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STUDIES ON THE INHALATION TOXICITY  
OF DYES PRESENT IN COLORED  
SMOKE MUNITIONS  
FINAL REPORT FOR PHASE IV STUDIES.  
90-DAY INHALATION EXPOSURES OF RATS TO DYE AEROSOLS

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U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
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| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br>The U.S. Army has an interest in the potential inhalation toxicity of yellow dye (SY) and a yellow/green dye mixture (SY/SG) used in colored smoke munitions. Rats were exposed by inhalation to aerosols of SY or SY/SG generated in a respirable particle size range (2.1-4.2 $\mu$ m mass median aerodynamic diameter) for 6 hr/day, 5 days/week for a period of 90 days. The objective was to determine an exposure concentration that produced no observable adverse effects. Nominal exposure concentrations selected for both dye exposures were 0, 1, 10, and 100 mg/m <sup>3</sup> . Actual concentrations were within 10% of these nominal |                                             |                                                                                           |

concentrations. Animals exposed to the highest concentration of SY (100 mg/m<sup>3</sup>) had only a slight decrease in body weight gain of 4 percent compared to control animals and an accumulation of foamy macrophages in lungs. Exposure to the lower concentrations of SY dye elicited no observed response. Animals exposed to the highest level of SY/SG dye (100 mg/m<sup>3</sup>) had pulmonary inflammation (as judged by increased lactate dehydrogenase activity, protein and neutrophil numbers in lung lavage fluid) with histopathological evidence of mild Type II pulmonary epithelial cell hyperplasia and proliferation of foamy alveolar macrophages. Some of the animals exposed to the medium concentration of SY/SG dye mixture (10 mg/m<sup>3</sup>) produced similar, but milder histopathological results. Thus, the no-observable-adverse effects level for inhalation exposure to SY dye was 10 mg/m<sup>3</sup> while that of SY/SG dye was 1 mg/m<sup>3</sup> under the exposure regime used.



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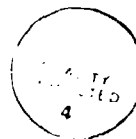
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## EXECUTIVE SUMMARY

The U. S. Army has an interest in the potential inhalation toxicity of a yellow dye (SY) and a yellow/green dye mixture (SY/SG) used in colored smoke munitions. The chemical name of the major component of the yellow dye is 2-(2'quinolinyi)-1,3-indandione (QI) (C.I. Solvent Yellow 33, C.I. 47000) and the major component of the green dye is 1,4-di-p-toluidinoanthraquinone (TA) (C.I. Solvent Green 3, C.I. 61565). SY contains only QI, while the SY/SG dye mixture contains 30 percent QI and 70 percent TA. To test the inhalation toxicity of these materials, exposure atmospheres of SY or SY/SG were generated in a respirable particle size range and used for inhalation exposures of F344 rats at three concentrations for 6 hr/day, 5 days/week for a period of 90 days. The purpose of these studies was to find a no-observable-adverse-effect level for each dye material. Animals were observed for signs of toxicity at the end of each exposure and after a 30-day post-exposure recovery period. For these studies, the biological indicators of toxicity were gross clinical observations, changes in body weight gain, respiratory function measurements, biochemical and cellular analyses of bronchoalveolar lavage fluid, lung tissue enzyme and connective tissue biochemistry, blood and serum chemistries, and histopathology of selected tissues. This report describes the results of these investigations.

In the 90-day inhalation exposure to SY dye, rats were exposed to aerosols of SY dye at average concentrations of  $1.0 \pm 0.2$ ,  $10.8 \pm 1.8$  or  $100 \pm 17 \text{ mg/m}^3$  ( $\bar{x} \pm \text{SD}$ ). The average particle size of these aerosols ranged from 2.1 to 4.0  $\mu\text{m}$  (mass median aerodynamic diameter) with the higher exposure concentrations having the larger particle size. The geometric standard

deviation ( $\sigma_g$ ) of all dye aerosols was approximately 2.0. After exposures, it was found that very little SY dye (QI) was retained in the lungs, indicating the SY dye was rapidly cleared. Exposure-related histopathological lesions consisted of the accumulation of foamy alveolar macrophages in lungs of rats exposed to the highest concentration of SY dye. Pigments, probably metabolites of quinoline dye, were present in the nasal cavity, liver and kidneys. Lesser deposits of pigments were seen in the medium exposure concentration group. No reaction was seen to these deposits and they were not considered an adverse effect. The body weights of the animals exposed to the highest concentration averaged 4 percent less than controls ( $p \leq 0.05$ ) at the end of the exposure, but returned to control values after the 30-day recovery period. Except for these differences, no other toxicologically significant effects were seen.

Rats were exposed to aerosols of SY/SG dye mixture having average concentrations of  $1.1 \pm 0.5$ ,  $10.2 \pm 3.1$  or  $101 \pm 23 \text{ mg/m}^3$  ( $\bar{X} \pm \text{SD}$ ). The average particle size of these aerosols ranged from 2.8 to 4.2  $\mu\text{m}$  (mass median aerodynamic diameter) with a  $\sigma_g$  of approximately 2.0. As with the studies on SY dye exposures, it was found that the QI component of the SY/SG dye mixture cleared from lungs at a very rapid rate. However, the SG portion of the SY/SG dye mixture was retained in lungs for a much longer time. Rats exposed to the highest concentration of SY/SG dye mixture had a significantly lower body weight after the 90-day exposures than controls, approximately 7 percent less. Analysis of bronchoalveolar lavage fluid showed an influx of neutrophils and increased enzyme activities, indicating that a mild pulmonary inflammatory response occurred in high level SY/SG exposed rats. Exposure-related histopathological lesions consisted of minimal to slight Type

II pulmonary epithelial cell hyperplasia and proliferation of foamy alveolar macrophages and lymphoid hyperplasia in the tracheobronchial lymph nodes of rats exposed to the highest concentration of SY/SG dye. This mild response was also seen in some of the medium dose animals, but no lesions were observed in the low dose animals. No other adverse effects were observed.

Pigments, probably metabolites of quinoline dye, were found in the nasal cavity, liver and kidneys of the high and medium exposure groups. This pigment deposition was not considered an adverse effect.

In summary, minimal histopathological lesions were observed in rats exposed to up to  $100 \text{ mg/m}^3$  of SY dye for 65 days over a 90-day period. In rats exposed to the SY/SG dye mixture, an exposure concentration of  $10 \text{ mg/m}^3$  was sufficient to induce some histopathological lesions in the lung. Thus, the no-observable-adverse effects level of SY was  $10 \text{ mg/m}^3$ , and for SY/SG it was  $1 \text{ mg/m}^3$  under the above exposure conditions. It is apparent that the SY/SG dye mixture was more toxic to the lung than is the SY dye. This is at least partially due to the longer retention time in the lung for the SG portion of the dye mixture as compared to the SY.

## PREFACE

The authors acknowledge the outstanding contributions of all members of the Inhalation Toxicology Research Institute, without whose help these studies could not have been completed. Histopathological examination of tissues was performed at Experimental Pathology Laboratories, Inc., Herndon, Virginia, by Dr. Deborah Banas, Diplomate ACVP. In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Users of Laboratory Animals," prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 80-23, Revised 1980). This research was conducted in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. This research was conducted in accordance with the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (FDA, 1978). These studies were inspected by the ITRI Quality Assurance Unit, and the results in the final report were audited for completeness and accuracy of reporting to the raw data. This final report is in accordance to the experimental methods described in study protocols and standard operating procedures. This research was supported by the U. S. Army Medical Research and Development Command under a Memorandum of Understanding Agreement No. AT(29-2)-2138/3807 with the Lovelace Inhalation Toxicology Research Institute, which is operated for the U. S. Department of Energy under DOE Contract No. DE-AC04-76EV01013.

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## INTRODUCTION

The U. S. Army needs to obtain information on the inhalation toxicity of the dyes present in colored smoke munitions. The major concern is for the health of munition production workers who could be exposed to fine dusts containing the dyes during production of the smoke munition. In the project, "Studies on the Inhalation Toxicity of Dyes Present in Colored Smoke Munitions (Project Order No. 83PP3807)," the Lovelace Inhalation Toxicology Research Institute (ITRI) studied the inhalation toxicity of two dye materials: a yellow dye (SY) and yellow/green dye mix (SY/SG). The chemical name of the yellow dye is 2-(2'-quinoliny)-1,3-indandione (QI). Various synonyms used for the dye include C.I. solvent yellow 33, C.I. 47000 and D & C yellow No. 11. The green dye is 1,4-di-p-toluidinanthraquinone (TA) and is also called C.I. solvent green 3, C.I. 61565 and D & C Green No. 6. The yellow/green dye mix contains approximately 30 percent yellow dye and 70 percent green dye. The smoke munitions contain 42 percent by mass of the dyes. The balance of the munition's mass is composed of potassium chlorate, magnesium carbonate and sucrose.

The work was conducted in four phases. Phase I included standardization of methods for generation of aerosols of the test materials and the physical/chemical characterization of the aerosols. Phase II consisted of range-finding experiments to determine acute toxic effects from exposure to high concentrations of the dyes and to select exposure concentrations for the next two phases of the study. In Phase III, four-week exposures of animals to varying concentrations of the dyes were used to determine the lowest exposure concentration that will produce pathological changes. Phase IV was a 90-day

subchronic study to determine a no-observable-adverse effects level (NOAEL) of exposure.

This is a final report of the work completed in Phase IV of these studies.

### 90-DAY INHALATION EXPOSURE TO SY DYE

Nominal exposure concentrations selected for this study were 0, 1, 10, and 100 mg/m<sup>3</sup> given for 6 hours/day, 5 days/week, for a period of 90 days. These concentrations were selected on the basis of the results from the 4-week exposures to SY dye (Phase III).<sup>1</sup> The highest level was selected as a concentration expected to produce minimal toxic responses. The lowest level was selected as the lowest concentration that could be consistently maintained. The middle level was selected as a concentration that differs by a factor of 10 from the low and high levels.

#### Statistical Analyses

Where possible, computer software packages such as BMDP, RSI or Path/Tox were used for data handling and analysis. Standard tests applied to the experimental data were one-way analyses of variance followed by tests for the equality of means, such as simple t-tests or multiple comparison t-tests.<sup>2</sup> Usually a confidence level of 0.05 was used, although in some cases significance was expressed in much smaller or much larger values.

#### Chemicals

SY was supplied by the U. S. Army Medical Bioengineering Research and Development Laboratory (Fort Detrick, Frederick, MD). The purity of this dye material (Q1) was 93 percent and was used without further purification.

#### Animals

Male and female Fischer-344 (F344/N) rats, 15-20 weeks of age were used for this study. The rats were obtained from an existing colony at the Inhalation Toxicology Research Institute. Disease surveillance monitoring of the rat breeding colony is conducted at quarterly intervals. Thirty weanling

F344 rats (15 males, 15 females) are assigned to one of 23 available rat housing rooms. Room assignments are made from a randomized list of animal rooms. Of the thirty animals assigned to a room, 10 (5 of each sex) are sacrificed for surveillance at 3 months of age, 10 at one year of age, and 10 at 2 years of age. This system results in 3 age groups and 3 animal rooms being surveyed every 3 months. The animals are anesthetized and blood is collected prior to sacrifice. The serum is diluted, heat-inactivated and submitted to Microbiological Associates (Bethesda, MD) for serologic testing for Sendai virus, rat corona-virus/Sialodacryodentitis virus (RCV/SDAV), Reovirus type 3 (Reo 3), Theiler's encephalomyelitis virus (GD VII), Toolan's H-1 virus (H-1), Kilham rat virus (KRV), Lymphocytic choriomeningitis (LCM) and Mycoplasma pulmonis. Bacterial cultures are also performed on swabs or tissue samples from the nasal cavity, lung, spleen, liver, kidney and cecum. Media have been selected to identify the major bacterial pathogens of rodents. Following collection of samples for bacterial culture, a complete necropsy is performed. Tissues from all major organs and any gross lesions are collected and processed for histopathology. During the necropsy, the skin is examined grossly for signs of ectoparasites, skin scrapings are taken if indicated, and a section of skin is processed for histopathology. Fecal material and/or cecal contents are examined for internal parasites by fecal floatation.

At the age for experimental use, rats were moved to Hazleton 2000 exposure chambers for at least 3 weeks before exposures to acclimate them to that environment and to ascertain their physical well being. Rats were assigned to experimental groups by a randomization program on the Path/Tox computer system (Xybion Medical Systems Corp., Cedar Knolls, NJ) according to

body weight. Rats were uniquely identified using ear tags. During these studies all animals were given food (Wayne Lab Blox) and water ad libitum except that food was withheld during exposure periods.

Inhalation exposure chambers were maintained at  $75 \pm 3^{\circ}\text{F}$  and 35-70 percent relative humidity. This temperature was above that normally found in an animal room ( $72 \pm 2^{\circ}\text{F}$ ) in order to compensate for body heat loss due to chamber airflow. Chamber airflow rate, temperature, humidity, and pressure relative to the room were monitored throughout this study. Temperature and humidity measuring devices were calibrated and checked before initiation of the study. At the time of sacrifice rats were euthanized by intraperitoneal injections of T-61 euthanasia solution.

#### Animal Exposures

Aerosols of SY dye material were generated using a Jet-O-Mizer air jet mill as previously described.<sup>3,4</sup> Four Hazleton 2000 chambers (Hazleton Systems, Inc., Aberdeen, MD) containing 6 tiers of animal cages (10-16 rats per tier) were used for these whole-body inhalation exposure studies. For these studies, 392 rats (196 males and 196 females) were entered into each exposure chamber in four groups (1 control and 3 treated groups). Immediately after the last day of exposures, a portion of the animals (132 males and 132 females) were taken for toxicological evaluations, while the remaining animals from each of the four exposure groups were held for 30 days to determine if animals could recover from any exposure-related toxic responses.

The SY exposure concentration was determined gravimetrically from filter samples taken daily from each exposure chamber. Particle size of the dye material was measured using a Lovelace Multi-Jet cascade impactor. These particle size measurements were taken each day during the first week of

exposure and then at the intervals shown in Table 1. Concentration and size characteristics of the exposure atmospheres for each exposure chamber for each exposure day are shown in Table 1. The daily concentrations were  $1.0 \pm 0.2$ ,  $10.8 \pm 1.8$  and  $100 \pm 17 \text{ mg/m}^3$  ( $\bar{X} \pm \text{SD}$ ). The coefficient of variation of daily aerosol concentrations was between 17 and 20 percent.

#### Clinical Observations

Detailed clinical observations were performed on all animals before exposures to ensure that they were in good health. Detailed clinical observations were also done twice daily throughout the exposure period and during the 30-day recovery period. The animals were also observed twice daily for morbidity and mortality. No clinical abnormalities were noticed and all animals survived to sacrifice times.

#### Animal Body Weights

During the 90-day exposures, a subset of both male and female rats ( $n = 20$  per sex) from each exposure chamber (including the control chamber) were weighed on a weekly basis. This same subset of animals were held for the 30-day recovery time and also weighed at the end of this recovery period. Body weights measured throughout the study are summarized in Table 2. Before exposures, animal weights did not differ among the different exposure groups. However, after exposures rats exposed to the highest level of SY dye ( $100 \text{ mg/m}^3$ ) gained weight at a slightly slower rate than controls. At the end of exposures, these high level exposed rats weighed approximately 4 percent less than the control animals (for the null hypothesis  $P < 0.05$  in Dunnett's multiple comparisons procedure). During the 30-day post-exposure recovery period, the weights of male rats exposed to the highest level of SY dye returned to control male animal weight values, whereas the body weights of



Table 1  
SY Aerosol Concentration and Size Characteristics for the  
90-Day Inhalation Study

|     |    | LOW     |                   |              | MEDIUM               |            |            | HIGH                 |            |            |
|-----|----|---------|-------------------|--------------|----------------------|------------|------------|----------------------|------------|------------|
|     |    | Conc    | MMAD <sup>a</sup> |              | Conc.                | MMAD       |            | Conc.                | MMAD       |            |
|     |    | (mg / ) | ( $\mu$ m)        | $\sigma_g^b$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ |
| Day | 1  | 1.7     | 2.3               | 2.0          | 14.5                 | 2.5        | 1.9        | 76                   | 3.5        | 1.9        |
|     | 2  | 0.7     | 2.2               | 2.0          | 7.4                  | 2.7        | 2.0        | 52                   | 3.8        | 1.8        |
|     | 3  | 0.8     | 2.2               | 2.0          | 10.1                 | 2.9        | 2.0        | 100                  | 4.4        | 2.0        |
|     | 4  | 1.0     | 2.2               | 2.0          | 10.2                 | 2.8        | 2.0        | 107                  | 4.4        | 2.1        |
|     | 5  | 1.1     | 2.1               | 2.0          | 10.8                 | 2.6        | 2.0        | 112                  | 4.4        | 1.9        |
|     | 6  | 1.1     |                   |              | 8.6                  |            |            | 126                  |            |            |
|     | 7  | 1.0     | 2.3               | 2.4          | 13.1                 | 2.6        | 2.0        | 89                   | 4.1        | 1.9        |
|     | 8  | 1.1     |                   |              | 11.7                 |            |            | 98                   |            |            |
|     | 9  | 1.3     |                   |              | 10.7                 |            |            | 115                  |            |            |
|     | 10 | 0.9     |                   |              | 10.9                 |            |            | 87                   |            |            |
|     | 11 | 1.1     | 2.1               | 1.9          | 12.1                 | 2.8        | 1.9        | 102                  | 3.3        | 1.8        |
|     | 12 | 1.1     |                   |              | 11.4                 |            |            | 85                   |            |            |
|     | 13 | 0.9     |                   |              | 12.2                 |            |            | 95                   |            |            |
|     | 14 | 0.6     |                   |              | 12.4                 |            |            | 104                  |            |            |
|     | 15 | 1.3     |                   |              | 16.6                 |            |            | 151                  |            |            |
|     | 16 | 0.6     | 2.0               | 1.9          | 13.8                 | 2.8        | 1.9        | 86                   | 4.0        | 1.8        |
|     | 17 | 0.9     |                   |              | 13.2                 |            |            | 108                  |            |            |
|     | 18 | 1.0     |                   |              | 16.3                 |            |            | 133                  |            |            |
|     | 19 | 1.1     |                   |              | 9.8                  |            |            | 108                  |            |            |
|     | 20 | 0.7     |                   |              | 10.4                 |            |            | 78                   |            |            |
|     | 21 | 1.1     |                   |              | 10.2                 |            |            | 64                   |            |            |
|     | 22 | 1.1     | 2.1               | 1.9          | 10.1                 | 2.9        | 2.0        | 98                   | 4.3        | 1.9        |
|     | 23 | 1.1     |                   |              | 11.0                 |            |            | 122                  |            |            |
|     | 24 | 0.9     |                   |              | 9.4                  |            |            | 90                   |            |            |
|     | 25 | 1.2     |                   |              | 8.9                  |            |            | 97                   |            |            |
|     | 26 | 0.9     |                   |              | 8.1                  |            |            | 95                   |            |            |
|     | 27 | 0.9     | 2.1               | 1.8          | 12.0                 | 2.9        | 2.0        | 115                  | 4.5        | 1.9        |
|     | 28 | 0.8     |                   |              | 12.0                 |            |            | 86                   |            |            |
|     | 29 | 1.1     |                   |              | 13.5                 |            |            | 91                   |            |            |
|     | 30 | 1.1     |                   |              | 9.4                  |            |            | 100                  |            |            |
|     | 31 | 1.3     |                   |              | 12.7                 |            |            | 103                  |            |            |
|     | 32 | 1.5     |                   |              | 12.4                 |            |            | 100                  |            |            |
|     | 33 | 1.0     | 2.0               | 2.0          | 10.9                 | 2.8        | 2.0        | 95                   | 4.4        | 2.0        |
|     | 34 | 1.1     |                   |              | 8.9                  |            |            | 96                   |            |            |
|     | 35 | 1.4     |                   |              | 9.0                  |            |            | 113                  |            |            |
|     | 36 | 1.0     |                   |              | 9.6                  |            |            | 94                   |            |            |
|     | 37 | 1.1     |                   |              | 10.7                 |            |            | 96                   |            |            |
|     | 38 | 1.0     | 2.0               | 1.9          | 9.8                  | 2.5        | 2.0        | 78                   | 3.7        | 2.2        |
|     | 39 | 0.9     |                   |              | 9.9                  |            |            | 78                   |            |            |

Table 1 (Continued)

|           | LOW                  |                   |                         | MEDIUM               |            |            | HIGH                 |            |            |
|-----------|----------------------|-------------------|-------------------------|----------------------|------------|------------|----------------------|------------|------------|
|           | Conc.                | MMAD <sup>a</sup> |                         | Conc.                | MMAD       |            | Conc.                | MMAD       |            |
|           | (mg/m <sup>3</sup> ) | ( $\mu$ m)        | $\sigma_g$ <sup>b</sup> | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ |
| Day 40    | 1.2                  |                   |                         | 10.7                 |            |            | 94                   |            |            |
| 41        | 1.3                  |                   |                         | 10.3                 |            |            | 103                  |            |            |
| 42        | 1.3                  |                   |                         | 11.5                 |            |            | 71                   |            |            |
| 43        | 0.9                  | 2.0               | 2.1                     | 9.6                  | 3.2        | 2.0        | 66                   | 3.7        | 2.0        |
| 44        | 1.1                  |                   |                         | 12.8                 |            |            | 120                  |            |            |
| 45        | 1.2                  |                   |                         | 10.8                 |            |            | 109                  |            |            |
| 46        | 0.9                  |                   |                         | 10.0                 |            |            | 96                   |            |            |
| 47        | 0.9                  |                   |                         | 10.8                 |            |            | 97                   |            |            |
| 48        | 0.9                  | 2.1               | 1.9                     | 10.5                 | 3.1        | 1.9        | 90                   | 3.9        | 2.0        |
| 49        | 1.1                  |                   |                         | 10.3                 |            |            | 98                   |            |            |
| 50        | 0.8                  |                   |                         | 9.6                  |            |            | 99                   |            |            |
| 51        | 1.3                  |                   |                         | 9.8                  |            |            | 100                  |            |            |
| 52        | 1.2                  |                   |                         | 10.8                 |            |            | 105                  |            |            |
| 53        | 1.2                  |                   |                         | 12.2                 | 3.6        | 2.1        | 113                  | 3.6        | 1.8        |
| 54        | 1.0                  | 2.1               | 2.2                     | 12.5                 |            |            | 135                  |            |            |
| 55        | 0.9                  |                   |                         | 8.1                  |            |            | 103                  |            |            |
| 56        | 0.8                  |                   |                         | 10.4                 |            |            | 117                  |            |            |
| 57        | 0.9                  |                   |                         | 9.4                  |            |            | 96                   |            |            |
| 58        | 1.1                  | 2.3               | 2.2                     | 9.8                  | 2.8        | 2.1        | 112                  | 4.2        | 2.1        |
| 59        | 1.0                  |                   |                         | 8.7                  |            |            | 129                  |            |            |
| 60        | 1.1                  |                   |                         | 10.5                 |            |            | 115                  |            |            |
| 61        | 0.9                  |                   |                         | 10.3                 |            |            | 100                  |            |            |
| 62        | 0.9                  | 2.1               | 2.1                     | 10.8                 | 3.1        | 2.1        | 82                   | 3.4        | 2.0        |
| 63        | 0.9                  |                   |                         | 7.2                  |            |            | 98                   |            |            |
| 64        | 0.9                  |                   |                         | 8.5                  |            |            | 105                  |            |            |
| 65        | 1.0                  |                   |                         | 9.7                  |            |            | 122                  |            |            |
| $\bar{X}$ | 1.0                  | 2.1               | 2.0                     | 10.8                 | 2.9        | 2.0        | 100                  | 4.0        | 2.0        |
| SD        | $\pm 0.2$            | $\pm 0.1$         | $\pm 0.1$               | $\pm 1.8$            | $\pm 0.3$  | $\pm 0.1$  | $\pm 17$             | $\pm 0.4$  | $\pm 0.1$  |

Daily chamber concentrations were determined by the mean of 3 two-hour samples taken during the day.

<sup>a</sup>MMAD = mass median aerodynamic diameter

<sup>b</sup> $\sigma_g$  = geometric standard deviation

Table 2

Weekly Average Weights<sup>a</sup> of Male and Female Rats for the  
90-Day SV Inhalation Exposure Study

| Week | Control                    |          | Low<br>(1.0 mg/m <sup>3</sup> ) |          | Medium<br>(10.8 mg/m <sup>3</sup> ) |          | High<br>(100 mg/m <sup>3</sup> ) |                       |
|------|----------------------------|----------|---------------------------------|----------|-------------------------------------|----------|----------------------------------|-----------------------|
|      | Male                       | Female   | Male                            | Female   | Male                                | Female   | Male                             | Female                |
|      |                            |          |                                 |          |                                     |          |                                  |                       |
| 0    | 322 ± 39                   | 204 ± 15 | 320 ± 38                        | 203 ± 10 | 318 ± 41                            | 203 ± 10 | 320 ± 48                         | 203 ± 11              |
| 2    | 327 ± 26                   | 203 ± 5  | 324 ± 19                        | 202 ± 13 | 323 ± 20                            | 202 ± 9  | 327 ± 14                         | 203 ± 7               |
| 3    | 342 ± 24                   | 217 ± 16 | 330 ± 24                        | 216 ± 12 | 333 ± 20                            | 219 ± 12 | 332 ± 40                         | 215 ± 12              |
| 4    | Valid weights not obtained |          |                                 |          | 368 ± 14                            | 211 ± 12 | 346 ± 18                         | 204 ± 8               |
| 5    | 369 ± 17                   | 214 ± 10 | 375 ± 19                        | 216 ± 9  | 369 ± 14                            | 212 ± 11 | 351 ± 17 <sup>b</sup>            | 206 ± 9 <sup>b</sup>  |
| 6    | 369 ± 19                   | 212 ± 10 | 376 ± 17                        | 215 ± 10 | 368 ± 16                            | 210 ± 10 | 352 ± 18 <sup>b</sup>            | 204 ± 7 <sup>b</sup>  |
| 7    | 376 ± 20                   | 216 ± 9  | 383 ± 16                        | 216 ± 9  | 377 ± 14                            | 215 ± 10 | 361 ± 18 <sup>b</sup>            | 209 ± 8               |
| 8    | 384 ± 15                   | 219 ± 8  | 384 ± 16                        | 221 ± 8  | 378 ± 16                            | 212 ± 14 | 367 ± 17 <sup>b</sup>            | 212 ± 8               |
| 9    | 386 ± 13                   | 219 ± 8  | 389 ± 15                        | 217 ± 8  | 382 ± 15                            | 217 ± 9  | 362 ± 23 <sup>b</sup>            | 211 ± 9               |
| 10   | 392 ± 15                   | 224 ± 7  | 397 ± 15                        | 223 ± 7  | 389 ± 19                            | 223 ± 10 | 369 ± 20 <sup>b</sup>            | 214 ± 9 <sup>b</sup>  |
| 11   | 394 ± 18                   | 228 ± 7  | 402 ± 15                        | 227 ± 7  | 393 ± 16                            | 222 ± 9  | 374 ± 19 <sup>b</sup>            | 217 ± 8 <sup>b</sup>  |
| 12   | 397 ± 18                   | 225 ± 8  | 402 ± 16                        | 224 ± 7  | 395 ± 15                            | 222 ± 9  | 377 ± 20 <sup>b</sup>            | 217 ± 10 <sup>b</sup> |
| 13   | 392 ± 18                   | 223 ± 10 | 393 ± 13                        | 217 ± 8  | 388 ± 18                            | 220 ± 10 | 377 ± 17 <sup>b</sup>            | 211 ± 9 <sup>b</sup>  |
| 17   | 408 ± 16                   | 228 ± 10 | 406 ± 18                        | 223 ± 10 | 410 ± 17                            | 226 ± 10 | 399 ± 18                         | 220 ± 8 <sup>b</sup>  |

<sup>a</sup>Average animal weight (grams) ± SD, n = 20.

<sup>b</sup>Shown to be significantly lower than the control group of the same week interval using Dunnett's multiple comparisons at P ≤ 0.05.

female rats exposed to the highest level of SY dye remained significantly lower than control female body weights.

#### Lung Content of QI After Exposure to SY Dye

On the day after the last exposure day, lungs from six rats (three male and three female) from each chamber (low, medium and high concentration) were analyzed for QI content. Animals were sacrificed and lungs removed, with care to avoid contamination with yellow dye on the pelt. Each lung was homogenized in 1.5 mL of acetonitrile and centrifuged, and the supernatant was removed. The pellet was resuspended in 2 mL acetonitrile, centrifuged, and the supernatant removed. This procedure was repeated three more times. Preliminary experiments in which excised control lung lobes were directly injected with a syringe with a known amount of SY dye dissolved in acetonitrile prior to homogenization showed that this extraction procedure removed 94 percent of the QI. The combined supernatants were diluted to 10 mL and analyzed for QI by HPLC using the following conditions:

- reverse phase column (Alltech C-18, 10 $\mu$ ; 25 cm x 4.6 mm)
- 9:1 acetonitrile:water mobile phase (1 mL/min)
- UV detection at 435 nm

The results, shown in Table 3, demonstrate that very little QI was retained in the lung. Thus, the majority of the QI deposited in lungs during exposures was cleared at a rapid rate. Assuming 10 percent pulmonary deposition of inhaled SY dye aerosol<sup>5</sup> and a minute volume of 200 mL/min, 720  $\mu$ g of SY dye/day should have been deposited in animals exposed to the high concentration. Of the amount calculated to be deposited during only the last day of exposure, only ~ 0.2 percent remained 16 hours after exposure. This finding is similar to the results found in the four-week exposure of rats to SY dye aerosols (Phase III).<sup>1</sup>

Table 3

## Lung Burden of QI After a 90-Day Exposure to SY Dye

|               | Aerosol<br>Concentration<br><u>(mg/m<sup>3</sup>)</u> | Lung Burden<br>Mean $\pm$ SE (n = 3)<br><u>(<math>\mu</math>g/lung)</u> |
|---------------|-------------------------------------------------------|-------------------------------------------------------------------------|
| <u>Male</u>   | 1                                                     | 0.050 $\pm$ 0.030                                                       |
|               | 10                                                    | 0.20 $\pm$ 0.10                                                         |
|               | 100                                                   | 1.3 $\pm$ 0.3                                                           |
| <u>Female</u> | 1                                                     | 0.025 $\pm$ 0.007                                                       |
|               | 10                                                    | 0.10 $\pm$ 0.04                                                         |
|               | 100                                                   | 1.3 $\pm$ 0.2                                                           |

### Respiratory Function

The respiratory function of 8 male rats and 8 female rats at each exposure level (control, low, medium and high) was measured before exposures began, at the end of the 90-day exposures and at 30 days after the end of exposures, using methods previously published.<sup>6</sup> Each rat was anesthetized with halothane in air, intubated with orotracheal and esophageal catheters and placed prone in a plethysmograph. Breathing patterns and dynamic lung mechanics were measured during spontaneous breathing. Prior to each subsequent test procedure, the rat was hyperinflated manually to +20 cm H<sub>2</sub>O transpulmonary pressure to stimulate pulmonary stretch receptors, and the various inflation-deflation cycles were performed during the ensuing periods of apnea. The rat resumed spontaneous respiration between each procedure and its anesthetic depth and breathing pattern were stabilized. Measurements included all physiologic subdivisions of lung volume, quasistatic (slow) pressure-volume relationships, carbon monoxide (CO) diffusing capacity, forced exhalation and single-breath N<sub>2</sub> washout. Thirty-seven variables were measured or calculated for each rat, providing information on various aspects of lung respiratory function: ventilation, lung mechanics, gas distribution and gas exchange.

All data were summarized by measurement period and exposure group. The group data were compared at each measurement time using analysis of variance (BMDP Statistical Software, University of California, Los Angeles). Values for each exposed group were compared to those of the controls by the Student's t-test adjusted for multiple comparisons using the Bonferroni inequality. The criterion for statistical significance was set at the 95 percent confidence level for all comparisons.

The results are summarized in Tables 4 (pre-exposure), 5 (immediately after exposure) and 6 (30 days after exposure). Mean values different from control means at the 95 percent confidence level are indicated in the tables with an asterisk. There were no significant differences among the groups before exposure (Table 4). At the end of exposure (Table 5), the only significant difference was a lower volume-normalized CO diffusing capacity in the high level group as compared to controls. A slightly lower diffusing capacity and slightly higher alveolar volume (measured by gas dilution during the diffusing capacity test) combined to produce the significant difference. At 30 days after the end of exposure (Table 6), the only significant difference was a lower volume-normalized forced expiratory flowrate at 10% of forced vital capacity (i.e., flow rate at low lung volume). As with diffusing capacity, this resulted from nonsignificant differences in the two variables used to calculate the parameter.

These results indicate very little effect of the 90-day SY dye exposure on respiratory function. Values for single parameters differed significantly between controls and high-level exposed rats after exposure and 30 days later. However, these differences did not comprise a recognizable pattern of physiological change, nor were they supported by trends in related parameters. Thus, in the absence of supportive significant differences or consistent trends, the high exposure level can be considered to have caused no decrement in respiratory function.

TABLE 4  
Respiratory Function of Rats Before SY Dye Exposures\*

| Variable                                                   | Units                      | Control $\pm$ SE | Low $\pm$ SE | Medium $\pm$ SE | High $\pm$ SE |
|------------------------------------------------------------|----------------------------|------------------|--------------|-----------------|---------------|
| Body weight                                                | g                          | 269              | 274          | 275             | 274           |
| Minute volume                                              | ml/kg                      | 337              | 302          | 319             | 297           |
| Dynamic lung compliance                                    | ml/cm H <sub>2</sub> O     | 0.44             | 0.41         | 0.43            | 0.39          |
| Quasistatic chord compliance                               | ml/cm H <sub>2</sub> O     | 0.95             | 0.93         | 0.99            | 0.97          |
| Total lung capacity (TLC)                                  | ml                         | 15.4             | 14.0         | 15.3            | 15.4          |
| TLC/body weight                                            | ml/kg                      | 60.1             | 55.5         | 57.6            | 57.7          |
| Vital capacity (VC)                                        | ml                         | 13.2             | 12.7         | 13.3            | 13.1          |
| VC/TLC                                                     | ml/ml                      | 0.85             | 0.86         | 0.87            | 0.85          |
| Functional residual capacity (FRC)                         | ml                         | 3.0              | 3.4          | 3.4             | 3.6           |
| FRC/TLC                                                    | ml/ml                      | 0.24             | 0.23         | 0.22            | 0.24          |
| Residual volume (RV)                                       | ml                         | 2.2              | 2.1          | 2.0             | 2.3           |
| RV/TLC                                                     | ml/ml                      | 0.15             | 0.14         | 0.13            | 0.15          |
| CO diffusing capacity (DLCO)                               | ml/min/mm Hg               | 0.309            | 0.296        | 0.289           | 0.277         |
| DLCO/alveolar volume                                       | ml/min/mm Hg/ml            | 0.021            | 0.020        | 0.020           | 0.019         |
| Forced vital capacity (FVC)                                | ml                         | 13.5             | 13.2         | 13.7            | 13.4          |
| Percent of FVC exhaled in 0.1 sec                          | percent                    | 50               | 51           | 52              | 48            |
| Mean alveolar flowrate (MAEF)                              | ml/sec                     | 62               | 62           | 65              | 48            |
| MAEF/FVC                                                   | ml/sec/ml                  | 4.5              | 4.5          | 4.6             | 3.7           |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | ml/sec                     | 21               | 19           | 20              | 15            |
| FEF10/FVC                                                  | ml/sec/ml                  | 1.5              | 1.4          | 1.4             | 1.1           |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /ml | 0.57             | 0.68         | 0.62            | 0.56          |

\*There were no significant differences between treated and control groups at  $P < 0.05$ .



TABLE 5  
Respiratory Function of Rats at the End of 90-Day SY Dye Exposures

| Variable                                                   | Units                      | Control $\pm$ SE | Low $\pm$ SE | Medium $\pm$ SE | High $\pm$ SE |
|------------------------------------------------------------|----------------------------|------------------|--------------|-----------------|---------------|
| Body weight                                                | g                          | 313 22           | 305 22       | 302 20          | 297 21        |
| Minute volume                                              | mL/kg                      | 328 22           | 314 17       | 318 21          | 305 21        |
| Dynamic lung compliance                                    | mL/cm H <sub>2</sub> O     | 0.54 0.04        | 0.51 0.04    | 0.50 0.05       | 0.53 0.05     |
| Quasistatic chord compliance                               | mL/cm H <sub>2</sub> O     | 1.18 0.06        | 1.11 0.06    | 1.17 0.07       | 1.15 0.06     |
| Total lung capacity (TLC)                                  | mL                         | 17.2 0.8         | 16.2 0.8     | 17.3 0.9        | 16.9 0.8      |
| TLC/body weight                                            | mL/kg                      | 56.6 1.8         | 54.4 1.7     | 58.3 1.7        | 59.7 2.1      |
| Vital capacity (VC)                                        | mL                         | 15.4 0.8         | 14.8 0.8     | 15.7 0.8        | 15.4 0.7      |
| VC/TLC                                                     | mL/mL                      | 0.90 0.01        | 0.92 0.01    | 0.91 0.01       | 0.91 0.02     |
| Functional residual capacity (FRC)                         | mL                         | 3.4 0.2          | 3.0 0.2      | 3.4 0.2         | 3.3 0.2       |
| FRC/TLC                                                    | mL/mL                      | 0.20 0.01        | 0.19 0.01    | 0.20 0.01       | 0.20 0.01     |
| Residual volume (RV)                                       | mL                         | 1.8 0.2          | 1.4 0.2      | 1.6 0.2         | 1.7 0.1       |
| RV/TLC                                                     | mL/mL                      | 0.10 0.01        | 0.09 0.01    | 0.09 0.01       | 0.10 0.01     |
| CO diffusing capacity (DLCO)                               | mL/min/mm Hg               | 0.306 0.016      | 0.283 0.017  | 0.284 0.017     | 0.265 0.017   |
| DLCO/alveolar volume                                       | mL/min/mm Hg/mL            | 0.019 0.001      | 0.018 0.001  | 0.018 0.001     | 0.017* 0.001  |
| Forced vital capacity (FVC)                                | mL                         | 16.0 0.8         | 15.3 0.8     | 16.1 0.8        | 15.9 0.8      |
| Percent of FVC exhaled in 0.1 sec                          | percent                    | 61 2             | 63 2         | 61 2            | 59 2          |
| Mean alveolar flowrate (MAEF)                              | mL/sec                     | 87 7             | 86 4         | 87 4            | 83 4          |
| MAEF/FVC                                                   | mL/sec/mL                  | 5.5 0.4          | 5.7 0.2      | 5.6 0.4         | 5.2 0.2       |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | mL/sec                     | 21 2             | 21 2         | 23 1            | 20 2          |
| FEF10/FVC                                                  | mL/sec/mL                  | 1.3 0.1          | 1.4 0.1      | 1.4 0.1         | 1.2 0.1       |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /mL | 0.45 0.05        | 0.57 0.05    | 0.52 0.05       | 0.52 0.04     |

\*Different from control mean at  $P < 0.05$ .

TABLE 6

Respiratory Function of Rats 30 Days After the End of 90-Day SY Dye Exposures

| Variable                                                   | Units                      | Control $\pm$ SE | Low $\pm$ SE | Medium $\pm$ SE | High $\pm$ SE |
|------------------------------------------------------------|----------------------------|------------------|--------------|-----------------|---------------|
| Body weight                                                | g                          | 317              | 316          | 319             | 312           |
| Minute volume                                              | mL/kg                      | 283              | 309          | 308             | 300           |
| Dynamic lung compliance                                    | mL/cm H <sub>2</sub> O     | 0.56             | 0.62         | 0.61            | 0.69          |
| Quasistatic chord compliance                               | mL/cm H <sub>2</sub> O     | 1.12             | 1.13         | 1.22            | 1.20          |
| Total lung capacity (TLC)                                  | mL                         | 16.2             | 16.6         | 17.7            | 17.6          |
| TLC/body weight                                            | mL/kg                      | 53.8             | 54.6         | 57.6            | 56.4          |
| Vital capacity (VC)                                        | mL                         | 14.7             | 15.2         | 16.1            | 15.9          |
| VC/TLC                                                     | mL/mL                      | 0.90             | 0.92         | 0.91            | 0.90          |
| Functional residual capacity (FRC)                         | mL                         | 3.1              | 3.1          | 3.3             | 3.4           |
| FRC/TLC                                                    | mL/mL                      | 0.20             | 0.19         | 0.19            | 0.20          |
| Residual volume (RV)                                       | mL                         | 1.6              | 1.4          | 1.5             | 1.7           |
| RV/TLC                                                     | mL/mL                      | 0.11             | 0.08         | 0.09            | 0.10          |
| CO diffusing capacity (DLCO)                               | mL/min/mm Hg               | 0.297            | 0.298        | 0.298           | 0.309         |
| DLCO/alveolar volume                                       | mL/min/mm Hg/mL            | 0.018            | 0.019        | 0.017           | 0.018         |
| Forced vital capacity (FVC)                                | mL                         | 15.8             | 16.3         | 17.0            | 16.8          |
| Percent of FVC exhaled in 0.1 sec                          | percent                    | 64               | 62           | 60              | 57            |
| Mean midexpiratory flowrate (MMEF)                         | mL/sec                     | 88               | 94           | 88              | 88            |
| MMEF/FVC                                                   | mL/sec/mL                  | 5.5              | 5.9          | 5.3             | 5.3           |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | mL/sec                     | 23               | 20           | 18              | 19            |
| FEF10/FVC                                                  | mL/sec/mL                  | 1.5              | 1.2          | 1.1             | 1.2*          |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /mL | 0.67             | 0.61         | 0.55            | 0.55          |

\*Different from control mean at  $P < 0.05$ .

From the results of the 4-week exposure of rats to SY (Phase III),<sup>1</sup> we suggested it was important to look for indications of emphysematous changes in rats exposed to SY for a longer time. In the 90-day exposed rats there was no indication of any development of emphysematous lesions.

#### Lung Biochemistry

Lung damage was assessed by the analysis of bronchoalveolar lavage (BAL) fluid. Previous studies have shown this to be a useful method to detect an inflammatory response in lungs following inhalation of toxic materials.<sup>7</sup>

Analysis of BAL fluid was done after 6 weeks as well as after 13 weeks of exposure and at the 17 week time point (30 days after end of exposure). Parameters measured in BAL fluid included total and differential cell counts, lactate dehydrogenase,  $\beta$ -glucuronidase, acid phosphatase and total protein. There was no indication of any inflammatory response in the lung at any time point (Table 7). There was a slight decrease in the number of macrophages recovered from some of the exposed animals. However, the significance of this is unknown since there was no concomitant increase in lysosomal enzymes or in lactate dehydrogenase to indicate that macrophages had been lysed. Statistical analysis of these data was by analysis of variance followed by Bonferroni pairwise comparisons of means.

Lung tissue and lavage fluid proteinolytic activity were also measured in control rats and rats exposed to SY dye aerosols. The data were compared statistically using the Student's t-test corrected for 3 comparisons. Results showed no differences in these activities between control and exposed rats after the 90-day exposures (Table 8) or after the 30-day recovery period (Table 9).

