotine door. The smaller (4-1/2 x 9-1/2 x 7-1/2 in), dark compartment was of black plexiglass and had a grid floor wired for delivery of foot shock. The "safe" compartment was 7 1/2 x 9-1/2 x 7-1/2 in and was clear plexiglass. The apparatus was housed in a sound-attenuating chamber (Coulbourn Instruments, Lehigh Valley, PA, Model E10-20). A compound conditioning stimulus was provided by a cue light located in the top of the smaller compartment and a tone delivered through a speaker (Coulbourn E12-01) located in the right rear corner of the sound attenuating chamber. Tone generation was via a Coulbourn generator (S81-06) and amplifier (S82-24). Foot shock (.75mA) was delivered via BRS-Foringer (Lehigh Valley, PA) shock generator and scrambler (SG-901, SC-902). Other support equipment included various timers and switches for programming the delivery of shock, tone, and light presentations, a printout counter (BRS-Foringer POC-112) for recording of data, and a photocell-sensor and control assembly (Lafayette Model 5811).

During the acquisition phase of this procedure, each animal was given four consecutive training trials. On each trial, the animal was placed in the smaller compartment; the guillotine door was raised and the light, tone and shock were turned on. The animal could escape the shock and turn off the conditioning stimuli by moving 3 inches into the safe compartment where a photobeam-sensor unit was located. If the animal did not escape within 20 sec, the trial was terminated and the three stimuli turned off. Approximately 10 min following its last acquisition trial, each animal received two consecutive test trials. For a test trial, the onset of the conditioning stimuli (light and tone) preceded the onset of shock by 10 sec. During this interval, the animal could avoid shock and terminate the conditioning stimuli by moving to the safe compartment. After shock onset, the animal could escape if it moved to the safe compartment within 10 sec or if it failed to escape, shock, tone, and light were turned off at the end of this time.

Expression of data: Three activity counts were analyzed for locomotor activity in the figure-eight maze. These were activity counts for the first 10 min, activity counts for the second 10 min, and the sum of these two or total activity counts for the 20 min test period. Fore- and hindlimb grip strength was measured in grams force on each of three trials. The data were expressed as mean forelimb and hindlimb grip strength for each animal with the means being derived by averaging across the three trials. The data points considered in analysis of the one-way active escape-avoidance were as follows:

Time (sec) to escape shock on each of four training trials
Number of times shock was escaped during training
Time (sec) to avoid or escape shock on each of two test trials
Number of times shock was avoided during testing
Number of times shock was escaped or avoided during testing

For training a maximum time to escape of 10 sec was utilized and during testing the maximum time recorded was 20 sec.

The abbreviations used in reporting the data for neurobehavioral measures are given in Table 4.

### 2.3.4. Genetic Toxicology: Micronucleus Test

#### 2.3.4.1. Red Blood Cell Assay

The blood samples were prepared for analysis with a modification of the method of R. Schlegel and J. MacGregor (Mut. Res. 104:367, 1982). The rats were gently restrained by hand while the tip of the tail was snipped off with dissecting scissors. Three drops of blood were dispensed into a small well of a porcelain dish by gently "milking" the tail. The blood was mixed immediately with three drops of calf serum. Blood smears were made on duplicate pre-labeled, methanol-cleaned glass slides and allowed to air-dry for at least 12 hours.

The slides were fixed in methanol, rinsed twice in deionized, distilled water and stained for 10 minutes with Giemsa (1 part Giemsa + 5 parts distilled water, prepared fresh and filtered through Whatman No. 1 paper). After thorough rinsing and drying, the slides were cleared in xylene and coverslips were affixed with permount. Cells were counted under 40X magnification, and the number of micronuclei (MN) per 1000 blood erythrocytes were tabulated.

#### 2.3.4.2. Bone Marrow Assay

Bone marrow cells were harvested following the method of M. Von Ledebur and S. Schmid (Mut. Res. 12:109, 1973). A femur was removed *in toto* from each rat by cutting through the pelvis and tibia and carefully separating the distal end of the bone from the knee with gentle traction. The bone was cleaned of muscle and tissue with gauze. A 5-ml plastic centrifuge tube was filled with fetal calf serum. A small volume of serum was aspirated into a 3 ml syringe through a 20 gauge needle which was inserted subsequently a few mm into the proximal end of the femur (distal end remains closed). The femur was submerged completely in the serum tube while alternate aspirations and flushings evacuated the

Table 4

IDENTIFICATIONS OF ABBREVIATIONS FROM COMPUTER-GENERATED TABLES AND MODE OF EXPRESSING THE DATA FOR NEUROBEHAVIORAL PARAMETERS

| Test Endpoint | Expression of Data |
|---|---|
| **Locomotor Activity** | |
| Act-1st 10' | Activity counts in the figure-8 maze for the first 10 min of testing |
| Act-2nd 10' | Activity counts in the figure-8 maze for the second 10 min of testing |
| Act-Tot 20' | Activity counts in the figure-8 maze for the total of 20 min of testing |
| **Grip Strength** | |
| FL Grip | Forelimb grip strength (g force), average of 3 trials |
| HL Grip | Hindlimb grip strength (g force), average of 3 trials |
| **Escape-Avoidance** | |
| TrTr1-Time | Time (sec) to escape on training trial 1 |
| TrTr2-Time | Time (sec) to escape on training trial 2 |
| TrTr3-Time | Time (sec) to escape on training trial 3 |
| TrTr4-Time | Time (sec) to escape on training trial 4 |
| No. ESC-Tr | Number of escapes out of 4 trials during training |
| TeTr-1 Time | Time (sec) to avoid or escape on test trial 1 |
| TeTr-2 Time | Time (sec) to avoid or escape on test trial 2 |
| No. AVD-Te | Number of trials out of 2 test trials on which the animal avoided shock |
| No. ESC-Te | Number of trials out of 2 test trials on which the animal either avoided or escaped shock. |

bone cavity and produced a fine suspension of cells. The cells were centrifuged at 250 xg for 5 minutes and the supernatant decanted, leaving only a small volume to resuspend the cells. Smears were made on duplicate slides.

The cells were prepared for analysis following the method of Hayashi *et al.* (Mut. Res. 120:241, 1983). Briefly, The slides were stained in Acridine Orange (A.O.) working solution (2 parts of 0.1% aqueous stock A.O. + 30 parts Sorenson's buffer pH 6.8, prepared fresh and filtered through 0.2 um membrane filter). The slides were rinsed in buffer 3 times and coverslips were affixed with buffer and the margins were sealed with rubber cement. The slides were examined the same day using a fluorescent microscope with a BG-12 excitation filter. The number of micronucleated cells was tabulated for polychromatic erythrocytes (PCE) as well as normochromatic erythrocytes (NCE).

Expression of data: The genotoxic response was expressed as mean number of micronuclei in bone marrow polychromatic erythrocytes and in circulating blood cells (normachromatic erythrocytes). The abbreviations used to identify each parameter in the computer generated tables are summarized in Table 5.

## 3. STATISTICAL APPROACH AND EXPERIMENTAL DESIGN

When a sufficient amount of information is available about the biological effects of a given compound, completely balanced randomized designs are essential for drawing inference from experimental data. In these experiments, levels of one or more design variables or "factors" are examined with all possible combinations of every other factor, therefore providing full information regarding main effects of each design variable (eg. concentration) and higher order interactions (eg. concentration by frequency of exposure).

In some experiments, we know very little about the biologically effective concentrations of an experimental compound and even less about the effect of that compound when used in various combinations with other factors such as, in our case, the frequency and duration of exposure. In these cases it is recommended to proceed in two stages.

In the first stage a subset of combinations of conditions are tested. From these preliminary data, a mathematical model is constructed which will predict optimal combinations of design variables (e.g. concentration, duration and frequency of exposure). If the predicted maximum is far away from the values chosen for the pilot study, new combinations closer to the predicted values may be tested. In this way the range of biologically effective combinations of the design variables may be

Table 5

IDENTIFICATIONS OF ABBREVIATIONS FROM COMPUTER-GENERATED TABLES AND MODE OF EXPRESSING THE DATA FOR GENETIC TOXICOLOGY PARAMETERS

| Assay | Expression of Data |
|---|---|
| RBC MN N 8X<br>RBC MN N 16X<br>RBC MN N 2R | Number of micronuclei (MN) per 1000 RBC normocytes (N) after 8 (8X) or 16 exposures (16X) or after 14 day recovery (2R) |
| BM MN P | Number of MN per 1000 bone marrow (BM) polychromatic erythrocytes (P) after 8X, 16X, or 2R |
| BM MN N | Number of MN per 1000 BM N after 8X, 16X or 2R |
| BM MN P + N | Sum of (BM MN P) + (BM MN N) after 8X, 16X, or 2R |

identified quickly and economically (i.e., all possible combinations of the design variables do not have to be tested).

In the second stage of analysis, a confirmatory study with increased sample size is conducted. Based on the results of the preliminary investigation, a much more focused selection of conditions may be chosen. The number of treatment combinations is of course greatly reduced, since the preliminary study has already identified treatment combinations that produce maximal responses.

The previously described experimental procedure is known as "response surface modeling." Statistically, the method involves fitting a response surface model to the experimental data using least squares, and moving to the area of experimentation along a path of steepest ascent until it is near a stationary point. This point is then explored in much greater detail.

Experimentally, the current study has involved three separate experiments and four phases of statistical analysis. In the following, details of each study and corresponding analyses are described.

## 3.1. CHARACTERIZING THE RESPONSE SURFACE: STUDY NO. Z9

This first experiment was used to characterize the response surface. The purpose of this study was to identify combinations of concentration, frequency and duration that yield maximal biological effects. Results of this study were then used to select more specific levels of concentration, frequency and duration for more detailed studies in larger samples of animals.

The following experimental design parameters were selected to be applied in various combinations in a 4-week exposure study.

- o Animals: Four male rats per treatment group.
- o Exposure Concentration: Three RP/BR aerosol concentrations C1<C2<C3 (C1=0.4 mg/l, C2=0.75 mg/l, C3=1.0 mg/l) and filtered air control (C0).
- o Exposure Duration: 1 hr and 3.5 hr.
- o Exposure Frequency: F1(XX), exposure on two consecutive days; F2 (XXXX), exposure on four consecutive days; F3 (X00X), two exposure days separated by two days rest.
- o Biological endpoints: Pulmonary bactericidal activity (BC); Lavage: pulmonary free cells

and lavage fluid protein (LAV); Behavioral tests (BEH); Standard toxicology (TOX).

- o Biological endpoints were tested after the last exposure or in case of one exposure group (C3, F2, 3.5 hr) also after a 14-day recovery period (R) following the last exposure.

- o Controls for all exposure conditions and all endpoints were exposed to filtered air for 3.5 hr at F2 (XXXX).

All animals were exposed for four weeks. Exposures to concentrations C1, C2 and C3 were simultaneous; however different frequency groups were scheduled separately. Post exposure experiments were conducted on the days of the last exposures for all endpoints except for BEH tests which were done one day after the last exposures. Recovery experiments were conducted 14 days after the last exposure for all endpoints except for BEH tests which were done 15 days after the last exposure.

In order to facilitate the time-consuming and labor-intensive processes of the BC, LAV, BEH, and TOX endpoints, the exposures were staggered. Biological endpoints for three exposure concentrations and two exposure periods were handled on the same day, but exposures of animals for the different frequency experiments for each endpoint were scheduled individually. Details of the exposure and assay dates for the different endpoints and the actual animal numbers assigned for each group were summarized in tables included in the experimental protocol.

## 3.2. EXPANDED STUDY DESIGN WITH MALE RATS: STUDY NO. 79-S

The conclusions of the preliminary statistical analysis by response surface method of the data of Study No. 79 demonstated relatively few compound-related effects and those that were observed generally exhibited complete recovery after 14 days. The data also indicated that neither exposure duration nor frequency produced major changes in effects observed at a given concentration. Based on this statistical evaluation, the experimental conditions for the supplemental study No. 79-S were selected as follows:

- o Animals: 15 per treatment group.

- o Exposure Concentration: 0, 0.75, 1.00 and 1.30 mg/l (C0, C1, C2 and C3). Because of mortalities observed after one or two exposures to 1.3 mg/l RP/BR aerosol, this target concentration was lowered to

1.2 mg/l after consultation with the Sponsor. The change was effective on the third day of exposure.

- o Exposure Duration: 2.25 hr/day
- o Exposure Frequency: Exposures on four consecutive days
- o Exposure Period: Four weeks
- o Biological Endpoints: Pulmonary response parameters (*in vivo* bactericidal activity, pulmonary free cell numbers, cellular ATP and protein levels, ecto-enzyme activities, phagocytosis, pulmonary lavage fluid protein levels), general toxicology (clinical and morphological pathology) and neurobehavioral activity tests were performed on the last exposure day to C0 and to RP/BR aerosol concentrations of C1, C2 and C3.
- o Recovery Period: Additional rats exposed to C0, C2 C3 were tested after a 14 day recovery period following the last exposure.

To utilize project personnel in conducting all endpoint experiments most efficiently, the four daily inhalation exposures within each week were staggered by conducting them with various groups of animals from Monday through Thursday and Tuesday through Friday, respectively.

## 3.3. EXPANDED STUDY DESIGN WITH FEMALE RATS: STUDY NO.79-SF

Study No. 79-SF was conducted to examine female rats under similar exposure conditions to those that were used for males in Study No. 79-S. Because of mortalities observed in the male rats upon exposure to the highest RP/BR concentration (1.3 and 1.2 mg/l respectively as described above) the exposure concentrations for this study were lowered. The experimental design for Study No. 79-SF was as follows:

- o Animals: The number of rats used was 15 per treatment group except for the genetic toxicology assays in which 4 or 5 were used.
- o Exposure Concentration: 0, 0.40, 0.75, and 1.00 mg/l (C0, C1, C2 and C3).
- o Exposure Duration: 2.25 hr/day.

- Exposure Frequency: Exposures on four consecutive days.

- Exposure Period: All treatment groups were exposed for four weeks before measuring biological endpoints except those for the genetic toxicology assays which were also tested after two weeks of exposures.

- Biological Endpoints: The micronucleus test (*in vivo* rat bone marrow method) for cytogenetic evaluation after RP/BR exposure was added to the endpoints used in Study No. 79S. Only two neurobehavioral assays were conducted for this study. These were locomotor activity and one-way active avoidance. (The fore- and hindlimb grip strength assay showed no effects in prior studies). The biological endpoints for pulmonary bactericidal activity, pulmonary lavage parameters, neurobehavioral activity and standard toxicology were tested on the last (sixteenth) exposure day to exposure concentrations of C0, C1, C2 and C3. Genetic toxicology assays were conducted on rats from C0 and C3 exposure groups on the eighth and the last exposure days.

- Recovery Period: Additional rats were exposed to C0, C2 and C3 to be tested after a 14 day recovery period following the last exposure.

To utilize project personnel in conducting all endpoint experiments most efficiently, the inhalation exposures were staggered over a five-week period. In addition, the four daily exposures within each week were also staggered by conducting them with various groups of animals from Monday through Thursday and Tuesday through Friday.

## 3.4. STATISTICAL PROCEDURES

The statistical analysis of these data proceeded in three stages. (1) the analysis of the initial response surface (Study No. 79), (2) the analysis of the expanded confirmatory experiment with male rats (Study No. 79-S), and (3) the analysis of the expanded confirmatory experiment with female rats (Study No. 79-SF).

The first study (Study No. 79) was used to obtain an initial characterization of the response surface. In light of the large number of measured parameters and the large number of experimental

design conditions (i.e. concentration, duration, frequency and recovery), the following statistical strategy was used. First, three-factor fixed effect univariate analyses of variance were computed for each outcome variable separately for rats tested immediately after the last exposure and for those tested after a 14-day recovery (treatment and recovery sacrifice animals). The three factors were concentration, duration and frequency. Second, extensive post-hoc comparisons were computed for individual treatment conditions (e.g. control versus high dose in frequency 1 and duration 1 etc) and for various combined marginal distributions (e.g. control versus high dose averaging over frequency and duration). These latter comparisons were only interpreted in the absence of significant higher order interactions (e.g. concentration by duration). In light of this strategy, significant main effects and interactions are reported for each parameter at the treatment sacrifice, and the recovery status of that effect is then reported by examining the significance of the parallel analysis in recovery animals. In studies that followed this preliminary experiment, increased sample sizes and fewer experimental conditions allowed us to treat recovery as a factor in the design and directly estimate concentration by recovery interactions using both multivariate and univariate test statistics.

In the first study all parameters exhibiting significant interactions are first reported and then remaining parameters that only exhibited main effects of concentration are discussed. Otherwise the general statistical methodology used in each stage of the analysis was essentially the same. In each study and the overall analysis, a three-stage hypothesis testing model was used. First, each logically related set of response variables that were simultaneously measured in the same animals was analyzed by a three factor (Study 79), or two-factor (Studies 79-S and 79-SF) multivariate analysis of variance (MANOVA). A significant main effect of treatment infers that there were significant differences between treatment groups averaging over recovery and non-recovery animals. A significant treatment by recovery interaction infers that the effect of treatment differed in recovery and non-recovery animals. In many but not all cases, this effect indicates that significant recovery occurred. In Study No. 79 the frequency by treatment and duration by treatment interactions were also examined. The presence of these higher order effects would indicate that the effect of exposure depended on the specific frequency, duration or both.

Second, in the presence of a significant multivariate test statistic, individual univariate analyses of variance (ANOVA) were performed in each response variable separately. The logic of the specific tests of hypotheses is identical to the multivariate test, except that these tests are now focused on individual parameters (eg. bactericidal activity) and not the entire response set (e.g.

all pulmonary response parameters).

Third, for Study Nos. 79S and 79-SF in the presence of significant multivariate and univariate tests, individual post hoc comparisons (i.e. each treatment group compared to its respective control in terms of every individual parameter, for recovery and non-recovery animals separately) were performed. These statistics (Dunnett's test) aid in interpreting exactly where significant between-group differences occurred. Tests of linear dose-response relations are also performed at this stage using Pearson product moment correlation coefficients (in non-recovery animals only).

The statistical significance of post-hoc comparisons of exposed relative to control groups was indicated by the presence of asterisks in the summary tables of results. The placement of an asterisk was based on the significance of Dunnett's test. In Study No. 79 the significance of all post-hoc comparisons was reported regardless of the significance of main effects and interactions. This was done because of the complexity of the design at this early stage of the study and the exploratory nature of hypothesis testing in the first phase of constructing the response surface. In the confirmatory studies (79S and 79SF) post-hoc comparisons were only conducted in the presence of a significant main effect or interaction. In light of the more confirmatory nature of these studies, asterisks on summary tables only appear for parameters exhibiting significant F statistics.

A type one error of $p \leq 0.05$ was assigned a priori for all statistical comparisons. For purposes of display, the number of significant digits for a specific parameter was kept constant across conditions. In rare cases two means that may look similar or even identical may yield different statistical results (ie. one post-hoc comparison is significant whereas the other is not). The apparent inconsistency is due to rounding. For example data reported for two treatment groups as $0.10 \pm 0.01$ and $0.10 \pm 0.01$ and controls $0.11 \pm 0.01$ may actually reflect true values of $Tx_1 = 0.100 \pm 0.010$, $Tx_2 = 0.104 \pm 0.005$ and $0.105 \pm 0.005$ for controls. The result might be significant for $Tx_1$ but would clearly not be significant for $Tx_2$.

## 4. OBJECTIVES AND RESULTS

### 4.1. THE EXPERIMENTAL TEST ATMOSPHERE

The experimental test atmosphere characterization data are summarized in Tables 6, 7 and 8 for study numbers 79, 79-S and 79-SF respectively. The means and standard deviations for RP/BR aerosol mass concentrations, the corresponding MMAD and $\mu g$ for particle size and the percent phosphoric acid levels of the aerosols were measured in each of the exposure chambers as

Table 6

MASS CONCENTRATION, PARTICLE SIZE AND PERCENT PHOSPHORIC ACID LEVELS IN RP/BR AEROSOLS CALCULATED FOR STUDY NO. 79[a]

| | | | RP/BR Aerosol | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mass Conc. Determined from:[b] | | | | | | Particle Size[b] | | | | | | % $H_3PO_4$[c] | | |
| | | | Filter Collected Samples | | | Photosensor Readings | | | MMAD[d] | | | $\sigma_g$ | | | | | |
| Chamber No. | Exposure Duration Hr. | Targeted Aerosol Mass Conc. mg/l | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N | Mean | + SD | N | Mean | ± SD | N |
| 1 | 1 | 0.40 | 0.39 | 0.02 | 26 | 0.41 | 0.01 | 26 | 0.45 | 0.08 | 26 | 1.96 | 0.28 | 26 | - | - | - |
| 2 | 1 | 0.75 | 0.78 | 0.03 | 26 | 0.74 | 0.02 | 26 | 0.54 | 0.07 | 26 | 1.94 | 0.25 | 26 | - | - | - |
| 3 | 1 | 1.00 | 1.01 | 0.07 | 26 | 1.01 | 0.02 | 26 | 0.53 | 0.09 | 26 | 1.97 | 0.21 | 26 | - | - | - |
| 1 | 3.5 | 0.40 | 0.39 | 0.02 | 26 | 0.40 | 0.01 | 26 | 0.44 | 0.07 | 26 | 1.94 | 0.23 | 26 | 63.77 | 2.29 | 5 |
| 2 | 3.5 | 0.75 | 0.75 | 0.03 | 26 | 0.73 | 0.02 | 26 | 0.53 | 0.07 | 26 | 1.90 | 0.28 | 26 | 65.80 | 5.79 | 5 |
| 3 | 3.5 | 1.00 | 1.01 | 0.06 | 26 | 1.01 | 0.01 | 26 | 0.53 | 0.08 | 26 | 1.94 | 0.22 | 26 | 66.81 | 5.57 | 5 |

[a] Exposures were staggered over 5 weeks at the specified frequencies of F1, F2 or F3. For details see text.

[b] Calculated from the daily means over 26 exposure days.

[c] Calculated from one filter-collected sample per week at the 3.5 hr duration over a 5-week period

[d] Mass median aerodynamic diameter, um

N Number of samples

Table 7

MASS CONCENTRATION, PARTICLE SIZE AND PERCENT PHOSPHORIC ACID LEVELS IN RP/BR AEROSOLS
CALCULATED FOR STUDY NO. 795[a]

| | | RP/BR Aerosol | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mass Conc. Determined From:[b] | | | | | | Particle Size[b] | | | | | | % $H_3PO_4$[c] | | |
| | | Filter Collected Samples | | | Photosensor Readings | | | MMAD[d] | | | σg | | | | | |
| Chamber No. | Targeted Aerosol Mass Conc. mg/l | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N |
| 1 | 0.75 | 0.75 | 0.03 | 20 | 0.75 | 0.01 | 20 | 0.63 | 0.09 | 20 | 1.74 | 0.28 | 20 | 68.44 | 7.37 | 4 |
| 2 | 1.00 | 1.02 | 0.04 | 20 | 0.99 | 0.02 | 20 | 0.64 | 0.05 | 20 | 1.58 | 0.26 | 20 | 61.52 | 5.36 | 4 |
| 3 | 1.20 | 1.22 | 0.08 | 20 | 1.21 | 0.04 | 20 | 0.64 | 0.06 | 20 | 1.66 | 0.20 | 20 | 70.44 | 5.28 | 4 |
| 4 | 1.00 | 1.02 | 0.03 | 12 | 0.99 | 0.02 | 12 | 0.60 | 0.07 | 13 | 1.73 | 0.14 | 12 | 65.71 | 1.74 | 4 |
| 5 | 1.20 | 1.20 | 0.04 | 12 | 1.20 | 0.03 | 12 | 0.63 | 0.09 | 13 | 1.71 | 0.20 | 12 | 66.91 | 2.55 | 4 |

[a] Male rats were exposed for 2.25 hr/day on four consecutive days per week (Monday through Thursday or Tuesday through Friday) for a total of four weeks. In Chamber Nos. 4 and 5 exposures were conducted Tuesday through Thursday only.

[b] Calculated from the daily means over the entire exposure period.

[c] Calculated from one filter-collected aerosol sample per week over the entire exposure period.

[d] Mass median aerodynamic diameter, um

N Number of samples

Table 8

MASS CONCENTRATION, PARTICLE SIZE AND PERCENT PHOSPHORIC ACID LEVELS IN RP/BR AEROSOLS
CALCULATED FOR STUDY NO. 79 - SF[a]

| | | RP/BR Aerosol | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mass Conc. determined from[b] | | | | | | Particle Size[b] | | | | | | % $H_3PO_4$[c] | | |
| | | Filter Collected Samples | | | Photosensor Readings | | | MMAD[d] | | | σg | | | | | |
| Chamber No. | Targeted Aerosol Mass Conc. mg/l | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N | Mean | ± SD | N |
| 1 | 0.40 | 0.41 | 0.02 | 25 | 0.41 | 0.02 | 25 | 0.53 | 0.07 | 24 | 1.87 | 0.19 | 24 | 72.68 | 5.41 | 5 |
| 2 | 0.75 | 0.74 | 0.02 | 25 | 0.75 | 0.02 | 25 | 0.59 | 0.06 | 25 | 1.93 | 0.26 | 25 | 69.96 | 4.55 | 5 |
| 3 | 1.00 | 1.06 | 0.02 | 25 | 0.98 | 0.02 | 25 | 0.59 | 0.05 | 25 | 1.87 | 0.15 | 25 | 70.22 | 2.77 | 5 |
| 4 | 0.75 | 0.73 | 0.02 | 12 | 0.74 | 0.02 | 12 | 0.58 | 0.05 | 12 | 1.88 | 0.19 | 12 | 68.38 | 3.98 | 4 |
| 5 | 1.00 | 1.09 | 0.04 | 12 | 0.97 | 0.03 | 12 | 0.62 | 0.08 | 12 | 1.86 | 0.17 | 12 | 73.98 | 1.02 | 4 |

[a] Female rats were exposed for 2.25 hr/day on four consecutive days per week (Monday through Thursday or Tuesday through Friday) for a total of four weeks. For Chambers Nos. 1, 2 and 3 exposures were staggered over a five-week period. In Chamber Nos. 4 and 5 exposures were conducted Tuesday through Thursday over a four-week period.

[b] Calculated from the daily means over the entire exposure period.

[c] Calculated from one filter-collected aerosol sample per week over the entire exposure period.

[d] Mass median aerodynamic diameter, um

N Number of samples

described in Section 2.2.3. The overall means for the entire exposure period for aerosol mass concentration (from gravimetric filter-collected samples and from the integrated time averages of the continuous photosensor readings, respectively) and for particle size were calculated from daily means for each chamber. The phosphoric acid levels were determined from one filter-collected sample analysis per week per chamber.

For Study No. 79, the exposure data are summarized in Table 6. The RP/BR aerosol exposures were conducted at target concentrations of 0.40, 0.75 and 1.00 mg/l in three inhalation chambers at 1 hr and 3.5 hr durations on Mondays through Fridays staggered over a five-week period at the specified frequencies of F1, F2 or F3 as described in the experimental design. The first exposure was on a Friday to accomodate the F3 schedule using Saturday and Sunday as the rest days between the two exposures. Thus the total number of days on which exposures were conducted over a five-week period at a given concentration and duration including all three frequencies used was 26. The phosphoric acid levels were determined from 5 samples, one filter-collected sample per week, during the 3.5 hr exposures.

Study No. 79-S was conducted at target concentrations of 0.75, 1.00 and 1.20 mg/l in five inhalation chambers at 2.25 hr/day, on four consecutive days/week, for a period of four weeks. The high dose originally selected was 1.30 mg/l, however after a concentration overrun on the first exposure day followed by mortalities on the second day (for details see Section 4.3.2) the target concentration was lowered to 1.20 mg/l on Day 3. Table 7 includes data collected throughout the entire study. Because of the labor-intensive nature of the biologic endpoint experiments the groups of rats were staggered for exposures Mondays through Thursdays and Tuesdays through Fridays. Chambers 1, 2 and 3 were used on 5 days per week and Chambers 4 and 5 were used Tuesdays, Wednesdays and Thursdays. The mean mass concentration and particle size values for each target concentration were calculated from 20 daily means (5 days/week for four weeks) for Chamber Nos. 1, 2 and 3 and from 12 daily means (3 days/week for four weeks) for Chamber Nos. 4 and 5. Phosphoric acid levels were determined from one filter-collected sample per chamber per week.

For Study No. 79-SF, (Table 8), female rats were exposed in five inhalation chambers at RP/BR aerosol target concentrations of 0.40, 0.75 and 1.00 mg/l for 2.25 hr/day on 4 consecutive days/weeks, Mondays through Thursdays or Tuesdays through Fridays for a total of four weeks. For Chamber Nos. 1, 2 and 3 the exposures were staggered over a five-week period. In Chamber Nos. 4 and 5 exposures were conducted Tuesdays through Thursdays over a four-week period. Thus, the aerosol mean mass concentration and particle size were calculated from 25 daily means for Chamber Nos. 1, 2 and 3 and 12 daily means for Chambers 4 and 5. The phosphoric

acid levels were determined from samples collected weekly from Chambers 1, 2 and 3, over a five-week period, and from Chambers 4 and 5 over a four-week period.

The data indicate that the target concentrations were well maintained at each exposure level throughout each of the three studies. Mean RP/BR mass concentrations were consistently within 4% of the target value when measured gravimetrically, and within 3% of the required concentration when determined using the light scattering photosensor. Standard deviations of the daily mean concentrations were below ± 8% in every instance when calculated for either sampling method. Excellent agreement between the gravimetric and light scattering methods were demonstrated with variations in mean daily concentration between each method being approximately equivalent in magnitude to the deviations due to actual concentration fluctuation measured within each method. The particle size data indicate excellent aerosol stability throughout the exposures with the mean ranging from 0.44 to 0.64 μm and mean σg from 1.66 to 1.97. Phosphoric acid levels ranged from 61 to 74% $H_3PO_4$. The variation from sample to sample is generally thought to include the inherent errors due to sampling and chemical analysis in addition to the actual fluctuation in phosphoric acid levels in the chambers.

## 4.2 CHARACTERIZATION OF THE RESPONSE SURFACE: STUDY NO. Z9

The objective of this study was to define the experimental conditions in terms of combinations of exposure concentration; duration and frequency that produce maximal effects in the biologic response parameters selected for the project. The choice of response surface modeling as the statistical approach made it possible to work with a low subject number (n=4) for this initial study as necessitated by the need to test a large number of experimental design conditions coupled with multiple biological endpoints at the end of the exposures as well as after a recovery period. Based on the results more specific conditions were to be selected for subsequent studies with increased sample size to find the most sensitive biologic response parameters to be used in the subchronic exposures in the final phase of the research program.

Response surface modeling allows the investigator to proceed in stages so that the greatest amount of statistical power (i.e. sample size) can be placed at the location on the surface producing the maximal biological activity. In light of this, it is often useful to begin with modest sample sizes and increase them as the surface becomes better defined. This is particularly important because at early stages in the experimental design we are examining many parameters under many conditions, whereas at the end of the experiment we have narrowed our view to a specific set of response parameters under specially chosen experimental conditions.

In the current study we selected a design consisting of four concentrations (including control), three frequencies, and two durations tested immediately after the last exposure, and two concentrations (high dose and control), one frequency and one duration tested after a recovery period. This design yielded 26 treatment groups each with a sample size of four animals. Obviously, an n of four is inadequate to test the four-way interaction of concentration by duration by frequency by recovery. This sample size is adequate, however, for tests of main effects and two-way interactions. For example, the main effect of concentration has a relative sample size of 24 animals per dosage group and control (since the design is completely balanced). The concentration by frequency and concentration by duration interactions also have adequate sample sizes. In light of this, the selected sample size in the first study yields more than adequate statistical power for an initial characterization of the response surface involving main effects and all possible two-way interactions. Further studies using more specific experimental conditions had appropriately increased sample sizes.

The three RP/BR aerosol concentrations of 0.40 (C1), 0.75 (C2) and 1.0 (C3) mg/l were selected on the basis of the results of the preliminary range finding studies of Phase II. Durations of 1 and 3.5 hr were used already in some of the Phase II exposures. The selection of exposure frequencies per week was intended to broaden the range of the effect of the inhalation by subjecting the rats to the smoke at the same concentrations and for similar durations on two consecutive days ($F_1$), four consecutive days ($F_2$), or two days separated by two days of rest ($F_3$). Maximally stressed controls inhaling filtered air for 3.5 hr/day on four consecutive days/week were used with all exposure combinations. The total exposure period was four weeks followed by two weeks of recovery with biologic assays conducted at both time points (details of this design are described in section 3.1).

The experimental data are summarized in Tables A-1 to A-43 of Appendix A. The tables were computer-generated from the results of the experimental data entered for statistical analysis. Because of table print-out programming limitations there are for each group of biological response parameters, separate tables comparing the values measured at the three test concentrations relative to controls for each frequency-duration combination (i.e. six tables for the combination of three frequencies with two durations) for assays conducted immediately after the last exposure plus an additional table for the results of the post- recovery assays. Thus there are seven tables each for pulmonary response, neurobehavioral activity, clinical chemistry and hematology parameters, body weights and body weight gains, and there is one table for food consumption.

For the data summarized in these tables <u>post-hoc</u> comparisons (i.e.

Dunnett's test) were computed automatically without regard for the statistical significance of relevant main effects and interactions. For the purpose of interpretation, however, we are only permitted to draw inference from post-hoc comparisons that are associated with significant main effects or interactions. In this preliminary study several scattered significant post-hoc comparisons were observed in the absence of significant main effects and interactions. These post-hoc comparisons are consistent with chance expectations (given the large number of multiple comparisons) and should therefore not be interpreted. In fact, only a small number of significant main effects and an even smaller number of significant interactions were found. These results are presented in the following.

### 4.2.1. Pulmonary Response Parameters

A significant concentation by duration interaction was observed for ATP/cells ($p \leq 0.006$), ATP/protein ($p \leq 0.002$) and pulmonary bactericidal activity ($p \leq 0.002$). Bactericidal activity and ATP were in general decreased, however, this effect appeared to be more pronounced for the 1-hr duration in medium and high-dose animals. In addition, a significant concentration by frequency interaction ($p \leq 0.05$) revealed that ATP/protein values were more significantly decreased in F3 animals. However this effect appeared to be due to an unusual high control value for this parameter in F3 exposures. Similarly, the significantly increased percent macrophage values (from differential counts) in the immediate as well as recovery sacrifice animals was due to markedly lower than historical control values.

### 4.2.2. Behavioral Measures

Locomotor activity counts of the low and high dose animals were significantly increased over controls for the second 10-minute interval of testing in the figure-eight maze ($p \leq 0.02$). Complete recovery was observed from this effect. A significant concentration by duration interaction was observed for total activity counts during the 20-minute test period. This effect was due to greater increases in counts for the 1-hour exposure duration.

### 4.2.3. Hematology and Clinical Chemistry

Relatively few effects were found for these parameters. Several concentration by duration interactions were seen due to some low outlying values in the medium dose 1-hr duration group. These effects are small and most likely artificial.

The only strong main effect of concentation was for BUN values ($p \leq 0.0001$) which were decreased in all concentration groups. This effect exhibited full recovery. BUN levels are usually elevated

under conditions of insufficient renal clearance. On rare occasions, slight decreases are observed, usually in debilitated animals. Therefore, on the basis of these BUN data renal injury is not anticipated. In addition, medium dose inorganic phosphorus levels were decreased relative to controls.

A few concentrations by frequency interactions were also observed. Cholesterol values ($p \leq 0.003$) were decreased in F1 animals and increased in F3 animals relative to controls. No recovery was observed from this effect. Sodium ($p \leq 0.004$) and total protein values ($p \leq 0.03$) were increased in F3 treatment animals relative to controls. This effect was absent after the recovery period.

#### 4.2.4. Body Weights

A significant decrease in body weight gains (N=18) was observed at F2 frequency for medium ($p \leq 0.02$) and high dose ($p \leq 0.002$) animals after the first week of exposures (Test day 8). Low dose animals first exhibited a significant difference from controls on Test day 15 ($p \leq 0.003$). These effects did not increase over the course of the study and recovery animals did not return to control levels. In light of this, we conclude that an initial body weight decrease occurred and these animals never quite caught up (i.e., rates of change did not differ between groups).

#### 4.2.5. Conclusion

Relatively few compound-related effects were observed. Those that were observed, in general, also exhibited complete recovery. The exceptions to this rule were decreases in initial body weights, and decreased cholesterol which did not return to within control values in recovery animals. Given the large number of parameters tested, these effects could have occurred by chance. Furthermore, when interactions did occur, main effects were, in general, absent. This finding further points to the fact that these interactions were spurious. Conversely, strong main effects only occurred for parameters which did not have interactions. Thus it could be concluded that both duration and frequency did not appear to produce major changes in the effects of exposure dose. The most pronounced effects were found for body weight, pulmonary bactericidal activity and BUN values. These effects were seen for all three concentrations with the exception of bactericidal activity values which occurred at medium and high concentations only.

### 4.3. DEFINITIVE PRINCIPAL STUDIES WITH MALE AND FEMALE RATS: STUDY NOS. 79S AND 79SF

In the second and third extended studies with male and female rats respectively more detailed examination of dose response relations were made for a single duration and frequency combination that was

selected on the basis of the findings of the first experiment. The outcome of these showed that since frequency and duration did not affect results significantly, F2 (exposures on four consecutive days per week) was selected to explore the "worst case" situation and 2.25 hr, the logarithmic mean between the previously tested 1 and 3.5 hr was chosen as the single duration. The RP/BR exposure concentrations of 0.75, 1.00 and 1.20 mg/l were used in the first study for male rats and and this range was lowered to 0.40, 0.75 and 1.0 mg/l for the second study with female rats. The increased sample size of n=15 used in these two studies allowed us to directly estimate the recovery effect (i.e. concentration by recovery interaction) and to also obtain multivariate test statistics in addition to the previously reported univariate results.

### 4.3.1. Pulmonary Response Parameters

Male rats were exposed to filtered air or RP/BR aerosol at concentrations of 0.75, 1.00 or 1.20 mg/l for 2.25 hr/day, 4 days/week for 4 weeks. Within one hour or 14 days after the last exposure (only control, medium and high-dose treatment groups were included in the recovery) the rats were killed, pulmonary free cells and lavage fluid were collected from their lungs by tracheobronchial lavage and a series of assays were conducted on the separated cells and the lavage fluid as described in the methodology section. Other rats from each treatment group were used for determination of *in vivo* pulmonary bactericidal activity.

The results are summarized in Tables 9 through 12. The statistical evaluation for the main effects and the *post-hoc* comparisons are described in Tables 9 and 10 respectively. The means with associated standard deviations for all pulmonary response parameters examined in male rats immediately after the last exposure and after a 14-day recovery period are shown in Tables 11 and 12. Significant differences ($p \leq 0.05$) from the *post-hoc* comparisons are indicated in Tables 11 and 12.

The significant multivariate concentration by recovery interaction found for these data (Table 9) indicates differing responses in rats examined immediately after the last exposure and those tested after a 14-day recovery period. Significant univariate interactions were found for ug protein/$10^5$cells ($p \leq 0.02$), ATP/$10^5$cells ($p \leq 0.001$), ATP/ug protein ($p \leq 0.001$), lavage fluid protein ($p \leq 0.008$), phagocytosis of $^{51}$Cr-CRBC ($p \leq 0.002$) and the activity of the ectoenzyme $APD_1$ ($p \leq 0.02$). In addition, significant main effects of concentration were found for the ectoenzyme activities of 5'-N ($p \leq 0.001$) and LAP ($p \leq 0.05$) (Table 9). Subsequently individual *post-hoc* comparisons for these parameters were made (Table 10).

No significant univariate interactions or main effects were

Table 9

PULMONARY RESPONSE PARAMETERS
STATISTICAL DATA FOR MAIN TREATMENT EFFECT AND TREATMENT BY RECOVERY INTERACTION

| Study No. (Sex) | Two-factor MANOVA[a] (for all response parameters measured in one animal) | | Two-factor ANOVA[a] (for individual response parameters) | |
|---|---|---|---|---|
| | Main Effect of Treatment[b] | Treatment by Recovery Interaction[c] | Main Effect of Treatment[b] | Treatment by Recovery Interaction[c] |
| 79-S (M) | | p<0.001 | 5'N (p<0.001)<br>LAP (p<0.05) | prot/cell (p<0.02)<br>ATP/cell (p<0.001)<br>ATP/prot (p<0.001)<br>lav prot (p<0.008)<br>APD1 (p<0.02)<br>phagocyt (p<0.002) |
| 79-SF (F) | | p<0.001 | APD1 (p<0.005)<br>5'N (p<0.01) | tot cells (p<0.004)<br>tot cells/BW (p<0.003)<br>prot/cell (p<0.02)<br>ATP/cell (p<0.001)<br>ATP/prot (p<0.001)<br>lav prot (p<0.002)<br>LAP (p<0.003) |

[a] The two factors are treatment and recovery.

[b] Significant effect of treatment averaging over animals tested after the last exposure and those tested after the recovery period.

[c] Significant difference in effect of treatment between animals tested after the last exposure and those tested after the recovery period.

Table 10

SIGNIFICANT POST-HOC COMPARISONS FROM THE STATISTICAL EVALUATION OF PULMONARY RESPONSE PARAMETERS TESTED IN STUDIES 79-S AND 79-SF

| | Male Rats[a] | | | | | Female Rats[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Post Exposure | | | Post Recovery | | Post Exposure | | | Post Recovery | |
| Endpoint Assay | 0.75 | 1.0 | 1.2 | 1.0 | 1.2 | 0.40 | 0.75 | 1.0 | 0.75 | 1.0 |
| % BC | | | | | | | | | | |
| TOT CELLS | | | | | | | ↑ | ↑ | | |
| TOT CELL/g BW | | | | | | | ↑ | ↑ | | |
| % MACROPHAGE | | | | | | | | | | |
| PROT/$10^5$ CELL | | | ↑ | | | | ↑ | ↓ | | |
| ATP/$10^5$ CELL | ↑ | ↑ | ↑ | | | ↑ | ↑ | | | ↑ |
| ATP/uG PROT | ↑ | ↑ | ↑ | | ↑ | ↑ | ↑ | | | ↑ |
| PHAGO | ND | ↓ | | | ↑ | ND | | | | |
| LAVPROT/g BW | | | ↑ | | | | | ↑ | | ↓ |
| LAP | | | | | | | | ↓ | | |
| APD1 | | | | ↓ | ↓ | ↑ | | | | |
| S[illegible]-N | ↓ | ↓ | ↓ | ↓ | ↓ | | | ↓ | ↓ | |

[a] Significant ($p<0.05$) increase (↑) or decrease (↓) relative to control in male or female rats exposed to the specified RP/BR aerosol concentrations (mg/L) and tested immediately after the last exposure or after a 14-day recovery following the last exposure.

ND Not done

Table 11

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS
TESTED IMMEDIATELY AFTER FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|---|
| % BC | 79.66 ± 9.99 ( 15) | 78.21 ± 13.73 ( 15) | 83.25 ± 12.39 ( 15) | 82.59 ± 12.61 ( 15) |
| TOT CELLS | 16.60 ± 9.55 ( 15) | 17.34 ± 3.86 ( 14) | 15.17 ± 3.31 ( 15) | 10.57 ± 4.26 ( 15) |
| TOTCELL/g BW | 59.60 ± 38.86 ( 15) | 64.81 ± 15.68 ( 14) | 56.76 ± 13.06 ( 15) | 53.14 ± 17.17 ( 15) |
| %MACROPHAGES | 100 ± 1 ( 15) | 99 ± 1 ( 14) | 99 ± 1 ( 15) | 99 ± 1 ( 15) |
| PROT/10⁶CELL | 20.40 ± 4.96 ( 15) | 18.65 ± 3.21 ( 14) | 21.09 ± 3.14 ( 15) | 25.57 ± 4.26 ( 15)* |
| ATP/10⁶ CELL | 0.30 ± 0.25 ( 15) | 0.67 ± 0.15 ( 14)* | 0.75 ± 0.22 ( 13)* | 0.80 ± 0.42 ( 15)* |
| ATP/ug PROT | 1.41 ± 0.96 ( 15) | 3.62 ± 0.77 ( 14)* | 3.62 ± 1.13 ( 13)* | 3.09 ± 1.48 ( 15)* |
| PHAGO [CPM] | 11054 ± 1310 ( 15) | ---- ± 0 ( 0) | 10097 ± 580 ( 15)* | 10755 ± 833 ( 15) |
| LAVPROT/g BW | 11.14 ± 4.28 ( 15) | 13.66 ± 4.80 ( 14) | 14.37 ± 2.79 ( 15) | 16.45 ± 2.71 ( 15)* |
| LAP | 20.38 ± 12.61 ( 15) | 18.42 ± 10.86 ( 13) | 15.54 ± 6.25 ( 15) | 14.90 ± 6.24 ( 15) |
| APDI | 2.09 ± 1.39 ( 15) | 2.20 ± 1.40 ( 13) | 2.13 ± 0.94 ( 15) | 1.76 ± 0.85 ( 15) |
| 5'-N | 2.87 ± 1.94 ( 15) | 1.71 ± 1.12 ( 13)* | 1.29 ± 0.79 ( 15)* | 0.99 ± 0.52 ( 15)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 12

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS
TESTED 14 DAYS POST-EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|
| % BC | 73.34 ± 11.91 ( 16) | 78.81 ± 9.68 ( 16) | 80.08 ± 8.16 ( 16) |
| TOT CELLS | 17.78 ± 8.55 ( 15) | 16.88 ± 4.54 ( 15) | 16.99 ± 4.72 ( 15) |
| TOTCELL/g BW | 56.17 ± 27.20 ( 15) | 53.74 ± 15.38 ( 15) | 58.79 ± 18.53 ( 15) |
| %MACROPHAGES | 98 ± 3 ( 15) | 99 ± 1 ( 15) | 99 ± 1 ( 15) |
| PROT/10⁶CELL | 17.82 ± 2.75 ( 15) | 17.41 ± 1.88 ( 15) | 17.43 ± 5.40 ( 15) |
| ATP/10⁶ CELL | 0.69 ± 0.26 ( 15) | 0.53 ± 0.14 ( 15) | 0.88 ± 0.36 ( 15) |
| ATP/ug PROT | 3.83 ± 1.12 ( 15) | 3.04 ± 0.86 ( 15) | 4.99 ± 0.83 ( 15)* |
| PHAGO [CPM] | 13411 ± 2232 ( 15) | 13518 ± 2078 ( 15) | 18487 ± 6843 ( 15)* |
| LAVPROT/g BW | 11.62 ± 4.28 ( 15) | 10.93 ± 2.01 ( 15) | 11.59 ± 2.82 ( 15) |
| LAP | 24.24 ± 12.29 ( 14) | 19.24 ± 29.84 ( 15) | 12.49 ± 4.97 ( 15) |
| APDI | 1.57 ± 0.65 ( 14) | 0.79 ± 0.31 ( 15)* | 0.95 ± 0.61 ( 15)* |
| 5'-N | 3.02 ± 1.65 ( 14) | 1.63 ± 1.14 ( 15)* | 1.68 ± 0.67 ( 15)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

observed for total pulmonary free cell yield, cells/g body weight, % macrophages, or % bactericidal activity of alveolar macrophages to inhaled [35]S-*K. pneumoniae*, thus *post-hoc* comparisons were not applicable.

A review of the data in Tables 11 and 12 demonstrate that there were significant increases for cellular ATP levels, expressed as ATP/cells or ATP/protein, at all three concentrations tested immediately after the last exposure. Only ATP/protein from rats exposed to 1.2 mg/l RP/BR remained significantly different from control after the recovery period. There was a significant increase in cellular protein levels measured after the last exposure to 1.2 mg/l of the aerosol and this effect was no longer observed after the recovery period. A significant increase in the protein level of the pulmonary lavage fluid after exposures to 1.2 mg/l also exhibited complete recovery. (An increase in lung protein is usually ascribed to transudation of serum due to capillary damage, in the absence of actual measurements of protein types).

Significantly decreased phagocytosis observed in AM from rats after inhalation of 1.0 mg/l of RP/BR was no longer seen after recovery. The significant increase in phagocytosis shown in the 1.2 mg/l treatment group after recovery is an unrealistically great effect with an unusually big standard deviation due to three high outlier values and should be therefore ignored. On the other hand the lack of increases in total cell counts and cell counts per body weight in the pulmonary lavage of the exposed rats may be attributable to the high outlier values in the control cell counts. If two outlier values which are skewing the means and inflating the standard deviations in the control group were deleted, the mean $\pm$ SD(n) for the controls immediately after exposure would be $13.12 \pm 2.60(13)$ for total cells and $45.50 \pm 9.67(13)$ for total cells/g BW respectively and pronounced increases with exposure would be noticeable for both parameters.

When activities of the plasma membrane-associated enzymes (ectoenzymes) of AM from rats exposed to various concentrations of RP/BR were examined a dose dependent decrease in LAP activity was observed in all treatment groups compared to controls. LAP activities of exposed rats were approximately 90, 76 and 73% of control values. After the recovery period LAP activity in AM of the 1.20 mg/l-treatment group was still only 52% of control levels. None of these changes were significant. 5'-N activities were significantly decreased in all treatment groups immediately after the last exposure and remained significantly depressed following the two week recovery period. APDI activities of AM from rats sacrificed immediately following treatment remained near normal levels. AM from rats recovering from 1.00 and 1.20 mg/l RP/BR exposure had respectively, only 50 and 62% APDI activity as compared to control values. These decreases were statistically

significant.

There were significant linear dose response relationships for ATP/cells (r=0.58), ATP/protein (r=0.54), lavage protein (r=0.45) and the ectoenzyme 5'-N (r= -0.52) when these parameters were determined immediately after the last exposure.

Female rats were exposed to filtered air or to RP/BR aerosol at concentrations of 0.40, 0.75, or 1.00 mg/l for 2.25 hr/day, 4 days/week for 4 weeks. Within one hour or 14 days after the last exposure the rats were killed and the same assays were conducted as described for the male rats. No low-dose animals were included in the recovery groups.

Statistical evaluation of the data showed no significant interactions or main effects for % macrophages, *in vivo* bactericidal activity of alveolar macrophages to inhaled [35]S-*K. pneumoniae*, or *in vitro* phagocytosis of $^{51}$Cr-CRBC indicating that these experimental parameters were not affected by the exposures.

A significant multivariate treatment by recovery interaction was found as shown in Table 9, once again indicating differing responses in terminal-sacrifice and recovery-sacrifice animals. Significant univariate (one parameter at a time) treatment by recovery interactions were shown for total cells ($p \leq 0.004$), ug protein/$10^5$cells ($p \leq 0.02$), ATP/$10^5$cells ($p \leq 0.001$), ATP/ug protein ($p \leq 0.001$), total cells/g body weight ($p \leq 0.003$), lavage fluid protein ($p \leq 0.002$) and the ectoenzyme LAP ($p \leq 0.003$). In addition, simple main effects of dosage were found for the other two ectoenzymes: APDI ($p \leq 0.005$) and 5'-N ($p \leq 0.01$).

*Post-hoc* comparisons between treatment groups for these parameters are shown in Tables 10, 13 and 14. The means and standard deviations and significant differences ($p \leq 0.05$) from controls for all experimental data determined after the last exposure and after the recovery period are summarized in Tables 13 and 14 respectively. Total cell counts and cell counts per body weights were significantly increased in the pulmonary lavage from female rats immediately after exposure to 0.75 or 1.0 mg/l, while differential counts remained unaffected indicating unaltered cellular distribution. Since 97 to 99% of the cells were macrophages this means an increased number of AM in the lungs following the exposures. After the 14-day recovery period the counts were no longer different from the controls. Cellular protein levels were significantly decreased at the corresponding concentrations suggesting lower protein content in the newly influxed cells. This effect also disappeared after recovery.

ATP/cells and ATP/protein were significantly increased immediately after exposure to 0.4 or 0.75 mg/l of the aerosol and in AM from rats exposed to 1.0 mg/l after recovery. Although the pattern of

## Table 13

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
PULMONARY DEFENSE PARAMETERS OF FEMALE SPRAGUE DAWLEY RATS
TESTED IMMEDIATELY AFTER FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| %BC | 90.39 ± 2.60 ( 13) | 85.12 ± 7.15 ( 13) | 86.65 ± 6.19 ( 15) | 88.46 ± 5.75 ( 15) |
| TOT CELLS | 9.34 ± 2.57 ( 15) | 9.91 ± 2.26 ( 15) | 11.63 ± 2.12 ( 15)* | 12.67 ± 3.65 ( 15)* |
| TOTCELL/g BW | 46.87 ± 12.53 ( 15) | 50.57 ± 12.48 ( 15) | 59.74 ± 11.82 ( 15)* | 63.22 ± 16.16 ( 15)* |
| %MACROPHAGES | 99 ± 2 ( 15) | 99 ± 2 ( 15) | 96 ± 2 ( 15) | 99 ± 1 ( 15) |
| PROT/10⁶CELL | 22.80 ± 3.80 ( 15) | 20.70 ± 2.61 ( 15) | 18.99 ± 2.73 ( 15)* | 19.29 ± 3.08 ( 15)* |
| ATP/10⁶ CELL | 0.51 ± 0.20 ( 15) | 0.76 ± 0.27 ( 15)* | 1.12 ± 0.13 ( 15)* | 0.55 ± 0.19 ( 15) |
| ATP/ug PROT | 2.26 ± 0.85 ( 15) | 3.64 ± 1.06 ( 15)* | 5.96 ± 0.86 ( 15)* | 2.90 ± 0.98 ( 15) |
| PHAGO [CPM] | 10638 ± 3618 ( 15) | ---- ± 0 ( 0)[b] | 9077 ± 1536 ( 15) | 9111 ± 1464 ( 15) |
| LAVPROT/g BW | 13.42 ± 2.04 ( 15) | 12.21 ± 3.89 ( 14) | 14.68 ± 4.82 ( 13) | 16.51 ± 3.14 ( 15)* |
| LAP | 9.63 ± 2.30 ( 15) | 8.15 ± 2.70 ( 15) | 8.13 ± 3.24 ( 15) | 6.28 ± 1.92 ( 15)* |
| APDI | 1.36 ± 0.69 ( 15) | 2.26 ± 1.48 ( 15)* | 2.16 ± 1.08 ( 15) | 1.20 ± 0.57 ( 15) |
| 5'-N | 2.89 ± 1.56 ( 15) | 2.17 ± 0.96 ( 15) | 2.42 ± 1.06 ( 15) | 1.52 ± 0.49 ( 15)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

b = not done

Table 14

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
PULMONARY DEFENSE PARAMETERS OF FEMALE SPRAGUE DAWLEY RATS
TESTED 14 DAYS POST-EXPOSURE
(MEAN AND STANDARD DEVIATION (n))

| ASSAY | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|
| %BC | 91.04 ± 7.87 ( 15) | 89.41 ± 7.99 ( 16) | 90.41 ± 4.94 ( 16) |
| TOT CELLS | 13.30 ± 5.98 ( 15) | 11.22 ± 2.76 ( 15) | 11.28 ± 2.21 ( 15) |
| TOTCELL/g BW | 61.43 ± 26.90 ( 15) | 52.16 ± 13.76 ( 15) | 51.41 ± 9.67 ( 15) |
| %MACROPHAGES | 97 ± 7 ( 15) | 99 ± 1 ( 15) | 98 ± 2 ( 15) |
| PROT/$10^5$CELL | 18.01 ± 2.74 ( 15) | 19.58 ± 3.24 ( 15) | 16.40 ± 2.51 ( 15) |
| ATP/$10^5$ CELL | 0.60 ± 0.25 ( 15) | 0.77 ± 0.26 ( 15) | 0.98 ± 0.25 ( 15)* |
| ATP/ug PROT | 3.40 ± 1.51 ( 15) | 3.93 ± 1.13 ( 15) | 6.06 ± 1.45 ( 15)* |
| PHAGO [CPM] | 32871 ± 8611 ( 15) | 35586 ± 6110 ( 15) | 30719 ± 4995 ( 15) |
| LAVPROT/g BW | 19.56 ± 7.82 ( 15) | 15.68 ± 3.27 ( 14) | 14.27 ± 2.27 ( 14)* |
| LAP | 10.38 ± 6.55 ( 14) | 12.69 ± 1.71 ( 15) | 10.98 ± 1.46 ( 15) |
| APDI | 1.07 ± 1.56 ( 15) | 2.21 ± 2.31 ( 15) | 2.21 ± 2.12 ( 15) |
| 5'-N | 6.04 ± 2.99 ( 15) | 4.28 ± 0.99 ( 15)* | 4.71 ± 1.69 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

these changes is not entirely clear the general increase in cellular ATP levels, also seen in the AM of male rats, indicates an increased energy supply that may be responsible for the unimpaired phagocytic and bactericidal activity observed after these repeated exposures. In contrast, after single exposures to the same RP/BR aerosol concentrations we measured highly significant decreases in pulmonary bactericidal activity in past as well as recent studies (see Phase II Report dated December 1983 and Appendix B Study No. 79 SC of present report). This suggests the development of an adaptation mechanism as a result of the multiple exposures to the RP/BR aerosol. We have made similar observations in other multiple aerosol exposure studies. (Aranyi et al., J. Tox. Environ. Health 15:163, 1985)

A significant increase in lavage fluid protein immediately after exposures to 1.0 mg/l suggests pulmonary cellular disruption or vascular permeability. The significant decrease seen after recovery in the 1.0 mg/l treatment group is most likely an artifact resulting from the unusually high mean and associated standard deviation for the corresponding control values.

In terms of ectoenzyme activities LAP was decreased in AM from rats exposed to 1.00 mg/l RP/BR. Recovery animals regained normal AM LAP levels. LAP control values of male rats are twice the value of female rats. This result is probably due to day-to-day variation in the assay (Morahan et al., 1980) and not indicative of a true difference in LAP activity between sexes. APD1 activity was significantly increased in AM from rats exposed to 0.4 mg/l RP/BR. There were no significant changes after recovery although APD1 levels were slightly higher in rats recovering from RP/BR exposure than in the corresponding controls. Rats breathing 1.00 mg/l RP/BR had significantly decreased 5'-N activity that was approximately 50% of the control level. Although most of the 5'-N activity was regained after recovery a significant depression from control levels still remained.

