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401 M Street, S.W.
Washington, D.C. 20460

Attention: Section 8(e) Coordinator

Re: Final Report on "Thirteen Week Subchronic Inhalation Toxicity (with Recovery) Study on Chromic Oxide and Basic Chrome Sulfate in Rats"
EPA Docket No. --- Unknown

Gentlemen:

The Industrial Health Foundation (IHF), acting as Agent for the IHF Chromium Chemicals Health and Environmental Committee, the membership of which consists of Harcros Chemical Group (American Chrome and Chemicals, British Chrome and Chemicals, and Wayne Chemical Corporation), AlliedSignal, Inc., Bayer AG, and Occidental Chemical Corporation, is submitting the final audited report on "Thirteen Week Subchronic Inhalation Toxicity (with Recovery) Study on Chromic Oxide and Basic Chrome Sulfate in Rats" in 4 volumes.

Should you need additional information, please contact me at 412-363-6600.

Sincerely,

Marianne C. Kaschak

Marianne C. Kaschak
Project Coordinator

88960000225

MCK/sk

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RESEARCH

THIRTEEN WEEK SUBCHRONIC INHALATION TOXICITY (WITH RECOVERY) STUDY ON CHROMIC OXIDE AND BASIC CHROME SULFATE IN RATS

TEST ARTICLE: Chromic Oxide and Basic Chrome Sulfate

PERFORMING LABORATORY: MPI Research
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LABORATORY STUDY IDENTIFICATION: 683-002

STUDY DIRECTOR: Roger J. Hilaski, M.A.

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SPONSOR REPRESENTATIVE: Michael J. Derelanko, Ph.D., D.A.B.T.

DATE OF STUDY COMPLETION: August 2, 1996

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1. SUMMARY: Thirteen Week Subchronic Inhalation Toxicity (with Recovery) Study on Chromic Oxide and Basic Chrome Sulfate in Rats

The objective of this study was to evaluate the subchronic toxicity of chromic oxide and basic chrome sulfate when administered to rats via nose-only inhalation exposure for thirteen (13) consecutive weeks. These test articles were selected as representative of various families of chromium compounds. The desired exposure levels were selected by the Sponsor to be multiples of the threshold limit value (TLV) for trivalent chrome and set at chrome equivalents of 3, 10 and 30 mg/m^3 for each test article. This study consisted of seven (7) groups of fifteen (15) male and fifteen (15) female Fischer 344 rats. One group (Group 1) served as the negative control (0 mg/m^3), three (3) treatment groups (Groups 2, 3 and 4) were exposed to chromic oxide (Cr_2O_3) and the three (3) other groups (Groups 5, 6 and 7) were exposed to basic chrome sulfate ($Cr_2(OH)_x(SO_4)_y \cdot Na_2SO_4 \cdot ZH_2O$).

The desired exposure levels were 4.4, 15 and 44 mg/m^3 for chromic oxide and 17, 58 and 175 for basic chrome sulfate. The exposures were conducted in 75 and 73-liter nose-only exposure chambers six (6) hours daily for thirteen (13) weeks (excluding weekends and holidays). Each animal was observed immediately prior to and following each exposure for overt toxicity and mortality. Body weights and clinical signs were recorded weekly for each rat. After 13 weeks of exposure, ten (10) males and ten (10) females from each group underwent hematologic, serum biochemical, urological, ophthalmologic and sperm characteristic (males only) evaluations, as well as a complete necropsy examination and histopathologic evaluations. After a thirteen (13) week post-exposure recovery period, the remaining animals also underwent a complete necropsy examination and limited histopathologic examinations.

During study weeks seven (7) and eight (8), an additional five (5) male and five (5) female Fischer rats were exposed for five (5) consecutive days at each exposure level. On the day following the fifth exposure, each rat was evaluated for various bronchoalveolar lavage fluid (BALF) parameters.