Table 7

Pulmonary Response of Rats Exposed to SY for 90 Days  
as Observed in Bronchoalveolar Lavage Fluid

( $\bar{X} \pm SE$ ,  $n = 12$ )

|                                         | Sacrifice <sup>b</sup><br>Week | Exposure Concentration (mg/m <sup>3</sup> ) |                |                |                |
|-----------------------------------------|--------------------------------|---------------------------------------------|----------------|----------------|----------------|
|                                         |                                | Control<br>0                                | Low<br>1.0     | Medium<br>10.8 | High<br>100    |
| Lactate Dehydrogenase,<br>mIU/g         | 6                              | 420 $\pm$ 40                                | 460 $\pm$ 60   | 530 $\pm$ 80   | 490 $\pm$ 30   |
|                                         | 13                             | 380 $\pm$ 30                                | 380 $\pm$ 40   | 370 $\pm$ 20   | 410 $\pm$ 50   |
|                                         | 17                             | 390 $\pm$ 30                                | 310 $\pm$ 20   | 330 $\pm$ 20   | 300 $\pm$ 20   |
| Acid Phosphatase,<br>mIU/g              | 6                              | 8.8 $\pm$ 1.1                               | 9.2 $\pm$ 1.0  | 12.7 $\pm$ 2.7 | 8.6 $\pm$ 1.3  |
|                                         | 13                             | 11.7 $\pm$ 1.8                              | 12.5 $\pm$ 2.4 | 10.3 $\pm$ 1.3 | 9.7 $\pm$ 1.5  |
|                                         | 17                             | 12.6 $\pm$ 0.6                              | 12.2 $\pm$ 1.6 | 10.1 $\pm$ 1.0 | 10.2 $\pm$ 0.5 |
| $\beta$ -Glucuronidase,<br>mIU/g        | 6                              | 1.8 $\pm$ 0.2                               | 1.7 $\pm$ 0.3  | 2.2 $\pm$ 0.4  | 1.6 $\pm$ 0.4  |
|                                         | 13                             | 2.5 $\pm$ 0.4                               | 1.9 $\pm$ 0.4  | 1.7 $\pm$ 0.2  | 1.6 $\pm$ 0.2  |
|                                         | 17                             | 1.7 $\pm$ 0.2                               | 1.6 $\pm$ 0.2  | 2.1 $\pm$ 0.2  | 1.4 $\pm$ 0.2  |
| Protein, mg/g                           | 6                              | 1.7 $\pm$ 0.1                               | 1.9 $\pm$ 0.1  | 2.0 $\pm$ 0.2  | 2.2 $\pm$ 0.3  |
|                                         | 13                             | 1.6 $\pm$ 0.1                               | 1.8 $\pm$ 0.1  | 1.5 $\pm$ 0.1  | 1.6 $\pm$ 0.1  |
|                                         | 17                             | 1.4 $\pm$ 0.1                               | 1.1 $\pm$ 0.1  | 1.9 $\pm$ 0.2  | 1.7 $\pm$ 0.1  |
| Macrophages,<br>10 <sup>3</sup> cells/g | 6                              | 1040 $\pm$ 110                              | 790 $\pm$ 100  | 960 $\pm$ 90   | 1000 $\pm$ 70  |
|                                         | 13                             | 850 $\pm$ 80                                | 560 $\pm$ 60*  | 570 $\pm$ 90   | 520 $\pm$ 50*  |
|                                         | 17                             | 880 $\pm$ 90                                | 680 $\pm$ 80   | 690 $\pm$ 70   | 560 $\pm$ 40*  |
| Neutrophils,<br>10 <sup>3</sup> cells/g | 6                              | 3 $\pm$ 2                                   | 9 $\pm$ 4      | 2 $\pm$ 1      | 3 $\pm$ 2      |
|                                         | 13                             | 28 $\pm$ 11                                 | 50 $\pm$ 36    | 7 $\pm$ 4      | 65 $\pm$ 40    |
|                                         | 17                             | 11 $\pm$ 6                                  | 4 $\pm$ 2      | 8 $\pm$ 5      | 3 $\pm$ 1      |

aValues represent total amounts of material recovered in BAL divided by the wet weight of the lung in g. There was no statistical difference in the mean wet weight of the lungs between the group. The values were normalized in this manner to take into account the difference in size of male versus female lung weights.

bAn interim sacrifice was made after 6 weeks of exposure and a second sacrifice was made at the end of the exposure (13 weeks). The 17 week sacrifice was of rats held for 1 month after the exposure to determine if there was recovery from any exposure-related injury.

\*Values differ from control values,  $P \leq 0.05$ , by Bonferroni pairwise comparison of means. The critical t-value necessary for rejection of the null hypothesis at  $P \leq 0.05$  was adjusted for comparison of the 3 treatment groups.

**Table 8**  
**Lung and Lavage Fluid Proteinolytic Activity in**  
**Rats Exposed to SY Dye for 90 Days**

|                          | <u>mg protein released/hr/g lung<sup>a</sup></u> |            |               |             |
|--------------------------|--------------------------------------------------|------------|---------------|-------------|
| <u>Lung Tissue:</u>      | <u>Control</u>                                   | <u>Low</u> | <u>Medium</u> | <u>High</u> |
| Total Acid Proteinase    | 10.3 ± 1.0                                       | 9.9 ± 1.3  | 10.3 ± 1.0    | 10.9 ± 1.0  |
| Cathepsin D <sup>b</sup> | 8.1 ± 0.8                                        | 8.4 ± 0.8  | 8.0 ± 0.9     | 8.5 ± 0.6   |
| Cathepsin B <sup>c</sup> | 2.2 ± 0.5                                        | 1.6 ± 0.6  | 2.3 ± 0.2     | 2.4 ± 0.6   |
| Total Neutral Proteinase | 1.9 ± 0.6                                        | 1.4 ± 0.2  | 1.2 ± 0.1     | 1.2 ± 0.1   |
| Macrophage               |                                                  |            |               |             |
| Elastase <sup>d</sup>    | 0.9 ± 0.6                                        | 0.4 ± 0.1  | 0.3 ± 0.1     | 0.3 ± 0.1   |
| Cathepsin G+ Neutrophil  |                                                  |            |               |             |
| Elastase <sup>e</sup>    | 1.0 ± 0.1                                        | 1.0 ± 0.1  | 1.0 ± 0.1     | 0.9 ± 0.1   |
| <u>Lavage Fluid:</u>     |                                                  |            |               |             |
| Total Acid Proteinase    | 3.5 ± 0.6                                        | 4.3 ± 0.5  | 4.0 ± 0.3     | 4.3 ± 0.5   |
| Cathepsin D              | 2.1 ± 0.4                                        | 3.0 ± 0.4  | 2.9 ± 0.8     | 2.7 ± 0.5   |
| Cathepsin B              | 1.4 ± 0.5                                        | 1.5 ± 0.4  | 1.1 ± 0.8     | 1.6 ± 0.4   |

<sup>a</sup>Mean ± SE (N = 5-6). No differences were seen when the data were compared using the Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

<sup>b</sup>not inhibited by leupeptin

<sup>c</sup>inhibited by leupeptin

<sup>d</sup>inhibited by 1,10 phenanthroline

<sup>e</sup>not inhibited by 1,10 phenanthroline

Table 9

Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed  
to SY Dye for 90 Days and Allowed to Recover for 30 Days

|                          | <u>mg protein released/hr/g lung<sup>a</sup></u> |            |                 |             |
|--------------------------|--------------------------------------------------|------------|-----------------|-------------|
| <u>Lung Tissue:</u>      | <u>Control</u>                                   | <u>Low</u> | <u>Medium</u>   | <u>High</u> |
| Total Acid Proteinase    | 9.6 ± 0.5                                        | 10.5 ± 1.1 | 9.8 ± 0.7       | 9.4 ± 0.6   |
| Cathepsin D <sup>c</sup> | 8.1 ± 0.6                                        | 8.4 ± 0.7  | 7.8 ± 0.5       | 8.3 ± 0.5   |
| Cathepsin B <sup>d</sup> | 1.4 ± 0.5                                        | 2.1 ± 0.5  | 2.0 ± 0.4       | 1.1 ± 0.4   |
| Total Neutral Proteinase | 0.3 ± 0.1                                        | 0.3 ± 0.1  | 0.2 ± 0.1       | 0.3 ± 0.1   |
| Macrophage               |                                                  |            |                 |             |
| Elastase <sup>e</sup>    | 0.1 ± 0.1                                        | 0.2 ± 0.1  | ND <sup>b</sup> | 0.2 ± 0.1   |
| Cathepsin G+ Neutrophil  |                                                  |            |                 |             |
| Elastase <sup>f</sup>    | 0.2 ± 0.1                                        | 0.1 ± 0.1  | 0.5 ± 0.2       | 0.1 ± 0.1   |
| <u>Lavage Fluid:</u>     |                                                  |            |                 |             |
| Total Acid Proteinase    | 2.8 ± 0.2                                        | 2.8 ± 0.3  | 2.6 ± 0.1       | 2.2 ± 0.1   |
| Cathepsin D              | 1.0 ± 0.2                                        | 1.0 ± 0.2  | 1.3 ± 0.5       | 0.5 ± 0.1   |
| Cathepsin B              | 1.8 ± 0.3                                        | 1.9 ± 0.3  | 1.4 ± 0.6       | 1.6 ± 0.2   |

<sup>a</sup>Mean ± SE (N = 5-6). No differences were seen when the data were compared using the Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

<sup>b</sup>ND = none detected.

<sup>c</sup>not inhibited by leupeptin

<sup>d</sup>inhibited by leupeptin

<sup>e</sup>inhibited by 1,10 phenanthroline

<sup>f</sup>not inhibited by 1,10 phenanthroline

### Lung Connective Tissue Biochemistry

Total lung collagen and airway fluid hydroxyproline content were measured in both control and SY dye exposed rats. Results showed no differences between control and exposed animals for these parameters after the 90-day exposure period (Table 10) or after the 30-day post-exposure recovery time (Table 11). Results were compared statistically using the Student's t-test corrected for 3 comparisons.

### Hematology and Serum Clinical Chemistries

Hematology and serum clinical chemistry determinations were done on rats exposed to SY over a 90-day period and on serum from exposed rats that were allowed to recover for 30 days. The parameters measured in these determinations are listed on Table 12. No hematologic parameters were affected by exposure to yellow dye. However, marginal reductions in serum alkaline phosphatase and serum glutamic pyruvic transaminase (SGPT) activities in serum were seen after 90 days of exposure to the highest concentration of SY dye (Table 13). These changes returned to normal after the 30-day recovery period (Table 14). Total bilirubin and cholesterol concentrations in serum were increased after 90 days of exposure to the highest level of yellow dye. The serum enzyme changes, along with increased bilirubin and cholesterol, suggest minimal hepatic dysfunction which was no longer present 30 days post-exposure. No other exposure levels were affected, and this increase was no longer present after the 30-day recovery period. Thyroxine was not significantly affected by exposure to yellow dye (Tables 13 and 14).

### Histopathology

Ten males and ten females from each exposure group and time were sacrificed by intraperitoneal injections of T61 and examined for gross

Table 10  
Lavage Fluid and Lung Tissue Collagen for Rats Exposed  
to SY Dye for 90 Days

|         | <u>Lavage Fluid Collagen<br/>(<math>\mu\text{g/g}</math>)*</u> | <u>Total Lung Collagen<br/>(<math>\text{mg/g}</math>)*</u> |
|---------|----------------------------------------------------------------|------------------------------------------------------------|
| Control | 31 $\pm$ 4                                                     | 18 $\pm$ 1                                                 |
| Low     | 34 $\pm$ 5                                                     | 19 $\pm$ 2                                                 |
| Medium  | 35 $\pm$ 5                                                     | 16 $\pm$ 1                                                 |
| High    | 38 $\pm$ 8                                                     | 15 $\pm$ 1                                                 |

\*Normalized to grams of lung weight (mean  $\pm$  SE; n = 5-6). No differences were seen when the data were compared using Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.



Table 11

Lavage Fluid and Lung Tissue Collagen for Rats Exposed  
to SY Dye for 90 Days Followed by 30 Days of Recovery

|         | <u>Lavage Fluid Collagen</u><br><u>(<math>\mu</math>g/g)*</u> | <u>Total Lung Collagen</u><br><u>(mg/g)*</u> |
|---------|---------------------------------------------------------------|----------------------------------------------|
| Control | 36 $\pm$ 3                                                    | 15 $\pm$ 1                                   |
| Low     | 30 $\pm$ 4                                                    | 17 $\pm$ 1                                   |
| Medium  | 38 $\pm$ 4                                                    | 16 $\pm$ 1                                   |
| High    | 35 $\pm$ 5                                                    | 15 $\pm$ 1                                   |

\*Normalized to grams of control lung weight (mean  $\pm$  SE; n = 6).  
No differences were seen when the data were compared using the  
Student's t-test corrected for 3 comparisons. Also, no  
differences were noted in lung weights among the different  
exposure groups.

Table 12

Hematology and Serum Clinical Chemistry Measurements on Rats  
Exposed by Inhalation to SY or SY/SG Dye Aerosols for 90 Days

a. Hematology:

- 1) Hematocrit
- 2) Hemoglobin concentration
- 3) Erythrocyte count
- 4) Erythrocyte indices (mean cellular volume, mean cellular hemoglobin, mean cellular hemoglobin concentration)
- 5) Leukocyte count, total
- 6) Leukocyte count, differential

b. Serum Chemistry:

- 1) Total protein and albumin
- 2) Serum gamma-glutamyl transpeptidase\*
- 3) Serum glutamic pyruvic transaminase
- 4) Serum alkaline phosphatase
- 5) Bilirubin (total)
- 6) Blood urea nitrogen
- 7) Creatinine
- 8) Calcium
- 9) Phosphorus
- 10) Sodium
- 11) Potassium
- 12) Chloride
- 13) Glucose
- 14) Cholesterol
- 15) Thyroxine ( $T_4$ )

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\*No activity detected following the SY/SG exposures. Therefore, not measured after the SY exposures.

Table 13  
Clinical Pathology Values of Rats  
Exposed to SY dye for 90 Days

( $\bar{X} \pm SE$ , n = 11-12)

| Biochemistry:                 | Control         |           | Low             |           | Medium          |           | High             |            |
|-------------------------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|------------------|------------|
| Alkaline Phosphatase (IU/L)   | 72              | $\pm 6$   | 67              | $\pm 7$   | 63              | $\pm 5$   | 57               | $\pm 4^*$  |
| SGPT (IU/L)                   | 40              | $\pm 7$   | 36              | $\pm 5$   | 33              | $\pm 2^*$ | 32               | $\pm 1^*$  |
| Total bilirubin (mg/dL)       | 0.29 $\pm$ 0.03 |           | 0.30 $\pm$ 0.05 |           | 0.35 $\pm$ 0.04 |           | 0.38 $\pm$ 0.03* |            |
| Thyroxine ( $\mu$ g/dL)       | 3.6             | $\pm 0.3$ | 3.7             | $\pm 0.4$ | 3.7             | $\pm 0.2$ | 3.9              | $\pm 0.5$  |
| Glucose (mg/dL)               | 230             | $\pm 40$  | 190             | $\pm 20$  | 190             | $\pm 20$  | 180              | $\pm 20$   |
| Cholesterol (mg/dL)           | 72              | $\pm 13$  | 78              | $\pm 16$  | 85              | $\pm 18$  | 113              | $\pm 13^*$ |
| BUN (mg/dL)                   | 21              | $\pm 2$   | 18              | $\pm 2$   | 19              | $\pm 2$   | 18               | $\pm 2$    |
| Creatinine (mg/dL)            | 0.63 $\pm$ 0.02 |           | 0.58 $\pm$ 0.05 |           | 0.58 $\pm$ 0.03 |           | 0.55 $\pm$ 0.04  |            |
| Inorganic Phosphorous (mg/dL) | 6.0             | $\pm 0.8$ | 5.7             | $\pm 0.5$ | 6.2             | $\pm 0.7$ | 6.0              | $\pm 0.6$  |
| Calcium (mg/dL)               | 11.0            | $\pm 1.4$ | 11.1            | $\pm 1.2$ | 10.4            | $\pm 0.4$ | 10.9             | $\pm 0.7$  |
| Total Protein (g/dL)          | 6.3             | $\pm 0.4$ | 6.3             | $\pm 0.4$ | 6.3             | $\pm 0.2$ | 6.5              | $\pm 0.3$  |
| Albumin (g/dL)                | 4.1             | $\pm 0.3$ | 4.2             | $\pm 0.2$ | 4.4             | $\pm 0.2$ | 4.5              | $\pm 0.3$  |

\*P  $\leq$  0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 13 (continued)  
Clinical Pathology Values of Rats  
Exposed to SY Dye for 90 Days

( $\bar{X} \pm SE$ , n = 11-12)

| <u>Biochemistry:</u>                                | <u>Control</u> | <u>Low</u>     | <u>Medium</u>  | <u>High</u>    |
|-----------------------------------------------------|----------------|----------------|----------------|----------------|
| Sodium<br>(meq/L)                                   | 148 $\pm$ 2    | 149 $\pm$ 1    | 149 $\pm$ 2    | 149 $\pm$ 2    |
| Potassium<br>(meq/L)                                | 6.0 $\pm$ 1.0  | 5.6 $\pm$ 0.3  | 5.5 $\pm$ 0.4  | 5.6 $\pm$ 0.4  |
| Chloride<br>(meq/L)                                 | 112 $\pm$ 2    | 112 $\pm$ 1    | 112 $\pm$ 2    | 111 $\pm$ 1    |
| <u>Hematology:</u>                                  |                |                |                |                |
| RBC<br>( $10^6/\text{mm}^3$ )                       | 7.1 $\pm$ 0.4  | 7.1 $\pm$ 0.3  | 7.1 $\pm$ 0.4  | 6.9 $\pm$ 0.5  |
| Hematocrit (%)                                      | 38 $\pm$ 1     | 38 $\pm$ 1     | 38 $\pm$ 2     | 36 $\pm$ 3     |
| Hemoglobin<br>(g/dL)                                | 13.8 $\pm$ 0.4 | 13.7 $\pm$ 0.4 | 13.8 $\pm$ 0.5 | 13.4 $\pm$ 0.4 |
| Mean Corpuscular<br>Volume ( $\mu\text{m}^3$ )      | 53 $\pm$ 1     | 53 $\pm$ 2     | 54 $\pm$ 2     | 53 $\pm$ 1     |
| Mean Corpuscular<br>Hemoglobin<br>Concentration (%) | 37 $\pm$ 1     | 37 $\pm$ 1     | 36 $\pm$ 1     | 37 $\pm$ 2     |
| WBC<br>( $10^3/\text{mm}^3$ )                       | 1.9 $\pm$ 0.8  | 1.8 $\pm$ 0.6  | 2.2 $\pm$ 0.6  | 2.1 $\pm$ 1.1  |
| Neutrophils<br>( $10^3/\text{mm}^3$ )               | 0.6 $\pm$ 0.3  | 0.5 $\pm$ 0.2  | 0.6 $\pm$ 0.2  | 0.6 $\pm$ 0.2  |
| Lymphocytes<br>( $10^3/\text{mm}^3$ )               | 1.3 $\pm$ 0.5  | 1.2 $\pm$ 0.3  | 1.6 $\pm$ 0.4  | 1.5 $\pm$ 0.9  |
| Eosinophils<br>( $10^3/\text{mm}^3$ )               | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Basophils<br>( $10^3/\text{mm}^3$ )                 | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |

\*P  $\leq$  0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 13 (continued)  
Clinical Pathology Values of Rats  
Exposed to SY Dye for 90 Days

( $\bar{X} \pm SE$ , n = 11-12)

| <u>Hematology:</u>                           | <u>Control</u> | <u>Low</u> | <u>Medium</u> | <u>High</u> |
|----------------------------------------------|----------------|------------|---------------|-------------|
| Monocytes<br>( $10^3/\text{mm}^3$ )          | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |
| Banded Neutrophils<br>( $10^3/\text{mm}^3$ ) | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |
| NRBC<br>( $10^3/\text{mm}^3$ )               | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |

\* $P \leq 0.05$  in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14  
Clinical Pathology Values of Rats Exposed to SY Dye  
for 90 Days and Allowed to Recover for 30 Days\*

( $\bar{x} \pm SE$ , n = 11-12)

| Biochemistry:                 | Control         | Low             | Medium          | High            |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Alkaline Phosphatase (IU/L)   | 72 $\pm$ 8      | 73 $\pm$ 9      | 70 $\pm$ 4      | 75 $\pm$ 7      |
| SGPT (IU/L)                   | 44 $\pm$ 5      | 49 $\pm$ 11     | 38 $\pm$ 4      | 41 $\pm$ 7      |
| Total bilirubin (mg/dL)       | 0.30 $\pm$ 0.11 | 0.33 $\pm$ 0.08 | 0.32 $\pm$ 0.12 | 0.40 $\pm$ 0.09 |
| Thyroxine ( $\mu$ g/dL)       | 3.1 $\pm$ 0.4   | 3.4 $\pm$ 0.6   | 3.4 $\pm$ 0.6   | 3.9 $\pm$ 0.6   |
| Glucose (mg/dL)               | 240 $\pm$ 50    | 250 $\pm$ 50    | 250 $\pm$ 40    | 250 $\pm$ 50    |
| Cholesterol (mg/dL)           | 96 $\pm$ 28     | 87 $\pm$ 25     | 92 $\pm$ 21     | 98 $\pm$ 20     |
| BUN (mg/dL)                   | 24 $\pm$ 1      | 24 $\pm$ 1      | 24 $\pm$ 1      | 25 $\pm$ 3      |
| Creatinine (mg/dL)            | 0.8 $\pm$ 0.2   | 0.8 $\pm$ 0.2   | 0.7 $\pm$ 0.2   | 0.7 $\pm$ 0.1   |
| Inorganic Phosphorous (mg/dL) | 6.7 $\pm$ 1.1   | 7.0 $\pm$ 1.1   | 7.0 $\pm$ 1.5   | 7.4 $\pm$ 1.4   |
| Calcium (mg/dL)               | 12.0 $\pm$ 0.4  | 12.1 $\pm$ 0.4  | 12.3 $\pm$ 0.7  | 12.0 $\pm$ 0.8  |
| Total Protein (g/dL)          | 7.9 $\pm$ 0.2   | 8.1 $\pm$ 0.7   | 7.9 $\pm$ 0.2   | 7.9 $\pm$ 0.4   |
| Albumin (g/dL)                | 5.0 $\pm$ 0.2   | 5.1 $\pm$ 0.7   | 5.0 $\pm$ 0.3   | 5.2 $\pm$ 0.3   |

\*There were no significant differences between treated and control groups at  $P < 0.05$  in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14 (continued)

Clinical Pathology Values of Rats Exposed to SY Dye  
for 90 Days and Allowed to Recover for 30 Days\*

( $\bar{X} \pm SE$ , n = 11-12)

| <u>Biochemistry:</u>                          | <u>Control</u> | <u>Low</u>     | <u>Medium</u>  | <u>High</u>    |
|-----------------------------------------------|----------------|----------------|----------------|----------------|
| Sodium (meq/L)                                | 147 $\pm$ 2    | 148 $\pm$ 3    | 148 $\pm$ 4    | 144 $\pm$ 9    |
| Potassium (meq/L)                             | 6.0 $\pm$ 0.7  | 5.7 $\pm$ 0.4  | 5.5 $\pm$ 0.4  | 5.6 $\pm$ 0.4  |
| Chloride (meq/L)                              | 110 $\pm$ 2    | 111 $\pm$ 2    | 110 $\pm$ 1    | 109 $\pm$ 3    |
| <u>Hematology:</u>                            |                |                |                |                |
| RBC ( $10^6/\text{mm}^3$ )                    | 7.4 $\pm$ 0.4  | 7.7 $\pm$ 0.4  | 7.7 $\pm$ 0.4  | 7.7 $\pm$ 0.5  |
| Hematocrit (%)                                | 40 $\pm$ 1     | 41 $\pm$ 1     | 41 $\pm$ 1     | 41 $\pm$ 3     |
| Hemoglobin (g/dL)                             | 14.1 $\pm$ 0.3 | 14.4 $\pm$ 0.4 | 14.5 $\pm$ 0.3 | 14.5 $\pm$ 0.3 |
| Mean Corpuscular Volume ( $\mu\text{m}^3$ )   | 53 $\pm$ 2     | 53 $\pm$ 2     | 54 $\pm$ 3     | 53 $\pm$ 2     |
| Mean Corpuscular Hemoglobin Concentration (%) | 36 $\pm$ 1     | 36 $\pm$ 1     | 35 $\pm$ 1     | 36 $\pm$ 1     |
| WBC ( $10^3/\text{mm}^3$ )                    | 2.4 $\pm$ 0.3  | 2.8 $\pm$ 0.1  | 3.1 $\pm$ 0.1  | 2.8 $\pm$ 0.1  |
| Neutrophils ( $10^3/\text{mm}^3$ )            | 0.7 $\pm$ 0.4  | 0.7 $\pm$ 0.3  | 0.8 $\pm$ 0.4  | 0.7 $\pm$ 0.4  |
| Lymphocytes ( $10^3/\text{mm}^3$ )            | 1.7 $\pm$ 0.6  | 2.0 $\pm$ 0.4  | 2.3 $\pm$ 0.7  | 2.1 $\pm$ 0.7  |
| Eosinophils ( $10^3/\text{mm}^3$ )            | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |

\*There were no significant differences between treated and control groups at  $P < 0.05$  in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14 (continued)  
Clinical Pathology Values of Rats Exposed to SY Dye  
for 90 Days and Allowed to Recover for 30 Days\*

( $\bar{X} \pm SE$ , n = 11-12)

| <u>Hematology:</u>                           | <u>Control</u> | <u>Low</u> | <u>Medium</u> | <u>High</u> |
|----------------------------------------------|----------------|------------|---------------|-------------|
| Basophils<br>( $10^3/\text{mm}^3$ )          | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |
| Monocytes<br>( $10^3/\text{mm}^3$ )          | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |
| Banded Neutrophils<br>( $10^3/\text{mm}^3$ ) | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |
| NRBC<br>( $10^3/\text{mm}^3$ )               | $\leq 0.1$     | $\leq 0.1$ | $\leq 0.1$    | $\leq 0.1$  |

\*There were no significant differences between treated and control groups at  $P < 0.05$  in Student-t statistic. Critical t-values were corrected for 3 comparisons.



lesions. Routine paraffin embedded, 5 micron, hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related effect. Histopathologic evaluation of tissues from animals exposed to SY was done at Experimental Pathology Laboratories, Inc., Herndon, VA, by Dr. Deborah Banas, Diplomate ACVP. The following is a summary of the findings. The complete histopathology report for this 90-day SY exposure study can be found in Appendix I.

#### Ninety-Day Exposure

Inhalation of SY dye at the high exposure concentration for 90 days resulted in submucosal pigment deposition in the nasal cavity of all rats. The pigment deposition was heaviest at medium and high levels. In the kidneys, an increase in granular pigment located in the cortical tubules was noted in all high dose rats. In the male rats, there was also an increase in the incidence of lesions characteristic of early chronic nephropathy, namely foci of regenerative tubular epithelium, casts, and foci of mononuclear cells. However, these lesions are commonly noted in rats of this age and strain and were only minimal to slight in severity. In the liver, minimal to slight granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile duct in all high dose rats. In the lung,

minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment were noted in the alveoli adjacent to the respiratory bronchioles in one male. This lesion was accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to SY at the medium exposure concentration, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at the medium level in three males and two females, and at the high concentration in five males and seven females. Pigment deposition in the kidneys was comparable to that of the controls. In the liver, minimal granules of pigment were noted in two females. No lesions attributable to treatment were noted in the sections of lung examined.

In the rats exposed to SY at the low exposure concentration, the nasal cavities of both sexes were examined. The livers of females were also examined. No compound-related histomorphologic alterations were noted in either of these tissues.

#### Thirty Day Recovery

Inhalation of SY dye at the high exposure concentration for 90 days, followed by a 30 day recovery period resulted in submucosal pigment deposition in the nasal cavities of all rats. This pigment deposition was heaviest at the medium and high levels, and was slightly less severe than was noted at the 90-day sacrifice. Increased pigment was noted in the kidney tubules and appeared to be less severe than that noted at the 90-day sacrifice. The incidence of early chronic nephropathy was comparable to that of the controls. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after the 90-day exposure. In the lungs, two males had minimal focal accumulations of foamy appearing alveolar macrophages

containing a minimal amount of pigment. These accumulations were accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to SY dye at the medium exposure concentration for 90 days followed by a 30-day recovery period, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at the medium level in two males and four females and at the high level in six males and eight females. Slight submucosal pigment was noted at the high level in an additional male. Pigment deposition in the kidneys was comparable to the controls. No lesions attributable to treatment were noted in the lung or liver.

In the rats exposed to SY dye at the low exposure concentration, only the nasal cavity was examined. No compound-related histomorphological alterations were noted in these sections.

The finding of pigments in the nasal cavity, kidney and liver was examined in more detail at ITRI. Special stains (Prussian Blue for iron, periodic acid Schiff (PAS) and Hall's stain for bile) were made on sections of kidney, liver and lung to differentiate administered dye material in the tissues from autogenous pigments found in normal rats. The pigments in the control kidneys and some of the pigments in the exposed rats stained faintly with PAS indicating that they were probably a natural phenomenon that has been previously described. The major portion of the pigments in the exposed rats did not stain. It is hypothesized that the pigments in the nose, liver and kidney are metabolites of quinoline dye. Metabolism studies have shown that the dye is metabolized by the liver and excreted by the kidney. The pigment in the nasal cavity is present only under the olfactory epithelium, the epithelium where mixed function oxidases are concentrated. No pigments were

found in the tracheobronchial lymph nodes indicating that the dye was soluble enough to leave the lung before particle translocation to the lymph node took place.

Spontaneous disease lesions and incidental findings such as retinal degeneration, focal acinar atrophy of the pancreas, nematodiasis and nonsuppurative myocarditis occurred in a few rats in both control and treated groups at both sacrifice intervals. These lesions were distributed with approximately equal frequency in test and control rats, and thus were not exposure related (see Appendix I).

## 90-DAY INHALATION EXPOSURE TO SY/SG DYE

Nominal exposure concentrations selected for this study were 0, 1, 10 and 100 mg/m<sup>3</sup> given 6 hours/day, 5 days/week, for a period of 90 days. These exposure concentrations were selected on the basis of the same criteria as the 90 day SY dye exposure previously mentioned.

### Statistical Analyses

Where possible, computer software packages such as BMDP, RSI or Path/Tox were used for data handling and analysis. Standard tests applied to the experimental data were one-way analyses of variance, followed by tests for the equality of means, such as simple t-tests or multiple comparison t-tests<sup>2</sup> for the equality of medians. Usually a confidence level of 0.05 was used, although in some cases significance was expressed in much smaller or much larger values.

### Chemicals

SY/SG was supplied by the U. S. Army Medical Bioengineering Research and Development Laboratory (Fort Detrick, Frederick, MD). The purity of this dye material (QI and TA combined) was 95 percent and was used without further purification.

### Animals and Animal Exposures

Male and female Fischer-344 (F344/Crl) rats, 15-20 weeks of age with an age range of  $\pm 2$  weeks, were used for this study. These animals were obtained from an existing colony raised at the Inhalation Toxicology Research Institute in which the disease surveillance monitoring of the colony was as previously described in this report. Rats were then acclimatized in exposure chambers, randomized into experimental groups, and cared for as described previously in this report for the 90 day inhalation exposure study of SY dye.

Animals were exposed to 3 levels of SY/SG dye material generated by a Jet-O-Mizer air jet mill as previously described.<sup>3,4</sup> The arrangement and entry groups of animals in the four Hazleton 2000 whole-body inhalation chambers used for this study (3 exposure and 1 air control), and chamber environment monitoring and maintenance were as previously described in this report for the 90 day inhalation study of SY dye. Concentration and size characteristics of the exposure atmospheres for each of the 63 exposure days are shown in Table 15. The SY/SG aerosol concentration was determined gravimetrically from filter samples taken daily from each exposure chamber. Aerosol size of the dye material was measured with a Lovelace Multi-Jet cascade impactor each day during the first week of exposure and at intervals as shown in Table 15 thereafter.

#### Clinical Observations

Detailed clinical observations were performed on all animals before exposures to ensure that they were in good health. Detailed clinical observations were also done at 6 weeks after the initiation of exposures, at the end of the 90 day exposures and after the 30 day recovery period. The animals were also observed twice daily for morbidity and mortality. No clinical abnormalities were noticed and all animals survived to sacrifice times.

#### Animal Body Weights

During this 3-month exposure, subsets of both male and female rats (n = 20 per sex) from each exposure chamber (including the control chamber) were weighed on a weekly basis. All animals were weighed after the last day of exposure. Those animals not sacrificed after the last day of exposure and held for the 30-day recovery were weighed at the end of this recovery period. Body weights measured throughout the study are summarized in Table 16. These

Table 15

SY/SG Aerosol Concentration and Size Characteristics for the  
90-Day Inhalation Study

| Day | LOW                  |                   |              | MEDIUM               |            |            | HIGH                 |            |            |
|-----|----------------------|-------------------|--------------|----------------------|------------|------------|----------------------|------------|------------|
|     | Conc.                | MMAD <sup>a</sup> |              | Conc.                | MMAD       |            | Conc.                | MMAD       |            |
|     | (mg/m <sup>3</sup> ) | ( $\mu$ m)        | $\sigma_g^b$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ |
| 1   | 2.0                  | 3.1               | 1.9          | 16.4                 | 2.9        | 1.8        | 125                  | 5.0        | 2.0        |
| 2   | 1.1                  | 3.1               | 2.3          | 10.2                 | 2.9        | 1.9        | 85                   | 4.8        | 2.1        |
| 3   | 1.5                  | 3.5               | 2.2          | 7.4                  | 3.1        | 2.0        | 62                   | 4.3        | 2.0        |
| 4   | 1.1                  | 3.3               | 2.5          | 13.1                 | 3.3        | 1.9        | 66                   | 4.2        | 2.0        |
| 5   | 1.3                  | 3.2               | 2.4          | 11.0                 | 3.2        | 2.0        | 106                  | 4.4        | 1.9        |
| 6   | 1.3                  |                   |              | 9.0                  |            |            | 101                  |            |            |
| 7   | 0.7                  | 2.0               | 1.9          | 12.5                 |            |            | 113                  |            |            |
| 8   | 1.3                  |                   |              | 14.1                 | 3.3        | 2.0        | 86                   | 4.1        | 1.9        |
| 9   | 0.8                  |                   |              | 6.0                  |            |            | 72                   |            |            |
| 10  | 1.1                  |                   |              | 12.0                 |            |            | 107                  |            |            |
| 11  | 1.7                  |                   |              | 9.8                  |            |            | 97                   |            |            |
| 12  | 1.9                  |                   |              | 10.0                 |            |            | 61                   | 3.9        | 2.8        |
| 13  | 1.7                  |                   |              | 9.9                  | 3.0        | 1.8        | 78                   |            |            |
| 14  | 0.8                  | 2.5               | 2.4          | 9.8                  |            |            | 95                   |            |            |
| 15  | 0.9                  |                   |              | 10.8                 |            |            | 123                  |            |            |
| 16  | 0.4                  |                   |              | 10.2                 |            |            | 97                   |            |            |
| 17  | 1.7                  | 2.8               | 2.0          | 12.2                 |            |            | 80                   |            |            |
| 18  | 1.1                  |                   |              | 12.0                 | 2.8        | 1.9        | 102                  |            |            |
| 19  | 0.9                  |                   |              | 10.1                 |            |            | 104                  | 3.6        | 1.8        |
| 20  | 1.2                  |                   |              | 11.2                 |            |            | 93                   |            |            |
| 21  | 0.5                  | 2.4               | 2.0          | 11.3                 |            |            | 84                   |            |            |
| 22  | 0.9                  |                   |              | 9.4                  | 2.7        | 2.0        | 86                   |            |            |
| 23  | 0.6                  |                   |              | 9.4                  |            |            | 96                   | 4.0        | 1.9        |
| 24  | 0.8                  |                   |              | 10.0                 |            |            | 55                   |            |            |
| 25  | 1.2                  |                   |              | 13.2                 |            |            | 8                    |            |            |
| 26  | 1.7                  | 3.2               | 2.1          | 9.5                  |            |            | 119                  |            |            |
| 27  | 1.0                  |                   |              | 9.6                  | 3.1        | 2.1        | 132                  |            |            |
| 28  | 0.7                  |                   |              | 1.8                  |            |            | 107                  | 4.4        | 2.0        |
| 29  | 0.7                  |                   |              | 5.3                  |            |            | 113                  |            |            |
| 30  | 1.0                  |                   |              | 9.9                  |            |            | 142                  |            |            |
| 31  | 1.0                  | 2.7               | 2.1          | 14.0                 |            |            | 123                  |            |            |
| 32  | 0.8                  |                   |              | 12.8                 | 3.1        | 1.8        | 105                  |            |            |
| 33  | 1.0                  |                   |              | 13.3                 |            |            | 98                   | 4.2        | 1.9        |
| 34  | 0.7                  |                   |              | 13.1                 |            |            | 98                   |            |            |
| 35  | 0.6                  |                   |              | 9.6                  |            |            | 131                  |            |            |
| 36  | 0.7                  | 2.4               | 2.0          | 10.4                 |            |            | 90                   |            |            |
| 37  | 0.9                  |                   |              | 12.5                 | 3.0        | 1.9        | 98                   |            |            |
| 38  | 0.7                  |                   |              | 10.2                 |            |            | 101                  | 3.8        | 1.8        |
| 39  | 1.1                  |                   |              | 7.3                  |            |            | 132                  |            |            |
| 40  | 1.0                  |                   |              | 9.4                  |            |            | 117                  |            |            |

Table 15 (Continued)

|             | LOW                  |                   |                         | MEDIUM               |            |            | HIGH                 |            |            |
|-------------|----------------------|-------------------|-------------------------|----------------------|------------|------------|----------------------|------------|------------|
|             | Conc.                | MMAD <sup>a</sup> |                         | Conc.                | MMAD       |            | Conc.                | MMAD       |            |
|             | (mg/m <sup>3</sup> ) | ( $\mu$ m)        | $\sigma_g$ <sup>b</sup> | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ | (mg/m <sup>3</sup> ) | ( $\mu$ m) | $\sigma_g$ |
| Day 41      | 0.3                  | 2.4               | 2.1                     | 2.2                  |            |            | 108                  |            |            |
| 42          | 0.8                  |                   |                         | 10.9                 | 2.7        | 2.2        | 116                  |            |            |
| 43          | 1.0                  |                   |                         | 7.1                  |            |            | 69                   | 4.2        | 1.9        |
| 44          | 0.4                  |                   |                         | 3.6                  |            |            | 135                  |            |            |
| 45          | 0.8                  |                   |                         | 8.7                  |            |            | 130                  |            |            |
| 46          | 0.8                  | 2.6               | 1.9                     | 13.5                 |            |            | 131                  |            |            |
| 47          | 1.0                  |                   |                         | 11.0                 | 3.0        | 1.9        | 122                  |            |            |
| 48          | 0.9                  |                   |                         | 11.6                 |            |            | 109                  | 3.8        | 1.8        |
| 49          | 0.6                  |                   |                         | 13.4                 |            |            | 90                   |            |            |
| 50          | 0.9                  |                   |                         | 13.8                 |            |            | 80                   |            |            |
| 51          | 1.1                  | 2.5               | 1.9                     | 12.7                 |            |            | 93                   |            |            |
| 52          | 1.4                  |                   |                         | 7.1                  | 3.0        | 2.0        | 121                  |            |            |
| 53          | 1.4                  |                   |                         | 11.1                 |            |            | 111                  |            |            |
| 54          | 1.4                  |                   |                         | 9.7                  |            |            | 137                  |            |            |
| 55          | 3.5                  |                   |                         | 11.5                 |            |            | 102                  | 3.9        | 1.8        |
| 56          | 0.8                  |                   |                         | 13.4                 |            |            | 103                  |            |            |
| 57          | 1.6                  | 2.9               | 2.1                     | 11.5                 |            |            | 120                  |            |            |
| 58          | 0.9                  |                   |                         | 10.2                 | 2.8        | 1.9        | 101                  |            |            |
| 59          | 0.8                  |                   |                         | 15.1                 |            |            | 126                  | 4.1        | 1.7        |
| 60          | 0.9                  |                   |                         | 12.8                 |            |            | 113                  |            |            |
| 61          | 0.6                  | 2.7               | 1.8                     | 9.5                  |            |            | 80                   |            |            |
| 62          | 1.1                  |                   |                         | 3.4                  | 2.7        | 1.9        | 100                  |            |            |
| 63          | 1.1                  |                   |                         | 1.8                  |            |            | 100                  | 4.3        | 1.8        |
| $\bar{x}^c$ | 1.1                  | 2.8               | 2.1                     | 10.2                 | 3.0        | 1.9        | 101                  | 4.2        | 1.9        |
| SD          | $\pm 0.5$            | $\pm 0.4$         | $\pm 0.2$               | $\pm 3.1$            | $\pm 0.2$  | $\pm 0.1$  | $\pm 23$             | $\pm 0.4$  | $\pm 0.2$  |

Daily chamber concentrations were determined by the mean of 3 two-hour samples taken during the day.

<sup>a</sup>MMAD = mass median aerodynamic diameter

<sup>b</sup> $\sigma_g$  = geometric standard deviation

<sup>c</sup>Mean values from day 1 through day 63



Table 16  
Weekly Average Weights<sup>a</sup> of Male and Female Rats for the  
90-Day SY/SG Inhalation Exposure Study

|         | Control  |          | Low<br>(1.1 mg/m <sup>3</sup> ) |          | Medium<br>(10.2 mg/m <sup>3</sup> ) |          | High<br>(101 mg/m <sup>3</sup> ) |                      |
|---------|----------|----------|---------------------------------|----------|-------------------------------------|----------|----------------------------------|----------------------|
|         | Male     | Female   | Male                            | Female   | Male                                | Female   | Male                             | Female               |
| Week -3 | 258 ± 26 | 157 ± 11 | 253 ± 30                        | 156 ± 13 | 260 ± 26                            | 157 ± 11 | 251 ± 23                         | 158 ± 13             |
| 0       | 262 ± 30 | 166 ± 10 | 254 ± 15                        | 158 ± 6  | 255 ± 19                            | 161 ± 9  | 248 ± 18                         | 156 ± 8              |
| 2       | 263 ± 43 | 176 ± 9  | 277 ± 12                        | 167 ± 6  | 271 ± 18                            | 166 ± 9  | 257 ± 18                         | 160 ± 8              |
| 3       | 273 ± 40 | 174 ± 18 | 289 ± 15                        | 171 ± 7  | 282 ± 21                            | 169 ± 11 | 265 ± 19                         | 166 ± 7              |
| 4       | 273 ± 51 | 182 ± 13 | 291 ± 15                        | 172 ± 6  | 288 ± 20                            | 174 ± 9  | 267 ± 19                         | 168 ± 6 <sup>b</sup> |
| 5       | 288 ± 34 | 180 ± 14 | 291 ± 15                        | 173 ± 9  | 294 ± 22                            | 177 ± 8  | 274 ± 19                         | 170 ± 7 <sup>b</sup> |
| 6       | 299 ± 36 | 187 ± 13 | 303 ± 15                        | 181 ± 7  | 298 ± 22                            | 180 ± 6  | 279 ± 18                         | 173 ± 7 <sup>b</sup> |
| 7       | 300 ± 29 | 187 ± 11 | 307 ± 14                        | 183 ± 8  | 284 ± 30                            | 181 ± 11 | 287 ± 18                         | 176 ± 7 <sup>b</sup> |
| 8       | 319 ± 37 | 198 ± 10 | 318 ± 13                        | 190 ± 7  | 312 ± 23                            | 191 ± 9  | 292 ± 19 <sup>b</sup>            | 177 ± 7 <sup>b</sup> |
| 9       | 319 ± 36 | 195 ± 15 | 319 ± 14                        | 189 ± 8  | 316 ± 22                            | 187 ± 12 | 299 ± 19                         | 179 ± 7 <sup>b</sup> |
| 10      | 321 ± 36 | 199 ± 9  | 322 ± 15                        | 191 ± 7  | 322 ± 23                            | 192 ± 10 | 302 ± 19                         | 181 ± 8 <sup>b</sup> |
| 11      | 320 ± 36 | 192 ± 10 | 321 ± 15                        | 187 ± 6  | 319 ± 22                            | 189 ± 9  | 299 ± 18                         | 178 ± 7 <sup>b</sup> |
| 12      | 332 ± 40 | 198 ± 11 | 327 ± 14                        | 191 ± 8  | 325 ± 23                            | 194 ± 6  | 303 ± 17 <sup>b</sup>            | 180 ± 6 <sup>b</sup> |
| 13      | 327 ± 33 | 196 ± 11 | 325 ± 17                        | 186 ± 6  | 322 ± 21                            | 190 ± 8  | 301 ± 18 <sup>b</sup>            | 178 ± 6 <sup>b</sup> |
| 17      | 342 ± 23 | 193 ± 11 | 330 ± 25                        | 190 ± 15 | 333 ± 22                            | 191 ± 12 | 316 ± 26 <sup>b</sup>            | 186 ± 14             |

<sup>a</sup>Average animal weight (grams) ± SD, n = 20.