Alterations in murine peritoneal ectoenzyme levels have been associated with acquisition of tumoricidal activity or change in resident macrophage status (Morahan et al., J. Immunol., 125:1312, 1980). The plasma membrane-localized enzyme, 5'N, has been characterized as a marker of macrophage development (Edelson, Lymphokines 3:57, 1981). Resident macrophages contain high levels of this enzyme, while stimulated or activated macrophages have decreased levels. The decreased level of 5'N has been associated with decreased synthesis of enzyme as well as increased membrane recycling. Decreased levels of APD1, another macrophage ectoenzyme, have been associated with enhanced macrophage anti-tumor function in peritoneal macrophages of mice. The relationship of macrophage function to ectoenzyme activity has not yet been established in rats. However, if the relationship in rat alveolar macrophages is similar to that of mouse peritoneal macrophages these data indicate that alveolar macrophages of rats

exposed to RP/BR aerosol are stimulated and may have enhanced anti-tumor capacity.

These data are similar to the results found in male rats which indicated that RP/BR exposure may have stimulated rat macrophages as well as enhanced anti-tumor capacity.

A review of the various summarized assay parameters (Table 13) measured immediately after the last exposure generally shows dose response trends. When evaluated statistically the tests for linear dose response relations were significant for total cells ($r=0.47$), cells/BW ($r=0.47$), protein/cells ($r=-0.42$), ATP/protein ($r=0.37$), lavage fluid protein ($r=0.30$), LAP ($r=-0.38$) and 5'-N ($r=-0.37$). Although statistically significant none of these effects are particularly striking.

### 4.3.2. Standard Toxicology

Male and female rats were exposed to filtered air or RP/BR aerosol as previously described. Treatment-related clinical observations were wheezing and/or labored breathing (20/132) and hunched posture (5/132) for several male rats at the high dose. No treatment-related clinical signs were apparent for the female rats exposed to RP/BR. Discharge from the eye(s), nose and mouth was recorded for a few rats of both sexes at all dose levels and control groups.

Mortality: In the study with male rats 16 out of 132 died in the high exposure group. The original target concentration for the high dose was 1.3 mg/l, however on the first day, in one exposure chamber holding 74 rats, the RP/BR concentration was accidentally increased to 1.65 mg/l for 70 minutes of the 2.25 hr exposure period and subsequently was readjusted to 1.3 mg/l for the remaining 65 minutes. On the following day the concentration in this chamber was maintained at the targeted 1.3 mg/l. Because of mortalities occurring during the first two days, the concentration was lowered on Day 3 to 1.2 mg/l for the remaining 14 exposures. By the completion of the studies a total of 12/74 or 16.2% of the rats died that were exposed in this chamber, eight of these after the first two exposures. According to the staggered exposure schedule, exposures were also started on Day 2 at 1.3 mg/l in a second chamber for 58 additional rats and were continued after Day 3 with 15 exposures to 1.2 mg/l. From this group 3/58, or 5.2% of the rats died but only one of these died after the single exposure to 1.3 mg/l. The ten rats that died during the first three days of exposures were replaced on Days 3 and 4 with rats of similar body weight (as determined at randomization), therefore these animals have never been exposed to concentrations higher than 1.2 mg/l and received a maximum of 14 exposures. One of these animals died representing 1% of this treatment group. Thus these data demonstrate that the short accidental exposure to 1.65 mg/l

produced a high increase in mortality as can be seen from the 16.2% relative to 5.2% mortality values observed among rats that were exposed in the two chambers. The effect of 1.3 versus 1.2 mg/l is difficult to evaluate since there were not enough exposure days at 1.3 mg/l.

In the study with female rats where the highest dose was 1.0 mg/l and no concentration overrun occurred, one out of 131 (0.8%) animals died following eight exposures to 0.75 mg/l, the medium dose of RP/BR.

Necropsy and histopathology of these rats that died as a result of the exposures showed that most of them had congestion of the nasal turbinates, lung, liver and kidneys as can be expected in animals that were not exsanguinated at the time of death. For further details see the end of this section and Appendix C.

Body weights: For the male rats there were decreases in body weights and in body weight gains in almost all treatment groups. These changes were generally consistent for the rats designated for assays following the last exposure (Tables 15 and 17) and the recovery animals (Tables 16 and 18). The decreased body weights and body weight gain were seen at all exposure levels from the onset of the second week of exposures (Test Day 8) throughout the exposure period. After 14 days of recovery body weights were similar for control animals and those exposed to 1.0 mg/l. Although a statistically significant reduction in absolute and relative body weights compared to controls was still apparent at the end of the recovery period for rats at the 1.2 mg/l exposure level, these rats gained as much weight as the controls from the final exposure through the end of the recovery period (Test Day 39).

Exposure of female rats to RP/BR aerosol did not appear to affect body weight. Similar values were in general observed for control and treated rats at all time points tested (Tables 19 and 20). Statistically significant differences were however seen when body weight gains were analysed (Tables 21 and 22). This was apparently due to a significantly lower mean body weight for the control animals on Test Day 1 and not due to aerosol exposure.

Food consumption: A reduction in food intake prior to the last exposure was observed for the male rats at the 1.0 and 1.2 mg/l exposure levels, however it was not seen after the recovery period (Table 23). Food consumption did not appear to be affected in female rats by exposure to RP/BR aerosol (Table 24).

Results for clinical pathology are summarized in Tables 25 through 36. The statistical evaluation for the main effects and the post-hoc comparisons for hematology and clinical chemistry are described in Tables 25 through 28. The means with associated

Table 15

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS
TESTED THROUGHOUT THE EXPOSURE PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 0.75 mg/L | | 1.0 mg/L | | 1.2 mg/L | |
|---|---|---|---|---|---|---|---|---|
| RANDOM[b] | 74 ± | 9 ( 66) | 74 ± | 9 ( 65) | 74 ± | 9 ( 66) | 74 ± | 9 ( 66) |
| 1 | 165 ± | 13 ( 66) | 170 ± | 16 ( 65) | 166 ± | 14 ( 66) | 170 ± | 15 ( 66) |
| 8 | 206 ± | 15 ( 66) | 202 ± | 16 ( 65) | 196 ± | 15 ( 66)* | 196 ± | 18 ( 66)* |
| 15 | 248 ± | 15 ( 66) | 240 ± | 19 ( 65)* | 233 ± | 15 ( 66)* | 233 ± | 15 ( 65)* |
| 22 | 280 ± | 16 ( 66) | 265 ± | 21 ( 65)* | 262 ± | 15 ( 66)* | 260 ± | 17 ( 65)* |
| FINAL[b] | 288 ± | 16 ( 66) | 270 ± | 20 ( 65)* | 268 ± | 16 ( 66)* | 264 ± | 17 ( 64)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table 16

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BP AEROSOLS ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD [MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 1.0 mg/L | | 1.2 mg/L | |
|---|---|---|---|---|---|---|
| RANDOM[b] | 73 ± | 9 ( 66) | 74 ± | 9 ( 66) | 73 ± | 9 ( 66) |
| 1 | 165 ± | 15 ( 66) | 166 ± | 18 ( 66) | 166 ± | 14 ( 65) |
| 8 | 200 ± | 17 ( 66) | 200 ± | 15 ( 66) | 190 ± | 19 ( 66)* |
| 15 | 247 ± | 18 ( 66) | 239 ± | 15 ( 66)* | 228 ± | 17 ( 62)* |
| 22 | 276 ± | 18 ( 66) | 270 ± | 15 ( 66) | 257 ± | 18 ( 62)* |
| FINAL[b] | 285 ± | 18 ( 66) | 274 ± | 17 ( 66)* | 263 ± | 17 ( 62)* |
| 29 | 301 ± | 19 ( 66) | 289 ± | 18 ( 66)* | 275 ± | 18 ( 62)* |
| 36 | 318 ± | 23 ( 66) | 310 ± | 20 ( 66) | 296 ± | 20 ( 62)* |
| 39 | 324 ± | 22 ( 65) | 321 ± | 22 ( 65) | 304 ± | 21 ( 62)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2 25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table 17

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS
TESTED THROUGHOUT THE EXPOSURE PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 0.75 mg/L | | 1.0 mg/L | | 1.2 mg/L | |
|---|---|---|---|---|---|---|---|---|
| 8 | 41 ± | 6 ( 66) | 32 ± | 6 ( 65)* | 30 ± | 6 ( 66)* | 26 ± | 11 ( 66)* |
| 15 | 83 ± | 7 ( 66) | 70 ± | 9 ( 65)* | 67 ± | 8 ( 66)* | 62 ± | 10 ( 65)* |
| 22 | 116 ± | 10 ( 66) | 95 ± | 13 ( 65)* | 96 ± | 12 ( 66)* | 89 ± | 13 ( 65)* |
| FINAL[b] | 123 ± | 12 ( 66) | 99 ± | 13 ( 65)* | 102 ± | 13 ( 66)* | 93 ± | 15 ( 64)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAY OF FINAL EXPOSURE

Table 18

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BP AEROSOLS ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD [MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 1.0 mg/L | | 1.2 mg/L | |
|---|---|---|---|---|---|---|
| 8 | 35 ± | 5 ( 66) | 34 ± | 11 ( 66) | 24 ± | 14 ( 65)* |
| 15 | 82 ± | 8 ( 66) | 73 ± | 12 ( 66)* | 62 ± | 12 ( 61)* |
| 22 | 111 ± | 11 ( 66) | 105 ± | 14 ( 66)* | 92 ± | 15 ( 61)* |
| FINAL[b] | 120 ± | 11 ( 66) | 108 ± | 17 ( 66)* | 98 ± | 14 ( 61)* |
| 29 | 136 ± | 13 ( 66) | 124 ± | 17 ( 66)* | 109 ± | 15 ( 61)* |
| 36 | 152 ± | 18 ( 66) | 144 ± | 19 ( 66)* | 130 ± | 18 ( 61)* |
| 39 | 159 ± | 19 ( 65) | 155 ± | 19 ( 65) | 139 ± | 19 ( 61)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAY OF FINAL EXPOSURE

Table 19

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON WEEKLY BODY WEIGHTS (G) OF FEMALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 0.4 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|---|---|
| RANDOM[b] | 126 ± | 10 ( 71) | 126 ± | 10 ( 66) | 126 ± | 10 ( 66) | 126 ± | 10 ( 71) |
| 1 | 151 ± | 11 ( 71) | 156 ± | 14 ( 66)* | 159 ± | 14 ( 66)* | 158 ± | 12 ( 71)* |
| 8 | 167 ± | 11 ( 71) | 168 ± | 13 ( 66) | 171 ± | 12 ( 66) | 170 ± | 13 ( 71) |
| 15 | 184 ± | 13 ( 71) | 183 ± | 14 ( 66) | 185 ± | 14 ( 66) | 184 ± | 13 ( 71) |
| 22 | 198 ± | 13 ( 71) | 196 ± | 14 ( 66) | 200 ± | 13 ( 66) | 199 ± | 14 ( 71) |
| FINAL[b] | 201 ± | 13 ( 71) | 200 ± | 15 ( 66) | 205 ± | 15 ( 66) | 203 ± | 14 ( 71) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table 20

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON WEEKLY BODY WEIGHTS (G) OF FEMALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD [MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|
| RANDOM[b] | 126 ± | 10 ( 65) | 126 ± | 10 ( 65) | 126 ± | 10 ( 65) |
| 1 | 151 ± | 13 ( 65) | 153 ± | 13 ( 65) | 155 ± | 13 ( 65) |
| 8 | 168 ± | 14 ( 65) | 167 ± | 13 ( 65) | 168 ± | 13 ( 65) |
| 15 | 184 ± | 15 ( 65) | 182 ± | 14 ( 64) | 184 ± | 17 ( 65) |
| 22 | 196 ± | 15 ( 65) | 198 ± | 14 ( 64) | 198 ± | 14 ( 65) |
| FINAL[b] | 203 ± | 15 ( 65) | 202 ± | 15 ( 64) | 203 ± | 14 ( 65) |
| 29 | 205 ± | 14 ( 65) | 210 ± | 12 ( 64) | 209 ± | 14 ( 65) |
| 36 | 213 ± | 15 ( 65) | 220 ± | 16 ( 64) | 219 ± | 32 ( 65) |
| 39 | 215 ± | 15 ( 65) | 222 ± | 16 ( 64)* | 224 ± | 15 ( 65)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table 21

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
WEEKLY BODY WEIGHT GAINS (G) OF FEMALE SPRAGUE DAWLEY RATS
TESTED THROUGHOUT THE EXPOSURE PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 17 ± 5 ( 71) | 13 ± 5 ( 66)* | 12 ± 7 ( 66)* | 12 ± 5 ( 71)* |
| 15 | 33 ± 8 ( 71) | 27 ± 7 ( 66)* | 26 ± 8 ( 66)* | 26 ± 6 ( 71)* |
| 22 | 47 ± 10 ( 71) | 40 ± 7 ( 66)* | 42 ± 8 ( 66)* | 41 ± 8 ( 71)* |
| FINAL[b] | 51 ± 10 ( 71) | 45 ± 8 ( 66)* | 46 ± 9 ( 66)* | 45 ± 8 ( 71)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAY OF FINAL EXPOSURE

## Table 22

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON WEEKLY BODY WEIGHT GAINS (G) OF FEMALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD [MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|
| 8 | 17 ± | 5 ( 65) | 14 ± | 7 ( 65) | 13 ± | 8 ( 65)* |
| 15 | 32 ± | 7 ( 65) | 30 ± | 6 ( 64) | 29 ± | 14 ( 65)* |
| 22 | 45 ± | 9 ( 65) | 45 ± | 9 ( 64) | 43 ± | 7 ( 65) |
| FINAL[b] | 52 ± | 8 ( 65) | 50 ± | 11 ( 64) | 48 ± | 9 ( 65) |
| 29 | 54 ± | 10 ( 65) | 57 ± | 13 ( 64) | 54 ± | 10 ( 65) |
| 36 | 62 ± | 11 ( 65) | 68 ± | 12 ( 64)* | 67 ± | 14 ( 64) |
| 39 | 64 ± | 12 ( 65) | 69 ± | 12 ( 64)* | 69 ± | 11 ( 65)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = DAY OF FINAL EXPOSURE

Table 23

EFFECT OF MULTIPLE EXPOSURES TO RP/BR AEROSOLS ON
FOOD CONSUMPTION (G/DAY) OF MALE SPRAGUE DAWLEY RATS
MEASURED AT THE FINAL EXPOSURE (FC 1) AND 14 DAYS POST-EXPOSURE (FC 2)
[MEAN AND STANDARD DEVIATION (n)]

| DAY OF TEST | 0.0 mg/L | | 1.0 mg/L | | 1.2 mg/L | |
|---|---|---|---|---|---|---|
| FC 1 | 27 ± | 4 ( 51) | 24 ± | 3 ( 51)* | 23 ± | 4 ( 60)* |
| FC 2 | 25 ± | 4 ( 64) | 26 ± | 3 ( 64) | 25 ± | 2 ( 60) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 24

EFFECT OF MULTIPLE EXPOSURES TO RP/BR AEROSOLS ON
FOOD CONSUMPTION (G/DAY) OF FEMALE SPRAGUE DAWLEY RATS
MEASURED AT THE FINAL EXPOSURE (FC 1) AND 14 DAYS POST-EXPOSURE (FC 2)
[MEAN AND STANDARD DEVIATION (n)]

| DAY OF TEST | 0.0 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|
| FC 1 | 22 ± | 4 ( 61) | 22 ± | 3 ( 64) | 22 ± | 5 ( 65) |
| FC 2 | 20 ± | 3 ( 65) | 21 ± | 3 ( 64) | 21 ± | 3 ( 65) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 25

HEMATOLOGY

STATISTICAL DATA FOR MAIN TREATMENT EFFECT AND TREATMENT BY RECOVERY INTERACTION

| Study No. (Sex) | Two-factor MANOVA[a] (for all parameters measured in one animal) | | Two-factor ANOVA[a] (for individual parameters) | | | |
|---|---|---|---|---|---|---|
| | Main Effect of Treatment[b] | Treatment by Recovery Interaction[c] | Main Effect of Treatment[b] | | Treatment by Recovery Interaction[c] | |
| 79S (M) | | p <0.001 | HGB | (p <0.001) | WBC | (p <0.001) |
| | | | | | RBC | (p <0.001) |
| | | | | | HCT | (p <0.001) |
| | | | | | MCV | (p <0.001) |
| | | | | | MCH | (p <0.001) |
| | | | | | MCHC | (p <0.001) |
| 79SF (F) | p <0.009 | NS | WBC | (p <0.03) | | |
| | | | RBC | (p <0.001) | | |
| | | | HGB | (p <0.001) | | |
| | | | HCT | (p <0.001) | | |
| | | | M. NEU | (p <0.006) | | |
| | | | LYMPH | (p <0.01) | | |

[a] The two factors are treatment and recovery.

[b] Significant effect of treatment averaging over animals tested after the last exposure and those tested after the recovery period.

[c] Significant difference in effect of treatment between animals tested after the last exposure and those tested after the recovery period.

Table 26

SIGNIFICANT POST-HOC COMPARISONS FROM THE STATISTICAL EVALUATION OF HEMATOLOGY PARAMETERS TESTED IN STUDIES 79-S AND 79-SF

| Endpoint Assay | Male Rats[a] | | | | | Female Rats[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Post Exposure | | | Post Recovery | | Post Exposure | | | Post Recovery | |
| | 0.75 | 1.0 | 1.2 | 1.0 | 1.2 | 0.40 | 0.75 | 1.0 | 0.75 | 1.0 |
| HCT %rbc | ↑ | ↑ | | | | ↑ | ↑ | ↑ | ↑ | ↑ |
| HGB g/dl | ↑ | ↑ | ↑ | | | | ↑ | | ↑ | |
| MCV $um^3$ | ↓ | ↓ | ↓ | | | | | | | |
| MCH pg | ↓ | ↓ | ↓ | | | | | | | |
| MCHC g/dl | ↓ | ↓ | | | | | | | | |
| RBCx$10^6$/$mm^3$ | ↑ | ↑ | ↑ | | | | ↑ | ↑ | ↑ | |
| WBCx$10^3$/$mm^3$ | ↓ | ↓ | | ↑ | ↑ | | | | ↑ | |
| PLTx$10^3$/$mm^3$ | ↓ | ↓ | | | | | | | | |
| IM NEU %WBC | | | | | | | | | | |
| M NEU %WBC | | | | | | | ↓ | | | |
| LYMPH %WBC | | | | | | | ↑ | | ↑ | |
| MON %WBC | | | | | | | | | | |
| EOS %WBC | | | | | | | | | | |
| NRBC/100 WBC | | | | | | | | | | |

[a] Significant ($p<0.05$) increase (↑) or decrease (↓) relative to control in male or female rats exposed to the specified RP/BR aerosol concentrations (mg/L) and tested immediately after the last exposure or after a 14-day recovery following the last exposure.

Table 27

CLINICAL CHEMISTRY

STATISTICAL DATA FOR MAIN TREATMENT EFFECT AND TREATMENT BY RECOVERY INTERACTION

| Study No. (Sex) | Two-factor MANOVA[a] (for all response parameters measured in one animal) | | Two-factor ANOVA[a] (for individual response parameters) | | | |
|---|---|---|---|---|---|---|
| | Main Effect of Treatment[b] | Treatment by Recovery Interaction[c] | Main Effect of Treatment[b] | | Treatment by Recovery Interaction[c] | |
| 79S (M) | | p <0.001 | ALB | (p <0.004) | T BIL | (p <0.05) |
| | | | AL PHOS. | (p <0.005) | CHOL | (p <0.004) |
| | | | D BIL | (p <0.001) | CPK | (p <0.01) |
| | | | BUN | (p <0.001) | Na | (p <0.001) |
| | | | GLU | (p <0.001) | K | (p <0.01) |
| | | | T PRO | (p <0.05) | | |
| | | | GLOB | (p <0.001) | | |
| | | | ALB/GLOB | (p <0.001) | | |
| 79SF (F) | p <0.001 | p <0.05 | ALP | (p <0.002) | Alk. Phosph. | (p <0.001) |
| | | | D [illegible]L | (p <0.01) | | |
| | | | T [illegible]IL | (p <0.001) | | |
| | | | CHOL | (p <0.001) | | |
| | | | BUN | (p <0.001) | | |
| | | | TRIG | (p <0.001) | | |

[a] The two factors are treatment and recovery.

[b] Significant effect of treatment averaging over animals tested after the last exposure and those tested after the recovery period.

[c] Significant difference in effect of treatment between animals tested after the last exposure and those tested after the recovery period.

Table 28

SIGNIFICANT POST-HOC COMPARISONS FROM THE STATISTICAL EVALUATION OF CLINICAL CHEMISTRY PARAMETERS TESTED IN STUDIES 79-S AND 79-SF

| Endpoint Assay | Male Rats[a] | | | | | Female Rats[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Post Exposure | | | Post Recovery | | Post Exposure | | | Post Recovery | |
| | 0.75 | 1.0 | 1.2 | 1.0 | 1.2 | 0.40 | 0.75 | 1.0 | 0.75 | 1.0 |
| GLU mg/dl | † | † | | | | | | | | |
| BUN mg/dl | ↓ | ↓ | ↓ | ↓ | | ↓ | ↓ | ↓ | ↓ | ↓ |
| ALT IU/l | | | | | | | | | | |
| TRIG mg/dl | | | | | | ↓ | ↓ | ↓ | | ↓ |
| T PRO g/dl | | | | | | | | | | |
| ALB g/dl | † | † | | | | | | | ↓ | ↓ |
| CHOL mg/dl | ↓ | ↓ | ↓ | | | ↓ | ↓ | ↓ | | ↓ |
| D BIL mg/dl | | | | | | | ↓ | | | |
| T BIL mg/dl | | | | | | | ↓ | | | |
| AL PHOS IU/l | | | | | † | | | ↓ | ↓ | ↓ |
| Ca mg/dl | | | | | | | | | | |
| P mg/dl | | | | | | | | | | |
| Na mMol/l | † | † | | | | | | | | |
| K mMol/l | † | | | | | | | | | |
| Cl Meq/l | | | | | | | | | | |
| CPK IU/l | † | | | | | | | | | |
| GLOB g/dl | ↓ | ↓ | ↓ | | ↓ | | | | | |
| ALB/GLOB | † | † | † | | † | | | | | |

[a] Significant ($p<0.05$) increase (†) or decrease (↓) relative to control in male or female rats exposed to the specified RP/BR aerosol concentrations (mg/L) and tested immediately after the last exposure or after a 14-day recovery following the last exposure.

standard deviations for all clinical pathology data immediately after the last exposure and after a 14 day recovery period are shown in Tables 29 through 36.

Hematology: For male rats tested immediately after the final exposure statistically significant increases in hematocrit, RBC, and hemoglobin concentration were, in general, seen at all exposure levels of the RP/BR aerosol. The greatest response however occurred at the lowest level, 0.75 mg/l. As the dose increased, a lesser response was seen. This "dose-related" phenomenon was also apparent for the observed leukopenia. The relative proportion of WBC cell types were however similar among all groups. Platelets counts were similar between control and high exposure level animals. The observed decrease in platelet counts for animals exposed to the low or medium levels was apparently due to a technical problem in the counting procedure. The platelet samples for these animals were counted after the recommended time between setup and analysis (Table 29).

None of the above mentioned changes were seen when male rats were subsequently tested 14 days post-exposure. All hematology parameters were similar for control and treated males with the exception of WBC counts. Although leukocytosis was seen at the two exposure levels tested, 1.0 and 1.2 mg/l, a greater response at the lower level was observed. The relative proportion of WBC cell types were again similar among control and treated male rats (Table 30).

For female rats RBC counts and hemoglobin levels were significantly increased for non-recovery rats exposed to 0.75 but not 1.0 mg/l (Table 31). These changes were still apparent when the recovery animals were tested (Table 32). The hematocrit was elevated at all exposure levels for both the non-recovery and recovery rats. Animals exposed to 0.75 mg/l demonstrated the greatest change relative to controls. Lymphocytosis was also apparent at this exposure level for both the rats sacrificed following the last exposure and after 14 days recovery.

Clinical Chemistry: For the male rats hyperglycemia and elevated serum sodium levels were apparent at the 0.75 and 1.0 mg/l exposure levels. Although serum glucose levels were somewhat higher for males at the 1.2 mg/l level compared to controls, this increase was not statistically significant. A slight increase in serum potassium was also observed at the lowest dose tested. Slight reductions in BUN and serum cholesterol levels were seen at all exposure levels although dose-response relationships were not apparent. Although total protein levels were unaffected by exposure to RP/BR aerosol, serum globulin levels were reduced with the albumin/globulin ratio increased at all exposure levels (Table 33).

Table 29

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON HEMATOLOGY
OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER FINAL EXPOSURE
(MEAN AND STANDARD DEVIATION (n))

| HEMATOLOGY VALUES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|---|
| HCT %rbc | 39.9 ± 0.8 ( 15) | 43.8 ± 2.3 ( 14)* | 42.5 ± 1.1 ( 15)* | 40 9 ± 0.8 ( 14) |
| HGB g/dl | 15.3 ± 0.3 ( 15) | 16.5 ± 0.8 ( 14)* | 16.2 ± 0.4 ( 15)* | 15.8 ± 0.4 ( 14)* |
| MCV um³ | 60 ± 1 ( 15) | 59 ± 1 ( 14)* | 59 ± 1 ( 15)* | 59 ± 1 ( 14)* |
| MCH pg | 22.3 ± 0.6 ( 15) | 21.4 ± 0.4 ( 14)* | 21.5 ± 0 1 ( 15)* | 21.8 ± 0.4 ( 14)* |
| MCHC g/dl | 38.4 ± 0.4 ( 15) | 37.7 ± 0.4 ( 14)* | 37.9 ± 0.3 ( 15)* | 38.7 ± 0.4 ( 14) |
| RBCx10⁶/mm³ | 6.86 ± 0.21 ( 15) | 7.71 ± 0.39 ( 14)* | 7.47 ± 0.25 ( 15)* | 7.23 ± 0.16 ( 14)* |
| WBCx10³/mm³ | 7.0 ± 1.2 ( 15) | 5.6 ± 1.9 ( 14)* | 5.3 ± 1.4 ( 15)* | 6.6 ± 1.4 ( 14) |
| PLTx10³/mm³ | 533 ± 70 ( 15) | 281 ± 37 ( 14)* | 436 ± 142 ( 15)* | 540 ± 100 ( 14) |
| IM NEU %WBC | 0 ± 0 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) | 0 ± 0 ( 15) |
| M NEU %WBC | 8 ± 4 ( 15) | 10 ± 5 ( 14) | 10 ± 5 ( 15) | 7 ± 3 ( 14) |
| LYMPH %WBC | 91 ± 4 ( 15) | 89 ± 5 ( 14) | 90 ± 5 ( 15) | 92 ± 3 ( 14) |
| MON %WBC | 0 ± 1 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) | 0 ± 0 ( 15) |
| EOS %WBC | 0 ± 1 ( 15) | 1 ± 1 ( 14) | 1 ± 1 ( 15) | 0 ± 1 ( 15) |
| NRBC/100 WBC | 0 ± 0 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) | 0 ± 0 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS FOR 4 WEEKS

## Table 30

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON HEMATOLOGY OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE (MEAN AND STANDARD DEVIATION (n))

| HEMATOLOGY VALUES | 0.0 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|
| HCT %rbc | 41.1 ± 0.9 ( 16) | 41.0 ± 1.4 ( 16) | 41.5 ± 1.8 ( 14) |
| HGB g/dl | 15.9 ± 0.5 ( 16) | 16.0 ± 0.7 ( 16) | 16.0 ± 0.6 ( 14) |
| MCV um³ | 57 ± 1 ( 16) | 57 ± 1 ( 16) | 57 ± 1 ( 14) |
| MCH pg | 20.9 ± 0.6 ( 16) | 21.2 ± 0.5 ( 16) | 21.1 ± 0.3 ( 14) |
| MCHC g/dl | 38.6 ± 0.8 ( 16) | 39.0 ± 0.7 ( 16) | 38.5 ± 0.5 ( 14) |
| RBCx10⁶/mm³ | 7.57 ± 0.28 ( 16) | 7.51 ± 0.35 ( 16) | 7.53 ± 0.34 ( 14) |
| WBCx10³/mm³ | 6.4 ± 1.3 ( 16) | 8.1 ± 2.1 ( 16)* | 7.7 ± 1.0 ( 14)* |
| PLTx10³/mm³ | 453 ± 83 ( 16) | 420 ± 51 ( 16) | 431 ± 70 ( 14) |
| IM NEU %WBC | 0 ± 0 ( 16) | 0 ± 0 ( 16) | 0 ± 0 ( 14) |
| M NEU %WBC | 1 ± 0 ( 66) | 4 ± 0 ( 66) | 5 ± 0 ( 66) |
| LYMPH %WBC | 87 ± 5 ( 16) | 88 ± 7 ( 16) | 89 ± 6 ( 14) |
| MON %WBC | 0 ± 1 ( 16) | 0 ± 1 ( 16) | 0 ± 0 ( 14) |
| ECS %WBC | 1 ± 1 ( 16) | 1 ± 1 ( 16) | 1 ± 1 ( 14) |
| NRBC/100 WBC | 0 ± 0 ( 16) | 0 ± 0 ( 16) | 0 ± 0 ( 14) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS FOR 4 WEEKS

Table 31

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON HEMATOLOGY
OF FEMALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT % | 40.1 ± 1.7 ( 15) | 41.5 ± 1.9 ( 15)* | 42.8 ± 1.9 ( 14)* | 41.8 ± 1.3 ( 15)* |
| HGB g/dl | 15.1 ± 0.5 ( 15) | 15.6 ± 0.7 ( 15) | 15.9 ± 0.8 ( 14)* | 15.6 ± 0.5 ( 15) |
| MCV um³ | 57 ± 2 ( 15) | 57 ± 2 ( 15) | 57 ± 1 ( 14) | 57 ± 2 ( 15) |
| MCH pg | 21.0 ± 0.6 ( 15) | 21.2 ± 0.7 ( 15) | 21.0 ± 0.7 ( 14) | 20.9 ± 0.5 ( 15) |
| MCHC g/dl | 37.8 ± 0.5 ( 15) | 37.7 ± 0.4 ( 15) | 37.3 ± 0.5 ( 14) | 37.5 ± 0.5 ( 15) |
| RBCx $10^6$/mm³ | 7.12 ± 0.30 ( 15) | 7.31 ± 0.27 ( 15) | 7.54 ± 0.32 ( 14)* | 7.42 ± 0.22 ( 15)* |
| WBCx $10^3$/mm³ | 6.1 ± 1.4 ( 15) | 7.2 ± 1.7 ( 15) | 6.5 ± 1.7 ( 14) | 5.8 ± 1.3 ( 15) |
| PLTx $10^3$/mm³ | 437 ± 53 ( 15) | 468 ± 63 ( 15) | 471 ± 81 ( 14) | 484 ± 58 ( 15) |
| IM NEU %WBC | 0 ± 0 ( 15) | 0 ± 0 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) |
| M NEU %WBC | 10 ± 4 ( 15) | 9 ± 4 ( 15) | 7 ± 4 ( 14)* | 8 ± 4 ( 15) |
| LYMPH %WBC | 88 ± 4 ( 15) | 90 ± 4 ( 15) | 92 ± 4 ( 14)* | 90 ± 5 ( 15) |
| MON %WBC | 0 ± 1 ( 15) | 0 ± 0 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) |
| EOS %WBC | 1 ± 1 ( 15) | 1 ± 1 ( 15) | 1 ± 1 ( 14) | 1 ± 1 ( 15) |
| NRBC/100 WBC | 0 ± 0 ( 15) | 0 ± 0 ( 15) | 0 ± 0 ( 14) | 0 ± 0 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 32

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON HEMATOLOGY OF FEMALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE [MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|
| HCT % | 40.4 ± 1.6 ( 15) | 42.2 ± 1.2 ( 13)* | 41.6 ± 1.3 ( 15)* |
| HGB g/dl | 15.0 ± 0.6 ( 15) | 15.7 ± 0.5 ( 13)* | 15.3 ± 0.5 ( 15) |
| MCV um³ | 56 ± 2 ( 15) | 57 ± 2 ( 13) | 57 ± 1 ( 15 |
| MCH pg | 20.7 ± 0.7 ( 15) | 21.1 ± 0.8 ( 13) | 21.0 ± 0.6 ( 15) |
| MCHC g/dl | 37.3 ± 0.4 ( 15) | 37.3 ± 0.8 ( 13) | 37.0 ± 0.5 ( 15) |
| RBCx $10^6$/mm³ | 7.19 ± 0.28 ( 15) | 7.41 ± 0.20 ( 13)* | 7.26 ± 0.21 ( 15) |
| WBCx $10^3$/mm³ | 4.3 ± 0.9 ( 15) | 5.5 ± 1.7 ( 13)* | 5.3 ± 1.4 ( 15) |
| PLTx $10^3$/mm³ | 463 ± 56 ( 15) | 447 ± 60 ( 13) | 462 ± 70 ( 15) |
| IM NEU %WBC | 0 ± 0 ( 15) | 0 ± 0 ( 13) | 0 ± 0 ( 15) |
| M NEU %WBC | 12 ± 7 ( 15) | 7 ± 5 ( 13) | 9 ± 5 ( 15) |
| LYMPH %WBC | 87 ± 6 ( 15) | 91 ± 5 ( 13)* | 90 ± 5 ( 15) |
| MON %WBC | 0 ± 0 ( 15) | 0 ± 0 ( 13) | 0 ± 0 ( 15) |
| EOS %WBC | 2 ± 1 ( 15) | 1 ± 1 ( 13) | 1 ± 1 ( 15) |
| NRBC/100 WBC | 0 ± 0 ( 15) | 0 ± 0 ( 13) | 0 ± 0 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

## Table 33

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON CLINICAL CHEMISTRY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER FINAL EXPOSURE [MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 181 ± 22 ( 15) | 209 ± 29 ( 11)* | 227 ± 35 ( 15)* | 200 ± 31 ( 14) |
| BUN mg/dl | 21 ± 3 ( 15) | 17 ± 1 ( 11)* | 17 ± 3 ( 15)* | 18 ± 2 ( 14)* |
| ALT IU/l | 52 ± 7 ( 15) | 49 ± 13 ( 11) | 53 ± 10 ( 14) | 48 ± 6 ( 14) |
| TRIG mg/dl | 64.4 ± 13.6 ( 15) | 54.6 ± 15.9 ( 11) | 69.6 ± 37.6 ( 15) | 69.9 ± 24.1 ( 14) |
| T PRO g/dl | 5.6 ± 0.2 ( 15) | 5.6 ± 0.2 ( 11) | 5.6 ± 0.2 ( 14) | 5.4 ± 0.3 ( 14) |
| [illegible] g/dl | 3.6 ± 0.1 ( 15) | 3.7 ± 0.1 ( 11)* | 3.7 ± 0.1 ( 15)* | 3.7 ± 0.1 ( 14) |
| CHOL mg/dl | 88 ± 9 ( 15) | 72 ± 10 ( 11)* | 69 ± 7 ( 15)* | 70 ± 9 ( 14)* |
| D BIL mg/dl | 0.10 ± 0.0[illegible] 15) | 0.09 ± 0.03 ( 12) | 0.09 ± 0.02 ( 15) | 0.10 ± 0.03 ( 14) |
| T BIL mg/dl | 0.20 ± 0.0[illegible] 15) | 0.21 ± 0.08 ( 12) | 0.18 ± 0.02 ( 15) | 0.20 ± 0.02 ( 14) |
| AL PHOS IU/l | 231 ± 36 ( 15) | 210 ± 55 ( 11) | 223 ± 41 ( 14) | 241 ± 21 ( 14) |
| Ca mg/dl | 10.8 ± 0.5 ( 15) | 10.8 ± 0.4 ( 11) | 10.7 ± 0.2 ( 15) | 10.7 ± 0.3 ( 14) |
| P mg/dl | 9.2 ± 0.7 ( 15) | 9.5 ± 0.9 ( 12) | 9.1 ± 0.5 ( 15) | 8.9 ± 0.6 ( 14) |
| Na mMol/l | 143 ± 2 ( 15) | 147 ± 3 ( 13)* | 149 ± 2 ( 15)* | 143 ± 1 ( 14) |
| K mMol/l | 4.4 ± 0.4 ( 15) | 5.3 ± 1.1 ( 13)* | 4.9 ± 0.6 ( 15) | 4.6 ± 0.2 ( 14) |
| Cl Meq/l | 101 ± 1 ( 15) | 101 ± 1 ( 11) | 101 ± 2 ( 14) | 101 ± 1 ( 14) |
| CPK IU/l | 349 ± 104 ( 15) | 556 ± 329 ( 10)* | 533 ± 199 ( 14) | 483 ± 148 ( 14) |
| GLOB g/dl | 2.1 ± 0.2 ( 15) | 1.9 ± 0.1 ( 11)* | 1.9 ± 0.1 ( 14)* | 1.8 ± 0.2 ( 14)* |
| ALB/GLOB | 1.7 ± 0.1 ( 15) | 2.0 ± 0.1 ( 11)* | 2.0 ± 0.1 ( 14)* | 2.1 ± 0.1 ( 14)* |

* = SIGNIFICANTLY FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS FOR 4 WEEKS

Table 34

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON CLINICAL CHEMISTRY OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|
| GLU mg/dl | 170 ± 33 ( 16) | 186 ± 31 ( 16) | 189 ± 16 ( 14) |
| BUN mg/dl | 25 ± 4 ( 16) | 21 ± 3 ( 16)* | 22 ± 4 ( 14) |
| ALT IU/l | 44 ± 9 ( 16) | 44 ± 11 ( 16) | 48 ± 10 ( 14) |
| TRIG mg/dl | 47.6 ± 23.2 ( 16) | 54.3 ± 24.5 ( 16) | 65.3 ± 43.4 ( 14) |
| T PRO g/dl | 5.3 ± 0.2 ( 16) | 5.3 ± 0.2 ( 16) | 5.2 ± 0.2 ( 14) |
| ALB g/dl | 3.5 ± 0.1 ( 16) | 3.6 ± 0.2 ( 16) | 3.6 ± 0.1 ( 14) |
| CHOL mg/dl | 78 ± 11 ( 16) | 74 ± 7 ( 16) | 73 ± 6 ( 14) |
| D BIL mg/dl | 0.05 ± 0.01 ( 16) | 0.05 ± 0.01 ( 16) | 0.05 ± 0.01 ( 14) |
| T BIL mg/dl | 0.15 ± 0.04 ( 16) | 0.16 ± 0.04 ( 16) | 0.14 ± 0.03 ( 14) |
| AL PHOS IU/l | 167 ± 32 ( 16) | 193 ± 32 ( 16) | 206 ± 36 ( 14)* |
| Ca mg/dl | 9.9 ± 0.3 ( 16) | 10.0 ± 0.2 ( 16) | 10.2 ± 0.2 ( 14) |
| P mg/dl | 9.3 ± 1.6 ( 16) | 9.3 ± 2.3 ( 16) | 9.1 ± 1.9 ( 14) |
| Na mMol/l | 147 ± 3 ( 16) | 148 ± 3 ( 16) | 147 ± 3 ( 14) |
| K mMol/l | 4.9 ± 0.9 ( 16) | 4.5 ± 0.4 ( 16) | 4.5 ± 0.3 ( 14) |
| Cl Meq/l | 102 ± 2 ( 16) | 102 ± 2 ( 16) | 102 ± 1 ( 14) |
| CPK IU/l | 882 ± 903 ( 16) | 585 ± 583 ( 16) | 549 ± 647 ( 13) |
| GLOB g/dl | 1.8 ± 0.2 ( 16) | 1.7 ± 0.1 ( 16) | 1.6 ± 0.1 ( 14)* |
| ALB/GLOB | 2.0 ± 0.2 ( 16) | 2.1 ± 0.2 ( 16) | 2.2 ± 0.1 ( 14)* |

* = SIGNIFICANTLY FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS FOR 4 WEEKS

## Table 35

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON CLINICAL CHEMISTRY OF FEMALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| CLIN. CHEM. VALUES | 0.0 mg/L | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 282 ± 113 ( 14) | 276 ± 98 ( 14) | 294 ± 80 ( 13) | 253 ± 39 ( 15) |
| BUN mg/dl | 22 ± 3 ( 14) | 18 ± 3 ( 14)* | 17 ± 2 ( 13)* | 17 ± 2 ( 15)* |
| ALT IU/l | 43 ± 9 ( 13) | 51 ± 9 ( 15)* | 48 ± 7 ( 13) | 47 ± 9 ( 15) |
| TRIG mg/dl | 68 ± 32 ( 13) | 46 ± 18 ( 14)* | 42 ± 15 ( 13)* | 36 ± 12 ( 15)* |
| T PRO g/dl | 6.1 ± 0.5 ( 14) | 6.0 ± 0.3 ( 14) | 6.0 ± 0.3 ( 13) | 6.0 ± 0.4 ( 15) |
| ALB g/dl | 4.2 ± 0.3 ( 14) | 4.1 ± 0.3 ( 14) | 4.1 ± 0.1 ( 13) | 4.1 ± 0.3 ( 15) |
| CHOL mg/dl | 106 ± 12 ( 14) | 88 ± 11 ( 14)* | 96 ± 11 ( 13)* | 95 ± 12 ( 15)* |
| D BIL mg/dl | 0.07 ± 0.03 ( 14) | 0.08 ± 0.03 ( 14) | 0.05 ± 0.02 ( 13)* | 0.06 ± 0.03 ( 15) |
| T BIL mg/dl | 0.22 ± 0.06 ( 14) | 0.21 ± 0.08 ( 14) | 0.13 ± 0.05 ( 13)* | 0.17 ± 0.08 ( 15) |
| AL PHOS IU/l | 131 ± 20 ( 14) | 124 ± 18 ( 14) | 114 ± 18 ( 13) | 111 ± 23 ( 15)* |
| Ca mg/dl | 11.2 ± 0.8 ( 14) | 11.1 ± 0.9 ( 14) | 11.3 ± 0.8 ( 13) | 10.9 ± 0.5 ( 15) |
| P mg/dl | 9.0 ± 1.4 ( 14) | 8.6 ± 1.1 ( 14) | 9.2 ± 1.0 ( 13) | 8.4 ± 1.1 ( 15) |
| Na mMol/l | 147 ± 3 ( 14) | 146 ± 3 ( 14) | 146 ± 2 ( 13) | 146 ± 3 ( 15) |
| K mMol/l | 7.2 ± 2.1 ( 14) | 6.1 ± 1.6 ( 14) | 6.2 ± 1.0 ( 13) | 5.9 ± 1.2 ( 15) |
| Cl Meq/l | 99 ± 3 ( 14) | 98 ± 2 ( 13) | 98 ± 2 ( 13) | 100 ± 2 ( 15) |
| CPK IU/l | 555 ± 378 ( 14) | 655 ± 223 ( 14) | 621 ± 332 ( 13) | 755 ± 454 ( 15) |
| GLOB g/dl | 1.8 ± 0.2 ( 14) | 1.9 ± 0.2 ( 14) | 1.9 ± 0.2 ( 13) | 1.9 ± 0.3 ( 15) |
| ALB/GLOB | 2.3 ± 0.3 ( 14) | 2.2 ± 0.2 ( 14) | 2.2 ± 0.2 ( 13) | 2.2 ± 0.3 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 36

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON CLINICAL CHEMISTRY OF FEMALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| CLIN. CHEM. VALUES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|
| GLU mg/dl | 194 ± 32 ( 14) | 232 ± 29 ( 13)* | 233 ± 38 ( 14)* |
| BUN mg/dl | 26 ± 5 ( 14) | 22 ± 2 ( 13)* | 22 ± 2 ( 14)* |
| ALT IU/l | 55 ± 14 ( 14) | 49 ± 5 ( 13) | 50 ± 7 ( 14) |
| TRIG mg/dl | 50 ± 19 ( 14) | 39 ± 11 ( 13) | 36 ± 12 ( 14)* |
| T PRO g/dl | 6.2 ± 0.2 ( 14) | 5.9 ± 0.3 ( 13)* | 6.0 ± 0.3 ( 14) |
| ALB g/dl | 4.1 ± 0.2 ( 14) | 4.0 ± 0.2 ( 13)* | 4.0 ± 0.1 ( 14)* |
| CHOL mg/dl | 111 ± 13 ( 14) | 101 ± 15 ( 13) | 93 ± 11 ( 14)* |
| D BIL mg/dl | 0.09 ± 0.02 ( 14) | 0.08 ± 0.03 ( 13) | 0.10 ± 0.07 ( 14) |
| T BIL mg/dl | 0.21 ± 0.04 ( 14) | 0.18 ± 0.03 ( 13) | 0.21 ± 0.08 ( 14) |
| AL PHOS IU/l | 113 ± 22 ( 14) | 140 ± 18 ( 13)* | 140 ± 31 ( 14)* |
| Ca mg/dl | 11.3 ± 0.5 ( 14) | 11.4 ± 0.4 ( 13) | 11.4 ± 0.4 ( 14) |
| P mg/dl | 7.1 ± 1.3 ( 14) | 7.7 ± 1.1 ( 13) | 7.2 ± 0.9 ( 14) |
| Na mMol/l | 145 ± 2 ( 14) | 143 ± 4 ( 13) | 145 ± 3 ( 14) |
| K mMol/l | 4.3 ± 0.4 ( 14) | 4.4 ± 0.8 ( 13) | 4.7 ± 0.9 ( 14) |
| Cl Meq/l | 102 ± 2 ( 14) | 102 ± 2 ( 13) | 102 ± 2 ( 12) |
| CPK IU/l | 496 ± 169 ( 14) | 496 ± 258 ( 13) | 572 ± 234 ( 14) |
| GLOB g/dl | 2.0 ± 0.2 ( 14) | 2.0 ± 0.2 ( 13) | 2.0 ± 0.2 ( 14) |
| ALB/GLOB | 2.0 ± 0.2 ( 14) | 2.0 ± 0.2 ( 13) | 2.0 ± 0.2 ( 14) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

When male rats were tested 14 days post-exposure, the changes discussed above were no longer apparent with the exception of the globulin and subsequent A/G ratio changes at the 1.2 mg/l level. In addition, slight reductions in BUN were still observed at the exposure levels tested. Although not previously seen after the final exposure, serum alkaline phosphatase levels showed a dose-related increase at the recovery sampling time (Table 34).

In female rats serum alkaline phosphatase levels were reduced, compared to control animals, for sacrifice rats at the 1.0 and probably at the 0.75 mg/l exposure level (Table 35). By contrast, recovery rats at these levels showed slight increase relative to controls (Table 36). Slight reduction in total and direct bilirubin were seen for sacrifice but not recovery rats at the 0.75 but not 1.0 mg/l exposure level. The lack of dose-response relationship suggests that this may be a spurious observation. Serum cholesterol, triglycerides, and BUN levels were significantly decreased for the sacrifice animals. Following the recovery period, dose-related reductions for these parameters were still evident. No other clinical chemistry variables appeared to be altered following exposure to RP/BR.

Statistically significant linear dose response relationships were found, when measured immediately after the last exposure, in clinical pathology for RBC ($r=0.48$), MCV ($r=-0.46$), MCH ($r=-0.43$), BUN ($r=-0.45$), and Cholesterol ($r=-0.66$) in male rats and for RBC ($r=0.42$), HGB ($r=0.32$), HCT ($r=0.42$) and MCHC ($r=-0.32$) in female rats. Although significant, even the largest coefficients are not particularly impressive.

Necropsy and histopathology observations: Detailed reports on histopathology including incidence tables prepared by Dr. W. Iverson of EPL, consultant pathologist and on necropsy and gross pathology observations prepared by Dr. V. Rac, staff pathologist are included in Appendix C. A brief summary of the main results follows.

In Study No. 79 in which male rats were exposed to 0.4, 0.75, or 1.0 mg/l RP/BR aerosols for 1 or 3.5 hr per day, 2 or 4 times per week for 4 weeks, treatment-related gross necropsy lesions in the lungs, red discoloration with varying patterns of distribution, were found in rats necropsied immediately after the last exposure but not in the recovery groups. The small group size makes it difficult to determine whether these observed lesions were significantly affected by varying exposure concentrations, frequency or duration of the exposure.

Histopathologically no treatment related changes were seen in the nasal turbinates, trachea or pulmonary lymph nodes. In addition, heart, eyes, kidneys, adrenals, liver, esophagus, stomach, duodenum and urinary bladder were free of treatment-related changes.

Changes were seen in the lung, however, where the primary lesion was terminal bronchiolar fibrosis which first became evident when the rats were exposed to 0.4 mg/l of aerosol for 3.5 hr/day for 4 consecutive days. The lesion increased in incidence and severity with increased concentrations and length of exposure and did not exhibit recovery during the 14-day holding interval after exposure.

Masson's trichrome special stain was used to confirm and grade the amount of collagen in the terminal bronchioles and associated alveoli in the affected animals. The results indicate that part, but not all, of the thickening of the terminal bronchioles and associated alveoli was due to fibrosis - the formation of new collagen fibers in excess of what would normally be present. One additional pulmonary lesion which may be treatment-related was the peribronchiolar and perivascular infiltration of eosinophils.

In Study No. 79S, male rats were exposed to 0.75, 1.0 or $\geq$1.2 mg/l RP/BR aerosols for 2.25 hr per day, 4 consecutive days per week for 4 weeks. In this study no treatment-related gross lesions were observed in scheduled necropsies. In rats that died spontaneously after exposure of the highest concentration, gross morphologic lesions were confined to red fluid in the thoracic cavity, red discoloration of various intensity and distribution in the lungs, and dark red liver. Congestion of the lungs, nasal turbinates, liver and kidneys was seen microscopically in these rats, as expected in animals not exsanguinated at the time of necropsy.

Histopathologically all treated animals, both terminal and recovery sacrifices, had lung lesions described as mild to moderate terminal bronchiolar fibrosis. The lesion was more severe in animals that received $\geq$1.2 mg/l and in rats recovering from 1.0 mg/l RP/BR than those exposed to lower doses. Examination of lungs from selected animals indicated that fibrosis, as evidenced by a Masson's trichrome stain, was a component of the terminal bronchiolar fibrosis previously identified in the study. As the thickening, which comprised this lesion became more severe, increased amounts of collagen were present in these areas. Fourteen days after the final exposure, several of the animals recovering from exposure to the two higher dosage levels had a slight increase in inflammation of the posterior nasal turbinates relative to controls. There were no treatment-related changes observed in any other tissues.

In Study No. 79-SF, female rats were exposed to 0.4, 0.75, or 1.0 mg/l RP/BR aerosols for 2.25 hr per day, 4 consecutive days per week for 4 weeks. No treatment-related gross lesions were found in rats in any of the necropsies. Once again the primary treatment-related change seen histologically was in the lung and was diagnosed as minimal to mild terminal bronchiolar fibrosis. These changes were seen in rats that were exposed to 0.75 or 1.0 mg/l but not in those that received 0.4 mg/l of the RP/BR aerosols. The lesion was slightly more severe in the high dose animals, and

once again was due, in both the 0.75 and 1.0 mg/l exposure groups, to the formation of new collagen fibers in excess of what would normally be present. Fibrosis does not account for all of the thickening seen in the changes designated "terminal bronchiolar fibrosis". A treatment-related increase in peribronchiolar eosinophilic infiltrate appeared to regress during the 14-day recovery period. No treatment-related changes were found in the tissues examined outside of the respiratory tract.

### 4.3.3. Neurobehavioral Activity

The studies which examined the behavioral effects of RP/BR aerosols have been consistent in indicating either significant increases in locomotor activity in the residential maze or trends in that direction. The most pronounced effect was seen when groups of 15 male rats were exposed to concentrations of 0.75, 1.0 and 1.2 mg/l for 2.25 hr/day on 4 consecutive days for 4 weeks. In this study, there was no interaction between treatment and recovery for neurobehavioral parameters by either the multivariate or univariate analyses, however, the multivariate analysis yielded a significant effect of treatment ($p \leq 0.001$). The treatment effect was significant for the univariate analysis for all three locomotor activity parameters ($p \leq 0.001$). Immediately following exposure, activity of all treatment groups was elevated compared to control values when activity for the total 20 min period was considered (Figure 1). All treatment groups also had activity levels higher than control values when the first 10 min of activity measurement was analyzed separately (Table 37). In addition for the second 10-min of the activity measuring session, male rats in high and low dose groups were significantly more active than controls and the value for the middle dose group fell just short of significant elevation. The effect of RP/BR aerosols on locomotor activity of male rats persisted through recovery. Considering the total 20-min session, the dose-response curve for recovery was essentially parallel to that obtained immediately following exposure (Figure 1). As this is the case, the higher activity counts at recovery for both control and treated groups are most likely due to the fact that the animals were 2 weeks older. The statistical analysis indicated significant elevations at recovery for all 3 activity measures at 1.0 mg/l and during the first 10 min and total of 20 min at 1.2 mg/l (Table 38). Expressed as a percentage of control activity, the mean values for male treated groups were 30 to 60% higher than control values immediately following exposure and approximately 30 to 40% higher at the recovery evaluations.

For female rats exposed to RP/BP aerosol concentrations of 0.4, 0.75, and 1.0 mg/l, the results of the multivariate analysis was not significant for either treatment or the treatment by recovery interaction. Under the statistical procedures utilized, this would preclude consideration of the univariate analyses. However, in that significant effects on locmotor activity were observed in male

Figure 1

LOCOMOTOR ACTIVITY OF MALE
SPRAQUE-DAWLEY RATS FOR THE 20-MINUTE TESTING SESSION

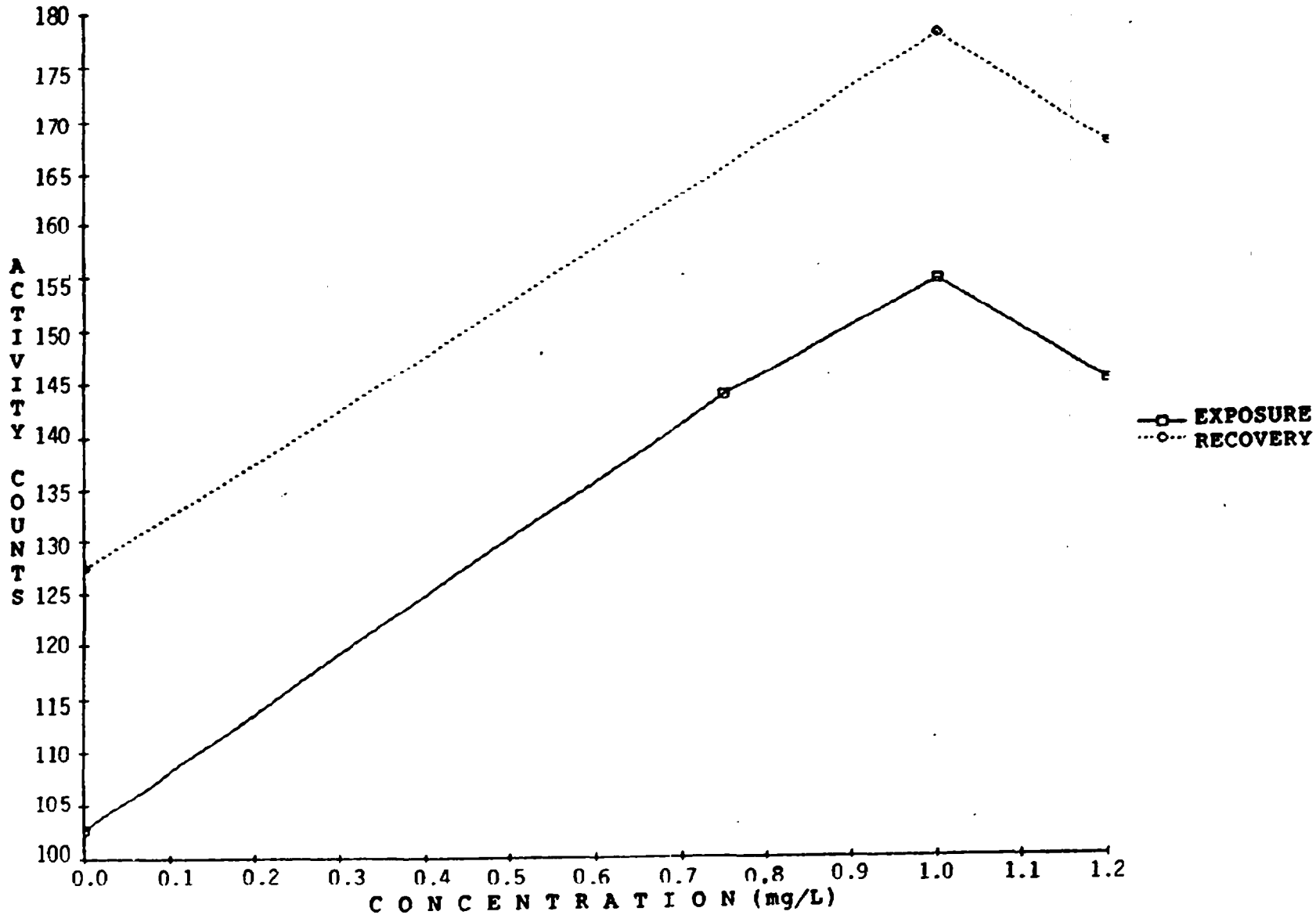


Table 37

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE [MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 69.73 ± 29.58 ( 15) | 97.33 ± 16.26 ( 15)* | 111.93 ± 22.75 ( 15)* | 101.23 ± 19.53 ( 13)* |
| Act-2nd 10' | 32.93 ± 10.18 ( 15) | 46.47 ± 12.82 ( 15)* | 42.60 ± 12.15 ( 15) | 43.92 ± 13.98 ( 13)* |
| Act-Tot 20' | 102.67 ± 34.62 ( 15) | 143.80 ± 24.70 ( 15)* | 154.53 ± 30.14 ( 15)* | 145.15 ± 22.53 ( 13)* |
| Fl Grip | 896.7 ± 191.3 ( 15) | 902.1 ± 303.2 ( 15) | 868.4 ± 169.4 ( 15) | 869.7 ± 146.8 ( 14) |
| Hl Grip | 511.67 ±102.75 ( 15) | 494.67 ± 96.62 ( 15) | 474.73 ± 73.20 ( 15) | 434.29 ± 80.26 ( 14)* |
| TrTr 1-Time | 3.47 ± 2.56 ( 15) | 5.40 ± 3.91 ( 15) | 5.86 ± 3.37 ( 14) | 3.29 ± 2.73 ( 14) |
| TrTr 2-Time | 4.53 ± 3.70 ( 15) | 3.93 ± 3.95 ( 15) | 5.47 ± 4.22 ( 15) | 6.64 ± 3.30 ( 14) |
| TrTr 3-Time | 4.21 ± 3.72 ( 14) | 7.60 ± 3.85 ( 15) | 5.73 ± 4.27 ( 15) | 4.86 ± 4.24 ( 14) |
| TrTr 4-Time | 5.40 ± 4.05 ( 15) | 5.64 ± 4.77 ( 14) | 4.27 ± 4.03 ( 15) | 5.85 ± 3.87 ( 13) |
| No. ESC-Tr | 3.20 ± 1.01 ( 15) | 2.20 ± 1.08 ( 15)* | 2.60 ± 1.24 ( 15) | 2.79 ± 1.05 ( 14) |
| TeTr 1-Time | 13.53 ± 5.34 ( 15) | 17.60 ± 3.52 ( 15)* | 14.87 ± 4.63 ( 15) | 14.50 ± 3.98 ( 14) |
| TeTr 2-Time | 11.79 ± 4.76 ( 14) | 15.67 ± 4.85 ( 15) | 12.27 ± 4.46 ( 15) | 13.50 ± 5.83 ( 14) |
| No. ESC-Te | 1.57 ± 0.65 ( 14) | 0.93 ± 0.80 ( 15)* | 1.53 ± 0.64 ( 15) | 1.57 ± 0.76 ( 14) |
| No. AVD-Te | 0.43 ± 0.76 ( 14) | 0.13 ± 0.35 ( 15) | 0.13 ± 0.35 ( 15) | 0.14 ± 0.36 ( 14) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 38

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE [MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L | 1.0 mg/L | 1.2 mg/L |
|---|---|---|---|
| Act-1st 10' | 90.07 ± 35.82 ( 14) | 125.29 ± 22.07 ( 14)* | 119.31 ± 27.76 ( 13)* |
| Act-2nd 10' | 37.21 ± 14.83 ( 14) | 52.57 ± 14.31 ( 14)* | 48.08 ± 12.34 ( 13) |
| Act-Tot 20' | 127.29 ± 45.73 ( 14) | 177.86 ± 28.93 ( 14)* | 167.38 ± 32.62 ( 13)* |
| Hi Grip | 956.1 ± 163.9 ( 15) | 956.7 ± 218.6 ( 15) | 851.9 ± 112.2 ( 13) |
| Hi Grip | 541.93 ± 71.81 ( 15) | 553.20 ± 84.77 ( 15) | 516.85 ± 99.18 ( 13) |
| TrTr 1-Time | 3.64 ± 2.98 ( 14) | 4.33 ± 3.85 ( 15) | 4.00 ± 3.03 ( 13) |
| TrTr 2-Time | 4.00 ± 3.42 ( 15) | 5.67 ± 4.39 ( 15) | 3.08 ± 4.01 ( 12) |
| TrTr 3-Time | 5.36 ± 4.18 ( 14) | 7.40 ± 4.19 ( 15) | 4.67 ± 4.42 ( 12) |
| TrTr 4-Time | 5.73 ± 3.49 ( 15) | 7.53 ± 3.44 ( 15) | 3.08 ± 3.71 ( 13) |
| No. ESC-Tr | 3.00 ± 1.07 ( 15) | 2.33 ± 1.18 ( 15) | 3.15 ± 1.14 ( 13) |
| TeTr 1-Time | 12.60 ± 5.70 ( 15) | 16.13 ± 4.37 ( 15) | 12.08 ± 4.87 ( 13) |
| TeTr 2-Time | 12.33 ± 7.18 ( 15) | 15.73 ± 5.62 ( 15) | 9.69 ± 3.84 ( 13) |
| No. ESC-Te | 1.53 ± 0.74 ( 15) | 1.00 ± 0.85 ( 15) | 1.85 ± 0.38 ( 13) |
| No. AVD-Te | 0.47 ± 0.74 ( 15) | 0.07 ± 0.26 ( 15) | 0.38 ± 0.51 ( 13) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

rats, it seems appropriate to note that the univariate analyses of those variables related to locomotor activity in females indicated a significant treatment effect for the total 20-min activity measuring session ($p \leq 0.01$) and for each of the 10-min segments ($p \leq 0.05$). Activity was elevated immediately following exposure for the group of females exposed to 0.4 mg/l (lowest concentration) for both activity measurment segments and for the group exposed to 1.0 mg/l (highest concentration) for the second 10-min segment (Table 39). Expressed as a percentage of control activity, the mean values for female treated groups ranged from 12% to 53% higher with, as noted above, the low dose group being more affected. Neither of the groups tested at recovery showed any effect of exposure to RP/BP aerosols (Table 40).