Six animals died on exposure day 1 as a direct result of the restraint tubes. These animals were replaced with animals of similar weight from the same purchase order shipment. One mortality occurred to a Group 7 male which was exposed to the high level of basic chrome sulfate (168 mg/m^3) for four days. This was an unusual situation because no other mortalities or severe clinical signs of toxicity occurred for any other animal exposed to basic chrome sulfate either at the time of this animal's death or during the remaining 12 weeks of exposure. Although no abnormalities were observed at necropsy, the cause of this death may have been related to stress induced by the exposure procedure which caused the deaths of the above six rats. For these reasons, the cause of death cannot be clearly established. Therefore, it does not seem appropriate to consider this mortality as a test material-related death.

No exposure-related effects of significance were observed in the clinical observations or ophthalmologic evaluations. Exposure-related reduced body weight gains, some statistically significant at the $p \leq .01$ level, were observed in the mid and high exposure levels for basic chrome sulfate. At the terminal sacrifice, the control group males had

gained approximately 51% in mean body weight, while the Group 5, 6, and 7 males gained approximately 50%, 46% and 39%, respectively. The Group 7 females gained 33% compared to a 38% weight gain in the control group females. At the recovery sacrifice, the Group 6 and 7 males continued to exhibit a mean body weight that was significantly lower than the control group, but the approximate weight gains for the recovery period were slightly greater than the control group males (26% for control group, 29 - 32% for Groups 5, 6 and 7). The female mean body weights and body weight gains in Groups 5, 6 and 7 were comparable to the control group at the recovery sacrifice. After 13 weeks of exposure, the mean body weights of animals exposed to chromic oxide were comparable to the control group with the males gaining 50% in each group and the females gaining 35 - 38%. During the recovery period, the body weight gains continued to be similar to the control group. Group 2, 3, and 4 males gained 27 - 29% compared to 26% for the control group males, and the females gained 20 - 21% compared to 20% for the control group females.

No apparent exposure related effects were noted for sperm motility, sperm morphology and concentration for either test material.

Most hematology, serum biochemistry, and urinalysis values from all treatment groups were similar to the control group. Increased leukocytes and segmented neutrophils, some statistically significant, were noted in Groups 6 and 7 males and females. Other findings noted were considered incidental.

No exposure-related changes in BALF parameters were observed for animals exposed to chromic oxide, however a yellow crystalline material was present within the mononuclear cells from Groups 2, 3 and 4 believed to be test material stained during the preparation of the tissue slides. The BALF values from animals exposed to basic chrome sulfate showed several treatment related effects, including decreased total nucleated cell counts, increased protein and lactate dehydrogenase activity, increased cell debris and lysed cells.

Macroscopic examination at the terminal sacrifice showed green discoloration in the lungs and lymph nodes of animals exposed to chromic oxide and a corresponding gray discoloration in the animals exposed to basic chrome sulfate. Some of the discoloration was resolved by the recovery sacrifice.

Statistically significant increases ($p \leq 0.01$) in the mean lung/trachea organ weights, lung/trachea to body weight ratios and lung/trachea to brain weight ratios were noted for the chromic oxide, Group 4 males and the basic chrome sulfate, Group 5, 6 and 7 males and females at terminal sacrifice. These organ weight changes corresponded to changes observed microscopically. At the recovery sacrifice, the basic chrome Group 5, 6 and 7, males and females continued to exhibit statistically significant increases ($p \leq 0.01$ for all but Group 5 females, which showed a significance of $p \leq 0.05$) in the lung/trachea organ weights. Changes in the weights of some other organs were observed primarily in Group 7 males and females. These changes were generally very small with no corresponding microscopic pathology. They could not be clearly related to a direct effect of the test material.

Exposure-related microscopic changes were observed in the lungs, lymphoid tissue and mediastinal lymph nodes at the terminal sacrifice for all groups, males and females, exposed to chromic oxide. Exposure-related microscopic changes were observed in the lungs, larynx, mediastinal lymph node and nasal cavity at the terminal sacrifice of all groups, males and females, exposed to basic chrome sulfate. These changes varied from trace to severe and from focal to diffuse.