<sup>b</sup>Shown to be significantly lower than the control group of the same week interval using Dunnett's multiple comparisons procedure. P value ≤ 0.01.

data show that rats exposed to the highest level of SY/SG dye gained weight at a significantly slower rate than controls, with female rats showing a difference in weight gain earlier than male rats. At the end of the 90-day exposures, high level exposed rats weighed approximately 7% less than control animals. However, after the 30-day post-exposure recovery period, there were no statistically significant differences in the weights of female rats among the four groups, while those of male rats exposed to the highest level of SY/SG dye remained significantly lower than male control animal weights.

#### Lung Content of QI and TA After Exposure to SY/SG Dye

At the end of the 3-month exposure, six rats (3 males and 3 females) from each chamber were sacrificed. Following each sacrifice, lungs were removed, homogenized in acetonitrile, the homogenate centrifuged, and the supernatant removed. The tissue pellet was then re-extracted with acetonitrile until no more dye was removed. The pooled acetonitrile extracts were analyzed for the major chemicals in the SY/SG dye mixture [2-(2'-quinoliny)-1,3-indandione (QI) and 1,4-di-p-toluidinoanthraquinone (TA)] by high pressure liquid chromatography. Conditions were:

- reverse phase C<sub>18</sub> column, 25 cm x 4.6 mm.
- mobile phase; 9:1 acetonitrile:water to 100% acetonitrile gradient in 10 min, hold at 100% for 10 minutes
- flow rate, 1 mL/min
- detection: UV at 435 and 620 nm

Data in Table 17 indicate that virtually no QI remained in the lungs of rats sacrificed the day after the last day of exposure. However, in these same animals, approximately 19% of the calculated amount of TA that would have deposited in lungs during these exposures was found in lungs at every exposure level (Table 18).

Table 17  
Lung Content of QI and TA After the 90-Day  
Inhalation Exposure to SY/SG Dye Mixture

| Aerosol<br>Concentration<br>(mg/m <sup>3</sup> ) | Lung Concentration<br>(µg/g Lung ± SE) |            |
|--------------------------------------------------|----------------------------------------|------------|
|                                                  | QI                                     | TA         |
| <u>Male</u>                                      |                                        |            |
| Control                                          | nd <sup>a</sup>                        | < 0.15     |
| 1                                                | nd                                     | 43 ± 4     |
| 10                                               | nd                                     | 480 ± 20   |
| 100                                              | nd                                     | 3400 ± 50  |
| <u>Female</u>                                    |                                        |            |
| Control                                          | nd                                     | < 0.18     |
| 1                                                | nd                                     | 39 ± 2     |
| 10                                               | nd                                     | 370 ± 40   |
| 100                                              | nd                                     | 2800 ± 200 |

<sup>a</sup>nd=not detected at sensitivity of assay. Samples were assayed by high performance liquid chromatography with the sensitivity adjusted for the concentration of the TA. At these sensitivities, the assay would have detected as low as 0.1 µg QI/g lung in the low, 2.0 µg QI/g lung in the medium and 14 µg QI/g lung in the high level exposed lungs.

Table 18  
Lung Burden of TA After a 90-Day  
Exposure to SY/SG Dye Mixture

|               | Aerosol<br>Concentration<br>(mg/m <sup>3</sup> ) | Lung Burdens<br>Mean $\pm$ SE (n = 3)<br>(mg/Lung) | Calculated*<br>Amount<br>Deposited<br>(mg/Lung) | Percent<br>Retained |
|---------------|--------------------------------------------------|----------------------------------------------------|-------------------------------------------------|---------------------|
| <u>Male</u>   |                                                  |                                                    |                                                 |                     |
|               | 1                                                | 0.06 $\pm$ 0.003                                   | 0.32                                            | 19 $\pm$ 1          |
|               | 10                                               | 0.68 $\pm$ 0.03                                    | 3.2                                             | 21 $\pm$ 1          |
|               | 100                                              | 5.70 $\pm$ 0.08                                    | 31.8                                            | 18 $\pm$ 4          |
| <u>Female</u> |                                                  |                                                    |                                                 |                     |
|               | 1                                                | 0.04 $\pm$ 0.001                                   | 0.24                                            | 17 $\pm$ 1          |
|               | 10                                               | 0.41 $\pm$ 0.05                                    | 2.4                                             | 17 $\pm$ 2          |
|               | 100                                              | 3.86 $\pm$ 0.34                                    | 23.8                                            | 16 $\pm$ 3          |

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\*Assuming 63 6-hr exposures, 200 mL minute vol for males and 150 mL for females, 10% lung deposition, and 70 percent of SY/SG is TA.

In addition, 8 other groups of 6 rats (3 males and 3 females) were sacrificed 3, 7, 14, 30, 60, 90, 160 and 230 days after the last day of exposure and lungs were analyzed for SY/SG dye components. Again, virtually no QI was detected, but the quantity of TA found in lungs was significant at each of these post-exposure sacrifice times (Table 19 and Figure 1). This indicates that TA clears from lungs at a much slower rate than QI.

#### Respiratory Function

Respiratory function data from measurements of rats before exposures, immediately after exposures and 30 days after exposure; to SY/SG dye were analyzed by analysis of variance and comparison of the mean of each (low, medium and high) treated group to that of controls using the Student's t-test and the Bonferroni adjustment for multiple comparisons. A probability level of  $P < 0.05$  was used as the criterion for statistical significance of all comparisons. The results are summarized in Tables 20-22. Not all variables measured are listed; data for body weight and the variables reflecting the major facets of respiratory function are presented. There were 16 rats per group before exposure and 14-16 at subsequent measurement times. The rats measured after exposure were the same as those measured before.

There were no significant differences between pre-exposure data from control or treated rats (Table 20). There were no physiologically meaningful differences between respiratory function of treated and control rats at the end of exposure (Table 21). As reported in Table 16, there was a dose-related trend toward lower body weights for treated rats than for controls, and the same trend was observed among the respiratory function groups. Since there were no significant differences among non-normalized function data between treated and control rats, there was a tendency for the weight-normalized

Table 19  
Lung Retention of TA at Various Times After the 90-Day  
Exposure to SY/SG Dye Mixture

| Days After<br>Exposure | Total Lung Content of TA in mg <sup>a</sup> |                 |
|------------------------|---------------------------------------------|-----------------|
|                        | Male                                        | Female          |
| 0                      | 5.7 ± 0.1 (100)                             | 3.9 ± 0.3 (100) |
| 3                      | 5.3 ± 0.6 (93)                              | 3.6 ± 0.4 (92)  |
| 7                      | 5.8 ± 0.8 (102)                             | 3.9 ± 0.2 (100) |
| 14                     | 6.1 ± 0.5 (107)                             | 3.6 ± 0.2 (92)  |
| 30                     | 5.9 ± 0.2 (104)                             | 3.3 ± 0.4 (85)  |
| 60                     | 3.6 ± 0.4 (63)                              | 3.4 ± 0.3 (87)  |
| 90                     | 3.3 ± 0.5 (58)                              | 2.8 ± 0.4 (72)  |
| 160                    | 3.9 ± 0.5 (69)                              | 2.6 ± 0.1 (66)  |
| 230                    | 3.6 ± 0.5 (63)                              | 2.1 ± 0.1 (55)  |

<sup>a</sup>Means ± SE (n = 3). Numbers in parentheses are the percent of 0-day values.

Figure 1

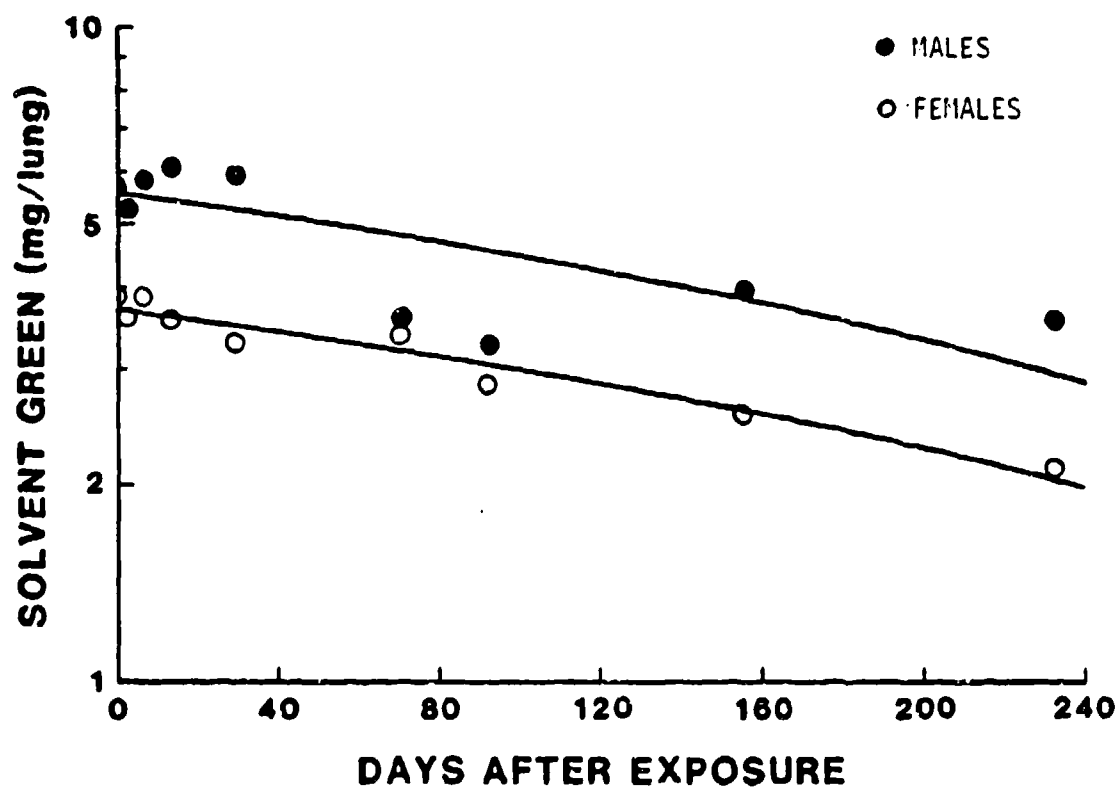


Table 20

Respiratory Function of Rats Before the SY/SG Dye Exposures\*

| Variable                                                   | Units                      | Control $\pm$ SE | Low $\pm$ SE | Medium $\pm$ SE | High $\pm$ SE |
|------------------------------------------------------------|----------------------------|------------------|--------------|-----------------|---------------|
| Body weight                                                | g                          | 210              | 156          | 196             | 190           |
| Minute volume                                              | ml/kg                      | 382              | 430          | 411             | 379           |
| Dynamic lung compliance                                    | ml/cm H <sub>2</sub> O     | 0.29             | 0.29         | 0.31            | 0.28          |
| Quasistatic chord compliance                               | ml/cm H <sub>2</sub> O     | 0.62             | 0.55         | 0.56            | 0.61          |
| Total lung capacity (TLC)                                  | ml                         | 12.2             | 11.3         | 12.0            | 11.9          |
| TLC/body weight                                            | ml/kg                      | 59.9             | 59.9         | 63.5            | 64.3          |
| Vital capacity (VC)                                        | ml                         | 9.8              | 9.1          | 9.5             | 9.7           |
| VC/TLC                                                     | ml/ml                      | 0.80             | 0.80         | 0.80            | 0.81          |
| Functional residual capacity (FRC)                         | ml                         | 3.3              | 3.3          | 3.5             | 3.3           |
| FRC/TLC                                                    | ml/ml                      | 0.28             | 0.29         | 0.29            | 0.28          |
| Residual volume (RV)                                       | ml                         | 2.4              | 2.2          | 2.4             | 2.2           |
| RV/TLC                                                     | ml/ml                      | 0.20             | 0.20         | 0.20            | 0.19          |
| CO diffusing capacity (DLCO)                               | ml/min/mm Hg               | 0.196            | 0.176        | 0.190           | 0.169         |
| DLCO/alveolar volume                                       | ml/min/mm Hg/ml            | 0.018            | 0.017        | 0.018           | 0.017         |
| Forced vital capacity (FVC)                                | ml                         | 9.5              | 9.0          | 9.8             | 9.8           |
| Percent of FVC exhaled in 0.1 sec                          | Percent                    | 49               | 44           | 51              | 52            |
| Mean midexpiratory flowrate (MEF)                          | ml/sec                     | 41               | 32           | 48              | 48            |
| MEF/FVC                                                    | ml/sec/ml                  | 4.1              | 3.6          | 4.8             | 4.8           |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | ml/sec                     | 11               | 10           | 13              | 13            |
| FEF10/FVC                                                  | ml/sec/ml                  | 1.1              | 1.1          | 1.3             | 1.4           |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /ml | 0.93             | 0.98         | 0.89            | 0.78          |

\*There were no significant differences between treated and control groups at  $P < 0.05$ .



Table 21

Respiratory Function of Rats at the End of 90-Day SY/SG Exposures\*

| Variable                                                   | Units                      | Control $\pm$ SE | Low $\pm$ SE | Medium $\pm$ SE | High $\pm$ SE |
|------------------------------------------------------------|----------------------------|------------------|--------------|-----------------|---------------|
| Body weight                                                | g                          | 256              | 249          | 255             | 217           |
| Minute volume                                              | ml/kg                      | 368              | 329          | 373             | 377           |
| Dynamic lung compliance                                    | ml/cm H <sub>2</sub> O     | 0.32             | 0.32         | 0.32            | 0.35          |
| Quasistatic chord compliance                               | ml/cm H <sub>2</sub> O     | 0.69             | 0.71         | 0.73            | 0.72          |
| Total lung capacity (TLC)                                  | ml                         | 13.3             | 13.5         | 13.5            | 13.1          |
| TLC/body weight                                            | ml/kg                      | 53.9             | 57.1         | 54.4            | 62.1          |
| Vital capacity (VC)                                        | ml                         | 11.0             | 11.2         | 11.5            | 11.0          |
| VC/TLC                                                     | ml/ml                      | 0.83             | 0.83         | 0.85            | 0.84          |
| Functional residual capacity (FRC)                         | ml                         | 3.4              | 3.6          | 3.3             | 3.4           |
| FRC/TLC                                                    | ml/ml                      | 0.26             | 0.27         | 0.25            | 0.26          |
| Residual volume (RV)                                       | ml                         | 2.3              | 2.3          | 2.0             | 2.1           |
| RV/TLC                                                     | ml/ml                      | 0.18             | 0.17         | 0.15            | 0.16          |
| CO diffusing capacity (DLCO)                               | ml/min/mm Hg               | 0.212            | 0.239        | 0.241           | 0.195         |
| DLCO/alveolar volume                                       | ml/min/mm Hg/ml            | 0.018            | 0.020        | 0.019           | 0.016         |
| Forced vital capacity (FVC)                                | ml                         | 10.7             | 10.9         | 11.3            | 10.7          |
| Percent of FVC exhaled in 0.1 sec                          | percent                    | 47               | 52           | 50              | 52            |
| Mean midexpiratory flowrate (MMEF)                         | ml/sec                     | 42               | 48           | 46              | 46            |
| MMEF/VC                                                    | ml/sec/ml                  | 3.9              | 4.4          | 4.1             | 4.4           |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | ml/sec                     | 13               | 15           | 13              | 13            |
| FEF10/FVC                                                  | ml/sec/ml                  | 1.2              | 1.3          | 1.2             | 1.3           |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /ml | 0.83             | 0.79         | 0.75            | 0.73          |

\*There were no significant differences between treated and control groups at  $P < 0.05$ .

Table 22

Respiratory Function of Rats 30 Days After the End of 90-Day SY-SG Dye Exposures\*

| Variable                                                   | Units                      | Control $\pm$ SE |       | Low $\pm$ SE |       | Medium $\pm$ SE |       | High $\pm$ SE |       |
|------------------------------------------------------------|----------------------------|------------------|-------|--------------|-------|-----------------|-------|---------------|-------|
| Body weight                                                | g                          | 262              | 19    | 255          | 19    | 259             | 20    | 223           | 16    |
| Minute volume                                              | mL/kg                      | 295              | 27    | 302          | 28    | 322             | 33    | 336           | 26    |
| Dynamic lung compliance                                    | mL/cm H <sub>2</sub> O     | 0.37             | 0.03  | 0.39         | 0.03  | 0.35            | 0.02  | 0.39          | 0.02  |
| Quasistatic chord compliance                               | mL/cm H <sub>2</sub> O     | 0.77             | 0.04  | 0.77         | 0.05  | 0.77            | 0.05  | 0.74          | 0.05  |
| Total lung capacity (TLC)                                  | mL                         | 14.1             | 0.6   | 14.1         | 0.6   | 14.1            | 0.7   | 13.5          | 0.6   |
| TLC/body weight                                            | mL/kg                      | 56.3             | 2.3   | 58.0         | 3.0   | 56.9            | 2.3   | 62.4          | 2.7   |
| Vital capacity (VC)                                        | mL                         | 11.7             | 0.5   | 11.9         | 0.6   | 11.9            | 0.6   | 11.5          | 0.5   |
| VC/TLC                                                     | mL/mL                      | 0.83             | 0.01  | 0.84         | 0.01  | 0.84            | 0.01  | 0.85          | 0.01  |
| Functional residual capacity (FRC)                         | mL                         | 3.5              | 0.1   | 3.7          | 0.1   | 3.6             | 0.2   | 3.4           | 0.1   |
| FRC/TLC                                                    | mL/mL                      | 0.25             | 0.01  | 0.27         | 0.01  | 0.25            | 0.01  | 0.25          | 0.01  |
| Residual volume (RV)                                       | mL                         | 2.4              | 0.1   | 2.2          | 0.1   | 2.3             | 0.2   | 2.0           | 0.2   |
| RV/TLC                                                     | mL/mL                      | 0.17             | 0.01  | 0.16         | 0.01  | 0.16            | 0.01  | 0.15          | 0.01  |
| CO diffusing capacity (DLCO)                               | mL/min/mm Hg               | 0.257            | 0.018 | 0.253        | 0.016 | 0.257           | 0.015 | 0.209         | 0.015 |
| DLCO/alveolar volume                                       | mL/min/mm Hg/mL            | 0.020            | 0.001 | 0.019        | 0.001 | 0.020           | 0.001 | 0.016*        | 0.001 |
| Forced vital capacity (FVC)                                | mL                         | 12.1             | 0.5   | 12.2         | 0.7   | 12.5            | 0.6   | 12.0          | 0.6   |
| Percent of FVC exhaled in 0.1 sec                          | percent                    | 55               | 2     | 54           | 2     | 54              | 3     | 56            | 3     |
| Mean midexpiratory flowrate (MMEF)                         | mL/sec                     | 60               | 5     | 57           | 5     | 62              | 6     | 64            | 3     |
| MMEF/FVC                                                   | mL/sec/mL                  | 5.0              | 0.4   | 4.7          | 0.4   | 5.1             | 0.5   | 5.6           | 0.4   |
| Forced expiratory flowrate at 10% of FVC (FEF10)           | mL/sec                     | 18               | 2     | 16           | 2     | 19              | 2     | 18            | 1     |
| FEF10/FVC                                                  | mL/sec/mL                  | 1.4              | 0.1   | 1.4          | 0.2   | 1.5             | 0.2   | 1.6           | 0.1   |
| Slope of phase III of single-breath N <sub>2</sub> washout | percent N <sub>2</sub> /mL | 0.71             | 0.07  | 0.63         | 0.07  | 0.65            | 0.05  | 0.65          | 0.07  |

\*Significantly different from control at  $P < 0.05$ .

values to be higher in treated rats. This trend only reached statistical significance for CO diffusing capacity/kg (not shown). There was little evidence of impairment of respiratory function at 30 days after the end of exposure (Table 22).

Only one statistically significant ( $P < 0.05$ ) difference among the group means was detected by analysis of variance. The CO diffusing capacity normalized by alveolar volume was lower in the high level rats than in the other groups. The diffusing capacity itself was lower than that of controls, but only at the  $P < 0.10$  level. There were no trends toward group differences in lung volume subdivisions. This means that there might have been a slight reduction in diffusing capacity (alveolar-capillary gas exchange) in the high level rats, but it was a combination of slight changes in opposite directions in two parameters that made the volume-normalized diffusing capacity significantly different. There were no other indications of function loss in exposed rats. Therefore, taken with the lack of function differences seen immediately after exposure, this result does not suggest that there was a physiologically significant effect of SY/SG dye exposure on respiratory function in this 90-day exposure study.

#### Lung Biochemistry

Bronchoalveolar lavage fluid (BAL) was analyzed for indicators of injury after 6 and 13 weeks of exposure and after 30 days of recovery from the exposure. These results are summarized in Table 23. The data indicate an inflammatory response only in the lungs of rats exposed to the highest concentration ( $100 \text{ mg/m}^3$ ). The inflammatory response was present after 6 weeks of exposure and, based on BAL analysis, did not appear to worsen by 13 weeks. Analysis of BAL from rats one month after the end of the exposure

Table 23

## Pulmonary Response of Rats Exposed to SV/SG for 90 Days

## As Observed in Bronchoalveolar Lavage Fluid

 $(\bar{X} \pm SE, n = 12)$ 

|                                         | Sacrifice <sup>b</sup><br>Week | Exposure Concentration (mg/m <sup>3</sup> ) |            |  |              |             |  |
|-----------------------------------------|--------------------------------|---------------------------------------------|------------|--|--------------|-------------|--|
|                                         |                                | Control<br>0                                | Low<br>1.1 |  | Medium<br>10 | High<br>101 |  |
|                                         |                                |                                             |            |  |              |             |  |
| Lactate Dehydrogenase,<br>mIU/g         | 6                              | 490 ± 40                                    | 510 ± 30   |  | 520 ± 30     | 1210 ± 50*  |  |
|                                         | 13                             | 390 ± 30                                    | 400 ± 30   |  | 450 ± 30     | 930 ± 50*   |  |
|                                         | 17                             | 370 ± 20                                    | 380 ± 20   |  | 380 ± 20     | 780 ± 40*   |  |
| Acid Phosphatase,<br>mIU/g              | 6                              | 9.7 ± 0.8                                   | 12.2 ± 1.8 |  | 11.0 ± 1.8   | 16.1 ± 2.2  |  |
|                                         | 13                             | 9.2 ± 0.7                                   | 11.4 ± 0.7 |  | 10.9 ± 0.8   | 11.5 ± 1.0  |  |
|                                         | 17                             | 7.9 ± 0.6                                   | 8.3 ± 0.8  |  | 7.1 ± 0.7    | 7.4 ± 0.6   |  |
| β-Glucuronidase,<br>mIU/g               | 6                              | 1.5 ± 0.2                                   | 1.9 ± 0.4  |  | 1.7 ± 0.2    | 7.2 ± 0.3*  |  |
|                                         | 13                             | 2.2 ± 0.8                                   | 1.7 ± 0.2  |  | 1.5 ± 0.2    | 5.7 ± 0.8*  |  |
|                                         | 17                             | 0.9 ± 0.1                                   | 1.1 ± 0.3  |  | 1.2 ± 0.2    | 3.4 ± 0.5*  |  |
| Protein, mg/g                           | 6                              | 1.5 ± 0.2                                   | 1.9 ± 0.2  |  | 2.3 ± 0.3    | 3.4 ± 0.3*  |  |
|                                         | 13                             | 1.1 ± 0.2                                   | 1.0 ± 0.2  |  | 1.6 ± 0.4    | 3.2 ± 0.6*  |  |
|                                         | 17                             | 0.9 ± 0.1                                   | 1.4 ± 0.3  |  | 1.4 ± 0.2    | 2.0 ± 0.2*  |  |
| Macrophages,<br>10 <sup>3</sup> cells/g | 6                              | 730 ± 60                                    | 620 ± 50   |  | 860 ± 90     | 770 ± 110   |  |
|                                         | 13                             | 600 ± 60                                    | 510 ± 60   |  | 460 ± 80     | 1000 ± 160* |  |
|                                         | 17                             | 450 ± 40                                    | 430 ± 40   |  | 580 ± 70     | 580 ± 70    |  |
| Neutrophils,<br>10 <sup>3</sup> cells/g | 6                              | 5 ± 2                                       | 30 ± 25    |  | 23 ± 5       | 1300 ± 130* |  |
|                                         | 13                             | 0 ± 0                                       | 7 ± 3      |  | 13 ± 7       | 470 ± 100*  |  |
|                                         | 17                             | 7 ± 3                                       | 1 ± 1      |  | 35 ± 35      | 290 ± 50*   |  |

a values represent total amounts of material recovered in BAL divided by the net weight of the lung in g. There was no statistical difference in the mean net weight of the lungs between the group. The values were normalized in this manner to take into account the difference in size of male versus female weights.

b An interim sacrifice was made after 6 weeks of exposure and a second sacrifice was made at the end of the exposure (13 weeks). The 17 week sacrifice was of rats held for 1 month after the exposure to determine if there was recovery from any exposure-related injury.

\* Values differ from control values,  $p \leq 0.05$ , by Bonferroni pairwise comparison of means. The critical t-value necessary for rejection of the null hypothesis at  $p \leq 0.05$  was adjusted for

indicated that the inflammation was still present in the rats exposed to the high concentration of SY/SG (Table 23). This is not surprising, since the SG portion of the dye had not cleared from the lung at this time (Table 19).

Lung tissue and lavage fluid proteolytic activities were also measured in control rats and rats exposed to SY/SG dye aerosols. Acid proteinase activity was higher at the highest dose level after 90 days exposure to green dye (Table 24). This change was still present after 30 days recovery (Table 25). The increased activity was related to cathepsin D and probably associated with modest inflammation. Neutral proteinase activity tended to be increased at the same times, however, these data are extremely variable and thus significance, if any, cannot be defined.

#### Lung Connective Tissue Biochemistry

The collagen contents of bronchoalveolar fluid and of lung tissue were determined at the end of the 90-day exposure (Table 26) and after a 30-day recovery period (Table 27). Total lung collagen was not affected by exposure to SY/SG dye mixture. Lavage fluid collagen was increased after 90 days of exposure to the highest two levels of SY/SG dye mixture, suggesting that there was an increased turnover of the extracellular collagenous matrix. However, after 90 days of exposure and a 30-day recovery period, no differences were noted in rats exposed to the highest two levels of SY/SG dye mixture. The low level of green dye exposure did not affect rat lavage fluid collagen at any time.

#### Hematology and Serum Clinical Chemistries

Hematology and clinical chemistry measurements were made on 12 control rats and 12 rats at each concentration at the end of the 90-day exposure (Table 28) and after a 30 day recovery period (Table 29). Results showed slight changes in inorganic phosphorous which were not dose related. Parallel

Table 24  
Lung and Lavage Fluid Proteinolytic Activity in  
Rats Exposed to SY/SG Dye for 90 Days

| <u>Lung Tissue:</u>      | <u>mg protein released/hr/g lung<sup>a</sup></u> |            |               |                         |
|--------------------------|--------------------------------------------------|------------|---------------|-------------------------|
|                          | <u>Control</u>                                   | <u>Low</u> | <u>Medium</u> | <u>High</u>             |
| Total Acid Proteinase    | 13.0 ± 1.0                                       | 13.0 ± 1.0 | 11.2 ± 0.6    | 16.2 ± 0.8 <sup>b</sup> |
| Cathepsin D <sup>d</sup> | 8.1 ± 0.5                                        | 8.9 ± 0.7  | 7.8 ± 0.5     | 10.7 ± 0.4 <sup>b</sup> |
| Cathepsin B <sup>e</sup> | 4.9 ± 0.7                                        | 4.1 ± 1.0  | 3.4 ± 0.5     | 5.4 ± 0.8               |
| Total Neutral Proteinase | 1.3 ± 0.1                                        | 1.7 ± 0.1  | 0.8 ± 0.1     | 1.5 ± 0.1               |
| Macrophage               |                                                  |            |               |                         |
| Elastase <sup>f</sup>    | 0.4 ± 0.1                                        | 0.5 ± 0.1  | 0.1 ± 0.2     | 0.1 ± 0.1               |
| Cathepsin G & Neutrophil |                                                  |            |               |                         |
| Elastase <sup>g</sup>    | 0.9 ± 0.1                                        | 1.1 ± 0.1  | 0.8 ± 0.1     | 1.3 ± 0.1 <sup>b</sup>  |
| <u>Lavage Fluid:</u>     |                                                  |            |               |                         |
| Total Acid Proteinase    | 1.2 ± 0.5                                        | 1.2 ± 0.4  | 1.2 ± 0.3     | 1.7 ± 0.3               |
| Cathepsin D              | 1.3 ± 0.5                                        | 0.7 ± 0.2  | 1.1 ± 0.3     | 1.4 ± 0.2               |
| Cathepsin B              | ND <sup>c</sup>                                  | 0.5 ± 0.3  | 0.2 ± 0.4     | 0.3 ± 0.2               |

<sup>a</sup>Mean ± SE; (N = 8). No differences were noted in lung weights among the different exposure groups.

<sup>b</sup>p ≤ 0.05 in Student-t statistic; corrected for 3 comparisons.

<sup>c</sup>ND = none detected

<sup>d</sup>not inhibited by leupeptin

<sup>e</sup>inhibited by leupeptin

<sup>f</sup>inhibited by 1,10 phenanthroline

<sup>g</sup>not inhibited by 1,10 phenanthroline

Table 25

Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed  
to SY/SG Dye for 90 Days After the 30 Day Recovery Period

| <u>Lung Tissue:</u>                            | <u>mg protein released/hr/g lung<sup>a</sup></u> |                        |                        |                         |
|------------------------------------------------|--------------------------------------------------|------------------------|------------------------|-------------------------|
|                                                | <u>Control</u>                                   | <u>Low</u>             | <u>Medium</u>          | <u>High</u>             |
| Total Acid Proteinase                          | 8.3 ± 0.7                                        | 9.5 ± 0.7              | 9.5 ± 0.5              | 12.1 ± 0.8 <sup>b</sup> |
| Cathepsin D <sup>c</sup>                       | 6.7 ± 0.5                                        | 8.0 ± 0.6              | 8.9 ± 0.5 <sup>b</sup> | 11.0 ± 0.6 <sup>b</sup> |
| Cathepsin B <sup>d</sup>                       | 1.5 ± 0.6                                        | 1.5 ± 0.4              | 0.6 ± 0.2              | 1.1 ± 0.4               |
| Total Neutral Proteinase                       | 0.6 ± 0.1                                        | 1.0 ± 0.1 <sup>g</sup> | 1.1 ± 0.1 <sup>g</sup> | 1.2 ± 0.1 <sup>g</sup>  |
| Macrophage Elastase <sup>e</sup>               | 0.2 ± 0.1                                        | 0.4 ± 0.1              | 0.5 ± 0.1 <sup>b</sup> | 0.4 ± 0.1               |
| Cathepsin G & Neutrophil Elastase <sup>f</sup> | 0.4 ± 0.1                                        | 0.7 ± 0.1              | 0.6 ± 0.1              | 0.9 ± 0.1 <sup>b</sup>  |
| <u>Lavage Fluid:</u>                           |                                                  |                        |                        |                         |
| Total Acid Proteinase                          | 1.4 ± 0.8                                        | 1.7 ± 0.3              | 1.4 ± 0.4              | 1.6 ± 0.1               |
| Cathepsin D                                    | 0.7 ± 0.1                                        | 1.1 ± 0.2              | 0.9 ± 0.3              | 1.4 ± 0.1               |
| Cathepsin B                                    | 0.7 ± 1.0                                        | 0.6 ± 0.3              | 0.5 ± 0.4              | 0.4 ± 0.2               |

<sup>a</sup>Mean ± SE; (N = 8). No differences were noted in lung weights among the different exposure groups.

<sup>b</sup>p ≤ 0.05 in Student-t statistic; corrected for 3 comparisons.

<sup>c</sup>not inhibited by leupeptin

<sup>d</sup>inhibited by leupeptin

<sup>e</sup>inhibited by 1,10 phenanthroline

<sup>f</sup>not inhibited by 1,10 phenanthroline

<sup>g</sup>within the range of historical controls (0.2-2.5 mg protein released/hr/g lung)

Table 26  
Lavage Fluid and Lung Tissue Collagen for Rats  
Exposed to SY/SG Dye for 90 Days

( $\bar{X} \pm SE$ , n = 6-8)

|         | Lavage<br>Fluid<br>Collagen<br>( $\mu\text{g/g}$ )* | Total Lung<br>Collagen<br>( $\text{mg/g}$ )* |
|---------|-----------------------------------------------------|----------------------------------------------|
| Control | 30 $\pm$ 4                                          | 20 $\pm$ 2                                   |
| Low     | 17 $\pm$ 6                                          | 20 $\pm$ 3                                   |
| Medium  | 48 $\pm$ 4**                                        | 16 $\pm$ 3                                   |
| High    | 57 $\pm$ 6**                                        | 17 $\pm$ 2                                   |

\*Normalized to grams of lung weight. No differences were noted in lung weights among the different exposure groups.

\*\*P  $\leq$  0.05 in Student-t test. Critical t-values were corrected for 3 comparisons.



Table 27

## Lavage Fluid and Lung Tissue Collagen for Rats

Exposed to SY/SG Dye for 90 Days and Allowed to Recover for 30 Days

 $(\bar{X} \pm SE, n = 6-8)$ 

|         | Lavage<br>Fluid<br>Collagen<br>( $\mu\text{g/g}$ )* | Total Lung<br>Collagen<br>( $\text{mg/g}$ )* |
|---------|-----------------------------------------------------|----------------------------------------------|
| Control | $33 \pm 5$                                          | $16 \pm 1$                                   |
| Low     | $23 \pm 7$                                          | $17 \pm 2$                                   |
| Medium  | $31 \pm 5$                                          | $17 \pm 2$                                   |
| High    | $43 \pm 5$                                          | $16 \pm 2$                                   |

\*Normalized to grams of lung weight. No differences were noted in lung weights among the different exposure groups.

Table 28

Clinical Pathology Values in Rats After 90 Day Exposure to SY/SG Dye

 $(\bar{X} \pm SE; n = 11-12)$ 

| Biochemistry:                        | Control                          |     | Low         |       | Medium      |       | High        |       |
|--------------------------------------|----------------------------------|-----|-------------|-------|-------------|-------|-------------|-------|
| Alkaline Phosphatase (IU/L)          | 88                               | ± 5 | 78          | ± 2   | 77          | ± 3   | 61          | ± 2*  |
| SGPT (IU/L)                          | 54                               | ± 8 | 54          | ± 9   | 44          | ± 3   | 40          | ± 4   |
| Total Bilirubin (mg/dL)              | 0.22 ± 0.02                      |     | 0.24 ± 0.02 |       | 0.23 ± 0.02 |       | 0.30 ± 0.04 |       |
| Cholesterol (mg/dL)                  | 71                               | ± 7 | 58          | ± 5   | 83          | ± 11  | 123         | ± 23* |
| Thyroxine (µg/dL)                    | 3.4 ± 0.3                        |     | 3.9 ± 0.2   |       | 4.0 ± 0.6   |       | 3.3 ± 0.1   |       |
| Glucose (mg/dL)                      | 187                              | ± 8 | 220         | ± 13* | 260         | ± 21* | 270         | ± 23* |
| BUN (mg/dL)                          | 21                               | ± 1 | 21          | ± 1   | 22          | ± 1   | 22          | ± 1   |
| Creatinine (mg/dL)                   | 0.58 ± 0.02                      |     | 0.61 ± 0.02 |       | 0.61 ± 0.02 |       | 0.63 ± 0.02 |       |
| Inorganic Phosphorus (mg/dL)         | 5.0 ± 0.3                        |     | 5.5 ± 0.2   |       | 6.5 ± 0.6*  |       | 6.1 ± 0.4*  |       |
| Calcium (mg/dL)                      | 10.4 ± 0.1                       |     | 10.9 ± 0.1  |       | 11.0 ± 0.1  |       | 11.9 ± 0.3  |       |
| Total Protein (g/dL)                 | 6.3 ± 0.1                        |     | 6.8 ± 0.1*  |       | 6.9 ± 0.2*  |       | 7.2 ± 0.2*  |       |
| Albumin (g/dL)                       | 4.0 ± 0.1                        |     | 4.5 ± 0.1*  |       | 4.5 ± 0.1*  |       | 4.8 ± 0.1*  |       |
| Gamma Glutamyl Transpeptidase (IU/L) | No Significant Activity Detected |     |             |       |             |       |             |       |

\*Value differs from control at  $P < 0.05$  in Students' t-test. Critical t-values were corrected for 3 comparisons.

Table 28 (continued)

Clinical Pathology Values in Rats After 90 Day Exposure to SY/SG Dye

 $(\bar{X} \pm SE; n = 11-12)$ 

| Hematology:                                         | Control        | Low            | Medium         | High           |
|-----------------------------------------------------|----------------|----------------|----------------|----------------|
| RBC<br>( $10^6/\text{mm}^3$ )                       | $7.8 \pm 0.1$  | $7.7 \pm 0.1$  | $7.8 \pm 0.2$  | $7.7 \pm 0.2$  |
| Hematocrit (%)                                      | $42 \pm 1$     | $41 \pm 1$     | $42 \pm 1$     | $42 \pm 1$     |
| Hemoglobin<br>(g/dL)                                | $14.8 \pm 0.1$ | $14.8 \pm 0.2$ | $14.7 \pm 0.2$ | $14.8 \pm 0.1$ |
| Mean Corpuscular<br>Volume ( $\mu\text{m}^3$ )      | $54 \pm 1$     | $54 \pm 1$     | $54 \pm 1$     | $54 \pm 1$     |
| Mean Corpuscular<br>Hemoglobin<br>Concentration (%) | $35.0 \pm 0.4$ | $36.0 \pm 0.3$ | $35.0 \pm 0.3$ | $35.5 \pm 0.3$ |
| WBC<br>( $10^3/\text{mm}^3$ )                       | $6.2 \pm 0.5$  | $5.4 \pm 0.4$  | $4.5 \pm 0.6$  | $4.8 \pm 0.5$  |
| Neutrophils<br>( $10^3/\text{mm}^3$ )               | $1.1 \pm 0.2$  | $1.1 \pm 0.1$  | $1.0 \pm 0.1$  | $1.4 \pm 0.1$  |
| Lymphocytes<br>( $10^3/\text{mm}^3$ )               | $4.8 \pm 0.3$  | $4.3 \pm 0.3$  | $3.4 \pm 0.5$  | $3.3 \pm 0.3$  |
| Eosinophils<br>( $10^3/\text{mm}^3$ )               | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Basophils<br>( $10^3/\text{mm}^3$ )                 | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Monocytes<br>( $10^3/\text{mm}^3$ )                 | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Banded Neutrophils<br>( $10^3/\text{mm}^3$ )        | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| NRBC<br>( $10^3/\text{mm}^3$ )                      | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |

\*Value differs from control at  $P < 0.05$  in Students' t-test. Critical t-values were corrected for 3 comparisons.

Table 29  
Clinical Pathology Values in Rats After 90 Day Exposure  
to SY/SG Dye and Allowed to Recover for 30 Days

( $\bar{X} \pm SE$ ; n = 12)

| Biochemistry:                        | Control                          |   |    | Low         |   |    | Medium      |   |    | High        |   |    |
|--------------------------------------|----------------------------------|---|----|-------------|---|----|-------------|---|----|-------------|---|----|
| Alkaline Phosphatase (IU/L)          | 85                               | ± | 2  | 74          | ± | 3  | 74          | ± | 5  | 72          | ± | 6  |
| SGPT (IU/L)                          | 42                               | ± | 2  | 47          | ± | 5  | 39          | ± | 3  | 39          | ± | 2  |
| Total Bilirubin (mg/dL)              | 0.28 ± 0.01                      |   |    | 0.32 ± 0.02 |   |    | 0.30 ± 0.03 |   |    | 0.26 ± 0.02 |   |    |
| Cholesterol (mg/dL)                  | 74                               | ± | 6  | 71          | ± | 7  | 70          | ± | 7  | 75          | ± | 7  |
| Thyroxine (µg/dL)                    | 1.77 ± 0.11                      |   |    | 1.77 ± 0.15 |   |    | 1.70 ± 0.17 |   |    | 2.71 ± 0.19 |   |    |
| Glucose (mg/dL)                      | 220                              | ± | 10 | 220         | ± | 10 | 210         | ± | 20 | 230         | ± | 10 |
| BUN (mg/dL)                          | 22                               | ± | 1  | 22          | ± | 1  | 22          | ± | 1  | 23          | ± | 1  |
| Creatinine (mg/dL)                   | 0.54 ± 0.02                      |   |    | 0.59 ± 0.02 |   |    | 0.58 ± 0.01 |   |    | 0.58 ± 0.02 |   |    |
| Inorganic Phosphorus (mg/dL)         | 5.3 ± 0.3                        |   |    | 5.1 ± 0.3   |   |    | 5.2 ± 0.3   |   |    | 5.9 ± 0.3   |   |    |
| Calcium (mg/dL)                      | 12.1 ± 0.3                       |   |    | 11.8 ± 0.2  |   |    | 11.8 ± 0.4  |   |    | 12.4 ± 0.2  |   |    |
| Total Protein (g/dL)                 | 6.6 ± 0.1                        |   |    | 6.5 ± 0.1   |   |    | 6.7 ± 0.2   |   |    | 6.9 ± 0.1   |   |    |
| Albumin (g/dL)                       | 4.3 ± 0.1                        |   |    | 4.4 ± 0.1   |   |    | 4.4 ± 0.1   |   |    | 4.5 ± 0.1   |   |    |
| Gamma Glutamyl Transpeptidase (IU/L) | No Significant Activity Detected |   |    |             |   |    |             |   |    |             |   |    |

Table 29 (continued)  
Clinical Pathology Values in Rats After 90 Day Exposure  
to SY/SG Dye and Allowed to Recover for 30 Days\*

( $\bar{X} \pm SE$ ; n = 12)

| Hematology.                                         | Control        | Low            | Medium         | High           |
|-----------------------------------------------------|----------------|----------------|----------------|----------------|
| RBC<br>( $10^6/\text{mm}^3$ )                       | $8.1 \pm 0.2$  | $8.0 \pm 0.2$  | $8.3 \pm 0.1$  | $8.3 \pm 0.3$  |
| Hematocrit (%)                                      | $44 \pm 1$     | $43 \pm 1$     | $44 \pm 1$     | $44 \pm 1$     |
| Hemoglobin<br>(g/dL)                                | $15.0 \pm 0.1$ | $15.2 \pm 0.1$ | $15.3 \pm 0.2$ | $15.5 \pm 0.2$ |
| Mean Corpuscular<br>Volume ( $\mu\text{m}^3$ )      | $54 \pm 1$     | $54 \pm 1$     | $53 \pm 1$     | $53 \pm 1$     |
| Mean Corpuscular<br>Hemoglobin<br>Concentration (%) | $34.6 \pm 0.3$ | $35.4 \pm 0.2$ | $34.7 \pm 0.2$ | $35.8 \pm 1.0$ |
| WBC<br>( $10^3/\text{mm}^3$ )                       | $5.4 \pm 0.6$  | $4.9 \pm 0.4$  | $3.7 \pm 0.3$  | $4.6 \pm 0.5$  |
| Neutrophils<br>( $10^3/\text{mm}^3$ )               | $1.6 \pm 0.7$  | $0.9 \pm 0.1$  | $1.0 \pm 0.2$  | $1.3 \pm 0.3$  |
| Lymphocytes<br>( $10^3/\text{mm}^3$ )               | $4.1 \pm 0.3$  | $3.9 \pm 0.3$  | $2.6 \pm 0.2$  | $3.3 \pm 0.2$  |
| Eosinophils<br>( $10^3/\text{mm}^3$ )               | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Basophils<br>( $10^3/\text{mm}^3$ )                 | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Monocytes<br>( $10^3/\text{mm}^3$ )                 | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| Banded Neutrophils<br>( $10^3/\text{mm}^3$ )        | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |
| NRBC<br>( $10^3/\text{mm}^3$ )                      | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     | $\leq 0.1$     |

\*There were no significant differences between treated and control groups at  $P \leq 0.05$ .

and slight changes in albumin and total protein appeared to be dose related. Cholesterol was increased only at the highest dose. Glucose showed the largest change of the parameters examined and this was a dose related increase. The cause of these changes is unknown, but appears to have little clinical significance in light of the normal BUN, creatinine and SGPT levels indicating normal kidney and liver function. Serum electrolytes (sodium, potassium and chloride) were not analyzed because an insufficient volume of serum was obtained.