None of the other neurobehavioral parameters indicated consistent effects although there were occasional instances of either a significant parameter in the univariate analysis or in post-hoc comparisons where the preceding analysis failed to yield significant results. These are considered cases of spurious significance. Tables 37-40 also show mean values for all neurobehavioral parameters considered for both male and female rats.

The results of the overall statistical evaluation and the following significant post-hoc comparisons are summarized in Tables 41 and 42 respectively.

### 4.3.4. Genetic Toxicology: Micronucleus Analysis

A micronucleus (MN) analysis was performed on bone marrow polychromatic erythrocytes (PCE) and normachromatic erythrocytes (N) and on circulating red blood cells (RBC) of filtered air- and 1.0 mg/l RP/BR-exposed female rats after 8 and 16 exposures and after a two-week recovery period following 16 exposures.

Micronuclei form in response to clastogenic events. As an assay for detecting clastogens, MN are usually counted in the polychromatic erythrocytes from bone marrow and in circulating RBC's in mice. The RBC-MN assay is not usually performed on rats since it is generally understood that the MN are efficiently removed from the RBC by their spleens. We performed the assay on bone marrow cells and on RBC in rats as a test of this dictum and to determine if RP/BR aerosol is a clastogen.

Due to the small sample on which the genetic toxicology parameters were measured, multivariate tests of the hypotheses were not used because of their extremely limited power under such conditions. In light of this, differences between control and high dose animals were reported as f-statistics only (i.e. post-hoc comparisons).

A statistically significant clastogenic response was measured in

Table 39

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON NEUROBEHAVIORAL ACTIVITY OF FEMALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 73.43 ± 19.75 ( 14) | 93.67 ± 18.93 ( 15)[b] | 84.50 ± 20.66 ( 14) | 81.87 ± 24.42 ( 15) |
| Act-2nd 10' | 29.86 ± 7.50 ( 14) | 45.53 ± 13.96 ( 15)[b] | 37.50 ± 13.05 ( 14) | 39.93 ± 11.11 ( 15)[b] |
| Act-Tot 20' | 103.29 ± 22.39 ( 14) | 139.20 ± 29.28 ( 15)[b] | 122.00 ± 22.30 ( 14) | 121.80 ± 27.84 ( 15) |
| TrTr 1-Time | 2.80 ± 2.76 ( 15) | 2.00 ± 1.85 ( 15) | 2.21 ± 2.39 ( 14) | 3.60 ± 2.75 ( 15) |
| TrTr 2-Time | 4.53 ± 3.93 ( 15) | 2.87 ± 2.88 ( 15) | 4.71 ± 3.75 ( 14) | 2.27 ± 2.46 ( 15) |
| TrTr 3-Time | 5.33 ± 3.54 ( 15) | 4.00 ± 3.91 ( 15) | 5.14 ± 4.02 ( 14) | 3.73 ± 3.63 ( 15) |
| TrTr 4-Time | 5.40 ± 4.15 ( 15) | 5.07 ± 3.90 ( 15) | 5.42 ± 4.14 ( 12) | 1.87 ± 1.51 ( 15) |
| No. ESC-Tr | 3.20 ± 0.86 ( 15) | 3.60 ± 0.51 ( 15) | 3.00 ± 1.00 ( 13) | 3.80 ± 0.41 ( 15) |
| TeTr 1-Time | 10.85 ± 6.15 ( 13) | 7.67 ± 5.00 ( 15) | 10.86 ± 6.15 ( 14) | 9.20 ± 6.55 ( 15) |
| TeTr 2-Time | 6.54 ± 3.99 ( 13) | 7.87 ± 5.46 ( 15) | 6.86 ± 5.67 ( 14) | 9.33 ± 4.64 ( 15) |
| No. ESC-Te | 1.92 ± 0.28 ( 13) | 1.87 ± 0.52 ( 15) | 1.86 ± 0.36 ( 14) | 1.87 ± 0.35 ( 15) |
| No. AVD-Te | 1.00 ± 0.71 ( 13) | 1.07 ± 0.88 ( 15) | 0.86 ± 0.66 ( 14) | 1.07 ± 0.88 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS
b = See comments in text

Table 40

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON
NEUROBEHAVIORAL ACTIVITY OF FEMALE SPRAGUE DAWLEY RATS
TESTED 14 DAYS POST-EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL[1] MEASURES | 0.0 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|
| Act-1st 10' | 79.79 ± 18.80 ( 14) | 91.07 ± 17.75 ( 15) | 88.73 ± 17.59 ( 15) |
| Act-2nd 10' | 32.79 ± 16.96 ( 14) | 42.93 ± 16.33 ( 15) | 40.20 ± 15.32 ( 15) |
| Act-Tot 20' | 112.57 ± 33.30 ( 14) | 134.00 ± 27.32 ( 15) | 128.93 ± 29.29 ( 15) |
| TrTr 1-Time | 3.00 ± 2.80 ( 15) | 2.20 ± 1.42 ( 15) | 2.27 ± 2.76 ( 15) |
| TrTr 2-Time | 4.00 ± 2.96 ( 14) | 4.43 ± 3.76 ( 14) | 3.21 ± 3.21 ( 14) |
| TrTr 3-Time | 3.33 ± 3.18 ( 15) | 3.07 ± 2.70 ( 14) | 2.73 ± 2.66 ( 15) |
| TrTr 4-Time | 4.27 ± 3.63 ( 15) | 6.14 ± 4.04 ( 14) | 3.87 ± 4.26 ( 15) |
| No. ESC-Tr | 3.67 ± 0.49 ( 15) | 3.13 ± 0.99 ( 15) | 3.67 ± 0.49 ( 15) |
| TeTr 1-Time | 8.93 ± 5.46 ( 15) | 11.07 ± 6.67 ( 15) | 10.00 ± 5.28 ( 15) |
| TeTr 2-Time | 7.64 ± 5.50 ( 14) | 8.80 ± 5.16 ( 15) | 7.87 ± 5.08 ( 15) |
| No. ESC-Te | 1.86 ± 0.36 ( 14) | 1.73 ± 0.46 ( 15) | 1.87 ± 0.35 ( 15) |
| No. AVD-Te | 1.07 ± 0.92 ( 14) | 0.80 ± 0.86 ( 15) | 0.93 ± 0.88 ( 15) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK FOR 4 WEEKS

Table 41

NEUROBEHAVIORAL

STATISTICAL DATA FOR MAIN TREATMENT EFFECT AND TREATMENT BY RECOVERY INTERACTION

| Study No. (Sex) | Two-factor MANOVA[a] (for all response parameters measured in one animal) | | Two-factor ANOVA[a] (for individual response parameters) | |
|---|---|---|---|---|
| | Mean Effect of Treatment[b] | Treatment by Recovery Interaction[c] | Main Effect of Treatment[b] | Treatment by Recovery Interaction[c] |
| 79S (M) | p <0.001 | | Activity-1st 10' (p <0.001)[d]<br>Activity-2nd 10' (p <0.001)[d]<br>Activity Total 20 (p <0.001)[d] | |
| 79SF (F) | | | | |

[a] The two factors are treatment and recovery

[b] Significant effect of treatment averaging over animals tested after the last exposure and those tested after the recovery period.

[c] Significant difference in effect of treatment betweeen animals tested after the last exposure and those tested after the recovery period.

[d] Activity for the first or second 10-min of the activity measurement session or for the total 20-min evaluation.

Table 42

SIGNIFICANT POST-HOC COMPARISONS FROM THE STATISTICAL EVALUATION OF NEUROBEHAVIORAL RESPONSE PARAMETERS TESTED IN STUDIES 79-S AND 79-SF

| Endpoint Assay[b] | Male Rats[a] | | | | | Female Rats[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Post Exposure | | | Post Recovery | | Post Exposure | | | Post Recovery | |
| | 0.75 | 1.0 | 1.2 | 1.0 | 1.2 | 0.40 | 0.75 | 1.0 | 0.75 | 1.0 |
| ACT.1st 10' | ↑ | ↑ | ↑ | ↑ | ↑ | | | | | |
| ACT.2nd 10' | ↑ | | ↑ | ↑ | | | | | | |
| ACT.total 20' | ↑ | ↑ | ↑ | ↑ | ↑ | | | | | |

Multivariate analysis not significant

[a] Significant ($p<0.05$) increase ( ) or decrease ( ) relative to control in male and female rats exposed to the specified RB/PR aerosol concentrations (mg/L) and tested immediately after the last exposure or after a 14-day recovery following the last exposure.

[b] Activity for the first or second 10-min of the activity measurement session or for the total 20 min evaluation.

NS Not significant

both bone marrow and RBC of rats that received 8 inhalation exposures to 1.0 mg/l of RP/BR aerosol for 2.25 hr over a 2-week period. However, no significant clastogenic response was found after 16 exposures over a 4-week period or after a 2-week recovery period following the 16 exposures (Tables 43 and 44 and Figures 2 and 3).

The results indicate that RP/BR aerosol is a weak clastogen for female Sprague-Dawley rats. However, the negative results found after 16 exposures and after the 2-week recovery period suggest that the rats recruit biochemical pathways to detoxify and clear the genotoxic fractions and that under the exposure regimen used, the adaptation is in effect after 16 exposures. The negative response after the recovery period also indicates that there is not a delayed response 2-weeks following the exposure. Since equivalent results were found using RBC or bone marrow cells, it suggests that female Sprague-Dawley rats may not remove MN from RBC as efficiently as other strains, and/or that the RP/BR exposure altered the biology of the spleen such that MN were not removed and/or that the dictum that rat spleens remove MN from RBC is not a generalized phenomena in rats. The low number of MN in the normocytes indicates that the artifact problem common with the rat bone marrow/Giemsa technique, was resolved with the Acridine Orange staining technique. Therefore, the conclusion is that the positive response found after 8 exposures is real and not artifactual.

## 5. SUMMARY CONCLUSIONS

Combinations of exposure concentrations, durations and frequencies were tested in four-week inhalation exposures followed by two weeks of recovery to define the most suitable conditions for this investigation and to select the most sensitive biologic response parameters for the subsequent subchronic studies. Response surface modeling was used for the experimental design and statistical analysis of the data. Results of preliminary testing suggested that exposure duration and frequency did not have major effects. Subsequently male and female Sprague-Dawley rats were exposed in separate studies to RP/BR aerosols ranging from 0.40 to 1.20 mg/l (0.40, 0.75 and 1.0 mg/l for females and 0.75, 1.0 and 1.2 mg/l for males) or to filtered air for 2.25 hr/day on four days/week for four weeks. Aerosol exposure monitoring data demonstrated well maintained target concentrations and excellent particle size stability.

During the exposure period, wheezing and labored breathing were observed in male rats exposed to the high dose. Decreased body weights, body weight gains and reduced food consumption seen in male rats only at all concentration levels during the exposures returned to normal after the recovery period. Although an overall

Table 43

EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON MICRONUCLEUS ANALYSIS OF BONE MARROW OF FEMALE SPRAGUE DAWLEY RATS TESTED AFTER EITHER 8 OR 16 EXPOSURES OR AFTER A 2-WEEK RECOVERY PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L | 1.0 mg/L |
|---|---|---|
| BM MN P 8X | 1.24 ± 0.96 ( 4) | 2.98 ± 0.82 ( 4)* |
| BM MN N 8X | 1.90 ± 0.92 ( 4) | 1.15 ± 1.37 ( 4) |
| BM MN P+N 8X | 3.15 ± 1.11 ( 4) | 4.14 ± 1.42 ( 4) |
| BM MN P 16X | 2.00 ± 1.87 ( 5) | 1.99 ± 1.22 ( 5) |
| BM MN N 16X | 1.10 ± 1.67 ( 5) | 0.39 ± 0.86 ( 5) |
| BM MN P+N 16X | 3.09 ± 2.51 ( 5) | 2.37 ± 1.50 ( 5) |
| BM MN P 2R | 2.20 ± 1.30 ( 5) | 1.98 ± 0.70 ( 5) |
| BM MN N 2R | 0.97 ± 0.89 ( 5) | 1.04 ± 1.09 ( 5) |
| BM MN P+N 2R | 3.17 ± 1.44 ( 5) | 3.02 ± 1.08 ( 5) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK

Table 44

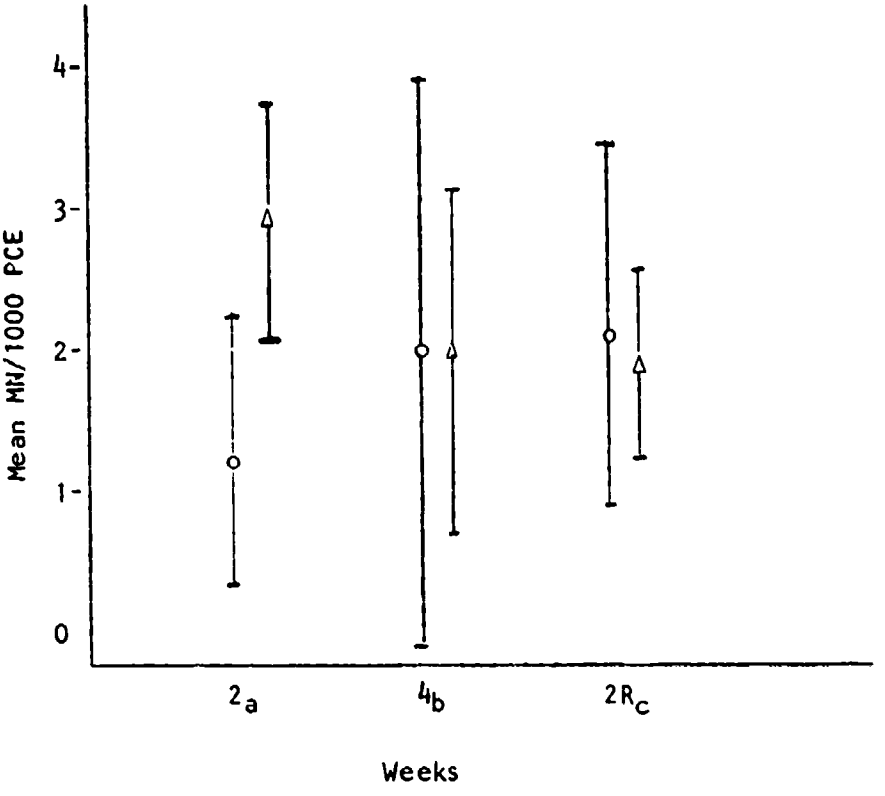
EFFECT OF MULTIPLE EXPOSURES[a] TO RP/BR AEROSOLS ON MICRONUCLEUS ANALYSIS OF RED BLOOD CELLS OF FEMALE SPRAGUE DAWLEY RATS TESTED AFTER EITHER 8 OR 16 EXPOSURES OR AFTER A 2-WEEK RECOVERY PERIOD
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L | 1.0 mg/L |
|---|---|---|
| RBC MN N 8X | 1.19 ± 1.08 ( 5) | 3.58 ± 1.13 ( 5)* |
| RBC MN N 16X | 2.40 ± 0.54 ( 5) | 2.60 ± 1.14 ( 5) |
| RBC MN N 2R | 1.40 ± 0.55 ( 5) | 2.40 ± 0.89 ( 5) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = 2.25 HR/DAY ON 4 CONSECUTIVE DAYS/WEEK

Figure 2

MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES OF FEMALE SPRAGUE-DAWLEY RATS FOLLOWING INHALATION EXPOSURE TO RP/BR AEROSOL




o negative control

Δ exposed animals

a 8 exposures of 1.0 mg/l RP/BR for 2.25 hr/exposure

b 16 exposures of 1.0 mg/l RP/BR for 2.25 hr/exposure

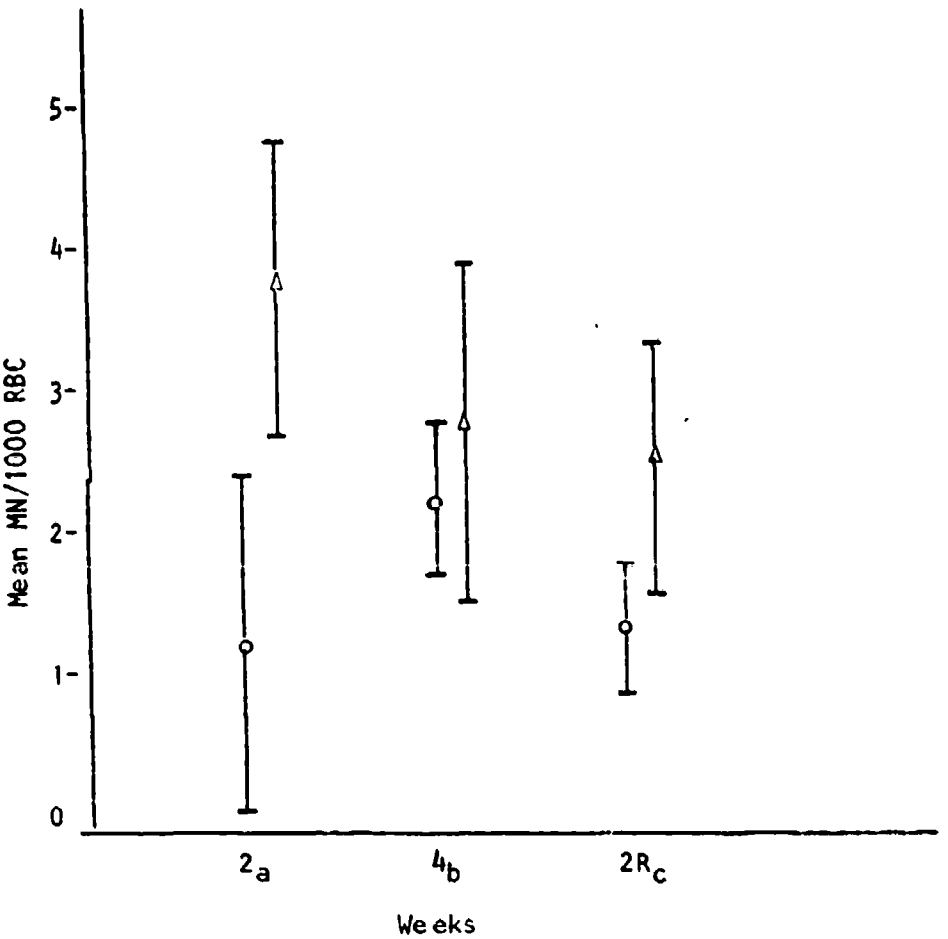
c 2 week recovery

MN Micronucleus

PCE Polychromatic erythrocyte

Figure 3

MICRONUCLEI IN RED BLOOD CELLS OF FEMALE SPRAGUE-DAWLEY RATS FOLLOWING INHALATION EXPOSURE TO RP/BR AEROSOL




o negative control

Δ exposed animals

a 8 exposures of 1.0 mg/l RP/BR for 2.25 hr/exposure

b 16 exposures of 1.0 mg/l RP/BR for 2.25 hr/exposure

c 2 week recovery

MN Micronucleus

RBC Red blood cells

mortality of 12.1% was observed in male rats exposed to the high dose (1.3 and 1.2 mg/l for two and 14 days, respectively), this was due to a 70-minute concentration overrun to 1.65 mg/l of RP/BR in one of the chambers on the first day of the exposures. The 5.2% value observed in a second chamber reflects the effect of the exposure more realistically. In female rats only a single death was observed during the entire study and this 0.8% mortality occurred in the medium (0.75 mg/l) dose.

Various biological endpoints were examined immediately after the last exposure, and for selected treatment groups after a 14-day recovery period. Although some statistically significant effects were found for clinical pathology, most of these were biologically non-significant due to their absolute value being within, or close to the published normal ranges. The most consistent changes were decreases for BUN and cholesterol levels in rats of both sexes and in triglicerides for female rats only, with the latter two parameters showing partial recovery. However, no treatment-related histopathological changes were found in any tissue outside the respiratory tract.

Examination of the pulmonary free cells collected by lung lavage (97-99% were alveolar macrophages) showed an increase or an increasing trend in total numbers, increased cellular ATP levels and decreased ectoenzyme activity for 5'nucleotidase after most of the RP/BR exposures of both sexes, suggesting increased energy levels as well as potential activation for the macrophages. Protein levels in the lavage fluid were elevated after the high doses. Pulmonary bactericidal activity to inhaled [35]S-*K.pneumoniae* was not affected by the exposures in either of the sexes. Histopathologically mild to moderate terminal broncheolar fibrosis was found in rats of both sexes exposed to the medium and high doses. Except for the fibrosis and the 5'nucleotidase activity most of these changes were reversible.

Of the neurobehavioral parameters examined only locomotor activity was significantly affected by treatment with RP/BR aerosols. Male rats showed increased motor activity at all concentrations and incomplete recovery after two weeks at some concentrations. In females there was a trend toward increased activity but no evidence of effects after the recovery period. None of the other behavioral endpoints were altered by the exposures.

In female rats only a micronucleus analysis was performed on bone marrow polychromatic erythrocytes and normachromatic erythrocytes and on circulating red blood cells. The assays were performed on animals exposed for two or four weeks and after a two-week recovery period following four weeks of exposures. The results showed a significant clastogenic response in both bone marrow and RBC of rats that were exposed for two weeks to the RP/BR aerosol. No effects were found after four weeks of exposures or after a

two-week recovery period following the four weeks of exposures suggesting that the rats recruit biochemical pathways to detoxify and clear the genotoxic fractions and an adaptation is in effect.

# APPENDIX A
# TABLES FOR STUDY NUMBER 79

Table A-1

EFFECT OF TWO CONSECUTIVE DAILY 4-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 77.51 ± 7.16 ( 8) | 81.94 ± 2.22 ( 4) | 50.50 ± 9.93 ( 4)* | 50.43 ± 17.36 ( 4)* |
| TOT CELLS | 15.99 ± 5.60 ( 4) | 12.05 ± 2.27 ( 4) | 6.62 ± 0.34 ( 4)* | 10.45 ± 3.71 ( 4) |
| TOTCELL/g BW | 53.60 ± 15.71 ( 4) | 41.19 ± 6.46 ( 4) | 23.31 ± 2.23 ( 4)* | 40.20 ± 17.62 ( 4) |
| %MACROPHAGES | 98 ± 1 ( 4) | 99 ± 1 ( 4) | 98 ± 3 ( 4) | 100 ± 1 ( 4) |
| PROT/10⁶CELL | 21.66 ± 0.54 ( 4) | 21.86 ± 3.68 ( 4) | 22.11 ± 3.22 ( 4) | 21.45 ± 0.79 ( 4) |
| ATP/10⁶ CELL | 0.66 ± 0.19 ( 4) | 0.66 ± 0.17 ( 4) | 0.63 ± 0.14 ( 4) | 0.78 ± 0.04 ( 4) |
| ATP/ug PROT | 3.03 ± 0.85 ( 4) | 3.04 ± 0.83 ( 4) | 2.94 ± 1.05 ( 4) | 3.63 ± 0.12 ( 4) |
| LAVPROT/g BW | 14.07 ± 3.28 ( 4) | 12.74 ± 1.60 ( 4) | 11.10 ± 2.41 ( 4) | 14.19 ± 1.43 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-2

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 77.51 ± 7.16 ( 8) | 74.91 ± 10.22 ( 4) | 60.25 ± 19.02 ( 4) | 51.54 ± 11.97 ( 4)* |
| TOT CELLS | 15.99 ± 5.60 ( 4) | 12.38 ± 2.59 ( 4) | 13.01 ± 3.71 ( 4) | 13.97 ± 3.18 ( 4) |
| TOTCELL/g BW | 50.60 ± 15.71 ( 4) | 42.30 ± 10.96 ( 4) | 51.21 ± 16.52 ( 4) | 52.70 ± 11.94 ( 4) |
| %MACROPHAGES | 98 ± 1 ( 4) | 99 ± 2 ( 4) | 96 ± 1 ( 4)* | 100 ± 1 ( 4) |
| PROT/10⁶CELL | 21.66 ± 0.54 ( 4) | 18.34 ± 6.40 ( 4) | 22.23 ± 3.48 ( 4) | 21.78 ± 2.47 ( 4) |
| ATP/10⁶ CELL | 0.66 ± 0.19 ( 4) | 0.67 ± 0.24 ( 4) | 0.88 ± 0.13 ( 4) | 0.66 ± 0.08 ( 4) |
| ATP/ug PROT | 3.03 ± 0.85 ( 4) | 3.68 ± 0.35 ( 4) | 3.95 ± 0.07 ( 4)* | 3.05 ± 0.20 ( 4) |
| LAVPROT/g BW | 14.07 ± 3.28 ( 4) | 12.88 ± 0.83 ( 3) | 16.14 ± 3.55 ( 4) | 21.51 ± 7.68 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-3

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE-DAWLEY RATS[a] TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 80.46 ± 5.03 ( 8) | 81.52 ± 6.61 ( 4) | 68.64 ± 9.62 ( 4) | 65.69 ± 10.15 ( 4)* |
| TOT CELLS | 14.73 ± 7.34 ( 4) | 12.27 ± 1.40 ( 4) | 8.95 ± 1.96 ( 4) | 10.38 ± 1.86 ( 4) |
| TOTCELL/g BW | 48.02 ± 23.54 ( 4) | 41.90 ± 2.64 ( 4) | 32.03 ± 7.96 ( 4) | 36.25 ± 5.07 ( 4) |
| %MACROPHAGES | 95 ± 6 ( 4) | 98 ± 1 ( 4) | 97 ± 2 ( 4) | 100 ± 1 ( 4) |
| PROT/$10^6$CELL | 21.71 ± 7.80 ( 4) | 21.34 ± 1.67 ( 4) | 20.91 ± 1.15 ( 4) | 22.05 ± 3.46 ( 4) |
| ATP/$10^6$ CELL | 0.71 ± 0.25 ( 4) | 0.42 ± 0.09 ( 4) | 0.39 ± 0.08 ( 4)* | 0.54 ± 0.17 ( 4) |
| ATP/ug PROT | 3.29 ± 0.18 ( 4) | 1.94 ± 0.37 ( 4)* | 1.88 ± 0.32 ( 4)* | 2.49 ± 0.68 ( 4) |
| LAVPROT/g BW | 15.98 ± 9.12 ( 4) | 10.56 ± 1.38 ( 4) | 10.99 ± 1.37 ( 4) | 15.78 ± 4.47 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-4

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 80.46 ± 5.03 ( 8) | 77.20 ± 10.95 ( 4) | 88.38 ± 4.46 ( 4) | 85.86 ± 6.54 ( 4) |
| TOT CELLS | 14.73 ± 7.34 ( 4) | 14.11 ± 2.48 ( 4) | 18.28 ± 1.34 ( 4) | 16.33 ± 3.72 ( 4) |
| TOTCELL/g BW | 48.02 ± 23.54 ( 4) | 48.38 ± 10.46 ( 4) | 65.81 ± 4.45 ( 4) | 61.44 ± 11.53 ( 4) |
| %MACROPHAGES | 95 ± 6 ( 4) | 97 ± 1 ( 4) | 98 ± 1 ( 4) | 99 ± 1 ( 4) |
| PROT/$10^6$CELL | 21.71 ± 7.80 ( 4) | 21.24 ± 1.95 ( 4) | 19.51 ± 1.55 ( 4) | 22.67 ± 4.76 ( 4) |
| ATP/$10^6$ CELL | 0.71 ± 0.25 ( 4) | 0.64 ± 0.04 ( 4) | 0.90 ± 0.07 ( 4) | 0.78 ± 0.12 ( 4) |
| ATP/ug PROT | 3.29 ± 0.18 ( 4) | 3.04 ± 0.14 ( 4) | 4.63 ± 0.11 ( 4)* | 3.52 ± 0.55 ( 4) |
| LAVPROT/g BW | 15.98 ± 9.12 ( 4) | 11.34 ± 0.58 ( 4) | 19.55 ± 2.32 ( 4) | 16.63 ± 5.27 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-5

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 89.93 ± 4.89 ( 8) | 93.18 ± 4.75 ( 4) | 87.87 ± 3.76 ( 4) | 80.82 ± 3.41 ( 4)* |
| TOT CELLS | 16.35 ± 6.88 ( 4) | [illegible]13 ± 1.25 ( 4) | 9.42 ± 2.00 ( 4) | 10.02 ± 4.93 ( 4) |
| TOTCELL/g BW | 55.47 ± 21.89 ( 4 | [illegible] 5.75 ( 4) | 33.36 ± 8.05 ( 4) | 33.68 ± 16.44 ( 4) |
| %MACROPHAGES | 98 ± 2 ( 4 | 9[illegible] ± 1 ( 4) | 96 ± 2 ( 4) | 98 ± 2 ( 4) |
| PROT/10³CELL | 18.67 ± 2.97 ( 4) | [illegible]77 ± [illegible] 4) | 20.62 ± 3.16 ( 4) | 19.40 ± 6.71 ( 4) |
| ATP/10³ CELL | 0.97 ± 0.16 ( 4) | 0.[illegible] ± 0.[illegible] | 0.70 ± 0.15 ( 4) | 0.66 ± 0.17 ( 4) |
| [illegible] PROT | 5.18 ± 0.40 ( 4) | 3.49 ± 0.67 ( 4)* | 3.37 ± 0.45 ( 4)* | 3.52 ± 0.62 ( 4)* |
| LA[illegible] /g BW | 11.85 ± 4.88 ( 4) | 9.89 ± 1.63 ( 4) | 9.98 ± 1.12 ( 4) | 11.22 ± 1.08 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-6

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D2) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| % BC | 89.93 ± 4.89 ( 8) | 86.59 ± 2.58 ( 4) | 69.20 ± 9.13 ( 4)* | 65.11 ± 15.87 ( 4)* |
| TOT CELLS | 16.35 ± 6.88 ( 4) | 13.07 ± 3.57 ( 4) | 11.79 ± 1.19 ( 4) | 12.64 ± 2.54 ( 4) |
| TOTCELL/g BW | 55.47 ± 21.99 ( 4) | 44.01 ± 12.76 ( 4) | 40.09 ± 4.16 ( 4) | 43.00 ± 10.21 ( 4) |
| %MACROPHAGES | 98 ± 2 ( 4) | 97 ± 2 ( 4) | 99 ± 2 ( 4) | 98 ± 1 ( 4) |
| PROT/$10^6$CELL | 18.67 ± 2.97 ( 4) | 19.59 ± 3.39 ( 4) | 22.63 ± 3.22 ( 4) | 20.42 ± 3.90 ( 4) |
| ATP/$10^6$ CELL | 0.97 ± 0.16 ( 4) | 0.71 ± 0.22 ( 4) | 1.03 ± 0.11 ( 4) | 0.92 ± 0.20 ( 4) |
| ATP/ug PROT | 5.18 ± 0.40 ( 4) | 3.70 ± 1.35 ( 4)* | 4.57 ± 0.46 ( 4) | 4.48 ± 0.42 ( 4) |
| LAVPROT/g BW | 11.65 ± 4.88 ( 4) | 10.75 ± 1.18 ( 4) | 11.90 ± 1.11 ( 4) | 11.31 ± 1.97 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-7

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| ASSAY | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| % BC | 81.85 ± 7.83 ( 4) | 80.75 ± 3.16 ( 4) | 87.13 ± 5.37 ( 4) |
| TOT CELLS | 18.59 ± 14.26 ( 4) | 10.02 ± 1.92 ( 4) | 20.64 ± 2.32 ( 4) |
| TOTCELL/g BW | 53.43 ± 43.70.( 4) | 29.74 ± 6.27 ( 4) | 67.56 ± 8.44 ( 4) |
| %MACROPHAGES | 96 ± 4 ( 4) | 100 ± 1 ( 4) | 100 ± 1 ( 4) |
| PROT/10⁶CELL | 18.11 ± 3.77 ( 4) | 15.30 ± 1.93 ( 4) | 17.85 ± 2.30 ( 4) |
| ATP/10⁶ CELL | 0.61 ± 0.15 ( 4) | 0.61 ± 0.20 ( 4) | 0.92 ± 0.09 ( 4)* |
| ATP/ug PROT | 3.51 ± 1.20 ( 4) | 3.99 ± 1.13 ( 4) | 5.28 ± 1.19 ( 4) |
| LAVPROT/g BW | 19.38 ± 11.32 ( 4) | 13.06 ± 2.65 ( 4) | 15.59 ± 2.09 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-8

EFFECT OF TWO CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 85.25 ± 12.69 ( 4) | 100.00 ± 20.64 ( 4) | 80.75 ± 8.54 ( 4) | 90.50 ± 14.25 ( 4) |
| Act-2nd 10' | 15.25 ± 3.86 ( 4) | 40.50 ± 9.68 ( 4)* | 31.75 ± 4.79 ( 4)* | 36.00 ± 12.94 ( 4)* |
| Act-Tot 20' | 100.50 ± 13.70 ( 4) | 140.50 ± 27.50 ( 4)* | 112.50 ± 11.90 ( 4) | 126.50 ± 20.34 ( 4) |
| F1 Grip | 1018.8 ± 272.7 ( 4) | 897.8 ± 194.5 ( 4) | 1079.3 ± 159.0 ( 4) | 975.0 ± 251.2 ( 4) |
| H1 Grip | 514.00 ± 86.59 ( 4) | 473.25 ± 78.71 ( 4) | 480.00 ± 99.12 ( 4) | 448.25 ± 74.96 ( 4) |
| TrTr 1-Time | 7.00 ± 3.46 ( 4) | 6.00 ± 4.69 ( 4) | 6.33 ± 4.73 ( 3) | 5.00 ± 4.16 ( 4) |
| TrTr 2-Time | 4.25 ± 4.35 ( 4) | 3.50 ± 4.51 ( 4) | 6.00 ± 3.16 ( 4) | 6.00 ± 4.69 ( 4) |
| TrTr 3-Time | 4.75 ± 3.30 ( 4) | 5.25 ± 2.50 ( 4) | 6.50 ± 2.65 ( 4) | 5.25 ± 4.43 ( 4) |
| TrTr 4-Time | 3.00 ± 4.69 ( 4) | 3.25 ± 4.57 ( 4) | 4.25 ± 4.03 ( 4) | 2.25 ± 2.63 ( 4) |
| No. ESC-Tr | 3.25 ± 0.50 ( 4) | 3.00 ± 1.15 ( 4) | 2.75 ± 1.89 ( 4) | 3.00 ± 0.00 ( 4) |
| TeTr 1-Time | 15.50 ± 5.26 ( 4) | 13.50 ± 8.54 ( 4) | 8.50 ± 5.07 ( 4) | 10.75 ± 0.96 ( 4) |
| TeTr 2-Time | 9.00 ± 8.21 ( 4) | 8.00 ± 4.55 ( 4) | 8.25 ± 6.65 ( 4) | 6.50 ± 4.80 ( 4) |
| No. ESC-Te | 1.25 ± 0.96 ( 4) | 1.50 ± 0.58 ( 4) | 2.00 ± 0.00 ( 4) | 2.00 ± 0.00 ( 4) |
| No. AVD-Te | 0.50 ± 0.58 ( 4) | 0.75 ± 0.96 ( 4) | 0.75 ± 0.96 ( 4) | 0.50 ± 0.58 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-9

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 85.25 ± 12.69 ( 4) | 96.25 ± 19.14 ( 4) | 92.00 ± 17.76 ( 4) | 91.00 ± 24.75 ( 4) |
| Act-2nd 10' | 15.25 ± 3.86 ( 4) | 30.25 ± 6.24 ( 4) | 29.75 ± 8.62 ( 4) | 35.50 ± 14.62 ( 4)* |
| Act-Tot 20' | 100.50 ± 13.70 ( 4) | 126.50 ± 18.70 ( 4) | 121.75 ± 24.10 ( 4) | 126.50 ± 35.76 ( 4) |
| F1 Grip | 1018.8 ± 272.7 ( 4) | 795.8 ± 143.9 ( 4) | 900.0 ± 193.2 ( 4) | 1077.3 ± 101.1 ( 4) |
| H1 Grip | 514.00 ± 86.59 ( 4) | 436.00 ± 95.45 ( 4) | 493.50 ± 53.13 ( 4) | 474.00 ± 72.10 ( 4) |
| TrTr 1-Time | 7.00 ± 3.46 ( 4) | 6.00 ± 4.90 ( 4) | 6.50 ± 4.12 ( 4) | 6.50 ± 3.87 ( 4) |
| TrTr 2-Time | 4.25 ± 4.35 ( 4) | 6.50 ± 4.43 ( 4) | 7.25 ± 4.86 ( 4) | 5.25 ± 4.11 ( 4) |
| TrTr 3-Time | 4.75 ± 3.30 ( 4) | 6.75 ± 4.03 ( 4) | 5.00 ± 3.56 ( 4) | 3.50 ± 3.51 ( 4) |
| TrTr 4-Time | 3.00 ± 4.69 ( 4) | 6.25 ± 4.50 ( 4) | 5.00 ± 5.77 ( 4) | 3.50 ± 4.43 ( 4) |
| No. ESC-Tr | 3.25 ± 0.50 ( 4) | 2.50 ± 1.91 ( 4) | 2.75 ± 0.50 ( 4) | 3.25 ± 0.96 ( 4) |
| TeTr 1-Time | 15.50 ± 5.26 ( 4) | 11.00 ± 6.38 ( 4) | 10.75 ± 0.96 ( 4) | 11.25 ± 2.06 ( 4) |
| TeTr 2-Time | 9.00 ± 8.21 ( 4) | 9.00 ± 10.03 ( 4) | 12.75 ± 4.86 ( 4) | 8.00 ± 4.32 ( 4) |
| No. ESC-Te | 1.25 ± 0.96 ( 4) | 1.50 ± 1.00 ( 4) | 1.75 ± 0.50 ( 4) | 2.00 ± 0.00 ( 4) |
| No. AVD-Te | 0.50 ± 0.58 ( 4) | 1.00 ± 0.82 ( 4) | 0.00 ± 0.00 ( 4) | 0.75 ± 0.96 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-10

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 95.50 ± 24.57 ( 4) | 101.50 ± 18.28 ( 4) | 80.50 ± 14.20 ( 4) | 114.50 ± 14.84 ( 4) |
| Act-2nd 10' | 25.50 ± 17.56 ( 4) | 40.00 ± 19.03 ( 4) | 28.25 ± 8.77 ( 4) | 59.00 ± 17.36 ( 4)* |
| Act-Tot 20' | 121.00 ± 27.31 ( 4) | 141.50 ± 27.26 ( 4) | 108.75 ± 21.75 ( 4) | 173.50 ± 28.41 ( 4)* |
| F1 Grip | 1025.0 ± 275.1 ( 4) | 1035.5 ± 168.4 ( 4) | 1023.0 ± 271.7 ( 4) | 868.8 ± 87.6 ( 4) |
| H1 Grip | 434.00 ±121.26 ( 4) | 422.50 ± 92.87 ( 4) | 420.75 ± 40.19 ( 4) | 413.25 ± 89.41 ( 4) |
| TrTr 1-Time | 5.00 ± 2.16 ( 4) | 3.50 ± 3.51 ( 4) | 6.00 ± 2.94 ( 4) | 3.00 ± 1.41 ( 4) |
| TrTr 2-Time | 3.25 ± 3.40 ( 4) | 3.50 ± 1.73 ( 4) | 10.00 ± 0.00 ( 4)* | 6.25 ± 3.30 ( 4) |
| TrTr 3-Time | 3.75 ± 2.87 ( 4) | 4.00 ± 4.36 ( 3) | 6.00 ± 2.71 ( 4) | 8.75 ± 2.50 ( 4) |
| TrTr 4-Time | 2.75 ± 3.10 ( 4) | 5.50 ± 5.26 ( 4) | 7.25 ± 2.75 ( 4) | 7.25 ± 4.86 ( 4) |
| No. ESC-Tr | 4.00 ± 0.00 ( 4) | 3.25 ± 0.50 ( 4) | 2.25 ± 0.50 ( 4)* | 2.75 ± 0.96 ( 4)* |
| TeTr 1-Time | 8.00 ± 7.02 ( 4) | 7.50 ± 4.04 ( 4) | 15.50 ± 5.20 ( 4) | 15.50 ± 1.73 ( 4) |
| TeTr 2-Time | 8.50 ± 5.57 ( 4) | 12.00 ± 6.16 ( 4) | 11.50 ± 7.05 ( 4) | 11.75 ± 6.24 ( 4) |
| No. ESC-Te | 2.00 ± 0.00 ( 4) | 1.75 ± 0.50 ( 4) | 1.25 ± 0.50 ( 4) | 1.75 ± 0.50 ( 4) |
| No. AVD-Te | 1.00 ± 0.00 ( 4) | 0.75 ± 0.50 ( 4) | 0.25 ± 0.50 ( 4) | 0.25 ± 0.50 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

# Table A-11

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 95.50 ± 24.57 ( 4) | 101.50 ± 16.09 ( 4) | 103.50 ± 16.82 ( 4) | 88.25 ± 12.71 ( 4) |
| Act-2nd 10' | 25.50 ± 17.56 ( 4) | 36.75 ± 10.63 ( 4) | 25.50 ± 6.03 ( 4) | 41.50 ± 4.65 ( 4) |
| Act-Tot 20' | 121.00 ± 27.31 ( 4) | 138.25 ± 25.05 ( 4) | 129.00 ± 19.66 ( 4) | 129.75 ± 17.21 ( 4) |
| Fl Grip | 1025.0 ± 275.1 ( 4) | 1033.5 ± 159.4 ( 4) | 968.8 ± 254.9 ( 4) | 933.5 ± 77.9 ( 4) |
| Hl Grip | 434.00 ±121.26 ( 4) | 524.00 ± 73.69 ( 4) | 496.50 ± 20.87 ( 4) | 405.25 ± 72.43 ( 4) |
| TrTr 1-Time | 5.00 ± 2.16 ( 4) | 2.25 ± 2.06 ( 4) | 2.50 ± 1.00 ( 4) | 2.75 ± 2.87 ( 4) |
| TrTr 2-Time | 3.25 ± 3.40 ( 4) | 7.00 ± 4.24 ( 4) | 7.75 ± 2.22 ( 4) | 1.50 ± 1.73 ( 4) |
| TrTr 3-Time | 3.75 ± 2.87 ( 4) | 6.67 ± 5.77 ( 3) | 7.25 ± 4.86 ( 4) | 9.50 ± 1.00 ( 4) |
| TrTr 4-Time | 2.75 ± 3.10 ( 4) | 7.25 ± 3.20 ( 4) | 6.50 ± 2.65 ( 4) | 2.00 ± 2.16 ( 4) |
| No. ESC-Tr | 4.00 ± 0.00 ( 4) | 2.25 ± 1.50 ( 4) | 3.00 ± 1.41 ( 4) | 3.50 ± 0.58 ( 4) |
| TeTr 1-Time | 8.00 ± 7.02 ( 4) | 16.00 ± 4.24 ( 4) | 16.25 ± 4.79 ( 4) | 11.75 ± 3.59 ( 4) |
| TeTr 2-Time | 8.50 ± 5.57 ( 4) | 13.50 ± 4.36 ( 4) | 13.75 ± 4.27 ( 4) | 11.25 ± 8.06 ( 4) |
| No. ESC-Te | 2.00 ± 0.00 ( 4) | 1.50 ± 0.58 ( 4) | 1.25 ± 0.96 ( 4) | 1.75 ± 0.50 ( 4) |
| No. AVD-Te | 1.00 ± 0.00 ( 4) | 0.00 ± 0.00 ( 4) | 0.25 ± 0.50 ( 4) | 0.75 ± 0.96 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-12

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 80.50 ± 16.82 ( 4) | 114.25 ± 20.71 ( 4)* | 75.75 ± 15.90 ( 4) | 85.25 ± 12.39 ( 4) |
| Act-2nd 10' | 31.50 ± 12.71 ( 4) | 63.00 ± 13.27 ( 4)* | 45.25 ± 10.34 ( 4) | 44.50 ± 6.86 ( 4) |
| Act-Tot 20' | 112.00 ± 25.23 ( 4) | 177.25 ± 25.47 ( 4)* | 121.00 ± 24.12 ( 4) | 129.75 ± 15.82 ( 4) |
| Fl Grip | 937.8 ± 224.3 ( 4) | 923.0 ± 109.7 ( 4) | 881.3 ± 119.7 ( 4) | 956.0 ± 89.1 ( 4) |
| Hl Grip | 421.75 ±121.92 ( 4) | 377.25 ± 82.33 ( 4) | 517.50 ± 82.61 ( 4) | 519.25 ± 55.21 ( 4) |
| TrTr 1-Time | 1.67 ± 0.58 ( 3) | 7.00 ± 3.83 ( 4) | 2.75 ± 2.36 ( 4) | 5.50 ± 4.12 ( 4) |
| TrTr 2-Time | 1.75 ± 1.71 ( 4) | 9.00 ± 2.00 ( 4)* | 5.00 ± 4.76 ( 4) | 4.25 ± 1.89 ( 4) |
| TrTr 3-Time | 2.50 ± 2.52 ( 4) | 4.00 ± 4.24 ( 4) | 3.50 ± 2.38 ( 4) | 4.00 ± 4.55 ( 4) |
| TrTr 4-Time | 1.00 ± 0.00 ( 3) | 6.00 ± 3.74 ( 4) | 1.67 ± 0.58 ( 3) | 5.50 ± 5.26 ( 4) |
| No. ESC-Tr | 3.50 ± 0.58 ( 4) | 2.25 ± 1.50 ( 4) | 3.50 ± 0.58 ( 4) | 3.00 ± 0.00 ( 4) |
| TeTr 1-Time | 10.50 ± 1.00 ( 4) | 9.50 ± 8.19 ( 4) | 12.75 ± 4.99 ( 4) | 8.50 ± 4.43 ( 4) |
| TeTr 2-Time | 9.75 ± 4.19 ( 4) | 13.00 ± 5.48 ( 4) | 6.75 ± 5.56 ( 4) | 6.50 ± 3.70 ( 4) |
| No. ESC-Te | 2.00 ± 0.00 ( 4) | 1.75 ± 0.50 ( 4) | 1.75 ± 0.50 ( 4) | 2.00 ± 0.00 ( 4) |
| No. AVD-Te | 0.50 ± 0.58 ( 4) | 0.75 ± 0.96 ( 4) | 0.75 ± 0.50 ( 4) | 1.25 ± 0.96 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

# Table A-13

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D2) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a] [MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| Act-1st 10' | 80.50 ± 16.82 ( 4) | 82.75 ± 17.33 ( 4) | 105.75 ± 10.18 ( 4) | 80.25 ± 30.19 ( 4) |
| Act-2nd 10' | 31.50 ± 12.71 ( 4) | 35.00 ± 4.69 ( 4) | 36.50 ± 7.85 ( 4) | 29.25 ± 22.47 ( 4) |
| Act-Tot 20' | 112.00 ± 25.23 ( 4) | 117.75 ± 18.15 ( 4) | 142.25 ± 11.79 ( 4) | 109.50 ± 46.25 ( 4) |
| Fl Grip | 937.8 ± 224.3 ( 4) | 973.0 ± 238.3 ( 4) | 950.0 ± 70.7 ( 4) | 966.5 ± 107.3 ( 4) |
| Hl Grip | 421.75 ±121.92 ( 4) | 400.75 ±111.75 ( 4) | 463.25 ± 79.93 ( 4) | 386.75 ±153.45 ( 4) |
| TrTr 1-Time | 1.67 ± 0.58 ( 3) | 4.00 ± 4.08 ( 4) | 5.25 ± 3.77 ( 4) | 1.50 ± 1.91 ( 4) |
| TrTr 2-Time | 1.75 ± 1.71 ( 4) | 6.00 ± 4.55 ( 4) | 4.25 ± 3.95 ( 4) | 4.50 ± 3.87 ( 4) |
| TrTr 3-Time | 2.50 ± 2.52 ( 4) | 4.75 ± 5.50 ( 4) | 4.50 ± 3.00 ( 4) | 5.00 ± 3.46 ( 4) |
| TrTr 4-Time | 1.00 ± 0.00 ( 3) | 4.50 ± 3.79 ( 4) | 2.50 ± 2.52 ( 4) | 2.25 ± 3.20 ( 4) |
| No. ESC-Tr | 3.50 ± 0.58 ( 4) | 3.25 ± 0.96 ( 4) | 3.75 ± 0.50 ( 4) | 3.50 ± 1.00 ( 4) |
| TeTr 1-Time | 10.50 ± 1.00 ( 4) | 5.33 ± 6.66 ( 3) | 6.50 ± 4.12 ( 4) | 8.75 ± 8.30 ( 4) |
| TeTr 2-Time | 9.75 ± 4.19 ( 4) | 7.75 ± 2.75 ( 4) | 4.50 ± 4.12 ( 4) | 8.50 ± 8.19 ( 4) |
| No. ESC-Te | 2.00 ± 0.00 ( 4) | 1.75 ± 0.50 ( 4) | 2.00 ± 0.00 ( 4) | 1.50 ± 0.58 ( 4) |
| No. AVD-Te | 0.50 ± 0.58 ( 4) | 1.25 ± 0.50 ( 4) | 1.50 ± 0.58 ( 4) | 1.25 ± 0.96 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-14

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON NEUROBEHAVIORAL ACTIVITY OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| BEHAVIORAL MEASURES | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| Act-1st 10' | 88.75 ± 30.35 ( 4) | 112.25 ± 23.61 ( 4) | 85.75 ± 16.94 ( 4) |
| Act-2nd 10' | 32 75 ± 20.84 ( 4) | 55.25 ± 27.11 ( 4) | 37.50 ± 13.96 ( 4) |
| Act-Tot 20' | 121.50 ± 50.38 ( 4) | 167.50 ± 49.83 ( 4) | 123.25 ± 25.45 ( 4) |
| F1 Grip | 1389.5 ± 162.2 ( 4) | 1320.8 ± 135.1 ( 4) | 1097.8 ± 96.1 ( 4)* |
| H1 Grip | 624.25 ±126.59 ( 4) | 596.25 ± 62.84 ( 4) | 664.25 ±152.46 ( 4) |
| TrTr 1-Time | 5.25 ± 4.03 ( 4) | 7.00 ± 4.24 ( 4) | 5.75 ± 4.92 ( 4) |
| TrTr 2-Time | 4.75 ± 2.87 ( 4) | 7.00 ± 3.83 ( 4) | 6.25 ± 4.79 ( 4) |
| TrTr 3-Time | 6.00 ± 4.08 ( 4) | 7.00 ± 2.58 ( 4) | 2.50 ± 1.73 ( 4) |
| TrTr 4-Time | 6.00 ± 4.90 ( 4) | 6.75 ± 3.95 ( 4) | 7.00 ± 3.83 ( 4) |
| No. ESC-Tr | 3.00 ± 1.41 ( 4) | 2.25 ± 1.50 ( 4) | 2.75 ± 0.96 ( 4) |
| TeTr 1-Time | 8.00 ± 4.00 ( 4) | 9.50 ± 2.65 ( 4) | 13.25 ± 6.65 ( 4) |
| TeTr 2-Time | 13.25 ± 8.42 ( 4) | 6.75 ± 5.19 ( 4) | 14.75 ± 4.27 ( 4) |
| No. ESC-Te | 1.75 ± 0.50 ( 4) | 2.00 ± 0.00 ( 4) | 1.50 ± 0.58 ( 4) |
| No. AVD-Te | 0.50 ± 1.00 ( 4) | 1.25 ± 0.50 ( 4) | 0.25 ± 0.50 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-15

EFFECT OF TWO CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
(MEAN AND STANDARD DEVIATION (n))

| CLIN CHEM VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 257 ± 72 ( 4) | 232 ± 17 ( 4) | 222 ± 22 ( 2) | 253 ± 17 ( 4) |
| BUN mg/dl | 20 ± 2 ( 4) | 19 ± 2 ( 4) | 17 ± 2 ( 2) | 20 ± 2 ( 4) |
| ALT IU/l | 55 ± 10 ( 4) | 68 ± 16 ( 4) | 91 ± 49 ( 2) | 59 ± 5 ( 4) |
| TRIG mg/dl | 73.0 ± 12.4 ( 4) | 60.0 ± 20.7 ( 4) | 66.0 ± 0.0 ( 2) | 67.0 ± 20.9 ( 4) |
| T PRO g/dl | 5.4 ± 0.1 ( 4) | 5.3 ± 0.1 ( 4) | 5.2 ± 0.3 ( 2) | 5.1 ± 0.1 ( 4) |
| ALB g/dl | 3.5 ± 0.1 ( 4) | 3.7 ± 0.1 ( 4) | 3.6 ± 0.2 ( 2) | 3.6 ± 0.1 ( 4) |
| CHOL mg/dl | 90 ± 14 ( 4) | 79 ± 4 ( 4) | 68 ± 9 ( 2)* | 79 ± 8 ( 4) |
| D BIL mg/dl | 0.04 ± 0.01 ( 4) | 0.04 ± 0.01 ( 4) | 0.06 ± 0.01 ( 2)* | 0.06 ± 0.01 ( 4)* |
| T BIL mg/dl | 0.12 ± 0.01 ( 4) | 0.14 ± 0.01 ( 4) | 0.20 ± 0.01 ( 2)* | 0.18 ± 0.01 ( 4)* |
| AL PHOS IU/l | 208 ± 13 ( 4) | 243 ± 34 ( 4) | 240 ± 108 ( 2) | 217 ± 14 ( 4) |
| Ca mg/dl | 10.2 ± 0.4 ( 4) | 9.7 ± 0.4 ( 4) | 10.0 ± 1.1 ( 2) | 9.7 ± 0.1 ( 4) |
| P mg/dl | 9.0 ± 0.7 ( 4) | 8.5 ± 0.6 ( 4) | 8.7 ± 0.5 ( 2) | 8.9 ± 0.5 ( 4) |
| Na mMol/l | 144 ± 1 ( 4) | 143 ± 2 ( 4) | 143 ± 3 ( 2) | 143 ± 1 ( 4) |
| K mMol/l | 4.9 ± 1.0 ( 4) | 4.6 ± 0.7 ( 4) | 4.8 ± 0.5 ( 2) | 4.9 ± 0.4 ( 4) |
| Cl Meq/l | 100 ± 3 ( 4) | 100 ± 2 ( 4) | 102 ± 2 ( 2) | 101 ± 2 ( 4) |
| CPK IU/l | 315 ± 125 ( 4) | 430 ± 93 ( 4) | 273 ± 54 ( 2) | 510 ± 198 ( 4) |
| GLOB g/dl | 1.9 ± 0.1 ( 4) | 1.6 ± 0.1 ( 4)* | 1.5 ± 0.1 ( 2)* | 1.5 ± 0.1 ( 4)* |
| ALB/GLOB | 1.9 ± 0.1 ( 4) | 2.2 ± 0.1 ( 4)* | 2.3 ± 0.1 ( 2)* | 2.3 ± 0.2 ( 4)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-16