For animals exposed to chromic oxide, black pigment within macrophages and in the peribronchial lymphoid tissue and mediastinal lymph nodes, was observed microscopically in all treated groups, males and females. The pigment observed in stained hematoxylin and eosin tissue slides was presumed to be the test article. The presence of the pigment corresponded to the green discoloration seen macroscopically. Associated with this pigment were trace to moderate exposure-related microscopic changes in the lungs and mediastinal lymph nodes. These included interstitial inflammation, septal cell hyperplasia and lymphoid hyperplasia. (the effects at the low level were limited to lymphoid hyperplasia). The changes observed are similar to those previously reported for other insoluable, respirable particles (Lee, et al., 1986; Muhle, et al., 1991). The trachea and nasal cavity were generally unaffected from exposure to chromic oxide.

At the recovery sacrifice of the chromic oxide-exposed animals, black pigment persisted with approximately the same incidence and severity as observed at the terminal sacrifice. At the low level (4.4 mg/m^3), two of the males had septal cell hyperplasia and or chronic interstitial inflammation associated with aggregates of pigmented macrophages. However, pigment accumulation was not associated with pathological effects in three of the five males and all of the females exposed previously to chromic oxide. Microscopic observations in these animals found only scattered macrophages containing intracytoplasmic pigment and accumulation of similar pigment in the peribronchial and mediastinal lymph tissue. Septal cell hyperplasia and chronic interstitial inflammation persisted in rats exposed at the mid and high levels but the severity of the lesions was decreased as compared to the terminal sacrifice animals at these levels. The presence of pigment in the lymphoid tissue suggests pulmonary clearance of the pigment via the lymphatic system.

After 13 weeks of exposure to basic chrome sulfate, trace to severe exposure-related changes were observed microscopically in the nasal cavity, larynx, lungs and mediastinal lymph node in all groups and both sexes. The changes noted include interstitial and granulomatous inflammation, septal cell hyperplasia, foreign material deposition, intraalveolar accumulation of macrophages with foamy/granular-appearing acidophilic cytoplasm and histiocytosis. Some of these effects may be related to the acidity of the basic chrome sulfate.

At the recovery sacrifice of the basic chrome sulfate-exposed animals, the exposure-related changes continued in the larynx, lungs and mediastinal lymph node with the incidence and severity approximately equal to the terminal sacrifice animals for most changes observed. Peribronchial histiocytosis in low level females, and foreign material and granulomatous inflammation in the lungs of low and mid level males and females were decreased or resolved. Foreign material was not observed in the larynx of

low level males and females, and mid level males. Nasal cavity findings were resolved in all animals with the exception of trace suppurative exudate randomly seen in a few rats.

This study indicates that there are significant differences in toxicity between insoluble chromic oxide and soluble basic chrome sulfate with subchronic inhalation in rats. The effects seen with chromic oxide appeared to be a pathological response to the accumulation of insoluble, respirable particles in the lung and lymphatic tissue. In contrast, the effects of basic chrome sulfate were relatively more severe and in part may be related to the acidic nature of this material. The effects of both materials were limited to the respiratory tract and for chromic oxide generally appear to be reversible under the exposure conditions of this study. While the effects seen with basic chrome sulfate may be reversible, the length of the recovery period in this study was insufficient to make a definitive determination.

Due to the microscopic effects observed in some of the animals exposed to the low level of chromic oxide, a No Observable Adverse Effect Level (NOAEL) was not established. However, the low incidence and minimal severity of the pathological effects in the low level animals suggest that a level of 4.4 mg/m^3 is very near a NOAEL for subchronic exposure to chromic oxide. A No Observable Adverse Effect Level (NOAEL) was not established for basic chrome sulfate in this study.