No significant differences were seen in any of the measured clinical chemistry endpoints between each group of dye exposed rats and control animals 30 days after the last day of exposure. Thus, the serum biochemistry changes that were observed immediately following the 90-day exposures to SY/SG dye (Table 28) were apparently reversible during this 30-day post-exposure recovery period (Table 29).

#### Histopathology

Ten males and ten females from each exposure and time were sacrificed by intraperitoneal injections with T61 and examined for gross lesions. Routine paraffin embedded, 5 micron, hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related

effect. Histopathologic evaluation of tissues from animals exposed to SY/SG was done at Experimental Pathology Laboratories, Inc., Herndon, VA, by Dr. Deborah Banas, Diplomate ACVP. The following is a summary of the findings. The complete histopathology report for this 90-day SY/SG exposure study can be found in Appendix II.

#### Ninety-Day Exposure

Inhalation of SY/SG dye mixture at  $100 \text{ mg/m}^3$  six hours/day, five days/week for 13 weeks resulted in changes in the lungs, nasal cavity, tracheobronchial lymph nodes, kidneys, and liver. In the lungs, slight to moderate accumulations of foamy appearing alveolar macrophages containing minimal to slight amounts of pigment were noted in the alveoli adjacent to the respiratory bronchioles in all high dose rats. These accumulations of alveolar macrophages were accompanied by slight to moderate hyperplasia of Type II cells (granular pneumocytes). In the nasal cavity, submucosal pigment deposition was noted at most levels of the nasal cavities of nearly all high dose rats. The pigment deposition was heaviest at Level III and Level IV. (Level I is the most anterior portion of the nasal cavity and Level IV is the most posterior. Level IV is mainly olfactory tissue.) In the tracheobronchial lymph node, hyperplasia of foamy macrophages (reticuloendothelial cells) with minimal pigment deposition and slight to moderately severe lymphoid hyperplasia were present. In the kidneys, an increase in granular pigment present in the cortical tubules was noted in all high dose rats. In the liver, minimal granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile ducts in all high dose rats.

In the rats exposed to SY/SG mixture at  $10 \text{ mg/m}^3$ , only lung, nasal cavity, tracheobronchial lymph node, liver, and kidneys were examined. Minimal lung lesions similar to those noted in the high dose rats occurred in three males and three females. The lesions were single lesions and tended to be at the margins of the lung lobes. In the nasal cavity, minimal submucosal pigment was noted at Level III in one male and four females, and at Level IV in two females. In tracheobronchial lymph nodes, hyperplasia of foamy macrophages with minimal pigment deposition was noted in two males and two females. Lymphoid hyperplasia was noted in an additional male. Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females.

In the rats exposed to SY/SG dye mixture at  $1 \text{ mg/m}^3$ , the lungs and nasal cavities from both sexes were examined. The livers from females were also examined. No compound-related histomorphologic alterations were noted in any of these tissues.

The pigments in the tissues of the exposed rats are similar to the pigments seen after exposure to SY dye alone.

#### Thirty-Day Recovery

Inhalation of SY/SG dye mixture at  $100 \text{ mg/m}^3$  for 90 days followed by a 30-day recovery period resulted in lung lesions similar to those noted after 90 days, but marginally less severe. Additionally, in the lungs, a few of the foamy macrophages containing pigment were present in the peribronchial lymphoid cuffs, a feature not present after 90 days exposure. In the nasal cavity, submucosal pigment deposition was present at most levels in nearly all high dose rats, but appeared to be slightly less severe than was noted after 90 days. In the tracheobronchial lymph nodes, hyperplasia of foamy



macrophages containing a minimal amount of pigment was slightly more severe than was noted after 90 days exposure. The extent of lymphoid hyperplasia was similar to that at the end of exposure. In the kidney tubules, the increased tubular pigment was less severe than was noted after 90 days. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after 90 days exposure.

In the rats exposed to SY/SG dye mixture at  $10 \text{ mg/m}^3$  for 90 days followed by a 30-day recovery period, only lung, nasal cavity, tracheobronchial lymph node, liver and kidneys were examined. Lesions similar to those noted at this level after 90 days exposure were present. Minimal lung lesions were noted in two rats of each sex and submucosal pigment deposition was noted in the nasal cavity of single rats of each sex at Level II, six males and five females at Level III, and two males and six females at Level IV. Lymphoid hyperplasia was present in the tracheobronchial lymph node of one male, but hyperplasia of foamy macrophages was not present in any of the lymph nodes examined. Pigment was noted in the kidneys and was comparable to that of the controls. Thus, this does not appear to be exposure related. No pigment deposition was noted in the liver.

No compound-related histomorphologic alterations were noted in the lungs and nasal cavities of rats exposed to  $1 \text{ mg/m}^3$  for 90 days followed by a 30-day recovery period.

Spontaneous disease lesions and incidental findings such as nonsuppurative myocarditis, testicular atrophy, prostatitis, and nematodiasis occurred in a few rats in both control and treated groups at both sacrifice intervals. These lesions were distributed with approximately equal frequency in test and control rats, and thus were not exposure related (see Appendix II).

SUMMARY OF THE 90-DAY REPEATED  
INHALATION EXPOSURE OF RATS TO DYE AEROSOLS

Male and female F344 rats were exposed by inhalation to  $1.0 \pm 0.2$ ,  $10.8 \pm 1.8$  or  $100 \pm 17 \text{ mg/m}^3$  (mean  $\pm$  SD) of SY dye aerosol for 6 hr/day, 5 days/wk for a period of 90 days. The average particle size of these aerosols ranged from 2.1 to 4.0  $\mu\text{m}$  (mass median aerodynamic diameter). Following exposures, lung concentrations of QI were measured, which indicated that very little SY dye was retained in lungs and thus the amount deposited had cleared at a very rapid rate. Exposed animals were also evaluated for changes in respiratory function, biochemical indications of lung tissue damage, changes in blood chemistries, and histopathological lesions. At the end of the exposure, both male and female rats exposed to the highest concentration of SY dye had slightly, but statistically significant lower body weights than control animals. These lower body weights of male rats exposed to the highest concentration of SY returned to control values during the 30-day recovery period, while those of female rats did not. Exposure-related histopathological lesions in rats exposed to the highest concentration of SY dye ( $100 \text{ mg/m}^3$ ) consisted of pigment deposition in the nasal cavity, liver, and kidney. In the lungs, accumulation of foamy alveolar macrophages containing minimal pigment was noted in one male. After a four-week recovery period, the amount of pigment deposited was slightly decreased. Minimal lung lesions were noted in two rats. Exposure of rats to  $10 \text{ mg/m}^3$  of SY dye did not result in lesions. Only pigment deposition in the nasal cavity was noted and to a much lesser degree than was noted at the high dose exposure. After a four-week recovery period, the pigment deposition in the nasal cavity was

still present. No compound-related histomorphological changes were seen in the tissues examined from rats exposed to  $1 \text{ mg/m}^3$  of SY dye. No other toxicologically significant effects were observed in exposed animals as compared to control rats. Therefore, the no-observable-adverse effects level for SY dye inhalation exposures was  $10 \text{ mg/m}^3$  for this particular exposure regime.

Male and female F344 rats were also exposed by inhalation to  $1.1 \pm 0.5$ ,  $10.2 \pm 3.1$  or  $101 \pm 23 \text{ mg/m}^3$  (mean  $\pm$  SD) of SY/SG dye aerosol for 6 hr/day, 5 days/wk for a period of 90 days. The average particle size of these aerosols ranged from 2.8 to  $4.2 \mu\text{m}$  (mass median aerodynamic diameter). After exposures, the SY portion of this dye mixture (QI) cleared from lungs at a rapid rate, but substantial amounts of the SG portion of this dye mixture (TA) remained in lungs for an extended period after the exposure. As in the 90-day exposure study to SY dye, rats exposed to the highest concentration of SY/SG dye mixture gained weight at a slower rate than the other experimental groups of animals. However, after the 30-day post-exposure period, only females returned to control body weight values. Analysis of bronchoalveolar lavage fluid indicated an inflammatory response only in the lungs of rats exposed to the highest concentration of SY/SG dye ( $100 \text{ mg/m}^3$ ), which was present after 6 weeks of exposure, did not worsen after 13 weeks of exposure, and was still present after the 30-day recovery period. Increased acid proteinase in the highest two exposure levels at the end of exposure suggested an inflammatory response. However, after 30-day post-exposure period, only the highest exposure level was still increased, suggesting a gradual reduction in severity over time. Exposure-related histopathological lesions in rats exposed to the highest concentration of SY/SG dye (100

mg/m<sup>3</sup>) consisted of accumulations of foamy alveolar macrophages containing minimal amounts of pigment in the lungs. These accumulations were accompanied by hyperplasia of Type II pneumocytes. Similarly, foamy macrophages with pigment had accumulated in the tracheobronchial lymph nodes. Pigment deposition was noted in the nasal cavity, liver, and kidney. After a 30-day recovery period, these lesions were decreased in severity with the exception of foamy macrophages in the tracheobronchial lymph nodes which were slightly increased. Exposure of rats to 10 mg/m<sup>3</sup> of SY/SG dye resulted in minimal lesions in the lungs and tracheobronchial lymph nodes of a few rats and pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a 30-day recovery period, these minimal lesions were essentially unchanged. No compound-related histomorphological changes were seen in the tissues examined from animals exposed to 1 mg/m<sup>3</sup> of SY/SG dye mixture. Therefore, the no-observable-adverse effects level for SY/SG dye inhalation exposures was 1 mg/m<sup>3</sup>.

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## GLOSSARY

Green component of yellow/green dye: green dye, solvent green, SG

Major compound in yellow dye: 2-(2'-quinoliny)-1,3-indandione, QI

Major compound in green dye: 1,4-di-p-toluidinoanthraquinone, TA

Stock yellow dye: yellow dye solvent yellow, SY

Stock yellow/green dye: yellow/green dye mix, SY/SG

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# APPENDIX I

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

LOVELACE PROJECT NUMBER RZ-79

13 WEEK AND 17 WEEK INHALATION STUDY ON  
SOLVENT YELLOW DYE

PATHOLOGY REPORT

Submitted to:

Lovelace Biomedical and Environmental  
Research Institute, Inc.  
Albuquerque, New Mexico 87185

February 17, 1986

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PATHOLOGY SUMMARY

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

## LOVELACE PROJECT NUMBER RZ-79

13 WEEK AND 17 WEEK INHALATION STUDY ON  
SOLVENT YELLOW DYE

## PATHOLOGY SUMMARY

A histopathologic evaluation of selected tissues from male and female rats exposed to Solvent Yellow Dye was conducted to provide information on the inhalation toxicity of dyes present in colored smoke munitions. The experimental design for this study was as follows:

| Group | Concentration                 | Number of Animals       |                           |                         |                           |
|-------|-------------------------------|-------------------------|---------------------------|-------------------------|---------------------------|
|       |                               | 13-Week Sacrifice Males | 13-Week Sacrifice Females | 17-Week Sacrifice Males | 17-Week Sacrifice Females |
| C     | Control                       | 10                      | 10                        | 10                      | 10                        |
| L     | Low Exposure Concentration    | 10                      | 10                        | 10                      | 10                        |
| M     | Medium Exposure Concentration | 10                      | 10                        | 10                      | 10                        |
| H     | High Exposure Concentration   | 10                      | 10                        | 10                      | 10                        |

According to protocol, routine hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related effect.

In general, the tissues called for to be examined by protocol are represented in the Histopathology Incidence Tables. Only a few tissues were inadvertently missed at the time of necropsy or lost during histologic processing. In some instances, the posterior portion of the nasal cavity had been damaged and complete sections of four levels of the nasal cavity could not be obtained.

Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. All lesions are summarized by treatment groups in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time the necropsies were performed.

## RESULTS

### 13-Week Sacrifice

Inhalation of Solvent Yellow Dye at the high exposure concentration for 13 weeks resulted in submucosal pigment deposition in the nasal cavity of all rats. The pigment deposition was heaviest at Level III and Level IV. In the kidneys, an increase in granular pigment located in the cortical tubules was noted in all high dose rats. In the male rats, there was also an increase in the incidence of lesions



-characteristic of early chronic nephropathy, namely foci of regenerative tubular epithelium, casts, and foci of mononuclear cells. However, these lesions are commonly noted in rats of this age and strain and were only minimal to slight in severity. In the liver, minimal to slight granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile duct in all high dose rats. In the lung, minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment were noted in the alveoli adjacent to the respiratory bronchioles in one male. This lesion was accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to Solvent Yellow Dye at the medium exposure concentration, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at Level III in three males and two females, and at Level IV in five males and seven females. Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females. No lesions attributable to treatment were noted in the sections of lung examined.

In the rats exposed to Solvent Yellow Dye at the low exposure concentration, the nasal cavity was examined from both sexes; the liver was also examined from the females. No compound-related histomorphologic alterations were noted in either of these tissues.

#### 17-Week Sacrifice

Inhalation of Solvent Yellow Dye at the high exposure concentration for 13 weeks followed by a four-week recovery period resulted

- in submucosal pigment deposition in the nasal cavity of all rats. This pigment deposition was heaviest at Level III and Level IV and was slightly less severe than was noted at the 13-week sacrifice. In the kidney tubules, increased tubular pigment was noted and appeared to be less severe than that noted at the 13-week sacrifice. The incidence of early chronic nephropathy was comparable to that of the controls. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after 13 weeks exposure. In the lungs, two males had minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment. These accumulations were accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to Solvent Yellow Dye at the medium exposure concentration for 13 weeks followed by a four week recovery period, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at Level III in two males and four females and at Level IV in six males and eight females. Slight submucosal pigment was noted at Level IV in an additional male. Pigment deposition in the kidneys was comparable to the controls. No lesions attributable to treatment were noted in the lung or liver.

In the rats exposed to Solvent Yellow Dye at the low exposure concentration, only the nasal cavity was examined. No compound-related histomorphological alterations were noted in these sections.

Spontaneous disease lesions and incidental findings occurred in rats in both control and treated groups at both sacrifice intervals.

- These lesions were distributed with approximately equal frequency in test and control rats.

### CONCLUSIONS

Exposure of rats to Solvent Yellow Dye at the high exposure concentration for 13 weeks resulted in pigment deposition in the nasal cavity, liver, and kidney. In the lungs, accumulation of foamy alveolar macrophages containing minimal pigment was noted in one male. After a four-week recovery period, the pigment deposition was slightly decreased in severity. Minimal lung lesions were noted in two rats.

Exposure of Solvent Yellow Dye at the medium exposure concentration for 13 weeks resulted in pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a four-week recovery period, the pigment deposition in the nasal cavity was still present.

Exposure of rats to Solvent Yellow Dye at the low exposure concentration did not result in any compound-related histomorphologic changes in the tissues examined.

*Deborah A. Banas*  
DEBORAH A. BANAS, D.V.M., M.S.  
Veterinary Pathologist

*February 17, 1986*

DAB/wk

SUMMARY INCIDENCE TABLES

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE  
REPORT CERTIFICATION

Client Name Lovelace Biomedical and Environ-  
mental Research Institute, Inc. Client Study No. RZ-79

Study Director Dr. Larry A. Ackerman Pathologist Dr. Deborah A. Banas

Study Title 13 Week and 17 Week Inhalation Study on Solvent Yellow Dye

Test Article Solvent Yellow Dye Species Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on April 23, 1985 through August 27, 1985. All findings were reported to the Study Director and Management.

Janet Milazzo

2/17/86

## SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

|                                      | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|--------------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL I                 |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                       | 1          |            |            |            |
| Hemorrhage                           | 2          | 2          | 5          | 2          |
| Submucosal Pigment Deposition        |            | 4          |            |            |
| Nonsuppurative Rhinitis              |            |            | 1          |            |
| Hyperplasia of Goblet Cells          |            |            | 1          |            |
| Suppurative Exudate                  |            |            |            | 1          |
| Inflammation of Nasolacrimal<br>Duct |            |            |            |            |
| NASAL CAVITY-LEVEL II                |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                       | 1          |            |            |            |
| Hemorrhage                           | 1          | 3          | 4          | 2          |
| Submucosal Pigment Deposition        |            | 10         |            |            |
| Inflammation of Nasolacrimal<br>Duct |            | 1          |            |            |
| Nonsuppurative Rhinitis              |            |            | 1          |            |
| Cystic Glands                        |            |            |            | 1          |
| NASAL CAVITY-LEVEL III               |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                           | 1          | 1          | 1          | 1          |
| Submucosal Pigment Deposition        |            | 10         |            | 3          |
| Nonsuppurative Rhinitis              |            |            | 1          |            |
| Cystic Glands                        |            |            | 1          |            |
| Inflammation of Nasolacrimal<br>Duct |            |            |            |            |

# SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

|                               | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|-------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL IV         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                | 1          |            |            |            |
| Hemorrhage                    | 1          |            | 1          |            |
| Submucosal Pigment Deposition |            | 10         |            | 5          |
| LIVER (NO. EXAMINED)          | (10)       | (10)       |            | (10)       |
| Foci of Mononuclear Cells     | 5          | 6          |            | 3          |
| Bile Duct Hyperplasia         |            | 1          |            | 1          |
| Pigment Deposition            |            | 10         |            |            |
| Infarction                    |            |            |            | 1          |
| KIDNEY (NO. EXAMINED)         | (10)       | (10)       |            | (10)       |
| Regenerative Tubular          |            |            |            |            |
| Epithelium                    | 3          | 8          |            | 5          |
| Casts                         | 5          | 9          |            | 7          |
| Pigment Deposition            | 10         | 10         |            | 10         |
| Foci of Mononuclear Cells     | 4          | 8          |            | 4          |
| Tubular Mineralization        |            |            |            |            |
| Cyst                          |            |            |            |            |
| LUNG (NO. EXAMINED)           | (10)       | (10)       |            | (10)       |
| Pigment Deposition            |            | 1          |            |            |
| Hyperplasia of Type II Cells  |            | 1          |            |            |
| Peribronchial Lymphoid        |            |            |            |            |
| Hyperplasia                   | 8          | 9          |            | 10         |
| Accumulations of Foamy        |            |            |            |            |
| Macrophages                   |            | 1          |            |            |

## SUMMARY INCIDENCE TABLE

R2-79  
13 Week Sacrifice  
Male Rats

|                                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|------------------------------------------------|------------|------------|------------|------------|
| BRAIN (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)                       | (10)       | (10)       |            |            |
| ADRENAL (NO. EXAMINED)                         | (10)       | (8)        |            |            |
| Vacuolated Cortical Cells                      | 1          |            |            |            |
| EYE (NO. EXAMINED)                             | (10)       | (10)       |            |            |
| Retinal Degeneration                           |            | 1          |            |            |
| THYROID (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| LARYNX (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      |            | 3          |            |            |
| TRACHEA (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      |            | 2          |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL<br>(NO. EXAMINED) | (10)       | (10)       |            |            |
| Lymphoid Hyperplasia                           | 1          |            |            |            |
| Hemorrhage                                     |            |            |            |            |
| Pigment Deposition                             |            |            |            |            |
| HEART (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis                     | 3          | 1          |            |            |
| Dilatation                                     |            | 1          |            |            |



# SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

|                                         | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|-----------------------------------------|------------|------------|------------|------------|
| SPLEEN (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| Focal Acinar Atrophy                    |            | 1          |            |            |
| LYMPH NODE, POPLITEAL<br>(NO. EXAMINED) | (10)       | (10)       |            |            |
| Pigment Deposition                      |            | 2          |            |            |
| Lymphoid Hyperplasia                    |            |            |            |            |
| Hemorrhage                              |            |            |            |            |
| STOMACH (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| DUODENUM (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| CECUM (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            | 2          | 1          |            |            |
| COLON (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            | 1          |            |            |            |
| SKIN (NO. EXAMINED)                     | (10)       | (10)       |            |            |
| TESTIS (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| EPIDIDYMIS (NO. EXAMINED)               | (10)       | (10)       |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |

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# SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

|                                      | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|--------------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL I                 |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                       |            |            |            |            |
| Hemorrhage                           | 1          |            | 1          | 3          |
| Submucosal Pigment Deposition        |            | 4          |            |            |
| Nonsuppurative Rhinitis              | 2          | 2          |            |            |
| Hyperplasia of Goblet Cells          |            | 1          |            |            |
| Suppurative Exudate                  |            |            |            |            |
| Inflammation of Nasolacrimal<br>Duct |            |            | 1          | 1          |
| NASAL CAVITY-LEVEL II                |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                       |            | 1          |            |            |
| Hemorrhage                           | 2          |            | 1          |            |
| Submucosal Pigment Deposition        |            | 10         |            |            |
| Inflammation of Nasolacrimal<br>Duct |            |            | 1          |            |
| Nonsuppurative Rhinitis              | 2          | 1          |            | 1          |
| Cystic Glands                        |            |            |            |            |
| NASAL CAVITY-LEVEL III               |            |            |            |            |
| (NO. EXAMINED)                       | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                           |            |            |            |            |
| Submucosal Pigment Deposition        |            | 10         |            | 2          |
| Nonsuppurative Rhinitis              |            |            |            | 1          |
| Cystic Glands                        |            |            |            |            |
| Inflammation of Nasolacrimal<br>Duct |            |            | 1          |            |

# SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

|                                       | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|---------------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL IV                 |            |            |            |            |
| (NO. EXAMINED)                        | (10)       | (10)       | (10)       | (10)       |
| Serous Exudate                        |            |            |            |            |
| Hemorrhage                            |            |            |            |            |
| Submucosal Pigment Deposition         |            | 10         |            | 7          |
| LIVER (NO. EXAMINED)                  | (10)       | (10)       | (10)       | (10)       |
| Foci of Mononuclear Cells             | 4          | 3          | 3          | 6          |
| Bile Duct Hyperplasia                 |            |            |            |            |
| Pigment Deposition                    |            | 10         |            | 2          |
| Infarction                            |            |            |            |            |
| KIDNEY (NO. EXAMINED)                 | (10)       | (10)       |            | (10)       |
| Regenerative Tubular<br>Epithelium    |            |            |            |            |
| Casts                                 | 1          |            |            | 1          |
| Pigment Deposition                    | 8          | 10         |            | 10         |
| Foci of Mononuclear Cells             | 2          | 2          |            | 2          |
| Tubular Mineralization                | 10         | 10         |            | 10         |
| Cyst                                  |            |            |            | 1          |
| LUNG (NO. EXAMINED)                   | (10)       | (10)       |            | (10)       |
| Pigment Deposition                    |            |            |            |            |
| Hyperplasia of Type II Cells          |            |            |            |            |
| Peribronchial Lymphoid<br>Hyperplasia | 10         | 9          |            | 9          |
| Accumulations of Foamy<br>Macrophages |            |            |            |            |

## SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

|                                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|------------------------------------------------|------------|------------|------------|------------|
| BRAIN (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)                       | (10)       | (10)       |            |            |
| ADRENAL (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Vacuolated Cortical Cells                      |            |            |            |            |
| EYE (NO. EXAMINED)                             | (10)       | (10)       |            |            |
| Retinal Degeneration                           |            |            |            |            |
| THYROID (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| LARYNX (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      |            | 1          |            |            |
| TRACHEA (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      |            | 1          |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL<br>(NO. EXAMINED) | (9)        | (8)        |            |            |
| Lymphoid Hyperplasia                           |            |            |            |            |
| Hemorrhage                                     | 3          | 3          |            |            |
| Pigment Deposition                             | 4          | 2          |            |            |
| HEART (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis                     | 2          | 1          |            |            |
| Dilatation                                     |            |            |            |            |

## SUMMARY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

|                                         | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|-----------------------------------------|------------|------------|------------|------------|
| SPLEEN (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| Focal Acinar Atrophy                    |            |            |            |            |
| LYMPH NODE, POPLITEAL<br>(NO. EXAMINED) | (8)        | (9)        |            |            |
| Pigment Deposition                      |            | 1          |            |            |
| Lymphoid Hyperplasia                    |            | 1          |            |            |
| Hemorrhage                              |            | 1          |            |            |
| STOMACH (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| DUODENUM (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| CECUM (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            |            |            |            |            |
| COLON (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            | 1          |            |            |            |
| SKIN (NO. EXAMINED)                     | (10)       | (10)       |            |            |
| UTERUS (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| Dilatation                              | 1          | 2          |            |            |
| OVARY (NO. EXAMINED)                    | (10)       | (10)       |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |



RZ-79  
13 Week Sacrifice  
Female Rats

[illegible]

HISTOPATHOLOGY INCIDENCE TABLES



| <u>GROUP</u> | <u>CONCENTRATION</u>          |
|--------------|-------------------------------|
| C            | Control                       |
| L            | Low Exposure Concentration    |
| M            | Medium Exposure Concentration |
| H            | High Exposure Concentration   |

# HISTOPATHOLOGY INCIDENCE TABLE

62-79  
3 Week Sacrifice  
Male Rats

Group C

|                                   | ANUM<br>BER | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-----------------------------------|-------------|---|---|---|---|---|---|---|---|---|
|                                   |             | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                   |             | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                                   |             | - | - | - | - | - | - | - | - | - |
|                                   |             | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |             | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| ASAL CAVITY-LEVEL I               |             | X | X | X | X | X | X |   | X | X |
| Serous Exudate                    |             |   |   |   |   |   | 1 |   |   |   |
| Hemorrhage                        |             |   |   |   |   |   | 1 |   | 3 |   |
| Submucosal Pigment Deposition     |             |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |             |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells       |             |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate               |             |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |             |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL II              |             | X | X | X | X | X | X |   | X | X |
| Serous Exudate                    |             |   |   |   |   |   | 1 |   |   |   |
| Hemorrhage                        |             |   |   |   |   |   |   |   | 3 |   |
| Submucosal Pigment Deposition     |             |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |             |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |             |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |             |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL III             |             | X | X | X | X | X | X | X | X | X |
| Hemorrhage                        |             |   |   |   |   |   |   |   | 2 |   |
| Submucosal Pigment Deposition     |             |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |             |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |             |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |             |   |   |   |   |   |   |   |   |   |

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EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group C

| A<br>N<br>I<br>M<br>A<br>L    | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-------------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                               |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                               |                            | - | - | - | - | - | - | - | - | - | - |
|                               |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL IV         |                            | X | X | X | X | X | X |   | X | X |   |
| Serous Exudate                |                            |   |   |   |   |   |   | 1 |   |   |   |
| Hemorrhage                    |                            |   |   |   |   |   |   |   |   | 2 |   |
| Submucosal Pigment Deposition |                            |   |   |   |   |   |   |   |   |   |   |
| LIVER                         |                            |   |   | X | X | X |   | X |   | X |   |
| Foci of Mononuclear Cells     |                            | 1 | 1 |   |   |   | 1 |   | 1 |   | 1 |
| Bile Duct Hyperplasia         |                            |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |   |   |   |   |   |   |   |   |   |   |
| Infarction                    |                            |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                        |                            |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular          |                            |   |   |   |   |   |   |   |   |   |   |
| Epithelium                    |                            | 1 |   |   |   |   |   | 1 | 1 |   |   |
| Casts                         |                            | 1 | 1 |   |   |   | 1 | 1 | 1 |   |   |
| Pigment Deposition            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
| Foci of Mononuclear Cells     |                            |   |   | 1 | 1 |   | 1 |   |   |   | 1 |
| Tubular Mineralization        |                            |   |   |   |   |   |   |   |   |   |   |
| Cyst                          |                            |   |   |   |   |   |   |   |   |   |   |
| LUNG                          |                            | X |   |   |   |   |   |   |   |   | X |
| Pigment Deposition            |                            |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells  |                            |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |                            |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   |                            |   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
| Accumulations of Foamy        |                            |   |   |   |   |   |   |   |   |   |   |
| Macrophages                   |                            |   |   |   |   |   |   |   |   |   |   |

11-2

EPL

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

A = Atypical X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group C

AN  
NU  
ME  
RA  
L

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                              |   |   |   |   |   |   |   |   |   |   |
|------------------------------|---|---|---|---|---|---|---|---|---|---|
| BRAIN                        | X | X | X | X | X | X | X | X | X | X |
| PITUITARY                    | X | X | X | X | X | X | X | X | X | X |
| ADRENAL                      | X | X | X | X | X | X | X | X | X |   |
| Vacuolated Cortical Cells    |   |   |   |   |   |   |   |   |   | 1 |
| EYE                          | X | X | X | X | X | X | X | X | X | X |
| Retinal Degeneration         |   |   |   |   |   |   |   |   |   |   |
| THYROID                      | X | X | X | X | X | X | X | X | X | X |
| LARYNX                       | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                      | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL | X |   | X | X | X | X | X | X | X | X |
| Lymphoid Hyperplasia         |   |   | 2 |   |   |   |   |   |   |   |
| Hemorrhage                   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition           |   |   |   |   |   |   |   |   |   |   |
| HEART                        |   | X |   |   | X | X | X | X | X | X |
| Nonsuppurative Myocarditis   | 2 |   | 2 | 1 |   |   |   |   |   |   |
| Dilatation                   |   |   |   |   |   |   |   |   |   |   |

11-3

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

5 = Severe

1 = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group C

AN  
NUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

SPLEEN

X X X X X X X X X X X

PANCREAS

X X X X X X X X X X X

Focal Acinar Atrophy

LYMPH NODE, POPLITEAL

X X X X X X X X X X X

Pigment Deposition

Lymphoid Hyperplasia

Hemorrhage

STOMACH

X X X X X X X X X X X

DUODENUM

X X X X X X X X X X X

CECUM

X X X X X X X X X X

Nematodiasis

P P

COLON

X X X X X X X X X X

Nematodiasis

P

SKIN

X X X X X X X X X X X

TESTIS

X X X X X X X X X X X

11-4

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe/High

**250**



2.



5

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group H

|                                   | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-----------------------------------|---|---|---|---|---|---|---|---|---|---|
| A                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| N                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| I                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| M                                 | - | - | - | - | - | - | - | - | - | - |
| B                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| E                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| R                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I              | X |   |   | X |   |   |   |   | X | X |
| Serous Exudate                    |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |   |   | 3 |   | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition     |   | 2 |   |   |   | 1 | 1 | 1 |   |   |
| Nonsuppurative Rhinitis           |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells       |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate               |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II             |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |   | 1 | 2 |   | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition     | 3 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 2 |
| Inflammation of Nasolacrimal Duct |   |   |   |   |   |   | 2 |   |   |   |
| Nonsuppurative Rhinitis           |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |   |   |   |   |   | 1 |   |   |   |   |
| Submucosal Pigment Deposition     | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 2 |
| Nonsuppurative Rhinitis           |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |   |   |   |   |   |   |   |   |   |   |

11-6

EPL

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderate to Severe High  
5 = Severe High 1 = Incomplete Section

A = Analysis X = Not Examined  
3 = Moderate 4 = Moderate to Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

82-79  
13 Week Sacrifice  
Male Rats

Group H

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

## BLASAL CAVITY-LEVEL IV

Serous Exudate

Hemorrhage

Submucosal Pigment Deposition

3 3 3 3 3 4 3 3 3 3

## LIVER

Foci of Mononuclear Cells

1 1 1 2 1 1

Bile Duct Hyperplasia

2

Pigment Deposition

1 1 1 1 1 1 1 1 1 1

Infarction

## KIDNEY

Regenerative Tubular

Epithelium

2 2 1 1 2 2 1 1

Casts

1 2 2 1 1 2 2 2 1

Pigment Deposition

3 3 3 3 3 3 3 3 3 3

Foci of Mononuclear Cells

1 1 1 1 1 1 1 1 1

Tubular Mineralization

Cyst

## LUNG

X

Pigment Deposition

1

Hyperplasia of Type II Cells

1

Peribronchial Lymphoid

Hyperplasia

1 1 1 1 1 1 1 1 1

Accumulations of Foamy

Macrophages

1

II-7

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

5 = Severe

High 1 = Incomplete Section



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group H

|                              | A<br>N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                              |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                              |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                              |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                              |                                 | - | - | - | - | - | - | - | - | - | - |
|                              |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                              |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                              |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| BRAIN                        |                                 | X | X | X | X | X | X | X | X | X | X |
| PITUITARY                    |                                 | X | X | X | X | X | X | X | X | X | X |
| ADRENAL                      |                                 | X | X | X | X | N | X | X | X | X | N |
| Vacuolated Cortical Cells    |                                 |   |   |   |   |   |   |   |   |   |   |
| EYE                          |                                 | X | X | X | X | X | X |   | X | X | X |
| Retinal Degeneration         |                                 |   |   |   |   |   |   | 3 |   |   |   |
| THYROID                      |                                 | X | X | X | X | X | X | X | X | X | X |
| LARYNX                       |                                 | X |   | X | X |   | X | X |   | X | X |
| Foci of Mononuclear Cells    |                                 | 1 |   |   | 1 |   |   | 1 |   |   |   |
| TRACHEA                      |                                 |   |   | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |                                 | 1 | 1 |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL |                                 | X | X | X | X | X | X | X | X | X | X |
| Lymphoid Hyperplasia         |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                   |                                 |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition           |                                 |   |   |   |   |   |   |   |   |   |   |
| HEART                        |                                 | X | X |   | X | X | X | X | X |   | X |
| Nonsuppurative Myocarditis   |                                 |   |   |   |   |   |   |   |   | 1 |   |
| Dilatation                   |                                 |   |   | 3 |   |   |   |   |   |   |   |

11-8

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 = Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group H

|                       | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-----------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
|                       |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                       |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                       |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                       |                            |                            | - | - | - | - | - | - | - | - | - | - | - | - |
|                       |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                       |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                       |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |   |   |
| SPLEEN                |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| PANCREAS              |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| Focal Acinar Atrophy  |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, POPLITEAL |                            |                            | X | X |   |   | X | X | X | X | X | X | X | X |
| Pigment Deposition    |                            |                            |   |   |   |   | 1 | 1 |   |   |   |   |   |   |
| Lymphoid Hyperplasia  |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage            |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| STOMACH               |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| DUODENUM              |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| CECUM                 |                            |                            | X |   | X | X | X | X | X | X | X | X | X | X |
| Nematodiasis          |                            |                            |   |   |   |   | P |   |   |   |   |   |   |   |
| COLON                 |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| Nematodiasis          |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| SKIN                  |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| TESTIS                |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |

11-9

EPL

Experimental Pathology Laboratories, Inc

Key

P - Present

1 - Minimal

5 - Severe High

N - No Section

2 - Slight

1 - Incomplete Section

A - Autolysis

3 - Moderate

X - Not Remarkable

4 - Moderately Severe High

**Group H**

AN  
NUM  
BER

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group L

|                                   | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|-----------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |   |
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |   |
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |   |
|                                   |                                 | - | - | - | - | - | - | - | - | - |   |
|                                   |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
|                                   |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|                                   |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I              |                                 |   |   |   | X |   | X | X | X | X |   |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 | 1 | 1 | 4 |   | 1 |   |   |   | 1 |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   |   |   | 2 |   |
| Hyperplasia of Goblet Cells       |                                 |   |   | 1 |   |   |   |   |   |   |   |
| Suppurative Exudate               |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |
|                                   |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II             |                                 |   |   |   | X |   | X |   | X | X | X |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 | 1 | 2 | 3 |   | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   | 1 |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   |   |   |   |   |
|                                   |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                                 | X | X |   | X | X | X |   | X | X | X |
| Hemorrhage                        |                                 |   |   | 2 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   | 1 |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   | 1 |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |

II-11

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe high I = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

## HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Male Rats

Group L

[illegible]

11-12

EPL

Experimental Pathology Laboratories, Inc.

Key    P = Present            N = No Section  
         1 = Minor            2 = Slight  
         5 = Severe High    1 = Incomplete Section

A - Asymptomatic      3 - Moderate  
 3 - Moderate      4 - Moderate, Severe

# HISTOPATHOLOGY INCIDENCE TABLE

79-79  
3 Week Sacrifice  
Male Rats

Group M

|                                   | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | - | - | - | - | - | - | - | - | - |
|                                   |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|                                   |                            |                            |   |   |   |   |   |   |   |   | 9 |
| ASAL CAVITY-LEVEL I               |                            |                            | X | X | X | X |   | X |   | X | X |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   | 2 |   | 2 |   |   |   |
| Submucosal Pigment Deposition     |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells       |                            |                            |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate               |                            |                            |   |   |   |   |   |   |   | 1 |   |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II             |                            |                            | X | X |   | X | X | X |   | X | X |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   | 1 |   |   | 1 |   |   |   |
| Submucosal Pigment Deposition     |                            |                            |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                            |                            |   |   | 1 |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                            |                            | X |   |   | X | X |   | X | X | X |
| Hemorrhage                        |                            |                            |   |   |   |   |   | 1 |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 1 | 1 |   |   | 1 |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                            |                            |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |

II-13

EPL

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
5 - Severe High 1 - Incomplete Section

A - Autolysis X - Not Remarkable  
3 - Moderate 4 - Moderately Severe High

| <u>GROUP</u> | <u>CONCENTRATION</u>          |
|--------------|-------------------------------|
| C            | Control                       |
| L            | Low Exposure Concentration    |
| M            | Medium Exposure Concentration |
| H            | High Exposure Concentration   |

# HISTOPATHOLOGY INCIDENCE TABLE

PZ-79  
3 Week Sacrifice  
Male Rats

Group M

| ANIMAL NUMBER | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |  |
|---------------|---|---|---|---|---|---|---|---|---|---|--|
|               | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
|               | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
|               | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
|               | - | - | - | - | - | - | - | - | - | - |  |
|               | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |
|               | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |  |
|               | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |  |
|               |   | X |   |   | X | X |   | X | X |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
| on            |   | 1 | 1 |   | 1 |   |   | 1 | 1 |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               | X | X |   |   | X |   | X |   | X | X |  |
|               |   |   | 1 | 1 |   | 1 |   |   |   |   |  |
|               |   |   | 1 |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   | P |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |
|               |   |   |   |   |   |   |   |   |   |   |  |

II-14

EPL

Experimental Pathology Laboratories, Inc.