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
(MEAN AND STANDARD DEVIATION (n))

| CLIN CHEM VALUES | 0.0 mg/L[b] | | | 0.4 mg/L | | | 0.75 mg/L | | | 1.0 mg/L | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GLU mg/dl | 257 ± | 72 | ( 4) | 249 ± | 17 | ( 4) | 263 ± | 25 | ( 4) | 270 ± | 29 | ( 4) |
| BUN mg/dl | 20 ± | 2 | ( 4) | 16 ± | 1 | ( 4)* | 16 ± | 1 | ( 4)* | 13 ± | 1 | ( 4)* |
| ALT IU/l | 55 ± | 10 | ( 4) | 59 ± | 16 | ( 4) | 54 ± | 8 | ( 4) | 58 ± | 15 | ( 4) |
| TRIG mg/dl | 73.0 ± | 12.4 | ( 4) | 69.8 ± | 19.7 | ( 4) | 67.8 ± | 9.4 | ( 4) | 56.8 ± | 8.5 | ( 4) |
| T PRO g/dl | 5.4 ± | 0.1 | ( 4) | 5.4 ± | 0.2 | ( 4) | 5.5 ± | 0.1 | ( 4) | 5.5 ± | 0.3 | ( 4) |
| ALB g/dl | 3.5 ± | 0.1 | ( 4) | 3.7 ± | 0.1 | ( 4) | 3.6 ± | 0.1 | ( 4) | 3.7 ± | 0.1 | ( 4) |
| CHOL mg/dl | 90 ± | 14 | ( 4) | 61 ± | 20 | ( 4)* | 77 ± | 6 | ( 4) | 84 ± | 9 | ( 4) |
| D BIL mg/dl | 0.04 ± | 0.01 | ( 4) | 0.06 ± | 0.02 | ( 4) | 0.04 ± | 0.01 | ( 4) | 0.04 ± | 0.01 | ( 4) |
| T BIL mg/dl | 0.12 ± | 0.01 | ( 4) | 0.18 ± | 0.04 | ( 4)* | 0.14 ± | 0.01 | ( 4) | 0.14 ± | 0.03 | ( 4) |
| AL PHOS IU/l | 208 ± | 13 | ( 4) | 178 ± | 32 | ( 4) | 175 ± | 8 | ( 4) | 186 ± | 27 | ( 4) |
| Ca mg/dl | 10.2 ± | 0.4 | ( 4) | 9.9 ± | 0.3 | ( 4) | 10.0 ± | 0.3 | ( 4) | 9.9 ± | 0.3 | ( 4) |
| P mg/dl | 9.0 ± | 0.7 | ( 4) | 9.1 ± | 0.5 | ( 4) | 9.4 ± | 0.2 | ( 4) | 9.1 ± | 0.3 | ( 4) |
| Na mMol/l | 144 ± | 1 | ( 4) | 145 ± | 1 | ( 4) | 143 ± | 1 | ( 4) | 142 ± | 1 | ( 4)* |
| K mMol/l | 4.9 ± | 1.0 | ( 4) | 4.7 ± | 0.4 | ( 4) | 4.6 ± | 0.2 | ( 4) | 4.3 ± | 0.2 | ( 4) |
| Cl Meq/l | 100 ± | 3 | ( 4) | 100 ± | 1 | ( 4) | 101 ± | 1 | ( 4) | 102 ± | 2 | ( 4) |
| CPK IU/l | 315 ± | 125 | ( 4) | 412 ± | 87 | ( 4) | 512 ± | 113 | ( 4) | 365 ± | 218 | ( 4) |
| GLOB g/dl | 1.9 ± | 0.1 | ( 4) | 1.7 ± | 0.1 | ( 4) | 1.8 ± | 0.1 | ( 4) | 1.8 ± | 0.2 | ( 4) |
| ALB/GLOB | 1.9 ± | 0.1 | ( 4) | 2.1 ± | 0.2 | ( 4) | 2.0 ± | 0.1 | ( 4) | 2.0 ± | 0.3 | ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-17

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 240 ± 24 ( 4) | 212 ± 12 ( 4) | 236 ± 21 ( 4) | 237 ± 25 ( 4) |
| BUN mg/dl | 22 ± 2 ( 4) | 18 ± 1 ( 4)* | 19 ± 1 ( 4)* | 19 ± 1 ( 4) |
| ALT IU/l | 49 ± 5 ( 4) | 64 ± 21 ( 4) | 70 ± 14 ( 4) | 74 ± 17 ( 4) |
| TRIG mg/dl | 73.8 ± 22.4 ( 4) | 58.5 ± 5.8 ( 4) | 58.3 ± 3.8 ( 4) | 57.3 ± 10.3 ( 4) |
| T PRO g/dl | 5.3 ± 0.2 ( 4) | 5.3 ± 0.1 ( 4) | 5.4 ± 0.1 ( 4) | 5.6 ± 0.3 ( 4) |
| ALB g/dl | 3.4 ± 0.1 ( 4) | 3.5 ± 0.1 ( 4) | 3.5 ± 0.1 ( 4) | 3.6 ± 0.1 ( 4)* |
| CHOL mg/dl | 75 ± 8 ( 4) | 71 ± 10 ( 4) | 73 ± 4 ( 4) | 81 ± 12 ( 4) |
| D BIL mg/dl | 0.04 ± 0.01 ( 4) | 0.06 ± 0.01 ( 4) | 0.06 ± 0.01 ( 4) | 0.05 ± 0.01 ( 4) |
| T BIL mg/dl | 0.13 ± 0.02 ( 4) | 0.14 ± 0.02 ( 4) | 0.15 ± 0.01 ( 4) | 0.17 ± 0.02 ( 4)* |
| AL PHOS IU/l | 207 ± 23 ( 4) | 226 ± 23 ( 4) | 222 ± 22 ( 4) | 240 ± 11 ( 4) |
| Ca mg/dl | 10.7 ± 0.3 ( 4) | 10.4 ± 0.1 ( 4) | 10.1 ± 0.1 ( 4)* | 10.6 ± 0.1 ( 4) |
| P mg/dl | 9.3 ± 0.4 ( 4) | 7.9 ± 0.6 ( 4)* | 7.6 ± 0.4 ( 4)* | 8.4 ± 0.3 ( 4) |
| Na mMol/l | 144 ± 1 ( 4) | 141 ± 1 ( 4)* | 138 ± 2 ( 4)* | 140 ± 3 ( 4)* |
| K mMol/l | 4.6 ± 0.2 ( 4) | 4.2 ± 0.3 ( 4) | 4.2 ± 0.3 ( 4) | 4.8 ± 0.9 ( 4) |
| Cl Meq/l | 99 ± 1 ( 4) | 100 ± 1 ( 4) | 101 ± 1 ( 4) | 99 ± 1 ( 4) |
| CPK IU/l | 365 ± 101 ( 4) | 442 ± 216 ( 4) | 332 ± 81 ( 4) | 407 ± 173 ( 4) |
| GLOB g/dl | 1.9 ± 0.1 ( 4) | 1.8 ± 0.1 ( 4) | 1.9 ± 0.1 ( 4) | 2.0 ± 0.2 ( 4) |
| ALB/GLOB | 1.8 ± 0.1 ( 4) | 1.9 ± 0.2 ( 4) | 1.8 ± 0.1 ( 4) | 1.8 ± 0.1 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-18

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 240 ± 24 ( 4) | 227 ± 21 ( 4) | 255 ± 55 ( 4) | 238 ± 30 ( 4) |
| BUN mg/dl | 22 ± 2 ( 4) | 16 ± 1 ( 4)* | 15 ± 2 ( 4)* | 14 ± 0 ( 4)* |
| ALT IU/l | 49 ± 5 ( 4) | 58 ± 14 ( 4) | 54 ± 10 ( 4) | 62 ± 15 ( 4) |
| TRIG mg/dl | 73.8 ± 22.4 ( 4) | 68.3 ± 18.8 ( 4) | 85.5 ± 70.0 ( 4) | 41.5 ± 8.7 ( 4) |
| T PRO g/dl | 5.3 ± 0.2 ( 4) | 5.6 ± 0.3 ( 4) | 5.7 ± 0.1 ( 4) | 5.6 ± 0.3 ( 4) |
| ALB g/dl | 3.4 ± 0.1 ( 4) | 3.5 ± 0.1 ( 4) | 3.6 ± 0.0 ( 4)* | 3.6 ± 0.1 ( 4)* |
| CHOL mg/dl | 75 ± 8 ( 4) | 74 ± 7 ( 4) | 77 ± 7 ( 4) | 75 ± 4 ( 4) |
| D BIL mg/dl | 0.04 ± 0.01 ( 4) | 0.06 ± 0.01 ( 4) | 0.05 ± 0.03 ( 4) | 0.05 ± 0.01 ( 4) |
| T BIL mg/dl | 0.13 ± 0.02 ( 4) | 0.16 ± 0.02 ( 4) | 0.15 ± 0.05 ( 4) | 0.15 ± 0.01 ( 4) |
| AL PHOS IU/l | 207 ± 23 ( 4) | 173 ± 11 ( 4) | 206 ± 18 ( 4) | 195 ± 21 ( 4) |
| Ca mg/dl | 10.7 ± 0.3 ( 4) | 11.1 ± 0.3 ( 4) | 11.5 ± 0.7 ( 4)* | 10.6 ± 0.1 ( 4) |
| P mg/dl | 9.3 ± 0.4 ( 4) | 9.1 ± 0.6 ( 4) | 9.5 ± 0.7 ( 4) | 8.9 ± 0.6 ( 4) |
| Na mMol/l | 144 ± 1 ( 4) | 146 ± 1 ( 4) | 146 ± 1 ( 4) | 146 ± 1 ( 4) |
| K mMol/l | 4.6 ± 0.2 ( 4) | 4.8 ± 0.7 ( 4) | 5.3 ± 0.8 ( 4) | 4.8 ± 0.5 ( 4) |
| Cl Meq/l | 99 ± 1 ( 4) | 98 ± 1 ( 4) | 99 ± 3 ( 4) | 98 ± 1 ( 4) |
| CPK IU/l | 365 ± 101 ( 4) | 268 ± 46 ( 4) | 361 ± 112 ( 4) | 318 ± 117 ( 4) |
| GLOB g/dl | 1.9 ± 0.1 ( 4) | 2.1 ± 0.3 ( 4) | 2.1 ± 0.1 ( 4) | 2.0 ± 0.2 ( 4) |
| ALB/GLOB | 1.8 ± 0.1 ( 4) | 1.7 ± 0.2 ( 4) | 1.7 ± 0.1 ( 4) | 1.8 ± 0.2 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-19

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 238 ± 20 ( 4) | 291 ± 93 ( 4) | 232 ± 13 ( 4) | 250 ± 15 ( 4) |
| BUN mg/dl | 20 ± 3 ( 4) | 23 ± 5 ( 4) | 18 ± 2 ( 4) | 18 ± 2 ( 4) |
| ALT IU/l | 56 ± 15 ( 4) | 67 ± 23 ( 4) | 57 ± 8 ( 4) | 65 ± 16 ( 4) |
| TRIG mg/dl | 64.5 ± 28.2 ( 4) | 70.0 ± 11.6 ( 4) | 60.0 ± 16.2 ( 4) | 58.0 ± 5.7 ( 4) |
| T PRO g/dl | 5.2 ± 0.1 ( 4) | 5.6 ± 0.4 ( 4) | 5.4 ± 0.3 ( 4) | 5.6 ± 0.1 ( 4) |
| ALB g/dl | 3.5 ± 0.1 ( 4) | 3.7 ± 0.1 ( 4) | 3.7 ± 0.2 ( 4) | 3.8 ± 0.1 ( 4 |
| CHOL mg/dl | 50 ± 8 ( 4) | 72 ± 9 ( 4)* | 68 ± 4 ( 4)* | 64 ± 8 ( 4) |
| D BIL mg/dl | 0.05 ± 0.02 ( 4) | 0.06 ± 0.02 ( 4) | 0.05 ± 0.01 ( 4) | 0.06 ± 0.01 ( 4) |
| T BIL mg/dl | 0.15 ± 0.03 ( 4) | 0.20 ± 0.03 ( 4)* | 0.18 ± 0.01 ( 4) | 0.19 ± 0.01 ( 4) |
| AL PHOS IU/l | 193 ± 35 ( 4) | 193 ± 24 ( 4) | 201 ± 38 ( 4) | 209 ± 19 ( 4) |
| Ca mg/dl | 9.6 ± 0.5 ( 4) | 10.3 ± 0.7 ( 4) | 9.8 ± 0.1 ( 4) | 10.0 ± 0.1 ( 4) |
| P mg/dl | 9.5 ± 0.1 ( 4) | 9.2 ± 1.1 ( 4) | 8.5 ± 0.4 ( 4) | 9.2 ± 0.4 ( 4) |
| Na mMol/l | 142 ± 2 ( 4) | 143 ± 2 ( 4) | 144 ± 1 ( 4) | 144 ± 2 ( 4) |
| K mMol/l | 4.8 ± 0.4 ( 4) | 5.5 ± 1.7 ( 4) | 4.4 ± 0.4 ( 4) | 4.6 ± 0.4 ( 4) |
| Cl Meq/l | 101 ± 1 ( 4) | 100 ± 2 ( 4) | 102 ± 0 ( 4) | 101 ± 1 ( 4) |
| CPK IU/l | 334 ± 79 ( 4) | 352 ± 65 ( 4) | 274 ± 119 ( 4) | 513 ± 236 ( 4) |
| GLOB g/dl | 1.6 ± 0.1 ( 4) | 1.9 ± 0.3 ( 4) | 1.7 ± 0.1 ( 4) | 1.8 ± 0.1 ( 4) |
| ALB/GLOB | 2.2 ± 0.1 ( 4) | 2.0 ± 0.2 ( 4) | 2.2 ± 0.1 ( 4) | 2.1 ± 0.2 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-20

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D2) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| GLU mg/dl | 238 ± 20 ( 4) | 254 ± 17 ( 4) | 274 ± 21 ( 4) | 255 ± 36 ( 4) |
| BUN mg/dl | 20 ± 3 ( 4) | 16 ± 2 ( 4) | 17 ± 4 ( 4) | 16 ± 2 ( 4) |
| ALT IU/l | 56 ± 15 ( 4) | 48 ± 8 ( 4) | 45 ± 7 ( 4) | 48 ± 3 ( 4) |
| TRIG mg/dl | 64.5 ± 28.2 ( 4) | 64.3 ± 7.5 ( 4) | 84.8 ± 40.2 ( 4) | 76.0 ± 15.6 ( 4) |
| T PRO g/dl | 5.2 ± 0.1 ( 4) | 5.5 ± 0.1 ( 4)* | 5.5 ± 0.1 ( 4)* | 5.5 ± 0.2 ( 4)* |
| ALB g/dl | 3.5 ± 0.1 ( 4) | 3.7 ± 0.1 ( 4)* | 3.7 ± 0.1 ( 4)* | 3.7 ± 0.1 ( 4)* |
| CHOL mg/dl | 50 ± 8 ( 4) | 63 ± 14 ( 4) | 50 ± 5 ( 4) | 62 ± 4 ( 4) |
| D BIL mg/dl | 0.05 ± 0.02 ( 4) | 0.05 ± 0.02 ( 4) | 0.04 ± 0.01 ( 4) | 0.05 ± 0.01 ( 4) |
| T BIL mg/dl | 0.15 ± 0.03 ( 4) | 0.18 ± 0.03 ( 4) | 0.16 ± 0.02 ( 4) | 0.15 ± 0.02 ( 4) |
| AL PHOS IU/l | 193 ± 35 ( 4) | 172 ± 5 ( 4) | 176 ± 19 ( 4) | 227 ± 23 ( 4) |
| Ca mg/dl | 9.6 ± 0.5 ( 4) | 10.3 ± 0.4 ( 4) | 10.3 ± 0.4 ( 4) | 10.4 ± 0.3 ( 4)* |
| P mg/dl | 9.5 ± 0.1 ( 4) | 9.3 ± 0.1 ( 4) | 9.1 ± 0.2 ( 4)* | 9.2 ± 0.2 ( 4)* |
| Na mMol/l | 142 ± 2 ( 4) | 144 ± 1 ( 4) | 143 ± 1 ( 4) | 142 ± 2 ( 4) |
| K mMol/l | 4.8 ± 0.4 ( 4) | 4.8 ± 0.2 ( 4) | 4.5 ± 0.4 ( 4) | 4.6 ± 0.2 ( 4) |
| Cl Meq/l | 101 ± 1 ( 4) | 100 ± 3 ( 4) | 100 ± 1 ( 4) | 100 ± 1 ( 4) |
| CPK IU/l | 334 ± 79 ( 4) | 558 ± 233 ( 4) | 352 ± 122 ( 4) | 440 ± 209 ( 4) |
| GLOB g/dl | 1.6 ± 0.1 ( 4) | 1.8 ± 0.1 ( 4) | 1.7 ± 0.1 ( 4) | 1.7 ± 0.1 ( 4) |
| ALB/GLOB | 2.2 ± 0.1 ( 4) | 2.1 ± 0.1 ( 4) | 2.2 ± 0.1 ( 4) | 2.1 ± 0.1 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-21

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON CLINICAL CHEMISTRY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| CLIN CHEM VALUES | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| GLU mg/dl | 197 ± 14 ( 4) | 226 ± 4 ( 3) | 224 ± 31 ( 4) |
| BUN mg/dl | 25 ± 1 ( 4) | 21 ± 3 ( 3)* | 26 ± 1 ( 4) |
| ALT IU/l | 90 ± 33 ( 4) | 83 ± 22 ( 3) | 81 ± 53 ( 4) |
| TRIG mg/dl | 88.8 ± 17.5 ( 4) | 90.0 ± 17.1 ( 3) | 95.0 ± 62.5 ( 4) |
| T PRO g/dl | 5.6 ± 0.1 ( 4) | 5.7 ± 0.2 ( 3) | 5.5 ± 0.1 ( 4) |
| ALB g/dl | 3.5 ± 0.2 ( 4) | 3.8 ± 0.2 ( 3) | 3.6 ± 0.1 ( 4) |
| CHOL mg/dl | 87 ± 11 ( 4) | 68 ± 4 ( 3) | 70 ± 12 ( 4) |
| D BIL mg/dl | 0.11 ± 0.02 ( 4) | 0.09 ± 0.02 ( 3) | 0.07 ± 0.02 ( 4)* |
| T BIL mg/dl | 0.20 ± 0.03 ( 4) | 0.17 ± 0.02 ( 3) | 0.16 ± 0.03 ( 4) |
| AL PHOS IU/l | 212 ± 34 ( 4) | 238 ± 16 ( 3) | 239 ± 42 ( 4) |
| Ca mg/dl | 10.2 ± 0.5 ( 4) | 10.2 ± 0.4 ( 3) | 10.7 ± 0.5 ( 4) |
| P mg/dl | 7.2 ± 0.7 ( 4) | 7.5 ± 0.4 ( 3) | 7.7 ± 0.5 ( 4) |
| Na mMol/l | 145 ± 1 ( 4) | 145 ± 2 ( 3) | 145 ± 2 ( 4) |
| K mMol/l | 4.3 ± 0.1 ( 4) | 4.0 ± 0.1 ( 3)* | 4.2 ± 0.2 ( 4) |
| Cl Meq/l | 99 ± 1 ( 4) | 100 ± 2 ( 3) | 98 ± 0 ( 4) |
| CPK IU/l | 478 ± 226 ( 4) | 254 ± 47 ( 3) | 452 ± 323 ( 4) |
| GLOB g/dl | 2.0 ± 0.2 ( 4) | 2.0 ± 0.1 ( 3) | 1.9 ± 0.1 ( 4) |
| ALB/GLOB | 1.7 ± 0.3 ( 4) | 1.9 ± 0.0 ( 3) | 1.9 ± 0.1 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-22

EFFECT OF TWO CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 41.5 ± 1.5 ( 4) | 42.0 ± 0.4 ( 4) | 41.6 ± 1.6 ( 4) | 42.0 ± 1.1 ( 4) |
| HGB g/dl | 15.6 ± 0.5 ( 4) | 15.7 ± 0.2 ( 4) | 15.5 ± 0.4 ( 4) | 15.7 ± 0.2 ( 4) |
| MCV um³ | 58 ± 2 ( 4) | 59 ± 1 ( 4) | 59 ± 2 ( 4) | 58 ± 1 ( 4) |
| MCH pg | 21.4 ± 0.3 ( 4) | 21.5 ± 0.5 ( 4) | 21.6 ± 0.7 ( 4) | 21.5 ± 0.4 ( 4) |
| MCHC g/dl | 37.5 ± 0.9 ( 4) | 37.2 ± 0.6 ( 4) | 36.9 ± 0.4 ( 4) | 37.3 ± 0.6 ( 4) |
| RBCx10⁶/mm³ | 7.28 ± 0.20 ( 4) | 7.31 ± 0.17 ( 4) | 7.15 ± 0.33 ( 4) | 7.34 ± 0.19 ( 4) |
| WBCx10³/mm³ | 7.5 ± 2.3 ( 4) | 6.6 ± 1.1 ( 4) | 6.0 ± 3.4 ( 4) | 5.9 ± 2.3 ( 4) |
| PLTx10³/mm³ | 463 ± 35 ( 4) | 462 ± 93 ( 4) | 400 ± 77 ( 4) | 461 ± 107 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 7 ± 3 ( 4) | 5 ± 4 ( 4) | 7 ± 5 ( 4) | 13 ± 8 ( 4) |
| LYMPH %WBC | 93 ± 2 ( 4) | 94 ± 5 ( 4) | 93 ± 5 ( 4) | 87 ± 8 ( 4) |
| MON %WBC | 1 ± 1 ( 4) | 0 ± 1 ( 4) | 0 ± 1 ( 4) | 0 ± 0 ( 4) |
| EOS %WBC | 0 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-23

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 41.5 ± 1.5 ( 4) | 43.7 ± 0.7 ( 4) | 43.9 ± 0.5 ( 4) | 42.6 ± 2.0 ( 4) |
| HGB g/dl | 15.6 ± 0.5 ( 4) | 16.2 ± 0.2 ( 4) | 16.6 ± 0.3 ( 4)* | 16.0 ± 0.8 ( 4) |
| MCV um³ | 58 ± 2 ( 4) | 59 ± 1 ( 4) | 59 ± 1 ( 4) | 58 ± 2 ( 4) |
| MCH pg | 21.4 ± 0.3 ( 4) | 21.4 ± 0.4 ( 4) | 21.9 ± 0.5 ( 4) | 21.5 ± 0.6 ( 4) |
| MCHC g/dl | 37.5 ± 0.9 ( 4) | 37.1 ± 0.3 ( 4) | 37.6 ± 0.4 ( 4) | 37.6 ± 0.1 ( 4) |
| RBCx10⁶/mm³ | 7.28 ± 0.20 ( 4) | 7.59 ± 0.21 ( 4) | 7.59 ± 0.25 ( 4) | 7.47 ± 0.43 ( 4) |
| WBCx10³/mm³ | 7.5 ± 2.3 ( 4) | 6.9 ± 1.1 ( 4) | 7.3 ± 0.8 ( 4) | 6.1 ± 1.0 ( 4) |
| PLTx10³/mm³ | 463 ± 35 ( 4) | 552 ± 240 ( 4) | 346 ± 41 ( 4) | 543 ± 76 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 7 ± 3 ( 4) | 8 ± 4 ( 4) | 6 ± 3 ( 4) | 2 ± 1 ( 4) |
| LYMPH %WBC | 93 ± 2 ( 4) | 92 ± 4 ( 4) | 93 ± 3 ( 4) | 97 ± 2 ( 4) |
| MON %WBC | 1 ± 1 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| EOS %WBC | 0 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 0 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-24

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a] [MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 41.9 ± 1.8 ( 4) | 41.2 ± 0.7 ( 4) | 41.8 ± 0.7 ( 4) | 42.5 ± 0.7 ( 4) |
| HGB g/dl | 15.9 ± 0.6 ( 4) | 15.6 ± 0.3 ( 4) | 15.7 ± 0.2 ( 4) | 16.2 ± 0.3 ( 4) |
| MCV um³ | 58 ± 1 ( 4) | 58 ± 1 ( 4) | 58 ± 1 ( 4) | 57 ± 1 ( 4)* |
| MCH pg | 21.7 ± 0.4 ( 4) | 21.6 ± 0.3 ( 4) | 21.3 ± 0.5 ( 4) | 21.3 ± 0.3 ( 4) |
| MCHC g/dl | 37.9 ± 0.8 ( 4) | 37.7 ± 0.2 ( 4) | 37.4 ± 0.4 ( 4) | 38.2 ± 0.4 ( 4) |
| RBCx10⁶/mm³ | 7.33 ± 0.26 ( 4) | 7.22 ± 0.12 ( 4) | 7.39 ± 0.18 ( 4) | 7.66 ± 0.07 ( 4) |
| WBCx10³/mm³ | 7.7 ± 0.6 ( 4) | 6.9 ± 0.9 ( 4) | 5.9 ± 0.8 ( 4)* | 5.5 ± 1.3 ( 4)* |
| PLTx10³/mm³ | 511 ± 90 ( 4) | 503 ± 44 ( 4) | 528 ± 46 ( 4) | 578 ± 112 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 7 ± 4 ( 4) | 7 ± 3 ( 4) | 7 ± 3 ( 4) | 7 ± 3 ( 4) |
| LYMPH %WBC | 93 ± 3 ( 4) | 93 ± 4 ( 4) | 93 ± 4 ( 4) | 93 ± 3 ( 4) |
| MON %WBC | 0 ± 1 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| EOS %WBC | 0 ± 1 ( 4) | 0 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-25

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 41.9 ± 1.8 ( 4) | 43.0 ± 2.5 ( 4) | 42.7 ± 1.0 ( 4) | 44.9 ± 1.7 ( 4) |
| HGB g/dl | 15.9 ± 0.6 ( 4) | 16.3 ± 0.9 ( 4) | 16.2 ± 0.3 ( 4) | 16.7 ± 0.5 ( 4) |
| MCV um³ | 58 ± 1 ( 4) | 57 ± 2 ( 4) | 57 ± 1 ( 4) | 58 ± 2 ( 4) |
| MCH pg | 21.7 ± 0.4 ( 4) | 21.1 ± 0.7 ( 4) | 21.2 ± 0.5 ( 4) | 21.4 ± 0.7 ( 4) |
| MCHC g/dl | 37.9 ± 0.8 ( 4) | 37.8 ± 0.2 ( 4) | 37.8 ± 0.3 ( 4) | 37.2 ± 0.4 ( 4) |
| RBCx10⁶/mm³ | 7.33 ± 0.26 ( 4) | 7.74 ± 0.38 ( 4) | 7.62 ± 0.23 ( 4) | 7.85 ± 0.42 ( 4) |
| WBCx10³/mm³ | 7.7 ± 0.6 ( 4) | 7.3 ± 1.6 ( 4) | 8.0 ± 1.7 ( 4) | 6.1 ± 1.8 ( 4) |
| PLTx10³/mm³ | 511 ± 90 ( 4) | 469 ± 49 ( 4) | 552 ± 27 ( 4) | 497 ± 92 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 7 ± 4 ( 4) | 10 ± 6 ( 4) | 8 ± 4 ( 4) | 11 ± 8 ( 4) |
| LYMPH %WBC | 93 ± 3 ( 4) | 89 ± 7 ( 4) | 92 ± 4 ( 4) | 89 ± 8 ( 4) |
| MON %WBC | 0 ± 1 ( 4) | 0 ± 0 ( 4) | 0 ± 1 ( 4) | 0 ± 0 ( 4) |
| EOS %WBC | 0 ± 1 ( 4) | 1 ± 2 ( 4) | 0 ± 1 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-26

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 42.1 ± 0.4 ( 4) | 44.0 ± 5.1 ( 4) | 41.0 ± 0.7 ( 4) | 41.9 ± 1.0 ( 4) |
| HGB g/dl | 15.6 ± 0.3 ( 4) | 16.5 ± 2.0 ( 4) | 15.5 ± 0.5 ( 4) | 15.8 ± 0.3 ( 4) |
| MCV um³ | 59 ± 1 ( 4) | 56 ± 2 ( 4) | 57 ± 2 ( 4) | 58 ± 1 ( 4) |
| MCH pg | 21.4 ± 0.3 ( 4) | 20.9 ± 0.9 ( 4) | 21.3 ± 0.6 ( 4) | 21.6 ± 0.1 ( 4) |
| MCHC g/dl | 37.0 ± 0.2 ( 4) | 37.5 ± 0.6 ( 4) | 37.7 ± 0.9 ( 4) | 37.7 ± 0.5 ( 4) |
| RBCx10⁶/mm³ | 7.30 ± 0.22 ( 4) | 7.96 ± 1.16 ( 4) | 7.30 ± 0.25 ( 4) | 7.34 ± 0.15 ( 4) |
| WBCx10³/mm³ | 7.2 ± 1.3 ( 4) | 6.9 ± 1.8 ( 4) | 5.7 ± 0.6 ( 4) | 6.8 ± 1.1 ( 4) |
| PLTx10³/mm³ | 432 ± 37 ( 4) | 647 ± 107 ( 4)* | 647 ± 82 ( 4)* | 599 ± 49 ( 4)* |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 6 ± 4 ( 4) | 9 ± 3 ( 4) | 14 ± 3 ( 4)* | 6 ± 3 ( 4) |
| LYMPH %WBC | 94 ± 5 ( 4) | 91 ± 3 ( 4) | 85 ± 3 ( 4)* | 94 ± 3 ( 4) |
| MON %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 1 ( 4) |
| EOS %WBC | 1 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-27

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D2) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED IMMEDIATELY AFTER THE FINAL EXPOSURE[a]
[MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| HCT %rbc | 42.1 ± 0.4 ( 4) | 43.3 ± 1.4 ( 4) | 44.0 ± 1.1 ( 4)* | 43.5 ± 0.6 ( 4) |
| HGB g/dl | 15.6 ± 0.3 ( 4) | 16.1 ± 0.4 ( 4) | 16.5 ± 0.5 ( 4)* | 16.3 ± 0.4 ( 4) |
| MCV um³ | 59 ± 1 ( 4) | 57 ± 3 ( 4) | 59 ± 1 ( 4) | 59 ± 1 ( 4) |
| MCH pg | 21.4 ± 0.3 ( 4) | 21.0 ± 0.9 ( 4) | 21.9 ± 0.3 ( 4) | 21.7 ± 0.3 ( 4) |
| MCHC g/dl | 37.0 ± 0.2 ( 4) | 37.2 ± 0.3 ( 4) | 37.4 ± 0.2 ( 4) | 37.5 ± 0.4 ( 4) |
| RBCx10⁶/mm³ | 7.30 ± 0.22 ( 4) | 7.72 ± 0.43 ( 4) | 7.56 ± 0.18 ( 4) | 7.54 ± 0.24 ( 4) |
| WBCx10³/mm³ | 7.2 ± 1.3 ( 4) | 6.9 ± 1.9 ( 4) | 5.3 ± 4.0 ( 4) | 7.2 ± 0.9 ( 4) |
| PLTx10³/mm³ | 432 ± 37 ( 4) | 440 ± 46 ( 4) | 362 ± 28 ( 4) | 379 ± 49 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 6 ± 4 ( 4) | 6 ± 3 ( 4) | 7 ± 1 ( 4) | 9 ± 4 ( 4) |
| LYMPH %WBC | 94 ± 5 ( 4) | 94 ± 3 ( 4) | 92 ± 2 ( 4) | 91 ± 4 ( 4) |
| MON %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 1 ( 4) |
| EOS %WBC | 1 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) | 1 ± 1 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

## Table A-28

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON HEMATOLOGY PARAMETERS OF MALE SPRAGUE DAWLEY RATS TESTED 14 DAYS POST-EXPOSURE[a] [MEAN AND STANDARD DEVIATION (n)]

| HEMATOLOGY VALUES | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| HCT %rbc | 40.8 ± 0.8 ( 4) | 40.6 ± 0.6 ( 4) | 40.2 ± 1.2 ( 4) |
| HGB g/dl | 15.5 ± 0.3 ( 4) | 15.5 ± 0.4 ( 4) | 15.4 ± 0.3 ( 4) |
| MCV um³ | 56 ± 2 ( 4) | 54 ± 1 ( 4) | 56 ± 1 ( 4) |
| MCH pg | 21.0 ± 0.6 ( 4) | 20.5 ± 0.4 ( 4) | 21.1 ± 0.3 ( 4) |
| MCHC g/dl | 38.1 ± 0.4 ( 4) | 38.2 ± 0.4 ( 4) | 38.3 ± 0.9 ( 4) |
| RBCx10⁶/mm³ | 7.42 ± 0.11 ( 4) | 7.61 ± 0.30 ( 4) | 7.31 ± 0.20 ( 4) |
| WBCx10³/mm³ | 5.4 ± 0.8 ( 4) | 6.0 ± 1.0 ( 4) | 5.6 ± 1.2 ( 4) |
| PLTx10³/mm³ | 411 ± 86 ( 4) | 410 ± 141 ( 4) | 434 ± 36 ( 4) |
| IM NEU %WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| M NEU %WBC | 8 ± 3 ( 4) | 11 ± 5 ( 4) | 8 ± 3 ( 4) |
| LYMPH %WBC | 90 ± 2 ( 4) | 88 ± 7 ( 4) | 91 ± 4 ( 4) |
| MON %WBC | 0 ± 1 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |
| EOS %WBC | 1 ± 2 ( 4) | 2 ± 2 ( 4) | 2 ± 2 ( 4) |
| NRBC/100 WBC | 0 ± 0 ( 4) | 0 ± 0 ( 4) | 0 ± 0 ( 4) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

Table A-29

EFFECT OF TWO CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | | 0.4 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|---|---|
| RANDOM[c] | 100 ± | 10 ( 24) | 100 ± | 10 ( 18) | 101 ± | 10 ( 18) | 98 ± | 11 ( 18) |
| 1 | 203 ± | 27 ( 24) | 201 ± | 27 ( 18) | 200 ± | 28 ( 18) | 195 ± | 28 ( 18) |
| 8 | 242 ± | 27 ( 24) | 237 ± | 23 ( 18) | 229 ± | 30 ( 18) | 228 ± | 30 ( 18) |
| 15 | 275 ± | 23 ( 24) | 268 ± | 19 ( 18) | 260 ± | 26 ( 18) | 258 ± | 28 ( 18) |
| 22 | 299 ± | 23 ( 24) | 293 ± | 17 ( 18) | 285 ± | 28 ( 18) | 278 ± | 30 ( 18)* |
| FINAL[c] | 302 ± | 22 ( 24) | 295 ± | 19 ( 18) | 287 ± | 29 ( 18) | 277 ± | 30 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b - CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

## Table A-30

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | | 0.4 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|---|---|
| RANDOM[c] | 100 ± | 10 ( 24) | 100 ± | 11 ( 18) | 100 ± | 11 ( 18) | 100 ± | 9 ( 18) |
| 1 | 203 ± | 27 ( 24) | 200 ± | 27 ( 18) | 199 ± | 29 ( 18) | 193 ± | 24 ( 18) |
| 8 | 242 ± | 27 ( 24) | 236 ± | 26 ( 18) | 232 ± | 32 ( 18) | 222 ± | 22 ( 18) |
| 15 | 275 ± | 23 ( 24) | 268 ± | 21 ( 18) | 260 ± | 27 ( 18) | 256 ± | 18 ( 17)* |
| 22 | 299 ± | 23 ( 24) | 295 ± | 22 ( 18) | 284 ± | 29 ( 18) | 282 ± | 17 ( 17) |
| FINAL[c] | 302 ± | 22 ( 24) | 296 ± | 21 ( 18) | 285 ± | 27 ( 18) | 280 ± | 18 ( 17)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table A-31

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
(MEAN AND STANDARD DEVIATION (n))

| TEST DAY | 0.0 mg/L[b] | | 0.4 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|---|---|
| RANDOM[c] | 100 ± | 10 ( 24) | 100 ± | 12 ( 18) | 100 ± | 10 ( 18) | 101 ± | 9 ( 18) |
| 1 | 206 ± | 26 ( 24) | 201 ± | 30 ( 18) | 204 ± | 23 ( 18) | 206 ± | 27 ( 18) |
| 8 | 244 ± | 29 ( 24) | 234 ± | 29 ( 18) | 236 ± | 24 ( 18) | 235 ± | 29 ( 18) |
| 15 | 277 ± | 21 ( 24) | 263 ± | 26 ( 18) | 263 ± | 22 ( 18) | 266 ± | 27 ( 18) |
| 22 | 304 ± | 20 ( 24) | 286 ± | 27 ( 18) | 288 ± | 24 ( 18) | 287 ± | 28 ( 18) |
| FINAL[c] | 312 ± | 18 ( 24) | 295 ± | 28 ( 18) | 294 ± | 23 ( 18) | 293 ± | 28 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table A-32

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| RANDOM[c] | 100 ± 10 ( 24) | 99 ± 10 ( 18) | 100 ± 11 ( 18) | 99 ± 10 ( 18) |
| 1 | 206 ± 26 ( 24) | 203 ± 26 ( 18) | 203 ± 27 ( 18) | 199 ± 26 ( 18) |
| 8 | 244 ± 29 ( 24) | 238 ± 29 ( 18) | 226 ± 37 ( 18) | 220 ± 25 ( 18) |
| 15 | 277 ± 21 ( 24) | 268 ± 24 ( 18) | 262 ± 24 ( 18) | 249 ± 22 ( 18)* |
| 22 | 304 ± 20 ( 24) | 293 ± 26 ( 18) | 287 ± 23 ( 18) | 273 ± 25 ( 18)* |
| FINAL[c] | 312 ± 18 ( 24) | 301 ± 28 ( 18) | 296 ± 24 ( 18) | 276 ± 27 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY. 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table A-33

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a] [MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| RANDOM[c] | 100 ± 10 ( 24) | 100 ± 12 ( 18) | 100 ± 10 ( 18) | 100 ± 11 ( 18) |
| 1 | 195 ± 31 ( 24) | 194 ± 36 ( 18) | 197 ± 34 ( 18) | 200 ± 34 ( 18) |
| 8 | 232 ± 30 ( 24) | 228 ± 36 ( 18) | 230 ± 35 ( 18) | 230 ± 31 ( 18) |
| 15 | 267 ± 25 ( 24) | 261 ± 35 ( 18) | 263 ± 32 ( 18) | 265 ± 26 ( 18) |
| 22 | 293 ± 24 ( 24) | 283 ± 39 ( 18) | 288 ± 32 ( 18) | 292 ± 21 ( 18) |
| FINAL[c] | 302 ± 22 ( 24) | 290 ± 41 ( 18) | 296 ± 31 ( 18) | 303 ± 19 ( 18) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

Table A-34

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SE ARATED BY A 2-DAY INTERVAL (F3/D2) ON WEEKLY BODY WEIGHTS (G) OF MAL SPRAGUE DAWLLY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| RANDOM[c] | 100 ± 10 ( 24) | 100 ± 11 ( 18) | 100 ± 10 ( 18) | 99 ± 10 ( 18) |
| 1 | 195 ± 31 ( 24) | 194 ± 33 ( 18) | 196 ± 28 ( 18) | 195 ± 28 ( 18) |
| 8 | 232 ± 30 ( 24) | 227 ± 33 ( 18) | 229 ± 26 ( 18) | 226 ± 28 ( 18) |
| 15 | 267 ± 25 ( 24) | 261 ± 34 ( 14) | 259 ± 21 ( 18) | 253 ± 28 ( 18) |
| 22 | 293 ± 24 ( 24) | 289 ± 28 ( 18) | 286 ± 19 ( 18) | 279 ± 22 ( 18) |
| FINAL[c] | 302 ± 22 ( 24) | 299 ± 29 ( 18) | 295 ± 20 ( 18) | 291 ± 21 ( 18) |

• = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

## Table A-35

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON WEEKLY BODY WEIGHTS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| RANDOM[c] | 100 ± 11 ( 18) | 99 ± 10 ( 18) | 100 ± 10 ( 18) |
| 1 | 190 ± 13 ( 18) | 191 ± 13 ( 18) | 186 ± 20 ( 18) |
| 8 | 225 ± 17 ( 18) | 221 ± 15 ( 18) | 210 ± 18 ( 18)* |
| 15 | 267 ± 15 ( 18) | 255 ± 16 ( 18)* | 245 ± 17 ( 18)* |
| 22 | 298 ± 14 ( 18) | 281 ± 18 ( 18)* | 273 ± 18 ( 18)* |
| FINAL[c] | 309 ± 15 ( 18) | 288 ± 19 ( 18)* | 281 ± 19 ( 18)* |
| 29 | 321 ± 15 ( 18) | 299 ± 20 ( 18)* | 294 ± 19 ( 18)* |
| 36 | 340 ± 17 ( 18) | 321 ± 23 ( 18)* | 315 ± 22 ( 18)* |
| 39 | 348 ± 17 ( 18) | 329 ± 24 ( 18)* | 324 ± 21 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a - ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2)
c = DAYS OF RANDOMIZATION AND FINAL EXPOSURE RESPECTIVELY

## Table A-36

EFFECT OF TWO CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D1) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 39 ± 5 ( 24) | 36 ± 6 ( 18) | 29 ± 5 ( 18)* | 33 ± 5 ( 18)* |
| 15 | 72 ± 8 ( 24) | 67 ± 12 ( 18) | 61 ± 12 ( 18)* | 63 ± 11 ( 18)* |
| 22 | 96 ± 11 ( 24) | 92 ± 16 ( 18) | 86 ± 16 ( 18) | 83 ± 16 ( 18)* |
| FINAL[c] | 99 ± 13 ( 24) | 95 ± 15 ( 18) | 88 ± 16 ( 18) | 82 ± 16 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

## Table A-37

EFFECT OF TWO CONSECUTIVE DAILY 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F1/D2) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 39 ± 5 ( 24) | 35 ± 6 ( 18) | 33 ± 5 ( 18) | 29 ± 18 ( 18)* |
| 15 | 72 ± 8 ( 24) | 68 ± 14 ( 18) | 61 ± 10 ( 18)* | 65 ± 11 ( 17) |
| 22 | 96 ± 11 ( 24) | 94 ± 16 ( 18) | 85 ± 12 ( 18)* | 91 ± 12 ( 17) |
| FINAL[c] | 99 ± 13 ( 24) | 96 ± 16 ( 18) | 86 ± 14 ( 18)* | 89 ± 12 ( 17) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

## Table A-38

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 37 ± 6 ( 24) | 33 ± 8 ( 18) | 31 ± 6 ( 18)* | 28 ± 7 ( 18)* |
| 15 | 71 ± 10 ( 24) | 62 ± 13 ( 18)* | 58 ± 10 ( 18)* | 60 ± 11 ( 18)* |
| 22 | 98 ± 12 ( 24) | 85 ± 18 ( 18)* | 84 ± 12 ( 18)* | 81 ± 15 ( 18)* |
| FINAL[c] | 106 ± 15 ( 24) | 94 ± 18 ( 18) | 90 ± 13 ( 18)* | 87 ± 16 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

Table A-39

EFFECT OF FOUR CONSECUTIVE DAILY 3.5-HR KP/BR AEROSOL EXPOSURES PER WEEK (F2/D2) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | | 0.4 mg/L | | 0.75 mg/L | | 1.0 mg/L | |
|---|---|---|---|---|---|---|---|---|
| 8 | 37 ± | 6 ( 24) | 35 ± | 5 ( 18) | 23 ± | 21 ( 18)* | 21 ± | 4 ( 18)* |
| 15 | 71 ± | 10 ( 24) | 65 ± | 8 ( 18) | 59 ± | 11 ( 18)* | 50 ± | 8 ( 18)* |
| 22 | 98 ± | 12 ( 24) | 90 ± | 12 ( 18) | 84 ± | 17 ( 18)* | 74 ± | 11 ( 18)* |
| FINAL[c] | 106 ± | 15 ( 24) | 98 ± | 16 ( 18) | 93 ± | 18 ( 18)* | 77 ± | 13 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

## Table A-40

EFFECT OF TWO 1-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D1) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 37 ± 5 ( 24) | 34 ± 13 ( 18) | 34 ± 8 ( 18) | 30 ± 9 ( 13) |
| 15 | 72 ± 12 ( 24) | 67 ± 15 ( 18) | 66 ± 11 ( 18) | 65 ± 11 ( 18) |
| 22 | 98 ± 18 ( 24) | 89 ± 22 ( 18) | 91 ± 16 ( 18) | 92 ± 19 ( 18) |
| FINAL[c] | 107 ± 21 ( 24) | 97 ± 26 ( 18) | 99 ± 18 ( 18) | 103 ± 20 ( 18) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

Table A-41

EFFECT OF TWO 3.5-HR RP/BR AEROSOL EXPOSURES SEPARATED BY A 2-DAY INTERVAL (F3/D2) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE EXPOSURE PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 0.4 mg/L | 0.75 mg/L | 1.0 mg/L |
|---|---|---|---|---|
| 8 | 37 ± 5 ( 24) | 33 ± 5 ( 18) | 33 ± 7 ( 18) | 31 ± 5 ( 18)* |
| 15 | 72 ± 12 ( 24) | 66 ± 12 ( 14) | 63 ± 12 ( 18) | 58 ± 11 ( 18)* |
| 22 | 98 ± 18 ( 24) | 95 ± 18 ( 18) | 90 ± 17 ( 18) | 84 ± 13 ( 18)* |
| FINAL[c] | 107 ± 21 ( 24) | 105 ± 19 ( 18) | 99 ± 18 ( 18) | 96 ± 16 ( 18) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = AS SCHEDULED PER WEEK FOR 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

Table A-42

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON WEEKLY BODY WEIGHT GAINS (G) OF MALE SPRAGUE DAWLEY RATS TESTED THROUGHOUT THE STUDY AND 14 DAY RECOVERY PERIOD[a]
[MEAN AND STANDARD DEVIATION (n)]

| TEST DAY | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| 8 | 35 ± 7 ( 18) | 30 ± 5 ( 18)* | 24 ± 7 ( 18)* |
| 15 | 78 ± 8 ( 18) | 63 ± 9 ( 18)* | 60 ± 7 ( 18)* |
| 22 | 109 ± 9 ( 18) | 90 ± 13 ( 18)* | 87 ± 12 ( 18)* |
| FINAL[c] | 119 ± 10 ( 18) | 97 ± 14 ( 18)* | 95 ± 13 ( 18)* |
| 29 | 131 ± 12 ( 18) | 108 ± 16 ( 18)* | 108 ± 14 ( 18)* |
| 36 | 151 ± 12 ( 18) | 129 ± 18 ( 18)* | 129 ± 15 ( 18)* |
| 39 | 158 ± 12 ( 18) | 138 ± 20 ( 18)* | 138 ± 16 ( 18)* |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).
c = DAY OF FINAL EXPOSURE

Table A-43

EFFECT OF FOUR CONSECUTIVE DAILY 1-HR OR 3.5-HR RP/BR AEROSOL EXPOSURES PER WEEK (F2/D1, F2/D2) ON FOOD CONSUMPTION (G/DAY) OF MALE SPRAGUE DAWLEY RATS MEASURED AT THE FINAL EXPOSURE (FC 1) AND 14 DAYS POST-EXPOSURE[a] (FC 2) [MEAN AND STANDARD DEVIATION (n)]

| DAY OF TEST | 0.0 mg/L[b] | 1 HR 1.0 mg/L | 3.5 HR 1.0 mg/L |
|---|---|---|---|
| FC 1 | 27.1 ± 2.9 ( 18) | 24.1 ± 2.5 ( 18)* | 24.6 ± 3.0 ( 18)* |
| FC 2 | 28.4 ± 3.2 ( 18) | 29.1 ± 3.3 ( 18) | 29.1 ± 2.0 ( 18) |

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP
a = ANIMALS WERE EXPOSED FOR A TOTAL OF 4 WEEKS.
b = CONTROLS WERE EXPOSED 3.5 HRS/DAY, 4 DAYS/WEEK (F2/D2).

# APPENDIX B
# STUDIES COMPARING RATS FROM TWO BREEDING COLONIES

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## OBJECTIVES AND EXPERIMENTAL DESIGN

Previous to these comparison studies rats used in all studies were provided from the Madison, WI breeding colony of Harlan-Sprague Dawley, Inc. An inquiry was made to the supplier upon discovering that serum samples from these rats showed antibody titers to Pneumonia Virus of Mice (PVM). The supplier indicated that they had another breeding colony in Indianapolis, IN that was derived from the same genetic stock as the Madison colony that was PVM-free. In order to choose the most appropriate animals for the upcoming subchronic exposures, two comparison studies with representative animals from these two breeding colonies were conducted.

- o Gross physical examination and observation
- o Gross necropsy and follow-up histopathologic observation when indicted
- o Culture of respiratory tract (nasopharynx, tracheal aspirate and lung) for potential pathogens including mycoplasma.
- o Culture of intestinal tract for potential pathogens
- o Direct smear and fecal flotation of intestinal tract for endoparasites.
- o Examination of sera for standard murine virus profile (nine viruses: Reo, PVM, GDVII, mouse adeno., MHV, Toolan H-1, KRV, LCM and RCV).

In addition groups of male rats from the two facilities were exposed one time for 3.5 hrs to 1.0 mg/l of RP/BR aerosol. In Study No. 79-SC, following the exposure, the bactericidal activity assay was performed comparing the response of the animals from the two sources after receiving simultaneous bacterial aerosol challenge to $^{35}$S-*K. pneumoniae*. In a second study (SN79-SC2) male rats from the two breeding colonies were compared by measurement of pulmonary lavage parameters following a single 3.5 hr exposure to 1.0 mg/l of RP/BR. To facilitate the labor-intensive procedures involved in the pulmonary bactericidal activity and lavage assays, the rats were divided in each experiment into two groups and the RP/BR aerosol exposures staggered over two days. For the pulmonary bactericidal activity assay, two radioactive aerosol challenges were done on each of the

two consecutive RP/BR exposure days and 7 RP/BR-exposed and 7 control rats from the two colonies were assigned to each radioactive bacterial aerosol challenge. For comparison of pulmonary lavage parameters, eight rats from each facility were exposed to RP/BR aerosol or filtered air on each of the two experimental days. Within 1 hr after the exposure, pulmonary free cells were lavaged from the lungs and total and differential cell counts, cellular ATP and protein, lavage fluid protein, ectoenzyme activities, and phagocytosis of $^{51}$Cr-CRBC were measured.

## RESULTS

### Animals: Overall Health Status and Body Weights

For both comparison studies the two groups of rats received from the Harlan Sprague-Dawley, Inc., Madison, WI (Group M) and Indianapolis, IN (Group I) breeding facilities were housed in separate animal rooms and serviced by different animal care personnel to minimize possible cross contamination of the animals. The rats were observed at least once every working day. One rat from Group M died accidently. Another rat was lethargic, ataxic and lost weight and it was subsequently killed and necropsied. Grossly, dark red fluid was found in the urinary bladder. Microbiologically, *E. coli* was isolated from the ear swab and no pathogens were found in the caecal specimen. Presence of *E. coli* in animal specimen is common and not significant. With the exception of a crusted eye in one animal from Group I, all other animals appeared healthy.

When following a two-week quarantine period ten rats from each colony were killed and necropsied, no gross lesions were observed. Specimens submitted from rats from SN 79-SC for microbiological and parasitological testing were free of pathogenic microorganisms and endoparsites. All serum viral antibody titers were negative except for the rats from the Madison colony, all of which had positive titers to PVM.

All rats from both colonies were weighed on the day after arrival and again on Day 12 or 13 of the quarantine period as part of the randomization procedure. The data in Table B-1 show that although weights of rats received from both colonies were similar at arrival, rats from Indianapolis (PVM-free colony) gained 13-18 g, or about 20% more between the time of arrival and randomization.

### RP/BR Exposures

All rats received one 3.5 hr exposure to 1 mg/L of RP/BR aerosol or to filtered air. The RP/BR aerosol was monitored for mass concentration periodically by gravimetric filter collection and

Table B - 1

COMPARISONS OF MEAN BODY WEIGHTS (g) OF RATS
FROM THE INDIANOPOLIS (I) AND MADISON (M)
BREEDING COLONIES OF HARLAN/SPRAGUE-DAWLEY, INC.

| | | Body weights at Arrival | | | Body Weights at Randomization | | |
|---|---|---|---|---|---|---|---|
| Study | Source | Mean | ±SD | N | Mean | ±SD | N |
| 79-SC | I | 73 | 8 | 87 | 151 | 13 | 86 |
| | M | 71 | 9 | 77 | 131 | 16 | 75 |
| 79-SC2 | I | 64 | 4 | 42 | 156 | 8 | 42 |
| | M | 65 | 4 | 40 | 144 | 8 | 40 |

continuously with light scattering photosensors. Aerosol particle size was determined with a Quartz Crystal Microbalance-based cascade impactor. Percent total phosphorus was analyzed spectrophotometrically from the filter-collected aerosol samples. The aerosol data monitored during the exposures for Study Nos. 79-SC and 79-SC2 are summarized in Table B-2.

Pulmonary Bactericidal Activity (SN79-SC2)

For comparison of pulmonary bactericidal activity in the two rat colonies two aerosol challenges with $^{35}$S-*Klebsiella pneumoniae* were done on each of the two consecutive exposure days. Seven RP/BR-exposed and seven control rats from each of the two colonies were assigned to each radioactive challenge spray of which 2 were 0-hr controls and 5 were 3-hr experimental rats.

The results summarized in Table B-3 demonstrate highly significant decreases in bactericidal activity in the lungs of the exposed rats from both colonies relative to controls when analyzed by Student's t-test. When a three factor mixed-model analysis of variance was used to evaluate the data using treatment and source as fixed factors and replication as a random factor, a significant main effect of RP/BR exposure on bactericidal activity was found ($p \leq 0.001$). The overall mean $\pm$ SD (n) for control and exposed animals, respectively, was 85.89 $\pm$ 17.82 (40) and 36.46 $\pm$ 36.31 (40). In some exposed rats, more bacteria were present after the clearance period than at the time of deposition. Source of animals was not a statistically significant factor. The percentage decreases in the bactericidal activity of rats from the two colonies were quite similar. These decreases were also very similar to those we have reported in the preliminary studies of Phase II after single exposures of rats from the Madison, WI colony.

Pulmonary Lavage Parameters (SN79-SC2)

For the pulmonary lavage assays, the rats were divided into two groups and the RP/BR aerosol exposures staggered over two days. Eight rats from each breeding facility were exposed to RP/BR aerosol or filtered air on each of the two experimental days. Within 1 hr after the exposure, pulmonary free cells were lavaged from the lungs and total and differential cell counts, cellular ATP and protein, lavage fluid protein, ectoenzyme activities, and phagocytosis of $^{51}$Cr-CRBC were measured.

A three factor multivariate mixed-model analysis of variance was used to determine the effects of treatment on these pulmonary defense parameters. As for the bactericidal assay analysis, treatment and source were considered to be fixed effects and replication was considered a random factor. Following the multivariate test, individual univariate comparisons (one parameter

Table B - 2

MASS CONCENTRATION, PARTICLE SIZE AND PERCENT PHOSPHORIC ACID LEVELS IN RP/BR AEROSOLS CALCULATED FOR STUDY NOS. 79-SC AND 79-SC2[a]

| | RP/BR Aerosol | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mass Conc. Determined From[b] | | | | Particle Size[b] | | | | % $H_3PO_4$[c] | |
| | Filter Collected Samples | | Photosensor Readings | | MMAD[d] | | σg | | | |
| Study No. | Mean | ± SD | Mean | ± SD | Mean | ± SD | Mean | ± SD | Mean | ± SD |
| 79-SC | 1.03 | 0.07 | 1.00 | 0.02 | 0.60 | 0.06 | 1.78 | 0.15 | 75.75 | 0.21 |
| 79-SC2 | 1.04 | 0.03 | 0.99 | 0.02 | 0.58 | 0.07 | 1.94 | 0.31 | Not Done | |

[a] Male rats from the two breeding colonies were exposed once to 1 mg/L of RP/BR for 3.5 hr. Groups of animals were staggered for exposure over 2 days because of the labor-intensive procedures of the pulmonary lavage or bactericidal activity assays.

[b] Calculated from the daily means of 2 exposure days.

[c] Calculated from one filter sample collected during SN-79SC.

[d] Mass median aerodynamic diameter

Table B-3

COMPARISON OF THE EFFECT OF EXPOSURE TO RP/BR AEROSOL ON PULMONARY BACTERICIDAL ACTIVITY OF RATS FROM TWO HARLAN/SPRAGUE DAWLEY BREEDING COLONIES

| Origin of Rat Colony | % of Inhaled *K. pneumoniae* Killed in 3 hr | | |
|---|---|---|---|
| | Mean | ± SE | n |
| Indianapolis[a] | 81.1 | 5.4 | 20 |
| | 35.0*** | 7.7 | 20 |
| | 85.9 | 4.6 | 20 |
| Madison | 41.1*** | 9.2 | 20 |

[a]PVM-free colony.

Statistically significant difference from control determined by Student's t test after logarithmic transformation:
***p<0.001.

at a time) were made.

Summary statistics which combine the data from animals from both breeding colonies for control and treatment groups are displayed in Table B-4. The overall multivariate exposure effect was significant ($p \leq 0.001$). In RP/BR-exposed animals, ATP/cells and ATP/protein were increased relative to controls, whereas total cells, cells/BW, phagocytosis of 51Cr-CRBC, ADPI and 5'-ND were significantly decreased relative to controls.

When the effect of animal source was tested (i.e., comparison of two sources of animals), an overall multivariate treatment by source interaction was found ($p \leq 0.05$). Inspection of univariate results revealed several parameters which had different results for the two rat colonies: total cells ($p \leq 0.01$), protein per $10^5$ cells ($p \leq 0.04$) and cells per g body weight ($p \leq 0.02$). Total cells and cells per body weight showed the same decreasing trend following exposure for animals from both colonies as shown in the post hoc comparisons summarized for the two separate studies in Table B-5. As a result of higher cell counts however control values for both parameters in rats from the Indianapolis colony were higher than values for the Madison colony control rats. The values for these parameters after exposure were similar for both colonies indicating bigger changes in the Indianapolis colony rats. Protein per $10^5$ cells was slightly increased after RP/BR exposure in rats from Indianapolis, but slightly decreased in rats from the Madison colony whereas for lavage fluid protein this picture was reversed (Table B-5).