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2. QUALITY ASSURANCE STATEMENT

Below are the inspections conducted by the Quality Assurance Department and the dates the inspections were reported to the Study Director and Management:

Date(s) of Inspection	Study Phase Inspected	Date(s) Reported to Study Director/Management
10-18-94 to 10-19-94	Protocol Review	10-18-94, 11-09-94
10-18-94	Test Material Administration	11-09-94
10-18-94	Body Weight Measurement	11-09-94
10-18-94	Food Consumption Measurement	11-09-94
10-18-94	Particle Size Determinations	11-09-94
11-02-94	Pharmacotoxic Signs	12-12-94
11-08-94	Analytical Chemistry Operations	11-09-94, 12-12-94
11-22-94	Test Material Dispensation	12-12-94
12-05-94	Bronchoalveolar Lavage Evaluations	12-09-94, 1-04-95
12-05-94	Clinical Pathology Operations	1-04-95
1-12-95	Ophthalmoscopic Examination	2-03-95
1-16-95	Preparation for Blood and Urine Sample Collection	2-03-95
1-17-95	Urine Sample Collection	2-03-95
1-17-95	Sperm Evaluations	2-03-95
1-17-95	Necropsy	2-03-95
1-17-95	Blood Sample Collection	2-03-95
1-23-95	Sperm Morphology	2-03-95
1-26-95	Histology - Tissue Trimming	2-03-95
1-27-95	Histology - Embedding	2-03-95
1-30-95	Histology - Microtoming	2-03-95
3-16-95 to 4-14-95	Data Review	4-14-95,
7-28-95 to 8-03-95	Report Review	8-03-95
7-28-95 to 9-15-95	Data Review	9-15-95
8-21-95 to 8-22-95	Report Review	8-22-95
8-22-95 to 9-15-95	Report Review	9-15-95
9-05-95 to 9-06-95	Report Review	9-15-95
3-04-96 to 3-07-96	Report Review	3-07-96
7-19-96 to 7-22-96	Report Review	7-22-96

Leslie J. York, M.S.
Group Supervisor, Quality Assurance

8-2-96
Date

683-002

3. INTRODUCTION

3.1. OBJECTIVE

The objective of this study was to evaluate the subchronic toxicity of the two (2) test materials when administered to rats via nose-only inhalation exposure for thirteen consecutive weeks. The experimental design was based on guidelines of the Environmental Protection Agency: Toxic Substances Control Act Test Guidelines, Part 798 - Health Effects Testing Guidelines, Subpart B., Section 798.2450, September 1985.

3.2. SPECIES SELECTION

Charles River CDF® (Fischer 344) /Crl BR VAF/Plus® rats were used for this study. The rat is a universally used model for evaluating the subchronic toxicity of various classes of chemicals.

3.3. JUSTIFICATION FOR ROUTE OF ADMINISTRATION

Since inhalation is a potential route for human exposure, the experimental compound was administered via the inhalation route in nose-only exposure chambers.

4. SCHEDULE

Protocol Approved by Sponsor	October 6, 1994
Study Initiation (Protocol Sheet 1 Signed by Study Director)	October 13, 1994
Receipt of Animals	October 4, 1994
Receipt of Animals (BALF)	November 11, 1994
Study Randomization	October 14, 1994
BALF Randomization	November 29, 1994
Placement of Animals into Treatment Groups	October 14, 1994
Placement of BALF Animals into Treatment Groups	November 29, 1994
Commencement of Exposure	October 18, 1994
Last Day of Exposure	January 18, 1995
Terminal Necropsy	January 17-19, 1995
Recovery Necropsy	April 18-19, 1995
Draft Report	September 15, 1995

The following study calendar can be used to relate study events to calendar dates:

Table 4.1.