Key

0 = 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

RZ-79  
13 Week Sacrifice  
Female Rats

Group C

|                                   | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|-----------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |   |
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |   |
|                                   |                                 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |   |
|                                   |                                 | - | - | - | - | - | - | - | - | - |   |
|                                   |                                 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |   |
|                                   |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|                                   |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I              |                                 | X |   | X | X |   | X | X | X |   | X |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 |   |   |   |   |   |   |   | 2 |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   | 1 |   |   | 1 |   |   |   |   |   |
| Hyperplasia of Goblet Cells       |                                 |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate               |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |
|                                   |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II             |                                 | X |   |   | X | X | X | X | X |   | X |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 |   |   | 1 |   |   |   |   | 2 |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   | 2 | 1 |   |   |   |   |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   |   |   |   |   |
|                                   |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                                 | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                        |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   |   |   |

II-15

EPL

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
5 - Severe High 1 - Incomplete Section

A - Autolysis X - Not Remarkable  
3 - Moderate 4 - Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

42-79  
13 Week Sacrifice  
Female Rats

Group C

|                               | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
|                               |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                               |                            |                            | - | - | - | - | - | - | - | - | - | - | - | - |
|                               |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                               |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |   |   |
| NASAL CAVITY-LEVEL IV         |                            |                            | X | X | X | X | X | X | X | X | X | X | X | X |
| Serous Exudate                |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| LIVER                         |                            |                            |   | X |   |   | X | X | X | X | X |   |   |   |
| Foci of Mononuclear Cells     |                            |                            | 1 |   | 1 | 1 |   |   |   |   |   |   | 1 |   |
| Bile Duct Hyperplasia         |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Infarction                    |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                        |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular          |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Epithelium                    |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Casts                         |                            |                            |   |   |   |   | 1 |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 |   |   | 1 | 1 |   |   |
| Foci of Mononuclear Cells     |                            |                            |   |   |   | 1 |   | 1 |   |   |   |   |   |   |
| Tubular Mineralization        |                            |                            | 3 | 2 | 3 | 2 | 3 | 3 | 3 | 2 | 3 | 2 |   |   |
| Cyst                          |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| LUNG                          |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells  |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Accumulations of Foamy        |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Macrophages                   |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |

11-16

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe-High 1 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe-High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group C

ANIMAL

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| - | - | - | - | - | - | - | - | - | - |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                              |   |   |   |   |   |   |   |   |   |   |
|------------------------------|---|---|---|---|---|---|---|---|---|---|
| BRAIN                        | X | X | X | X | X | X | X | X | X | X |
| PITUITARY                    | X | X | X | X | X | X | X | X | X | X |
| ADRENAL                      | X | X | X | X | X | X | X | X | X | X |
| Vacuolated Cortical Cells    |   |   |   |   |   |   |   |   |   |   |
| EYE                          | X | X | X | X | X | X | X | X | X | X |
| Retinal Degeneration         |   |   |   |   |   |   |   |   |   |   |
| THYROID                      | X | X | X | X | X | X | X | X | X | X |
| LARYNX                       | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                      | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL |   |   |   | N | X | X |   |   |   | X |
| Lymphoid Hyperplasia         |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                   | 1 |   | 1 |   |   |   | 1 |   |   |   |
| Pigment Deposition           |   | 1 |   |   |   |   | 1 | 1 | 1 |   |
| HEART                        | X | X | X |   | X |   | X | X | X | X |
| Nonsuppurative Myocarditis   |   |   |   | 1 |   | 1 |   |   |   |   |
| Dilatation                   |   |   |   |   |   |   |   |   |   |   |

11-17

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

7-79  
3 Week Sacrifice  
Female Rats

Group C

|                       | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-----------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                       |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                       |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                       |                            |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                       |                            |                            | - | - | - | - | - | - | - | - | - |
|                       |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                       |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                       |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| PLEEN                 |                            |                            | X | X | X | X | X | X | X | X | X |
| PANCREAS              |                            |                            | X | X | X | X | X | X | X | X | X |
| Focal Acinar Atrophy  |                            |                            |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, POPLITEAL |                            |                            | N | X | X | X | X | X | N | X | X |
| Pigment Deposition    |                            |                            |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia  |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage            |                            |                            |   |   |   |   |   |   |   |   |   |
| STOMACH               |                            |                            | X | X | X | X | X | X | X | X | X |
| DUODENUM              |                            |                            | X | X | X | X | X | X | X | X | X |
| CECUM                 |                            |                            | X | X | X | X | X | X | X | X | X |
| Nematodiasis          |                            |                            |   |   |   |   |   |   |   |   |   |
| COLON                 |                            |                            | X | X | X |   | X | X | X | X | X |
| Nematodiasis          |                            |                            |   |   |   | P |   |   |   |   |   |
| SKIN                  |                            |                            | X | X | X | X | X | X | X | X | X |
| UTERUS                |                            |                            | X | X |   | X | X | X | X | X | X |
| Dilatation            |                            |                            |   |   | 3 |   |   |   |   |   |   |

11-18

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe High  
5 = Severe High I = Incomplete Section

A = Autolysis X = Not Examined  
3 = Moderate 4 = Moderately Severe High



### Group C

[illegible]

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group H

|                                   | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |                            |                            | - | - | - | - | - | - | - | - | - |
|                                   |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL I              |                            |                            | X |   |   | X | X |   |   | X | X |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 1 |   | 1 |   |   | 2 | 1 |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   | 1 |   |   | 3 |   |   |   |
| Hyperplasia of Goblet Cells       |                            |                            |   |   |   |   |   | 3 |   |   |   |
| Suppurative Exudate               |                            |                            |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II             |                            |                            |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   | 1 |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   | 2 |   |   |   |
| Cystic Glands                     |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                            |                            |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                            |                            |   |   |   |   |   |   |   |   |   |

11-20

EPL

Experimental Pathology Laboratories, Inc

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

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group H

|                               | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                               |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                            |                            | - | - | - | - | - | - | - | - | - |
|                               |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                               |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         |                            |                            |   |   |   |   |   |   |   |   |   |
| Serous Exudate                |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            | 3 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
| LIVER                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells     |                            |                            | 1 | 1 |   |   |   |   |   | 1 |   |
| Bile Duct Hyperplasia         |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |                            | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 |
| Infarction                    |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
| KIDNEY                        |                            |                            |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular          |                            |                            |   |   |   |   |   |   |   |   |   |
| Epithelium                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Casts                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Foci of Mononuclear Cells     |                            |                            |   |   | 1 |   | 1 |   |   |   |   |
| Tubular Mineralization        |                            |                            | 2 | 3 | 1 | 2 | 2 | 3 | 2 | 3 | 2 |
| Cyst                          |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
| LUNG                          |                            |                            |   |   |   |   |   | X |   |   |   |
| Pigment Deposition            |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells  |                            |                            |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   |                            |                            | 1 | 1 | 1 | 1 | 1 |   | 1 | 1 | 1 |
| Accumulations of Foamy        |                            |                            |   |   |   |   |   |   |   |   |   |
| Macrophages                   |                            |                            |   |   |   |   |   |   |   |   |   |

11-21

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

22-79  
13 Week Sacrifice  
Female Rats

Group H

|                              | A<br>N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|
|                              |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                              |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                              |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                              |                                 | - | - | - | - | - | - | - | - | - |
|                              |                                 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                              |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                              |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| BRAIN                        |                                 | X | X | X | X | X | X | X | X | X |
| PITUITARY                    |                                 | X | X | X | X | X | X | X | X | X |
| ADRENAL                      |                                 | X | X | X | X | X | X | X | X | X |
| Vacuolated Cortical Cells    |                                 |   |   |   |   |   |   |   |   |   |
| EYE                          |                                 | X | X | X | X | X | X | X | X | X |
| Retinal Degeneration         |                                 |   |   |   |   |   |   |   |   |   |
| THYROID                      |                                 | X | X | X | X | X | X | X | X | X |
| ARYNX                        |                                 | X | X |   | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |                                 |   |   | 1 |   |   |   |   |   |   |
| TRACHEA                      |                                 | X |   | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |                                 |   | 1 |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL |                                 | X | N |   | N |   | X |   | X | X |
| Lymphoid Hyperplasia         |                                 |   |   |   |   |   |   |   |   |   |
| Hemorrhage                   |                                 |   |   | 1 |   | 1 |   | 1 |   |   |
| Pigment Deposition           |                                 |   |   |   |   | 1 |   | 1 |   |   |
| HEART                        |                                 | X | X | X |   | X | X | X | X | X |
| Nonsuppurative Myocarditis   |                                 |   |   | 1 |   |   |   |   |   |   |
| Dilatation                   |                                 |   |   |   |   |   |   |   |   |   |

11-22

EPL

Experimental Pathology Laboratories, Inc.

Key  
+ = Present  
1 = Minimal  
5 = Severe/High  
N = No Section  
2 = Slight  
I = Incomplete Section

A = Autolysis  
3 = Moderate  
X = Not Representative  
4 = Moderately Severe/High



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group H

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                       |   |   |   |   |   |   |   |   |   |   |
|-----------------------|---|---|---|---|---|---|---|---|---|---|
| SPLEEN                | X | X | X | X | X | X | X | X | X | X |
| PANCREAS              | X | X | X | X | X | X | X | X | X | X |
| Focal Acinar Atrophy  |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, POPLITEAL |   |   | X | X | X | X | X | X | N | X |
| Pigment Deposition    | 1 |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia  | 2 |   |   |   |   |   |   |   |   |   |
| Hemorrhage            | 1 |   |   |   |   |   |   |   |   |   |
| STOMACH               | X | X | X | X | X | X | X | X | X | X |
| DUODENUM              | X | X | X | X | X | X | X | X | X | X |
| CECUM                 | X | X | X | X | X | X | X | X | X | X |
| Nematodiasis          |   |   |   |   |   |   |   |   |   |   |
| COLON                 | X | X | X | X | X | X | X | X | X | X |
| Nematodiasis          |   |   |   |   |   |   |   |   |   |   |
| SKIN                  | X | X | X | X | X | X | X | X | X | X |
| UTERUS                | X | X | X | X | X | X | X |   | X |   |
| Dilatation            |   |   |   |   |   |   |   | 2 |   | 3 |

11-23

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe/High

15

# I

5

1

3

五

11

1

1

•

五

Key    P = Present            N = No Section  
         1 = Minimal        2 = Significant  
         5 = Severe/High    I = Incomplete Section

A - Auto, 1  
3 - Manual  
2 - 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838,

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group L

|                                   | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-----------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                   |                                 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                   |                                 | - | - | - | - | - | - | - | - | - | - |
|                                   |                                 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                                   |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I              |                                 | X | X |   | X | X | X | X | X | X | X |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 |   |   | 1 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells       |                                 |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate               |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   | 1 |   |
| NASAL CAVITY-LEVEL II             |                                 | X | X |   | X | X | X | X | X | X | X |
| Serous Exudate                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                 |   |   | 1 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   | 2 |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                                 | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                        |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                 |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct |                                 |   |   |   |   |   |   |   |   | 2 |   |

11-25

EPL

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group L

ANNUAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| - | - | - | - | - | - | - | - | - | - |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

NASAL CAVITY-LEVEL IV

X X X X X X X X X X

Serous Exudate

Hemorrhage

Submucosal Pigment Deposition

LIVER

X X X X X X X

Foci of Mononuclear Cells

1 1 1

Bile Duct Hyperplasia

Pigment Deposition

Infarction

11-26

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 1 = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

R2-79  
13 Week Sacrifice  
Female Rats

Group M

|                               | A<br>N<br>I<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|-------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                               |                                 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                 | - | - | - | - | - | - | - | - | - | - |
|                               |                                 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                               |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I          |                                 | X | X |   | X | X |   |   | X |   | X |
| Serous Exudate                |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 |   |   | 1 |   |   |   | 1 |   | 2 |   |
| Submucosal Pigment Deposition |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                 |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells   |                                 |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |                                 |   |   |   |   |   |   |   |   |   |   |
| Duct                          |                                 |   |   |   |   |   | 1 |   |   |   |   |
| NASAL CAVITY-LEVEL II         |                                 | X | X | X | X | X |   | X | X | X | X |
| Serous Exudate                |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |                                 |   |   |   |   |   |   |   |   |   |   |
| Duct                          |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                 |   |   |   |   |   | 1 |   |   |   |   |
| Cystic Glands                 |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |                                 | X |   | X |   | X |   | X | X | X | X |
| Hemorrhage                    |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                 |   | 1 |   | 1 |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                 |   |   |   |   |   | 2 |   |   |   |   |
| Cystic Glands                 |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |                                 |   |   |   |   |   |   |   |   |   |   |
| Duct                          |                                 |   |   |   |   |   |   |   |   |   |   |

II-27

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Minimal

5 = Severe High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
13 Week Sacrifice  
Female Rats

Group M

|                                    | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|------------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
|                                    |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |                            |                            | - | - | - | - | - | - | - | - | - | - | - | - |
|                                    |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                                    |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |   |   |
| NASAL CAVITY-LEVEL IV              |                            |                            | I |   |   |   |   | X |   |   | I |   |   |   |
| Serous Exudate                     |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                            |                            | 1 |   | 1 | 1 | 1 | 1 |   | 1 |   | 1 |   |   |
| LIVER                              |                            |                            |   |   | X |   | X |   |   |   |   | X |   |   |
| Foci of Mononuclear Cells          |                            |                            | 1 | 1 |   | 1 |   | 1 |   | 1 | 1 |   |   |   |
| Bile Duct Hyperplasia              |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   | 1 | 1 |   |   |   |   |   |
| Infarction                         |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                             |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular Epithelium    |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Casts                              |                            |                            |   |   |   |   |   | 1 |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Foci of Mononuclear Cells          |                            |                            |   |   |   |   |   |   |   |   | 2 | 1 |   |   |
| Tubular Mineralization             |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |   |   |
| Cyst                               |                            |                            |   |   |   |   |   |   |   |   | P |   |   |   |
| LUNG                               |                            |                            |   |   | X |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                            |                            | 1 | 1 |   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Accumulations of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |   |   |   |   |   |

11-28

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

### 13 Week Sacrifice

Control

[illegible]



RZ-79  
13 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level: High Exposure

Species Rats Sex Males

Group Number H - Sacrificed

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations                                                             |
|---------------|--------------------------------|-----------------------------|--------------------------------------------------------------------------------------|
| 4001-130      | Skin                           | Yellow                      | No corresponding lesion                                                              |
|               | Popliteal lymph node           | Reddened, moderate          | No corresponding lesion                                                              |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion                                                              |
| 4001-131      | Popliteal lymph node           | Right, pink color           | No corresponding lesion                                                              |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion                                                              |
| 4001-132      | Skin                           | Yellow                      | No corresponding lesion                                                              |
|               | Popliteal lymph node           | Moderate dark gray          | Pigment deposition                                                                   |
|               | Lung                           | Pigment yellow minimal      | No corresponding lesion                                                              |
|               | Heart                          | Rounded and enlarged        | Dilatation                                                                           |
| 4001-133      | Skin                           | Yellow                      | No corresponding lesion                                                              |
|               | Popliteal lymph node           | Moderate dark gray          | Pigment deposition                                                                   |
|               | Lung                           | Pigment yellow minimum      | No corresponding lesion                                                              |
| 4001-134      | Skin                           | Yellow                      | No corresponding lesion                                                              |
|               | Popliteal lymph node           | Gray, mild                  | No corresponding lesion                                                              |
|               | Lung                           | Minimal yellow              | Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells |
| 4001-135      | Skin                           | Yellow                      | No corresponding lesion                                                              |

RZ-79  
13 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rats      Sex: Males      Group Number: H - Sacrificed      Dosage Level: High Exposure

| Animal Number        | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|----------------------|--------------------------------|-----------------------------|--------------------------|
| 4001-135<br>(Cont'd) | Popliteal lymph node           | Gray                        | No corresponding lesion  |
|                      | Lung                           | Pigment, yellow, minimal    | No corresponding lesion  |
| 4001-136             | Skin                           | Yellow                      | No corresponding lesion  |
|                      | Lung                           | Pigment, yellow, minimal    | No corresponding lesion  |
| 4001-137             | Skin                           | Yellow                      | No corresponding lesion  |
|                      | Lung                           | Pigment, yellow, minimal    | No corresponding lesion  |
| 4001-138             | Skin                           | Yellow                      | No corresponding lesion  |
|                      | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-139             | Skin                           | Yellow                      | No corresponding lesion  |
|                      | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
|                      |                                |                             |                          |
|                      |                                |                             |                          |
|                      |                                |                             |                          |
|                      |                                |                             |                          |
|                      |                                |                             |                          |
|                      |                                |                             |                          |
|                      |                                |                             |                          |



## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number: C - Sacrificed

**Species:**

[illegible]

**RZ-79**  
**13 Week Sacrifice**

**CORRELATION OF GROSS AND MICROSCOPIC FINDINGS**

Species: **Rats**      Sex: **Females**      Group Number: **H - Sacrificed**      Dosage Level: **High Exposure**

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations |
|---------------|--------------------------------|-----------------------------|--------------------------|
| 4001-630      | Skin                           | Yellow                      | No corresponding lesion  |
|               | Popliteal lymph node           | Left red, right gray        | Lymphoid hyperplasia     |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-631      | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-632      | Skin                           | Yellow                      | No corresponding lesion  |
|               | Tracheobronchial lymph node    | Reddened                    | Hemorrhage               |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-633      | Popliteal lymph node           | Gray                        | No corresponding lesion  |
| 4001-634      | Skin                           | Yellow                      | No corresponding lesion  |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-635      | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-636      | Skin                           | Yellow                      | No corresponding lesion  |
|               | Tracheobronchial lymph node    | Reddened                    | Hemorrhage               |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-637      | Lung                           | Minimal yellow pigment      | No corresponding lesion  |
| 4001-638      | Skin                           | Yellow                      | No corresponding lesion  |
|               | Lung                           | Minimal yellow pigment      | No corresponding lesion  |

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

### High Exposure:

[illegible]

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

### Medium Exposure

**Dosage Level:**

## M - Sacrificed

**Group Number**

## Females

**Sex:**

## Rats

[illegible]

SUMMARY INCIDENCE TABLES



## SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

|                               | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|-------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL I          |            |            |            |            |
| (NO. EXAMINED)                | (9)        | (10)       | (10)       | (10)       |
| Hemorrhage                    | 3          | 5          | 1          | 1          |
| Submucosal Pigment Deposition |            | 1          |            |            |
| Nonsuppurative Rhinitis       |            | 1          |            | 1          |
| Hyperplasia of Goblet Cells   |            | 1          |            | 2          |
| Cystic Glands                 |            |            |            | 2          |
| NASAL CAVITY-LEVEL II         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 3          | 2          |            | 2          |
| Submucosal Pigment Deposition |            | 10         |            |            |
| Nonsuppurative Rhinitis       |            | 1          |            | 2          |
| Foreign Body                  |            |            |            |            |
| NASAL CAVITY-LEVEL III        |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 1          | 2          | 1          |            |
| Submucosal Pigment Deposition |            | 10         |            | 2          |
| Nonsuppurative Rhinitis       |            | 1          |            |            |
| NASAL CAVITY-LEVEL IV         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Submucosal Pigment Deposition |            | 10         |            | 7          |
| Hemorrhage                    |            | 3          |            |            |
| Suppurative Exudate           |            | 1          |            |            |
|                               |            |            |            |            |
|                               |            |            |            |            |
|                               |            |            |            |            |
|                               |            |            |            |            |

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Experimental Pathology Laboratories, Inc.

## SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

|                                       | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|---------------------------------------|------------|------------|------------|------------|
| LIVER (NO. EXAMINED)                  | (10)       | (10)       |            | (10)       |
| Foci of Mononuclear Cells             | 2          | 8          |            | 2          |
| Pigment Deposition                    |            | 10         |            |            |
| Bile Duct Hyperplasia                 |            |            |            |            |
| KIDNEY (NO. EXAMINED)                 | (10)       | (10)       |            | (10)       |
| Pigment Deposition                    | 10         | 10         |            | 10         |
| Regenerative Tubular<br>Epithelium    | 9          | 10         |            | 7          |
| Casts                                 | 7          | 10         |            | 9          |
| Foci of Mononuclear Cells             | 4          | 8          |            | 6          |
| Cyst                                  |            | 1          |            |            |
| Tubular Mineralization                |            |            |            |            |
| LUNG (NO. EXAMINED)                   | (10)       | (10)       |            | (10)       |
| Hemorrhage                            |            | 2          |            |            |
| Pigment Deposition                    |            | 2          |            |            |
| Hyperplasia of Type II Cells          |            | 2          |            |            |
| Accumulations of Foamy<br>Macrophages |            | 2          |            |            |
| Peribronchial Lymphoid<br>Hyperplasia | 10         | 10         |            | 9          |
| BRAIN (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)              | (10)       | (10)       |            |            |
| Cyst                                  |            | 1          |            |            |

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EPL

Experimental Pathology Laboratories, Inc.

# SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

|                                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|------------------------------------------------|------------|------------|------------|------------|
| ADRENAL (NO. EXAMINED)                         | (10)       | (9)        |            |            |
| Vacuolated Cortical Cells                      | 5          | 3          |            |            |
| Hemorrhage                                     |            |            |            |            |
| EYE (NO. EXAMINED)                             | (10)       | (10)       |            |            |
| THYROID (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| LARYNX (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| Hemorrhage                                     | 1          |            |            |            |
| Foci of Mononuclear Cells                      |            |            |            |            |
| TRACHEA (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      |            |            |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL<br>(NO. EXAMINED) | (9)        | (9)        |            |            |
| Hemorrhage                                     | 1          |            |            |            |
| Pigment Deposition                             | 2          |            |            |            |
| HEART (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis                     | 5          | 6          |            |            |
| SPLEEN (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                        | (10)       | (10)       |            |            |
|                                                |            |            |            |            |
|                                                |            |            |            |            |
|                                                |            |            |            |            |

## SUMMARY INCIDENCE TABLE

12-79

17 Week Sacrifice

Male Rats

|                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|--------------------------------|------------|------------|------------|------------|
| LYMPH NODE, POPLITEAL          |            |            |            |            |
| NO. EXAMINED)                  | (10)       | (10)       |            |            |
| Hemorrhage                     | 1          |            |            |            |
| Pigment Deposition             | 1          |            |            |            |
| Lymphoid Hyperplasia           |            |            |            |            |
| STOMACH (NO. EXAMINED)         | (10)       | (10)       |            |            |
| DUODENUM (NO. EXAMINED)        | (10)       | (10)       |            |            |
| CECUM (NO. EXAMINED)           | (10)       | (10)       |            |            |
| Nematodiasis                   | 1          | 1          |            |            |
| Hemorrhage                     |            | 1          |            |            |
| COLON (NO. EXAMINED)           | (10)       | (10)       |            |            |
| Nematodiasis                   | 3          |            |            |            |
| Hemorrhage                     |            | 1          |            |            |
| SKIN (NO. EXAMINED)            | (10)       | (10)       |            |            |
| TESTIS (NO. EXAMINED)          | (10)       | (10)       |            |            |
| EPIDIDYMIS (NO. EXAMINED)      | (10)       | (10)       |            |            |
| PROSTATE (NO. EXAMINED)        | (10)       | (10)       |            |            |
| URINARY BLADDER (NO. EXAMINED) | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells      |            |            |            |            |

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[illegible]

RZ-79  
17 Week Sacrifice  
Male Rats

[illegible]

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## SUMMARY INCIDENCE TABLE

92-79

17 Week Sacrifice

Female Rats

|                               | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|-------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL I          |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 4          | 1          |            |            |
| Submucosal Pigment Deposition |            | 2          |            |            |
| Nonsuppurative Rhinitis       |            |            |            | 1          |
| Hyperplasia of Goblet Cells   | 1          |            | 1          | 1          |
| Cystic Glands                 |            |            |            |            |
| NASAL CAVITY-LEVEL II         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 3          | 1          |            |            |
| Submucosal Pigment Deposition |            | 10         |            |            |
| Nonsuppurative Rhinitis       |            |            |            |            |
| Foreign Body                  |            |            |            | 1          |
| NASAL CAVITY-LEVEL III        |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 1          | 1          |            |            |
| Submucosal Pigment Deposition |            | 10         |            | 4          |
| Nonsuppurative Rhinitis       |            |            |            |            |
| NASAL CAVITY-LEVEL IV         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Submucosal Pigment Deposition |            | 10         |            | 8          |
| Hemorrhage                    |            |            |            |            |
| Suppurative Exudate           |            |            |            |            |

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Experimental Pathology Laboratories, Inc.

## SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

|                                       | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|---------------------------------------|------------|------------|------------|------------|
| LIVER (NO. EXAMINED)                  | (10)       | (10)       |            | (10)       |
| Foci of Mononuclear Cells             | 3          | 5          |            | 4          |
| Pigment Deposition                    |            | 10         |            |            |
| Bile Duct Hyperplasia                 | 1          |            |            |            |
| KIDNEY (NO. EXAMINED)                 | (10)       | (10)       |            | (10)       |
| Pigment Deposition                    | 10         | 10         |            | 10         |
| Regenerative Tubular<br>Epithelium    |            | 1          |            |            |
| Casts                                 |            | 1          |            |            |
| Foci of Mononuclear Cells             | 2          | 2          |            | 2          |
| Cyst                                  |            |            |            |            |
| Tubular Mineralization                | 10         | 10         |            | 10         |
| LUNG (NO. EXAMINED)                   | (10)       | (10)       |            | (10)       |
| Hemorrhage                            |            |            |            |            |
| Pigment Deposition                    |            |            |            |            |
| Hyperplasia of Type II Cells          |            |            |            |            |
| Accumulations of Foamy<br>Macrophages |            |            |            |            |
| Peribronchial Lymphoid<br>Hyperplasia | 10         | 9          |            | 9          |
| BRAIN (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)              | (10)       | (10)       |            |            |
| Cyst                                  |            | 2          |            |            |

# SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

|                                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|------------------------------------------------|------------|------------|------------|------------|
| ADRENAL (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Vacuolated Cortical Cells                      |            |            |            |            |
| Hemorrhage                                     |            | 1          |            |            |
| EYE (NO. EXAMINED)                             | (10)       | (10)       |            |            |
| THYROID (NO. EXAMINED)                         | (10)       | (8)        |            |            |
| LARYNX (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| Hemorrhage                                     |            |            |            |            |
| Foci of Mononuclear Cells                      |            | 1          |            |            |
| TRACHEA (NO. EXAMINED)                         | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells                      | 1          | 1          |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL<br>(NO. EXAMINED) | (9)        | (10)       |            |            |
| Hemorrhage                                     | 4          | 3          |            |            |
| Pigment Deposition                             | 4          | 5          |            |            |
| HEART (NO. EXAMINED)                           | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis                     | 3          | 3          |            |            |
| SPLEEN (NO. EXAMINED)                          | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                        | (10)       | (10)       |            |            |
|                                                |            |            |            |            |
|                                                |            |            |            |            |
|                                                |            |            |            |            |



# SUMMARY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

|                                | Group<br>C | Group<br>H | Group<br>L | Group<br>M |
|--------------------------------|------------|------------|------------|------------|
| LYMPH NODE, POPLITEAL          |            |            |            |            |
| (NO. EXAMINED)                 | (7)        | (10)       |            |            |
| Hemorrhage                     |            |            |            |            |
| Pigment Deposition             |            |            |            |            |
| Lymphoid Hyperplasia           | 1          |            |            |            |
|                                |            |            |            |            |
| STOMACH (NO. EXAMINED)         | (10)       | (10)       |            |            |
|                                |            |            |            |            |
| DUODENUM (NO. EXAMINED)        | (10)       | (10)       |            |            |
|                                |            |            |            |            |
| CECUM (NO. EXAMINED)           | (10)       | (10)       |            |            |
| Nematodiasis                   |            |            |            |            |
| Hemorrhage                     |            |            |            |            |
|                                |            |            |            |            |
| COLON (NO. EXAMINED)           | (10)       | (10)       |            |            |
| Nematodiasis                   | 1          | 1          |            |            |
| Hemorrhage                     |            |            |            |            |
|                                |            |            |            |            |
| SKIN (NO. EXAMINED)            | (10)       | (10)       |            |            |
|                                |            |            |            |            |
| UTERUS (NO. EXAMINED)          | (10)       | (10)       |            |            |
| Dilatation                     |            | 1          |            |            |
|                                |            |            |            |            |
| OVARY (NO. EXAMINED)           | (10)       | (10)       |            |            |
| Parovarian Cyst                |            | 1          |            |            |
|                                |            |            |            |            |
| URINARY BLADDER (NO. EXAMINED) | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells      | 1          |            |            |            |
|                                |            |            |            |            |
|                                |            |            |            |            |

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HISTOPATHOLOGY INCIDENCE TABLES

| <u>GROUP</u> | <u>CONCENTRATION</u>          |
|--------------|-------------------------------|
| C            | Control                       |
| L            | Low Exposure Concentration    |
| M            | Medium Exposure Concentration |
| H            | High Exposure Concentration   |

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group C

ANIMAL

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                               |   |   |   |   |   |   |   |   |   |
|-------------------------------|---|---|---|---|---|---|---|---|---|
| NASAL CAVITY-LEVEL I          | X |   | X | X | X | X |   | N | X |
| Hemorrhage                    | 2 |   |   |   |   |   | 2 | 2 |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                 |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |   |   | X | X | X | X |   | X | X |
| Hemorrhage                    | 2 | 1 |   |   |   |   | 2 |   |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |
| Foreign Body                  |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        | X |   | X | X | X | X | X | X | X |
| Hemorrhage                    | 1 |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         | X | X | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |   |   |   |   |   |   |   |   |   |
| LIVER                         | X | X | X | X | X | X |   | X | X |
| Foci of Mononuclear Cells     |   |   |   |   |   |   | 1 | 1 |   |
| Pigment Deposition            |   |   |   |   |   |   |   |   |   |
| Bile Duct Hyperplasia         |   |   |   |   |   |   |   |   |   |

V-1

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  
4 = Moderately Severe/High

X = Not Remarkable

# HISTOPATHOLOGY INCIDENCE TABLE

22-79  
7 Week Sacrifice  
Male Rats

Group C

|                                    | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                    |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                    |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                    |                            |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                                    |                            |                            | - | - | - | - | - | - | - | - | - |
|                                    |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                    |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| KIDNEY                             |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Regenerative Tubular Epithelium    |                            |                            | 1 | 1 |   | 1 | 1 | 2 | 1 | 1 | 1 |
| Casts                              |                            |                            |   | 2 |   | 1 | 1 | 1 | 1 | 2 | 1 |
| Foci of Mononuclear Cells          |                            |                            |   | 1 |   |   | 1 |   |   |   | 1 |
| Cyst                               |                            |                            |   |   |   |   |   |   |   |   |   |
| Tubular Mineralization             |                            |                            |   |   |   |   |   |   |   |   |   |
| LUNG                               |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                            |                            |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                            |                            | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| BRAIN                              |                            |                            | X | X | X | X | X | X | X | X | X |
| PITUITARY                          |                            |                            | X | X | X | X | X | X | X | X | X |
| Cyst                               |                            |                            |   |   |   |   |   |   |   |   |   |
| ADRENAL                            |                            |                            |   | X |   | X | X |   | X | X |   |
| Vacuolated Cortical Cells          |                            |                            | 1 |   | 1 |   |   | 1 | 1 |   | 1 |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |

V-2

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group C

|                              | AN<br>N<br>I<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------|----------------------------------|---|---|---|---|---|---|---|---|---|
|                              |                                  | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                              |                                  | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                              |                                  | - | - | - | - | - | - | - | - | - |
|                              |                                  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                              |                                  | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                              |                                  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|                              |                                  | 9 |   |   |   |   |   |   |   |   |
| EYE                          |                                  | X | X | X | X | X | X | X | X | X |
| THYROID                      |                                  | X | X | X | X | X | X | X | X | X |
| LARYNX                       |                                  | X | X | X | X | X | X | X | X | X |
| Hemorrhage                   |                                  |   |   |   |   |   |   |   | 2 |   |
| Foci of Mononuclear Cells    |                                  |   |   |   |   |   |   |   |   |   |
| TRACHEA                      |                                  | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |                                  |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL |                                  | X |   | X | X | X | N |   | X | X |
| Hemorrhage                   |                                  | 1 |   |   |   |   |   |   |   |   |
| Pigment Deposition           |                                  | 1 |   |   |   |   | 2 |   |   |   |
| HEART                        |                                  |   |   |   | X |   | X | X | X | X |
| Nonsuppurative Myocarditis   |                                  | 1 | 1 | 2 |   | 1 |   |   |   | 1 |
| SPLEEN                       |                                  | X | X | X | X | X | X | X | X | X |
| PANCREAS                     |                                  | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL        |                                  | X | X | X | X | X | X | X | X | X |
| Hemorrhage                   |                                  |   |   |   |   |   |   |   | 2 |   |
| Pigment Deposition           |                                  |   |   |   |   |   |   |   | 1 |   |
| Lymphoid Hyperplasia         |                                  |   |   |   |   |   |   |   |   |   |

Y-3

EPL

Experimental Pathology Laboratories, Inc

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
5 - Severe/High 1 - Incomplete Section

A - Autolysis X - Not Remarkable  
3 - Moderate 4 - Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group C

|                           | ANIMAL<br>NUMBER | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|---------------------------|------------------|---|---|---|---|---|---|---|---|---|
|                           |                  | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                           |                  | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                           |                  | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                           |                  | - | - | - | - | - | - | - | - | - |
|                           |                  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                           |                  | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                           |                  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| STOMACH                   |                  | X | X | X | X | X | X | X | X | X |
| DUODENUM                  |                  | X | X | X | X | X | X | X | X | X |
| CECUM                     |                  | X | X | X | X |   | X | X | X | X |
| Nematodiasis              |                  |   |   |   |   | P |   |   |   |   |
| Hemorrhage                |                  |   |   |   |   |   |   |   |   |   |
| COLON                     |                  | X | X |   | X | X |   | X | X | X |
| Nematodiasis              |                  |   |   | P |   | P | P |   |   |   |
| Hemorrhage                |                  |   |   |   |   |   |   |   |   |   |
| SKIN                      |                  | X | X | X | X | X | X | X | X | X |
| TESTIS                    |                  | X | X | X | X | X | X | X | X | X |
| EPIDIDYMIS                |                  | X | X | X | X | X | X | X | X | X |
| PROSTATE                  |                  | X | X | X | X | X | X | X | X | X |
| URINARY BLADDER           |                  | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells |                  |   |   |   |   |   |   |   |   |   |
| FEMUR                     |                  | X | X | X | X | X | X | X | X | X |

V-4

EPL

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
3 - Severe High 4 - Incomplete Section

A - Autolysis X - Not Remarkable  
3 - Moderate 4 - Moderately Severe High



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group H

|                               | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                               |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                            |                            | - | - | - | - | - | - | - | - | - | - |
|                               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I          |                            |                            | X |   |   | X |   |   | X | X | X |   |
| Hemorrhage                    |                            |                            |   | 1 | 2 |   | 1 |   |   |   | 1 | 1 |
| Submucosal Pigment Deposition |                            |                            |   | 1 |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   | 1 |   |
| Hyperplasia of Goblet Cells   |                            |                            |   |   |   |   |   |   |   |   | 2 |   |
| Cystic Glands                 |                            |                            |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                            |                            |   | 1 |   |   | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   | 1 |   |
| Foreign Body                  |                            |                            |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                            |                            |   |   |   | 1 | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   | 1 |   |
| NASAL CAVITY-LEVEL IV         |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Hemorrhage                    |                            |                            |   |   |   | 1 | 1 |   |   |   | 1 |   |
| Suppurative Exudate           |                            |                            |   |   |   |   |   |   |   |   | 2 |   |
| LIVER                         |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells     |                            |                            |   | 1 | 1 | 1 | 1 |   | 1 | 1 | 1 | 1 |
| Pigment Deposition            |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 |
| Bile Duct Hyperplasia         |                            |                            |   |   |   |   |   |   |   |   |   |   |

V-5

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe

H =

# HISTOPATHOLOGY INCIDENCE TABLE

7-79  
7 Week Sacrifice  
Male Rats

Group H

|                                    | A<br>N<br>U<br>M<br>B<br>E<br>R | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|------------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                    |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                                 | - | - | - | - | - | - | - | - | - | - |
|                                    |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                                 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                    |                                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| KIDNEY                             |                                 |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                                 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 3 | 3 | 3 |
| Regenerative Tubular Epithelium    |                                 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 |
| Casts                              |                                 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 |
| Foci of Macular Cells              |                                 | 1 |   |   | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Cyst                               |                                 |   |   |   |   |   | P |   |   |   |   |
| Tubular Mineralization             |                                 |   |   |   |   |   |   |   |   |   |   |
| LUNG                               |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                                 | 1 |   | 1 |   |   |   |   |   |   |   |
| Pigment Deposition                 |                                 | 1 | 1 |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                                 | 1 | 1 |   |   |   |   |   |   |   |   |
| Accumulations of Foamy Macrophages |                                 | 1 | 1 |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                                 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| BRAIN                              |                                 | X | X | X | X | X | X | X | X | X | X |
| PITUITARY                          |                                 | X | X | X | X | X |   | X | X | X | X |
| Cyst                               |                                 |   |   |   |   |   | P |   |   |   |   |
| ADRENAL                            |                                 |   | X | N | X | X |   | X | X | X |   |
| Vacuolated Cortical Cells          |                                 | 1 |   |   |   |   | 1 |   |   |   | 1 |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |   |

V-6

EPL

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
3 - Severe/High 4 - Incomplete Section

A - Autopsy X - Not Remarkable  
3 - Moderate 4 - Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group H

ANUMBER  
M  
A  
L  
E  
R

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                              |   |   |   |   |   |   |   |   |   |   |
|------------------------------|---|---|---|---|---|---|---|---|---|---|
| EYE                          | X | X | X | X | X | X | X | X | X | X |
| THYROID                      | X | X | X | X | X | X | X | X | X | X |
| LARYNX                       | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                   |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                      | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL | X | X | X | X | X | X | N | X | X | X |
| Hemorrhage                   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition           |   |   |   |   |   |   |   |   |   |   |
| HEART                        |   |   | X |   |   | X | X |   |   | X |
| Nonsuppurative Myocarditis   | 1 | 1 |   | 1 | 1 |   |   | 1 | 1 |   |
| SPLEEN                       | X | X | X | X | X | X | X | X | X | X |
| PANCREAS                     | X | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL        | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition           |   |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia         |   |   |   |   |   |   |   |   |   |   |

V-7

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

RZ-79  
17 Week Sacrifice  
Male Rats

Group H

AN  
NU  
ME  
RA  
L

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

STOMACH

X X X X X X X X X X X

DUODENUM

X X X X X X X X X X X

CECUM

X X X X X X X X X

Nematodiasis

P

Hemorrhage

1

COLON

X X X X X X X X X X

Nematodiasis

Hemorrhage

3

SKIN

X X X X X X X X X X X

TESTIS

X X X X X X X X X X X

EPIDIDYMIS

X X X X X X X X X X X

PROSTATE

X X X X X X X X X X X

URINARY BLADDER

X X X X X X X X X X X

Foci of Mononuclear Cells

FEMUR

X X X X X X X X X X X

V-8

EPL

Experimental Pathology Laboratories, Inc

Key

P - Present

1 - Minimal

5 - Severe/High

N - No Section

2 - Slight

1 - Incomplete Section

A - Autolysis

3 - Moderate

X - Not Remarkable

4 - Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group L

|                               | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                               |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                               |                            |                            | - | - | - | - | - | - | - | - | - |
|                               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL I          |                            |                            | X | X | X | X | X | X | X | X | X |
| Hemorrhage                    |                            |                            | 1 |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells   |                            |                            |   |   |   |   |   |   |   |   |   |
| Cystic Glands                 |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |                            |                            | X | X | X | X | X | X | X | X | X |
| Hemorrhage                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   |   |
| Foreign Body                  |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |                            |                            | X | X | X | X | X |   | X | X | X |
| Hemorrhage                    |                            |                            |   |   |   |   |   | 1 |   |   |   |
| Submucosal Pigment Deposition |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         |                            |                            | X | X | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                            |                            |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |
|                               |                            |                            |   |   |   |   |   |   |   |   |   |

V-9

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe/High I = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

7-79  
7 Week Sacrifice  
Male Rats

Group M

|                               | A<br>N<br>N<br>U<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|-------------------------------|--------------------------------------|---|---|---|---|---|---|---|---|---|---|
|                               |                                      | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                                      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                      | - | - | - | - | - | - | - | - | - | - |
|                               |                                      | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                                      | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                                      | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I          |                                      | X | X |   | X |   |   |   | X | X |   |
| Hemorrhage                    |                                      |   |   |   |   | 2 |   |   |   |   |   |
| Submucosal Pigment Deposition |                                      |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                      |   |   |   |   |   | 1 |   |   |   |   |
| Hyperplasia of Goblet Cells   |                                      | 1 |   |   |   |   | 1 |   |   |   |   |
| Cystic Glands                 |                                      |   |   | 1 |   |   |   | 1 |   |   |   |
| NASAL CAVITY-LEVEL II         |                                      | X | X | X |   | X |   | X | X |   | X |
| Hemorrhage                    |                                      |   |   | 1 |   | 1 |   |   |   |   |   |
| Submucosal Pigment Deposition |                                      |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                      |   |   | 1 |   |   |   |   | 1 |   |   |
| Foreign Body                  |                                      |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |                                      | X | X | X |   | X | X | X | X | X |   |
| Hemorrhage                    |                                      |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                      | 1 |   |   | 1 |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |                                      |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         |                                      |   | X | X |   |   | X |   |   |   |   |
| Submucosal Pigment Deposition |                                      | 1 | 1 |   | 1 | 1 |   | 2 | 1 | 1 |   |
| Hemorrhage                    |                                      |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |                                      |   |   |   |   |   |   |   |   |   |   |
| LIVER                         |                                      | X | X |   | X |   | X | X | X | X | X |
| Foci of Mononuclear Cells     |                                      |   | 1 |   | 1 |   |   |   |   |   |   |
| Pigment Deposition            |                                      |   |   |   |   |   |   |   |   |   |   |
| Bile Duct Hyperplasia         |                                      |   |   |   |   |   |   |   |   |   |   |

V-10

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe High  
5 = Severe High I = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Male Rats

Group M

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - | - | - | - | - | - | - | - | - | - |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

## KIDNEY

Pigment Deposition

1 1 1 1 1 2 1 1 1 1

Regenerative Tubular

Epithelium

1 1 1 1 1 2 1

Casts

1 1 1 1 1 2 1 1

Foci of Mononuclear Cells

1 1 1 1 1 1

Cyst

Tubular Mineralization

## LUNG

X

Hemorrhage

Pigment Deposition

Hyperplasia of Type II Cells

Accumulations of Foamy

Macrophages

Peribronchial Lymphoid

Hyperplasia

1 2 1 1 1 1 1 1 1

V-11

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

5 = Severe

1 = Incomplete Section

| <u>GROUP</u> | <u>CONCENTRATION</u>          |
|--------------|-------------------------------|
| C            | Control                       |
| L            | Low Exposure Concentration    |
| M            | Medium Exposure Concentration |
| H            | High Exposure Concentration   |



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group C

AN  
I  
M  
B  
E  
R

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| - | - | - | - | - | - | - | - | - | - |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

|                               |   |   |   |   |   |   |   |   |   |   |
|-------------------------------|---|---|---|---|---|---|---|---|---|---|
| NASAL CAVITY-LEVEL I          |   |   | X | X | X | X |   | X |   |   |
| Hemorrhage                    | 2 | 1 |   |   |   |   | 2 |   | 1 |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells   |   |   |   |   |   |   |   | 1 |   |   |
| Cystic Glands                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |   |   | X | X | X | X | X |   | X | X |
| Hemorrhage                    | 2 |   |   |   |   |   | 1 |   | 1 |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |   |
| Foreign Body                  |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |   |   | X | X | X | X | X | X | X | X |
| Hemorrhage                    | 2 |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         |   |   | X | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |   |   |   |   |   |   |   |   |   |   |
| LIVER                         |   |   | X |   |   | X | X | X | X | X |
| Foci of Mononuclear Cells     |   | 1 |   | 1 |   |   |   |   |   | 1 |
| Pigment Deposition            |   |   |   |   |   |   |   |   |   |   |
| Bile Duct Hyperplasia         |   |   | 1 |   |   |   |   |   |   |   |

V-12

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Severe/High 4 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group C

|                                    | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                    |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                    |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                                    |                            |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                                    |                            |                            | - | - | - | - | - | - | - | - | - |
|                                    |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                                    |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                    |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| KIDNEY                             |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Regenerative Tubular Epithelium    |                            |                            |   |   |   |   |   |   |   |   |   |
| Casts                              |                            |                            |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells          |                            |                            |   |   |   |   | 1 |   | 1 |   |   |
| Cyst                               |                            |                            |   |   |   |   |   |   |   |   |   |
| Tubular Mineralization             |                            |                            | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 |
| LUNG                               |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                            |                            |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| BRAIN                              |                            |                            | X | X | X | X | X | X | X | X | X |
| PITUITARY                          |                            |                            | X | X | X | X | X | X | X | X | X |
| Cyst                               |                            |                            |   |   |   |   |   |   |   |   |   |
| ADRENAL                            |                            |                            | X | X | X | X | X | X | X | X | X |
| Vacuolated Cortical Cells          |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |

V-13

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

5 = Severe

1 = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group C

|                              | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                              |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                              |                            |                            | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|                              |                            |                            | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|                              |                            |                            | - | - | - | - | - | - | - | - | - |
|                              |                            |                            | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                              |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                              |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| EYE                          |                            |                            | X | X | X | X | X | X | X | X | X |
| THYROID                      |                            |                            | X | X | X | X | X | X | X | X | X |
| LARYNX                       |                            |                            | X | X | X | X | X | X | X | X | X |
| Hemorrhage                   |                            |                            |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells    |                            |                            |   |   |   |   |   |   |   |   |   |
| TRACHEA                      |                            |                            | X | X |   | X | X | X | X | X | X |
| Foci of Mononuclear Cells    |                            |                            |   |   | 1 |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL |                            |                            | X | X |   | X | N |   |   | X | X |
| Hemorrhage                   |                            |                            |   |   | 1 |   |   | 2 | 1 |   | 1 |
| Pigment Deposition           |                            |                            |   |   | 1 |   |   | 2 | 1 |   | 2 |
| HEART                        |                            |                            | X | X | X | X | X |   | X | X |   |
| Nonsuppurative Myocarditis   |                            |                            |   |   |   |   | 1 |   |   | 1 | 1 |
| SPLEEN                       |                            |                            | X | X | X | X | X | X | X | X | X |
| PANCREAS                     |                            |                            | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL        |                            |                            | N | X | N | X | N | X |   | X | X |
| Hemorrhage                   |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition           |                            |                            |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia         |                            |                            |   |   |   |   |   | 2 |   |   |   |

V-14

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe High  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Not Removable  
3 = Moderate 4 = Moderately Severe High

**2.**

1

五

1

1



**Key**

N - No Section

2 - Sign:

1 - Incomplete Section.