Finally a significant main effect of source was found for ATP per $10^5$ cells ($p \leq 0.05$). This means that cellular ATP content was significantly lower for rats from the Indianapolis colony than the Madison animals in both RP/BR-exposed and control groups although cells from both colonies showed the same increases in this parameters after exposure (see Table B-5).

## CONCLUSIONS

We have found that there was a difference in terms of weight gain between the two breeding colonies during the quarantine period; the PVM-free group (Indianapolis) gained weight faster. Pulmonary bactericidal activity was significantly decreased relative to controls in both groups and the source of animals was not a statistically significant factor. In terms of pulmonary lavage parameters however there was a significant difference in responses due to animal source. The results of the lavage studies demonstrate that changes in the test criteria compared showed generally similar trends for two colonies except for protein per cells and protein per lavage fluid. The other apparent differences

Table B-4

EFFECTS OF A SINGLE 3.5-HR EXPOSURE TO 1 MG/L OF RP/BR AEROSOL ON COMBINED PULMONARY DEFENSE DATA FOR MALE SPRAGUE-DAWLEY RATS FROM TWO BREEDING COLONIES

| | Control | | | Exposed | | |
|---|---|---|---|---|---|---|
| Assay | Mean | ±SD | N | Mean | ±SD | N |
| TOT CELLS | 119.38 | 38.70 | 32 | 84.12*** | 23.81 | 32 |
| TOT CELL/g BW | 74.90 | 22.26 | 32 | 52.96*** | 15.37 | 32 |
| % MACROPHAGES | 98.90 | 1.33 | 31 | 99.09 | 1.25 | 32 |
| PROT/$10^5$ CELL | 19.39 | 3.52 | 32 | 20.00 | 4.93 | 31 |
| ATP/$10^5$ CELL | 0.61 | 0.26 | 32 | 1.00*** | 0.44 | 32 |
| ATP/ug PROT | 3.16 | 1.29 | 32 | 4.33*** | 1.59 | 31 |
| PHAGO [CPM x $10^3$] | 10.47 | 1.23 | 32 | 9.94* | 1.11 | 32 |
| LAV PROT/g BW | 24.26 | 10.12 | 31 | 23.35 | 6.60 | 32 |
| LAP | 14.54 | 4.77 | 28 | 13.35 | 5.18 | 29 |
| ADPI | 24.42 | 7.07 | 31 | 21.12* | 6.97 | 31 |
| 5'-N | 6.55 | 2.79 | 31 | 4.70** | 2.73 | 31 |

Significant difference from controls.

*p<0.05
**p<0.01
***p<0.001

Table C-5

COMPARISON OF EFFECTS OF A SINGLE 3.5-HR EXPOSURE TO 1 mg/L OF RP/BK AEROSOL ON PULMONARY DEFENSE PARAMETERS OF MALE SPRAGUE-DAWLEY RATS FROM THE INDIANOPOLIS AND MADISON BREEDING COLONIES OF HARLAN/SPRAGUE-DAWLEY, INC.

| | Madison | | | | | | Indianapolis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | Exposed | | | Control | | | Exposed | | |
| Assay | Mean | ±SD | N | Mean | ±SD | N | Mean | ±SD | N | Mean | ±SD | N |
| TOT CELLS | 100.93 | 35.33 | 16 | 82.26 | 22.36 | 16 | 137.83 | 33.47 | 16 | 85.98*** | 25.78 | 16 |
| TOT CELL/g BW | 66.30 | 22.84 | 16 | 53.59 | 14.69 | 16 | 83.49 | 18.58 | 16 | 52.34*** | 16.48 | 16 |
| % MACROPHAGES | 99.07 | 1.03 | 15 | 99.25 | 1.13 | 16 | 98.75 | 1.57 | 16 | 98.94 | 1.39 | 16 |
| PROT/$10^5$ CELL | 20.26 | 4.33 | 16 | 18.86 | 3.08 | 15 | 18.53 | 2.29 | 16 | 21.08 | 6.11 | 16 |
| ATP/$10^5$ CELL | 0.69 | 0.24 | 16 | 1.13 | 0.46 | 16 | 0.53 | 0.25 | 16 | 0.87** | 0.38 | 16 |
| ATP/ug PROT | 3.52 | 1.35 | 16 | 4.58 | 1.96 | 15 | 2.80 | 1.16 | 16 | 4.11** | 1.18 | 16 |
| PHAGO [CPM x $10^3$] | 10.73 | 1.12 | 16 | 10.05* | 0.70 | 16 | 10.22 | 1.30 | 16 | 9.84 | 1.43 | 16 |
| LAV PROT/g BW | 26.09 | 11.53 | 15 | 22.29 | 7.45 | 16 | 22.55 | 8.60 | 16 | 24.41 | 5.68 | 16 |
| LAP | 15.53 | 5.71 | 14 | 13.20 | 5.08 | 14 | 13.56 | 3.54 | 14 | 13.49 | 5.46 | 15 |
| ADPI | 24.77 | 8.66 | 15 | 22.20 | 6.91 | 15 | 24.10 | 5.47 | 16 | 20.11 | 7.09 | 16 |
| 5'-N | 6.09 | 3.19 | 15 | 5.05 | 3.03 | 15 | 6.97 | 2.39 | 16 | 4.36** | 2.46 | 16 |

Significant difference from controls: *p<0.05, **p<0.01, ***p<0.001

(total cells, cells per body weight, and ATP per cells) were for parameters which showed the same direction of response after RP/BR exposure for animals from both breeding colonies. However when in post hoc comparisons the effects of RP/BR exposure were evaluated in each of the two colonies (Table B-5) several significant changes relative to controls were found in the Indianapolis group whereas no significant differences were observed for the same parameters in rats obtained from Madison. This suggests that the PVM-free colony from Indianapolis is somewhat more susceptible to the exposures. As a result of these studies it appears to be feasible to select the PVM-free colony for the subchronic studies since in general the responses were similar to those observed in the Madison (PVM positive) colony. However, in view of the fact that the PVM-free rats appeared to be more responsive in the pulmonary lavage assays we should be careful in selecting the highest exposure dose to avoid encountering unexpecting mortality rates during the subchronic exposures.

# APPENDIX C
# MORPHOLOGICAL PATHOLOGY

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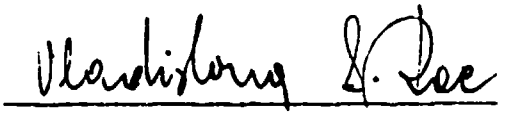
STUDY NUMBER 79
NECROPSY REPORT

STUDY NUMBER 79
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PATHOLOGY SYNOPSIS

Treatment-related lesions were observed at necropsy in the lungs of the rats exposed to the aerosols of RP/BR combustion products. A red discoloration with varying patterns of distribution (mottled, multifocal, focal, diffusely red, and multiple red foci) were observed in the lungs in the initial exposure groups. The lesions were not seen in the lungs of the rats in the recovery groups, which received similar treatment. The small group size makes it difficult to determine whether the lesions observed in the lungs were significantly affected by varying exposure concentrations of the aerosol, frequency of exposure, or duration of the exposure. Microscopic examinations of tissues revealed treatment-related lesions in the lung as terminal bronchial fibrosis. The lesion was characterized by thickening of the alveolar walls. The lesion increased in incidence and severity with increased concentrations and length of exposure to the test material. After a fourteen-day recovery period following the test exposure did not reduce the incidence or severity of the lesion. The peribronchial and perivascular infiltration of eosinophils may also be treatment-related. The exposure to RP/BR for four weeks via inhalation at the concentrations and for the duration of exposure did not produce any treatment-related lesions in the nasal turbinates, trachea, pulmonary lymph nodes, heart, eyes, kidneys, adrenals, liver, esophagus, stomach, duodenum, or urinary bladder.



Vladislava S. Rac, M.S., D.V.M.
Scientific Advisor
Veterinary Pathologist

# GROSS NECROPSY OBSERVATIONS

Phase III - Study Number 79

## INTRODUCTION

In accordance with the experimental protocol, examination of organs was performed on 96 male Sprague-Dawley rats for IITRI Project L6139, Study Number 79 Phase III. The experimental design is presented in the histopathology report.

A summary of gross observations is presented in Table Groups A and B. The tables in Group A compare each of the aerosol exposure concentrations with various exposure frequencies (F1, F2, F3), while the tables in Group B compare each exposure frequency with various exposure concentrations of the aerosol (0.0, 0.4, 0.75, and 1.0 mg/l) for both the initial exposure and recovery groups.

## RESULTS AND DISCUSSION

Gross lesions were observed primarily in the lungs, urinary bladder, thymus, and mandibular lymph nodes in both the initial exposure and recovery groups. The gross lesions involving the lungs appeared to be treatment-related. A red discoloration with varying patterns of distributions (mottled, multifocal, focal, and diffusly red) was most often observed in the lungs of rats in the initial exposure group. Multiple red foci were present in the lungs of 3/4 rats in the initial exposure group at the 1.0 mg/l exposure concentration, at the 3.5 hour exposure duration, at the F2 exposure frequency. The lesion was not seen in lungs of rats in the recovery group which had received similar treatment. However, it should be noted that multiple red foci were observed in the lungs of 2/4 rats at both the 0.4 and 0.75 mg/l exposure concentration, at F1 and F2 exposure frequencies, at the 1.0 hour exposure duration. Mottled brown and tan lungs were also observed in a few rats. Calculi were present in the urinary bladder of many of the rats regardless of the treatment received. Red discolorations were observed involving the mandibular lymph nodes and thymuses of a few rats.

## SUMMARY AND CONCLUSIONS

In summary, treatment-related lesions were observed in the lungs of rats exposured to the Aerosols of RP/BR combustion products. However, the small group size makes it very difficult to determine if the lesions

observed in the lungs were significantly affected by varying exposure concentrations of the aerosols, frequency of exposure, or duration of exposure. Lesions were not observed in the lungs of rats in the recovery group at the 1.0 mg/l exposure concentration. All other lesions (except those in the thymus) were regarded as incidental findings and were present in both the control and treated groups.

Florida Lorne S. Lee

# TABLE GROUP A

Project No.: L06139
Exposure Concentration (mg/l): 0.0

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| Number of Rats Examined | | 0 | 0 | 0 | 0 | 12 | 0 |
| No Gross Lesions | | 0 | 0 | 0 | 0 | 8 | 0 |
| | | | | | | | |
| LUNGS | | | | | | | |
| Mottled red/red | | | | | | | |
| Multiple red foci | | | | | | | |
| Red focus | | | | | | | |
| Tan foci | | | | | | | |
| Mottled brown/tan | | | | | | | |
| | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | | | | | | |
| Red foci | | | | | | | |
| | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | | | | |
| | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Concentration (mg/l): 0.0

| ORGAN<br>Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | Duration of Exposure: 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| LIVER | | | | | | | |
| White raised area (nodule) | | | | | | | |
| Red focus | | | | | | | |
| | | | | | | | |
| KIDNEYS | | | | | | | |
| Nodule | | | | | | | |
| | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | |
| Enlarged | | | | | | | |
| | | | | | | | |
| URINARY BLADDER | | | | | | | |
| Calculi | | | | | | 1 | |
| | | | | | | | |
| TESTIS | | | | | | | |
| Not apparent | | | | | | | |
| | | | | | | | |
| PROSTATE | | | | | | | |
| Enlarged | | | | | | | |
| | | | | | | | |

Project No.: L0E139
Exposure Concentration (mg/l): 0.0

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| SEMINAL VESICLES | | | | | | | |
| White material adhered to | | | | | | 1 | |
| Edematous | | | | | | | |
| | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | |
| Mottled red/red | | | | | | 3 | |
| Enlarged | | | | | | | |
| Multiple red foci | | | | | | | |
| | | | | | | | |
| TAIL | | | | | | | |
| Red abrasion | | | | | | | |
| | | | | | | | |
| HIND LEG | | | | | | | |
| Musculature - red area | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 0.4

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| Number of Rats Examined | | 4 | 4 | 4 | 4 | 4 | 4 |
| No Gross Lesions | | 1 | 1 | 2 | 2 | 0 | 1 |
| | | | | | | | |
| LUNGS | | | | | | | |
| Mottled red/red | | 1 | | 2 | | 1 | |
| Multiple red foci | | 2 | 1 | | | | |
| Red focus | | | | | 1 | 1 | |
| Tan foci | | | | | | | |
| Mottled brown/tan | | | | | | | |
| | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | 1 | | | 1 | 1 | |
| Red foci | | | | | | 1 | |
| | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | 1 | | | |
| | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | 1 | | | |

Project No.: L06139
Exposure Concentration (mg/l): 0.4

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| LIVER | | | | | | | |
| White raised area (nodule) | | | | | | | |
| Red focus | | | | | | | |
| KIDNEYS | | | | | | | |
| Nodule | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | |
| Enlarged | | | | | | | |
| URINARY BLADDER | | | | | | | |
| Calculi | | | 2 | | 2 | 2 | 1 |
| TESTIS | | | | | | | |
| Not apparent | | | | | | | |
| PROSTATE | | | | | | | |
| Enlarged | | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 0.4

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: Duration of Exposure: 1.0 Hours F1 | F2 | F3 | 3.5 Hours F1 | F2 | F3 |
|---|---|---|---|---|---|---|
| SEMINAL VESICLES | | | | | | |
| White material adhered to | | | | | | |
| Edematous | | | | | | |
| | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | |
| Mottled red/red | 1 | | | 2 | | 1 |
| Enlarged | | | | | 1 | |
| Multiple red foci | | | | | | |
| | | | | | | |
| TAIL | | | | | | |
| Red abrasion | | | | | | 1 |
| | | | | | | |
| HIND LEG | | | | | | |
| Musculature - red area | | | | | | 1 |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Project No.: L06139
*Exposure Concentration (mg/l): 0.75*

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| Number of Rats Examined | | 4 | 4 | 4 | 4 | 4 | 4 |
| No Gross Lesions | | 1 | 0 | 4 | 1 | 2 | 2 |
| | | | | | | | |
| LUNGS | | | | | | | |
| Mottled red/red | | | | | | | |
| Multiple red foci | | | 2 | | | | |
| Red focus | | | | | 1 | | |
| Tan foci | | | | | | | |
| Mottled brown/tan | | 2 | | | | | |
| | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | 2 | | | | | |
| Red foci | | | 1 | | | | |
| | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | | | | |
| | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 0.75

## Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| LIVER | | | | | | | |
| White raised area (nodule) | | | | | | | |
| Red focus | | | | | | | |
| KIDNEYS | | | | | | | |
| Nodule | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | |
| Enlarged | | | 1 | | | | |
| URINARY BLADDER | | | | | | | |
| Calculi | | 2 | 1 | | 1 | 2 | 1 |
| TESTIS | | | | | | | |
| Not apparent | | | | | | | |
| PROSTATE | | | | | | | |
| Enlarged | | | | | 1 | | |

Project No.: L06139
Exposure Concentration (mg/l): 0.75

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Duration of Exposure: 1.0 Hours F1 | 1.0 Hours F2 | 1.0 Hours F3 | 3.5 Hours F1 | 3.5 Hours F2 | 3.5 Hours F3 |
|---|---|---|---|---|---|---|
| SEMINAL VESICLES | | | | | | |
| White material adhered to | | | | | | 1 |
| Edematous | | | | | | |
| | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | |
| Mottled red/red | 1 | 2 | | | | 1 |
| Enlarged | | | | | | |
| Multiple red foci | | | | | | |
| | | | | | | |
| TAIL | | | | | | |
| Red abrasion | | | | | | |
| | | | | | | |
| HIND LEG | | | | | | |
| Musculature - red area | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 1.0

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| Number of Rats Examined | | 4 | 4 | 4 | 4 | 4 | 4 |
| No Gross Lesions | | 1 | 2 | 1 | 1 | 0 | 1 |
| | | | | | | | |
| LUNGS | | | | | | | |
| Mottled red/red | | 1 | 1 | | | | |
| Multiple red foci | | | | 1 | | 3 | 1 |
| Red focus | | 1 | | | | | |
| Tan foci | | | | | | | |
| Mottled brown/tan | | 1 | | | 1 | | |
| | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | | | 1 | | | |
| Red foci | | | | 1 | | | |
| | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | | | | |
| | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 1.0

## Necropsy Observations
Rats Killed After the Last Exposure

| Organ Lesion | Exposure Frequency: Duration of Exposure: 1.0 Hours F1 | 1.0 Hours F2 | 1.0 Hours F3 | 3.5 Hours F1 | 3.5 Hours F2 | 3.5 Hours F3 |
|---|---|---|---|---|---|---|
| LIVER | | | | | | |
| White raised area (nodule) | | | | | | |
| Red focus | | | | | | |
| | | | | | | |
| KIDNEYS | | | | | | |
| Nodule | | | 1 | | | |
| | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | |
| Enlarged | | | | | | |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| Calculi | 1 | | 1 | 2 | 2 | 1 |
| | | | | | | |
| TESTIS | | | | | | |
| Not apparent | | | | 1 | | |
| | | | | | | |
| PROSTATE | | | | | | |
| Enlarged | 1 | | | | | |
| | | | | | | |

Project No.: L06139
Exposure Concentration (mg/l): 1.0

Necropsy Observations
Rats Killed After the Last Exposure

| ORGAN Lesion | Exposure Frequency: Duration of Exposure: 1.0 Hours F1 | F2 | F3 | 3.5 Hours F1 | F2 | F3 |
|---|---|---|---|---|---|---|
| SEMINAL VESICLES | | | | | | |
| White material adhered to | | | 1 | | | 1 |
| Edematous | | | | | | |
| | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | |
| Mottled red/red | | 2 | 1 | | 1 | 2 |
| Enlarged | | | | | | |
| Multiple red foci | | | | | 1 | |
| | | | | | | |
| TAIL | | | | | | |
| Red abrasion | | | | | | |
| | | | | | | |
| HIND LEG | | | | | | |
| Musculature - red area | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

## Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 0.0

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours F1 | 1.0 Hours F2 | 1.0 Hours F3 | 3.5 Hours F1 | 3.5 Hours F2 | 3.5 Hours F3 |
|---|---|---|---|---|---|---|---|
| Number of Rats Examined | | 0 | 0 | 0 | 0 | 4 | 0 |
| No Gross Lesions | | 0 | 0 | 0 | 0 | 1 | 0 |
| LUNGS | | | | | | | |
| Mottled red/red | | | | | | | |
| Multiple red foci | | | | | | | |
| Red focus | | | | | | 1 | |
| Tan foci | | | | | | | |
| Mottled brown/tan | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | | | | | | |
| Red foci | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 0.0

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours F1 | 1.0 Hours F2 | 1.0 Hours F3 | 3.5 Hours F1 | 3.5 Hours F2 | 3.5 Hours F3 |
|---|---|---|---|---|---|---|---|
| LIVER | | | | | | | |
| White raised area (nodule) | | | | | | 1 | |
| Red focus | | | | | | 1 | |
| | | | | | | | |
| KIDNEYS | | | | | | | |
| Nodule | | | | | | | |
| | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | |
| Enlarged | | | | | | | |
| | | | | | | | |
| URINARY BLADDER | | | | | | | |
| Calculi | | | | | | 3 | |
| | | | | | | | |
| TESTIS | | | | | | | |
| Not apparent | | | | | | | |
| | | | | | | | |
| PROSTATE | | | | | | | |
| Enlarged | | | | | | | |
| | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 0.0

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours F1 | 1.0 Hours F2 | 1.0 Hours F3 | 3.5 Hours F1 | 3.5 Hours F2 | 3.5 Hours F3 |
|---|---|---|---|---|---|---|---|
| SEMINAL VESICLES | | | | | | | |
| White material adhered to | | | | | | | |
| Edematous | | | | | | | |
| | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | |
| Mottled red/red | | | | | | 3 | |
| Enlarged | | | | | | | |
| Multiple red foci | | | | | | | |
| | | | | | | | |
| TAIL | | | | | | | |
| Red abrasion | | | | | | | |
| | | | | | | | |
| HIND LEG | | | | | | | |
| Musculature - red area | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

## Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 1.0

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| Number of Rats Examined | | 0 | 4 | 0 | 0 | 4 | 0 |
| No Gross Lesions | | 0 | 2 | 0 | 0 | 2 | 0 |
| LUNGS | | | | | | | |
| Mottled red/red | | | | | | | |
| Multiple red foci | | | 2 | | | | |
| Red focus | | | | | | | |
| Tan foci | | | 1 | | | | |
| Mottled brown/tan | | | | | | | |
| THYMUS | | | | | | | |
| Mottled red | | | 1 | | | | |
| Red foci | | | | | | | |
| THORACIC CAVITY | | | | | | | |
| Contained abdominal viscera | | | | | | | |
| DIAPHRAGM | | | | | | | |
| Rupture | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 1.0

| ORGAN Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | Duration of Exposure: 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F1 | F2 | F3 |
| LIVER | | | | | | | |
| White raised area (nodule) | | | | | | | |
| Red focus | | | | | | | |
| KIDNEYS | | | | | | | |
| Nodule | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | |
| Enlarged | | | | | | | |
| URINARY BLADDER | | | | | | | |
| Calculi | | | 1 | | | 2 | |
| TESTIS | | | | | | | |
| Not apparent | | | | | | | |
| PROSTATE | | | | | | | |
| Enlarged | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Concentration (mg/l): 1.0

| ORGAN<br>Lesion | Exposure Frequency: | Duration of Exposure: 1.0 Hours | | | Duration of Exposure: 3.5 Hours | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | Fi | F2 | F3 |
| SEMINAL VESICLES | | | | | | | |
| White material adhered to | | | | | | | |
| Edematous | | | | | | | 1 |
| | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | |
| Mottled red/red | | | | | | | 2 |
| Enlarged | | | | | | | |
| Multiple red foci | | | | | | | |
| | | | | | | | |
| TAIL | | | | | | | |
| Red abrasion | | | | | | | |
| | | | | | | | |
| HIND LEG | | | | | | | |
| Musculature - red area | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

TABLE GROUP B

Necropsy Observations

## Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F1

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| Number of Rats Examined | | 0 | 4 | 4 | 4 | 0 | 4 | 4 | 4 |
| No Gross Lesions | | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 1 |
| LUNGS | | | | | | | | | |
| Mottled red/red | | | 1 | | 1 | | | | |
| Multiple red foci | | | 2 | | | | | | |
| Red focus | | | | | 1 | | 1 | 1 | |
| Tan foci | | | | | | | | | |
| Mottled brown/tan | | | | 2 | 1 | | | | 1 |
| THYMUS | | | | | | | | | |
| Mottled red | | | 1 | 2 | | | 1 | | |
| Red foci | | | | | | | | | |
| THORACIC CAVITY | | | | | | | | | |
| Contained abdominal viscera | | | | | | | | | |
| DIAPHRAGM | | | | | | | | | |
| Rupture | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F1

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | Duration of Exposure: 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| LIVER | | | | | | | | | |
| White raised area (nodule) | | | | | | | | | |
| Red focus | | | | | | | | | |
| | | | | | | | | | |
| KIDNEYS | | | | | | | | | |
| Nodule | | | | | | | | | |
| | | | | | | | | | |
| MESENTERIC LYMPH NODES | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | |
| Calculi | | | | 2 | 1 | | 2 | 1 | 2 |
| | | | | | | | | | |
| TESTIS | | | | | | | | | |
| Not apparent | | | | | | | | | 1 |
| | | | | | | | | | |
| PROSTATE | | | | | | | | | |
| Enlarged | | | | | 1 | | | 1 | |
| | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F1

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | Duration of Exposure: 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| SEMINAL VESICLES | | | | | | | | | |
| White material adhered to | | | | | | | | | |
| Edematous | | | | | | | | | |
| | | | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | | | |
| Mottled red/red | | | 1 | 1 | | | 2 | | |
| Enlarged | | | | | | | | | |
| Multiple red foci | | | | | | | | | |
| | | | | | | | | | |
| TAIL | | | | | | | | | |
| Red abrasion | | | | | | | | | |
| | | | | | | | | | |
| HIND LEG | | | | | | | | | |
| Musculature - red area | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F2

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| Number of Rats Examined | | 0 | 4 | 4 | 4 | 12 | 4 | 4 | 4 |
| No Gross Lesions | | 0 | 1 | 0 | 2 | 8 | 0 | 2 | 0 |
| LUNGS | | | | | | | | | |
| Mottled red/red | | | | | 1 | | 1 | | |
| Multiple red foci | | | 1 | 2 | | | | | 3 |
| Red focus | | | | | | | 1 | | |
| Tan foci | | | | | | | | | |
| Mottled brown/tan | | | | | | | | | |
| THYMUS | | | | | | | | | |
| Mottled red | | | | | | | 1 | | |
| Red foci | | | | 1 | | | 1 | | |
| THORACIC CAVITY | | | | | | | | | |
| Contained abdominal viscera | | | | | | | | | |
| DIAPHRAGM | | | | | | | | | |
| Rupture | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F2

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | Duration of Exposure: 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| LIVER | | | | | | | | | |
| White raised area (nodule) | | | | | | | | | |
| Red focus | | | | | | | | | |
| | | | | | | | | | |
| KIDNEYS | | | | | | | | | |
| Nodule | | | | | | | | | |
| | | | | | | | | | |
| MESENTERIC LYMPH NODES | | | | | | | | | |
| Enlarged | | | | 1 | | | | | |
| | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | |
| Calculi | | | 2 | 1 | | 1 | 2 | 2 | 2 |
| | | | | | | | | | |
| TESTIS | | | | | | | | | |
| Not apparent | | | | | | | | | |
| | | | | | | | | | |
| PROSTATE | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |

## Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F2

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| SEMINAL VESICLES | | | | | | | | | |
| White material adhered to | | | | | | 1 | | | |
| Edematous | | | | | | | | | |
| | | | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | | | |
| Mottled red/red | | | | 2 | 2 | 3 | | | 1 |
| Enlarged | | | | | | | 1 | | |
| Multiple red foci | | | | | | | | | 1 |
| | | | | | | | | | |
| TAIL | | | | | | | | | |
| Red abrasion | | | | | | | | | |
| | | | | | | | | | |
| HIND LEG | | | | | | | | | |
| Musculature - red area | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: LU6139
Exposure Frequency: F3

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| Number of Rats Examined | | 0 | 4 | 4 | 4 | 0 | 4 | 4 | 4 |
| No Gross Lesions | | 0 | 2 | 4 | 1 | 0 | 1 | 2 | 1 |
| | | | | | | | | | |
| LUNGS | | | | | | | | | |
| Mottled red/red | | | 2 | | | | | | |
| Multiple red foci | | | | | 1 | | | | 1 |
| Red focus | | | | | | | | | |
| Tan foci | | | | | | | | | |
| Mottled brown/tan | | | | | | | | | |
| | | | | | | | | | |
| THYMUS | | | | | | | | | |
| Mottled red | | | | | 1 | | | | |
| Red foci | | | | | 1 | | | | |
| | | | | | | | | | |
| THORACIC CAVITY | | | | | | | | | |
| Contained abdominal viscera | | | 1 | | | | | | |
| | | | | | | | | | |
| DIAPHRAGM | | | | | | | | | |
| Rupture | | | 1 | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure F uency: F3

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | Duration of Exposure: 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| LIVER | | | | | | | | | |
| White raised area (nodule) | | | | | | | | | |
| Red focus | | | | | | | | | |
| | | | | | | | | | |
| KIDNEYS | | | | | | | | | |
| Nodule | | | | | | | | | |
| | | | | | | | | | |
| MESENTERIC LYMPH NODES | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | |
| Calculi | | | | | | | 1 | 1 | 1 |
| | | | | | | | | | |
| TESTIS | | | | | | | | | |
| Not apparent | | | | | | | | | |
| | | | | | | | | | |
| PROSTATE | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project No.: L06139
Exposure Frequency: F3

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| SEMINAL VESICLES | | | | | | | | | |
| White material adhered to | | | | | | | | 1 | 1 |
| Edematous | | | | | | | | | |
| | | | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | | | |
| Mottled red/red | | | | | | | 1 | 1 | 2 |
| Enlarged | | | | | | | | | |
| Multiple red foci | | | | | | | | | |
| | | | | | | | | | |
| TAIL | | | | | | | | | |
| Red abrasion | | | | | | | 1 | | |
| | | | | | | | | | |
| HIND LEG | | | | | | | | | |
| Musculature - red area | | | | | | | 1 | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Frequency: F2

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| Number of Rats Examined | | 0 | 0 | 0 | 4 | 4 | 0 | 0 | 4 |
| No Gross Lesions | | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 2 |
| LUNGS | | | | | | | | | |
| Mottled red/red | | | | | | | | | |
| Multiple red foci | | | | | 1 | | | | |
| Red focus | | | | | | 1 | | | |
| Tan foci | | | | | 1 | | | | |
| Mottled brown/tan | | | | | | | | | |
| THYMUS | | | | | | | | | |
| Mottled red | | | | | 1 | | | | |
| Red foci | | | | | | | | | |
| THORACIC CAVITY | | | | | | | | | |
| Contained abdominal viscera | | | | | | | | | |
| DIAPHRAGM | | | | | | | | | |
| Rupture | | | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Frequency: F2

| ORGAN Lesion | Exposure Concentration: mg/l | Duration of Exposure: 1.0 hour | | | | Duration of Exposure: 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| LIVER | | | | | | | | | |
| White raised area (nodule) | | | | | | 1 | | | |
| Red focus | | | | | | 1 | | | |
| | | | | | | | | | |
| KIDNEYS | | | | | | | | | |
| Nodule | | | | | | | | | |
| | | | | | | | | | |
| MESENTERIC LYMPH NODES | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | |
| Calculi | | | | | 1 | 3 | | | 2 |
| | | | | | | | | | |
| TESTIS | | | | | | | | | |
| Not apparent | | | | | | | | | |
| | | | | | | | | | |
| PROSTATE | | | | | | | | | |
| Enlarged | | | | | | | | | |
| | | | | | | | | | |

Necropsy Observations
Recovery Group

Project No.: L06139
Exposure Frequency: F2

Exposure Concentration: mg/l

Duration of Exposure

| ORGAN Lesion | 1.0 hour | | | | 3.5 Hour | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.0 | 0.4 | 0.75 | 1.0 | 0.0 | 0.4 | 0.75 | 1.0 |
| SEMINAL VESICLES | | | | | | | | |
| White material adhered to | | | | | | | | |
| Edematous | | | | | | | | 1 |
| | | | | | | | | |
| MANDIBULAR LYMPH NODES | | | | | | | | |
| Mottled red/red | | | | | 3 | | | 2 |
| Enlarged | | | | | | | | |
| Multiple red foci | | | | | | | | |
| | | | | | | | | |
| TAIL | | | | | | | | |
| Red abrasion | | | | | | | | |
| | | | | | | | | |
| HIND LEG | | | | | | | | |
| Musculature - red area | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
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# EPL PATHOLOGY SYNOPSIS

## IITRI PROJECT NUMBER L06139
## PHASE III STUDY 79

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT

Submitted to:

IIT Research Institute
Chicago, Illinois 60616

January 23, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O.Iverson

Study Title: Repeated Inhalation Exposure Studies to Aerosols of RP/BR Combustion Products in Rats

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on January 11-13, and 20 1984. All findings were reported to the Study Director and Management.

Betty L. Flankenhorn

Betty L. Flankenhorn

January 20, 1984

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**IITRI PROJECT NUMBER L06139**
**PHASE III STUDY 79**

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY SUMMARY

Microscopic examinations were performed on selected tissues from male Sprague-Dawley rats. The purpose of this study was to evaluate the effects of exposure concentration, duration, frequency, and recovery time of the repeated exposure of rats to aerosols of combustion products of Red Phosphorus/Butyl Rubber (RP/BR) on various biologic endpoints. This report contains the histopathologic findings. The experimental design for this study was as follows:

| Group Code | Exposure Class Conc. | Hours/Day | Exposure Frequency | Recovery | Number of Rats |
|---|---|---|---|---|---|
| I | 0 | 3.5 | F2 | No | 12 |
| IR | 0 | 3.5 | F2 | Yes | 4 |
| II | C1 | 1.0 | F1,2,3 | No | 12 |
| III | C1 | 3.5 | F1,2,3 | No | 12 |
| IV | C2 | 1.0 | F1,2,3 | No | 12 |
| V | C2 | 3.5 | F1,2,3 | No | 12 |
| VI | C3 | 1.0 | F1,2,3 | No | 12 |
| VIR | C3 | 1.0 | F2 | Yes | 4 |
| VII | C3 | 3.5 | F1,2,3 | No | 12 |
| VIIR | C3 | 3.5 | F2 | Yes | 4 |

All animals were exposed for four weeks. Recovery animals were then untreated for an additional fourteen days. The aerosol concentrations and exposure frequencies were as follows:

| | | |
|---|---|---|
| C1 | = | 0.4 mg/L |
| C2 | = | 0.75 mg/L |
| C3 | = | 1.0 mg/L |
| F1 | = | exposure on two consecutive days |
| F2 | = | exposure on four consecutive days |
| F3 | = | two exposure days separated by two days rest |

All rats were necropsied and gross and histologic evaluations of the respiratory tract were conducted. According to protocol, the following tissues were trimmed and processed to paraffin blocks: trachea, pulmonary lymph nodes, each lung lobe, nasal turbinates and gross lesions. The paraffin blocks were then shipped to Experimental Pathology Laboratories, Inc. where hematoxylin and eosin stained slides were prepared and examined.

**RESULTS**

The microscopic changes and a detailed listing of all tissues evaluated are presented in the Histopathology Incidence Tables. All lesions are summarized by treatment group and presented in the Summary Incidence Tables. A correlation of lesions observed at necropsy with the corresponding microscopic observation, where possible, is presented in the Correlation of Gross and Microscopic Findings Tables. The gross observations in these tables were transcribed from the necropsy sheets provided with the paraffin blocks.

The primary treatment-related change seen histologically in the study was in the lung and diagnosed as "terminal bronchiolar fibrosis". The lesion consisted of thickening of the alveolar walls where the terminal bronchiole, lined by cuboidal epithelium, joined the alveolar sacs. The thickening consisted of a heterogeneous eosinophilic material compatible with collagen, containing small numbers of cells. Larger cells with prominent nuclei frequently lined the affected area. These cells appeared to be macrophages or activated Type II pneumocytes. The lesion was first detectable at a very minimal level in all of the Group III (0.4mg/l) rats that received exposure on four consecutive days. It was not seen in the F1 or F3 exposures in this treatment group. The rats in all exposures in Group V (0.75mg/l) had terminal bronchiolar fibrosis. In the F2 animals in this group the lesion was mild in severity. At least three of four animals in each of the exposure groups in Group VI also had the lesion. All Group VII animals at all exposure frequencies had moderate terminal bronchiolar fibrosis. The fourteen day recovery period given the animals in Group VIR and Group VIIR did not affect the incidence or severity of the lesion.

An additional change that was seen in only treated animals in some of the exposure frequencies in all treatment groups was the presence of a minimal to mild eosinophilic infiltrate around the airways and blood vessels. The infiltrate consisted primarily of eosinophils with small numbers of neutrophils and

lymphcytes intermixed. The highest incidence seen was 2/4 animals and occurred in Groups IV, V, and VI. The presence of alveolar macrophages was noted in both control and treated rats. The highest incidence (4/4) was seen in F2 Group VII.

All other changes seen in this study occurred in both control and treated animals or were present in such low incidence as to not be considered treatment related.

## CONCLUSIONS

The results of this microscopic examination indicate that administration of RP/BR to rats for four weeks via inhalation at the concentrations and for the durations of exposure used in this study did not produce treatment related changes in the nasal turbinate, trachea, or pulmonary lymph nodes.

Treatment related changes were seen in the lung. The primary lesion seen was terminal bronchiolar fibrosis which first became evident when the rats were exposed to 0.4 mg/l of aerosol for 3.5 hours/day for four consecutive days. The lesion increased in incidence and severity with increased concentrations and length of exposure of the test material. Holding the animals for a fourteen day recovery period following the last exposure did not reduce the incidence or severity of the lesion. An additional pulmonary lesion was seen in some of the treated animals and may be treatment related. This was the peribronchiolar and perivascular infiltration of eosinophils and

was diagnosed "eosinophilic infiltrate".

W.O. Iverson, D.V.M.
Diplomate ACVP

January 23, 1974

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP I & I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | I<br>F2 | | IR<br>F2 | | |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (12) | | (4) | | |
| Hemorrhage | | 1 | | 1 | | |
| Acute Inflammation | | 1 | | 0 | | |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (12) | | (4) | | |
| Hemorrhage | | 4 | | 2 | | |
| Exudate | | 1 | | 0 | | |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (12) | | (4) | | |
| Hemorrhage | | 0 | | 0 | | |
| Lymphocytic Infiltrate | | 0 | | 0 | | |
| Squamous Metaplasia | | 0 | | 0 | | |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (11) | | (4) | | |
| Hemorrhage | | 3 | | 4 | | |
| Edema | | 2 | | 2 | | |
| Lymphocytic Hyperplasia | | 4 | | 4 | | |
| Macrophage Hyperplasia | | 2 | | 1 | | |
| Lymphocytic Infiltrate | | 0 | | 0 | | |
| | | | | | | |
| | | | | | | |
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| | | | | | | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

## SUMMARY INCIDENCE TABLE

GROUP I & I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | I<br>F2 | | IR<br>F2 | | |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (12) | | (4) | | |
| Atelectasis | | 6 | | 3 | | |
| Hemorrhage | | 0 | | 0 | | |
| Focal Lymphocyte Aggregate | | 4 | | 0 | | |
| Alveolar Macrophages | | 2 | | 1 | | |
| Interstitial Inflammation | | 3 | | 1 | | |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 0 | | 0 | | |
| Eosinophilic Infiltrate | | 0 | | 0 | | |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (12) | | (4) | | |
| Lymphocytic Hyperplasia | | 2 | | 3 | | |
| Macrophage Hyperplasia | | 0 | | 0 | | |
| Edema | | 0 | | 0 | | |
| Hemorrhage | | 3 | | 3 | | |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | ( 1) | | (0) | | |
| Ejaculate | | 1 | | 0 | | |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | ( 1) | | (3) | | |
| Concretion | | 0 | | 3 | | |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | ( 0) | | (1) | | |
| Necrosis | | 0 | | 1 | | |
| Hemorrhage | | 0 | | 1 | | |

PROJECT 106139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP I & I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | I<br>F2 | | IR<br>F2 | | |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| Hemorrhage | | 0 | | 0 | | |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| Erosion | | 0 | | 0 | | |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| Hemorrhage | | 0 | | 0 | | |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| Edema | | 0 | | 0 | | |
| Lymphocytic Hyperplasia | | 0 | | 0 | | |
| Macrophage Hyperplasia | | 0 | | 0 | | |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | | (0) | | |
| Edema | | 0 | | 0 | | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | II<br>F1 | | II<br>F2 | | II<br>F3 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 1 |
| Acute Inflammation | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 2 | | 1 | | 3 |
| Exudate | | 0 | | 0 | | 0 |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 1 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| Squamous Metaplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 0 |
| Edema | | 1 | | 3 | | 2 |
| Lymphocytic Hyperplasia | | 3 | | 2 | | 3 |
| Macrophage Hyperplasia | | 2 | | 2 | | 0 |
| Lymphocytic Infiltrate | | 0 | | 1 | | 0 |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP II 0.4 MG/L

1.0 HOURS/DAY

| Group<br>Exposure Frequency | | II<br>F1 | | II<br>F2 | | II<br>F3 |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Atelectasis | | 2 | | 1 | | 3 |
| Hemorrhage | | 0 | | 0 | | 1 |
| Focal Lymphocyte Aggregate | | 0 | | 1 | | 0 |
| Alveolar Macrophages | | 1 | | 1 | | 0 |
| Interstitial Inflammation | | 0 | | 1 | | 2 |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 0 | | 0 | | 0 |
| Eosinophilic Infiltrate | | 1 | | 1 | | 1 |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (1) | | (0) | | (0) |
| Lymphocytic Hyperplasia | | 1 | | 0 | | 0 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| Edema | | 0 | | 0 | | 0 |
| Hemorrhage | | 1 | | 0 | | 0 |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Ejaculate | | 0 | | 0 | | 0 |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (0) | | (2) | | (0) |
| Concretion | | 0 | | 2 | | 0 |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Necrosis | | 0 | | 0 | | 0 |
| Hemorrhage | | 0 | | 0 | | 0 |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | II<br>F1 | | II<br>F2 | | II<br>F3 |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (1) | | (0) | | (0) |
| Hemorrhage | | 1 | | 0 | | 0 |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Erosion | | 0 | | 0 | | 0 |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Hemorrhage | | 0 | | 0 | | 0 |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| Lymphocytic Hyperplasia | | 0 | | 0 | | 0 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS SUMMARY INCIDENCE TABLE

GROUP III 0.4 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | III<br>F1 | | III<br>F2 | | III<br>F3 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 1 |
| Acute Inflammation | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 1 | | 0 | | 2 |
| Exudate | | 0 | | 0 | | 0 |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 0 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| Squamous Metaplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 1 | | 0 | | 1 |
| Edema | | 1 | | 1 | | 4 |
| Lymphocytic Hyperplasia | | 3 | | 2 | | 3 |
| Macrophage Hyperplasia | | 1 | | 2 | | 1 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | III<br>F1 | | III<br>F2 | | III<br>F3 |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Atelectasis | | 2 | | 1 | | 3 |
| Hemorrhage | | 1 | | 0 | | 1 |
| Focal Lymphocyte Aggregate | | 1 | | 1 | | 1 |
| Alveolar Macrophages | | 1 | | 1 | | 2 |
| Interstitial Inflammation | | 1 | | 0 | | 1 |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 0 | | 4 | | 0 |
| Eosinophilic Infiltrate | | 1 | | 1 | | 1 |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (2) | | (1) | | (1) |
| Lymphocytic Hyperplasia | | 2 | | 1 | | 1 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| Edema | | 0 | | 0 | | 0 |
| Hemorrhage | | 2 | | 0 | | 1 |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Ejaculate | | 0 | | 0 | | 0 |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (2) | | (2) | | (1) |
| Concretion | | 1 | | 1 | | 1 |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Necrosis | | 0 | | 0 | | 0 |
| Hemorrhage | | 0 | | 0 | | 0 |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP III 0.4 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | III<br>F1 | | III<br>F2 | | III<br>F3 |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (1) | | (2) | | (0) |
| Hemorrhage | | 1 | | 2 | | 0 |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined | | (0) | | (0) | | (1) |
| Erosion | | 0 | | 0 | | 1 |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | | (0) | | (1) |
| Hemorrhage | | 0 | | 0 | | 1 |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| Lymphocytic Hyperplasia | | 0 | | 0 | | 0 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| | | | | | | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | IV<br>F1 | | IV<br>F2 | | IV<br>F3 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 1 |
| Acute Inflammation | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 1 | | 0 | | 1 |
| Exudate | | 0 | | 0 | | 0 |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 0 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| Squamous Metaplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 1 | | 2 | | 2 |
| Edema | | 3 | | 3 | | 1 |
| Lymphocytic Hyperplasia | | 1 | | 2 | | 4 |
| Macrophage Hyperplasia | | 1 | | 2 | | 3 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | IV<br>F1 | | IV<br>F2 | | IV<br>F3 |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Atelectasis | | 2 | | 2 | | 3 |
| Hemorrhage | | 1 | | 1 | | 1 |
| Focal Lymphocyte Aggregate | | 0 | | 1 | | 0 |
| Alveolar Macrophages | | 0 | | 1 | | 0 |
| Interstitial Inflammation | | 0 | | 1 | | 0 |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 0 | | 0 | | 0 |
| Eosinophilic Infiltrate | | 0 | | 2 | | 1 |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (1) | | (2) | | (0) |
| Lymphocytic Hyperplasia | | 1 | | 2 | | 0 |
| Macrophage Hyperplasia | | 0 | | 1 | | 0 |
| Edema | | 0 | | 0 | | 0 |
| Hemorrhage | | 1 | | 2 | | 0 |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Ejaculate | | 0 | | 0 | | 0 |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (2) | | (1) | | (0) |
| Concretion | | 2 | | 1 | | 0 |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Necrosis | | 0 | | 0 | | 0 |
| Hemorrhage | | 0 | | 0 | | 0 |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | IV<br>F1 | | IV<br>F2 | | IV<br>F3 |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (2) | | (1) | | (0) |
| Hemorrhage | | 2 | | 1 | | 0 |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Erosion | | 0 | | 0 | | 0 |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Hemorrhage | | 0 | | 0 | | 0 |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (1) | | (0) |
| Edema | | 0 | | 1 | | 0 |
| Lymphocytic Hyperplasia | | 0 | | 1 | | 0 |
| Macrophage Hyperplasia | | 0 | | 1 | | 0 |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| | | | | | | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP V 0.75 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | V<br>F1 | | V<br>F2 | | V<br>F3 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 0 |
| Acute Inflammation | | 0 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 2 | | 2 | | 1 |
| Exudate | | 0 | | 0 | | 0 |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 0 | | 0 | | 0 |
| Lymphocytic Infiltrate | | 0 | | 0 | | 0 |
| Squamous Metaplasia | | 0 | | 0 | | 1 |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Hemorrhage | | 2 | | 1 | | 1 |
| Edema | | 2 | | 2 | | 3 |
| Lymphocytic Hyperplasia | | 1 | | 3 | | 1 |
| Macrophage Hyperplasia | | 1 | | 2 | | 1 |
| Lymphocytic Infiltrate | | 1 | | 0 | | 0 |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | V<br>F1 | | V<br>F2 | | V<br>F3 |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | | (4) | | (4) |
| Atelectasis | | 0 | | 2 | | 2 |
| Hemorrhage | | 0 | | 0 | | 0 |
| Focal Lymphocyte Aggregate | | 1 | | 1 | | 1 |
| Alveolar Macrophages | | 0 | | 1 | | 1 |
| Interstitial Inflammation | | 2 | | 1 | | 2 |
| Terminal Bronchiolar Fibrosis | | 4 | | 4 | | 4 |
| Eosinophilic Infiltrate | | 2 | | 2 | | 0 |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (0) | | (1) |
| Lymphocytic Hyperplasia | | 0 | | 0 | | 1 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| Edema | | 0 | | 0 | | 0 |
| Hemorrhage | | 0 | | 0 | | 1 |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (0) | | (0) | | (1) |
| Ejaculate | | 0 | | 0 | | 1 |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (1) | | (2) | | (1) |
| Concretion | | 1 | | 2 | | 0 |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Necrosis | | 0 | | 0 | | 0 |
| Hemorrhage | | 0 | | 0 | | 0 |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

## SUMMARY INCIDENCE TABLE

| Group<br>Exposure Frequency | | V<br>F1 | | V<br>F2 | | V<br>F3 |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Hemorrhage | | 0 | | 0 | | 0 |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Erosion | | 0 | | 0 | | 0 |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Hemorrhage | | 0 | | 0 | | 0 |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| Edema | | 0 | | 0 | | 0 |
| Lymphocytic Hyperplasia | | 0 | | 0 | | 0 |
| Macrophage Hyperplasia | | 0 | | 0 | | 0 |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | | (0) | | (0) |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (1) | | (0) | | (0) |
| Edema | | 1 | | 0 | | 0 |
| | | | | | | |
| | | | | | | |
| | | | | | | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP VI & VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

| Group<br>Exposure Frequency | | VIR<br>F2 | VI<br>F1 | VI<br>F2 | VI<br>F3 | |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| Acute Inflammation | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 1 | 2 | 0 | 2 | |
| Exudate | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| Lymphocytic Infiltrate | | 0 | 1 | 0 | 0 | |
| Squamous Metaplasia | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 1 | 1 | 2 | 1 | |
| Edema | | 0 | 0 | 0 | 1 | |
| Lymphocytic Hyperplasia | | 2 | 1 | 0 | 3 | |
| Macrophage Hyperplasia | | 0 | 1 | 0 | 1 | |
| Lymphocytic Infiltrate | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
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| | | | | | | |
| | | | | | | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

## SUMMARY INCIDENCE TABLE

GROUP VI & VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

| Group<br>Exposure Frequency | | VIR<br>F2 | VI<br>F1 | VI<br>F2 | VI<br>F3 | |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Atelectasis | | 2 | 3 | 4 | 3 | |
| Hemorrhage | | 0 | 0 | 0 | 1 | |
| Focal Lymphocyte Aggregate | | 0 | 0 | 0 | 1 | |
| Alveolar Macrophages | | 1 | 0 | 1 | 0 | |
| Interstitial Inflammation | | 1 | 0 | 0 | 1 | |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 4 | 4 | 3 | 4 | |
| Eosinophilic Infiltrate | | 0 | 1 | 0 | 2 | |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | (0) | (2) | (1) | |
| Lymphocytic Hyperplasia | | 0 | 0 | 2 | 1 | |
| Macrophage Hyperplasia | | 0 | 0 | 0 | 0 | |
| Edema | | 0 | 0 | 0 | 0 | |
| Hemorrhage | | 0 | 0 | 2 | 1 | |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (1) | |
| Ejaculate | | 0 | 0 | 0 | 1 | |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (1) | (0) | (0) | (1) | |
| Concretion | | 0 | 0 | 0 | 1 | |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Necrosis | | 0 | 0 | 0 | 0 | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP VI & VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

| Group<br>Exposure Frequency | | VIR<br>F2 | VI<br>F1 | VI<br>F2 | VI<br>F3 | |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (1) | (0) | (0) | (2) | |
| Hemorrhage | | 0 | 0 | 0 | 2 | |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Erosion | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Edema | | 0 | 0 | 0 | 0 | |
| Lymphocytic Hyperplasia | | 0 | 0 | 0 | 0 | |
| Macrophage Hyperplasia | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | (1) | (0) | (0) | |
| Edema | | 0 | 1 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP VII & VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | VIIR<br>F2 | VII<br>F1 | VII<br>F2 | VII<br>F3 | |
|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| Acute Inflammation | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 0 | 0 | 0 | 1 | |
| Exudate | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| TRACHEA | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| Lymphocytic Infiltrate | | 0 | 0 | 0 | 0 | |
| Squamous Metaplasia | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
| PULMONARY LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Hemorrhage | | 1 | 0 | 0 | 1 | |
| Edema | | 1 | 3 | 0 | 1 | |
| Lymphocytic Hyperplasia | | 3 | 1 | 3 | 2 | |
| Macrophage Hyperplasia | | 0 | 2 | 0 | 1 | |
| Lymphocytic Infiltrate | | 0 | 0 | 0 | 0 | |
| | | | | | | |
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PROJECT L06139

PHASE III, STUDY 79

MALE RATS

## SUMMARY INCIDENCE TABLE

GROUP VII & VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | VIIR<br>F2 | VII<br>F1 | VII<br>F2 | VII<br>F3 | |
|---|---|---|---|---|---|---|
| LUNG | | | | | | |
| (Number Examined) | | (4) | (4) | (4) | (4) | |
| Atelectasis | | 2 | 1 | 2 | 2 | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| Focal Lymphocyte Aggregate | | 0 | 0 | 0 | 0 | |
| Alveolar Macrophages | | 0 | 1 | 4 | 0 | |
| Interstitial Inflammation | | 0 | 0 | 0 | 0 | |
| Terminal Bronchiolar | | | | | | |
| Fibrosis | | 4 | 4 | 4 | 4 | |
| Eosinophilic Infiltrate | | 0 | 1 | 0 | 0 | |
| | | | | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (2) | (0) | (2) | (2) | |
| Lymphocytic Hyperplasia | | 2 | 0 | 2 | 2 | |
| Macrophage Hyperplasia | | 1 | 0 | 0 | 1 | |
| Edema | | 0 | 0 | 0 | 1 | |
| Hemorrhage | | 2 | 0 | 2 | 1 | |
| | | | | | | |
| SEMINAL VESICLE | | | | | | |
| (Number Examined) | | (1) | (0) | (0) | (1) | |
| Ejaculate | | 0 | 0 | 0 | 1 | |
| | | | | | | |
| URINARY BLADDER | | | | | | |
| (Number Examined) | | (2) | (2) | (2) | (1) | |
| Concretion | | 1 | 1 | 2 | 1 | |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Necrosis | | 0 | 0 | 0 | 0 | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

SUMMARY INCIDENCE TABLE

GROUP VII & VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

| Group<br>Exposure Frequency | | VIIR<br>F2 | VII<br>F1 | VII<br>F2 | VII<br>F3 | |
|---|---|---|---|---|---|---|
| THYMUS | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| TAIL | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Erosion | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| HIND LEG | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Hemorrhage | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Edema | | 0 | 0 | 0 | 0 | |
| Lymphocytic Hyperplasia | | 0 | 0 | 0 | 0 | |
| Macrophage Hyperplasia | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| DIAPHRAGM | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| | | | | | | |
| PROSTATE | | | | | | |
| (Number Examined) | | (0) | (0) | (0) | (0) | |
| Edema | | 0 | 0 | 0 | 0 | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 355 | 356 | 357 | 358 | 383 | 384 | 385 | 386 | 411 | 412 | 413 | 414 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | X | | X | X | X | X | X | X | X | | X | X |
| Hemorrhage | | 2 | | | | | | | | | | |
| Acute Inflammation | | | | | | | | | | 2 | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | X | X | X | X | X | X | | X | | |
| Hemorrhage | | 3 | | | | | | | 1 | | 1 | 1 |
| Exudate | 1 | | | | | | | | | | | |
| | | | | | | | | | | | | |
| TRACHEA | X | X | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | |
| | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 355 | 356 | 357 | 358 | 383 | 384 | 385 | 386 | 411 | 412 | 413 | 414 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | N | X | | | | | X | | | | | X |
| Hemorrhage | | | | | | | | 1 | | 1 | 3 | |
| Edema | | | | | | | | | 1 | 2 | | |
| Lymphocytic Hyperplasia | | | 1 | 1 | 2 | 1 | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | 1 | 1 | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| LUNG | X | | | X | | | X | | | | | |
| Atelectasis | | 1 | | | | 1 | | 1 | | 2 | 2 | 1 |
| Hemorrhage | | | | | | | | | | | | |
| Focal Lymphocyte Aggregate | | | 1 | | 1 | 1 | | | | | | 1 |
| Alveolar Macrophages | | | | | 2 | 1 | | | | | | |
| Interstitial Inflammation | | | | | 3 | 2 | | | 1 | | | |
| Terminal Bronchiolar Fibrosis | | | | | | | | | | | | |
| Eosinophilic Infiltrate | | | | | | | | | | | | |
| | | | | | | | | | | | | |
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P1

Experimental Pathology Laboratories, Inc.

Key: P = Present; N = No Section; A = Autolysis; X = Not Remarkable
1 = Minimal; 2 = Slight; 3 = Moderate; 4 = Moderately Severe/High
5 = Severe/High; I = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | | 355 | 356 | 357 | 358 | 383 | 384 | 385 | 386 | 411 | 412 | 413 | 414 | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | 3 | | 2 | 1 | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | 2 | 1 | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SEMINAL VESICLE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | P | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Concretion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | | 355 | 356 | 357 | 358 | 383 | 384 | 385 | 386 | 411 | 412 | 413 | 414 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TAIL | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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PL | Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | | 355 | 356 | 357 | 358 | 383 | 384 | 385 | 386 | 411 | 412 | 413 | 414 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL | Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 439 | 440 | 441 | 442 |
|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | X | X | X |
| Hemorrhage | 1 | | | |
| Acute Inflammation | | | | |
| NASAL TURBINATE-LEVEL 2 | | X | | X |
| Hemorrhage | 1 | | 1 | |
| Exudate | | | | |
| TRACHEA | X | X | X | X |
| Hemorrhage | | | | |
| Lymphocytic Infiltrate | | | | |
| Squamous Metaplasia | | | | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 439 | 440 | 441 | 442 |
|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | | | | |
| Hemorrhage | 1 | 2 | 1 | 1 |
| Edema | | | 1 | 1 |
| Lymphocytic Hyperplasia | 1 | 2 | 1 | 2 |
| Macrophage Hyperplasia | | | | 1 |
| Lymphocytic Infiltrate | | | | |
| | | | | |
| LUNG | | | X | |
| Atelectasis | 1 | 1 | | 1 |
| Hemorrhage | | | | |
| Focal Lymphocyte Aggregate | | | | |
| Alveolar Macrophages | | 1 | | |
| Interstitial Inflammation | | 2 | | |
| Terminal Bronchiolar Fibrosis | | | | |
| Eosinophilic Infiltrate | | | | |
| | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 439 | 440 | 441 | 442 |
|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | |
| Hemorrhage | 2 | 3 | | 2 |
| Lymphocytic Hyperplasia | 3 | 3 | | 3 |
| Macrophage Hyperplasia | | | | |
| Edema | | | | |
| SEMINAL VESICLE | | | | |
| Ejaculate | | | | |
| URINARY BLADDER | | | | |
| Concretion | P | P | | P |
| LIVER | | | | |
| Necrosis | | 3 | | |
| Hemorrhage | | 2 | | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

Experimental Pathology Laboratories, Inc

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | 439 | 440 | 441 | 442 | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TAIL | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP I-RECOVERY 0.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | 439 | 440 | 441 | 442 | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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36

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

EPL Experimental Pathology Laboratories, Inc.

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

| Exposure Frequency: | F1 | | | F2 | | | | F3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 359 | 360 | 361 | 362 | 387 | 388 | 389 | 390 | 415 | 416 | 417 | 418 |
| NASAL TURBINATE-LEVEL 1 | X | X | X | X | X | X | X | X | X | X | X | |
| Hemorrhage | | | | | | | | | | | | 1 |
| Acute Inflammation | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | X | | X | X | X | X | | | X | | |
| Hemorrhage | 1 | | 1 | | | | | 1 | 1 | | 1 | 1 |
| Exudate | | | | | | | | | | | | |
| TRACHEA | X | X | X | X | X | X | X | X | X | | X | X |
| Hemorrhage | | | | | | | | | | 3 | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | |





EPL Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

| | Exposure Frequency: F1 | | | | | | | | | | | | F2 | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 359 | 360 | 361 | 362 | | | | | | 387 | 388 | 389 | 390 | | | | | | 415 | 416 | 417 | 418 | | | |
| PULMONARY LYMPH NODE(S) | | | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | 2 | | | | | | 2 | | 2 | 1 | | | | | | 1 | 1 | | | | | |
| Lymphocytic Hyperplasia | | | | | 1 | 1 | 1 | | | | | | | | 1 | 1 | | | | | | | 1 | 2 | 2 | | | |
| Macrophage Hyperplasia | | | | | | 1 | 1 | | | | | | 1 | 1 | | | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | | | 1 | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNG | | | | | | X | | | | | | | X | | X | | | | | | | | | | | | | |
| Atelectasis | | | | 1 | | | 1 | | | | | | | | | 2 | | | | | | 3 | | 2 | 2 | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | 1 | | | | | |
| Focal Lymphocyte Aggregate | | | | | | | | | | | | | | 3 | | | | | | | | | | | | | | |
| Alveolar Macrophages | | | | | 1 | | | | | | | | | 1 | | | | | | | | | | | | | | |
| Interstitial Inflammation | | | | | | | | | | | | | | 1 | | | | | | | | | | 2 | 1 | | | |
| Terminal Bronchiolar Fibrosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eosinophilic Infiltrate | | | | | 1 | | | | | | | | | 2 | | | | | | | | | | 2 | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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PL | Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT 106139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 359 | 360 | 361 | 362 | | | | | | 387 | 388 | 389 | 390 | | | | | 415 | 416 | 417 | 418 | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | 3 | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| SEMINAL VESICLE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| URINARY BLADDER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concretion | | | | | | | | | | | | P | | P | | | | | | | | | | | | | | | |
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| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 359 | 360 | 361 | 362 | 387 | 388 | 389 | 390 | 415 | 416 | 417 | 418 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | |
| Hemorrhage | 1 | | | | | | | | | | | |
| TAIL | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | |
| HIND LEG | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

EPL Experimental Pathology Laboratories, Inc.