First Day (Tuesday) of Study Week	Study Week	Study Days	Exposure Days	
10-18-94	1	1-7	1-5	
10-25-94	2	8-14	6-10	
11-01-94	3	15-21	11-15	
11-08-94	4	22-28	16-20	
11-15-94	5	29-35	21-25	
11-22-94	6	36-42	26-29	
11-29-94	7	43-49	30-36	
12-06-94	8	50-56	37-41	
12-13-94	9	57-63	42-46	
12-20-94	10	64-70	47-50	
12-27-94	11	71-77	51-54	
01-03-95	12	78-84	55-59	
01-10-95	13	85-91	60-64	
01-17-95	14	92-98	65-66	Begin
01-24-95	15	99-105	NA	Recovery
01-31-95	16	106-112	NA	Period
02-07-95	17	113-119	NA	
02-14-95	18	120-126	NA	
02-21-95	19	127-133	NA	
02-28-95	20	134-140	NA	
03-07-95	21	141-147	NA	
03-14-95	22	148-154	NA	
03-21-95	23	155-161	NA	
03-28-95	24	162-168	NA	
04-04-95	25	169-175	NA	
04-11-95	26	176-182	NA	
04-18-95	27	183-184	NA	

5. EXPERIMENTAL DESIGN

The study consisted of one (1) control group and six (6) treatment groups. Three treatment groups were exposed to different concentrations of chromic oxide and three were exposed to basic chrome sulfate. One treatment group was exposed to only one concentration of either test material. Exposures were conducted six (6) hours per day, five (5) days per week for approximately thirteen (13) consecutive weeks in nose-only exposure chambers. Each group consisted of fifteen (15) male and fifteen (15) female rats. An additional five (5) males and five (5) females were exposed for 5 days at each exposure level for BALF (bronchoalveolar lavage fluid) evaluations. Ten (10) males and ten (10) females from each group were euthanized after approximately thirteen (13) weeks of exposure, while five (5) male and five (5) female animals from each group were maintained for a thirteen (13) week post-exposure recovery period. During the exposure and post-exposure periods, observations for pharmacotoxic signs and body weights were recorded at various times. After thirteen (13) weeks of exposure, each group underwent hematologic, serum biochemical, urological, ophthalmologic, sperm characteristic (males only), a complete necropsy examination and histopathologic evaluations. The single animal that died on study underwent a complete necropsy on the day it was found dead. After a thirteen (13) week post-exposure recovery period, the remaining animals also underwent a complete necropsy examination. The experimental design is summarized in Appendix A.

6. MATERIALS AND METHODS

6.1. ANIMALS

6.1.1. Receipt And Maintenance

One hundred sixty (160) male and one hundred sixty (160) female CDF® (Fischer 344) /Crl BR VAF/Plus® rats were received from Charles River Laboratories, Raleigh, North Carolina on October 4, 1994. From these animals, 140 males and 140 females were selected on the basis of appropriate body weight and apparent good health. An additional shipment of forty (40) male and (40) female CDF® (Fischer 344)/Crl BR VAF/Plus® rats were received from Charles River Laboratories, Raleigh, North Carolina on November 15, 1994 for BALF evaluations. From these animals, 35 males (weighing from 195 to 221 g) and 35 females (weighing from 127 to 145 g) were selected on the basis of appropriate body weight and apparent good health. The animals were assigned randomly to control or treated groups. Animals in each group assigned for the recovery interval were also randomly selected. Each rat was identified by cage, group, sex, and individually by a Monel® metal ear tag bearing the animal number.

Upon arrival, the rats were group housed two to four of the same sex per cage in order to acclimate to the automatic watering system. After three days of group housing, the rats were individually housed. At all times the rats were maintained in environmentally controlled rooms with a 12 hour light/dark cycle.

During the acclimation period, non-exposure hours and recovery period, the animals were housed in an environmentally controlled animal room in which the temperature and relative humidity were recorded once daily.

6.1.2. Diet and Water

Water and diet (Rodent Laboratory Chow® No. 5002, Purina Mills, Inc., St. Louis, Missouri) were available *ad libitum*, except during actual exposures and prior to clinical pathology testing. Certification analysis of each lot of diet was performed by the supplier. The water supply is analyzed on a quarterly basis for the presence of heavy metals, pesticides and bacterial contaminants. The results of food and water analyses applicable to this study are retained in Archives.