A - Au'c'ys.s

3 - Moderate

$x = N^{-1} \sum_{i=1}^N \tilde{a}_i$

4 - Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group H

|                               | AN<br>NU<br>ME<br>R<br>AL | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|-------------------------------|---------------------------|---|---|---|---|---|---|---|---|---|---|
|                               |                           | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                           | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                               |                           | - | - | - | - | - | - | - | - | - | - |
|                               |                           | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|                               |                           | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               |                           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| NASAL CAVITY-LEVEL I          |                           | X | X |   |   | X | X | X | X | X |   |
| Hemorrhage                    |                           |   |   | 1 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                           |   |   | 1 |   |   |   |   |   | 1 |   |
| Nonsuppurative Rhinitis       |                           |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Goblet Cells   |                           |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                 |                           |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |                           |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                           |   |   | 1 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                           | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 2 |
| Nonsuppurative Rhinitis       |                           |   |   |   |   |   |   |   |   |   |   |
| Foreign Body                  |                           |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |                           |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                           |   |   | 1 |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                           | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 3 | 2 | 2 |
| Nonsuppurative Rhinitis       |                           |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV         |                           |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                           | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 3 |
| Hemorrhage                    |                           |   |   |   |   |   |   |   |   |   |   |
| Suppurative Exudate           |                           |   |   |   |   |   |   |   |   |   |   |
| LIVER                         |                           |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells     |                           |   | 1 |   | 1 |   | 1 |   | 1 |   | 1 |
| Pigment Deposition            |                           | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Bile Duct Hyperplasia         |                           |   |   |   |   |   |   |   |   |   |   |

V-16

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

5 - Severe

6 - High

7 - Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group H

| ANIMAL | NUMBER | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |   |
|--------|--------|---|---|---|---|---|---|---|---|---|---|
|        | 0      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|        | 0      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|        | 1      | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
|        | -      | - | - | - | - | - | - | - | - | - |   |
|        | 6      | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |   |
|        | 4      | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |   |
|        | 0      | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | 3 | 3 | 3 | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        | 1      |   |   |   |   |   |   |   |   |   |   |
|        | 1      |   |   |   |   |   |   |   |   |   |   |
|        | 1      | 1 |   |   |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        | 2      | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        | X      |   |   |   |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
| S      |        |   |   |   |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        | 1      | 1 | 1 |   | 1 | 1 | 1 | 1 | 1 | 1 |   |
|        | X      | X | X | X | X | X | X | X | X | X |   |
|        | X      |   | X | X | X | X | X |   |   | X |   |
|        | P      |   |   |   |   |   |   |   |   | P |   |
|        | X      | X |   | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        | 2      |   |   |   |   |   |   |   |   |   |   |

V-17

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Incomplete Section

A = Autolysis

3 = Moderate

X = Not Remarkable

4 = Moderately Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group H

ANNUAL  
NUMBER

4 4 4 4 4 4 4 4 4 4  
0 0 0 0 0 0 0 0 0 0  
0 0 0 0 0 0 0 0 0 0  
1 1 1 1 1 1 1 1 1 1  
- - - - - - - - - -  
6 6 6 6 6 6 6 6 6 6  
4 4 4 4 4 4 4 4 4 4  
0 1 2 3 4 5 6 7 8 9

EYE X X X X X X X X X X

THYROID N X N X X X X X X X

LARYNX X X X X X X X X X X

Hemorrhage

Foci of Mononuclear Cells 1

TRACHEA X X X X X X X X X X

Foci of Mononuclear Cells 1

LYMPH NODE, TRACHEOBRONCHIAL X X X X X

Hemorrhage 1 1 1

Pigment Deposition 1 1 2 1 1

HEART X X X X X X X X

Nonsuppurative Myocarditis 1 1 1

SPLEEN X X X X X X X X X X

PANCREAS X X X X X X X X X X

LYMPH NODE, POPLITEAL X X X X X X X X X X

Hemorrhage

Pigment Deposition

Lymphoid hyperplasia

EPL

Experimental Pathology Laboratory

Legend  
1 - Slight  
2 - Moderate  
3 - Severe

4 - Incomplete Section  
5 - Incomplete Section

A - Autopsy  
B - Biopsy  
C - Necropsy  
D - Mortality

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

Group H

| ANIMAL | NUMBER | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |   |
|--------|--------|---|---|---|---|---|---|---|---|---|---|
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|        |        | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
|        |        | - | - | - | - | - | - | - | - | - |   |
|        |        | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |   |
|        |        | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |   |
|        |        | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|        |        | X | X | X | X | X | X | X | X | X | X |
|        |        | X | X | X | X | X | X | X | X | X | X |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X | X |   |   |
| X      | X      | X | X | X | X | X | X | X |   |   |   |

V-19

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Incomplete Section

A = Analysis

3 = Moderate

4 = Moderately Severe/High

X = Not Remarkable

4 = Moderately Severe/High



### HISTOPATHOLOGY INCIDENCE TABLE

RZ-79  
17 Week Sacrifice  
Female Rats

**Group L**

[illegible]

V-20

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = Not Seen  
1 = Mild 2 = Sight  
3 = Severe 4 = Incomplete Section

A - Adult, 3 - Male, 2 - Female, 1 - Juvenile

# HISTOPATHOLOGY INCIDENCE TABLE

7-79  
7 Week Sacrifice  
Female Rats

Group M

ANNUAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - | - | - | - | - | - | - | - | - | - |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

## NASAL CAVITY-LEVEL I

|   |   |   |  |   |   |  |   |   |   |
|---|---|---|--|---|---|--|---|---|---|
| X | X | X |  | X | X |  | X | X | X |
|---|---|---|--|---|---|--|---|---|---|

Hemorrhage

Submucosal Pigment Deposition

Nonsuppurative Rhinitis

1

Hyperplasia of Goblet Cells

1

Cystic Glands

## NASAL CAVITY-LEVEL II

|   |   |   |   |   |  |   |   |   |   |
|---|---|---|---|---|--|---|---|---|---|
| X | X | X | X | X |  | X | X | X | X |
|---|---|---|---|---|--|---|---|---|---|

Hemorrhage

Submucosal Pigment Deposition

Nonsuppurative Rhinitis

Foreign Body

P

## NASAL CAVITY-LEVEL III

|   |   |  |   |   |  |   |  |   |  |
|---|---|--|---|---|--|---|--|---|--|
| X | X |  | X | X |  | X |  | X |  |
|---|---|--|---|---|--|---|--|---|--|

Hemorrhage

Submucosal Pigment Deposition

1

1

1

Nonsuppurative Rhinitis

## NASAL CAVITY-LEVEL IV

|   |  |  |  |  |  |  |  |  |  |
|---|--|--|--|--|--|--|--|--|--|
| X |  |  |  |  |  |  |  |  |  |
|---|--|--|--|--|--|--|--|--|--|

Submucosal Pigment Deposition

1

1

1

1

1

1

1

Hemorrhage

Suppurative Exudate

## LIVER

|   |   |   |  |   |  |   |   |  |  |
|---|---|---|--|---|--|---|---|--|--|
| X | X | X |  | X |  | X | X |  |  |
|---|---|---|--|---|--|---|---|--|--|

Foci of Mononuclear Cells

1

1

1

Pigment Deposition

Bile Duct Hyperplasia

V-21

J. 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 Examined  
4 = Moderate, Severe High



**Group M**

|        |        |   |   |   |   |   |   |   |   |   |
|--------|--------|---|---|---|---|---|---|---|---|---|
| ANIMAL | NUMBER | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|        |        | - | - | - | - | - | - | - | - | - |
|        |        | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|        |        | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|        |        | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

|                                    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|
| KIDNEY                             |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Regenerative Tubular Epithelium    |   |   |   |   |   |   |   |   |   |   |
| Casts                              |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells          |   |   |   | 1 |   |   | 1 |   |   |   |
| Cyst                               |   |   |   |   |   |   |   |   |   |   |
| Tubular Mineralization             | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 3 | 1 | 3 |
| LUNG                               |   |   |   | X |   |   |   |   |   |   |
| Hemorrhage                         |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |   |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy Macrophages |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia | 1 | 1 |   | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

V-22

**EPL**

Experimental Pathology Laboratories, Inc.

Key    P - Present            N - No Section  
         1 - Minimal        2 - Slight  
         3 - Severe High    1 - Incomplete Section

A = Autolysis      2 = Moderate  
3 = Moderate      4 = Moderate, Severe H<sub>2</sub>O

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

RZ-79  
17 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level: High Exposure

Group Number H - Sacrificed

Sex: Males

Species: Rats

| Animal Number | Client's Tissue Identification | Client's Gross Observations     | Microscopic Observations                                                                         |
|---------------|--------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------|
| 4001-140      | Lung                           | Dull pink, diffuse brown/yellow | Hemorrhage; accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells |
| 4001-141      | Lung                           | Diffuse yellow/brown            | Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells             |
| 4001-142      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-143      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-144      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-145      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-146      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-147      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-148      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
| 4001-149      | Lung                           | Diffuse yellow/brown            | No corresponding lesion                                                                          |
|               |                                |                                 |                                                                                                  |
|               |                                |                                 |                                                                                                  |
|               |                                |                                 |                                                                                                  |
|               |                                |                                 |                                                                                                  |
|               |                                |                                 |                                                                                                  |

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

**Sex:** **Mailes**

## M - Sacrificed

**Dosage Level:**

### Medium Exposure

[illegible]

RZ-79  
17 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level: High Exposure

Species: Rats Sex: Females

Group Number: H - Sacrificed

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations       |
|---------------|--------------------------------|-----------------------------|--------------------------------|
| 4001-640      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Pigment, yellow, minimal    | No corresponding lesion        |
|               | Ovary                          | Bilateral cysts             | No corresponding lesion        |
| 4001-641      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Pigment, yellow, minimal    | No corresponding lesion        |
| 4001-642      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Pigment, yellow, minimal    | No corresponding lesion        |
| 4001-643      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Tracheobronchial lymph node    | Reddened, enlarged          | Hemorrhage; pigment deposition |
|               | Lung                           | Yellow pigment, minimal     | No corresponding lesion        |
| 4001-644      | Skin                           | Yellow                      | No corresponding lesion        |
| 4001-645      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Pigment, yellow, minimal    | No corresponding lesion        |
| 4001-646      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Pigment, yellow, minimal    | No corresponding lesion        |
| 4001-647      | Skin                           | Yellow                      | No corresponding lesion        |
|               | Lung                           | Yellow pigment, minimal     | No corresponding lesion        |

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

**Dosage Level: High Exposure**

[illegible]



EPL

## APPENDIX II

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

LOVELACE INHALATION TOXICOLOGY  
RESEARCH INSTITUTE

90 DAY REPEATED INHALATION EXPOSURES OF  
RATS TO SOLVENT YELLOW-GREEN DYE MIXTURE

PATHOLOGY REPORT

Submitted to:

Lovelace Inhalation Toxicology  
Research Institute  
Albuquerque, New Mexico 87185

August 13, 1985

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## LOVELACE INHALATION TOXICOLOGY RESEARCH INSTITUTE

90 DAY REPEATED INHALATION EXPOSURES OF RATS TO  
SOLVENT YELLOW-GREEN DYE MIXTURE

## PATHOLOGY SUMMARY

A histopathologic evaluation of selected tissues from male and female rats exposed to Solvent Yellow-Green Dye Mixture was conducted to provide information on the inhalation toxicity of dyes present in colored smoke munitions. The experimental design for this study was as follows:

| Group | Treatment                     | Dose*<br>(mg/m <sup>3</sup> ) | Number of Animals |    |                 |     |
|-------|-------------------------------|-------------------------------|-------------------|----|-----------------|-----|
|       |                               |                               | 90 Day Sacrifice  |    | 30 Day Recovery |     |
|       |                               |                               | M                 | F  | M               | F   |
| L     | Controls                      | 0                             | 10                | 10 | 10              | 9** |
| M     | Low Exposure Concentration    | 1                             | 10                | 10 | 10              | 10  |
| N     | Medium Exposure Concentration | 10                            | 10                | 10 | 10              | 10  |
| O     | High Exposure Concentration   | 100                           | 10                | 10 | 10              | 10  |

\*Rats were exposed six hours/day, five days/week for thirteen weeks.

\*\*One animal escaped.

According to protocol, routine hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high

PATHOLOGY SUMMARY

dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related effect.

In general, the tissues called for to be examined by protocol are represented in the Histopathology Incidence Tables. Only a few tissues were inadvertently missed at the time of necropsy or lost during histologic processing. In some instances, the posterior portion of the nasal cavity had been damaged and complete sections of four levels of the nasal cavity could not be obtained.

Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. All lesions are summarized by treatment groups in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time the necropsies were performed.

## RESULTS

### Ninety-Day Exposure

Inhalation of Solvent Yellow-Green Dye Mixture at 100 mg/m<sup>3</sup> six hours/day, five days/week for thirteen weeks resulted in changes in the lungs, nasal cavity, tracheobronchial lymph node, kidneys, and liver. In the lungs, slight to moderate accumulations of foamy

appearing alveolar macrophages containing minimal to slight amounts of pigment were noted in the alveoli adjacent to the respiratory bronchioles in all high dose rats. These accumulations of alveolar macrophages were accompanied by slight to moderate hyperplasia of Type II cells (granular pneumocytes). In the nasal cavity, submucosal pigment deposition was noted at most levels in nearly all high dose rats. The pigment deposition was heaviest at Level III and Level IV. In the tracheobronchial lymph node, hyperplasia of foamy macrophages (reticuloendothelial cells) with minimal pigment deposition and slight to moderately severe lymphoid hyperplasia were present. In the kidneys, an increase in granular pigment present in the cortical tubules was noted in all high dose rats. In the liver, minimal granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile ducts in all high dose rats.

In the rats exposed to Solvent Yellow-Green Dye Mixture at 10 mg/m<sup>3</sup>, only lung, nasal cavity, tracheobronchial lymph node, liver, and kidneys were examined. Minimal lung lesions similar to those noted in the high dose rats occurred in three males and three females. The lesions were single lesions and tended to be at the margins of the lung lobes. In the nasal cavity, minimal submucosal pigment was noted at Level III in one male and four females, and at Level IV in two females. In tracheobronchial lymph nodes, hyperplasia of foamy macrophages with minimal pigment deposition was noted in two males and two females. Lymphoid hyperplasia was noted in an additional male.

- Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females.

In the rats exposed to Solvent Yellow-Green Dye Mixture at  $1 \text{ mg/m}^3$ , the lung and nasal cavity were examined from both sexes; the liver was also examined from the females. No compound-related histomorphologic alterations were noted in any of these tissues.

#### Thirty-Day Recovery

Inhalation of Solvent Yellow-Green Dye Mixture at  $100 \text{ mg/m}^3$  for ninety days followed by a thirty-day recovery period resulted in lung lesions similar to those noted after ninety days, but marginally less severe. Additionally, in the lungs, a few of the foamy macrophages containing pigment were present in the peribronchial lymphoid cuffs, a feature not present after ninety days exposure. In the nasal cavity, submucosal pigment deposition was present at most levels in nearly all high dose rats, but appeared to be slightly less severe than was noted after ninety days. In the tracheobronchial lymph nodes, hyperplasia of foamy macrophages containing a minimal amount of pigment was slightly more severe than was noted after ninety days exposure. Lymphoid hyperplasia was essentially comparable. In the kidney tubules, the increased tubular pigment was less severe than was noted after ninety days. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after ninety days exposure.

In the rats exposed to Solvent Yellow-Green Dye Mixture at  $10 \text{ mg/m}^3$  for ninety days followed by a thirty-day recovery period, only

lung, nasal cavity, tracheobronchial lymph node, liver and kidneys were examined. Lesions similar to those noted at this level after ninety days exposure were present. Minimal lung lesions were noted in two rats of each sex and submucosal pigment deposition was noted in the nasal cavity of single rats of each sex at Level II, six males and five females at Level III, and two males and six females at Level IV. In the tracheobronchial lymph node, of one male, lymphoid hyperplasia was present, but hyperplasia of foamy macrophages was not present in any of the lymph nodes examined. Pigment deposition in the kidneys was comparable to the controls and no pigment deposition was noted in the liver.

No compound-related histomorphologic alterations were noted in the lung and nasal cavity of rats exposed to  $1 \text{ mg/m}^3$  for ninety days followed by a thirty-day recovery period.

Spontaneous disease lesions and incidental findings occurred in rats in both control and treated groups at both sacrifice intervals. These lesions were distributed with approximately equal frequency in test and control rats.

#### CONCLUSIONS

Exposure of rats to Solvent Yellow-Green Dye Mixture at  $100 \text{ mg/m}^3$  for six hours/day, five days/week for thirteen weeks resulted in accumulations of foamy alveolar macrophages containing minimal amounts of pigment in the lungs. These accumulations were accompanied by hyperplasia of Type II pneumocytes. Similarly, foamy macrophages



with pigment had accumulated in the tracheobronchial lymph nodes. Pigment deposition was noted in the nasal cavity, liver, and kidney. After a thirty-day recovery period these lesions were decreased in severity with the exception of foamy macrophages in the tracheobronchial lymph nodes which were slightly increased.

Exposure of rats to Solvent Yellow-Green Dye Mixture at 10 mg/m<sup>3</sup> resulted in only minimal lesions in the lungs and tracheobronchial lymph nodes of a few rats and pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a thirty-day recovery period, these minimal lesions were essentially unchanged.

Exposure of rats to Solvent Yellow-Green Dye Mixture at 1 mg/m<sup>3</sup> did not result in any compound-related histomorphologic changes in the tissues examined.

*Deborah A. Banas*  
DEBORAH A. BANAS, D.V.M., M.S.  
Veterinary Pathologist

8/13/85

DAB/ras

**EPL**

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE  
REPORT CERTIFICATION

Client Name Lovelace Inhalation  
Toxicology Research Institute Client Study No. RZ-75

Study Director Dr. Larry Ackerman Pathologist Dr. Deborah Banas

Study Title 90 Day Repeated Inhalation Exposures of Rats to Solvent  
Yellow-Green Dye Mixture

Test Article Solvent Yellow-Green Dye Species Rats

All parts of the pathology phase of this study, including the final report, were reviewed by Experimental Pathology Laboratories Quality Assurance Unit on April 10, 1985 through August 13, 1985. All findings were reported to the Study Director and Management.

Janet Milazzo  
8/13/85

NINETY-DAY SACRIFICE  
SUMMARY INCIDENCE TABLES

## SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

|                               | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-------------------------------|------------|------------|------------|------------|
| LUNG (NO. EXAMINED)           | (10)       | (10)       | (10)       | (10)       |
| Accumulations of Foamy        |            |            |            |            |
| Macrophages                   |            | 10         |            | 2          |
| Hyperplasia of Type II Cells  |            | 10         |            | 1          |
| Pigment Deposition            |            | 10         |            | 3          |
| Adhesion                      |            |            |            |            |
| Hemorrhage                    |            |            |            | 2          |
| Peribronchial Lymphoid        |            |            |            |            |
| Hyperplasia                   | 10         | 10         | 8          | 10         |
| NASAL CAVITY-LEVEL I          |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    |            | 3          | 1          | 1          |
| Submucosal Pigment Deposition |            | 8          |            |            |
| Congestion                    |            |            |            |            |
| Serous Exudate                |            |            |            |            |
| Foreign Material              |            |            |            |            |
| Nonsuppurative Rhinitis       |            |            | 1          |            |
| Cystic Glands                 |            |            | 1          |            |
| NASAL CAVITY-LEVEL II         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (8)        | (9)        |
| Hemorrhage                    |            | 2          | 1          |            |
| Submucosal Pigment Deposition |            | 10         |            |            |
| Inflammation of Nasolacrimal  |            |            |            |            |
| Duct                          |            | 4          |            |            |
| Foreign Body                  |            | 1          |            |            |
| Focal Squamous Metaplasia     |            | 1          |            |            |
| Focal Inflammation            |            | 1          |            |            |
| Congestion                    |            |            |            |            |

# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

|                                   | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-----------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL II (CONTINUED) |            |            |            |            |
| Serous Exudate                    |            |            |            |            |
| Nonsuppurative Rhinitis           |            |            |            | 1          |
| Cystic Glands                     |            |            | 1          |            |
| NASAL CAVITY-LEVEL III            |            |            |            |            |
| (NO. EXAMINED)                    | (10)       | (8)        | (9)        | (9)        |
| Hemorrhage                        | 1          |            | 1          |            |
| Submucosal Pigment Deposition     |            | 8          |            | 1          |
| Serous Exudate                    |            |            |            |            |
| NASAL CAVITY-LEVEL IV             |            |            |            |            |
| (NO. EXAMINED)                    | (10)       | (10)       | (9)        | (8)        |
| Hemorrhage                        | 1          |            | 1          |            |
| Submucosal Pigment Deposition     |            | 10         |            |            |
| Serous Exudate                    |            |            |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL      |            |            |            |            |
| (NO. EXAMINED)                    | (7)        | (10)       | (9)        | (10)       |
| Hyperplasia of Foamy              |            |            |            |            |
| Macrophages                       |            | 9          |            | 2          |
| Lymphoid Hyperplasia              |            | 10         |            | 1          |
| Pigment Deposition                |            | 10         |            | 2          |
| Hemorrhage                        |            |            | 3          |            |
| KIDNEY (NO. EXAMINED)             |            |            |            |            |
| (NO. EXAMINED)                    | (10)       | (10)       |            | (10)       |
| Regenerative Tubular              |            |            |            |            |
| Epithelium                        | 5          | 6          |            | 6          |
| Casts                             |            | 3          |            | 1          |
| Cortical Infarct                  |            | 1          |            |            |

# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

|                           | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|---------------------------|------------|------------|------------|------------|
| KIDNEY (CONTINUED)        |            |            |            |            |
| Foci of Mononuclear Cells |            | 3          |            | 1          |
| Pigment Deposition        | 10         | 10         |            | 10         |
| LIVER (NO. EXAMINED)      | (10)       | (10)       |            | (10)       |
| Bile Duct Hyperplasia     | 1          |            |            |            |
| Foci of Mononuclear Cells | 2          | 3          |            | 2          |
| Cholangiofibrosis         | 1          |            |            |            |
| Pigment Deposition        |            | 10         |            |            |
| BRAIN (NO. EXAMINED)      | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)  | (10)       | (9)        |            |            |
| ADRENAL (NO. EXAMINED)    | (10)       | (10)       |            |            |
| Hemorrhage                | 1          |            |            |            |
| Vacuolated Cortical Cells |            | 1          |            |            |
| EYE (NO. EXAMINED)        | (10)       | (10)       |            |            |
| Corneal Subepithelial     |            |            |            |            |
| Basophilia                |            | 1          |            |            |
| THYROID (NO. EXAMINED)    | (9)        | (9)        |            |            |
| LARYNX (NO. EXAMINED)     | (9)        | (9)        |            |            |
| Foci of Mononuclear Cells |            | 2          |            |            |
|                           |            |            |            |            |
|                           |            |            |            |            |
|                           |            |            |            |            |
|                           |            |            |            |            |

# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

|                                        | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|----------------------------------------|------------|------------|------------|------------|
| TRACHEA (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| Hemorrhage                             | 1          |            |            |            |
| HEART (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis             | 8          | 3          |            |            |
| Pigment Deposition                     | 1          |            |            |            |
| SPLEEN (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                | (10)       | (10)       |            |            |
| LYMPH NODE, POPLITEAL<br>NO. EXAMINED) | (7)        | (9)        |            |            |
| STOMACH (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| DUODENUM (NO. EXAMINED)                | (10)       | (10)       |            |            |
| CECUM (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| Nematodiasis                           | 4          | 4          |            |            |
| COLON (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| Nematodiasis                           |            | 3          |            |            |
| SKIN (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| TESTIS (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| Atrophy                                | 1          | 1          |            |            |





# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

|                               | Group<br>L | Group<br>O | Group<br>M | Group<br>N |  |
|-------------------------------|------------|------------|------------|------------|--|
| UNG (NO. EXAMINED)            | (10)       | (10)       | (10)       | (10)       |  |
| Accumulations of Foamy        |            |            |            |            |  |
| Macrophages                   |            | 10         |            | 3          |  |
| Hyperplasia of Type II Cells  |            | 10         |            | 1          |  |
| Pigment Deposition            |            | 10         |            | 3          |  |
| Adhesion                      | 1          |            |            |            |  |
| Hemorrhage                    |            |            |            |            |  |
| Peribronchial Lymphoid        |            |            |            |            |  |
| Hyperplasia                   | 8          | 10         | 6          | 7          |  |
| NASAL CAVITY-LEVEL I          |            |            |            |            |  |
| (NO. EXAMINED)                | (9)        | (10)       | (10)       | (10)       |  |
| Hemorrhage                    |            |            |            |            |  |
| Submucosal Pigment Deposition |            | 4          |            |            |  |
| Congestion                    | 1          |            |            |            |  |
| Serous Exudate                | 1          |            |            |            |  |
| Foreign Material              |            | 1          |            |            |  |
| Nonsuppurative Rhinitis       |            |            |            |            |  |
| Cystic Glands                 |            |            |            |            |  |
| NASAL CAVITY-LEVEL II         |            |            |            |            |  |
| NO. EXAMINED)                 | (9)        | (10)       | (8)        | (9)        |  |
| Hemorrhage                    |            |            |            |            |  |
| Submucosal Pigment Deposition |            | 10         |            |            |  |
| Inflammation of Nasolacrimal  |            |            |            |            |  |
| Duct                          | 1          | 2          |            |            |  |
| Foreign Body                  |            |            |            |            |  |
| Focal Squamous Metaplasia     |            |            |            |            |  |
| Focal Inflammation            |            |            |            |            |  |
| Congestion                    | 1          |            |            |            |  |

# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

|                                   | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-----------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL II (CONTINUED) |            |            |            |            |
| Serous Exudate                    | 1          |            |            |            |
| Nonsuppurative Rhinitis           |            |            |            |            |
| Cystic Glands                     |            |            |            |            |
| NASAL CAVITY-LEVEL III            |            |            |            |            |
| (NO. EXAMINED)                    | (9)        | (10)       | (10)       | (9)        |
| Hemorrhage                        |            |            |            |            |
| Submucosal Pigment Deposition     |            | 10         |            | 4          |
| Serous Exudate                    | 1          |            |            |            |
| NASAL CAVITY-LEVEL IV             |            |            |            |            |
| (NO. EXAMINED)                    | (9)        | (10)       | (5)        | (7)        |
| Hemorrhage                        |            |            |            |            |
| Submucosal Pigment Deposition     |            | 10         |            | 2          |
| Serous Exudate                    | 1          |            |            |            |
| LYMPH NODE, TRACHEOBRONCHIAL      |            |            |            |            |
| (NO. EXAMINED)                    | (6)        | (8)        | (6)        | (8)        |
| Hyperplasia of Foamy              |            |            |            |            |
| Macrophages                       |            | 8          |            | 2          |
| Lymphoid Hyperplasia              | 1          | 8          |            |            |
| Pigment Deposition                |            | 8          |            | 2          |
| Hemorrhage                        |            |            |            | 2          |
| KIDNEY (NO. EXAMINED)             |            |            |            |            |
| (NO. EXAMINED)                    | (10)       | (10)       |            | (10)       |
| Regenerative Tubular              |            |            |            |            |
| Epithelium                        |            |            |            |            |
| Casts                             |            |            |            |            |
| Cortical Infarct                  |            |            |            |            |

# SUMMARY INCIDENCE TABLE

RZ-75  
Day Sacrifice  
Female Rats

|                           | Group<br>L | Group<br>O | Group<br>M | Group<br>N |  |
|---------------------------|------------|------------|------------|------------|--|
| KIDNEY (CONTINUED)        |            |            |            |            |  |
| Foci of Mononuclear Cells | 1          | 2          |            |            |  |
| Pigment Deposition        | 3          | 10         |            | 8          |  |
| LIVER (NO. EXAMINED)      | (10)       | (10)       | (10)       | (10)       |  |
| Bile Duct Hyperplasia     |            |            | 1          | 1          |  |
| Foci of Mononuclear Cells |            |            | 5          | 4          |  |
| Cholangiofibrosis         |            |            |            |            |  |
| Pigment Deposition        |            | 10         |            | 2          |  |
| BRAIN (NO. EXAMINED)      | (9)        | (10)       |            |            |  |
| PITUITARY (NO. EXAMINED)  | (8)        | (10)       |            |            |  |
| RENAL (NO. EXAMINED)      | (10)       | (10)       |            |            |  |
| Hemorrhage                |            |            |            |            |  |
| Vacuolated Cortical Cells |            |            |            |            |  |
| EYE (NO. EXAMINED)        | (9)        | (10)       |            |            |  |
| Corneal Subepithelial     |            |            |            |            |  |
| Basophilia                |            |            |            |            |  |
| THYROID (NO. EXAMINED)    | (10)       | (9)        |            |            |  |
| LARYNX (NO. EXAMINED)     | (10)       | (9)        |            |            |  |
| Foci of Mononuclear Cells |            | 2          |            |            |  |
|                           |            |            |            |            |  |
|                           |            |            |            |            |  |
|                           |            |            |            |            |  |

# SUMMARY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

|                                         | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-----------------------------------------|------------|------------|------------|------------|
| TRACHEA (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| Hemorrhage                              |            |            |            |            |
| HEART (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis              | 1          |            |            |            |
| Pigment Deposition                      |            |            |            |            |
| SPLEEN (NO. EXAMINED)                   | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| LYMPH NODE, POPLITEAL<br>(NO. EXAMINED) | (7)        | (8)        |            |            |
| STOMACH (NO. EXAMINED)                  | (10)       | (10)       |            |            |
| DUODENUM (NO. EXAMINED)                 | (10)       | (10)       |            |            |
| CECUM (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            | 4          | 1          |            |            |
| COLON (NO. EXAMINED)                    | (10)       | (10)       |            |            |
| Nematodiasis                            | 2          | 2          |            |            |
| SKIN (NO. EXAMINED)                     | (10)       | (10)       |            |            |
| OVARY (NO. EXAMINED)                    | (9)        | (10)       |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |
|                                         |            |            |            |            |

RZ-75  
90 Day Sacrifice  
Female Rats

1-10

NINETY-DAY SACRIFICE  
HISTOPATHOLOGY INCIDENCE TABLES

| <u>GROUP</u> | <u>DOSE<br/>(mg/m<sup>3</sup>)</u> | <u>TREATMENT</u>              |
|--------------|------------------------------------|-------------------------------|
| L            | 0                                  | Controls                      |
| M            | 1                                  | Low Exposure Concentration    |
| N            | 10                                 | Medium Exposure Concentration |
| O            | 100                                | High Exposure Concentration   |

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group L

ANIMAL

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

|                                    |                     |
|------------------------------------|---------------------|
| LUNG                               |                     |
| Accumulations of Foamy Macrophages |                     |
| Hyperplasia of Type II Cells       |                     |
| Pigment Deposition                 |                     |
| Adhesion                           |                     |
| Hemorrhage                         |                     |
| Peribronchial Lymphoid Hyperplasia | 2 1 2 1 1 1 1 1 1 1 |
| NASAL CAVITY-LEVEL I               | X X X X X X X X X X |
| Hemorrhage                         |                     |
| Submucosal Pigment Deposition      |                     |
| Congestion                         |                     |
| Serous Exudate                     |                     |
| Foreign Material                   |                     |
| Nonsuppurative Rhinitis            |                     |
| Cystic Glands                      |                     |
| NASAL CAVITY-LEVEL II              | X X X X X X X X X X |
| Hemorrhage                         |                     |
| Submucosal Pigment Deposition      |                     |
| Inflammation of Nasolacrimal Duct  |                     |
| Foreign Body                       |                     |
| Focal Squamous Metaplasia          |                     |
| Focal Inflammation                 |                     |

II-1

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

5 - Severe

6 - High

7 - Incomplete Section



# HISTOPATHOLOGY INCIDENCE TABLE

2-75  
90 Day Sacrifice  
Male Rats

Group L

| ANIMAL                           | NUMBER |   |   |   |   |   |   |   |   |   |
|----------------------------------|--------|---|---|---|---|---|---|---|---|---|
|                                  | 3      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  | 7      | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                  | 3      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  | 1      | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                  | -      | - | - | - | - | - | - | - | - | - |
|                                  | 0      | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                  | 0      | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                  | 9      | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| ASAL CAVITY-LEVEL II (CONTINUED) |        |   |   |   |   |   |   |   |   |   |
| Congestion                       |        |   |   |   |   |   |   |   |   |   |
| Serous Exudate                   |        |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis          |        |   |   |   |   |   |   |   |   |   |
| Cystic Glands                    |        |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL III            | X      | X | X | X | X | X | X | X | X | X |
| Hemorrhage                       |        |   |   |   |   |   |   |   |   | 2 |
| Submucosal Pigment Deposition    |        |   |   |   |   |   |   |   |   |   |
| Serous Exudate                   |        |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL IV             | X      | X | X | X | X | X | X | X | X | X |
| Hemorrhage                       |        |   |   |   |   |   |   |   |   | 2 |
| Submucosal Pigment Deposition    |        |   |   |   |   |   |   |   |   |   |
| Serous Exudate                   |        |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL     | N      | X | N | X | X | X | X | N | X | X |
| Hyperplasia of Foamy Macrophages |        |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia             |        |   |   |   |   |   |   |   |   |   |
| Pigment Deposition               |        |   |   |   |   |   |   |   |   |   |
| Hemorrhage                       |        |   |   |   |   |   |   |   |   |   |
| KIDNEY                           |        |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular Epithelium  |        |   |   |   |   |   |   |   |   |   |
| Casts                            | 1      | 1 | 1 | 1 |   |   |   |   |   | 1 |

II-2

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe High  
5 = Severe High 1 = Incomplete Section

A = Autopsy X = Not Autopsied  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Da Sacrifice  
Male Rats

Group L

|                                  | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|----------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                  |                                 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                  |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                  |                                 | - | - | - | - | - | - | - | - | - | - |
|                                  |                                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                  |                                 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                  |                                 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 |
| KIDNEY (CONTINUED)               |                                 |   |   |   |   |   |   |   |   |   |   |
| Cortical Infarct                 |                                 |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                                 |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition               |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| LIVER                            |                                 | X | X | X |   | X | X |   |   | X |   |
| Bile Duct Hyperplasia            |                                 |   |   |   | 1 |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                                 |   |   |   |   |   | 1 |   |   | 2 |   |
| Cholangiofibrosis                |                                 |   |   |   |   |   |   | 1 |   |   |   |
| Pigment Deposition               |                                 |   |   |   |   |   |   |   |   |   |   |
| BRAIN                            |                                 | X | X | X | X | X | X | X | X | X | X |
| PITUITARY                        |                                 | X | X | X | X | X | X | X | X | X | X |
| ADRENAL                          |                                 | X | X |   | X | X | X | X | X | X | X |
| Hemorrhage                       |                                 |   |   | 2 |   |   |   |   |   |   |   |
| Vacuolated Cortical Cells        |                                 |   |   |   |   |   |   |   |   |   |   |
| EYE                              |                                 | X | X | X | X | X | X | X | X | X | X |
| Corneal Subepithelial Basophilia |                                 |   |   |   |   |   |   |   |   |   |   |
| THYROID                          |                                 | X | X | X | X | X | X | N | X | X |   |

II-3

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderate to Severe High  
5 = Severe High 1 = Incomplete Section

A = Atypical X = Not Remarkable  
3 = Moderate 4 = Moderate to Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

2-75  
0 Day Sacrifice  
Male Rats

Group L

|                            | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|----------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                            | 7                               | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                            | 3                               | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                            | 1                               | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            | -                               | - | - | - | - | - | - | - | - | - | - |
|                            | 0                               | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                            | 0                               | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            | 9                               | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |   |
| ARYNX                      |                                 | X | X | X | X | X | X | X | N | X | X |
| Foci of Mononuclear Cells  |                                 |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                    |                                 | X | X | X |   | X | X | X | X | X | X |
| Hemorrhage                 |                                 |   |   |   | 2 |   |   |   |   |   |   |
| HEART                      |                                 |   |   |   | X |   |   |   |   |   | X |
| Nonsuppurative Myocarditis |                                 | 2 | 1 | 1 |   | 1 | 1 | 1 | 1 | 2 |   |
| Pigment Deposition         |                                 |   |   |   | 1 |   |   |   |   |   |   |
| SPLEEN                     |                                 | X | X | X | X | X | X | X | X | X | X |
| PANCREAS                   |                                 | X | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL      |                                 | X | X | X | X | X | X | N | N | X | N |
| STOMACH                    |                                 | X | X | X | X | X | X | X | X | X | X |
| DUODENUM                   |                                 | X | X | X | X | X | X | X | X | X | X |
| CECUM                      |                                 | X | X |   |   |   | X | X | X | X |   |
| Nematodiasis               |                                 |   |   |   | P | P | P |   |   |   | P |
| COLON                      |                                 | X | X | X | X | X | X | X | X | X | X |
| Nematodiasis               |                                 |   |   |   |   |   |   |   |   |   |   |

11-4

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present  
1 = Mild  
5 = Severe High  
N = No Section  
2 = Slight  
1 = Low Section

A = Absent  
3 = Moderate  
4 = Moderate Severe

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Group L

[illegible]

# HISTOPATHOLOGY INCIDENCE TABLE

2-75  
0 Day Sacrifice  
Male Rats

Group 0

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## LUNG

|                                    |   |   |   |   |   |   |   |   |   |   |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|
| Accumulations of Foamy Macrophages | 2 | 3 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |
| Hyperplasia of Type II Cells       | 2 | 3 | 3 | 2 | 2 | 3 | 3 | 3 | 2 | 3 |
| Pigment Deposition                 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 |
| Adhesion                           |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia | 2 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 2 |

## NASAL CAVITY-LEVEL I

|                               |   |   |   |   |   |   |  |   |   |   |
|-------------------------------|---|---|---|---|---|---|--|---|---|---|
| Hemorrhage                    | 1 |   |   |   | 2 |   |  |   | 2 |   |
| Submucosal Pigment Deposition | 1 | 1 | 1 | 1 |   | 1 |  | 1 | 2 | 2 |
| Congestion                    |   |   |   |   |   |   |  |   |   |   |
| Serous Exudate                |   |   |   |   |   |   |  |   |   |   |
| Foreign Material              |   |   |   |   |   |   |  |   |   |   |
| Nonsuppurative Rhinitis       |   |   |   |   |   |   |  |   |   |   |
| Cystic Glands                 |   |   |   |   |   |   |  |   |   |   |

## NASAL CAVITY-LEVEL II

|                                   |   |   |   |   |   |   |   |   |   |   |
|-----------------------------------|---|---|---|---|---|---|---|---|---|---|
| Hemorrhage                        | 1 |   |   |   |   |   |   |   |   | 2 |
| Submucosal Pigment Deposition     | 2 | 2 | 2 | 1 | 3 | 2 | 2 | 2 | 2 | 3 |
| Inflammation of Nasolacrimal Duct |   |   | 2 |   | 2 | 2 |   | 2 |   |   |
| Foreign Body                      |   |   |   |   |   |   |   | P |   |   |
| Focal Squamous Metaplasia         |   |   |   |   |   |   |   | 2 |   |   |
| Focal Inflammation                |   |   |   |   |   |   |   | 3 |   |   |

11-6

EPL

Experimental Pathology Laboratories, Inc

Key: 0 = Present  
1 = Minimal  
2 = Slight  
3 = Moderate  
4 = Severe  
5 = Severe High  
6 = No Section  
7 = Slight  
8 = Moderate  
9 = Incomplete Section

A = Alveoli  
B = Bronchi  
C = Capillaries  
D = Ducts  
E = Epithelium  
F = Fibroblasts  
G = Glands  
H = Hemorrhage  
I = Inflammation  
J = Joints  
K = Kidneys  
L = Lungs  
M = Muscles  
N = Nerves  
O = Osteoblasts  
P = Pigment  
Q = Squamous Metaplasia  
R = Rhinitis  
S = Serous Exudate  
T = Tissue  
U = Unidentified  
V = Vessels  
W = Wounds  
X = Unknown

133

**Group 0**

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

| NASAL CAVITY-LEVEL II (CONTINUED) |  |  |  |  |  |  |  |  |  |  |
|-----------------------------------|--|--|--|--|--|--|--|--|--|--|
| Congestion                        |  |  |  |  |  |  |  |  |  |  |
| Serous Exudate                    |  |  |  |  |  |  |  |  |  |  |
| Nonsuppurative Rhinitis           |  |  |  |  |  |  |  |  |  |  |
| Cystic Glands                     |  |  |  |  |  |  |  |  |  |  |
|                                   |  |  |  |  |  |  |  |  |  |  |
| NASAL CAVITY-LEVEL III            |  |  |  |  |  |  |  |  |  |  |
| Hemorrhage                        |  |  |  |  |  |  |  |  |  |  |
| Submucosal Pigment Deposition     |  |  |  |  |  |  |  |  |  |  |
| Serous Exudate                    |  |  |  |  |  |  |  |  |  |  |
|                                   |  |  |  |  |  |  |  |  |  |  |
| NASAL CAVITY-LEVEL IV             |  |  |  |  |  |  |  |  |  |  |
| Hemorrhage                        |  |  |  |  |  |  |  |  |  |  |
| Submucosal Pigment Deposition     |  |  |  |  |  |  |  |  |  |  |
| Serous Exudate                    |  |  |  |  |  |  |  |  |  |  |
|                                   |  |  |  |  |  |  |  |  |  |  |
| LYMPH NODE, TRACHEOBRONCHIAL      |  |  |  |  |  |  |  |  |  |  |
| Hyperplasia of Foamy              |  |  |  |  |  |  |  |  |  |  |
| Macrophages                       |  |  |  |  |  |  |  |  |  |  |
| Lymphoid Hyperplasia              |  |  |  |  |  |  |  |  |  |  |
| Pigment Deposition                |  |  |  |  |  |  |  |  |  |  |
| Hemorrhage                        |  |  |  |  |  |  |  |  |  |  |
|                                   |  |  |  |  |  |  |  |  |  |  |
| KIDNEY                            |  |  |  |  |  |  |  |  |  |  |
| Regenerative Tubular              |  |  |  |  |  |  |  |  |  |  |
| Epithelium                        |  |  |  |  |  |  |  |  |  |  |
| Casts                             |  |  |  |  |  |  |  |  |  |  |

# HISTOPATHOLOGY INCIDENCE TABLE

6-2-75  
 0 Day Sacrifice  
 Male Rats

Group 0

ANUMBER  
 I M B E R  
 A L

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## KIDNEY (CONTINUED)

Cortical Infarct

2

Foci of Mononuclear Cells

1 1 1

Pigment Deposition

3 3 3 3 2 2 3 3 3 3

## LIVER

Bile Duct Hyperplasia

Foci of Mononuclear Cells

1 1 1

Cholangiofibrosis

Pigment Deposition

1 1 1 1 1 1 1 1 1 1

## BRAIN

X X X X X X X X X X

## PITUITARY

N X X X X X N X X X

## ADRENAL

Hemorrhage

Vacuolated Cortical Cells

2

## EYE

Corneal Subepithelial

Basophilia

2

## THYROID

X X X X N X X X X X

11-8

EPL

Experimental Pathology Laboratories, Inc

Key P=Present N=No Section  
 1=Minimal 2=Spot  
 3=Severe High 4=Incomplete Section