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP II 0.4 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | | | | 359 | 360 | 361 | 362 | | | | | | 387 | 388 | 389 | 390 | | | | | | 415 | 416 | 417 | 418 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | N | | | | | |
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| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc

Key P = Present N = No Section A = Autolysis X = Not Remarkable
1 = Minimal 2 = Slight 3 = Moderate 4 = Moderately Severe/High
5 = Severe/High I = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | 363 | 364 | 365 | 366 | 391 | 392 | 393 | 394 | 419 | 420 | 421 | 422 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | X | X | X | X | X | X | X | X | X | X | X | |
| Hemorrhage | | | | | | | | | | | | 2 |
| Acute Inflammation | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | X | X | X | | X | X | X | X | | X | X | |
| Hemorrhage | | | | 2 | | | | | 1 | | | 2 |
| Exudate | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| TRACHEA | X | X | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc

Key P = Present N = No Section A = Autolysis X = Not Remarkable
1 = Minimal 2 = Slight 3 = Moderate 4 = Moderately Severe/High
5 = Severe/High I = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

| Exposure Frequency: | F1 | | | | | | | | | | | | F2 | | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 363 | 364 | 365 | 366 | | | | | | 391 | 392 | 393 | 394 | | | | | | | 419 | 420 | 421 | 422 | | | |
| PULMONARY LYMPH NODE(S) | | | | X | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Hemorrhage | | | | | 1 | | | | | | | | | | | | | | | | | | 1 | | | | | | |
| Edema | | | | | 2 | | | | | | | | | 2 | | | | | | | | | 2 | 1 | 2 | 1 | | | |
| Lymphocytic Hyperplasia | | | | | 1 | 2 | 1 | | | | | | 2 | 1 | | | | | | | | | | 1 | 1 | 1 | | | |
| Macrophage Hyperplasia | | | | | | 1 | | | | | | | | 1 | | 1 | | | | | | | 1 | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNG | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Atelectasis | | | | | | 2 | 3 | | | | | | | 2 | | | | | | | | | 1 | 1 | | 1 | | | |
| Hemorrhage | | | | 1 | | | | | | | | | | | | | | | | | | | | 1 | | | | | |
| Focal Lymphocyte Aggregate | | | | 1 | | | | | | | | | 1 | | | | | | | | | | | | 1 | | | | |
| Alveolar Macrophages | | | | | 1 | | | | | | | | 1 | | | | | | | | | | 1 | | | 1 | | | |
| Interstitial Inflammation | | | | | 2 | | | | | | | | | | | | | | | | | | 2 | | | | | | |
| Terminal Bronchiolar Fibrosis | | | | | | | | | | | | | 2 | 1 | 1 | 1 | | | | | | | | | | | | | |
| Eosinophilic Infiltrate | | | | 1 | | | | | | | | | | | | 1 | | | | | | | 1 | | | | | | |
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EPL | Experimental Pathology Laboratories, Inc

Key P = Present N = No Section A = Autolysis X = Not Remarkable
1 = Minimal 2 = Slight 3 = Moderate 4 = Moderately Severe/High
5 = Severe/High I = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

| Exposure Frequency: | F1 | | | | | | | | | | | F2 | | | | | | | | F3 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 363 | 364 | 365 | 366 | | | | | 391 | 392 | 393 | 394 | | | | | 419 | 420 | 421 | 422 | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | 3 | 4 | | | | | | | | | | | | | 3 | | | | | | |
| Lymphocytic Hyperplasia | | | | | | 4 | 4 | | | | | 3 | | | | | | | | 3 | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SEMINAL VESICLE | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | | | | | | | | | | | | | | | | |
| URINARY BLADDER | | | | | | X | | | | | | | | | X | | | | | | | | | | | |
| Concretion | | | | | | | P | | | | | | P | | | | | | | | | P | | | | |
| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | |



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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

PL

Experimental Pathology Laboratories, Inc.

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

| | Exposure Frequency: F1 | | | | | | | | | | | | F2 | | | | | | | | | F3 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 363 | 364 | 365 | 366 | | | | | | 391 | 392 | 393 | 394 | | | | | | 419 | 420 | 421 | 422 | | | | |
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | 2 | | | | | | | | 1 | 1 | | | | | | | | | | | | | | |
| TAIL | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | | | | | | | | | | | | 2 | | | | | | |
| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | 3 | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |





EPL Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP III 0.4 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 363 | 364 | 365 | 366 | 391 | 392 | 393 | 394 | 419 | 420 | 421 | 422 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | |
| KIDNEY | | | | | | | | | | | | |
| PROSTATE | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | |





EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

1.0 HOURS/DAY

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Frequency: | | | | F1 | | | | | | | | | F2 | | | | | | | | | F3 | | | | | | |
| ANIMAL NUMBER | | | | 367 | 368 | 369 | 370 | | | | | | 395 | 396 | 397 | 398 | | | | | | 423 | 424 | 425 | 426 | | | |
| NASAL TURBINATE-LEVEL 1 | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | 3 | | | | | |
| Acute Inflammation | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| NASAL TURBINATE-LEVEL 2 | | | | X | X | X | | | | | | | X | X | X | X | | | | | | X | | X | X | | | |
| Hemorrhage | | | | | | | 1 | | | | | | | | | | | | | | | | 3 | | | | | |
| Exudate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL | Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | 367 | 368 | 369 | 370 | 395 | 396 | 397 | 398 | 423 | 424 | 425 | 426 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | | | | | | | | | | | | |
| Hemorrhage | 1 | | | | 1 | 1 | | | | | 1 | 1 |
| Edema | 1 | 2 | 1 | | 1 | | 2 | 1 | 1 | | | |
| Lymphocytic Hyperplasia | | 1 | | | 1 | 1 | | | 1 | 3 | 2 | 2 |
| Macrophage Hyperplasia | | | | 1 | | | 1 | 1 | 1 | | 1 | 1 |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| LUNG | | X | | | | | | | X | | | |
| Atelectasis | | | 2 | 1 | | 1 | | 1 | | 1 | 1 | 1 |
| Hemorrhage | 2 | | | | | | 1 | | | | | 1 |
| Focal Lymphocyte Aggregate | | | | | 2 | | | | | | | |
| Alveolar Macrophages | | | | | 1 | | | | | | | |
| Interstitial Inflammation | | | | | 2 | | | | | | | |
| Terminal Bronchiolar Fibrosis | | | | | | | | | | | | |
| Eosinophilic Infiltrate | | | | | 1 | 1 | | | | | 1 | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

1.0 HOURS/DAY

| Exposure Frequency: | F1 | | | | | | | | | | | | F2 | | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 367 | 368 | 369 | 370 | | | | | | 395 | 396 | 397 | 398 | | | | | | | 423 | 424 | 425 | 426 | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | 2 | | | | | | | 1 | 3 | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | 4 | | | | | | | 1 | 3 | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | 2 | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SEMINAL VESICLE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| URINARY BLADDER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concretion | | | | | P | P | | | | | | | | | | P | | | | | | | | | | | | | |
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| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 367 | 368 | 369 | 370 | 395 | 396 | 397 | 398 | 423 | 424 | 425 | 426 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | |
| Hemorrhage | 1 | | 2 | | | | 1 | | | | | |
| TAIL | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | |
| HIND LEG | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | |
| Edema | | | | | 3 | | | | | | | |
| Lymphocytic Hyperplasia | | | | | 2 | | | | | | | |
| Macrophage Hyperplasia | | | | | 2 | | | | | | | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

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Experimental Pathology Laboratories, Inc

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP IV 0.75 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | | | | 367 | 368 | 369 | 370 | | | | | | 395 | 396 | 397 | 398 | | | | | | 423 | 424 | 425 | 426 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

| | Exposure Frequency: F1 | | | | | | | | | | | | F2 | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 371 | 372 | 373 | 374 | | | | | | 399 | 400 | 401 | 402 | | | | | | 427 | 428 | 429 | 430 | | | |
| NASAL TURBINATE-LEVEL 1 | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acute Inflammation | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | | | X | X | | | | | | X | X | | | | | | | | X | X | | X | | | |
| Hemorrhage | | | | 1 | 1 | | | | | | | | | | 1 | 3 | | | | | | | | 1 | | | | |
| Exudate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | X | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | | | | | | | | | | | | | | 1 | | | |
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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 371 | 372 | 373 | 374 | | | | | | 399 | 400 | 401 | 402 | | | | | | 427 | 428 | 429 | 430 | | | |
| PULMONARY LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Hemorrhage | | | | 1 | 1 | | | | | | | | | | 1 | | | | | | 1 | | | | | | | |
| Edema | | | 1 | | | 1 | | | | | | | | 2 | 1 | | | | | | 1 | 1 | 2 | | | | | |
| Lymphocytic Hyperplasia | | | | | 1 | | | | | | | 2 | 2 | 1 | | | | | | | | 1 | | | | | | |
| Macrophage Hyperplasia | | | | | 1 | | | | | | | | | 1 | 1 | | | | | | | | 1 | | | | | |
| Lymphocytic Infiltrate | | | | | | 1 | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNG | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Atelectasis | | | | | | | | | | | | | 1 | 3 | | | | | | | 1 | | 2 | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Focal Lymphocyte Aggregate | | | | 1 | | | | | | | | | | 1 | | | | | | | | 1 | | | | | | |
| Alveolar Macrophages | | | | | | | | | | | | 1 | | | | | | | | | | 1 | | | | | | |
| Interstitial Inflammation | | | | | 2 | 1 | | | | | | 1 | | | | | | | | | 1 | 1 | | | | | | |
| Terminal Bronchiolar Fibrosis | | | 1 | 1 | 2 | 1 | | | | | | 2 | 2 | 2 | 2 | | | | | | 1 | 1 | 1 | 2 | | | | |
| Eosinophilic Infiltrate | | | 1 | | 2 | | | | | | | | 1 | | 2 | | | | | | | | | | | | | |
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

| Exposure Frequency: | F1 | | | | | | | | | | | | F2 | | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 371 | 372 | 373 | 374 | | | | | | 399 | 400 | 401 | 402 | | | | | | | 427 | 428 | 429 | 430 | | | |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | 2 | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | 2 | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SEMINAL VESICLE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | | | | | | | | | | | | | P | | | | | | |
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| URINARY BLADDER | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Concretion | | | | P | | | | | | | | | P | | P | | | | | | | | | | | | | | |
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| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| | ANIMAL NUMBER | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 371 | 372 | 373 | 374 | | | | | | 399 | 400 | 401 | 402 | | | | | | 427 | 428 | 429 | 430 | | | |
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP V 0.75 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | | | | 371 | 372 | 373 | 374 | | | | | | 399 | 400 | 401 | 402 | | | | | 427 | 428 | 429 | 430 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

EPL

Experimental Pathology Laboratories, Inc.

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI 1.0 MG/L

1.0 HOURS/DAY

| Exposure Frequency: | F1 | | | | | | | | | | | | F2 | | | | | | | | | | | | F3 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | | | | 375 | 376 | 377 | 378 | | | | | | 403 | 404 | 405 | 406 | | | | | | | | | 431 | 432 | 433 | 434 | | | |
| NASAL TURBINATE-LEVEL 1 | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acute Inflammation | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | X | | | X | | | | | | X | X | X | X | | | | | | | | | X | X | | | | | |
| Hemorrhage | | | | | 1 | 1 | | | | | | | | | | | | | | | | | | | | | 1 | 1 | | | |
| Exudate | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| TRACHEA | | | | X | X | | X | | | | | | X | X | X | X | | | | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL | Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 375 | 376 | 377 | 378 | 403 | 404 | 405 | 406 | 431 | 432 | 433 | 434 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | X | | | | | X | | X | | | | |
| Hemorrhage | | | 1 | | 1 | | 1 | | | | | 1 |
| Edema | | | | | | | | | 1 | | | |
| Lymphocytic Hyperplasia | | 1 | | | | | | | | 1 | 2 | 1 |
| Macrophage Hyperplasia | | | | 1 | | | | | 1 | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| LUNG | | | | | | | | | | | | |
| Atelectasis | 1 | 2 | 1 | | 2 | 1 | 2 | 2 | 2 | | 1 | 1 |
| Hemorrhage | | | | | | | | | | 1 | | |
| Focal Lymphocyte Aggregate | | | | | | | | | | | 1 | |
| Alveolar Macrophages | | | | | | 1 | | | | | | |
| Interstitial Inflammation | | | | | | | | | | 2 | | |
| Terminal Bronchiolar Fibrosis | 1 | 1 | 1 | 2 | | 1 | 1 | 1 | 2 | 2 | 2 | 2 |
| Eosinophilic Infiltrate | | | | 3 | | | | | 2 | 1 | | |



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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 375 | 376 | 377 | 378 | 403 | 404 | 405 | 406 | 431 | 432 | 433 | 434 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | |
| Hemorrhage | | | | | 1 | | 1 | | | 2 | | |
| Lymphocytic Hyperplasia | | | | | 2 | | 2 | | | 3 | | |
| Macrophage Hyperplasia | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | |
| SEMINAL VESICLE | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | P | |
| URINARY BLADDER | | | | | | | | | | | | |
| Concretion | | | | | | | | | | | | P |
| LIVER | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | |

257



Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 375 | 376 | 377 | 378 | 403 | 404 | 405 | 406 | 431 | 432 | 433 | 434 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | 1 | | 1 |
| TAIL | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | |
| HIND LEG | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High; N = No Section, 2 = Slight, I = Incomplete Section; A = Autolysis, 3 = Moderate; X = Not Remarkable, 4 = Moderately Severe/High

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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE R[illegible]

GROUP VI 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | | | | 375 | 376 | 377 | 378 | | | | | | 403 | 404 | 405 | 406 | | | | | | 431 | 432 | 433 | 434 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | N | | | |
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| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | 3 | | | | | | | | | | | | | | | | | | | | | | |
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 443 | 444 | 445 | 446 |
|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | X | X | X | X |
| Hemorrhage | | | | |
| Acute Inflammation | | | | |
| | | | | |
| | | | | |
| NASAL TURBINATE-LEVEL 2 | X | X | X | |
| Hemorrhage | | | | 1 |
| Exudate | | | | |
| | | | | |
| | | | | |
| TRACHEA | X | X | X | X |
| Hemorrhage | | | | |
| Lymphocytic Infiltrate | | | | |
| Squamous Metaplasia | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 443 | 444 | 445 | 446 |
|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | | | X | X |
| Hemorrhage | | 1 | | |
| Edema | | | | |
| Lymphocytic Hyperplasia | 2 | 1 | | |
| Macrophage Hyperplasia | | | | |
| Lymphocytic Infiltrate | | | | |
| | | | | |
| LUNG | | | | |
| Atelectasis | | 1 | | 1 |
| Hemorrhage | | | | |
| Focal Lymphocyte Aggregate | | | | |
| Alveolar Macrophages | 1 | | | |
| Interstitial Inflammation | 2 | | | |
| Terminal Bronchiolar Fibrosis | 1 | 1 | 2 | 1 |
| Eosinophilic Infiltrate | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 443 | 444 | 445 | 446 |
|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | |
| Hemorrhage | | | | |
| Lymphocytic Hyperplasia | | | | |
| Macrophage Hyperplasia | | | | |
| Edema | | | | |
| | | | | |
| SEMINAL VESICLE | | | | |
| Ejaculate | | | | |
| | | | | |
| | | | | |
| URINARY BLADDER | | | | X |
| Concretion | | | | |
| | | | | |
| | | | | |
| LIVER | | | | |
| Necrosis | | | | |
| Hemorrhage | | | | |
| | | | | |



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Key: P = Present, 1 = Minimal, 5 = Severe/High; N = No Section, 2 = Slight, I = Incomplete Section; A = Autolysis, 3 = Moderate; X = Not Remarkable, 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | | 443 | 444 | 445 | 446 | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| TAIL | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VI-RECOVERY 1.0 MG/L

1.0 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 443 | 444 | 445 | 446 | | | | | | | | | | | | | | | | | | | | | | | |
| DIAPHRAGM | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PROSTATE | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |





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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

ANIMAL NUMBER

| | | | | 379 | 380 | 381 | 382 | | | | | | 407 | 408 | 409 | 410 | | | | | | 435 | 436 | 437 | 438 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acute Inflammation | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NASAL TURBINATE-LEVEL 2 | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | 1 | | | | |
| Exudate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | | | | X | X | X | X | | | | | | X | X | X | X | | | | | | X | X | X | X | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Infiltrate | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous Metaplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High; N = No Section, 2 = Slight, I = Incomplete Section; A = Autolysis, 3 = Moderate; X = Not Remarkable, 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 379 | 380 | 381 | 382 | 407 | 408 | 409 | 410 | 435 | 436 | 437 | 438 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | | | | | | X | | | X | | | |
| Hemorrhage | | | | | | | | | | | 1 | |
| Edema | | 2 | 2 | 1 | | | | | | 1 | | |
| Lymphocytic Hyperplasia | | | | 1 | 1 | | 1 | 1 | | 1 | | 1 |
| Macrophage Hyperplasia | 1 | | 1 | | | | | | | | 1 | |
| Lymphocytic Infiltrate | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| LUNG | | | | | | | | | | | | |
| Atelectasis | | 1 | | | 2 | | 1 | | | | 2 | 1 |
| Hemorrhage | | | | | | | | | | | | |
| Focal Lymphocyte Aggregate | | | | | | | | | | | | |
| Alveolar Macrophages | | | | 2 | 1 | 1 | 1 | 1 | | | | |
| Interstitial Inflammation | | | | | | | | | | | | |
| Terminal Bronchiolar Fibrosis | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Eosinophilic Infiltrate | | | | 2 | | | | | | | | |
| | | | | | | | | | | | | |
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Key: P = Present N = No Section A = Autolysis X = Not Remarkable
1 = Minimal 2 = Slight 3 = Moderate 4 = Moderately Severe/High
5 = Severe/High I = Incomplete Section

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Experimental Pathology Laboratories, Inc.

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 379 | 380 | 381 | 382 | 407 | 408 | 409 | 410 | 435 | 436 | 437 | 438 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | | | | | | | | | |
| Hemorrhage | | | | | | | 1 | 1 | 2 | | | |
| Lymphocytic Hyperplasia | | | | | | | 2 | I | 3 | | 3 | |
| Macrophage Hyperplasia | | | | | | | | | | | 1 | |
| Edema | | | | | | | | | | | 2 | |
| SEMINAL VESICLE | | | | | | | | | | | | |
| Ejaculate | | | | | | | | | | | | P |
| URINARY BLADDER | | | X | | | | | | | | | |
| Concretion | | P | | | P | | P | | P | | | |
| LIVER | | | | | | | | | | | | |
| Necrosis | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | |





EPL Experimental Pathology Laboratories, Inc

Key P = Present, 1 = Minimal, 5 = Severe/High; N = No Section, 2 = Slight, I = Incomplete Section; A = Autolysis, 3 = Moderate; X = Not Remarkable, 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | | | | 379 | 380 | 381 | 382 | | | | | | 407 | 408 | 409 | 410 | | | | | | 435 | 436 | 437 | 438 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| TAIL | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Erosion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIND LEG | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| MESENTERIC LYMPH NODE(S) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Macrophage Hyperplasia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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P L | Experimental Pathology Laboratories, Inc.

Key: P = Present, 1 = Minimal, 5 = Severe/High; N = No Section, 2 = Slight, I = Incomplete Section; A = Autolysis, 3 = Moderate; X = Not Remarkable, 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F1 F2 F3

| ANIMAL NUMBER | 379 | 380 | 381 | 382 | 407 | 408 | 409 | 410 | 435 | 436 | 437 | 438 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIAPHRAGM | | | | | | | | | | | | |
| KIDNEY | | | | | | | | | | | | |
| PROSTATE | | | | | | | | | | | | |
| Edema | | | | | | | | | | | | |





EPL Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| NASAL TURBINATE-LEVEL 1 | X | X | X | X |
| Hemorrhage | | | | |
| Acute Inflammation | | | | |
| | | | | |
| | | | | |
| NASAL TURBINATE-LEVEL 2 | X | X | X | X |
| Hemorrhage | | | | |
| Exudate | | | | |
| | | | | |
| TRACHEA | X | X | X | X |
| Hemorrhage | | | | |
| Lymphocytic Infiltrate | | | | |
| Squamous Metaplasia | | | | |
| | | | | |
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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

PL

Experimental Pathology Laboratories, Inc.

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

[illegible] III, STUDY 79

MALE RATS

GROUP VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| PULMONARY LYMPH NODE(S) | | | | |
| Hemorrhage | | | 2 | |
| Edema | | | 2 | |
| Lymphocytic Hyperplasia | 1 | 2 | | 1 |
| Macrophage Hyperplasia | | | | |
| Lymphocytic Infiltrate | | | | |
| | | | | |
| LUNG | | | | |
| Atelectasis | 1 | | | 1 |
| Hemorrhage | | | | |
| Focal Lymphocyte Aggregate | | | | |
| Alveolar Macrophages | | | | |
| Interstitial Inflammation | | | | |
| Terminal Bronchiolar Fibrosis | 3 | 3 | 3 | 3 |
| Eosinophilic Infiltrate | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII-RECOVERY 1.0 MG/T.

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| MANDIBULAR LYMPH NODE(S) | | | | |
| Hemorrhage | 2 | | | 3 |
| Lymphocytic Hyperplasia | 3 | | | 3 |
| Macrophage Hyperplasia | 1 | | | |
| Edema | | | | |
| | | | | |
| SEMINAL VESICLE | X | | | |
| Ejaculate | | | | |
| | | | | |
| | | | | |
| URINARY BLADDER | | | | X |
| Concretion | P | | | |
| | | | | |
| | | | | |
| LIVER | | | | |
| Necrosis | | | | |
| Hemorrhage | | | | |
| | | | | |





EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; I = Incomplete Section; A = Autolysis; 2 = Slight; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| THYMUS | | | | |
| Hemorrhage | | | | |
| | | | | |
| | | | | |
| TAIL | | | | |
| Erosion | | | | |
| | | | | |
| | | | | |
| HIND LEG | | | | |
| Hemorrhage | | | | |
| | | | | |
| | | | | |
| MESENTERIC LYMPH NODE(S) | | | | |
| Edema | | | | |
| Lymphocytic Hyperplasia | | | | |
| Macrophage Hyperplasia | | | | |
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EPL Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

GROUP VII-RECOVERY 1.0 MG/L

3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| DIAPHRAGM | | | | |
| KIDNEY | | | | |
| PROSTATE | | | | |
| Edema | | | | |





Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

PL | Experimental Pathology Laboratories, Inc.

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: I Dosage Level: 0.0 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 383 | Mandibular Lymph Node | Red | Hemorrhage |
| 385 | Mandibular Lymph Node | Red | Hemorrhage |
| 386 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 386 | Urinary Bladder | White calculus in bladder | No Corresponding Lesion |
| 384 | Seminal Vesicles | White material adhering to right seminal vesicle | Ejaculate |
| | | | |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: I-RECOVERY Dosage Level: 0.0 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 439 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 439 | Urinary Bladder | White calculus in lumen | Concretion |
| 440 | Mandibular Lymph Node | Dark red | Hemorrhage |
| 440 | Lung; Diaphragmatic Lobe | Red focus | Atelectasis |
| 440 | Liver; Left Lateral Lobe | Red focus with raised white material, dorsal surface | Necrosis |
| 440 | Urinary Bladder | White calculus in lumen | Concretion |
| 442 | Mandibular Lymph Node | Enlarged, red | Hemorrhage |
| 442 | Urinary Bladder | Calculi within | Concretion |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: II Dosage Level: 0.4 MG/L 1.0 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 359 | Thymus | Mottled red | Hemorrhage |
| 359 | Lung | Red focus on all lobes 0.2 x 0.2 | Atelectasis |
| | | to 0.1 x 0.1 cm | |
| 360 | Lung | Red foci | No Corresponding Lesion |
| 361 | Mandibular Lymph Node | Red | Hemorrhage |
| 361 | Lung | Mottled red | No Corresponding Lesion |
| 417 | Thoracic Cavity | Abdominal viscera within cavity | No Corresponding Lesion |
| 417 | Diaphragm | Ruptured | No Section |
| 417 | Lung | Left lobe red | Atelectasis |
| 418 | Lung | Mottled red | Atelectasis |
| 387 | Urinary Bladder | White calculus in lumen | Concretion |
| 388 | Lung | Red foci on left lobe and right | No Corresponding Lesion |
| | | intermediate lobe | |
| 389 | Urinary Bladder | White calculi within | Concretion |
| | | | |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: III Dosage Level: 0.4 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 365 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 365 | Lung, Left Lobe | Red focus | Atelectasis |
| 365 | Urinary Bladder | White calculus in lumen | No Corresponding Lesion |
| 365 | Thymus | Mottled red | Hemorrhage |
| 366 | Mandibular Lymph Node | Red | Hemorrhage |
| 366 | Urinary Bladder | White calculus in lumen | Concretion |
| 419 | Mandibular Lymph Node | Red | Hemorrhage |
| 420 | Tail | Red and scraped area 4.0 x 1.0 cm | Erosion |
| 420 | Right Hind Leg | Red area 1.5 x 0.8 cm involving | Hemorrhage |
| | | muscle above hock | |
| 422 | Urinary Bladder | Calculi within | Concretion |
| 391 | Mandibular Lymph Node | Enlarged | Lymphocytic Hyperplasia |
| 392 | Thymus | Mottled red | Hemorrhage |
| 392 | Lung | Mottled red | Atelectasis |
| 392 | Urinary Bladder | Calculi within | Concretion |
| 393 | Thymus | Red foci | Hemorrhage |
| 393 | Lung | Red focus on right apical lobe | No Corresponding Lesion |

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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: III Dosage Level: 0.4 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 394 | Urinary Bladder | White calculus in lumen | No Corresponding Lesion |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: IV Dosage Level: 0.75 MG/L 1.0 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 367 | Thymus | Mottled red | Hemorrhage |
| 367 | Lung | Mottled brown | No Corresponding Lesion |
| 368 | Urinary Bladder | Contains white calculi | Concretion |
| 369 | Mandibular Lymph Node | Red | Hemorrhage |
| 369 | Thymus | Mottled red | Hemorrhage |
| 369 | Lung | Mottled tan | Atelectasis |
| 369 | Urinary Bladder | White calculi in lumen | Concretion |
| 395 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 395 | Lung | Right diaphragmatic lobe, red foci | No Corresponding Lesion |
| 395 | Mesenteric Lymph Node | Enlarged 0.6 x 0.5 x 0.4 cm | Lymphocytic Hyperplasia |
| 396 | Mandibular Lymph Node | Red | Hemorrhage |
| 396 | Lung | Red foci on left lobe 0.3 x 0.3 cm | Atelectasis |
| 397 | Thymus | Red foci | Hemorrhage |
| 398 | Urinary Bladder | White calculus in lumen | Concretion |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: V Dosage Level: 0.75 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 427 | Urinary Bladder | White calculi in lumen | No Corresponding Lesion |
| 427 | Seminal Vesicles | White material around but not | Ejaculate |
| | | invading | |
| 429 | Mandibular Lymph Node | Red | Hemorrhage |
| 371 | Urinary Bladder | Calculi within | Concretion |
| 372 | Lung | Red focus on all lobes | No Corresponding Lesion |
| 373 | Prostate | Enlarged | Edema |
| 399 | Urinary Bladder | Contains white calculi | Concretion |
| 401 | Urinary Bladder | White calculus in lumen | Concretion |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VI Dosage Level: 1.0 MG/L 1.0 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 376 | Lung | Mottled red | Atelectasis |
| 376 | Urinary Bladder | White calculus in lumen | No Corresponding Lesion |
| 377 | Lung | Tan areas on dorsal portion of | No Corresponding Lesion |
| | | all lobes | |
| 377 | Prostate | Enlarged | Edema |
| 378 | Lung | One red focus on right inter- | No Corresponding Lesion |
| | | mediate lobe | |
| 432 | Mandibular Lymph Node | Red | Hemorrhage |
| 432 | Thymus | Red foci | Hemorrhage |
| 432 | Lung | Red foci on right diaphragmatic | Hemorrhage |
| | | lobe | |
| 434 | Thymus | Mottled red | Hemorrhage |
| 434 | Urinary Bladder | Contains calculi | Concretion |
| 434 | Kidney, Right | White nodule 0.2 x 0.2 x 0.1 cm | No Section |
| 403 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 405 | Mandibular Lymph Node | Red | Hemorrhage |
| 405 | Lung | Red | Atelectasis |

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VI Dosage Level: 1.0 MG/L 1.0 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 433 | Seminal Vesicles | White material growing around | Ejaculate |
| | | seminal vesicles but not | |
| | | invading organ | |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VI-RECOVERY Dosage Level: 1.0 MG/L 1.0 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Micros[illegible] Observations |
|---|---|---|---|
| 445 | Lung | Red foci on all lobes | No Corresponding Lesion |
| 446 | Lung | Tan foci on all lobes red with | No Corresponding Lesion |
| | | pinpoint foci on all lobes | |
| 446 | Thymus | Mottled red | No Corresponding Lesion |
| 446 | Urinary Bladder | Calculi within | No Corresponding Lesion |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VII Dosage Level: 1.0 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 435 | Mandibular Lymph Node | Red | Hemorrhage |
| 435 | Lung | Red foci | No Corresponding Lesion |
| 435 | Urinary Bladder | White calculi within | Concretion |
| 437 | Mandibular Lymph Node | Red | Hemorrhage |
| 438 | Lung | Anterior portion of left lobe - | No Corresponding Lesion |
| | | mottled tan | |
| 438 | Seminal Vesicles | White material around seminal | Ejaculate |
| | | vesicles but not invading organs | |
| 380 | Left Testis | Not apparent | No Section |
| 380 | Urinary Bladder | White calculus in lumen | Concretion |
| 381 | Urinary Bladder | White calculus in lumen | No Corresponding Lesion |
| 382 | Lung | Mottled tan | Alveolar Macrophages |
| 407 | Lung, All Lobes | Red foci | Atelectasis |
| 407 | Urinary Bladder | White calculus in lumen | Concretion |
| 408 | Lung | Red foci on all lobes | No Corresponding Lesion |
| 409 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 409 | Lung, All Lobes | Red foci | Atelectasis |

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VII Dosage Level: 1.0 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 409 | Urinary Bladder | White calculus in lumen | Concretion |
| 410 | Mandibular Lymph Node | Multiple red foci | Hemorrhage |
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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: RAT Sex: MALE Group Number: VII-RECOVERY Dosage Level: 1.0 MG/L 3.5 HOURS/DAY

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---|---|---|---|
| 447 | Mandibular Lymph Node | Mottled red | Hemorrhage |
| 447 | Seminal Vesicles | Edematous | No Corresponding Lesion |
| 447 | Urinary Bladder | White calculus in lumen | Concretion |
| 450 | Mandibular Lymph Node | Dark red | Hemorrhage |
| 450 | Urinary Bladder | White calculus in lumen | No Corresponding Lesion |
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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #1

Submitted to:

IIT Research Institute
Chicago, Illinois 60616

March 21, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O.Iverson

Study Title: Repeated Inhalation Exposure Studies to Aerosols of RP/BR Combustion Products in Rats, Amendment #1

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on March 20, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

March 21, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS AMENDMENT #1

## PATHOLOGY SUMMARY

Microscopic examinations were performed on specially stained sections of lung from male Sprague-Dawley rats. The purpose of these examinations was to confirm and grade the amount of collagen in the terminal bronchioles and associated alveoli. Two animals from each exposure group with previously reported terminal bronchiolar fibrosis were selected for examination. Two control animals were also selected. The paraffin blocks containing the right lung lobes from the selected animals were sectioned and stained with Masson's trichrome stain to demonstrate collagen. The slides were prepared and examined by Experimental Pathology Laboratories, Inc.

## RESULTS

The amount of stainable collagen in the alveolar walls was graded subjectively and recorded in the Histopathology Incidence Table. The Group and Exposure Frequency is also recorded at the top of each page.

The amount of collagen normally present in the alveolar

septa was recorded as "1", minimal. Some of the animals that had minimal to mild amounts of thickening of the terminal bronchiole and its associated alveolae did have a mild amount of collagen, i.e., grade 2, compared to the controls. In other animals the amount of stainable collagen present was not any greater than in the control animals, indicating that collagen fibers did not comprise all of the thickening present. Moderate amounts of collagen were present in most of the animals that were previously graded as 3 - terminal bronchiolar fibrosis.

## CONCLUSIONS

The results of this microscopic examination indicate that the thickening of the terminal bronchiole and its associated alveolae is indeed due, in part, to fibrosis - the formation of new collagen fibers in excess of what would normally be present. Fibrosis does not account for all of the thickening. In animals where the thickening was minimal, an increase in stainable collagen was not readily demonstrated. As the thickening became mild to moderate in severity, increased amounts of collagen in these areas were apparent.

W.O. Iverson, D.V.M.
Diplomate, A.C.V.P.

March 21, 1984

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

MASSON'S TRICHROME STAIN

| Group: | I R | | | III F2 | | | V F1 | | | V F2 | | | V F3 | | | VI R | | | VI F1 | | | VI F2 | | | VI F3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 441 | 442 | | 391 | 392 | | 373 | 374 | | 399 | 400 | | 429 | 430 | | 445 | 446 | | 377 | 378 | | 405 | 406 | | 431 | 432 | |
| LUNG | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar Septal Collagen | 1 | 1 | | 1 | 1 | | 2 | 1 | | 2 | 2 | | 1 | 1 | | 2 | 2 | | 1 | 1 | | 2 | 1 | | 1 | 1 | |

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Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79

MALE RATS

MASSON'S TRICHROME STAIN

| Group: | VII R | | | VII F1 | | | VII F2 | | | VII F3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 447 | 448 | | 379 | 380 | | 407 | 408 | | 437 | 438 | |
| LUNG | | | | | | | | | | | | |
| Alveolar Septal Collagen | 3 | 3 | | 3 | 3 | | 3 | 3 | | 3 | 3 | |

EPL | Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #2

Submitted to:

IIT Research Institute
Chicago, Illinois 60616

July 3, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O.Iverson

Study Title: Repeated Inhalation Exposure Studies to Aerosols of RP/BR Combustion Products in Rats, Amendment #2

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on July 3, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

July 3, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79

# REPEATED INHALATION EXPOSURE STUDIES TO AEROSOLS OF RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #2

## PATHOLOGY SUMMARY

Microscopic examinations were performed on selected tissues from male Sprague-Dawley rats. The purpose of these examinations was to determine if there were any treatment-related effects in tissues outside of the respiratory tract from the exposure of rats to aerosols of RP/BR combustion products. Tissues from rats which had received 0.0 mg/L or 1.0 mg/L for 3.5 hours/day for four consecutive days for four weeks and the respective recovery groups from these exposures, were selected for examination.

Paraffin blocks containing the following tissues were prepared at the Illinois Institute of Technology Research Institute: heart, eye, kidneys, adrenals, liver, esophagus, stomach, duodenum, and urinary bladder. The paraffin blocks were shipped to Experimental Pathology Laboratories, Inc., where hematoxylin and eosin stained slides were prepared and examined. A number of animals did not have urinary bladder present because it had been processed and examined as a part of the original pathology report for this study.

## RESULTS

The microscopic changes found and a detailed listing of all tissues evaluated are presented in the Histopathology Incidence Tables. All lesions are summarized by treatment group and presented in the Summary Incidence Tables.

No Changes were seen in the tissues examined which appeared to be related to the test material. Most lesions seen were present in the kidneys of both treated and control animals and consisted of early changes associated with chronic progressive nephropathy, a common degenerative renal disease of laboratory rats. The concretions seen in the urinary bladder of both treated and control animals are probably coagulated protein secreted by the male accessory sex glands at the time of euthanasia.

## CONCLUSIONS

The results of the additional microscopic examinations indicate that administration of RP/BR to rats for four weeks via inhalation at 1.0 mg/L for 3.5 hours per day for four consecutive days did not produce treatment related changes in the heart, eyes, kidneys, adrenals, liver, esophagus, stomach, duodenum, or urinary bladder.

W.O. Iverson, D.V.M.
Diplomate, ACVP

July 3, 1984

PROJECT L06139
PHASE III, STUDY 79
MALE RATS

## SUMMARY INCIDENCE TABLE

| GROUP: / EXPOSURE FREQUENCY: | I F2 | IR F2 | VII F2 | VIIR F2 | | |
|---|---|---|---|---|---|---|
| HEART | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| EYE | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| KIDNEY | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| Hyaline Casts | 4 | 4 | 3 | 3 | | |
| Tubular Hyperplasia | 1 | 2 | 1 | | | |
| Intratubular Mineralization | 3 | 3 | 1 | 2 | | |
| Lymphocytic Infiltrate | 1 | 1 | 1 | | | |
| | | | | | | |
| ADRENAL | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| LIVER | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| ESOPHAGUS | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| STOMACH | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| DUODENUM | | | | | | |
| (Number Examined) | (4) | (4) | (4) | (4) | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

PROJECT L06139
PHASE III, STUDY 79
MALE RATS

## SUMMARY INCIDENCE TABLE

| GROUP:<br>EXPOSURE FREQUENCY: | I<br>F2 | IR<br>F2 | VII<br>F2 | VIIR<br>F2 | | |
|---|---|---|---|---|---|---|
| URINARY BLADDER | | | | | | |
| (Number Examined) | (3) | (1) | (2) | (2) | | |
| Concretion | 1 | 1 | | 1 | | |

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP I 0.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 383 | 384 | 385 | 386 |
|---|---|---|---|---|
| HEART | X | X | X | X |
| EYE | X | X | X | X |
| KIDNEY | | | | |
| Hyaline Casts | 1 | 1 | 1 | 1 |
| Tubular Hyperplasia | 1 | | | |
| Intratubular Mineralization | | 1 | 1 | 1 |
| Lymphocytic Infiltrate | | 1 | | |
| ADRENAL | X | X | X | X |
| LIVER | X | X | X | X |
| ESOPHAGUS | X | X | X | X |
| STOMACH | X | X | X | X |
| DUODENUM | X | X | X | X |



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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP 1 0.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 383 | 384 | 385 | 386 |
|---|---|---|---|---|
| URINARY BLADDER | X | X | | N |
| Concretion | | | P | |





EPL | Experimental Pathology Laboratories, Inc.

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP I-RECOVERY 0.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 439 | 440 | 441 | 442 |
|---|---|---|---|---|
| HEART | X | X | X | X |
| EYE | X | X | X | X |
| KIDNEY | | | | |
| Hyaline Casts | 1 | 1 | 1 | 1 |
| Tubular Hyperplasia | | 1 | | 1 |
| Intratubular Mineralization | 1 | 2 | 1 | |
| Lymphocytic Infiltrate | | | | 1 |
| ADRENAL | X | X | X | X |
| LIVER | X | X | X | X |
| ESOPHAGUS | X | X | X | X |
| STOMACH | X | X | X | X |
| DUODENUM | X | X | X | X |





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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP I-RECOVERY 0.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 439 | 440 | 441 | 442 |
|---|---|---|---|---|
| URINARY BLADDER | N | N | | N |
| Concretion | | | P | |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP VII 1.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 407 | 408 | 409 | 410 |
|---|---|---|---|---|
| HEART | X | X | X | X |
| EYE | X | X | X | X |
| KIDNEY | X | | | |
| Hyaline Casts | | 1 | 1 | 1 |
| Tubular Hyperplasia | | | | 1 |
| Intratubular Mineralization | | | | 1 |
| Lymphocytic Infiltrate | | | | 1 |
| ADRENAL | X | X | X | X |
| LIVER | X | X | X | X |
| ESOPHAGUS | X | X | X | X |
| STOMACH | X | X | X | X |
| DUODENUM | X | X | X | X |





EPL | Experimental Pathology Laboratories, Inc

Key P = Present N = No Section A = Autolysis X = Not Remarkable
1 = Minimal 2 = Slight 3 = Moderate 4 = Moderately Severe/High
5 = Severe/High I = Incomplete Section

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP VII 1.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 407 | 408 | 409 | 410 |
|---|---|---|---|---|
| URINARY BLADDER | N | X | N | X |
| Concretion | | | | |



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Experimental Pathology Laboratories, Inc.

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Key P = Present
1 = Minimal
5 = Severe/High
N = No Section
2 = Slight
I = Incomplete Section
A = Autolysis
3 = Moderate
X = Not Remarkable
4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP VII-RECOVERY 1.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| HEART | X | X | X | X |
| EYE | X | X | X | X |
| KIDNEY | | | X | |
| Hyaline Casts | 1 | 1 | | 1 |
| Tubular Hyperplasia | | | | |
| Intratubular Mineralization | 1 | | | 1 |
| Lymphocytic Infiltrate | | | | |
| ADRENAL | X | X | X | X |
| LIVER | X | X | X | X |
| ESOPHAGUS | X | X | X | X |
| STOMACH | X | X | X | X |
| DUODENUM | X | X | X | X |

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Key: P = Present, 1 = Minimal, 5 = Severe/High, N = No Section, 2 = Slight, I = Incomplete Section, A = Autolysis, 3 = Moderate, X = Not Remarkable, 4 = Moderately Severe/High

P L
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# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139
PHASE III, STUDY 79
MALE RATS
GROUP VII-RECOVERY 1.0 MG/L
3.5 HOURS/DAY

Exposure Frequency: F2

| ANIMAL NUMBER | 447 | 448 | 449 | 450 |
|---|---|---|---|---|
| URINARY BLADDER | N | X | | N |
| Concretion | | | P | |





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STUDY NUMBER 795
NECROPSY REPORT

STUDY NUMBER 79S
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PATHOLOGY SYNOPSIS

Treatement-related gross morphologic lesions were observed in thoracic cavity and lungs in Sprague-Dawley rats from the experimental group that died spontaneously during the study. Microscopic examination of the tissues did not reveal any treatment-related changes in the heart, eyes, kidneys, adrenals, livers, esophagus, stomach, duodenum, urinary bladder, trachea and pulmonary lymph nodes. Inhalation of RP/BR by male rats for 2.25 hours per day for four consecutive days for four weeks at 0.75, 1.0 or 1.2-1.3 mg/l exposure levels induced terminal bronchiolar fibrosis in both terminal and recovery sacrifice. Inflammation of nasal turbinates was another change which was treatment-related. Most of the rats that died spontaneously had congestion of the nasal turbinates, lung and liver. Four of the sixteen rats which died spontaneously had very minimal terminal bronchiolar fibrosis.

Vladislava S. Rac

Vladislava S. Rac, M.S., D.V.M.
Scientific Advisor
Veterinary Pathologist

## GROSS NECROPSY OBSERVATIONS

### Phase III Study Number 79S

In accordance with experimental protocol, gross examinations of organs and tissues were performed on 120 male Sprague-Dawley rats in the toxicology group of Project L6139 Study Number 79, Supplemental (79S). The rats were divided into seven groups each containing male rats. The rats were exposed to various concentrations of RP/BR aerosol for 2.25 hours per day for four consecutive days for four week periods. Four of the seven groups of rats were sacrificed on the day of their last exposure while the rats in the remaining three groups (the recovery groups) were sacrificed 14 days following their last exposure. The groups, treatment, number of rats per group, and corresponding exposure concentration levels are outlined below.

| Treatment Group | Treatment | Number of Rats | Exposure Concentration Levels (mg/l) |
|---|---|---|---|
| 22 | Filtered Air | 15 | 0.0 |
| 23 | RP/BR Aerosol | 14 | 0.75 |
| 24 | RP/BR Aerosol | 15 | 1.0 |
| 25 | RP/BR Aerosol | 30[a] | 1.3 or 1.2 |
| 26 | Filtered Air | 16 | 0.0 |
| 27 | RP/BR Aerosol | 16 | 1.0 |
| 28 | RP/BR Aerosol | 14 | 1.3 or 1.2 |

### MATERIALS AND METHODS

The rats were anesthesized with Nembutal exsanguinate by way of the abdominal aorta and necropsied. The organs were examined and fixed in 10% neutral buffered formalin for a period of no less than 48 hours before further processing. The lungs were fixed by intratracheal perfusion of formalin.

The following tissues were collected at necropsy. Tissues marked with an asterisk (*) in the list below were processed by Histology Laboratory embedded in paraffin and resulting blocks were sent to EPL for further processing and microscopic examination.

| | | |
|---|---|---|
| Skin/Mammary Gland | Ileum | *Liver |
| Tongue | Jejunum | *Kidneys |
| Larynx | Mandibular Lymph Nodes | *Adrenal Glands |
| Parathyroid/Thyroid | *Eyes | Spleen |
| *Trachea | Brain | Pancreas |

[a] Includes spontaneous mortalities

| | | |
|---|---|---|
| *Esophagus | Spinal Cord (Cervical) | Cecum |
| *Heart | Pituitary Gland | Colon |
| Thymus | Ears (Tag) | Mesenteric Lymph Nodes |
| *Lungs | *Nasal Turbinates | Skeletal Muscle |
| *Urinary Bladder | *Respiratory Lymph Nodes | Sciatic Nerve |
| *Stomach | Sternum | Mandibular Glands |
| *Duodenum | Testes | |
| Salivary | | |
| Femur/Bone Marrow | | |

A summary of gross observations is presented by groups in the Necropsy Observations Tables.

PATHOLOGY RESULTS

Gross Observations: Treatment-related lesions were observed in rats that died spontaneously during the study. The lesions consisted of mottled red, dark red lungs, thoracid cavity containing red fluid, and dark red liver. No treatment-related changes were found at necropsy.

SUMMARY AND CONCLUSIONS

Treatment-related lesions were observed in lungs and liver of the rats that died during the study.

## Necropsy Observations
## Spontaneous Deaths

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN Lesion | Exposure Concentrations (mg/l) 0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| NUMBER OF RATS EXAMINED | 0 | 0 | 0 | 16 |
| NO GROSS LESIONS | 0 | 0 | 0 | 0 |
| | | | | |
| LUNGS | | | | |
| Mottled red | | | | 4/16 |
| Dark foci | | | | 1/16 |
| Dark red | | | | 11/16 |
| | | | | |
| THYMUS | | | | |
| Multiple red foci | | | | 1/16 |
| | | | | |
| THORACIC CAVITY | | | | |
| Contained dark red fluid | | | | 6/16 |
| | | | | |
| LIVER | | | | |
| Dark red | | | | 16/16 |
| Multifocal tan area | | | | 1/16 |
| Tan focus | | | | 1/16 |
| | | | | |
| | | | | |

Necropsy Observations
Spontaneous Deaths

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN Lesion | Exposure Concentrations (mg/l) 0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| KIDNEYS | | | | |
| Tan | | | | 2/16 |
| Red | | | | 1/16 |
| | | | | |
| SPLEEN | | | | |
| Dark red | | | | 1/16 |
| Pale red | | | | 1/16 |
| | | | | |
| STOMACH | | | | |
| Distended with gas | | | | 9/16 |
| Soft/flaccid | | | | 3/16 |
| | | | | |
| JEJUNUM | | | | |
| Distended | | | | 3/16 |
| | | | | |
| CECUM | | | | |
| Distended with gas | | | | 3/16 |
| | | | | |
| COLON | | | | |
| Distended with gas | | | | 1/16 |

Necropsy Observations
Spontaneous Deaths

Project L06139
Stucy Number 79-S
Test Article RP/BR

| ORGAN<br>Lesion | Exposure Concentrations (mg/l)<br>0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| URINARY BLADDER | | | | |
| Contained dark red fluid | | | | 1/16 |
| ABDOMINAL CAVITY | | | | |
| Contained red fluid | | | | 1/16 |
| PITUITARY GLAND | | | | |
| Dark red | | | | 1/16 |
| SKIN - Face | | | | |
| Crusty material (discharge) | | | | 1/16 |

## Necropsy Observations
## Rats Killed After the Last Exposure

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN<br>Lesion | Exposure Concentrations (mg/l)<br>0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| NUMBER OF RATS EXAMINED | 15 | 14 | 15 | 14 |
| NO GROSS LESIONS | 12 | 10 | 14 | 10 |
| | | | | |
| LUNGS | | | | |
| Depressed white/tan foci | | 1 | | |
| Red foci | | 1 | | |
| Gray raised areas | 1 | | | |
| | | | | |
| MANDIBULAR LYMPH NODES | | | | |
| Dark red | | 1 | | |
| Enlarged | | | | |
| | | | | |
| STOMACH | | | | |
| Distended with gas | 1 | | | |
| | | | | |
| URINARY BLADDER | | | | |
| Contained calculi | 1 | 1 | 1 | 2 |
| | | | | |
| CECUM | | | | |
| Mucosa - red | | | | |

Necropsy Observations
Rats Killed After the Last Exposure

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN Lesion | Exposure Concentrations (mg/l) 0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| RECTUM | | | | |
| Mucosa - red | | | | |
| | | | | |
| TESTES | | | | |
| Small | 1 | 1 | | 3 |
| Aplastic | | | | |

## Necropsy Observations
Recovery Group

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN Lesion | Exposure Concentrations (mg/l) 0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| NUMBER OF RATS EXAMINED | 16 | 0 | 16 | 14 |
| NO GROSS LESIONS | 12 | 0 | 13 | 12 |
| | | | | |
| LUNGS | | | | |
| Depressed white/tan foci | | | | |
| Red foci | | | | |
| Gray raised areas | 1 | | | |
| | | | | |
| MANDIBULAR LYMPH NODES | | | | |
| Dark red | | | 1 | |
| Enlarged | | | 1 | 1 |
| | | | | |
| STOMACH | | | | |
| Distended with gas | | | | |
| | | | | |
| URINARY BLADDER | | | | |
| Contained calculi | | | 1 | 1 |
| | | | | |
| CECUM | | | | |
| Mucosa - red | 2 | | 1 | |

Necropsy Observations
Recovery Group

Project L06139
Study Number 79-S
Test Article RP/BR

| ORGAN Lesion | Exposure Concentrations (mg/l) 0.0 | 0.75 | 1.0 | 1.3/1.2 |
|---|---|---|---|---|
| RECTUM | | | | |
| Mucosa - red | | | 1 | |
| | | | | |
| TESTES | | | | |
| Small | 1 | | | |
| Aplastic | 1 | | | |

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-S
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## EPL PATHOLOGY REPORT

Submitted To:

IIT Research Institute
Chicago, IL 60616

May 1, 1984

**EPL**

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79-5

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O. Iverson

Study Title: Inhalation Exposure Studies with RP/BR Combustion Products in Rats

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rat

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on April 25 through May 1, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

May 1, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-S
# INHALATION EXPOSURE STUDIES WITH RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY SUMMARY

Microscopic examinations were performed on selected tissues from male Sprague-Dawley rats. The purpose of this study was to evaluate the effects of exposure concentration and recovery time of the repeated exposure of rats to combustion products of Red Phosphorus/Butyl Rubber (RP/BR) on various biologic endpoints. This report contains the histopathologic findings. The experimental design for this study was as follows:

| Treatment Group | Code | Concentration mg/L | Recovery | Number of Rats |
|---|---|---|---|---|
| 22 | C0 | 0 | No | 15 |
| 23 | C1 | 0.75 | No | 14 |
| 24 | C2 | 1.0 | No | 15 |
| 25 | C3 | 1.3 or 1.2 | No | 30* |
| 26 | C0 | 0 | Yes | 16 |
| 27 | C2 | 1.0 | Yes | 16 |
| 28 | C3 | 1.3 or 1.2 | Yes | 14 |

* Sixteen of the Treatment Group 25 animals died spontaneously before the completion of all exposures.

All animals were exposed for 2.25 hours per day for four consecutive days for four weeks. Recovery animals were then untreated for an additional fourteen days.

The Group designations used in this report are as follows:

| Group | Code | Concentration mg/L | Recovery |
|---|---|---|---|
| 1 | C0 | 0 | No |
| 2 | C0 | 0 | Yes |
| 3 | C1 | 0.75 | No |
| 4 | C2 | 1.0 | No |
| 5 | C2 | 1.0 | Yes |
| 6 | C3 | 1.3 or 1.2 | No |
| 7 | C3 | 1.3 or 1.2 | Yes |

All animals in Groups 6 and 7 have a small case letter designation added to the animal number which specifies the exact exposure regimen that animal received. The exposure regimens are:

a. 1 exposure for 70 min. at 1.6 mg/L and 65 min at 1.3 mg/L

b. 1 exposure for 2.25 hr. at 1.3 mg/L

c. 14 exposures for 2.25 hr. at 1.2 mg/L

d. specified number of exposures for 2.25 hr. at 1.2 mg/L

All rats were necropsied and gross and histologic evaluations of the respiratory tract were conducted. According to protocol, the following tissues were trimmed and processed to paraffin blocks: trachea, pulmonary lymph nodes, each lung lobe, nasal turbinates and gross lesions. The paraffin blocks were then shipped to Experimental Pathology Laboratories, Inc. where hematoxylin and eosin stained slides were prepared and examined.

## RESULTS

The microscopic changes and a detailed listing of all tissues evaluated are presented in the Tabulated Animal Data Tables. All lesions are summarized by treatment group and presented in the Project Summary Tables. A correlation of lesions observed at necropsy with the corresponding microscopic observation, where possible, is presented in the Correlation of Gross and Micro Tables. The gross observations in these tables were transcribed from the necropsy sheets provided with the paraffin blocks.

The primary treatment-related change seen histologically in the study was in the lung and was diagnosed as "terminal bronchiolar fibrosis". The lesion consisted of thickening of the alveolar walls where the terminal bronchiole, lined by cuboidal epithelium, joined the alveolar sacs. The thickening consisted of a heterogeneous eosinophilic material compatible with collagen, containing small numbers of cells. Larger cells with prominent nuclei frequently lined the affected area. These cells appeared to be macrophages or activated Type II pneumocytes. All animals which were sacrificed in all the treated groups, both terminal and recovery sacrifice, had terminal bronchiolar fibrosis. The lesion was generally mild in Group 3 and 4 animals which received 0.75 or 1.0 mg/L respectively. Group 5, 6 or 7 animals had moderate fibrosis. A single animal in Groups 6 and 7 had severe terminal bronchiolar fibrosis. Four of the Group 6 animals which died spontanteously had very minimal thickening of

the terminal bronchioles. Another change which may be treatment related was inflammation of the nasal turbinates. This consisted of an increase in numbers of lymphocytes in the submucosa with infiltration of the mucosa by the same cells. Neutrophils were sometimes also present. The inflammation was usually only minimal in severity but approximately one-half of the C2 and C3 recovery animals had it in the most posterior section of the nasal turbinate (level 2). A substantial number of recovery control animals had inflammation in level 1 of the turbinate as did C2 and C3 recovery animals.

Most of the animals in the high dose group (Group 6) which died spontaneously had congestion of the nasal turbinates, lung and liver. This was to be expected in an animal that was not exsanguinated at the time of death. Four of the sixteen animals which died spontaneously had very minimal terminal bronchiolar fibrosis.

All other changes seen in this study occurred in both control and treated animals or were present in such low incidence as to not be considered treatment related.

## CONCLUSIONS

The results of these microscopic examinations indicate that the administration of RP/BR to rats for 2.25 hours per day for four consecutive days for four weeks at 0.75, 1.0, 1.2 or 1.3 mg/L produced mild to moderate terminal bronchiolar fibrosis. The lesion was more severe in animals that received $\geq$ 1.2 mg/L or

in the recovery animals that received 1.0 mg/L than in those that received lower doses. Several of the recovery animals that received 1.0, 1.2 or 1.3 mg/L of combustion products of RP/BR had a slight increase in inflammation of the posterior nasal turbinates relative to the recovery control animals. Most of the changes seen in sixteen high dose animals which died spontaneously were related to blood in the tissues (congestion). Four of these animals did have minimal thickening of terminal bronchioles.