6.1.3. Justification

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards and in consideration of applicable regulatory requirements.

6.2. TEST MATERIAL

6.2.1. Receipt And Description

The test material was received from British Chrome and Chemicals, Urlay Nook, Eaglescliffe, Cleveland, England, on May 31, 1994. The pertinent test material information follows:

Table 6.2.1.

Identification:	Basic Chrome Sulfate
Chemical Formula:	$Cr_2(OH)_x(SO_4)_y \cdot Na_2SO_4 \cdot ZH_2O$
Received:	5-31-94
Approx. Amount Received:	25 Kg
Code Number:	0109660
Physical Characteristics:	Dark Green Powder
Shelf life:	Presumed stable through end of study
Storage:	Room Temperature; keep dry
IRDC Number:	11520
Purity:	%(wt/wt) Cr(III) 25% as Cr_2O_3 %(wt/wt) Cr(VI) 0.0003%
Stability:	Stable
Identification:	Chromic Oxide 0512/93
Chemical Formula:	Cr_2O_3
Received:	5-31-94
Approx. Amount Received:	25 Kg
Batch Number:	O 512/93
Physical Characteristics:	Dark Green Powder
Shelf life:	Unlimited Storage Stability in sealed containers protected from moisture
Storage:	Room Temperature
IRDC Number:	11521
Purity:	%(wt/wt) Cr(III) 99% as Cr_2O_3 %(wt/wt) Cr(VI) <0.0001%
Stability:	Stable

The supplier assumes responsibility for appropriately defining the stability, purity, strength, composition and other characteristics of the test material.

6.2.2. Preparation

Each test material was removed from the shipping container and divided into smaller portions. These smaller portions allowed easier handling of the test material and precluded any potential contamination of the whole shipment. The basic chrome sulfate was divided equally into ten (10) individual plastic bags and the chromic oxide was divided equally into nine (9) individual plastic bags. Each plastic bag was kept in its own metal container. Since the basic chrome sulfate was quite hygroscopic, both materials were stored in separate unused $1m^3$ exposure chambers which were continuosly purged with a low-flow of dry compressed air.

6.3. TEST MATERIAL ADMINISTRATION

6.3.1. Exposure Methods

Exposures were conducted in nose-only exposure chambers. One system was dedicated for each group for the duration of the study. The chambers were operated under dynamic conditions. The chamber ventilation air for the chromic oxide was provided by the generation system and dilution air (figure 1). The chamber ventilation air for the basic chrome sulfate was provided for by the generation system, dilution air and mixing air (figure 2). For each exposure, the animals were removed from their home cages, placed in restraint tubes (the animals nose protruded from a small opening in the conical end) transported to the exposure room, placed in the exposure system and exposed for the requisite duration.

To facilitate animal identification, a system of color coding and numerical identification was used. The following colors were assigned to each group: Group 1 - blue; Group 2 - green; Group 3 - red; Group 4 - yellow; Group 5 - orange; Group 6 - brown; Group 7 - white. A clip with the appropriate color was assigned to each animal. This clip moved with the animal during transfer from the home cage to the exposure restraint tube and back to the home cage. The animal's unique identification number was listed on the color coded clip. In addition to the unique identification number, each clip also bore a more general number which was used to define the animal's tier location on the systematically rotated each week. Male and female animals occupied alternated port positions within a tier.

The restraint tubes and interior chamber walls were cleaned after each day's exposure.

6.3.2. Exposure Atmosphere Generation Methods

6.3.2.1. Chromic Oxide

Dust aerosol atmospheres of chromic oxide were generated using a system as illustrated in Figure 1. The system operated as follows: This low-output dust generator operated by spinning small glass beads over the surface of a packed "plug" of the test material pressed into a glass cylinder. The glass beads continually abraded a small amount of dust from the surface of the plug. The released dust was swept from the generator and piped to the exposure system inlet where dilution air reduced the concentration to the desired level. The dilution air was metered with a Fischer & Porter flow meter (No. 1-27-G-10/55).