A=Atrophic X=Extensive  
 1=Minimal 2=Spot  
 3=Severe High 4=Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group 0

| ANIMAL                     |   |   |   |   |   |   |   |   |   |   |
|----------------------------|---|---|---|---|---|---|---|---|---|---|
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|                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                            | - | - | - | - | - | - | - | - | - | - |
|                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                            | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| LARYNX                     | X |   | X | X | N | X |   | X | X | X |
| Foci of Mononuclear Cells  | 1 |   |   |   |   |   | 1 |   |   |   |
| TRACHEA                    | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                 |   |   |   |   |   |   |   |   |   |   |
| HEART                      |   |   | X | X | X |   | X | X | X | X |
| Nonsuppurative Myocarditis | 1 | 2 |   |   |   | 1 |   |   |   |   |
| Pigment Deposition         |   |   |   |   |   |   |   |   |   |   |
| SPLEEN                     | X | X | X | X | X | X | X | X | X | X |
| PANCREAS                   | X | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL      | X | X | X | X | X | N | X | X | X | X |
| STOMACH                    | X | X | X | X | X | X | X | X | X | X |
| DUODENUM                   | X | X | X | X | X | X | X | X | X | X |
| CECUM                      |   | X |   | X |   |   | X | X | X | X |
| Nematodiasis               | P |   | P |   | P | P |   |   |   |   |
| COLON                      |   |   | X |   | X | X | X | X | X | X |
| Nematodiasis               | P | P |   | P |   |   |   |   |   |   |

II-9

EPL

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section  
1 - Minimal 2 - Slight  
3 - Moderate 4 - Moderately Severe High  
5 - Severe High 6 - Incomplete Section

A - Autolysis X - Not Remarkable  
3 - Moderate 4 - Moderately Severe High



# HISTOPATHOLOGY INCIDENCE TABLE

Z-75  
30 Day Sacrifice  
Male Rats

Group 0

ANUMBER  
M  
A  
L  
R

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

KIN

X X X X X X X X X X

ESTIS

X X X X X X X X X

Atrophy

5

PIDIDYMIS

X X X X X X X X X

Spermatic Granuloma

P

Aspermia

P

PROSTATE

X X N X X X X X X X

Nonsuppurative Prostatitis

URINARY BLADDER

X X X X X X X X X X

FEMUR

X X N X X X X X X X

ADIPOSE TISSUE

X X X X X X X X X X

STERNUM

X

11-10

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Minimal

5 = Severe High

N = No Section

2 = Slight

1 = Incidental Section

A = Atrophic

3 = Moderate

4 = Moderate, Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group M

|                                    | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |   |
|------------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|---|
|                                    |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |   |   |
|                                    |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |   |
|                                    |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |   |   |
|                                    |                            |                            | - | - | - | - | - | - | - | - | - |   |   |
|                                    |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |   |
|                                    |                            |                            | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |
|                                    |                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |   |
| LUNG                               |                            |                            |   |   |   |   |   | X |   | X |   |   |   |
| Accumulations of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Adhesion                           |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 |   | 1 | 1 |   |   |
| NASAL CAVITY-LEVEL I               |                            |                            |   | X | X | X | X | X |   | X | X | X |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   | 1 |   |   |   |   |
| Submucosal Pigment Deposition      |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Congestion                         |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Foreign Material                   |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis            |                            |                            | 1 |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |                            |                            |   |   |   |   |   |   | 1 |   |   |   |   |
| NASAL CAVITY-LEVEL II              |                            |                            |   | X | X | X | N | X | N |   | X | X | X |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   | 2 |   |   |   |
| Submucosal Pigment Deposition      |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Foreign Body                       |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Focal Squamous Metaplasia          |                            |                            |   |   |   |   |   |   |   |   |   |   |   |
| Focal Inflammation                 |                            |                            |   |   |   |   |   |   |   |   |   |   |   |

II-11

EPL

Experimental Pathology Laboratories, Inc

Key P = Presort N = In Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderate to Severe High  
5 = Severe High 1 = Incomplete Section

A = Autopsy X = Not Examined  
3 = Moderate 4 = Moderate to Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group M

|                                   | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|-----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                   |                            |                            | - | - | - | - | - | - | - | - | - | - |
|                                   |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                   |                            |                            | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL II (CONTINUED) |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Congestion                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                            |                            |   |   |   |   |   |   | 1 |   |   |   |
| NASAL CAVITY-LEVEL III            |                            |                            | N | X | X | X | X | X |   | X | X | X |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   | 3 |   |   |   |
| Submucosal Pigment Deposition     |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV             |                            |                            | X | N | X | X | X | X |   | X | X | X |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   | 3 |   |   |   |
| Submucosal Pigment Deposition     |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL      |                            |                            | X | X | X |   | X | N |   | X | X |   |
| Hyperplasia of Foamy Macrophages  |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia              |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   | 1 |   |   | 2 |   | 1 |   |

11-12

EPL

Experimental Pathology Laboratories, Inc

Key: P = Present  
1 = Mild  
2 = Slight  
3 = Moderate  
4 = Moderate to Severe  
5 = Severe  
N = No Section  
2 = Slight  
3 = Moderate  
4 = Moderate to Severe  
5 = Severe  
1 = Mild  
2 = Slight  
3 = Moderate  
4 = Moderate to Severe  
5 = Severe

A = All  
3 = Moderate  
4 = Moderate to Severe  
5 = Severe

### HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group N

[illegible]

# HISTOPATHOLOGY INCIDENCE TABLE

Z-75  
90 Day Sacrifice  
Male Rats

Group N

| ANUM<br>BER                      |   |   |   |   |   |   |   |   |   |   |
|----------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                  | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                  | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  | - | - | - | - | - | - | - | - | - | - |
|                                  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                  | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                  | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| ASAL CAVITY-LEVEL II (CONTINUED) |   |   |   |   |   |   |   |   |   |   |
| Congestion                       |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                   |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis          |   |   |   |   | 1 |   |   |   |   |   |
| Cystic Glands                    |   |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL III            | X | X |   | X | X | X | X | X | N | X |
| Hemorrhage                       |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition    |   |   |   |   | 1 |   |   |   |   |   |
| Serous Exudate                   |   |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL IV             | X | X | X | X | X | X | N | X | N | X |
| Hemorrhage                       |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition    |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                   |   |   |   |   |   |   |   |   |   |   |
| MPH NODE, TRACHEOBRONCHIAL       | X |   |   |   | X | X | X | X | X | X |
| Hyperplasia of Foamy             |   |   |   |   |   |   |   |   |   |   |
| Macrophages                      |   |   |   |   | 1 | 1 |   |   |   |   |
| Lymphoid Hyperplasia             | 1 |   |   |   |   |   |   |   |   |   |
| Pigment Deposition               |   |   |   |   | 1 | 1 |   |   |   |   |
| Hemorrhage                       |   |   |   |   |   |   |   |   |   |   |
| DNEY                             |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular             |   |   |   |   |   |   |   |   |   |   |
| Epithelium                       | 1 |   |   | 1 | 1 | 1 |   | 1 |   | 1 |
| Casts                            |   |   |   |   | 1 |   |   |   |   |   |

11-14

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

N = No Section

A = Absent

X = Not Reported

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

1 = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Male Rats

Group N

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## KIDNEY (CONTINUED)

Cortical Infarct

Foci of Mononuclear Cells

1

Pigment Deposition

1 1 1 1 1 1 1 1 1 1

## LIVER

X X X X X X X X

Bile Duct Hyperplasia

Foci of Mononuclear Cells

1 1

Cholangiofibrosis

Pigment Deposition

11-15

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe  
5 = Severe High 1 = Incomplete Section

A = Atypical X = Not Remarkable  
3 = Moderate 4 = Moderately Severe

| <u>GROUP</u> | <u>DOSE<br/>(mg/m<sup>3</sup>)</u> | <u>TREATMENT</u>              |
|--------------|------------------------------------|-------------------------------|
| L            | 0                                  | Controls                      |
| M            | 1                                  | Low Exposure Concentration    |
| N            | 10                                 | Medium Exposure Concentration |
| O            | 100                                | High Exposure Concentration   |

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group L

|   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| N | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| U | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| M | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| B | - | - | - | - | - | - | - | - | - | - |
| E | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| R | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| L | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

|                                    |  |   |   |   |   |   |   |   |   |   |
|------------------------------------|--|---|---|---|---|---|---|---|---|---|
| LUNG                               |  |   |   |   |   | X |   |   |   | X |
| Accumulations of Foamy Macrophages |  |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |  |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |  |   |   |   |   |   |   |   |   |   |
| Adhesion                           |  |   |   |   | P |   |   |   |   |   |
| Hemorrhage                         |  |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |  | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 |   |
| NASAL CAVITY-LEVEL I               |  | X | X | X | X | N | X | X | X | X |
| Hemorrhage                         |  |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |  |   |   |   |   |   |   |   |   |   |
| Congestion                         |  |   |   |   |   |   |   |   | 3 |   |
| Serous Exudate                     |  |   |   |   |   |   |   |   | 3 |   |
| Foreign Material                   |  |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis            |  |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |  |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II              |  | X |   | X | X | N | X | X | X | X |
| Hemorrhage                         |  |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |  |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |  |   |   |   |   |   |   |   | 2 |   |
| Foreign Body                       |  |   |   |   |   |   |   |   |   |   |
| Focal Squamous Metaplasia          |  |   |   |   |   |   |   |   |   |   |
| Focal Inflammation                 |  |   |   |   |   |   |   |   |   |   |

II-16

EPL

Experimental Pathology Laboratories, Inc

Key P=Present N=No Section  
1=Minimal 2=Slight  
3=Moderate 4=Markedly Severe  
5=Severe High 1=Incomplete Section

A=Autolysis 3=Markedly Severe  
4=Markedly Severe High



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group L

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## NASAL CAVITY-LEVEL II (CONTINUED)

Congestion

3

Serous Exudate

3

Nonsuppurative Rhinitis

Cystic Glands

## NASAL CAVITY-LEVEL III

X X X X N X X X X

Hemorrhage

Submucosal Pigment Deposition

Serous Exudate

1

## NASAL CAVITY-LEVEL IV

X X X X N X X X X

Hemorrhage

Submucosal Pigment Deposition

Serous Exudate

1

## LYMPH NODE, TRACHEOBRONCHIAL

X X X X X N N N N

Hyperplasia of Foamy

Macrophages

Lymphoid Hyperplasia

2

Pigment Deposition

Hemorrhage

## KIDNEY

X X X X X X

Regenerative Tubular

Epithelium

Casts

II-17

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Minimal

5 = Severe/High

N = No Section

2 = Slight

1 = Intermediate Section

A = Absent

3 = Moderate

4 = Moderate to Severe/High

X = Not Examined

4 = Moderate to Severe/High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group L

ANUM  
BER  
AL

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## KIDNEY (CONTINUED)

Cortical Infarct

Foci of Mononuclear Cells

Pigment Deposition

## LIVER

Bile Duct Hyperplasia

Foci of Mononuclear Cells

Cholangiofibrosis

Pigment Deposition

## BRAIN

## PITUITARY

## ADRENAL

Hemorrhage

Vacuolated Cortical Cells

## EYE

Corneal Subepithelial

Basophilia

## THYROID

11-18

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Mild 2 = Slight  
3 = Moderate 4 = Marked 5 = Severe  
- = Incomplete Section

A = Autopsy X = Not Remarkable  
2 = Moderate 4 = Marked 5 = Severe

# HISTOPATHOLOGY INCIDENCE TABLE

52-75  
0 Day Sacrifice  
Female Rats

Group L

|                            | A<br>N<br>N<br>U<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|----------------------------|--------------------------------------|---|---|---|---|---|---|---|---|---|---|
|                            |                                      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                            |                                      | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                            |                                      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                            |                                      | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            |                                      | - | - | - | - | - | - | - | - | - | - |
|                            |                                      | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                            |                                      | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            |                                      | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| ARYNX                      |                                      | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells  |                                      |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                    |                                      | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                 |                                      |   |   |   |   |   |   |   |   |   |   |
| HEART                      |                                      | X | X | X | X | X |   |   | X | X | X |
| Nonsuppurative Myocarditis |                                      |   |   |   |   |   | 1 |   |   |   |   |
| Pigment Deposition         |                                      |   |   |   |   |   |   |   |   |   |   |
| SPLEEN                     |                                      | X | X | X | X | X | X | X | X | X | X |
| PANCREAS                   |                                      | X | X | X | X | X | X | X | X | X | X |
| LYMPH NODE, POPLITEAL      |                                      | X | X | X | N | X | X | N | N | X | X |
| STOMACH                    |                                      | X | X | X | X | X | X | X | X | X | X |
| THYROID                    |                                      | X | X | X | X | X | X | X | X | X | X |
| ECUM                       |                                      | X |   | X | X |   |   |   | X | X | X |
| Nematodiasis               |                                      |   | P |   |   | P | P | P |   |   |   |
| COLON                      |                                      | X | X |   | X | X | X | X |   | X | X |
| Nematodiasis               |                                      |   |   | P |   |   |   | P |   |   |   |

11-19

EPL

Experimental Pathology Laboratories, Inc

Key P - Present N - N Section  
1 - Minimal 2 - Slight  
5 - Severe High 1 - Incomplete Section

A - Adipose 1 - Incomplete Section  
3 - Moderate 4 - Moderate to Severe

100

Group L

[illegible]

# HISTOPATHOLOGY INCIDENCE TABLE

27-75  
30 Day Sacrifice  
Female Rats

Group 0

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

UNG

Accumulations of Foamy

Macrophages

Hyperplasia of Type II Cells

Pigment Deposition

Adhesion

Hemorrhage

Peribronchial Lymphoid

Hyperplasia

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 3 |
| 3 | 3 | 3 | 2 | 3 | 3 | 2 | 2 | 2 | 3 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 1 |

NASAL CAVITY-LEVEL I

Hemorrhage

Submucosal Pigment Deposition

Congestion

Serous Exudate

Foreign Material

Nonsuppurative Rhinitis

Cystic Glands

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X |   | X |   | X |   | X |   | X |
|   |   | 1 |   | 1 |   | 1 |   | 1 |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |

NASAL CAVITY-LEVEL II

Hemorrhage

Submucosal Pigment Deposition

Inflammation of Nasolacrimal

Duct

Foreign Body

Focal Squamous Metaplasia

Focal Inflammation

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|   |   |   |   | 1 |   |   |   |   | 2 |

11-21

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Marked  
5 = Severe High 1 = Incomplete Section

A = Adipose X = Squamous Metaplasia  
3 = Moderate 4 = Marked 5 = Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group 0

|                                   | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|-----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                   |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                   |                            |                            | - | - | - | - | - | - | - | - | - | - |
|                                   |                            |                            | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                   |                            |                            | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL II (CONTINUED) |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Congestion                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                            |                            |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 |   |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV             |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                            |                            | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 3 | 3 | 3 |
| Serous Exudate                    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL      |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Foamy              |                            |                            | N |   |   |   |   |   |   |   | N |   |
| Macrophages                       |                            |                            |   | 2 | 3 | 1 | 3 | 2 | 2 | 2 | 2 |   |
| Lymphoid Hyperplasia              |                            |                            |   | 2 | 3 | 4 | 3 | 2 | 2 | 4 | 3 |   |
| Pigment Deposition                |                            |                            |   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
| Hemorrhage                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                            |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular              |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Epithelium                        |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Casts                             |                            |                            |   |   |   |   |   |   |   |   |   |   |

11-22

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

N = No Section

A = Absent

3 = Moderate

1 = Minimal

2 = Slight

4 = Moderate

5 = Severe

5 = Severe High

1 = Incomplete Section

4 = Moderate Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

42-75  
90 Day Sacrifice  
Female Rats

Group 0

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## KIDNEY (CONTINUED)

Cortical Infarct

Foci of Mononuclear Cells

Pigment Deposition

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 |   |   |   |   |   |   |   |   |
| 2 | 3 | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 3 |

## LIVER

Bile Duct Hyperplasia

Foci of Mononuclear Cells

Cholangiofibrosis

Pigment Deposition

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|---|---|---|---|---|---|---|---|---|---|

## RAIN

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X | X | X | X | X | X | X | X | X |
|---|---|---|---|---|---|---|---|---|---|

## PITUITARY

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X | X | X | X | X | X | X | X | X |
|---|---|---|---|---|---|---|---|---|---|

## ADRENAL

Hemorrhage

Vacuolated Cortical Cells

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X | X | X | X | X | X | X | X | X |
|---|---|---|---|---|---|---|---|---|---|

## EYE

Corneal Subepithelial

Basophilia

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X | X | X | X | X | X | X | X | X |
|---|---|---|---|---|---|---|---|---|---|

## THYROID

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| X | X | X | X | X | X | X | N | X | X |
|---|---|---|---|---|---|---|---|---|---|

11-23

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

N = No Section

A = Atrophy

X = Not Determinable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe

5 = Severe

6 = High

7 = Severe High

8 = Severe High

9 = Severe High

## HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

## Group 0

[illegible]

11-24

EPL

Experimental Pathology Laboratories, Inc.

### Key

Թ. Նիկոնի

1 - Minimal

$$S = S(t, r, \theta)$$

N = No. Section

2 - 5. gnt

1 - 100% complete section

A = 2.5, 2.5, 2.5

3 - Major: JLE

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840. 84

4 - 1st Grade, Spelling List



25



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A = Agitation      2 = Moderate Pain  
3 = Moderate Pain      4 = Severe Pain

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group M

|                                    | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                    |                            | 7                          | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                    |                            | 3                          | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                            | 2                          | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                    |                            | -                          | - | - | - | - | - | - | - | - | - |
|                                    |                            | 5                          | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                    |                            | 0                          | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                            | 9                          | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| LUNG                               |                            |                            | X | X | X |   | X |   |   |   |   |
| Accumulations of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                            |                            |   |   |   |   |   |   |   |   |   |
| Adhesion                           |                            |                            |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                            |                            |   |   | 1 |   | 1 | 1 | 1 | 1 | 1 |
| NASAL CAVITY-LEVEL I               |                            |                            | X | X | X | X | X | X | X | X | X |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                            |                            |   |   |   |   |   |   |   |   |   |
| Congestion                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |                            |                            |   |   |   |   |   |   |   |   |   |
| Foreign Material                   |                            |                            |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis            |                            |                            |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |                            |                            |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II              |                            |                            | X | X | X | X | X | N | X | N | X |
| Hemorrhage                         |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                            |                            |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |                            |                            |   |   |   |   |   |   |   |   |   |
| Foreign Body                       |                            |                            |   |   |   |   |   |   |   |   |   |
| Focal Squamous Metaplasia          |                            |                            |   |   |   |   |   |   |   |   |   |
| Focal Inflammation                 |                            |                            |   |   |   |   |   |   |   |   |   |

11-26

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

N = No Section

A = Autopsy

X = Not Reportable

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderate to Severe

5 = Severe

High

1 = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

7-75  
0 Day Sacrifice  
Female Rats

Group M

|                                   | A<br>N<br>N<br>U<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|-----------------------------------|--------------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                   |                                      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                                      | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                   |                                      | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                   |                                      | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                   |                                      | - | - | - | - | - | - | - | - | - | - |
|                                   |                                      | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                   |                                      | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                   |                                      | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL II (CONTINUED) |                                      |   |   |   |   |   |   |   |   |   |   |
| Congestion                        |                                      |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                                      |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis           |                                      |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                     |                                      |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III            |                                      | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                        |                                      |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                      |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                                      |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL IV             |                                      | N | N | N | X | N | N | X | X | X | X |
| Hemorrhage                        |                                      |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition     |                                      |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                    |                                      |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL      |                                      | X | X | N | X | X | N | X | N | N | X |
| Hyperplasia of Foamy Macrophages  |                                      |   |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia              |                                      |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                |                                      |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                        |                                      |   |   |   |   |   |   |   |   |   |   |
| LIVER                             |                                      | X | X |   |   |   | X |   |   | X | X |
| Bile Duct Hyperplasia             |                                      |   |   | 1 |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells         |                                      |   |   | 1 | 1 | 1 |   | 1 | 1 |   |   |
| Cholangiofibrosis                 |                                      |   |   |   |   |   |   |   |   |   |   |

11-27

EPL

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe High

A = Absent X = Not Remarkable  
3 = Moderate 4 = Moderately Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

R2-75  
90 Day Sacrifice  
Female Rats

Group M

ANUMBER  
IMAL

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

LIVER (CONTINUED)

Pigment Deposition

11-28

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Moderately Severe  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Not Remarkable  
3 = Moderate 4 = Moderately Severe

# HISTOPATHOLOGY INCIDENCE TABLE

Z-75  
90 Day Sacrifice  
Female Rats

Group N

|                                    | A<br>N<br>I<br>M<br>B<br>E<br>R |   |   |   |   |   |   |   |   |   |   |
|------------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                    |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                                 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                    |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                                 | - | - | - | - | - | - | - | - | - | - |
|                                    |                                 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                    |                                 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                                 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| LUNG                               |                                 |   |   |   |   |   |   | X | X |   |   |
| Accumulations of Foamy Macrophages |                                 | 1 | 1 |   | 1 |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                                 |   | 1 |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                                 | 1 | 1 |   | 1 |   |   |   |   |   |   |
| Adhesion                           |                                 |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                                 | 1 |   | 1 | 1 | 1 | 1 |   |   | 1 |   |
| NASAL CAVITY-LEVEL I               |                                 | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                                 |   |   |   |   |   |   |   |   |   |   |
| Congestion                         |                                 |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |                                 |   |   |   |   |   |   |   |   |   |   |
| Foreign Material                   |                                 |   |   |   |   |   |   |   |   |   |   |
| Nonsuppurative Rhinitis            |                                 |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |                                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II              |                                 | X | X | X | X | X | X | X | X | N | X |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                                 |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |                                 |   |   |   |   |   |   |   |   |   |   |
| Foreign Body                       |                                 |   |   |   |   |   |   |   |   |   |   |
| Focal Squamous Metaplasia          |                                 |   |   |   |   |   |   |   |   |   |   |
| Focal Inflammation                 |                                 |   |   |   |   |   |   |   |   |   |   |

11-29

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
90 Day Sacrifice  
Female Rats

Group N

|                            |                            |   |   |   |   |   |   |   |   |   |   |
|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
| A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |   |
|                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|                            |                            | - | - | - | - | - | - | - | - | - |   |
|                            |                            | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |   |
|                            |                            | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |
|                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## NASAL CAVITY-LEVEL II (CONTINUED)

|                         |  |
|-------------------------|--|
| Congestion              |  |
| Serous Exudate          |  |
| Nonsuppurative Rhinitis |  |
| Cystic Glands           |  |

## NASAL CAVITY-LEVEL III

|                               |   |   |   |   |   |   |
|-------------------------------|---|---|---|---|---|---|
| Hemorrhage                    | X | N | X | X | X | X |
| Submucosal Pigment Deposition | 1 | 1 | 1 | 1 | 1 | 1 |
| Serous Exudate                |   |   |   |   |   |   |

## NASAL CAVITY-LEVEL IV

|                               |   |   |   |   |   |   |   |   |
|-------------------------------|---|---|---|---|---|---|---|---|
| Hemorrhage                    | X | X | N | N | X | X | X | N |
| Submucosal Pigment Deposition |   |   | 1 |   |   |   | 1 |   |
| Serous Exudate                |   |   |   |   |   |   |   |   |

## LYMPH NODE, TRACHEOBRONCHIAL

|                                  |   |   |   |   |   |   |
|----------------------------------|---|---|---|---|---|---|
| Hyperplasia of Foamy Macrophages | X | X | N | X | N | X |
| Lymphoid Hyperplasia             |   |   |   |   |   |   |
| Pigment Deposition               |   |   | 1 |   |   | 1 |
| Hemorrhage                       |   |   |   | 1 |   | 2 |

## KIDNEY

|                                 |  |   |   |
|---------------------------------|--|---|---|
| Regenerative Tubular Epithelium |  | X | X |
| Casts                           |  |   |   |

II-30

EPL

Experimental Pathology Laboratories, Inc

Key: P = Present, N = No Section, A = Absent, 1 = Minimal, 2 = Slight, 3 = Moderate, 4 = Moderately Severe, 5 = Severe, High, I = Incomplete Section

1 = Minimal, 2 = Slight, 3 = Moderate, 4 = Moderately Severe, 5 = Severe, High, I = Incomplete Section

# HISTOPATHOLOGY INCIDENCE TABLE

12-75  
90 Day Sacrifice  
Female Rats

Group N

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## KIDNEY (CONTINUED)

Cortical Infarct

Foci of Mononuclear Cells

Pigment Deposition

1 1 1 1 1 1 1 1 1

## LIVER

X X X X

Bile Duct Hyperplasia

1

Foci of Mononuclear Cells

1 1 1 1

Cholangiofibrosis

Pigment Deposition

1 1

11-31

EPL

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
3 = Moderate 4 = Marked  
5 = Severe High 1 = Incomplete Section

A = Atypical X = Not Remarkable  
3 = Moderate 4 = Marked  
5 = Severe High 1 = Incomplete Section

NINETY-DAY SACRIFICE

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES



RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Males

Species Rats

| Animal Number | Client's Tissue Identification | Client's Gross Observations     | Microscopic Observations                                                                                                                                                     |
|---------------|--------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3734-009      | Skin                           | Green hair                      | No corresponding lesion<br>Hyperplasia of foamy macrophages;<br>lymphoid hyperplasia; pigment deposition                                                                     |
|               | Tracheobronchial lymph node    | Dark brown                      |                                                                                                                                                                              |
|               | Lung                           | Mottled green areas             |                                                                                                                                                                              |
|               | Fatty tissue                   | Green tinted                    |                                                                                                                                                                              |
| 3734-010      | Skin                           | Green                           | No corresponding lesion<br>Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition                                                                        |
|               | Tracheobronchial lymph node    | Dark and enlarged 2x            |                                                                                                                                                                              |
|               | Lung                           | Diffuse moderate dye deposition |                                                                                                                                                                              |
|               | Stomach                        | Green contents                  |                                                                                                                                                                              |
| 3734-011      | All body fat                   | Green                           | No corresponding lesion<br>No corresponding lesion (adipose tissue)<br>No corresponding lesion<br>Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition |
|               | Skin                           | Green                           |                                                                                                                                                                              |
|               | Tracheobronchial lymph node    | Dark and enlarged 2x            |                                                                                                                                                                              |
|               | All body fat                   | Green                           |                                                                                                                                                                              |

RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Males

Species Rats

| Animal Number        | Client's Tissue Identification | Client's Gross Observations               | Microscopic Observations                                                             |
|----------------------|--------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------|
| 3734-011<br>(Cont'd) | Lung                           | Diffuse mild-moderate dye deposition      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3734-012             | Skin                           | Green                                     | No corresponding lesion                                                              |
|                      | Tracheobronchial lymph node    | Dark greenish brown color                 | Hyperplasia of foamy macrophages; lymphoid hyperplasia; pigment deposition           |
|                      | Lung                           | Dark greenish brown mottling in all lobes | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Fatty tissue                   | Green                                     | No corresponding lesion (adipose tissue)                                             |
| 3734-013             | Skin                           | Green                                     | No corresponding lesion                                                              |
|                      | Tracheobronchial lymph node    | Dark and enlarged 2x                      | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Diffuse moderate dye deposition           | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Stomach                        | Green contents                            | No corresponding lesion                                                              |
|                      | All body fat                   | Green                                     | No corresponding lesion (adipose tissue)                                             |
| 3734-014             | Skin                           | Green hair                                | No corresponding lesion                                                              |
|                      | Fat tissue                     | Green tinted                              | No corresponding lesion (adipose tissue)                                             |

RZ-75

90 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rats Sex: Males Group Number: 0 - Sacrificed Dosage Level: 100 mg/m<sup>3</sup>

| Animal Number        | Client's Tissue Identification | Client's Gross Observations  | Microscopic Observations                                                             |
|----------------------|--------------------------------|------------------------------|--------------------------------------------------------------------------------------|
| 3734-014<br>(Cont'd) | Tracheobronchial lymph node    | Dark brown                   | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Mottled brownish green areas | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3734-015             | Skin                           | Dark green                   | No corresponding lesion                                                              |
|                      | Tracheobronchial lymph node    | Dark brown                   | Lymphoid hyperplasia; pigment deposition                                             |
|                      | Lung                           | Dark brownish green mottling | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Fat                            | Greenish color               | No corresponding lesion (adipose tissue)                                             |
| 3734-016             | Skin                           | Green hair                   | No corresponding lesion                                                              |
|                      | Tracheobronchial lymph node    | Dark brown                   | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Mottled greenish brown areas | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Fat tissue                     | Green tinted                 | No corresponding lesion (adipose tissue)                                             |
| 3734-017             | Skin                           | Green                        | No corresponding lesion                                                              |
|                      | Testes                         | Small watery                 | Atrophy                                                                              |

RZ-75

90 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species **Rats** Sex **Males** Group Number **0 - Sacrificed** Dosage Level: **100 mg/m<sup>3</sup>**

| Animal Number        | Client's Tissue Identification | Client's Gross Observations           | Microscopic Observations                                                             |
|----------------------|--------------------------------|---------------------------------------|--------------------------------------------------------------------------------------|
| 3734-017<br>(Cont'd) | Tracheobronchial lymph node    | Dark brown                            | Hyperplasia of foamy macrophages; lymphoid hyperplasia; pigment deposition           |
|                      | Lung                           | Dark green and brown speckled pattern | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment            |
|                      | Fat                            | Discolored                            | No corresponding lesion (adipose tissue)                                             |
| 3734-018             | Skin                           | Green                                 | No corresponding lesion                                                              |
|                      | Tracheobronchial lymph node    | Dark and enlarged 3x                  | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Diffuse mild-moderate dye deposition  | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Stomach                        | Green contents                        | No corresponding lesion                                                              |
|                      | All body fat                   | Green                                 | No corresponding lesion (adipose tissue)                                             |
|                      |                                |                                       |                                                                                      |
|                      |                                |                                       |                                                                                      |
|                      |                                |                                       |                                                                                      |
|                      |                                |                                       |                                                                                      |

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## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number M - Sacrificed

Species Rats

[illegible]

RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level: 10 mg/m<sup>3</sup>

Group Number N - Sacrificed

Sex Males

Species Rats

| Animal Number | Client's Tissue Identification | Client's Gross Observations          | Microscopic Observations                                                             |
|---------------|--------------------------------|--------------------------------------|--------------------------------------------------------------------------------------|
| 3733-009      | Lung                           | Mottled brownish green areas         | No corresponding lesion                                                              |
| 3733-010      | Lung                           | Grayish tint to all lobes            | Pigment deposition                                                                   |
| 3733-011      | Lung                           | Brownish green color                 | No corresponding lesion                                                              |
| 3733-012      | Lung                           | Green/gray tint to all lobes         | No corresponding lesion                                                              |
| 3733-013      | Lung                           | Mottled brown areas                  | No corresponding lesion                                                              |
| 3733-014      | Lung                           | Mottled brownish discoloration       | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3733-015      | Lung                           | Brown mottled discoloration          | No corresponding lesion                                                              |
| 3733-016      | Lung                           | Greenish tint to all lobes           | Accumulations of foamy macrophages; pigment deposition                               |
| 3733-017      | Lung                           | Greenish brown mottled discoloration | No corresponding lesion                                                              |
| 3733-018      | Lung                           | Mottled brownish green discoloration | No corresponding lesion                                                              |
|               |                                |                                      |                                                                                      |
|               |                                |                                      |                                                                                      |
|               |                                |                                      |                                                                                      |
|               |                                |                                      |                                                                                      |
|               |                                |                                      |                                                                                      |
|               |                                |                                      |                                                                                      |

**90 Day Sacrifice**

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

| Species | Rats | Sex | Females | Group Number | L - Sacrificed | Dosage Level | 0 mg/m <sup>3</sup> |
|---------|------|-----|---------|--------------|----------------|--------------|---------------------|
|---------|------|-----|---------|--------------|----------------|--------------|---------------------|

[illegible]

RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats Sex Females Group Number 0 - Sacrificed Dosage Level 100 mg/m<sup>3</sup>

| Animal Number | Client's Tissue Identification | Client's Gross Observations       | Microscopic Observations                                                             |
|---------------|--------------------------------|-----------------------------------|--------------------------------------------------------------------------------------|
| 3734-509      | Skin                           | Green                             | No corresponding lesion                                                              |
|               | Tracheobronchial lymph node    | Dark brown                        | No section                                                                           |
|               | Lung                           | Heavy dye deposition in all lobes | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fatty tissues                  | Greenish discoloration            | No corresponding lesion (adipose tissue)                                             |
| 3734-510      | Tracheobronchial lymph node    | Dark brown                        | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Mottled brownish green areas      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3734-511      | Skin                           | Green hair                        | No corresponding lesion                                                              |
|               | Tracheobronchial lymph node    | Dark brown                        | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Mottled brownish green            | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fat tissue                     | Green tinted                      | No corresponding lesion (adipose tissue)                                             |
| 3734-512      | Tracheobronchial lymph node    | Dark and enlarged 2x              | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |



RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Species Rats Sex Females

Group Number 0 - Sacrificed

| Animal Number     | Client's Tissue Identification | Client's Gross Observations              | Microscopic Observations                                                                                              |
|-------------------|--------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| 3734-512 (Cont'd) | Skin                           | Green                                    | No corresponding lesion<br>Accumulations of foamy macrophages;<br>hyperplasia of type II cells;<br>pigment deposition |
|                   | Lung                           | Diffuse mild-moderate dye deposition     |                                                                                                                       |
|                   | Stomach                        | Green contents                           | No corresponding lesion<br>No corresponding lesion (adipose tissue)                                                   |
|                   | All body fat                   | Green                                    |                                                                                                                       |
| 3734-513          | Skin                           | Green                                    | No corresponding lesion<br>Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition                 |
|                   | Tracheobronchial lymph node    | Dark brown                               |                                                                                                                       |
|                   | Lung                           | Greenish brown color                     | Accumulations of foamy macrophages;<br>hyperplasia of type II cells;<br>pigment deposition                            |
| 3734-514          | Skin                           | Green                                    | No corresponding lesion<br>Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition                 |
|                   | Tracheobronchial lymph node    | Dark brown                               |                                                                                                                       |
|                   | Lung                           | Heavy speckled pattern of dye deposition | Accumulations of foamy macrophages;<br>hyperplasia of type II cells;<br>pigment deposition                            |
|                   | Fatty tissue                   | Green                                    | No corresponding lesion (adipose tissue)                                                                              |
| 3734-515          | Skin                           | Green hair                               | No corresponding lesion                                                                                               |

RZ-75  
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level: 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Females

Species Rats

| Animal Number     | Client's Tissue Identification | Client's Gross Observations           | Microscopic Observations                                                             |
|-------------------|--------------------------------|---------------------------------------|--------------------------------------------------------------------------------------|
| 3734-515 (Cont'd) | Lung                           | Mottled brown areas                   | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Fatty tissue                   | Green tinted                          | No corresponding lesion (adipose tissue)                                             |
| 3734-516          | Skin                           | Green                                 | No corresponding lesion                                                              |
|                   | Tracheobronchial lymph node    | Dark and enlarged 2x                  | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                   | Lung                           | Diffuse dye deposition, mild-moderate | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Stomach                        | Green contents                        | No corresponding lesion                                                              |
|                   | All body fat                   | Green                                 | No corresponding lesion (adipose tissue)                                             |
| 3734-517          | Skin                           | Dark green                            | No corresponding lesion                                                              |
|                   | Tracheobronchial lymph node    | Brownish green color                  | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                   | Lung                           | Dark brownish green color             | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Fatty tissue                   | Green color                           | No corresponding lesion (adipose tissue)                                             |
| 3734-518          | Skin                           | Green                                 | No corresponding lesion                                                              |

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## 90 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

| Species | Rats | Sex: | Females | Group Number | 0 - Sacrificed | Dosage Level | 100 mg/m <sup>3</sup> |
|---------|------|------|---------|--------------|----------------|--------------|-----------------------|
|---------|------|------|---------|--------------|----------------|--------------|-----------------------|

[illegible]

## 90 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

**Dosage Level: 1 mg/m<sup>3</sup>**

M - Sacrificed

**Sex:** Females

**Group Number**

Species Rats

[illegible]

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R2-75

90 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 10 mg/m<sup>3</sup>

Species Rats Sex Females

Group Number N - Sacrificed

| Animal Number | Client's Tissue Identification | Client's Gross Observations                                                                  | Microscopic Observations                                                             |
|---------------|--------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 3733-509      | Lung                           | Diffused brownish color with heavy green dye deposition                                      | Accumulations of foamy macrophages; pigment deposition                               |
| 3733-510      | Lung                           | Gray/green tint to all lobes, some concentrated foci scattered on all lobes                  | Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells |
| 3733-511      | Lung                           | Mottled brown areas                                                                          | No corresponding lesion                                                              |
| 3733-512      | Lung                           | Shows a diffuse brownish color with heavy focal dye deposition                               | Accumulations of foamy macrophages; pigment deposition                               |
| 3733-513      | Lung                           | Stuck to rib cage, mottled brown areas                                                       | No corresponding lesion                                                              |
| 3733-514      | Lung                           | Gray/green tint to all lobes                                                                 | No corresponding lesion                                                              |
| 3733-515      | Lung                           | Dull brown color                                                                             | No corresponding lesion                                                              |
| 3733-516      | Lung                           | Diffuse green tint to all lobes                                                              | No corresponding lesion                                                              |
| 3733-517      | Lung                           | Green/gray tint to all lobes, some more marked concentration in scattered areas of all lobes | No corresponding lesion                                                              |
| 3733-518      | Lung                           | Mottled brown discoloration                                                                  | No corresponding lesion                                                              |
|               |                                |                                                                                              |                                                                                      |
|               |                                |                                                                                              |                                                                                      |
|               |                                |                                                                                              |                                                                                      |
|               |                                |                                                                                              |                                                                                      |
|               |                                |                                                                                              |                                                                                      |

THIRTY-DAY SACRIFICE  
SUMMARY INCIDENCE TABLES

## SUMMARY INCIDENCE TABLE

RZ-75

30 Day Sacrifice

Male Rats

|                               | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-------------------------------|------------|------------|------------|------------|
| LUNG (NO. EXAMINED)           | (10)       | (10)       | (10)       | (10)       |
| Accumulations of Foamy        |            |            |            |            |
| Macrophages                   |            | 10         |            | 2          |
| Hyperplasia of Type II Cells  |            | 10         |            | 2          |
| Pigment Deposition            |            | 10         |            | 2          |
| Hemorrhage                    |            |            | 2          |            |
| Edema                         |            |            | 1          |            |
| Congestion                    |            |            |            |            |
| Peribronchial Lymphoid        |            |            |            |            |
| Hyperplasia                   | 8          | 9          | 8          | 9          |
| NASAL CAVITY-LEVEL I          |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 1          | 1          | 1          | 2          |
| Submucosal Pigment Deposition |            | 3          |            |            |
| Cystic Glands                 |            |            | 2          |            |
| NASAL CAVITY-LEVEL II         |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (10)       | (10)       |
| Hemorrhage                    | 1          | 1          | 1          |            |
| Submucosal Pigment Deposition |            | 10         |            | 1          |
| Serous Exudate                |            | 1          |            |            |
| Inflammation of Nasolacrimal  |            |            |            |            |
| Duct                          |            | 1          |            |            |
| NASAL CAVITY-LEVEL III        |            |            |            |            |
| (NO. EXAMINED)                | (10)       | (10)       | (9)        | (10)       |
| Submucosal Pigment Deposition |            | 10         |            | 6          |
| Hemorrhage                    |            |            | 1          |            |

IV-1

EPL

Experimental Pathology Laboratories, Inc.

## SUMMARY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Male Rats

|                                     | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-------------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL IV               |            |            |            |            |
| (NO. EXAMINED)                      | (10)       | (10)       | (10)       | (9)        |
| Submucosal Pigment Deposition       |            | 10         |            | 2          |
| Hemorrhage                          |            |            | 1          |            |
| LYMPH NODE, TRACHEOBRONCHIAL        |            |            |            |            |
| (NO. EXAMINED)                      | (7)        | (10)       |            | (8)        |
| Lymphoid Hyperplasia                |            | 10         |            | 1          |
| Hyperplasia of Foamy<br>Macrophages |            | 10         |            |            |
| Pigment Deposition                  |            | 10         |            |            |
| Hemorrhage                          |            |            |            |            |
| KIDNEY (NO. EXAMINED)               |            |            |            |            |
|                                     | (10)       | (10)       |            | (10)       |
| Regenerative Tubular<br>Epithelium  | 6          | 6          |            | 5          |
| Foci of Mononuclear Cells           | 3          | 4          |            | 2          |
| Casts                               | 1          | 5          |            | 3          |
| Pigment Deposition                  | 10         | 10         |            | 10         |
| Tubular Mineralization              |            | 1          |            |            |
| LIVER (NO. EXAMINED)                |            |            |            |            |
|                                     | (10)       | (10)       |            | (10)       |
| Foci of Mononuclear Cells           | 3          | 3          |            | 6          |
| Bile Duct Hyperplasia               | 1          | 1          |            | 1          |
| Focal Capsular Fibrosis             | 1          |            |            |            |
| Pigment Deposition                  |            | 10         |            |            |
| Hernia                              |            |            |            |            |

IV-2

EPL

Experimental Pathology Laboratories Inc.



## SUMMARY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Male Rats

|                            | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|----------------------------|------------|------------|------------|------------|
| BRAIN (NO. EXAMINED)       | (10)       | (10)       |            |            |
| PITUITARY (NO. EXAMINED)   | (10)       | (10)       |            |            |
| ADRENAL (NO. EXAMINED)     | (9)        | (10)       |            |            |
| Vacuolated Cortical Cells  | 5          | 4          |            |            |
| EYE (NO. EXAMINED)         | (10)       | (10)       |            |            |
| THYROID (NO. EXAMINED)     | (10)       | (10)       |            |            |
| LARYNX (NO. EXAMINED)      | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells  |            | 6          |            |            |
| TRACHEA (NO. EXAMINED)     | (10)       | (10)       |            |            |
| Foci of Mononuclear Cells  |            |            |            |            |
| HEART (NO. EXAMINED)       | (10)       | (10)       |            |            |
| Nonsuppurative Myocarditis | 7          | 2          |            |            |
| Interstitial Fibrosis      | 2          | 2          |            |            |
| SPLEEN (NO. EXAMINED)      | (10)       | (10)       |            |            |
| PANCREAS (NO. EXAMINED)    | (10)       | (10)       |            |            |
| LYMPH NODE, POPLITEAL      |            |            |            |            |
| (NO. EXAMINED)             | (10)       | (9)        |            |            |
| Pigment Deposition         | 1          | 2          |            |            |
| Lymphoid Hyperplasia       | 1          | 1          |            |            |

IV-3

EPL

Experimental Pathology Laboratories, Inc



RZ-75  
30 Day Sacrifice  
Male Rats

[illegible]

## SUMMARY INCIDENCE TABLE

RZ-75

30 Day Sacrifice

Female Rats

|                               | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-------------------------------|------------|------------|------------|------------|
| LUNG (NO. EXAMINED)           | (9)        | (10)       | (10)       | (10)       |
| Accumulations of Foamy        |            |            |            |            |
| Macrophages                   |            | 10         |            | 2          |
| Hyperplasia of Type II Cells  |            | 10         |            | 1          |
| Pigment Deposition            |            | 10         |            | 2          |
| Hemorrhage                    |            |            | 1          |            |
| Edema                         |            |            |            |            |
| Congestion                    |            |            | 2          |            |
| Peribronchial Lymphoid        |            |            |            |            |
| Hyperplasia                   | 5          | 10         | 5          | 10         |
| NASAL CAVITY-LEVEL I          |            |            |            |            |
| (NO. EXAMINED)                | (9)        | (9)        | (10)       | (10)       |
| Hemorrhage                    |            |            |            |            |
| Submucosal Pigment Deposition |            | 5          |            |            |
| Cystic Glands                 |            |            |            |            |
| NASAL CAVITY-LEVEL II         |            |            |            |            |
| (NO. EXAMINED)                | (9)        | (9)        | (10)       | (10)       |
| Hemorrhage                    |            |            |            |            |
| Submucosal Pigment Deposition |            | 9          |            | 1          |
| Serous Exudate                |            |            |            |            |
| Inflammation of Nasolacrimal  |            |            |            |            |
| Duct                          | 1          |            |            |            |
| NASAL CAVITY-LEVEL III        |            |            |            |            |
| (NO. EXAMINED)                | (9)        | (9)        | (9)        | (9)        |
| Submucosal Pigment Deposition |            | 9          |            | 5          |
| Hemorrhage                    |            |            |            |            |

IV-5

EPL

Experimental Pathology Laboratories, Inc.