W.O. Iverson, D.V.M.
W.O. Iverson, D.V.M.
Diplomate ACVP
May 1, 1984

## TABLE OF ABBREVIATIONS
## FOR PROJECT SUMMARY TABLES

| | | |
|---|---|---|
| N | - | Number Examined |
| LIVER- Centrilob. Valuolation | - | LIVER- Centrilobular Vacuolation |
| LUNG- Terminal Bronchiolar Fibro. | - | LUNG- Terminal Bronchiolar Fibrosis |
| MAN LN- Hemorrhage | - | MANDIBULAR LYMPH NODE- Hemorrhage |
| MAN LN- Lympho. Hyperplasia | - | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008 FATES: ALL
PAGE: 1 DAYS: ALL

| GROUP: | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 30 | 0 | 14 | 0 |
| NASAL TURBINATE - LEVEL 1 | N | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 29 | 0 | 13 | 0 |
| Inflammation | | 1 | 0 | 7 | 0 | 0 | 0 | 1 | 0 | 7 | 0 | 0 | 0 | 7 | 0 |
| Mineralization | | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 14 | 0 | 0 | 0 |
| Exudate | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| NASAL TURBINATE - LEVEL 2 | N | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 29 | 0 | 14 | 0 |
| Hemorrhage | | 2 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Exudate | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Mineralization | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Inflammation | | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 6 | 0 |
| Congestion | | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 |
| TRACHEA | N | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 30 | 0 | 14 | 0 |
| Lymphocytic Infiltrate | | 1 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 5 | 0 |
| Autolysis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| PULMONARY LYMPH NODE | N | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 30 | 0 | 14 | 0 |
| Hemorrhage | | 3 | 0 | 4 | 0 | 2 | 0 | 7 | 0 | 8 | 0 | 18 | 0 | 4 | 0 |
| Lymphocytic Hyperplasia | | 8 | 0 | 15 | 0 | 13 | 0 | 10 | 0 | 15 | 0 | 12 | 0 | 13 | 0 |
| Macrophage Hyperplasia | | 0 | 0 | 6 | 0 | 2 | 0 | 4 | 0 | 6 | 0 | 4 | 0 | 6 | 0 |
| LUNG | N | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 30 | 0 | 14 | 0 |
| Atelectasis | | 3 | 0 | 7 | 0 | 2 | 0 | 3 | 0 | 6 | 0 | 11 | 0 | 5 | 0 |
| Hemorrhage | | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 4 | 0 | 12 | 0 | 4 | 0 |
| Focal Lymphocyte Aggregate | | 0 | 0 | 3 | 0 | 1 | 0 | 1 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| Alveolar Macrophages | | 4 | 0 | 4 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 3 | 0 | 0 | 0 |
| Interstitial Inflammation | | 5 | 0 | 5 | 0 | 1 | 0 | 4 | 0 | 3 | 0 | 0 | 0 | 1 | 0 |
| Terminal Bronchiolar Fibro. | | 0 | 0 | 0 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 18 | 0 | 14 | 0 |
| Eosinophilic Infiltrate | | 1 | 0 | 2 | 0 | 3 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 1 | 0 |
| Congestion | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Osteoid | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Lymphocytic Aggregate | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008
PAGE: 2

FATES: ALL
DAYS: ALL

| GROUP: | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 30 | 0 | 14 | 0 |
| **OTHER TISSUES AND LESIONS:** | | | | | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| MAN LN- Hemorrhage | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| URINARY BLADDER- Normal | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| URINARY BLADDER- Concretion | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| LIVER- Necrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| LIVER- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 0 | 0 | 0 |
| LIVER- Centrilob. Vacuolation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| KIDNEY- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| KIDNEY- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| TESTIS- Tubular Atrophy | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| TESTIS- Mineralization | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| TESTIS- Aspermatogenesis | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TESTIS-Spermatidic Giant Cells | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SPLEEN- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| SPLEEN- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| JEJUNUM- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| PITUITARY- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| COLON- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| BRAIN- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| CECUM- Congestion | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CECUM- Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| RECTUM- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| STOMACH- Normal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 |
| CECUM- Normal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| THYMUS- Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| CECUM- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| URINARY BLADDER- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| STOMACH- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| STOMACH- Exfoliated Cells | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008
PAGE: 1

FATES: Terminal Sacrifice,Recovery Sacrifice
DAYS: ALL

| GROUP: | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| NASAL TURBINATE - LEVEL 1 | M 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 13 | 0 | 13 | 0 |
| Inflammation | 1 | 0 | 7 | 0 | 0 | 0 | 1 | 0 | 7 | 0 | 0 | 0 | 7 | 0 |
| Mineralization | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Congestion | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Exudate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| NASAL TURBINATE - LEVEL 2 | M 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 13 | 0 | 14 | 0 |
| Hemorrhage | 2 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Exudate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Mineralization | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Inflammation | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 6 | 0 |
| Congestion | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TRACHEA | M 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| Lymphocytic Infiltrate | 1 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 5 | 0 |
| Congestion | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PULMONARY LYMPH NODE | M 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| Hemorrhage | 3 | 0 | 4 | 0 | 2 | 0 | 7 | 0 | 8 | 0 | 3 | 0 | 4 | 0 |
| Lymphocytic Hyperplasia | 8 | 0 | 15 | 0 | 13 | 0 | 10 | 0 | 15 | 0 | 6 | 0 | 13 | 0 |
| Macrophage Hyperplasia | 0 | 0 | 6 | 0 | 2 | 0 | 4 | 0 | 6 | 0 | 1 | 0 | 6 | 0 |
| LUNG | M 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| Atelectasis | 3 | 0 | 7 | 0 | 2 | 0 | 3 | 0 | 6 | 0 | 3 | 0 | 5 | 0 |
| Hemorrhage | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 4 | 0 | 1 | 0 | 4 | 0 |
| Focal Lymphocyte Aggregate | 0 | 0 | 3 | 0 | 1 | 0 | 1 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| Alveolar Macrophages | 4 | 0 | 4 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Interstitial Inflammation | 5 | 0 | 5 | 0 | 1 | 0 | 4 | 0 | 3 | 0 | 0 | 0 | 1 | 0 |
| Terminal Bronchiolar Fibro. | 0 | 0 | 0 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| Eosinophilic Infiltrate | 1 | 0 | 2 | 0 | 3 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 1 | 0 |
| Osteoid | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Lymphocytic Aggregate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

## Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008
PAGE: 2

FATES: Terminal Sacrifice,Recovery Sacrifice
DAYS: ALL

| GROUP: | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | 15 | 0 | 16 | 0 | 14 | 0 | 15 | 0 | 16 | 0 | 14 | 0 | 14 | 0 |
| OTHER TISSUES AND LESIONS: | | | | | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| MAN LN- Hemorrhage | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| URINARY BLADDER- Normal | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| URINARY BLADDER- Concretion | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| TESTIS- Tubular Atrophy | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| TESTIS- Mineralization | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| TESTIS- Aspermatogenesis | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TESTIS-Spermatidic Giant Cells | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CECUM- Congestion | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CECUM- Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| RECTUM- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| STOMACH- Normal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CECUM- Normal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STOMACH- Exfoliated Cells | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008
PAGE: 1

FATES: Spontaneous Death
DAYS: ALL

| GROUP: | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| NASAL TURBINATE - LEVEL 1 | N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 14 | 0 | 0 | 0 |
| NASAL TURBINATE - LEVEL 2 | N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 |
| TRACHEA | N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Autolysis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| PULMONARY LYMPH NODE | N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Hemorrhage | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 0 | 0 | 0 |
| Lymphocytic Hyperplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 |
| Macrophage Hyperplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| LUNG | N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| Atelectasis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| Hemorrhage | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 |
| Alveolar Macrophages | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| Terminal Bronchiolar Fibro. | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Congestion | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S

## Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO.: 221-008
PAGE: 2

FATES: Spontaneous Death
DAYS: ALL

| GROUP: | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX: | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| NUMBER OF ANIMALS: | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 16 | 0 | 0 | 0 |
| OTHER TISSUES AND LESIONS: | | | | | | | | | | | | | | |
| LIVER- Necrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| LIVER- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 0 | 0 | 0 |
| LIVER- Centrilob. Vacuolation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| KIDNEY- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| KIDNEY- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| SPLEEN- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| SPLEEN- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| JEJUNUM- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| PITUITARY- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| COLON- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| BRAIN- Congestion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| STOMACH- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 |
| CECUM- Normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| THYMUS- Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| CECUM- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| URINARY BLADDER- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| STOMACH- Autolysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |

## TABLE OF ABBREVIATIONS
## FOR TABULATED ANIMAL DATA TABLES

| | | |
|---|---|---|
| N | - | Normal |
| P | - | Present |
| U | - | Unsuitable |
| * | - | Tissue Not Available |
| 1 | - | Minimal |
| 2 | - | Mild |
| 3 | - | Moderate |
| 4 | - | Marked |
| LIVER- Centrilob. Valuolation | - | LIVER- Centrilobular Vacuolation |
| LUNG- Terminal Bronchiolar Fibro. | - | LUNG- Terminal Bronchiolar Fibrosis |
| MAN LN- Hemorrhage | - | MANDIBULAR LYMPH NODE- Hemorrhage |
| MAN LN- Lympho. Hyperplasia | - | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |

INHALATION EXPOSURE STUDIES
WITH RP/B2 COMBUSTION PRODUCTS
PROJECT NUMBER 106139
PHASE III, STUDY 79-6
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 251-000 GROUP: 1 RATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID, mOl | 358 | 359 | 360 | 361 | 362 | 363 | 364 | 365 | 366 | 367 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | | N | N | N | N | N |
| Mineralization | - | - | - | - | 1 | - | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | | N | N | N | N |
| Mineralization | - | - | - | - | - | 1 | - | - | - | - |
| Inflammation | - | - | - | - | - | 1 | - | - | - | - |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | N | N | N | | | | N | | | N |
| Hemorrhage | - | - | - | - | - | - | - | - | 1 | - |
| Lymphocytic Hyperplasia | - | - | - | 2 | 1 | 2 | - | 1 | - | - |
| LUNG | N | N | N | | N | | | | | |
| Atelectasis | - | - | - | - | - | - | - | 2 | - | 1 |
| Hemorrhage | - | - | - | - | - | - | - | - | 1 | - |
| Alveolar Macrophages | - | - | - | 1 | - | 2 | 1 | - | - | 1 |
| Interstitial Inflammation | - | - | - | 2 | - | 3 | 1 | - | - | 1 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 368 | 369 | 370 | 371 | 372 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | N | N | N | N |
| Inflammation | 2 | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | | N | N | N | |
| Hemorrhage | 3 | - | - | - | 1 |
| TRACHEA | | N | N | N | N |
| Lymphocytic Infiltrate | 2 | - | - | - | - |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | 2 | 3 | - | - | - |
| Lymphocytic Hyperplasia | 2 | - | 1 | 1 | 1 |
| LUNG | | | N | N | |
| Atelectasis | 2 | - | - | - | - |
| Hemorrhage | - | - | - | - | 1 |
| Interstitial Inflammation | - | 1 | - | - | - |
| Eosinophilic Infiltrate | 1 | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 368 | 369 | 370 | 371 | 372 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| URINARY BLADDER- Normal | - | P | - | - | - |
| TESTIS- Tubular Atrophy | - | - | - | 3 | - |
| STOMACH- Normal | - | - | P | - | - |
| STOMACH- Exfoliated Cells | - | - | - | 1 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-6
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 85 | 418 | 419 | 420 | 421 | 422 | 423 | 424 | 425 | 426 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | | | | | N | N | N | N | N |
| Inflammation | 2 | - | 1 | 2 | 1 | - | - | - | - | - |
| Congestion | - | 1 | - | - | 1 | - | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | | N | | | N | N | N | N | N | N |
| Inflammation | 2 | - | - | - | - | - | - | - | - | - |
| Congestion | - | - | 1 | 1 | - | - | - | - | - | - |
| TRACHEA | | | | N | | N | | N | N | N |
| Lymphocytic Infiltrate | 2 | 2 | 2 | - | 2 | - | 2 | - | - | - |
| Congestion | - | - | - | - | 1 | - | - | - | - | - |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | - | - | - | - | 1 | - | - | 3 | 2 | - |
| Lymphocytic Hyperplasia | 1 | 2 | 3 | 2 | 2 | 1 | 1 | - | 2 | 3 |
| Macrophage Hyperplasia | 1 | - | - | - | - | 1 | - | - | 1 | 1 |
| LUNG | N | N | | | N | | | | | |
| Atelectasis | - | - | - | - | - | 2 | 1 | 1 | 1 | - |
| Focal Lymphocyte Aggregate | - | - | 1 | 1 | - | - | - | - | - | 2 |
| Alveolar Macrophages | - | - | - | 1 | - | - | - | - | - | 1 |
| Interstitial Inflammation | - | - | - | 1 | - | 1 | - | - | - | 2 |
| Osteoid | - | - | - | - | - | - | - | - | 1 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 2 RATES: Recovery Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 85 | 418 | 419 | 420 | 421 | 422 | 423 | 424 | 425 | 426 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| TESTIS- Tubular Atrophy | - | - | - | 4 | - | - | - | - | - | - |
| TESTIS- Mineralization | - | - | - | 1 | - | - | - | - | - | - |
| TESTIS- Aspermatogenesis | - | - | - | P | - | - | - | - | - | - |
| CECUM- Congestion | - | - | - | - | - | - | 1 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 2 RATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 427 | 428 | 429 | 430 | 431 | 432 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | | | | N | N |
| Inflammation | - | 2 | 1 | 1 | - | - |
| NASAL TURBINATE - LEVEL 2 | N | | N | N | N | N |
| Inflammation | - | 2 | - | - | - | - |
| TRACHEA | | | N | | N | N |
| Lymphocytic Infiltrate | 2 | 2 | - | 2 | - | - |
| PULMONARY LYMPH NODE | | | | | | |
| Hemorrhage | - | - | 1 | - | - | - |
| Lymphocytic Hyperplasia | 2 | 3 | 3 | 1 | 1 | 1 |
| Macrophage Hyperplasia | - | - | - | 1 | - | 1 |
| LUNG | | | | N | | |
| Atelectasis | 2 | - | - | - | 1 | 1 |
| Alveolar Macrophages | - | 2 | 2 | - | - | - |
| Interstitial Inflammation | - | 2 | 3 | - | - | - |
| Eosinophilic Infiltrate | - | - | 1 | - | - | 1 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 3 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 427 | 428 | 429 | 430 | 431 | 432 |
|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | |
| TESTIS- Tubular Atrophy | - | - | - | - | 1 | - |
| TESTIS-Spermatidic Giant Cells | - | - | - | - | 1 | - |
| CECUM- Normal | - | - | - | - | P | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 373 | 374 | 375 | 377 | 378 | 379 | 380 | 381 | 382 | 383 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | | N | N | N | N | | N | N |
| Mineralization | - | - | 1 | - | - | - | - | 1 | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | |
| Hemorrhage | - | - | - | - | - | - | - | - | - | 2 |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | N | | | | | | | | | |
| Hemorrhage | - | - | - | - | - | - | - | - | - | 1 |
| Lymphocytic Hyperplasia | - | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Macrophage Hyperplasia | - | - | - | - | - | - | 1 | - | - | - |
| LUNG | | | | | | | | | | |
| Hemorrhage | 1 | - | - | - | - | - | - | - | - | - |
| Alveolar Macrophages | - | 1 | - | - | - | - | - | - | - | - |
| Interstitial Inflammation | - | 1 | - | - | - | - | - | - | - | - |
| Terminal Bronchiolar Fibro. | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Eosinophilic Infiltrate | - | - | - | - | - | - | - | - | 1 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Tabulated Animal Data

PROJECT ID: 321-008 GROUP: 3 DATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 373 | 374 | 375 | 377 | 378 | 379 | 380 | 381 | 382 | 383 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| URINARY BLADDER- Normal | - | - | P | - | - | - | - | - | - | - |
| TESTIS- Tubular Atrophy | - | - | - | - | - | - | - | 3 | - | - |
| TESTIS- Aspermatogenesis | - | - | - | - | - | - | - | P | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 384 | 385 | 386 | 387 |
|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N |
| TRACHEA | N | N | N | N |
| PULMONARY LYMPH NODE | | | | |
| Hemorrhage | - | - | - | 1 |
| Lymphocytic Hyperplasia | 1 | 1 | 1 | 1 |
| Macrophage Hyperplasia | - | - | - | 1 |
| LUNG | | | | |
| Atelectasis | - | 2 | - | 1 |
| Focal Lymphocyte Aggregate | - | - | 1 | - |
| Terminal Bronchiolar Fibro. | 2 | 2 | 2 | 2 |
| Eosinophilic Infiltrate | 1 | 3 | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 3 DATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 384 | 385 | 386 | 387 |
|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | 2 | - |
| MAN LN- Hemorrhage | - | - | 2 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 388 | 389 | 390 | 391 | 392 | 393 | 394 | 395 | 396 | 397 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | | N | N | N | N |
| Inflammation | - | - | - | - | - | 1 | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | | N |
| Hemorrhage | - | - | - | - | - | - | - | - | 1 | - |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | N | | |
| Hemorrhage | 1 | - | - | 3 | - | - | 3 | - | 2 | 2 |
| Lymphocytic Hyperplasia | 1 | - | 1 | - | 2 | 2 | 1 | - | 1 | - |
| Macrophage Hyperplasia | 1 | 1 | - | - | - | - | - | - | 1 | - |
| LUNG | | | | | | | | | | |
| Atelectasis | - | - | - | - | 2 | - | 2 | - | - | - |
| Focal Lymphocyte Aggregate | - | - | - | - | - | 1 | - | - | - | - |
| Alveolar Macrophages | - | - | - | - | - | - | - | 1 | - | 1 |
| Interstitial Inflammation | 1 | - | - | - | 1 | 1 | - | 1 | - | - |
| Terminal Bronchiolar Fibro. | 3 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 3 |
| Eosinophilic Infiltrate | - | - | - | - | - | - | - | - | 1 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 398 | 399 | 400 | 401 | 402 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | | N | N |
| Mineralization | - | - | 1 | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | - | - | - | 1 | 2 |
| Lymphocytic Hyperplasia | 1 | 1 | 1 | 2 | - |
| Macrophage Hyperplasia | - | 1 | - | - | - |
| LUNG | | | | | |
| Atelectasis | 1 | - | - | - | - |
| Terminal Bronchiolar Fibro. | 2 | 2 | 2 | 2 | 2 |

INHALATION EXPOSURE STUDIES
WITH RP/ER COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 4 DATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 398 | 399 | 400 | 401 | 402 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| URINARY BLADDER- Concretion | P | " | " | " | " |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L0G139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 106 | 433 | 434 | 435 | 436 | 437 | 438 | 439 | 440 | 441 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | | | N | N | N | | N | |
| Inflammation | - | - | 3 | 3 | - | - | - | 2 | - | 2 |
| Exudate | - | - | 2 | 1 | - | - | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | | | N | N | N | | | |
| Inflammation | - | - | 1 | 1 | - | - | - | 1 | 1 | 2 |
| TRACHEA | | N | | | | N | N | | N | |
| Lymphocytic Infiltrate | 1 | - | 1 | 4 | 1 | - | - | 2 | - | 2 |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | - | - | 2 | - | 1 | - | 1 | - | 1 | 2 |
| Lymphocytic Hyperplasia | 2 | 2 | 2 | 3 | 2 | - | 2 | 2 | 2 | 1 |
| Macrophage Hyperplasia | - | - | - | - | - | 2 | - | 1 | - | - |
| LUNG | | | | | | | | | | |
| Atelectasis | 2 | - | - | - | - | 1 | - | - | 2 | - |
| Hemorrhage | - | - | - | - | - | - | 1 | - | - | 1 |
| Focal Lymphocyte Aggregate | - | - | - | 1 | 1 | - | - | - | 1 | - |
| Alveolar Macrophages | - | 2 | - | - | - | - | - | - | 3 | - |
| Interstitial Inflammation | - | 2 | - | - | - | - | - | - | 2 | - |
| Terminal Bronchiolar Fibro. | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 3 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 106 | 433 | 434 | 435 | 436 | 437 | 438 | 439 | 440 | 441 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | 4 | - | - | - | - | - | - | - |
| MAN LN- Hemorrhage | - | - | 1 | - | - | - | - | - | - | - |
| URINARY BLADDER- Concretion | - | - | - | - | - | - | - | P | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 442 | 443 | 444 | 445 | 446 | 447 |
|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | | | N | |
| Inflammation | - | - | 1 | 1 | - | 1 |
| NASAL TURBINATE - LEVEL 2 | | N | | | N | |
| Inflammation | 1 | - | 1 | 1 | - | 2 |
| TRACHEA | | N | | | N | |
| Lymphocytic Infiltrate | 1 | - | 1 | 1 | - | 1 |
| PULMONARY LYMPH NODE | | | | | | |
| Hemorrhage | 1 | - | - | 3 | - | 1 |
| Lymphocytic Hyperplasia | 1 | 2 | 2 | 2 | 3 | 2 |
| Macrophage Hyperplasia | 2 | 1 | 1 | - | 1 | - |
| LUNG | | | | | | |
| Atelectasis | 3 | - | 1 | - | - | 1 |
| Hemorrhage | - | - | - | 1 | - | 1 |
| Focal Lymphocyte Aggregate | - | 1 | - | - | 1 | - |
| Interstitial Inflammation | - | - | - | - | 1 | - |
| Terminal Bronchiolar Fibro. | 2 | 3 | 3 | 3 | 2 | 2 |
| Eosinophilic Infiltrate | - | - | - | 2 | 2 | - |

INHALATION EXPOSURE STUDIES
WITH RF/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 442 | 443 | 444 | 445 | 446 | 447 |
|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | |
| CECUM- Hemorrhage | - | - | - | 1 | - | - |
| RECTUM- Normal | - | - | - | P | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 231-008 GROUP: 6 RATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 404abc | 405abc | 406 | 408abc | 409abc | 410abc | 411abc | 412abc | 413abc | 414abc |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | N | N | | | | N | N | N | N | |
| Hemorrhage | - | - | - | 1 | 1 | - | - | - | - | - |
| Lymphocytic Hyperplasia | - | - | 1 | 1 | 1 | - | - | - | - | - |
| Macrophage Hyperplasia | - | - | - | - | - | - | - | - | - | 1 |
| LUNG | | | | | | | | | | |
| Atelectasis | - | - | - | - | - | - | 2 | - | - | - |
| Hemorrhage | - | - | - | - | - | - | - | 1 | - | - |
| Terminal Bronchiolar Fibro. | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Eosinophilic Infiltrate | - | - | - | 1 | - | - | - | - | - | - |
| Lymphocytic Aggregate | - | - | - | 1 | - | - | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 404abc | 405abc | 406 | 408abc | 409abc | 410abc | 411abc | 412abc | 413abc | 414abc |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| URINARY BLADDER- Normal | - | - | - | - | - | - | - | - | P | - |
| URINARY BLADDER- Concretion | - | P | - | - | - | - | - | - | - | - |
| TESTIS- Tubular Atrophy | - | - | 2 | - | 1 | - | - | - | 4 | - |
| TESTIS- Mineralization | - | - | - | - | 3 | - | - | - | 4 | - |

INHALATION EXPOSURE STUDIES
WITH RP/SR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 6 DATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 416abc | 468c | 469c | 470c |
|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N |
| TRACHEA | N | N | N | N |
| PULMONARY LYMPH NODE | N | | | |
| Lymphocytic Hyperplasia | - | 1 | 1 | 1 |
| LUNG | | | | |
| Atelectasis | 2 | - | - | 2 |
| Terminal Bronchiolar Fibro. | 3 | 4 | 3 | 3 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 73b | 141bd | 202ab | 298a | 303ab | 345abd | 349abd | 356b | 403ab | 407abd |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | | N | | | | | | | |
| Congestion | 1 | 1 | - | 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| NASAL TURBINATE - LEVEL 2 | | N | N | | N | | | | | |
| Congestion | 1 | - | - | 2 | - | 1 | 1 | 2 | 1 | 1 |
| TRACHEA | N | | | | N | | N | N | | N |
| Autolysis | - | 1 | 2 | - | - | 3 | - | - | - | - |
| Congestion | - | 1 | 1 | 1 | - | - | - | - | 1 | - |
| PULMONARY LYMPH NODE | | | | | N | | | | | |
| Hemorrhage | 1 | 2 | 2 | 3 | - | 1 | 1 | 2 | 1 | 2 |
| Lymphocytic Hyperplasia | 2 | - | - | 1 | - | - | 1 | 2 | 1 | - |
| Macrophage Hyperplasia | - | - | - | - | - | 1 | - | - | - | - |
| LUNG | | | | | | | | | | |
| Atelectasis | 2 | - | - | - | 1 | 1 | - | 1 | - | 3 |
| Hemorrhage | - | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 2 | 2 |
| Alveolar Macrophages | - | - | - | - | - | 1 | 1 | 1 | - | - |
| Terminal Bronchiolar Fibro. | - | 1 | - | - | - | 1 | 1 | - | - | - |
| Congestion | 2 | 2 | 4 | 3 | 3 | 4 | 2 | 2 | 4 | 4 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 321-008 GROUP: 6 FATES: Spontaneous Death
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 73b | 141bd | 202ab | 298ab | 303ab | 345abd | 349abd | 356b | 403ab | 407abd |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| LIVER- Necrosis | - | - | - | - | - | - | 1 | - | - | - |
| LIVER- Congestion | 2 | 2 | 1 | 1 | 2 | 3 | 2 | 2 | 1 | 1 |
| LIVER- Centrilob. Vacuolation | 1 | - | 2 | 1 | - | - | - | - | - | - |
| KIDNEY- Congestion | - | - | - | - | - | 3 | - | - | - | - |
| KIDNEY- Autolysis | - | - | - | - | - | 2 | - | - | - | - |
| SPLEEN- Normal | - | - | - | - | - | - | P | - | - | - |
| JEJUNUM- Autolysis | - | - | - | 3 | 3 | - | - | - | - | - |
| COLON- Autolysis | 2 | - | - | - | - | - | - | - | - | - |
| BRAIN- Congestion | - | - | - | - | - | 1 | - | - | - | - |
| STOMACH- Normal | P | P | P | - | P | - | - | - | P | P |
| CECUM- Autolysis | 2 | - | - | - | - | - | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. #0: | 415ab | 417ab | 454ab | 455a | 458abd | 467c |
|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | | | N | | |
| Congestion | 1 | 1 | 1 | - | 1 | 1 |
| NASAL TURBINATE - LEVEL 2 | | | | N | | |
| Congestion | 1 | 1 | 1 | - | 1 | 1 |
| TRACHEA | | | | N | | |
| Autolysis | 1 | 2 | 1 | - | 3 | 3 |
| Congestion | 1 | 2 | 1 | - | 2 | - |
| PULMONARY LYMPH NODE | | | | | | |
| Hemorrhage | 3 | 2 | 1 | 1 | 1 | 3 |
| Lymphocytic Hyperplasia | - | - | - | 1 | - | - |
| Macrophage Hyperplasia | 2 | - | 1 | - | - | - |
| LUNG | | | | | | |
| Atelectasis | - | 2 | 2 | - | - | 2 |
| Hemorrhage | - | 2 | - | 2 | - | - |
| Terminal Bronchiolar Fibro. | - | - | - | - | - | 2 |
| Congestion | 4 | 4 | 4 | 3 | 4 | 3 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 415ab | 417ab | 454ab | 455a | 458abd | 467c |
|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | |
| LIVER- Necrosis | - | - | - | - | 3 | 3 |
| LIVER- Congestion | 2 | - | 1 | 1 | 2 | 2 |
| LIVER- Centrilob. Vacuolation | - | 1 | - | - | - | - |
| KIDNEY- Congestion | - | - | - | - | - | 3 |
| KIDNEY- Autolysis | - | - | - | - | - | 2 |
| SPLEEN- Congestion | - | - | - | 1 | - | - |
| JEJUNUM- Autolysis | - | - | - | 4 | - | - |
| PITUITARY- Congestion | - | - | - | 3 | - | - |
| BRAIN- Congestion | - | - | - | - | - | 2 |
| STOMACH- Normal | P | P | P | P | - | - |
| CECUM- Normal | P | - | - | - | - | - |
| THYMUS- Hemorrhage | - | 1 | - | - | - | - |
| CECUM- Autolysis | - | - | 1 | - | - | - |
| URINARY BLADDER- Autolysis | - | - | - | - | 3 | - |
| STOMACH- Autolysis | - | - | - | - | 2 | 3 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 321-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 448abc | 449abc | 450abc | 451abc | 452abc | 453abc | 456abc | 457abc | 459abc | 460abc |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | | | U | | N | N | N | P | |
| Inflammation | 1 | 1 | 1 | - | 2 | - | - | - | - | 2 |
| NASAL TURBINATE - LEVEL 2 | | | N | N | | N | N | N | N | |
| Inflammation | 1 | 1 | - | - | 1 | - | - | - | - | 1 |
| TRACHEA | | | | N | N | N | N | N | | N |
| Lymphocytic Infiltrate | 1 | 1 | 3 | - | - | - | - | - | 1 | - |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | - | 1 | 1 | - | - | 1 | - | - | - | - |
| Lymphocytic Hyperplasia | 3 | 3 | 3 | 3 | 3 | 1 | 2 | - | 2 | 1 |
| Macrophage Hyperplasia | 2 | 1 | - | - | - | - | 1 | 1 | - | - |
| LUNG | | | | | | | | | | |
| Atelectasis | 2 | - | 1 | - | - | - | - | - | 2 | - |
| Hemorrhage | - | 1 | - | - | - | 1 | - | 1 | - | 1 |
| Interstitial Inflammation | - | - | - | 1 | - | - | - | - | - | - |
| Terminal Bronchiolar Fibro. | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 |
| Osteoid | - | P | - | - | - | - | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-003 GROUP: 7 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 448abc | 449abc | 450abc | 451abc | 452abc | 453abc | 456abc | 457abc | 459abc | 460abc |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | 3 | - | - | - | - | - | - | - |
| URINARY BLADDER- Concretion | - | - | - | - | - | P | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH EP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

| ANIMAL ID. NO: | 461abc | 462abc | 463bc | 471c |
|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | | | N |
| Inflammation | - | 2 | 2 | - |
| NASAL TURBINATE - LEVEL 2 | N | | | N |
| Exudate | - | 1 | - | - |
| Inflammation | - | 1 | 1 | - |
| TRACHEA | N | | N | N |
| Lymphocytic Infiltrate | - | 1 | - | - |
| PULMONARY LYMPH NODE | | | | |
| Hemorrhage | - | - | 1 | - |
| Lymphocytic Hyperplasia | 2 | 2 | 2 | 1 |
| Macrophage Hyperplasia | 1 | 1 | - | - |
| LUNG | | | | |
| Atelectasis | 2 | - | - | 2 |
| Terminal Bronchiolar Fibro. | 3 | 3 | 3 | 3 |
| Eosinophilic Infiltrate | 2 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 358 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 359 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 360 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 361 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 362 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 363 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 364 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 365 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 366 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 367 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 368 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 369 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Contains Calculi | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 1 FATES: Terminal Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 370 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Several White Depressed Areas on All Lobes | NO COROLLARY CHANGE DETECTED |
| >STOMACH: Void of Ingesta | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 371 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >STOMACH: Bloated and Gas Filled | STOMACH- Exfoliated Cells |
| >R. TESTIS: Small 1.0 X 0.8 cm x 0.4 cm | TESTIS- Tubular Atrophy |

ANIMAL ID. NO: 372 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 85 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 418 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 419 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 420 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >TESTES: Left, Aplasia. | TESTIS- Tubular Atrophy |

ANIMAL ID. NO: 421 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 422 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 423 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >CECUM: Mucosa Reddish | CECUM- Congestion |

ANIMAL ID. NO: 424 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 425 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 426 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Scattered Gray Raised Areas. | LUNG- Interstitial Inflammation |

ANIMAL ID. NO: 427 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 428 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 429 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 430 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 431 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >TESTE - LEFT: Small 1.8 x 1.3 x 1.5 cm | TESTIS- Tubular Atrophy |
| >CECUM: Mucosa Reddish | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C0

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 2 FATES: Recovery Sacrifice
PAGE 6 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 432 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 373 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 374 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 375 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Contains Calculi | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 377 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 378 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 379 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG - LEFT LOBE: Tan Depressed Area Along Edge Scattered Red Pinpoint Foci | NO COROLLARY CHANGE DETECTED |
| >LUNG - CARDIAC LOBE: Scattered Red Pinpoint Foci | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 380 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 381 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >TESTE - RIGHT: Small 1.2 x 1.0 x 0.6 cm | TESTIS- Tubular Atrophy |

ANIMAL ID. NO: 382 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 383 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 384 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 385 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C1

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 3 FATES: Terminal Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 386 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODES: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL ID. NO: 387 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 388 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 389 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 390 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 391 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 392 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 393 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 394 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 395 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 396 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice,
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 397 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 398 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Contains Calculi | URINARY BLADDER- Concretion |

ANIMAL ID. NO: 399 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 4 FATES: Terminal Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 400 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 401 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 402 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 106 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 433 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 434 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged, Dark Red | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 435 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 436 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 437 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 438 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 439 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Calculi | URINARY BLADDER- Concretion |

ANIMAL ID. NO: 440 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 441 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 442 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 443 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 444 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 445 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >CECUM: Mucosa- 0.2 x 0.5 cm Dark Red Area | CECUM- Hemorrhage |
| >RECTUM: Mucosa- 1.0 x 1.0 cm Dark Red Area | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 446 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C2

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 5 FATES: Recovery Sacrifice
PAGE 6 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 447 PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 404abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 405abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Contains Calculi | URINARY BLADDER- Concretion |

ANIMAL ID. NO: 406 PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >TESTIS II: Very Small | TESTIS- Tubular Atrophy |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
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CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 408abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 409abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >TESTE - LEFT: Small 0.2 x 0.2 x 0.2 cm | TESTIS- Tubular Atrophy; Mineralization |

ANIMAL ID. NO: 410abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 411abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 412abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 413abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LEFT TESTIS (II): Small 0.5 cm x 0.3 cm | TESTIS- Tubular Atrophy; Mineralization |
| >URINARY BLADDER: Contains Calculi | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 414abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 416abc PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 468c PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Terminal Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 469c PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 470c PATHOLOGIST: WOI
ANIMAL FATE: Terminal Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 73b PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THORACIC CAVITY: Severe Red Fluid (Amount) | No Section |
| >LUNGS: Dark Red. | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >CECUM: Partially Gas Filled. | NO COROLLARY CHANGE DETECTED |
| >STOMACH: Partially Gas Filled. | NO COROLLARY CHANGE DETECTED |
| >COLON: Partially Gas Filled. | COLON- Autolysis |

ANIMAL ID. NO: 141bd PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NOSE: Crusty Discharge Around | No Section |
| >EYES: Crusty Discharge Around | No Section |
| >THORACIC AND ABDOMINAL CAVITIES: Severe Red Fluid. | No Section |
| >LUNGS: Dark Mottled Red. | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >STOMACH: Empty; Gas Filled. | NO COROLLARY CHANGE DETECTED |
| >MOUTH: Crusty Discharge Around | No Section |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 202ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LIVER: Dark Red. | LIVER- Congestion |
| >LUNGS: Dark Red. | LUNG- Congestion; Hemorrhage |
| >STOMACH: Flaccid. | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 298ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LIVER: Dark Red | LIVER- Congestion |
| >JEJUNUM: Slightly Bloated. | JEJUNUM- Autolysis |

ANIMAL ID. NO: 303ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LIVER: Dark Red. | LIVER- Congestion |
| >LUNGS: Dark Red. | LUNG- Congestion |
| >STOMACH: Gas Filled; Empty. | NO COROLLARY CHANGE DETECTED |
| >JEJUNUM: Empty; Gas Filled. | JEJUNUM- Autolysis |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 345abd PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Severe Mottled Red. | LUNG- Congestion |
| >KIDNEYS: Tan. | KIDNEY- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >BRAIN: Soft. | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 349abd PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THORACIC CAVITY: Moderate Red Fluid | No Section |
| >LUNGS: Mottled Red. | LUNG- Congestion |
| >SPLEEN: Pale Red. | NO COROLLARY CHANGE DETECTED |
| >LIVER: Dark Red. Tan Focus 0.2 x 0.2 cm On The Dorsal Surface Of The Median Lobe. | LIVER- Necrosis |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 356b PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THORACIC CAVITY: Filled With Dark Red Fluid | No Section |
| >LUNGS: Dark Red | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |

ANIMAL ID. NO: 403ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Dark Red. | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >STOMACH: Flaccid | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 407abd PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THORACIC CAVITY: Severe Red Fluid. | No Section |
| >LUNGS: Dark Red. | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >STOMACH: Flaccid. | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 415ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Dark Red | LUNG- Congestion |
| >STOMACH: Gas Filled | NO COROLLARY CHANGE DETECTED |
| >CECUM: Gas Filled | NO COROLLARY CHANGE DETECTED |
| >LIVER: Dark Red | LIVER- Congestion |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
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## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 6 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 417ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Dark Red. | LUNG- Congestion |
| >THYMUS: Scattered Dark Red Foci. | THYMUS- Hemorrhage |
| >LIVER: Dark Red. | NO COROLLARY CHANGE DETECTED |
| >STOMACH: Bloated. Gas Filled. | NO COROLLARY CHANGE DETECTED |

ANIMAL ID. NO: 454ab PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Dark Red | LUNG- Congestion |
| >STOMACH: Gas Filled | NO COROLLARY CHANGE DETECTED |
| >CECUM: Gas Filled | CECUM- Autolysis |
| >LIVER: Dark Red. | LIVER- Congestion |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
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## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 7 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 455a PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THORACIC CAVITY: Contained Dark Red Fluid. | No Section |
| >LUNGS: Scattered Dark Areas, Some Pinpoint, Throughout. | LUNG- Hemorrhage |
| >SPLEEN: Dark Red. | SPLEEN- Congestion |
| >STOMACH: Bloated and Gas Filled. | NO COROLLARY CHANGE DETECTED |
| >LIVER: Extremely Dark Red. | LIVER- Congestion |
| >JEJUNUM: Bloated. Gas Filled. | JEJUNUM- Autolysis |
| >PITUITARY GLAND: Dark Red. | PITUITARY GLAND- Congestion |

ANIMAL ID. NO: 458abd PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Dark Red. | LUNG- Congestion |
| >LIVER: Dark Red. | LIVER- Congestion |
| >URINARY BLADDER: Filled With Dark Red Fluid. Aspirated 0.4 cc. | NO COROLLARY CHANGE DETECTED |
| >STOMACH: Gas Filled. | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 6 FATES: Spontaneous Death
PAGE 8 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 467c PATHOLOGIST: WOI
ANIMAL FATE: Spontaneous Death

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNGS: Mottled Red. | LUNG- Congestion |
| >LIVER: Dark Red, Basically, With Some Scattered Tan Areas. | LIVER- Necrosis; Congestion |
| >STOMACH: Bloated. Gas Filled. | STOMACH- Autolysis |
| >LEFT KIDNEY: Tan Posterior, Dark Red Anterior. | KIDNEY- Congestion |
| >BRAIN: Softer. | NO COROLLARY CHANGE DETECTED |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 1 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 448abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 449abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 450abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged | MANDIBULAR LYMPH NODE- Lymphocyti Hyperplasia |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 2 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 451abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 452abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 453abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >URINARY BLADDER: Contained Calculi | URINARY BLADDER- Concretion |

INHALATION EXPOSURE STUDIES
WITH RF/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 3 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 456abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

>NO OBSERVABLE ABNORMALITIES. NOT APPLICABLE

ANIMAL ID. NO: 457abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

>NO OBSERVABLE ABNORMALITIES. NOT APPLICABLE

ANIMAL ID. NO: 459abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

>NO OBSERVABLE ABNORMALITIES. NOT APPLICABLE

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 4 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 460abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 461abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVAELE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 462abc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Correlation of Gross and Micro

PROJECT ID: 221-008 GROUP: 7 FATES: Recovery Sacrifice
PAGE 5 SEX: MALE DAYS: ALL

ANIMAL ID. NO: 463bc PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL ID. NO: 471c PATHOLOGIST: WOI
ANIMAL FATE: Recovery Sacrifice

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-S
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #1

Submitted To:

IIT Research Institute
Chicago, IL 60616

July 20, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79-S

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O.Iverson

Study Title: Repeated Inhalation Exposure Studies With RP/BR Combustion Products in Rats, Pathology Report Amendment #1

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on July 20, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

July 20, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-S
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #1

## PATHOLOGY SUMMARY

Microscopic examinations were performed on selected tissues from male Sprague-Dawley rats. The purpose of these examinations was to determine if there were any treatment-related effects in tissues outside of the respiratory tract from the exposure of rats to RP/BR combustion products. Microscopic examinations were also performed on specially stained sections of lung from selected rats in this study. The purpose of these examinations was to confirm and grade the amount of collagen in the terminal bronchioles and associated alveoli. Tissues from selected rats which had received 0.0 mg/L, 0.75 mg/L, 1.0 mg/L, or 1.2 or 1.3 mg/L for 2.25 hours per day for four consecutive days for four weeks, and the respective recovery groups from these exposures, were examined.

Paraffin blocks containing the following tissues were prepared at the Illinois Institute of Technology Research Institute: heart, eyes, kidneys, adrenals, liver, esophagus, stomach, duodenum, urinary bladder, and lung. Paraffin blocks were shipped to Experimental Pathology Laboratories, Inc. where hematoxylin and eosin stained slides were prepared and examined. The paraffin blocks containing the right lung lobes from selected animals were sectioned and stained with Masson's trichrome stain to demonstrate collagen. Several animals did not have liver, stomach or urinary bladder

present because they had been processed and examined as a part of the original pathology report for this study.

**RESULTS**

The microscopic changes found and a detailed listing of all tissues evaluated are presented in the Tabulated Animal Data Tables. The amount of stainable collagen present in the alveolar walls of the lung was graded subjectively and is recorded in the Histopathology Incidence Tables. All lesions are summarized by treatment group and presented in the Project Summary Tables.

No changes were seen in the tissues examined outside of the respiratory tract which appeared to be related to the test material. Most lesions seen were present in the kidneys of both treated and control animals and consisted of early changes associated with chronic progressive nephropathy, a common degenerative renal disease of laboratory rats. The concretions seen in the urinary bladder of both treated and control animals were probably coagulated protein secreted by the male accessory sex glands at the time of euthanasia. A number of rats in the group which received 1.3 mg/L or more died spontaneously and exhibited congestion in the heart, kidney, and adrenal.

The amount of collagen normally present in the alveolar septa was recorded as "1", minimal. Some of the animals that had minimal to mild amounts of thickening of the terminal bronchiole and its associated alveoli did have a mild amount of collagen, i.e., grade 2, compared to the

controls. Mild to moderate amounts of collagen were present in most of the animals that were previously graded as grade 3 terminal bronchiolar fibrosis, that is, those animals that received 1.3 or 1.2 mg/L and survived until the terminal sacrifice.

## CONCLUSIONS

The results of these microscopic examinations indicate that the administration of combustion products of RP/BR to rats under the conditions of this experiment did not produce treatment-related lesions in the heart, eyes, kidneys, adrenals, liver, esophagus, stomach, duodenum or urinary bladder. Examination of lung from selected animals indicated that fibrosis, as evidenced by a Masson's trichrome stain, is a component of the lesion "terminal bronchiolar fibrosis" previously identified in the study. As the thickening which comprised this lesion became more severe, increased amounts of collagen were present in these areas.

W.O. Iverson, D.V.M.
Veterinary Pathologist

July 20, 1984

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 221-008 FATES: TERMINAL SACRIFICE,RECOVERY SACRIFICE
PAGE 1 DAYS: ALL SEX: MALE

| GROUP: | | C0 | | C0 R | | C3 | | C3 R | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 15 | | 16 | | 13 | | 14 | |
| | | # | % | # | % | # | % | # | % |
| HEART | No Ex | 15 | | 16 | | 13 | | 14 | |
| Inflammation | | 1 | (7) | 1 | (6) | 0 | (0) | 0 | (0) |
| EYE | No Ex | 15 | | 16 | | 12 | | 14 | |
| Inflammation | | 1 | (7) | 0 | (0) | 0 | (0) | 0 | (0) |
| KIDNEY | No Ex | 15 | | 16 | | 13 | | 14 | |
| Hyaline Casts | | 8 | (53) | 9 | (56) | 8 | (62) | 9 | (64) |
| Tubular Hyperplasia | | 5 | (33) | 7 | (44) | 3 | (23) | 5 | (36) |
| Intratubular Mineralization | | 10 | (67) | 13 | (81) | 5 | (38) | 9 | (64) |
| Lymphocytic Infiltrate | | 8 | (53) | 5 | (31) | 3 | (23) | 1 | (7) |
| ADRENAL | No Ex | 15 | | 16 | | 13 | | 14 | |
| Accessory Cortical Tissue | | 1 | (7) | 1 | (6) | 1 | (8) | 1 | (7) |
| LIVER | No Ex | 15 | | 16 | | 13 | | 14 | |
| Extramedullary Hematopoiesis | | 1 | (7) | 0 | (0) | 0 | (0) | 0 | (0) |
| Eosinophilic Infiltrate | | 1 | (7) | 0 | (0) | 0 | (0) | 0 | (0) |
| Subacute Inflammation | | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (7) |
| ESOPHAGUS | No Ex | 15 | | 16 | | 13 | | 14 | |
| STOMACH | No Ex | 13 | | 16 | | 13 | | 14 | |
| Exfoliated Cells | | 0 | (0) | 1 | (6) | 0 | (0) | 0 | (0) |
| DUODENUM | No Ex | 14 | | 16 | | 13 | | 14 | |
| URINARY BLADDER | No Ex | 14 | | 16 | | 11 | | 13 | |
| Concretion | | 2 | (14) | 4 | (25) | 0 | (0) | 1 | (8) |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 321-008 FATES: SPONTANEOUS DEATH
PAGE 1 DAYS: ALL SEX: MALE

| GROUP: | | C0 | | C0 R | | C3 | | C3 R | |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 0 | | 0 | | 16 | | 0 | |
| | | # | % | # | % | # | % | # | % |
| HEART | No Ex | 0 | | 0 | | 16 | | 0 | |
| Congestion | | 0 | | 0 | | 13 | (81) | 0 | |
| EYE | No Ex | 0 | | 0 | | 16 | | 0 | |
| Congestion | | 0 | | 0 | | 2 | (13) | 0 | |
| KIDNEY | No Ex | 0 | | 0 | | 15 | | 0 | |
| Congestion | | 0 | | 0 | | 15 | (100) | 0 | |
| Intratubular Mineralization | | 0 | | 0 | | 5 | (33) | 0 | |
| ADRENAL | No Ex | 0 | | 0 | | 16 | | 0 | |
| Congestion | | 0 | | 0 | | 12 | (75) | 0 | |
| LIVER | No Ex | 0 | | 0 | | 0 | | 0 | |
| ESOPHAGUS | No Ex | 0 | | 0 | | 16 | | 0 | |
| STOMACH | No Ex | 0 | | 0 | | 4 | | 0 | |
| DUODENUM | No Ex | 0 | | 0 | | 15 | | 0 | |
| Autolysis | | 0 | | 0 | | 2 | (13) | 0 | |
| URINARY BLADDER | No Ex | 0 | | 0 | | 15 | | 0 | |
| Concretion | | 0 | | 0 | | 1 | (7) | 0 | |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-9
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: CO SEX: MALE DAYS: ALL
FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 358 | 359 | 360 | 361 | 362 | 363 | 364 | 365 | 366 | 367 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | N | N | N | N |
| KIDNEY | | | N | | | | | | | |
| Hyaline Casts | 1 | 1 | - | 1 | 1 | 1 | 1 | 1 | - | - |
| Tubular Hyperplasia | 1 | - | - | 1 | - | - | - | - | 2 | 1 |
| Intratubular Mineralization | - | - | - | 1 | 1 | - | 2 | 1 | 1 | 1 |
| Lymphocytic Infiltrate | 1 | - | - | 1 | 1 | 1 | - | - | - | 1 |
| ADRENAL | N | | N | N | N | N | N | N | N | N |
| Accessory Cortical Tissue | - | P | - | - | - | - | - | - | - | - |
| LIVER | N | | N | N | N | N | N | N | N | N |
| Extramedullary Hematopoiesis | - | 1 | - | - | - | | - | - | - | - |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | | | N | N | N | N | N |
| Concretion | - | - | - | P | P | - | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: CO SEX: MALE DAYS: ALL
DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 368 | 369 | 370 | 371 | 372 |
|---|---|---|---|---|---|
| HEART | N | N | N | | N |
| Inflammation | - | - | - | 1 | - |
| EYE | | N | N | N | N |
| Inflammation | 2 | - | - | - | - |
| KIDNEY | | | | | |
| Hyaline Casts | - | - | - | 1 | - |
| Tubular Hyperplasia | - | - | - | 1 | - |
| Intratubular Mineralization | - | 1 | 1 | 1 | 1 |
| Lymphocytic Infiltrate | 1 | - | 1 | 1 | - |
| ADRENAL | N | N | N | N | N |
| LIVER | N | N | | N | N |
| Eosinophilic Infiltrate | - | - | 1 | - | - |
| ESOPHAGUS | N | N | N | N | N |
| STOMACH | N | N | A | A | N |
| DUODENUM | N | N | N | A | N |
| URINARY BLADDER | N | A | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER 106139
PHASE III, STUDY 79-9
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: CO R SEX: MALE DAYS: ALL
FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 85 | 418 | 419 | 420 | 421 | 422 | 423 | 424 | 425 | 426 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | N | | N | N | N | N | N | N | N | N |
| Inflammation | - | 1 | - | - | - | - | - | - | - | - |
| EYE | N | N | N | N | N | N | N | N | N | N |
| KIDNEY | | | | | | | | | | |
| Hyaline Casts | 1 | - | - | - | 1 | 2 | - | 2 | 1 | 1 |
| Tubular Hyperplasia | - | 1 | - | - | 1 | 1 | - | 1 | - | - |
| Intratubular Mineralization | - | 1 | - | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Lymphocytic Infiltrate | - | - | 1 | 1 | 1 | - | - | - | - | - |
| ADRENAL | N | | N | N | N | N | N | N | N | P |
| Accessory Cortical Tissue | - | P | - | - | - | - | - | - | - | - |
| LIVER | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | |
| Exfoliated Cells | - | - | - | - | - | - | - | - | - | 1 |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | | | N | N | N | |
| Concretion | - | - | - | - | P | P | - | - | - | P |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- CO

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: CO R SEX: MALE DAYS: ALL
FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 427 | 428 | 429 | 430 | 431 | 432 |
|---|---|---|---|---|---|---|
| HEART | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N |
| KIDNEY | | | | | | |
| Hyaline Casts | 1 | - | 1 | - | 1 | - |
| Tubular Hyperplasia | 1 | 1 | - | - | 1 | - |
| Intratubular Mineralization | 1 | - | 1 | 1 | 1 | 1 |
| Lymphocytic Infiltrate | - | 1 | - | - | - | 1 |
| ADRENAL | N | N | N | N | N | N |
| LIVER | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | | N | N |
| Concretion | - | - | - | P | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 SEX: MALE DAYS: ALL
FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 404 | 405 | 408 | 409 | 410 | 411 | 412 | 413 | 414 | 416 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | A | N | N | N | N | N | N | N | N | N |
| KIDNEY | | | | | | | N | N | | |
| Hyaline Casts | - | 1 | - | 1 | 1 | - | - | - | 1 | 1 |
| Tubular Hyperplasia | - | 1 | - | 1 | - | - | - | - | - | 1 |
| Intratubular Mineralization | 1 | 1 | - | - | 1 | 1 | - | - | - | - |
| Lymphocytic Infiltrate | - | - | 1 | 1 | - | - | - | - | - | 1 |
| ADRENAL | N | | N | N | N | N | N | N | N | N |
| Accessory Cortical Tissue | - | P | - | - | - | - | - | - | - | - |
| LIVER | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | A | N | N | N | N | N | A | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 SEX: MALE DAYS: ALL
FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 468 | 469 | 470 |
|---|---|---|---|
| HEART | N | N | N |
| EYE | N | N | N |
| KIDNEY | | | |
| Hyaline Casts | 1 | 1 | 1 |
| Intratubular Mineralization | - | - | 1 |
| ADRENAL | N | N | N |
| LIVER | N | N | N |
| ESOPHAGUS | N | N | N |
| STOMACH | N | N | N |
| DUODENUM | N | N | N |
| URINARY BLADDER | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 R SEX: MALE DAYS: ALL
FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 448 | 449 | 450 | 451 | 452 | 453 | 456 | 457 | 459 | 460 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | N | N | N | N |
| KIDNEY | | | | | | N | | | | |
| Hyaline Casts | - | 1 | 1 | 1 | - | - | 1 | - | 1 | 1 |
| Tubular Hyperplasia | - | 1 | - | - | 1 | - | - | - | - | 1 |
| Intratubular Mineralization | 1 | 1 | 1 | 1 | - | - | - | - | - | 1 |
| Lymphocytic Infiltrate | - | - | - | - | - | - | - | 1 | - | - |
| ADRENAL | N | N | N | N | N | N | N | | N | N |
| Accessory Cortical Tissue | - | - | - | - | - | - | - | P | - | - |
| LIVER | N | N | N | N | N | N | N | | N | N |
| Subacute Inflammation | - | - | - | - | - | - | - | 1 | - | - |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N | * | N | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 R SEX: MALE DAYS: ALL
FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 461 | 462 | 463 | 471 |
|---|---|---|---|---|
| HEART | N | N | N | N |
| EYE | N | N | N | N |
| KIDNEY | | | | |
| Hyaline Casts | 1 | 1 | - | 1 |
| Tubular Hyperplasia | - | 1 | - | 1 |
| Intratubular Mineralization | 1 | 1 | 1 | 1 |
| ADRENAL | N | N | N | N |
| LIVER | N | N | N | N |
| ESOPHAGUS | N | N | N | N |
| STOMACH | N | N | N | N |
| DUODENUM | N | N | N | N |
| URINARY BLADDER | N | N | N | |
| Concretion | - | - | - | P |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

# Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 SEX: MALE DAYS: ALL
FATES: SPONTANEOUS DEATH

| ANIMAL ID. NO: | 73 | 141 | 202 | 298 | 303 | 345 | 349 | 356 | 403 | 407 |
|---|---|---|---|---|---|---|---|---|---|---|
| HEART | | N | | N | | | | | | |
| Congestion | 1 | - | 2 | - | 2 | 1 | 1 | 2 | 1 | 1 |
| EYE | N | N | N | N | N | | N | N | N | N |
| Congestion | - | - | - | - | - | 1 | - | - | - | - |
| KIDNEY | | | | | | A | | | | |
| Congestion | 1 | 2 | 1 | 2 | 2 | - | 2 | 2 | 2 | 1 |
| Intratubular Mineralization | - | 1 | - | - | - | - | - | 1 | 1 | - |
| ADRENAL | N | N | N | | | | | | | |
| Congestion | - | - | - | 1 | 1 | 3 | 1 | 1 | 1 | 1 |
| LIVER | A | A | A | A | A | A | A | A | A | A |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | A | A | A | N | A | N | N | N | A | A |
| DUODENUM | N | N | N | N | | N | N | N | N | N |
| Autolysis | - | - | - | - | P | - | - | - | - | - |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-S
CONCENTRATION -- C3

## Tabulated Animal Data

PROJECT ID: 221-008 GROUP: C3 SEX: MALE DAYS: ALL
FATES: SPONTANEOUS DEATH

| ANIMAL ID. NO: | 415 | 417 | 454 | 455 | 458 | 467 |
|---|---|---|---|---|---|---|
| HEART | | N | | | | |
| Congestion | 2 | - | 2 | 1 | 1 | 2 |
| EYE | N | N | | N | N | N |
| Congestion | - | - | 2 | - | - | - |
| KIDNEY | | | | | | |
| Congestion | 2 | 1 | 1 | 2 | 1 | 2 |
| Intratubular Mineralization | - | 1 | - | - | 1 | - |
| ADRENAL | | | | | | N |
| Congestion | 2 | 1 | 2 | 1 | 1 | - |
| LIVER | A | A | A | A | A | A |
| ESOPHAGUS | N | N | N | N | N | N |
| STOMACH | A | A | A | A | A | A |
| DUODENUM | N | N | A | N | N | |
| Autolysis | - | - | - | - | - | P |
| URINARY BLADDER | N | N | N | | A | N |
| Concretion | - | - | - | P | - | - |

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79-S

MALE RATS

MASSON'S TRICHROME STAIN

| | CO Group I | | | | | CO R Group II | | | | | C 1 Group III | | | | | C2 Group IV | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 358 | 359 | 360 | 361 | 362 | 418 | 419 | 420 | 421 | 422 | 373 | 374 | 375 | 377 | 378 | 388 | 389 | 390 | 391 | 392 |
| LUNG | | | | | | | | | | | | | | | | | | | | |
| Alveolar Septal Collagen | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 |





EPL Experimental Pathology Laboratories, Inc.

Key P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79-S

MALE RATS

MASSON'S TRICHROME STAIN

| | C2 R Group V | | | | | | C3 Group VI | | | | | | C3 R Group VII | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 106 | 433 | 434 | 435 | 436 | | 404 | 405 | 406 | 408 | 409 | | 448 | 449 | 456 | 451 | 452 | |
| LUNG | | | | | | | | | | | | | | | | | | |
| Alveolar Septal Collagen | 2 | 3 | 3 | 3 | 2 | | 3 | 3 | 3 | 3 | 2 | | 2 | 2 | 2 | 3 | 3 | |





EPL Experimental Pathology Laboratories, Inc

Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

STUDY NUMBER 79SF
NECROPSY REPORT

IIT RESEARCH INSTITUTE

STUDY NUMBER 79SF
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PATHOLOGY SYNOPSIS

No compound-related gross pathologic lesions were observed in Sprague-Dawley rats from the experimental groups sacrificed after treatment which they received, and the recovery groups sacrificed 14 days following their last exposure.

Microscopic examination of the tissue did not reveal any treatment-related changes in the trachea, pulmonary lymph nodes, nasal turbinates, adrenals, urinary bladder, duodenum, esophagus, stomach, eyes, heart, kidneys, and liver. Inhalation of RP/BR by female rats for 2.25 hours per day for four consecutive days for four weeks at 0.75 or 1.0 mg/l induced minimal to mild terminal bronchiolar fibrosis. The severity of the lesions was slightly increased in rats that received 1.0 mg/l of RP/BR. The treatment-related increase of peribronchiolar eosinophilic infiltrate in treated rats did regress in the recovery groups of rats.

Vladislava S. Rac

Vladislava S. Rac, M.S., D.V.M.
Scientific Advisor
Veterinary Pathologist

# GROSS NECROPSY OBSERVATIONS

## Phase III Study Number 79SF

In accordance with experimental protocol, gross examinations of organs and tissues were performed on 105 female Sprague-Dawley rats in the toxicology group of Project L06139, Study Number 79, Supplemental (79-SF). The rats were divided into seven groups each containing 15 female rats. The rats were exposed to varing concentrations of RP/BR aerosol for 2.25 hrs/day for four consecutive days over a four week period. Four of the seven groups of rats were sacrificed on the day of their last exposure, while the rats in the remaining three groups (the recovery groups) were sacrificed 14 days following their last exposure. The groups, treatment, number of rats per group, and corresponding exposure concentration levels are outlined below.

| Treatment Group | Treatment | Number of Rats | Exposure Concentration Levels (mg/l) |
|---|---|---|---|
| TOX-$C_0$ | Filter Air | 15 | 0.0 |
| TOX-$C_1$ | RP/BR Aerosol | 15 | 0.40 |
| TOX-$C_2$ | RP/BR Aerosol | 15 | 0.75 |
| TOX-$C_3$ | RP/BR Aerosol | 15 | 1.00 |
| R-TOX-$C_0$ | Filter Air | 15 | 0.0 |
| R-TOX-$C_2$ | RP/BR Aerosol | 15 | 0.75 |
| R-TOX-$C_3$ | RP/BR Aerosol | 15 | 1.00 |

## MATERIALS AND METHODS

The rats were anesthetized with Nembutal exsanguinate by way of the abdominal aorta and necropsied. The organs were examined and fixed in 10% neutral buffered formalin for a period of no less than 48 hrs before further processing. The lungs were fixed by intratracheal perfusion of formalin.

The following tissues were collected at necropsy. Tissues marked with an asterisk (*) in the list below were processed by Histology, and the resulting blocks were sent to EPL for further processing and microscopic examination.

Skin/Mammary Gland
Tongue
Larynx
Parathyroid
*Trachea
*Esophagus
*Heart
Thymus
*Lungs

Ovaries
Uterus
*Urinary Bladder
*Stomach
*Duodenum
Jejunum
Ileum

Mandibular Lymph Nodes
*Eyes
Brain
Cervical Cord
Pituitary
Ears (tag)
*Nasal Turbinates

| | | |
|---|---|---|
| *Respiratory Lymph Nodes | Cecum | Sternum |
| *Liver | Colon | Femur/Bone Marrow |
| *Kidneys | Mesenteric Lymph Nodes | |
| *Adrenal Glands | Skeletal Muscles | |
| Spleen | Sciatic Nerve | |
| Pancreas | Mandibular Salivary Glands | |

A summary of the gross observations is presented for the rats killed immediately after the last exposure and those killed after the recovery period, respectively, in the following two Necropsy Observations Tables.

## PATHOLOGY RESULTS

Gross Observations: Treatment-related lesions were not observed either in the exposure group sacrificed on the day of last exposure or in the recovery group. The gross lesions observed were mild and seen with the same frequency in both the control and exposure groups. These lesions included: dark red foci and grey areas in the lungs; dark red and enlarged mandibular lymph nodes; mottled red thymuses and distended uteri.

## SUMMARY AND CONCLUSIONS

Treatment-related lesions were not observed in either the exposure groups sacrificed the day of the last exposure or those sacrificed 14 days later. The gross lesions that were observed were mild and occurred with similar frequency in both the control and treated groups.

Necropsy Observations Tables
Rats Killed After the Last Exposure

L6139
Phase III
Study Number: 79
Supplemental (79-SF)

Exposure Concentrations (mg/l)

| ORGAN Lesions. | $C_0$ (0.0) | $C_1$ (0.40) | $C_2$ (0.75) | $C_3$ (1.00) |
|---|---|---|---|---|
| Number of Rats Examined | 15 | 15 | 15 | 15 |
| No Gross Lesions | 11 | 4 | 9 | 10 |
| | | | | |
| LUNGS | | | | |
| Dark red foci/focus | 1 | 2 | 2 | |
| Raised grey foci | 3 | 2 | | |
| Tan focus/foci | | 2 | | |
| | | | | |
| MANDIBULAR LYMPH NODES | | | | |
| Dark red | 1 | 4 | 3 | 3 |
| Enlarged | | 2 | | 1 |
| | | | | |
| THYMUS | | | | |
| Mottled red | | 1 | | |
| Dark red foci | | 1 | | 1 |
| | | | | |
| MANDIBULAR SALIVARY GLANDS | | | | |
| Dark red | | | | 1 |
| | | | | |
| | | | | |

Necropsy Observations Tables
Rats Killed After the Last Exposure

L6139
Phase III
Study Number: 79
Supplemental (79-SF)

Exposure Concentrations (mg/l)

| ORGAN Lesions | $C_0$ (0.0) | $C_1$ (0.40) | $C_2$ (0.75) | $C_3$ (1.00) |
|---|---|---|---|---|
| UTERUS | | | | |
| Distended/dilated with clear fluid | 1 | 2 | 1 | 1 |
| Red | | 1 | | |
| | | | | |
| PERIBRONCHIAL LYMPH NODES | | | | |
| Dark red | | | | 1 |

L6139
Phase III
Study Number: 79
Supplemental (79-SF)

Recovery Group

Exposure Concentrations (mg/l)

| ORGAN Lesions | $C_0$ (0.0) | $C_1$ (0.40) | $C_2$ (0.75) | $C_3$ (1.00) |
|---|---|---|---|---|
| Number of Rats Examined | 15 | 0 | 15 | 15 |
| No Gross Lesions | 3 | 0 | 4 | 7 |
| LUNGS | | | | |
| Dark red foci/focus | 1 | | | |
| Mottled red | 1 | | 1 | 1 |
| MANDIBULAR LYMPH NODES | | | | |
| Dark red | 9 | | 8 | 6 |
| Enlarged | 1 | | 3 | 3 |
| THYMUS | | | | |
| Mottled red | 2 | | 2 | 1 |
| Dark red foci | 1 | | 3 | 3 |
| Dark red | 1 | | | |
| PERIBRONCHIAL LYMPH NODES | | | | |
| Dark red | 1 | | | |

L6139
Phase III
Study Number: 79
Supplemental (79-SF)

Recovery Group

Exposure Concentrations (mg/l)

| ORGAN Lesions | $C_0$ (0.0) | $C_1$ (0.40) | $C_2$ (0.75) | $C_3$ (1.00) |
|---|---|---|---|---|
| UTERUS | | | | |
| Distended/dilated with clear fluid | 3 | | 3 | |
| OVARIES | | | | |
| Small | 1 | | | |
| SPLEEN | | | | |
| Dark red | | | 1 | |
| RESPIRATORY LYMPH NODES | | | | |
| Enlarged | | | 1 | |
| LIVER | | | | |
| Dark red | | | 1 | |
| THORAX AND ABDOMIN | | | | |
| Contained red fluid | | | 1 | |

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-SF
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## EPL PATHOLOGY REPORT

Submitted To:

IIT Research Institute
Chicago, IL 60616

June 26, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79-SF

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O. Iverson

Study Title: Inhalation Exposure Studies with RP/BR Combustion Products in Rats

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rat

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on June 22 through June 26, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

June 26, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-SF
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## PATHOLOGY SUMMARY

Microscopic examinations were performed on selected tissues from female Sprague-Dawley rats. The purpose of this study was to evaluate the effects of exposure concentration and recovery time of the repeated exposure of rats to combustion products of Red Phosphorus/Butyl Rubber (RP/BR) on various biologic endpoints. This report contains the histopathologic findings. The experimental design for this study was as follows:

| Treatment Group | Code | Concentration mg/L | Recovery | Number of Rats |
|---|---|---|---|---|
| 22 | C0 | 0 | No | 15 |
| 23 | C1 | 0.40 | No | 15 |
| 24 | C2 | 0.75 | No | 15 |
| 25 | C3 | 1.0 | No | 15 |
| 26 | C0 | 0 | Yes | 15 |
| 27 | C2 | 0.75 | Yes | 15* |
| 28 | C3 | 1.0 | Yes | 15 |

* One of the Treatment Group 27 animals died spontaneously before the completion of all exposures.

All animals were exposed for 2.25 hours per day for four consecutive days for four weeks. Recovery animals were then untreated for an additional fourteen days.

All rats were necropsied and gross and histologic evaluations of the respiratory tract were conducted. According to protocol, the following tissues from all animals were trimmed and processed to paraffin blocks: trachea, pulmonary lymph nodes, each lung lobe, nasal turbinates and gross lesions. The following additional tissues were also processed to blocks from all animals in Groups 22, 25, 26 and 28: adrenals, urinary bladder, duodenum, esophagus, eyes, heart, kidneys, liver, and stomach. The paraffin blocks were then shipped to Experimental Pathology Laboratories, Inc. where hematoxylin and eosin stained slides were prepared and examined.

**RESULTS**

The microscopic changes and a detailed listing of all tissues evaluated are presented in the Tabulated Animal Data Tables. All lesions are summarized by treatment group and presented in the Project Summary Tables. A correlation of lesions observed at necropsy with the corresponding microscopic observation, where possible, is presented in the Correlation of Gross and Micro Tables. The gross observations in these tables were transcribed from the necropsy sheets provided with the paraffin blocks.

The primary treatment-related change seen histologically in the study was in the lung and was diagnosed as "terminal bronchiolar fibrosis". The lesion consisted of a minimal thickening of the alveolar walls where the terminal bronchiole,

lined by cuboidal epithelium, joined the alveolar sacs. The thickening consisted of a heterogeneous eosinophilic material compatible with collagen, containing small numbers of cells. All animals which were sacrificed in the treated groups 24, 25, 27 and 28, both terminal and recovery sacrifices, had terminal bronchiolar fibrosis. The lesion was generally minimal to mild in Group 25 and 28 animals which received 1.0 mg/L. Animals in Groups 24 and 27 had minimal terminal bronchiolar fibrosis which was only focal or multifocal in some animals. More of the treated animals had a peribronchiolar infiltrate of eosinophils than did the controls. This was especially true of the Group 23 and 24 animals which received .40 or .75 mg/L respectively. The treated recovery group tended to have less animals affected than did the regular sacrificed animals.

No changes were seen in the additional tissues examined from the control and high dose animals that appeared to be treatment related.

All other changes seen in this study occurred in both control and treated animals or were present in such low incidence as to not be considered treatment related.

## CONCLUSIONS

The results of these microscopic examinations indicate that the administration of RP/BR to female rats for 2.25 hours per day for four consecutive days for four weeks at 0.75 or 1.0 mg/L produced minimal to mild terminal bronchiolar fibrosis. The lesion was slightly more severe in animals that received 1.0 mg/L. There appeared to be a treatment-related increase in peribronchiolar eosinophilic infiltrate in treated animals that seemed to regress during the recovery period. No treatment-related changes were found in the tissues examined outside of the respiratory tract.

W.O. Iverson, D.V.M.
Diplomate ACVP
June 26, 1984

## TABLE OF ABBREVIATIONS
## FOR PROJECT SUMMARY TABLE

(COR) - C0 Recovery Group

(C2R) - C2 Recovery Group

(C3R) - C3 Recovery Group

No Ex - Number Examined

Lympho. Hyperplasia - Lymphocytic Hyperplasia

MAN LN - Mandibular Lymph Node

MAN SALIVARY GLAND - Mandibular Salivary Gland

Terminal Bronchiolar Fibro. - Terminal Bronchiolar Fibrosis

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 221-009 FATES: ALL
DAYS: ALL SEX: FEMALE

| GROUP: | | 22 (C0) | | 26 (C0R) | | 23 (C1) | | 24 (C2) | | 27 (C2R) | | 25 (C3) | | 28 (C3R) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | |
| | | # | % | # | % | # | % | # | % | # | % | # | % | # | % |
| NASAL TURBINATE - LEVEL 1 | No Ex | 15 | | 15 | | 15 | | 15 | | 15 | | 14 | | 15 | |
| Mineralization | | 0 | (0) | 1 | (7) | 2 | (13) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| Exudate | | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (7) | 0 | (0) |
| NASAL TURBINATE - LEVEL 2 | No Ex | 15 | | 15 | | 15 | | 15 | | 15 | | 14 | | 15 | |
| Hemorrhage | | 1 | (7) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (14) | 1 | (7) |
| TRACHEA | No Ex | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | |
| PULMONARY LYMPHOCYTE | No Ex | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | |
| Hemorrhage | | 3 | (20) | 10 | (67) | 9 | (60) | 9 | (60) | 10 | (67) | 9 | (60) | 10 | (67) |
| Lymphocytic Hyperplasia | | 12 | (80) | 11 | (73) | 6 | (40) | 7 | (47) | 8 | (53) | 13 | (87) | 7 | (47) |
| Macrophage Hyperplasia | | 8 | (53) | 7 | (47) | 6 | (40) | 3 | (20) | 5 | (33) | 8 | (53) | 3 | (20) |
| Pigment | | 4 | (27) | 5 | (33) | 3 | (20) | 1 | (7) | 7 | (47) | 5 | (33) | 6 | (40) |
| Edema | | 0 | (0) | 1 | (7) | 2 | (13) | 3 | (20) | 5 | (33) | 1 | (7) | 5 | (33) |
| LUNG | No Ex | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | |
| Atelectasis | | 5 | (33) | 4 | (27) | 3 | (20) | 5 | (33) | 3 | (20) | 6 | (40) | 4 | (27) |
| Hemorrhage | | 2 | (13) | 2 | (13) | 0 | (0) | 1 | (7) | 2 | (13) | 0 | (0) | 2 | (13) |
| Focal Lymphocyte Aggregate | | 0 | (0) | 2 | (13) | 0 | (0) | 1 | (7) | 0 | (0) | 0 | (0) | 1 | (7) |
| Alveolar Macrophages | | 7 | (47) | 6 | (40) | 4 | (27) | 2 | (13) | 1 | (7) | 2 | (13) | 2 | (13) |
| Interstitial Inflammation | | 6 | (40) | 8 | (53) | 4 | (27) | 3 | (20) | 5 | (33) | 5 | (33) | 2 | (13) |
| Terminal Bronchiolar Fibro. | | 0 | (0) | 0 | (0) | 0 | (0) | 15 | (100) | 15 | (100) | 15 | (100) | 15 | (100) |
| Eosinophilic Infiltrate | | 2 | (13) | 4 | (27) | 10 | (67) | 12 | (80) | 5 | (33) | 7 | (47) | 2 | (13) |
| Congestion | | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (7) | 0 | (0) | 0 | (0) |
| HEART | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Mineralization | | 1 | (7) | 0 | (0) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| Inflammation | | 1 | (7) | 0 | (0) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| Fibrosis | | 0 | (0) | 1 | (7) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| EYE | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Corneal Hyperplasia | | 0 | (0) | 1 | (7) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 221-009 RATES: ALL
DAYS: ALL SEX: FEMALE

| GROUP: | | 22 (C0) | | 26 (C0R) | | 23 (C1) | | 24 (C2) | | 27 (C2R) | | 25 (C3) | | 28 (C3R) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | | 15 | |
| | | # | % | # | % | # | % | # | % | # | % | # | % | # | % |
| KIDNEY | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Congestion | | 1 | (7) | 0 | (0) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| Hyaline Casts | | 7 | (47) | 5 | (33) | 0 | | 0 | | 0 | | 3 | (20) | 8 | (53) |
| Tubular Hyperplasia | | 2 | (13) | 1 | (7) | 0 | | 0 | | 0 | | 0 | (0) | 4 | (27) |
| Intratubular Mineralization | | 3 | (20) | 5 | (33) | 0 | | 0 | | 0 | | 1 | (7) | 2 | (13) |
| Lymphocytic Infiltrate | | 2 | (13) | 2 | (13) | 0 | | 0 | | 0 | | 1 | (7) | 0 | (0) |
| Cyst | | 0 | (0) | 0 | (0) | 0 | | 0 | | 0 | | 1 | (7) | 0 | (0) |
| Tubular Vacuolation | | 0 | (0) | 1 | (7) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| ADRENAL | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Accessory Cortical Tissue | | 1 | (7) | 3 | (20) | 0 | | 0 | | 0 | | 1 | (7) | 1 | (7) |
| Congestion | | 0 | (0) | 2 | (13) | 0 | | 0 | | 0 | | 0 | (0) | 0 | (0) |
| LIVER | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Peritonitis | | 1 | (7) | 0 | (0) | 0 | | 0 | | 0 | | 0 | (0) | 1 | (7) |
| ESOPHAGUS | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| STOMACH | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |
| Exfoliated Cells | | 0 | (0) | 1 | (7) | 0 | | 0 | | 0 | | 1 | (7) | 0 | (0) |
| DUODENUM | No Ex | 13 | | 14 | | 0 | | 0 | | 0 | | 14 | | 15 | |
| URINARY BLADDER | No Ex | 15 | | 15 | | 0 | | 0 | | 0 | | 15 | | 15 | |

# Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 221-009 FATES: ALL
DAYS: ALL SEX: FEMALE

| GROUP: | 22 (C0) | 26 (C0R) | 23 (C1) | 24 (C2) | 27 (C2R) | 25 (C3) | 28 (C3R) |
|---|---|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| | # Z | # Z | # Z | # Z | # Z | # Z | # Z |
| OTHER TISSUES AND LESIONS: | | | | | | | |
| MAN LN- Macrophage Hyperplasia | 0 (0) | 8 (53) | 0 (0) | 2 (13) | 7 (47) | 0 (0) | 6 (40) |
| MAN LN- Lympho. Hyperplasia | 1 (7) | 9 (60) | 5 (33) | 3 (20) | 9 (60) | 3 (20) | 7 (47) |
| MAN LN- Hemorrhage | 1 (7) | 9 (60) | 5 (33) | 3 (20) | 9 (60) | 3 (20) | 7 (47) |
| MAN SALIVARY GLAND- Normal | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (7) | 0 (0) |
| THYMUS- Normal | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| THYMUS- Hemorrhage | 0 (0) | 4 (27) | 2 (13) | 0 (0) | 5 (33) | 1 (7) | 4 (27) |
| UTERUS- Hydrometra | 1 (7) | 4 (27) | 2 (13) | 1 (7) | 2 (13) | 1 (7) | 0 (0) |
| UTERUS- Congestion | 0 (0) | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| UTERUS- Normal | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 1 (7) | 0 (0) | 0 (0) |
| MAN LN- Edema | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| SPLEEN- Congestion | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (7) | 0 (0) | 0 (0) |
| LIVER- Congestion | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (7) | 0 (0) | 0 (0) |

## TABLE OF ABBREVIATIONS
## FOR TABULATED ANIMAL DATA TABLES

N - Normal

P - Present

U - Unsuitable

* - Tissue Not Available

1 - Minimal

2 - Mild

3 - Moderate

4 - Marked

Lympho. Hyperplasia - Lymphocytic Hyperplasia

MAN LN - Mandibular Lymph Node

MAN SALIVARY GLAND - Mandibular Salivary Gland

Terminal Bronchiolar Fibro. - Terminal Bronchiolar Fibrosis

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 1 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | | N | N | N | N | N | N | N | N | N |
| Hemorrhage | 2 | - | - | - | - | - | - | - | - | - |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | N | | | | | | | |
| Hemorrhage | - | - | - | 1 | - | - | - | - | - | - |
| Lymphocytic Hyperplasia | 2 | 1 | - | - | 1 | 2 | 2 | 1 | 2 | 2 |
| Macrophage Hyperplasia | 2 | - | - | 1 | 1 | 2 | 1 | 1 | - | - |
| Pigment | 1 | - | - | - | - | - | 1 | - | - | - |
| LUNG | N | N | | | | | | | | |
| Atelectasis | - | - | - | - | - | 1 | 1 | 1 | - | - |
| Hemorrhage | - | - | 1 | 1 | - | - | - | - | - | - |
| Alveolar Macrophages | - | - | - | - | 2 | 2 | 2 | - | 1 | 1 |
| Interstitial Inflammation | - | - | - | - | 3 | 3 | 2 | - | 1 | 1 |
| Eosinophilic Infiltrate | - | - | - | - | - | - | - | - | 1 | 1 |
| HEART | N | N | N | N | | N | N | N | N | N |
| Mineralization | - | - | - | - | 1 | - | - | - | - | - |
| EYE | N | N | N | N | N | N | N | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | | | | | N | | | | | N |
| Congestion | - | - | - | - | - | 1 | - | - | - | - |
| Hyaline Casts | 1 | 1 | 1 | 1 | - | - | - | 1 | - | - |
| Tubular Hyperplasia | - | 1 | - | - | - | - | 1 | - | - | - |
| Intratubular Mineralization | - | - | 1 | - | - | - | - | - | 1 | - |
| Lymphocytic Infiltrate | - | - | - | - | - | - | - | 1 | 1 | - |
| ADRENAL | N | N | N | N | N | | N | N | N | N |
| Accessory Cortical Tissue | - | - | - | - | - | P | - | - | - | - |
| LIVER | N | N | N | N | N | | N | N | N | N |
| Peritonitis | - | - | - | - | - | 1 | - | - | - | - |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | A | N | A | N | N |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | - | - | 2 | - | - | - | - | - |
| MAN LN- Hemorrhage | - | - | - | - | 2 | - | - | - | - | - |
| UTERUS- Hydrometra | - | - | - | - | - | 2 | - | - | - | - |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 365 | 366 | 367 | 368 | 369 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | 3 | - | 1 | - | - |
| Lymphocytic Hyperplasia | 1 | 2 | - | 1 | 2 |
| Macrophage Hyperplasia | - | - | - | 2 | 1 |
| Pigment | 2 | - | - | 1 | - |
| LUNG | N | | N | | |
| Atelectasis | - | - | - | 1 | 1 |
| Alveolar Macrophages | - | 2 | - | - | 1 |
| Interstitial Inflammation | - | 2 | - | - | - |
| HEART | N | N | | N | N |
| Inflammation | - | - | 1 | - | - |
| EYE | N | N | N | N | N |
| KIDNEY | N | | N | | |
| Hyaline Casts | - | 1 | - | 1 | - |
| Intratubular Mineralization | - | - | - | - | 1 |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 365 | 366 | 367 | 368 | 369 |
|---|---|---|---|---|---|
| ADRENAL | N | N | N | N | N |
| LIVER | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N |
| STOMACH | N | N | N | N | N |
| DUODENUM | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SE

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 26 (CO) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 415 | 416 | 417 | 418 | 419 | 420 | 421 | 422 | 423 | 424 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | 1 | 3 | 3 | 1 | - | 1 | - | 1 | 1 | 1 |
| Lymphocytic Hyperplasia | - | 1 | - | 2 | 1 | 2 | 2 | - | 2 | 2 |
| Macrophage Hyperplasia | 1 | - | 3 | - | 1 | 3 | 2 | - | 1 | - |
| Pigment | - | 1 | 1 | 1 | - | 2 | - | - | - | - |
| Edema | - | - | - | - | - | - | - | 1 | - | - |
| LUNG | | N | | N | | | | | | |
| Atelectasis | 2 | - | 1 | - | - | - | - | - | - | 2 |
| Hemorrhage | - | - | - | - | 1 | - | 1 | - | - | - |
| Focal Lymphocyte Aggregate | - | - | - | - | - | - | - | - | 1 | - |
| Alveolar Macrophages | - | - | - | - | - | 2 | - | - | - | - |
| Interstitial Inflammation | - | - | - | - | - | 2 | - | 1 | - | 1 |
| Eosinophilic Infiltrate | 1 | - | 1 | - | - | - | - | - | - | - |
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | | N | N | N | N |
| Corneal Hyperplasia | - | - | - | - | - | 2 | - | - | - | - |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 36 (CO) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 415 | 416 | 417 | 418 | 419 | 420 | 421 | 422 | 423 | 424 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | | N | | N | | N | | | | |
| Hyaline Casts | - | - | 1 | - | - | - | 1 | - | 1 | 1 |
| Tubular Hyperplasia | - | - | - | - | 1 | - | - | - | - | - |
| Intratubular Mineralization | - | - | 1 | - | 1 | - | - | 1 | - | - |
| Lymphocytic Infiltrate | 1 | - | - | - | - | - | - | - | - | - |
| Tubular Vacuolation | - | - | 1 | - | - | - | - | - | - | - |
| ADRENAL | N | N | N | N | N | | | N | | N |
| Accessory Cortical Tissue | - | - | - | - | - | P | - | - | P | - |
| Congestion | - | - | - | - | - | - | 1 | - | - | - |
| LIVER | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | | N | N | N | N | N | N |
| Exfoliated Cells | - | - | - | 1 | - | - | - | - | - | - |
| DUODENUM | N | N | N | A | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 26 (CO) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 415 | 416 | 417 | 418 | 419 | 420 | 421 | 422 | 423 | 424 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Macrophage Hyperplasia | 1 | 2 | - | - | - | - | 2 | - | 3 | - |
| MAN LN- Lympho. Hyperplasia | 2 | 1 | - | - | - | - | 3 | - | 3 | 4 |
| MAN LN- Hemorrhage | 2 | 3 | - | - | - | - | 3 | - | 3 | 2 |
| THYMUS- Normal | - | - | - | P | - | - | - | - | - | - |
| THYMUS- Hemorrhage | 2 | - | - | - | - | 1 | 1 | - | - | 2 |
| UTERUS- Hydrometra | - | - | 2 | - | - | 4 | - | - | - | - |
| UTERUS- Normal | P | - | - | - | - | - | - | - | - | - |
| MAN LN- Edema | - | - | - | - | - | - | - | - | - | 1 |

INHALATION EXPOSURE STUDIES
WITH RP/DR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 231-009 GROUP: 26 (CO) SEX: FEMALE DAYS: ALL
PAGE 4 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 425 | 426 | 427 | 428 | 429 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | | N | N |
| Mineralization | - | - | 1 | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | N |
| Hemorrhage | - | - | 1 | 2 | - |
| Lymphocytic Hyperplasia | 2 | 2 | 2 | 2 | - |
| Macrophage Hyperplasia | 2 | - | - | - | - |
| Pigment | - | - | - | 2 | - |
| LUNG | | | | | |
| Atelectasis | 2 | - | - | - | - |
| Focal Lymphocyte Aggregate | - | - | - | 1 | - |
| Alveolar Macrophages | 1 | 1 | 1 | 1 | 2 |
| Interstitial Inflammation | 1 | 2 | 2 | 1 | 3 |
| Eosinophilic Infiltrate | - | - | - | 1 | 1 |
| HEART | N | N | N | N | |
| Fibrosis | - | - | - | - | 1 |
| EYE | N | N | N | N | N |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 36 (CO) SEX: FEMALE DAYS: ALL
PAGE 5 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 425 | 426 | 427 | 428 | 429 |
|---|---|---|---|---|---|
| KIDNEY | N | | | N | |
| Hyaline Casts | - | 1 | - | - | - |
| Intratubular Mineralization | - | - | 1 | - | 1 |
| Lymphocytic Infiltrate | - | 1 | - | - | - |
| ADRENAL | N | | N | N | |
| Accessory Cortical Tissue | - | P | - | - | - |
| Congestion | - | - | - | - | 1 |
| LIVER | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N |
| STOMACH | N | N | N | N | N |
| DUODENUM | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N |

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 26 (CO) SEX: FEMALE DAYS: ALL
PAGE 6 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 425 | 426 | 427 | 428 | 429 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Macrophage Hyperplasia | 2 | 2 | - | 2 | 2 |
| MAN LN- Lympho. Hyperplasia | 4 | 3 | - | 3 | 2 |
| MAN LN- Hemorrhage | 4 | 3 | - | 3 | 3 |
| UTERUS- Hydrometra | 2 | 1 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/AR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-5E

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 1 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | | N | N | N | N | N | N | N | N | N |
| Mineralization | 1 | - | - | - | - | - | - | - | - | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | 2 | 2 | 1 | - | 1 | - | 1 | 1 | - | 1 |
| Lymphocytic Hyperplasia | - | - | - | 1 | - | 1 | - | - | 1 | - |
| Macrophage Hyperplasia | 1 | - | - | - | - | - | 2 | 2 | - | 1 |
| Pigment | 1 | 1 | - | - | - | - | - | - | - | - |
| Edema | - | - | - | - | - | - | - | 1 | - | - |
| LUNG | | | | | N | | | | | N |
| Atelectasis | 1 | - | - | - | - | 1 | - | - | - | - |
| Alveolar Macrophages | - | - | 1 | - | - | 1 | - | - | - | - |
| Interstitial Inflammation | - | | 1 | - | - | 2 | - | - | - | - |
| Eosinophilic Infiltrate | 1 | 1 | 1 | 1 | - | - | 1 | 2 | 1 | - |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 2 RATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Lymphno. Hyperplasia | - | - | 4 | 2 | 2 | - | - | - | - | - |
| MAN LN- Hemorrhage | - | - | 2 | 2 | 2 | - | - | - | - | - |
| UTERUS- Hydrometra | - | - | - | - | - | - | - | - | 2 | - |
| UTERUS- Congestion | - | - | - | - | - | 3 | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 3 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 380 | 381 | 382 | 383 | 384 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | | N |
| Mineralization | - | - | - | 1 | - |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | - | - | - | 1 | 1 |
| Lymphocytic Hyperplasia | 1 | 2 | 2 | - | - |
| Macrophage Hyperplasia | - | - | 1 | - | 1 |
| Pigment | - | - | - | 1 | - |
| Edema | - | - | - | 1 | - |
| LUNG | N | | | | |
| Atelectasis | - | 2 | - | - | - |
| Alveolar Macrophages | - | 1 | 1 | - | - |
| Interstitial Inflammation | - | 2 | 2 | - | - |
| Eosinophilic Infiltrate | - | 1 | - | 1 | 1 |

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 380 | 381 | 382 | 383 | 384 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | - | 2 | 1 |
| MAN LN- Hemorrhage | - | - | - | 1 | 3 |
| THYMUS- Hemorrhage | - | - | - | 2 | 2 |
| UTERUS- Hydrometra | - | 2 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH KP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 385 | 386 | 387 | 388 | 389 | 390 | 391 | 392 | 393 | 394 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | | N | |
| Hemorrhage | 1 | 2 | 1 | 1 | 1 | - | 1 | - | - | 2 |
| Lymphocytic Hyperplasia | - | 1 | - | - | - | 1 | 2 | 2 | - | 2 |
| Macrophage Hyperplasia | - | - | - | - | - | 1 | - | - | - | - |
| Pigment | 1 | - | - | - | - | - | - | - | - | - |
| Edema | - | - | - | - | 1 | - | - | - | - | - |
| LUNG | | | | | | | | | | |
| Atelectasis | 1 | - | - | - | 1 | 3 | - | - | - | 1 |
| Hemorrhage | - | 2 | - | - | - | - | - | - | - | - |
| Alveolar Macrophages | - | - | - | - | - | - | - | 1 | - | - |
| Interstitial Inflammation | - | 1 | - | - | - | - | - | 2 | - | - |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | 1 | 2 | 1 | 1 | 1 | - | - | 2 | 1 | 1 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 2 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 385 | 386 | 387 | 388 | 389 | 390 | 391 | 392 | 393 | 394 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Macrophage Hyperplasia | - | - | 1 | - | - | - | - | - | - | - |
| MAN LN- Lympho. Hyperplasia | - | - | 1 | - | - | - | - | - | - | - |
| MAN LN- Hemorrhage | - | - | 2 | - | - | - | - | - | - | - |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 3 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 395 | 396 | 397 | 398 | 399 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | - | 3 | 1 | - | - |
| Lymphocytic Hyperplasia | 1 | - | 3 | - | - |
| Macrophage Hyperplasia | - | - | - | 1 | 1 |
| Edema | - | 1 | - | - | 1 |
| LUNG | | | | | |
| Atelectasis | - | - | - | - | 1 |
| Focal Lymphocyte Aggregate | - | 1 | - | - | - |
| Alveolar Macrophages | - | - | 1 | - | - |
| Interstitial Inflammation | - | - | 1 | - | - |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | - | 1 | 1 | 1 | 1 |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 395 | 396 | 397 | 398 | 399 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Macrophage Hyperplasia | - | - | 1 | - | - |
| MAN LN- Lympho. Hyperplasia | 3 | - | 3 | - | - |
| MAN LN- Hemorrhage | 2 | - | 3 | - | - |
| UTERUS- Hydrometra | - | - | - | 3 | - |

INHALATION EXPOSURE STUDIES
WITH RP/BP COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 27 (02) SEX: FEMALE DAYS: ALL
PAGE 1 DATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

| ANIMAL ID. NO: | 430 | 431 | 432* | 433 | 434 | 435 | 436 | 437 | 438 | 439 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | N | | |
| Hemorrhage | 1 | 3 | 1 | - | 1 | 3 | - | - | 1 | 1 |
| Lymphocytic Hyperplasia | - | - | 2 | 1 | 1 | 1 | 2 | - | - | - |
| Macrophage Hyperplasia | 1 | 1 | - | - | - | - | 3 | - | 1 | - |
| Pigment | - | - | - | - | 2 | 1 | 1 | - | - | 1 |
| Edema | 2 | - | 1 | - | - | - | - | - | 2 | 1 |
| LUNG | | | | | | | | | | |
| Atelectasis | - | 1 | - | - | - | 1 | - | - | - | 1 |
| Hemorrhage | - | - | - | - | - | - | - | - | - | 1 |
| Alveolar Macrophages | - | - | - | - | - | - | 2 | - | - | - |
| Interstitial Inflammation | - | - | 1 | - | 1 | - | 3 | - | - | - |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | - | 1 | 1 | - | 1 | - | - | - | 1 | - |
| Congestion | - | - | 1 | - | - | - | - | - | - | - |

* Spontaneous Death

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 3 DATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

| ANIMAL ID. NO: | 430 | 431 | 432* | 433 | 434 | 435 | 436 | 437 | 438 | 439 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Macrophage Hyperplasia | 1 | 2 | - | 1 | - | 2 | - | - | - | 1 |
| MAN LN- Lympho. Hyperplasia | 3 | 3 | - | 3 | - | 3 | - | - | - | 3 |
| MAN LN- Hemorrhage | 3 | 3 | - | 2 | - | 3 | - | - | - | 3 |
| THYMUS- Hemorrhage | - | - | - | - | - | 1 | - | 1 | - | - |
| SPLEEN- Congestion | - | - | 3 | - | - | - | - | - | - | - |
| LIVER- Congestion | - | - | 3 | - | - | - | - | - | - | - |

* Spontaneous Death

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE, SPONTANEOUS DEATH

| ANIMAL ID. NO: | 440 | 441 | 442 | 443 | 444 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | N | |
| Hemorrhage | - | 2 | 1 | - | 2 |
| Lymphocytic Hyperplasia | 1 | 3 | - | - | 2 |
| Macrophage Hyperplasia | 1 | - | - | - | - |
| Pigment | 1 | 2 | - | - | 1 |
| Edema | - | - | 1 | - | - |
| LUNG | | | | | |
| Hemorrhage | 1 | - | - | - | - |
| Interstitial Inflammation | - | 1 | - | 1 | - |
| Terminal Bronchiolar Fibro. | 2 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | 1 | - | - | - | - |

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

| ANIMAL ID. NO: | 440 | 441 | 442 | 443 | 444 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Macrophage Hyperplasia | - | 1 | 2 | - | - |
| MAN LN- Lymph. Hyperplasia | 1 | 3 | 3 | 3 | - |
| MAN LN- Hemorrhage | 2 | 3 | 3 | 1 | - |
| THYMUS- Hemorrhage | 1 | 1 | 3 | - | - |
| UTERUS- Hydrometra | - | 3 | - | 3 | - |
| UTERUS- Normal | P | - | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SE

## Tabulated Animal Data

PROJECT ID: 321-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 1 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 400 | 401 | 402 | 403 | 404 | 405 | 406 | 407 | 408 | 409 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | A | N | | N | N | N | N | N | N |
| Exudate | - | - | - | 1 | - | - | - | - | - | - |
| NASAL TURBINATE - LEVEL 3 | N | A | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | | | | | | |
| Hemorrhage | 1 | - | - | 1 | - | 1 | - | 2 | - | 1 |
| Lymphocytic Hyperplasia | 1 | 2 | 1 | 1 | 1 | 2 | 1 | - | 1 | 1 |
| Macrophage Hyperplasia | - | 1 | - | 1 | 1 | 2 | - | 1 | - | - |
| Pigment | - | 1 | - | 1 | - | - | - | 1 | - | - |
| LUNG | | | | | | | | | | |
| Atelectasis | - | 1 | - | - | 1 | 1 | - | - | - | 3 |
| Alveolar Macrophages | - | 1 | - | - | - | - | - | 1 | - | - |
| Interstitial Inflammation | - | 1 | - | - | - | - | - | 2 | - | 1 |
| Terminal Bronchiolar Fibro. | 2 | 2 | 1 | 3 | 1 | 1 | 1 | 1 | 2 | 1 |
| Eosinophilic Infiltrate | - | 1 | - | 2 | - | - | - | - | 1 | 2 |
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | N | N | N | N |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 2 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 400 | 401 | 402 | 403 | 404 | 405 | 406 | 407 | 408 | 409 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | N | | N | | N | | N | N | N | N |
| Hyaline Casts | - | - | - | 1 | - | - | - | - | - | - |
| Intratubular Mineralization | - | 1 | - | - | - | - | - | - | - | - |
| Lymphocytic Infiltrate | - | - | - | 1 | - | - | - | - | - | - |
| Cyst | - | - | - | - | - | P | - | - | - | - |
| ADRENAL | N | N | N | | N | N | N | N | N | N |
| Accessory Cortical Tissue | - | - | - | P | - | - | - | - | - | - |
| LIVER | N | N | N | N | N | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 3 RATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 400 | 401 | 402 | 403 | 404 | 405 | 406 | 407 | 408 | 409 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Lympho. Hyperplasia | - | - | - | - | - | - | - | 2 | - | - |
| MAN LN- Hemorrhage | - | - | - | - | - | - | - | 3 | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 410 | 411 | 412 | 413 | 414 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | | N | |
| Hemorrhage | - | - | 2 | - | 2 |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | 2 | 1 | 1 | - | 1 |
| Lymphocytic Hyperplasia | - | 1 | 1 | 1 | 1 |
| Macrophage Hyperplasia | - | - | 1 | 1 | 1 |
| Pigment | 2 | 2 | - | - | - |
| Edema | 2 | - | - | - | - |
| LUNG | | | | | |
| Atelectasis | - | 1 | 1 | - | - |
| Interstitial Inflammation | - | 1 | - | 1 | - |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | 1 | 1 | - | 1 | - |
| HEART | N | N | N | N | N |
| EYE | N | N | N | N | N |
| KIDNEY | N | N | N | | |
| Hyaline Casts | - | - | - | 1 | 1 |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SE

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 5 DATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 410 | 411 | 412 | 413 | 414 |
|---|---|---|---|---|---|
| ADRENAL | N | N | N | N | N |
| LIVER | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N |
| STOMACH | N | N | N | N | |
| Exfoliated Cells | - | - | - | - | 2 |
| DUODENUM | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N |

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 6 FATES: TERMINAL SACRIFICE

| ANIMAL ID. NO: | 410 | 411 | 412 | 413 | 414 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Lympho. Hyperplasia | 2 | - | - | 3 | - |
| MAN LN- Hemorrhage | 3 | - | - | 3 | - |
| MAN SALIVARY GLAND- Normal | P | - | - | - | - |
| THYMUS- Hemorrhage | - | - | - | 1 | - |
| UTERUS- Hydrometra | - | 1 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 1 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 445 | 446 | 447 | 448 | 449 | 450 | 451 | 452 | 453 | 454 |
|---|---|---|---|---|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | N | N | N | N | N | N | N |
| TRACHEA | N | N | N | N | N | N | N | N | N | N |
| PULMONARY LYMPH NODE | N | | | | | | | | | |
| Hemorrhage | - | 1 | 2 | 1 | 1 | 1 | - | - | 1 | 1 |
| Lymphocytic Hyperplasia | - | - | 1 | - | - | 1 | - | 1 | - | 1 |
| Macrophage Hyperplasia | - | - | 1 | 1 | - | - | 1 | - | - | - |
| Pigment | - | - | - | - | - | 1 | - | - | 1 | 1 |
| Edema | - | 1 | - | - | 2 | - | 1 | - | 3 | - |
| LUNG | | | | | | | | | | |
| Atelectasis | - | - | - | 1 | - | - | - | - | 1 | 1 |
| Focal Lymphocyte Aggregate | - | - | - | - | - | - | - | 1 | - | - |
| Alveolar Macrophages | - | - | - | - | - | 1 | - | 1 | - | - |
| Interstitial Inflammation | - | - | - | - | - | 1 | - | 1 | - | - |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | - | - | - | - | - | - | 1 | - | - | - |
| HEART | N | N | N | N | N | N | N | N | N | N |
| EYE | N | N | N | N | N | N | N | N | N | N |

## Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 445 | 446 | 447 | 448 | 449 | 450 | 451 | 452 | 453 | 454 |
|---|---|---|---|---|---|---|---|---|---|---|
| KIDNEY | N | N | N | | N | | | | N | |
| Hyaline Casts | - | - | - | 1 | - | 1 | 1 | 1 | - | 1 |
| Tubular Hyperplasia | - | - | - | 1 | - | 1 | 1 | 1 | - | - |
| ADRENAL | N | N | N | N | N | N | N | N | N | N |
| LIVER | N | N | N | N | | N | N | N | N | N |
| Peritonitis | - | - | - | - | 1 | - | - | - | - | - |
| ESOPHAGUS | N | N | N | N | N | N | N | N | N | N |
| STOMACH | N | N | N | N | N | N | N | N | N | N |
| DUODENUM | N | N | N | N | N | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N | N | N | N | N | N |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 445 | 446 | 447 | 448 | 449 | 450 | 451 | 452 | 453 | 454 |
|---|---|---|---|---|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | | | | | | |
| MAN LN- Macrophage Hyperplasia | - | - | 2 | - | - | 1 | 2 | - | - | 1 |
| MAN LN- Lympho. Hyperplasia | - | - | 2 | 3 | - | 4 | 3 | - | - | 4 |
| MAN LN- Hemorrhage | - | - | 3 | 2 | - | 3 | 3 | - | - | 3 |
| THYMUS- Hemorrhage | - | - | - | 2 | - | - | 2 | - | - | 1 |

# Tabulated Animal Data

PROJECT ID: 221-009 GROUP: 38 (C3) SEX: FEMALE DAYS: ALL
PAGE 4 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 455 | 456 | 457 | 458 | 459 |
|---|---|---|---|---|---|
| NASAL TURBINATE - LEVEL 1 | N | N | N | N | N |
| NASAL TURBINATE - LEVEL 2 | N | N | N | | N |
| Hemorrhage | - | - | - | 1 | - |
| TRACHEA | N | N | N | N | N |
| PULMONARY LYMPH NODE | | | | | |
| Hemorrhage | 1 | - | 1 | 3 | - |
| Lymphocytic Hyperplasia | 1 | - | 1 | - | 1 |
| Pigment | 1 | 1 | - | 1 | - |
| Edema | 2 | - | - | - | - |
| LUNG | | | | | |
| Atelectasis | - | - | - | - | 1 |
| Hemorrhage | - | - | - | 1 | 1 |
| Terminal Bronchiolar Fibro. | 1 | 1 | 1 | 1 | 1 |
| Eosinophilic Infiltrate | - | 1 | - | - | - |
| HEART | N | N | N | N | N |
| EYE | N | N | N | N | N |
| KIDNEY | | N | | | |
| Hyaline Casts | 1 | - | 1 | - | 1 |
| Intratubular Mineralization | - | - | 1 | 1 | - |

## Tabulated Animal Data

PROJECT ID: 321-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 5 DATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 455 | 456 | 457 | 458 | 459 |
|---|---|---|---|---|---|
| ADRENAL | N | N | | N | N |
| Accessory Cortical Tissue | - | - | P | - | - |
| LIVER | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N |
| STOMACH | N | N | N | N | N |
| DUODENUM | N | N | N | N | N |
| URINARY BLADDER | N | N | N | N | N |

## Tabulated Animal Data

PROJECT ID: 321-009 GROUP: 38 (C3) SEX: FEMALE DAYS: ALL
PAGE 6 FATES: RECOVERY SACRIFICE

| ANIMAL ID. NO: | 455 | 456 | 457 | 458 | 459 |
|---|---|---|---|---|---|
| OTHER TISSUES AND LESIONS: | | | | | |
| MAN LN- Macrophage Hyperplasia | - | 3 | 1 | - | - |
| MAN LN- Lympho. Hyperplasia | - | 4 | 3 | - | - |
| MAN LN- Hemorrhage | - | 3 | 2 | - | - |
| THYMUS- Hemorrhage | - | 3 | - | - | - |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 22 (CO) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: TERMINAL SACRIFICE

ANIMAL NO: 355 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 356 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 357 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 358 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Several Dark Red Foci On Lungs | LUNG- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 22 (C0) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: TERMINAL SACRIFICE

ANIMAL NO: 359 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >LUNG: Lungs - Scattered 1.0 To 2.0 mm Raised Gray Foci | LUNG- Interstitial Inflammation |

ANIMAL NO: 360 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Left Lobe 0.3/0.3 cm Raised Gray Area Along W/Several Smaller Areas Scattered About @ 0.1/0.1 cm | LUNG- Interstitial Inflammation |
| >UTERUS: Uterine Horns Distended | UTERUS- Hydrometra |

ANIMAL NO: 361 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Several Pinpoint Raised Gray Loci | LUNG- Interstitial Inflammation |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 22 (C0) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

ANIMAL NO: 362 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 363 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 364 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 365 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 22 (C0) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

ANIMAL NO: 366 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 367 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 368 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 369 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 26 (C0) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: RECOVERY SACRIFICE

ANIMAL NO: 415 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Dark Red | THYMUS- Hemorrhage |
| >LUNG: Lungs - Mottled Red | NO COROLLARY CHANGE DETECTED |
| >UTERUS: Dilated | NO COROLLARY CHANGE DETECTED |

ANIMAL NO: 416 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Red Mandibular Lymph Nodes. | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 417 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >UTERUS: Horns Distended Contains Clear Fluid | UTERUS- Hydrometra |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 26 (C0) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: RECOVERY SACRIFICE

ANIMAL NO: 418 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THYMUS: Red Foci | NO COROLLARY CHANGE DETECTED |
| >DUODENUM: Separated From Stomach | No Section |

ANIMAL NO: 419 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 420 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE- Dark Red | No Section |
| >THYMUS- Mottled Red | THYMUS- Hemorrhage |
| >LUNG- Cardiac Lobe Of Lungs - Red Focus | NO COROLLARY CHANGE DETECTED |
| >UTERUS- Horns Distended And Filled With Fluid | UTERUS- Hydrometra |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 26 (CO) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE

ANIMAL NO: 421 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THYMIC LYMPH NODE: Thymic Lymph Nodes - Dark Red. | No Section |
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 422 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 423 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red, Enlarged | MANDIBULAR LYMPH NODE: Hemorrhage; Lymphocytic Hyperplasia |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 26 (C0) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: RECOVERY SACRIFICE

ANIMAL NO: 424 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Mottled Red. | THYMUS- Hemorrhage |

ANIMAL NO: 425 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >UTERUS: Dilated And Filled With Clear Fluid | UTERUS- Hydrometra |

ANIMAL NO: 426 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >UTERUS: Uterine Horns - Distended With Clear Fluid. | UTERUS- Hydrometra |
| >OVARY: Left, Small. | No Section |
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 26 (C0) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: RECOVERY SACRIFICE

ANIMAL NO: 427 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 428 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Red Mandibular Lymph Nodes. | MANDIBULAR LYMPH NODE- Hemorrhage |
| >KIDNEY: Rt. Kidney Cut Jaggedly | NO COROLLARY CHANGE DETECTED |
| >EYE: Very Little Optic Nerve Tissue Left On Eye. | NO COROLLARY CHANGE DETECTED |
| >BRAIN: Cerebrum Damaged. Lt. Hemisphere. | No Section |

ANIMAL NO: 429 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
PROJECT NUMBER L06139
PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: TERMINAL SACRIFICE

ANIMAL NO: 370 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 371 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Dark Red Focus On Left Lobe Of Lungs 1 mm | NO COROLLARY CHANGE DETECTED |

ANIMAL NO: 372 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: TERMINAL SACRIFICE

ANIMAL NO: 373 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Left Lobe 1.0 mm Tan Focus. | NO COROLLARY CHANGE DETECTED |
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 374 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged and Dark Red. | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia; Hemorrhage |

ANIMAL NO: 375 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Scattered 0.1 - 0.2 cm Grey Raised Foci | LUNG- Interstitial Inflammation |
| >UTERUS: Uterine Horns - Red | UTERUS- Congestion |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

ANIMAL NO: 376 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Pinpoint Raised Tan Foci | NO COROLLARY CHANGE DETECTED |

ANIMAL NO: 377 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 378 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >UTERUS: Horns Distended With Clear Fluid. | UTERUS- Hydrometra |

ANIMAL NO: 379 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
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## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

ANIMAL NO: 380 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 381 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Diaphragmatic Lobe - Pinpoint Dark Red Foci | LUNG- Atelectasis |
| >UTERUS: Slightly Distended Containing Clear Fluid | UTERUS- Hydrometra |

ANIMAL NO: 382 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Scattered Red Pinpoint Gray Foci | LUNG- Interstitial Inflammation |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 23 (C1) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: TERMINAL SACRIFICE

ANIMAL NO: 383 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |
| >THYMUS: Mottled Red | THYMUS- Hemorrhage |

ANIMAL NO: 384 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Scattered Dark Red Foci | THYMUS- Hemorrhage |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: TERMINAL SACRIFICE

ANIMAL NO: 385 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 386 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Left Lobe Of Lungs Has Dark Red Focus | LUNG- Hemorrhage |

ANIMAL NO: 387 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 388 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: TERMINAL SACRIFICE

ANIMAL NO: 389 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 390 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 391 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 392 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

ANIMAL NO: 393 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 394 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Several Dark Red Foci | NO COROLLARY CHANGE DETECTED |

ANIMAL NO: 395 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

ANIMAL NO: 396 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 397 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 398 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >UTERUS: Horns Distended, Contain Clear Liquid | UTERUS- Hydrometra |

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## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 24 (C2) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: TERMINAL SACRIFICE

ANIMAL NO: 399 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

INHALATION EXPOSURE STUDIES
WITH RP/BR COMBUSTION PRODUCTS
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PHASE III, STUDY 79-SF

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

ANIMAL NO: 430 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red, Enlarged | MANDIBULAR LYMPH NODE- Hemorrhage; Lymphocytic Hyperplasia |

ANIMAL NO: 431 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged And Dark Red | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia; Hemorrhage |

ANIMAL NO: 432 PATHOLOGIST: WOI
ANIMAL FATE: SPONTANEOUS DEATH

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Mottled Red. | LUNG- Congestion |
| >SPLEEN: Dark Red. | SPLEEN- Congestion |
| >LIVER: Severely Dark Red. | LIVER- Congestion |
| >ABDOMINAL CAVITY: Pools Of Red Fluid In The Abdominal Cavity. | NO COROLLARY CHANGE DETECTED |
| >THORACIC CAVITY: Pools Of Red Fluid In The Thoracic Cavity. | NO COROLLARY CHANGE DETECTED |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

ANIMAL NO: 433 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Red | MANDIBULAR LYMPH NODE- Congestion |

ANIMAL NO: 434 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 435 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Red Foci | THYMUS- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

ANIMAL NO: 436 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 437 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THYMUS: Red Foci | THYMUS- Hemorrhage |

ANIMAL NO: 438 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 439 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

ANIMAL NO: 440 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >UTERUS: Dilated | NO COROLLARY CHANGE DETECTED |
| >THYMUS: Red Foci | THYMUS- Hemorrhage |

ANIMAL NO: 441 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Mottled Red | THYMUS- Hemorrhage |
| >RESPIRATORY LYMPH NODE: Enlarged | PULMONARY LYMPH NODE- Lymphocytic Hyperplasia |
| >UTERUS: Uterus Horns - Distended Containing Clear Fluid | UTERUS- Hydrometra |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 27 (C2) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: RECOVERY SACRIFICE,SPONTANEOUS DEATH

ANIMAL NO: 442 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Mottled Red | THYMUS- Hemorrhage |

ANIMAL NO: 443 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |
| >UTERUS: Uterine Horns - Distended | UTERUS- Hydrometra |

ANIMAL NO: 444 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | No Section |

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## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: TERMINAL SACRIFICE

ANIMAL NO: 400 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 401 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 402 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 403 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: TERMINAL SACRIFICE

ANIMAL NO: 404 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 405 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 406 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 407 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |
| >LUNG: Lungs - Pinpoint Gray Raised Foci | LUNG- Interstitial Inflammation |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: TERMINAL SACRIFICE

ANIMAL NO: 408 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 409 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 410 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR SALIVARY GLAND: Mandibular Salivary Glands - Dark Red. | NO COROLLARY CHANGE DETECTED |
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: TERMINAL SACRIFICE

ANIMAL NO: 411 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >UTERUS: Horns Distended, Contain Clear Liquid | UTERUS- Hydrometra |

ANIMAL NO: 412 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 413 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged And Dark Red | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia; Hemorrhage |
| >THYMUS: Scattered Dark Red Foci. | THYMUS- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 25 (C3) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: TERMINAL SACRIFICE

ANIMAL NO: 414 PATHOLOGIST: WOI
ANIMAL FATE: TERMINAL SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >THYMIC LYMPH NODE: Thymic Lymph Nodes - Dark Red. | PULMONARY LYMPH NODE- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 1 FATES: RECOVERY SACRIFICE

ANIMAL NO: 445 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 446 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 447 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 448 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Red And Enlarged Mandibular Lymph Nodes. | MANDIBULAR LYMPH NODE- Hemorrhage; Lymphocytic Hyperplasia |
| >THYMUS: Red Foci | THYMUS- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 2 FATES: RECOVERY SACRIFICE

ANIMAL NO: 449 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >LUNG: Lungs - Mottled Red. | NO COROLLARY CHANGE DETECTED |

ANIMAL NO: 450 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Mandibular Lymph Nodes - Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |

ANIMAL NO: 451 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red. | MANDIBULAR LYMPH NODE- Hemorrhage |
| >THYMUS: Mottled Red | THYMUS- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 3 FATES: RECOVERY SACRIFICE

ANIMAL NO: 452 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 453 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 454 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |
| >THYMUS: Dark, Red Foci | THYMUS- Hemorrhage |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 4 FATES: RECOVERY SACRIFICE

ANIMAL NO: 455 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 456 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Enlarged | MANDIBULAR LYMPH NODE- Lymphocytic Hyperplasia |
| >THYMUS: Dark, Red Foci | THYMUS- Hemorrhage |

ANIMAL NO: 457 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >MANDIBULAR LYMPH NODE: Dark Red, Enlarged | MANDIBULAR LYMPH NODE- Hemorrhage; Lymphocytic Hyperplasia |

## Correlation of Gross & Micro

PROJECT ID: 221-009 GROUP: 28 (C3) SEX: FEMALE DAYS: ALL
PAGE 5 FATES: RECOVERY SACRIFICE

ANIMAL NO: 458 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

ANIMAL NO: 459 PATHOLOGIST: WOI
ANIMAL FATE: RECOVERY SACRIFICE

| REFERENCE TO NECROPSY RECORD: | RELATED HISTOPATHOLOGY: |
|---|---|
| >NO OBSERVABLE ABNORMALITIES. | NOT APPLICABLE |

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-SF
# INHALATION EXPOSURE STUDIES
# WITH RP/BR
# COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #1

Submitted To:

IIT Research Institute
Chicago, IL 60616

July 20, 1984

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

# QUALITY ASSURANCE REPORT CERTIFICATION

Client Name: IIT Research Institute

Client Study Number: L06139 Phase III Study 79-SF

Study Director: Dr. W.O. Iverson Pathologist: Dr. W.O.Iverson

Study Title: Repeated Inhalation Exposure Studies With RP/BR Combustion Products in Rats, Pathology Report Amendment #1

Test Article: Combustion Products of Red Phosphorus/Butyl Rubber

Species: Sprague-Dawley Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on July 20, 1984. All findings were reported to the Study Director and Management.

Betty L. Plankenhorn

Betty L. Plankenhorn

July 20, 1984

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# IITRI PROJECT NUMBER L06139
# PHASE III STUDY 79-SF
# INHALATION EXPOSURE STUDIES WITH RP/BR COMBUSTION PRODUCTS IN RATS

## PATHOLOGY REPORT AMENDMENT #1

## PATHOLOGY SUMMARY

Microscopic examinations were performed on specially stained sections of lung from female Sprague-Dawley rats. The purpose of these examinations was to confirm and grade the amount of collagen in the terminal bronchioles and associated alveoli. Five animals from each exposure group in this study were selected for examination. The paraffin blocks containing the right lung lobes from the selected animals were sectioned and stained with Masson's trichrome stain to demonstrate collagen. The slides were prepared and examined by Experimental Pathology Laboratories, Inc.

## RESULTS

The amount of stainable collagen present in the alveolar walls of the lung was graded subjectively and is recorded in the Histopathology Incidence Tables. The treatment group number is also recorded at the top of each page.

The amount of collagen normally present in the alveolar septa was recorded as "1", minimal. Some of the animals that had minimal to mild amounts of thickening of the terminal bronchiole and its associated alveoli did have a mild amount of collagen, i.e., grade 2, compared to the

controls. This occurred in those groups of animals treated with either 0.75 or 1.00 mg/L of combustion products of RP/BR. The amount of stainable collagen found in the group 23 animals, which had received 0.40 mg/L was not discernably different from that of the control animals (treatment groups number 22 and 26).

**CONCLUSIONS**

The results of this microscopic examination indicated that the thickening of the terminal bronchiole and its associated alveoli is due to the formation of new collagen fibers in excess of what would normally be present. Fibrosis does not account for all of the thickening seen in the change designated "terminal bronchiolar fibrosis". This staining substantiates the impression of terminal bronchiolar fibrosis in animals which received either 0.75 or 1.00 mg/L for 2.25 hours per day for 4 consecutive days for four weeks.

W.O. Iverson, D.V.M.
Veterinary Pathologist

July 20, 1984

# HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79-SF

FEMALE RATS

MASSON'S TRICHROME STAIN

| | Treatment Group No. 22 (C0) | | | | | | 23 (C1) | | | | | | 24 (C2) | | | | | | 25 (C3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 356 | 358 | 360 | 362 | 364 | | 371 | 373 | 375 | 377 | 379 | | 386 | 388 | 390 | 392 | 394 | | 401 | 403 | 405 | 407 | 409 | |
| LUNG | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar Septal Collagen | 1 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | 1 | 1 | | 1 | 2 | 2 | 1 | 2 | | 2 | 1 | 3 | 2 | 2 | |

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3

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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

## HISTOPATHOLOGY INCIDENCE TABLE

PROJECT L06139

PHASE III, STUDY 79-SF

FEMALE RATS

MASSON'S TRICHROME STAIN

| Treatment Group No. | 26 (C0 R) | | | | | | 27 (C2 R) | | | | | | 28 (C3 R) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANIMAL NUMBER | 416 | 418 | 420 | 422 | 424 | | 431 | 433 | 435 | 437 | 439 | | 446 | 448 | 450 | 452 | 454 | |
| LUNG | | | | | | | | | | | | | | | | | | |
| Alveolar Septal Collagen | 1 | 1 | 1 | 1 | 1 | | 2 | 2 | 1 | 2 | 2 | | 2 | 2 | 2 | 2 | 3 | |





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Key: P = Present; 1 = Minimal; 5 = Severe/High; N = No Section; 2 = Slight; I = Incomplete Section; A = Autolysis; 3 = Moderate; X = Not Remarkable; 4 = Moderately Severe/High

PERSONNEL SUPPORTED BY THIS PROJECT DURING THE PHASE III STUDIES

Catherine Aranyi, Principal Investigator
James D. Fenters, Co-Investigator

Joan Anderson
Jeannie Bradof
Marianna Furedi-Machacek
Robert Guerrero
E. L. Grove
Joseph B. Harder
Barry Levine
Patricia McGuire
William O'Shea
Kirit Parikh
Maurline Preache
Vladislava Rac
Josephine Reed
Alan Snelson
Carol Thompson
Stanley Vana

W. O. Iverson, Consultant Veterinary Pathologist, (EPL, Inc.)
Robert Gibbons, Consultant Biostatistician

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