# SUMMARY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

|                                     | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-------------------------------------|------------|------------|------------|------------|
| NASAL CAVITY-LEVEL IV               |            |            |            |            |
| (NO. EXAMINED)                      | (9)        | (9)        | (10)       | (10)       |
| Submucosal Pigment Deposition       |            | 8          |            | 6          |
| Hemorrhage                          |            |            |            |            |
| Lymph Node, TRACHEOBRONCHIAL        |            |            |            |            |
| (NO. EXAMINED)                      | (7)        | (10)       |            | (9)        |
| Lymphoid Hyperplasia                |            | 10         |            |            |
| Hyperplasia of Foamy<br>Macrophages |            | 10         |            |            |
| Pigment Deposition                  |            | 10         |            |            |
| Hemorrhage                          |            |            |            | 1          |
| KIDNEY (NO. EXAMINED)               | (9)        | (10)       |            | (10)       |
| Regenerative Tubular<br>Epithelium  |            | 1          |            | 2          |
| Foci of Mononuclear Cells           |            | 1          |            | 2          |
| Casts                               |            |            |            |            |
| Pigment Deposition                  | 9          | 10         |            | 7          |
| Tubular Mineralization              |            |            |            |            |
| LIVER (NO. EXAMINED)                | (9)        | (10)       |            | (10)       |
| Foci of Mononuclear Cells           | 4          | 3          |            | 2          |
| Bile Duct Hyperplasia               | 1          |            |            | 1          |
| Focal Capsular Fibrosis             |            | 1          |            |            |
| Pigment Deposition                  |            | 10         |            |            |
| Hernia                              |            | 1          |            |            |

# SUMMARY INCIDENCE TABLE

12-75

30 Day Sacrifice  
Female Rats

|                                         | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|-----------------------------------------|------------|------------|------------|------------|
| BRAIN (NO. EXAMINED)                    | (9)        | (9)        |            |            |
| PITUITARY (NO. EXAMINED)                | (9)        | (9)        |            |            |
| ADRENAL (NO. EXAMINED)                  | (9)        | (10)       |            |            |
| Vacuolated Cortical Cells               |            |            |            |            |
| EYE (NO. EXAMINED)                      | (9)        | (9)        |            |            |
| THYROID (NO. EXAMINED)                  | (9)        | (10)       |            |            |
| LARYNX (NO. EXAMINED)                   | (9)        | (10)       |            |            |
| Foci of Mononuclear Cells               | 2          |            |            |            |
| TRACHEA (NO. EXAMINED)                  | (9)        | (10)       |            |            |
| Foci of Mononuclear Cells               | 1          |            |            |            |
| HEART (NO. EXAMINED)                    | (9)        | (9)        |            |            |
| Nonsuppurative Myocarditis              |            | 1          |            |            |
| Interstitial Fibrosis                   |            |            |            |            |
| SPLEEN (NO. EXAMINED)                   | (9)        | (10)       |            |            |
| PANCREAS (NO. EXAMINED)                 | (9)        | (10)       |            |            |
| LYMPH NODE, POPLITEAL<br>(NO. EXAMINED) | (9)        | (10)       |            |            |
| Pigment Deposition                      |            |            |            |            |
| Lymphoid Hyperplasia                    |            |            |            |            |

IV-7

EPL

Experimental Pathology Laboratories, Inc.

100

RZ-75  
30 Day Sacrifice  
Female Rats

|                                | Group<br>L | Group<br>O | Group<br>M | Group<br>N |
|--------------------------------|------------|------------|------------|------------|
| STOMACH (NO. EXAMINED)         | (9)        | (10)       |            |            |
| DUODENUM (NO. EXAMINED)        | (9)        | (10)       |            |            |
| CECUM (NO. EXAMINED)           | (9)        | (10)       |            |            |
| Nematodiasis                   |            | 2          |            |            |
| COLON (NO. EXAMINED)           | (9)        | (10)       |            |            |
| Nematodiasis                   | 2          | 2          |            |            |
| SKIN (NO. EXAMINED)            | (6)        | (10)       |            |            |
| OVARY (NO. EXAMINED)           | (9)        | (10)       |            |            |
| Parovarian Cyst                | 2          | 1          |            |            |
| UTERUS (NO. EXAMINED)          | (9)        | (10)       |            |            |
| Dilatation                     | 2          | 2          |            |            |
| URINARY BLADDER (NO. EXAMINED) | (8)        | (10)       |            |            |
| FEMUR (NO. EXAMINED)           | (9)        | (10)       |            |            |
| ADIPOSE TISSUE (NO. EXAMINED)  |            | (9)        |            |            |

THIRTY-DAY SACRIFICE  
HISTOPATHOLOGY INCIDENCE TABLES

| <u>GROUP</u> | <u>DOSE<br/>(mg/m<sup>3</sup>)</u> | <u>TREATMENT</u>              |
|--------------|------------------------------------|-------------------------------|
| L            | 0                                  | Controls                      |
| M            | 1                                  | Low Exposure Concentration    |
| N            | 10                                 | Medium Exposure Concentration |
| O            | 100                                | High Exposure Concentration   |



# HISTOPATHOLOGY INCIDENCE TABLE

7-75  
30 Day Sacrifice  
Male Rats

Group L

|                                    | ANIMAL |   |   |   |   |   |   |   |   |   |   |
|------------------------------------|--------|---|---|---|---|---|---|---|---|---|---|
|                                    |        | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |        | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                    |        | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |        | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |        | - | - | - | - | - | - | - | - | - | - |
|                                    |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |        | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                    |        | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| UNG                                |        | X |   |   |   |   | X |   |   |   |   |
| Accumulations of Foamy Macrophages |        |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |        |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |        |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |        |   |   |   |   |   |   |   |   |   |   |
| Edema                              |        |   |   |   |   |   |   |   |   |   |   |
| Congestion                         |        |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |        | 1 |   | 1 | 1 | 1 | 1 |   | 1 | 1 | 1 |
| NASAL CAVITY-LEVEL I               |        | X | X | X | X | X | X | X |   | X | X |
| Hemorrhage                         |        |   |   |   |   |   |   |   | 3 |   |   |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |        |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II              |        | X | X | X | X | X | X | X |   | X | X |
| Hemorrhage                         |        |   |   |   |   |   |   |   | 2 |   |   |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |        |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |        |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III             |        | X | X | X | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |        |   |   |   |   |   |   |   |   |   |   |

V-1

EPL

Experimental Pathology Laboratories, Inc

Key

P - Present

1 - Minimal

5 - Severe High

N - No Section

2 - Slight

3 - Moderate

4 - Moderate to Severe High

A - Adipose

3 - Moderate

4 - Moderate to Severe High

5 - Severe High

X - Not Examined

4 - Moderate to Severe High

5 - Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Male Rats

Group L

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## NASAL CAVITY-LEVEL IV

X X X X X X X X X X

Submucosal Pigment Deposition

Hemorrhage

## LYMPH NODE, TRACHEOBRONCHIAL

X X X N N N X X X X

Lymphoid Hyperplasia

Hyperplasia of Foamy

Macrophages

Pigment Deposition

Hemorrhage

## KIDNEY

Regenerative Tubular

Epithelium

1 1 2 2 1 1

Foci of Mononuclear Cells

1 1 1

Casts

1

Pigment Deposition

1 1 1 1 1 1 1 1 1 1

Tubular Mineralization

## LIVER

X X X X X X

Foci of Mononuclear Cells

1 1 1

Bile Duct Hyperplasia

1

Focal Capsular Fibrosis

2

Pigment Deposition

Hernia

V-2

EPL

Experimental Pathology Laboratories, Inc.

Key P=Present N=No Section  
1=Minimal 2=Slight  
3=Severe High 4=Incomplete Section

A=Atypical X=Atypical  
3=Mod. Atypical 4=Mod. Atypical, Severe High

RZ-75  
30 Day Sacrifice  
Male Rats

A N  
N U  
I M  
M B  
A E  
L R

V-3

Experimental Pathology Laboratories, Inc.

Key    P = Present            N = No Section  
        1 = Normal         2 = Slight  
        5 = Severe to High    I = Incomplete Section

1. *Adaptation* – the ability of an organism to survive in its environment.  
 2. *Evolution* – the change in the characteristics of a population over time.  
 3. *Speciation* – the process by which new species are formed.  
 4. *Extinction* – the disappearance of a species from the Earth.  
 5. *Biological diversity* – the variety of life forms in a given area.  
 6. *Conservation* – the protection and management of natural resources.  
 7. *Endangered species* – species that are at risk of extinction.  
 8. *Wildlife* – animals and plants that live in the wild.  
 9. *Marine life* – organisms that live in the ocean.  
 10. *Terrestrial life* – organisms that live on land.  
 11. *Aquatic life* – organisms that live in water.  
 12. *Amphibian life* – organisms that can live both in water and on land.  
 13. *Reptilian life* – organisms that are cold-blooded and have scales.  
 14. *Bird life* – organisms that have feathers and can fly.  
 15. *Mammalian life* – organisms that have milk glands and are warm-blooded.  
 16. *Insect life* – organisms that have six legs and a segmented body.  
 17. *Fish life* – organisms that live in water and have gills.  
 18. *Plant life* – organisms that are photosynthetic and have roots.  
 19. *Fungal life* – organisms that are eukaryotic and have cell walls.  
 20. *Bacterial life* – organisms that are prokaryotic and lack a nucleus.

**Group L**

[illegible]

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
 ? = Minor 2 = Significant  
 S = Severe High 1 = Incomplete Section

A = Analysis      X = Not Applicable  
3 = Moderate      4 = Moderate, Severe



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Experimental Pathology Laboratories, Inc.

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EPL

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

1 - Agreeable      2 - Not Agreeable  
3 - Moderate      4 - Moderate, Strongly

# HISTOPATHOLOGY INCIDENCE TABLE

2Z-75  
30 Day Sacrifice  
Male Rats

Group 0

|                                  | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|
|                                  |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                  |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                  |                            |                            | - | - | - | - | - | - | - | - | - |
|                                  |                            |                            | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                  |                            |                            | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                  |                            |                            | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL IV            |                            |                            |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition    |                            |                            | 4 | 3 | 3 | 4 | 1 | 3 | 1 | 1 | 3 |
| Hemorrhage                       |                            |                            |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL     |                            |                            |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia             |                            |                            | 3 | 3 | 2 | 2 | 3 | 3 | 3 | 2 | 2 |
| Hyperplasia of Foamy Macrophages |                            |                            | 4 | 2 | 3 | 1 | 4 | 3 | 3 | 3 | 3 |
| Pigment Deposition               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hemorrhage                       |                            |                            |   |   |   |   |   |   |   |   |   |
| KIDNEY                           |                            |                            |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular Epithelium  |                            |                            | 1 |   |   | 1 | 1 | 1 |   | 1 | 2 |
| Foci of Mononuclear Cells        |                            |                            | 1 |   | 1 |   |   |   |   | 1 | 1 |
| Casts                            |                            |                            | 1 | 1 |   |   | 1 |   |   | 1 | 1 |
| Pigment Deposition               |                            |                            | 2 | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 |
| Tubular Mineralization           |                            |                            |   |   |   |   |   |   |   |   | 1 |
| LIVER                            |                            |                            |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                            |                            | 1 |   |   |   |   |   |   | 1 | 1 |
| Bile Duct Hyperplasia            |                            |                            | 1 |   |   |   |   |   |   |   |   |
| Focal Capsular Fibrosis          |                            |                            |   |   |   |   |   |   |   |   |   |
| Pigment Deposition               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hernia                           |                            |                            |   |   |   |   |   |   |   |   |   |





# HISTOPATHOLOGY INCIDENCE TABLE

2-75  
Day Sacrifice  
Male Rats

Group 0

| ANIMAL | NUMBER | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|--------|--------|---|---|---|---|---|---|---|---|---|---|
|        |        | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |   |
|        |        | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |
|        |        | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |   |
|        |        | - | - | - | - | - | - | - | - | - |   |
|        |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|        |        | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |   |
|        |        | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        |   |   | X | X |   | N | X | X | X | X |
|        | 1      |   |   |   | 1 |   |   |   |   |   |   |
|        | 3      |   |   |   |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X |   | X | X | X | X | X | X |   |
|        |        |   |   | P |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X |   | X | X | X | X | X | X |   |
|        |        |   |   | P |   |   |   |   |   |   |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |
|        |        |   |   |   |   |   |   |   |   |   |   |
|        |        | X | X | X | X | X | X | X | X | X |   |

V-9

EPL

Experimental Pathology Laboratories, Inc.

Key

1 - Mild

2 - Moderate

3 - Severe

4 - Very Severe

5 - Necrotic

6 - Unknown

7 - Absent

8 - Mild

9 - Severe

10 - Very Severe

11 - Necrotic

12 - Unknown

Group 0

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

[illegible]

F P L

Key      0 = Present      1 = 1st Section  
          1 = Mild        2 = 2nd  
          3 = Severe Hgt    1 = Indeterminate Section

$$\begin{aligned} A &= A_1 + A_2 + \dots + A_n & A &= A_1 + A_2 + \dots + A_n \\ B &= B_1 + B_2 + \dots + B_n & B &= B_1 + B_2 + \dots + B_n \end{aligned}$$

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Male Rats

Group M

| ANIMAL                             | NUMBER | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------------|--------|---|---|---|---|---|---|---|---|---|
|                                    |        | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| LUNG                               |        | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |        | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                    |        | - | - | - | - | - | - | - | - | - |
|                                    |        | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                                    |        | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                    |        | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| LUNG                               |        | X | X |   |   |   |   |   |   |   |
| Accumulations of Foamy Macrophages |        |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |        |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |        |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |        |   |   |   |   | 1 | 1 |   |   |   |
| Edema                              |        |   |   |   |   |   | 2 |   |   |   |
| Congestion                         |        |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |        |   |   | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| NASAL CAVITY-LEVEL I               |        | X | X |   | X | X | X |   | X | X |
| Hemorrhage                         |        |   |   |   |   |   |   |   | 1 |   |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |        |   |   | 1 |   |   |   | 1 |   |   |
| NASAL CAVITY-LEVEL II              |        | X | X | X | X | X | X | X | X | X |
| Hemorrhage                         |        |   |   |   |   |   |   |   | 2 |   |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |        |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |        |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III             |        | X | X | N | X | X | X | X | X | X |
| Submucosal Pigment Deposition      |        |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |        |   |   |   |   |   |   |   | 3 |   |

V-11

EPL

Experimental Pathology Laboratories, Inc.

Key

P=Present

1=Minimal

5=Severe High

N=Not Sectioned

2=Spot

1=Incomplete Section

A=Autopsy

1=Minimal

2=Spot

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Male Rats

Group M

ANIMAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| - | - | - | - | - | - | - | - | - | - |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

NASAL CAVITY-LEVEL IV

X X X X X X X X X X

Submucosal Pigment Deposition

Hemorrhage

2

V-12

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Minimal

5 = Severe

2 = Moderate

3 = Severe

4 = Severe with Necrosis

A = Absent

3 = Moderate

4 = Severe with Necrosis

# HISTOPATHOLOGY INCIDENCE TABLE

2-75  
30 Day Sacrifice  
Male Rats

Group N

|                               | A<br>N<br>U<br>M<br>B<br>E<br>R |                   |   |   |   |   |   |   |   |   |   |
|-------------------------------|---------------------------------|-------------------|---|---|---|---|---|---|---|---|---|
|                               |                                 | 3                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                                 | 7                 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                               |                                 | 3                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                                 | 3                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               |                                 | -                 | - | - | - | - | - | - | - | - | - |
|                               |                                 | 0                 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|                               |                                 | 1                 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                               |                                 | 9                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| UNG                           |                                 | X                 |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy        |                                 |                   |   |   |   |   |   |   |   |   |   |
| Macrophages                   |                                 | 1 1               |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells  |                                 | 1 1               |   |   |   |   |   |   |   |   |   |
| Pigment Deposition            |                                 | 1 1               |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 |                   |   |   |   |   |   |   |   |   |   |
| Edema                         |                                 |                   |   |   |   |   |   |   |   |   |   |
| Congestion                    |                                 |                   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |                                 |                   |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   |                                 | 1 1 1 1 1 1 1 1 1 |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL I           |                                 | X X X X X X X X X |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 | 1 2               |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                 |                   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                 |                                 |                   |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL II          |                                 | X X X X X X X X X |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 |                   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                 | 1                 |   |   |   |   |   |   |   |   |   |
| Serous Exudate                |                                 |                   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |                                 |                   |   |   |   |   |   |   |   |   |   |
| Duct                          |                                 |                   |   |   |   |   |   |   |   |   |   |
| ASAL CAVITY-LEVEL III         |                                 | X X X X           |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |                                 | 1 1 1 1 1 1       |   |   |   |   |   |   |   |   |   |
| Hemorrhage                    |                                 |                   |   |   |   |   |   |   |   |   |   |

V-13

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present  
1 = Mild  
5 = Severe

2 = Slight  
3 = Moderate  
4 = Severe

A = Absent  
B = Mild  
C = Moderate  
D = Severe

| <u>GROUP</u> | <u>DOSE<br/>(mg/m<sup>3</sup>)</u> | <u>TREATMENT</u>              |
|--------------|------------------------------------|-------------------------------|
| L            | 0                                  | Controls                      |
| M            | 1                                  | Low Exposure Concentration    |
| N            | 10                                 | Medium Exposure Concentration |
| O            | 100                                | High Exposure Concentration   |

30 Day Sacrifice  
Male Rats

A  
N  
I  
M  
A  
L

Y-14

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group L

|                                    | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|------------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|
|                                    |                                 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                    |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                    |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                                    |                                 | - | - | - | - | - | - | - | - | - |
|                                    |                                 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                    |                                 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                    |                                 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| LUNG                               |                                 |   | X |   | X |   |   | X | X |   |
| Accumulations of Foamy Macrophages |                                 |   |   |   |   |   |   |   |   |   |
| Hyperplasia of Type II Cells       |                                 |   |   |   |   |   |   |   |   |   |
| Pigment Deposition                 |                                 |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |
| Edema                              |                                 |   |   |   |   |   |   |   |   |   |
| Congestion                         |                                 |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid Hyperplasia |                                 | 1 |   | 1 |   | 1 | 1 |   |   | 1 |
| NASAL CAVITY-LEVEL I               |                                 | X | X | X | X | X | X | X | X | X |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                                 |   |   |   |   |   |   |   |   |   |
| Cystic Glands                      |                                 |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II              |                                 | X | X | X |   | X | X | X | X | X |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition      |                                 |   |   |   |   |   |   |   |   |   |
| Serous Exudate                     |                                 |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal Duct  |                                 |   |   |   | 2 |   |   |   |   |   |
| NASAL CAVITY-LEVEL III             |                                 | X | X | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition      |                                 |   |   |   |   |   |   |   |   |   |
| Hemorrhage                         |                                 |   |   |   |   |   |   |   |   |   |

V-15

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Mild

5 = Severe/high

N = N. Section

2 = High

1 = Incomplete Section

A = Ad. Les.

2 = Moderate

4 = High

A = Ad. Les.

4 = High

6 = High

1 = Mild

2 = Moderate

3 = High



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group L

|                                  | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|
| NASAL CAVITY-LEVEL IV            |                            |                            | X | X | X | X | X | X | X |
| Submucosal Pigment Deposition    |                            |                            |   |   |   |   |   |   |   |
| Hemorrhage                       |                            |                            |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL     |                            |                            | X | X | X | X | N | N | X |
| Lymphoid Hyperplasia             |                            |                            |   |   |   |   |   |   |   |
| Hyperplasia of Foamy Macrophages |                            |                            |   |   |   |   |   |   |   |
| Pigment Deposition               |                            |                            |   |   |   |   |   |   |   |
| Hemorrhage                       |                            |                            |   |   |   |   |   |   |   |
| KIDNEY                           |                            |                            |   |   |   |   |   |   |   |
| Regenerative Tubular Epithelium  |                            |                            |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                            |                            |   |   |   |   |   |   |   |
| Casts                            |                            |                            |   |   |   |   |   |   |   |
| Pigment Deposition               |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Tubular Mineralization           |                            |                            |   |   |   |   |   |   |   |
| LIVER                            |                            |                            |   | X | X | X | X |   |   |
| Foci of Mononuclear Cells        |                            |                            | 1 | 1 | 1 | 1 |   |   |   |
| Bile Duct Hyperplasia            |                            |                            |   |   |   |   |   | 1 |   |
| Focal Capsular Fibrosis          |                            |                            |   |   |   |   |   |   |   |
| Pigment Deposition               |                            |                            |   |   |   |   |   |   |   |
| Hernia                           |                            |                            |   |   |   |   |   |   |   |

V-16

EPL

Experimental Pathology Laboratories, Inc

Key: P = Present  
1 = Mild  
2 = Slight  
3 = Moderate  
4 = Severe  
5 = Severe High  
N = No Section  
I = Incomplete Section

A = Autopsy  
3 = Moderate  
4 = Moderate to Severe

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group L

|                            | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|----------------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|
|                            |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                            |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                            |                            |                            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                            |                            |                            | - | - | - | - | - | - | - | - |
|                            |                            |                            | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                            |                            |                            | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                            |                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| BRAIN                      |                            |                            | X | X | X | X | X | X | X | X |
| PITUITARY                  |                            |                            | X | X | X | X | X | X | X | X |
| ADRENAL                    |                            |                            | X | X | X | X | X | X | X | X |
| Vacuolated Cortical Cells  |                            |                            |   |   |   |   |   |   |   |   |
| EYE                        |                            |                            | X | X | X | X | X | X | X | X |
| THYROID                    |                            |                            | X | X | X | X | X | X | X | X |
| LARYNX                     |                            |                            | X | X |   | X | X | X |   | X |
| Foci of Mononuclear Cells  |                            |                            |   |   | 1 |   |   |   | 1 |   |
| TRACHEA                    |                            |                            | X | X | X | X | X |   | X | X |
| Foci of Mononuclear Cells  |                            |                            |   |   |   |   |   | 1 |   |   |
| HEART                      |                            |                            | X | X | X | X | X | X | X | X |
| Nonsuppurative Myocarditis |                            |                            |   |   |   |   |   |   |   |   |
| Interstitial Fibrosis      |                            |                            |   |   |   |   |   |   |   |   |
| SPLEEN                     |                            |                            | X | X | X | X | X | X | X | X |
| PANCREAS                   |                            |                            | X | X | X | X | X | X | X | X |

V-17

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present  
1 = Minimal  
5 = Severe High  
N = No Section  
2 = Slight  
I = Incomplete Section

4 = Moderate  
3 = Moderate  
4 = Moderate

# HISTOPATHOLOGY INCIDENCE TABLE

WZ-75  
30 Day Sacrifice  
Female Rats

Group L

|                       | ANUM<br>BER | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-----------------------|-------------|---|---|---|---|---|---|---|---|
|                       | 7           | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                       | 3           | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                       | 1           | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|                       | -           | - | - | - | - | - | - | - | - |
|                       | 5           | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                       | 1           | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                       | 9           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| LYMPH NODE, POPLITEAL |             | X | X | X | X | X | X | X | X |
| Pigment Deposition    |             |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia  |             |   |   |   |   |   |   |   |   |
| STOMACH               |             | X | X | X | X | X | X | X | X |
| DUODENUM              |             | X | X | X | X | X | X | X | X |
| CECUM                 |             | X | X | X | X | X | X | X | X |
| Nematodiasis          |             |   |   |   |   |   |   |   |   |
| COLON                 |             | X | X |   | X | X | X |   | X |
| Nematodiasis          |             |   |   | P |   |   |   | P |   |
| SKIN                  |             | N | X | N | X | N | X | X | X |
| OVARY                 |             | X |   |   | X | X | X | X | X |
| Parovarian Cyst       |             |   | P | P |   |   |   |   |   |
| UTERUS                |             | X |   | X | X | X |   | X | X |
| Dilatation            |             |   | 4 |   |   |   | 2 |   |   |
| URINARY BLADDER       |             | X | N | X | X | X | X | X | X |

V-18

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present    N = Nematodiasis    A = Absent    X = Mild    1 = Mild    2 = Moderate    3 = Moderate to Severe    4 = Severe    5 = Severe High    1 = Mild    2 = Moderate    3 = Moderate to Severe    4 = Severe    5 = Severe High

Group L

V-19

Experimental Pathology Laboratories, Inc.

Key: P = Present N = Not Specified  
1 = Minor 2 = Significant  
S = Severely Hurt 3 = Completely Destroyed

$$3 \sim A^{\frac{1}{2}} B^{\frac{1}{2}}, \quad 4 \sim \frac{A+B}{2}$$

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group 0

| ANUMBERAL                     | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-------------------------------|---|---|---|---|---|---|---|---|---|---|
|                               | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                               | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                               | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                               | - | - | - | - | - | - | - | - | - | - |
|                               | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                               | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                               | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|                               |   |   |   |   |   |   |   |   |   |   |
|                               |   |   |   |   |   |   |   |   |   |   |
| LUNG                          |   |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy        |   |   |   |   |   |   |   |   |   |   |
| Macrophages                   | 2 | 3 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |
| Hyperplasia of Type II Cells  | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Pigment Deposition            | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Edema                         |   |   |   |   |   |   |   |   |   |   |
| Congestion                    |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 1 |
| NASAL CAVITY-LEVEL I          |   | X | X |   | X |   |   | X | N |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition | 1 |   |   | 1 |   | 1 | 1 |   |   | 1 |
| Cystic Glands                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         |   |   |   |   |   |   |   |   | N |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 |   | 1 |
| Serous Exudate                |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |   |   |   |   |   |   |   |   |   |   |
| Duct                          |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |   |   |   |   |   |   |   |   | N |   |
| Submucosal Pigment Deposition | 2 | 3 | 2 | 3 | 3 | 3 | 2 | 3 |   | 2 |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |

V-20

EPL

Experimental Pathology Laboratories, Inc

Key: P = Present N = Not Section  
1 = Mild 2 = Severe  
3 = Moderate 4 = Marked  
5 = Severe High 1 = Inflammatory Section

A = Adipose X = Inflammatory  
3 = Moderate 4 = Marked 5 = Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group 0

|                                  | A<br>N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|----------------------------------|---------------------------------|---|---|---|---|---|---|---|---|---|---|
|                                  |                                 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                                  |                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                                  |                                 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                                  |                                 | - | - | - | - | - | - | - | - | - | - |
|                                  |                                 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                                  |                                 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                                  |                                 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| NASAL CAVITY-LEVEL IV            |                                 |   |   |   |   |   |   |   | X | N |   |
| Submucosal Pigment Deposition    |                                 | 3 | 1 | 1 | 2 | 1 | 1 | 3 |   |   | 2 |
| Hemorrhage                       |                                 |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODE, TRACHEOBRONCHIAL     |                                 |   |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia             |                                 | 2 | 3 | 3 | 3 | 3 | 2 | 4 | 2 | 4 | 2 |
| Hyperplasia of Foamy Macrophages |                                 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 3 | 2 |
| Pigment Deposition               |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hemorrhage                       |                                 |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                           |                                 |   |   |   |   |   |   |   |   |   |   |
| Regenerative Tubular Epithelium  |                                 |   |   | 1 |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                                 |   |   |   |   |   |   | 1 |   |   |   |
| Casts                            |                                 |   |   |   |   |   |   |   |   |   |   |
| Pigment Deposition               |                                 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Tubular Mineralization           |                                 |   |   |   |   |   |   |   |   |   |   |
| LIVER                            |                                 |   |   |   |   |   |   |   |   |   |   |
| Foci of Mononuclear Cells        |                                 |   |   | 1 |   |   | 1 | 1 |   |   |   |
| Bile Duct Hyperplasia            |                                 |   |   |   |   |   |   |   |   |   |   |
| Focal Capsular Fibrosis          |                                 |   |   |   |   |   | 2 |   |   |   |   |
| Pigment Deposition               |                                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Hernia                           |                                 |   |   |   |   |   | P |   |   |   |   |

V-21

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present N = No Section  
1 = Mild 2 = Slight  
3 = Moderate 4 = Severe  
5 = Severe High 1 = Incomplete Section

A = Aorta B = Blood Vessel C = Colon  
D = Duodenum E = Esophagus F = Fat  
G = Gallbladder H = Heart I = Intestine  
J = Kidney K = Liver L = Lung  
M = Muscle N = Nerve O = Ovary  
P = Pancreas Q = Skin R = Spleen  
S = Stomach T = Testis U = Uterus  
V = Vagina W = Ventricle X = X-ray  
Y = Yolk Z = Zygote

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group 0

| ANIMAL                     |   |   |   |   |   |   |   |   |   |   |
|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7                          | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3                          | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4                          | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| -                          | - | - | - | - | - | - | - | - | - | - |
| 5                          | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1                          | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9                          | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |   |
| BRAIN                      | X | X | X | X | X | X | X | X | N | X |
| PITUITARY                  | X | X | X | X | X | X | X | X | N | X |
| ADRENAL                    | X | X | X | X | X | X | X | X | X | X |
| Vacuolated Cortical Cells  |   |   |   |   |   |   |   |   |   |   |
| EYE                        | X | X | X | X | X | X | X | X | N | X |
| THYROID                    | X | X | X | X | X | X | X | X | X | X |
| LARYNX                     | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells  |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                    | X | X | X | X | X | X | X | X | X | X |
| Foci of Mononuclear Cells  |   |   |   |   |   |   |   |   |   |   |
| HEART                      | X | X | X | X | N | X | X | X | X |   |
| Nonsuppurative Myocarditis |   |   |   |   |   |   |   |   |   | 1 |
| Interstitial Fibrosis      |   |   |   |   |   |   |   |   |   |   |
| SPLEEN                     | X | X | X | X | X | X | X | X | X | X |
| PANCREAS                   | X | X | X | X | X | X | X | X | X | X |

V-22

EPL

Experimental Pathology Laboratories, Inc.

Key: P = Present, N = Not Seen, A = Autolysis, X = To Be Investigated  
1 = Mild, 2 = Slight, 3 = Moderate, 4 = Marked, 5 = Severe  
1 = Involving 1st Section, 2 = Involving 2nd Section, 3 = Involving 3rd Section, 4 = Involving 4th Section, 5 = Involving 5th Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group 0

|                       | A<br>N<br>I<br>M<br>A<br>L | N<br>U<br>M<br>B<br>E<br>R | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|-----------------------|----------------------------|----------------------------|---|---|---|---|---|---|---|---|---|---|
|                       |                            |                            | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|                       |                            |                            | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|                       |                            |                            | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
|                       |                            |                            | - | - | - | - | - | - | - | - | - | - |
|                       |                            |                            | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
|                       |                            |                            | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|                       |                            |                            | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| LYMPH NODE, POPLITEAL |                            |                            | X | X | X | X | X | X | X | X | X | X |
| Pigment Deposition    |                            |                            |   |   |   |   |   |   |   |   |   |   |
| Lymphoid Hyperplasia  |                            |                            |   |   |   |   |   |   |   |   |   |   |
| STOMACH               |                            |                            | X | X | X | X | X | X | X | X | X | X |
| DUODENUM              |                            |                            | X | X | X | X | X | X | X | X | X | X |
| CECUM                 |                            |                            | X | X | X | X | X |   | X | X | X |   |
| Nematodiasis          |                            |                            |   |   |   |   |   | P |   |   |   | P |
| COLON                 |                            |                            |   | X | X | X | X | X | X | X | X |   |
| Nematodiasis          |                            |                            | P |   |   |   |   |   |   |   |   | P |
| SKIN                  |                            |                            | X | X | X | X | X | X | X | X | X | X |
| OVARY                 |                            |                            | X | X | X | X | X | X |   | X | X |   |
| Parovarian Cyst       |                            |                            |   |   |   |   |   |   | P |   |   |   |
| UTERUS                |                            |                            | X | X |   |   | X | X | X | X | X | X |
| Dilatation            |                            |                            |   |   | 3 | 2 |   |   |   |   |   |   |
| URINARY BLADDER       |                            |                            | X | X | X | X | X | X | X | X | X | X |

V-23

EPL

Experimental Pathology Laboratories, Inc.

Key

P = Present

1 = Mild

5 = Severe High

N = No Section

2 = Significant

1 = Incomplete Section

A = Absent

3 = Moderate

4 = Moderate to Severe

X = Incomplete Section

4 = Moderate to Severe

4 = Moderate to Severe



# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group 0

ANNUAL  
NUMBER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

FEMUR

X X X X X X X X X X X

ADIPOSE TISSUE

X X X X X X X X X X

V-24

EPL

Experimental Pathology Laboratories, Inc

Key: P = Present N = No Section A = Absent 1 = Minimal 2 = Moderate 3 = Severe 4 = Severe +  
1 = Minimal 2 = Moderate 3 = Severe 4 = Severe +  
1 = Minimal Section 2 = Moderate Section 3 = Severe Section 4 = Severe + Section

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group M

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| - | - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |   |

## LUNG

X X X X

Accumulations of Foamy

Macrophages

Hyperplasia of Type II Cells

Pigment Deposition

Hemorrhage

1

Edema

Congestion

2

1

Peribronchial Lymphoid

Hyperplasia

1 1 1

1 1

## NASAL CAVITY-LEVEL I

X X X X X X X X X X

Hemorrhage

Submucosal Pigment Deposition

Cystic Glands

## NASAL CAVITY-LEVEL II

X X X X X X X X X X

Hemorrhage

Submucosal Pigment Deposition

Serous Exudate

Inflammation of Nasolacrimal

Duct

## NASAL CAVITY-LEVEL III

X X X X X N X X X X

Submucosal Pigment Deposition

Hemorrhage

V-25

EPL

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section  
1 = Minimal 2 = Slight  
5 = Severe High 1 = Incomplete Section

A = Autolysis X = Incomplete Section  
3 = Moderate 4 = Moderate to Severe High

# HISTOPATHOLOGY INCIDENCE TABLE

QZ-75  
30 Day Sacrifice  
Female Rats

Group M

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

ASAL CAVITY-LEVEL IV

X X X X X X X X X X X

Submucosal Pigment Deposition

Hemorrhage

V-26

EPL

Experimental Pathology Laboratories, Inc

Key P Present N=No Section  
1 Mild 2=Slight  
5 Severe High 1=Incomplete Section

A=Autopsy X=Not Examined  
3=Moderate 4=Markedly Severe

# HISTOPATHOLOGY INCIDENCE TABLE

RZ-75  
30 Day Sacrifice  
Female Rats

Group N

AN  
NUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

|                               |   |   |   |   |   |   |   |   |   |   |
|-------------------------------|---|---|---|---|---|---|---|---|---|---|
| LUNG                          |   |   |   |   |   |   |   |   |   |   |
| Accumulations of Foamy        |   |   |   |   |   |   |   |   |   |   |
| Macrophages                   |   |   |   |   |   |   | 1 | 1 |   |   |
| Hyperplasia of Type II Cells  |   |   |   |   |   |   |   | 1 |   |   |
| Pigment Deposition            |   |   |   |   |   |   | 1 | 1 |   |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Edema                         |   |   |   |   |   |   |   |   |   |   |
| Congestion                    |   |   |   |   |   |   |   |   |   |   |
| Peribronchial Lymphoid        |   |   |   |   |   |   |   |   |   |   |
| Hyperplasia                   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| NASAL CAVITY-LEVEL I          | X | X | X | X | X | X | X | X | X | X |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |   |   |   |   |   |   |   |   |   |   |
| Cystic Glands                 |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL II         | X | X |   | X | X | X | X | X | X | X |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |
| Submucosal Pigment Deposition |   |   | 1 |   |   |   |   |   |   |   |
| Serous Exudate                |   |   |   |   |   |   |   |   |   |   |
| Inflammation of Nasolacrimal  |   |   |   |   |   |   |   |   |   |   |
| Duct                          |   |   |   |   |   |   |   |   |   |   |
| NASAL CAVITY-LEVEL III        |   | X |   | X | X |   |   | X | N |   |
| Submucosal Pigment Deposition | 1 |   | 1 |   |   | 1 | 1 | 1 |   |   |
| Hemorrhage                    |   |   |   |   |   |   |   |   |   |   |

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EPL

Experimental Pathology Laboratories, Inc

Key

P= Present

1= Minimal

5= Severe High

N= No Section

2= Slight

1= Incomplete Section

A= Adipose

3= Moderate

X= Inflammatory

4= Moderately Severe

# HISTOPATHOLOGY INCIDENCE TABLE

QZ-75  
30 Day Sacrifice  
Female Rats

Group N

ANUM  
BER

|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| - | - | - | - | - | - | - | - | - | - |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

## NASAL CAVITY-LEVEL IV

Submucosal Pigment Deposition

Hemorrhage

## LYMPH NODE, TRACHEOBRONCHIAL

Lymphoid Hyperplasia

Hyperplasia of Foamy

Macrophages

Pigment Deposition

Hemorrhage

## KIDNEY

Regenerative Tubular

Epithelium

Foci of Mononuclear Cells

Casts

Pigment Deposition

Tubular Mineralization

## LIVER

Foci of Mononuclear Cells

Bile Duct Hyperplasia

Focal Capsular Fibrosis

Pigment Deposition

Hernia

V-28

EPL

Experimental Pathology Laboratories, Inc

Key

P = Present

1 = Minimal

5 = Severe High

2 = Moderate

3 = Severe

4 = Severe High

5 = Severe High

6 = Severe High

7 = Severe High

8 = Severe High

9 = Severe High

THIRTY-DAY SACRIFICE

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

## 30 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

**Dosage Level: 0 mg/m<sup>3</sup>**

Group Number L - Sacrificed

Sex Males

Species Rats

[illegible]

4Z-75  
30 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Males

Species Rats

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations                                                             |
|---------------|--------------------------------|-----------------------------|--------------------------------------------------------------------------------------|
| 3734-019      | Tracheobronchial lymph node    | Dark, moderate, enlarged    | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Popliteal lymph node           | Gray                        | Lymphoid hyperplasia; pigment deposition                                             |
|               | Lung                           | Diffuse mild gray color     | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Body fat                       | Green/gray                  | No corresponding lesion (adipose tissue)                                             |
| 3734-020      | Tracheobronchial lymph node    | Enlarged, mild, dark        | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Diffuse, moderate, gray     | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fat                            | Moderate, gray/green        | No corresponding lesion (adipose tissue)                                             |
| 3734-021      | Tracheobronchial lymph node    | Enlarged, mild, dark        | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Diffuse, moderate, gray     | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fat                            | Gray/green                  | No corresponding lesion (adipose tissue)                                             |
| 3734-022      | Body fat                       | Green/gray color            | No corresponding lesion (adipose tissue)                                             |



RZ-75

30 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Species Rats Sex Males

Group Number 0 - Sacrificed

| Animal Number        | Client's Tissue Identification | Client's Gross Observations  | Microscopic Observations                                                             |
|----------------------|--------------------------------|------------------------------|--------------------------------------------------------------------------------------|
| 3734-022<br>(Cont'd) | Tracheobronchial lymph node    | Enlarged, mild, dark         | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Popliteal lymph node           | Gray                         | Pigment deposition                                                                   |
|                      | Lung                           | Diffuse, mild-moderate, gray | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3734-023             | Tracheobronchial lymph node    | Enlarged, mild, dark         | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Diffuse, moderate, gray      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Fat                            | Green/gray                   | No corresponding lesion (adipose tissue)                                             |
| 3734-024             | Tracheobronchial lymph node    | Enlarged, mild, dark         | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                      | Lung                           | Diffuse, moderate, gray      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                      | Fat                            | Green/gray                   | No corresponding lesion (adipose tissue)                                             |
| 3734-025             | Tracheobronchial lymph node    | Enlarged, mild, dark         | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |

AZ-75

30 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Males

Species Rats

| Animal Number     | Client's Tissue Identification | Client's Gross Observations  | Microscopic Observations                                                             |
|-------------------|--------------------------------|------------------------------|--------------------------------------------------------------------------------------|
| 3734-025 (Cont'd) | Lung                           | Diffuse, moderate, gray      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Fat                            | Green/gray                   | No corresponding lesion (adipose tissue)                                             |
| 3734-026          | Tracheobronchial lymph node    | Dark, mild enlarged          | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                   | Lung                           | Diffuse, mild-moderate, gray | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Body fat                       | Green/gray                   | No corresponding lesion (adipose tissue)                                             |
| 3734-027          | Tracheobronchial lymph node    | Dark, mild enlarged          | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                   | Lung                           | Diffuse, mild-moderate, gray | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|                   | Body fat                       | Green/gray                   | No corresponding lesion (adipose tissue)                                             |
| 3734-028          | Tracheobronchial lymph node    | Enlarged, moderate, dark     | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|                   | Lung                           | Diffuse, moderate, gray      | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |

### 30 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

**Dosage level: 100 mg/m<sup>3</sup>**

Group Number 0 - Sacrificed

Sex Males

Species Rats

[illegible]



RZ-75

30 Day Sacrifice

## CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 10 mg/m<sup>3</sup>

Species Rats

Sex Males

Group Number N - Sacrificed

| Animal Number | Client's Tissue Identification | Client's Gross Observations               | Microscopic Observations                                                             |
|---------------|--------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------|
| 3733-019      | Lung                           | Diffuse gray coloring                     | No corresponding lesion                                                              |
| 3733-020      | Lung                           | Gray diffuse areas                        | No corresponding lesion                                                              |
| 3733-021      | Lung                           | Grayish tan colored areas                 | No corresponding lesion                                                              |
| 3733-022      | Lung                           | Diffuse gray/brown color                  | No corresponding lesion                                                              |
| 3733-023      | Lung                           | Brownish green patchy discoloration       | No corresponding lesion                                                              |
| 3733-024      | Lung                           | Gray diffuse areas                        | Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells |
| 3733-025      | Lung                           | Grayish brown areas with moderate redness | Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells |
| 3733-026      | Lung                           | Diffuse mild gray coloring                | No corresponding lesion                                                              |
| 3733-027      | Lung                           | Gray diffuse colored areas                | No corresponding lesion                                                              |
| 3733-028      | Lung                           | Grayish brown colored areas               | No corresponding lesion                                                              |
|               |                                |                                           |                                                                                      |
|               |                                |                                           |                                                                                      |
|               |                                |                                           |                                                                                      |
|               |                                |                                           |                                                                                      |

RZ-75  
30 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 100 mg/m<sup>3</sup>

Group Number 0 - Sacrificed

Sex Females

Species Rats

| Animal Number | Client's Tissue Identification | Client's Gross Observations | Microscopic Observations                                                             |
|---------------|--------------------------------|-----------------------------|--------------------------------------------------------------------------------------|
| 3734-519      | Tracheobronchial lymph node    | Enlarged, moderate, dark    | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Diffuse, gray, moderate     | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fat                            | Gray/green                  | No corresponding lesion (adipose tissue)                                             |
| 3734-520      | Tracheobronchial lymph node    | Enlarged, moderate, dark    | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Diffuse, gray               | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
| 3734-521      | Tracheobronchial lymph node    | Enlarged, mild, black       | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Lung                           | Diffuse, moderate, gray     | Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition |
|               | Fat                            | Green/gray                  | No corresponding lesion (adipose tissue)                                             |
| 3734-522      | Tracheobronchial lymph node    | Enlarged, mild, dark        | Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition           |
|               | Fat                            | Green/gray                  | No corresponding lesion (adipose tissue)                                             |