To prepare the plug of test material, the glass cylinder was placed on a balance and 10g of test material was added. The test material was manually pressed with a piston-like tool to a pressure equivalent to a weight of 8,000 g (as read on the balance). This process was repeated two more times to yield a total weight of approximately 30 g of test material in each plug.

After preparation, each plug was tested to ensure that the uniformity and consistency were acceptable. In a separate 160 L chamber, the plugs were used to generate and exposure atmosphere similar to Group 4 for approximately 1.5 hours. A new plug was used each week for Group 2 and each day for Groups 3 and 4.

The operating parameters for the low-output generation systems are shown below:

Table 6.3.2.a

	Group 2	Group 3	Group 4
Generator Cylinder Size (ml)	125	125	125
Beads			
Type	glass	glass	glass
Number	8	12	12
Size (mm)	6	3	3
Inlet Pressure (psig)	8	11	13
Airflow Output (L/min)	16	19	20
Dilution Air Flow Rate (L/min)	20-140	20-140	20-140

6.3.2.2. Basic Chrome Sulfate

The dust aerosol atmosphere of basic chrome sulfate was generated with a system similar to that shown in Figure 2. The auger-dust feeder consisted of a dust hopper with a motor-driven stirrer and an auger driven by a variable-speed motor. This dust-feeder dispensed test material at a known and constant rate to an air-micronizer (Fluid Energy, model 00). The micronizer broke up agglomerates of the test material to form an aerosol which was piped to the exposure system inlet. Dilution air was metered to the exposure system inlet with a Fischer & Porter flowmeter (No. 1-27-G-10/55). An air amplifier operating on the venturi principle was mounted in the inlet section of the exposure system. This device provided turbulence which improved dispersion of the aerosol. A 300 watt heat lamp, mounted approximately 9 inches away, warmed the auger dust feeder to reduce moisture absorption by the test material.

Operational parameters of the basic chrome sulfate generation systems are shown in the following table:

Table 6.3.2.2.

	Group 5	Group 6	Group 7
Stirrer Motor (rpm)	3	3	10
Auger			
Type	Teflon	Teflon	Stainless Steel
Size (OD in. x turns per inch)	1/4" x 20	1/4" x 20	1/4" x 2
Auger Motor			
Rated Maximum rpm	4.7	20	4.7
Speed Control Setting (%)	90	20	30
Actual rpm	5.1	4.8	1.4
Jet Mill			
Grinding Pressure (psig)	38	38	38
Inlet Pressure (psig)	36	36	36
Airflow Output (L/min)	77	71	73
Dilution Airflow Rate (L/min)	50-120	0-70	70-140
Air Amplifier			
Pressure (psig)	5	5	5
Airflow (L/min)	6	14	11

6.3.3. Exposure Atmosphere Analytical Methods

6.3.3.1. Actual Concentrations

Actual concentrations were measured by standard gravimetric methods. A sample was collected once per hour from each treatment group chamber during each six hour exposure. The duration of each sample was approximately fifty (50) minutes for Groups 2 - 6 and twenty (20) minutes for Group 7. Total volumes sampled were measured with dry gas meters. The difference in the filter pad pre- and post-sampling weights was calculated and divided by the sample volume. The following table lists the sampling parameters:

Table 6.3.3.1.a

Group Number	Approximate Sampling Flow Rate (L/min)	Approximate Sampling Duration (min)	Approximate Sample Volume (L)	Approximate Sample Volume (ft^3)	Number of Samples Collected per day
2	15	50	750	27	6
3	10	50	500	18	6
4	5	50	250	9	6
5	10	50	500	18	6
6	5	50	250	9	6
7	5	20	100	4	6

The anticipated range of variability in the daily and weekly mean exposure concentrations were as follows:

Table 6.3.3.1.b

Group Number	Desired Concentrations (mg/m^3)	Daily Mean (mg/m^3)	Weekly Mean (mg/m^3)	Chrome Equivalent Concentration (mg/m^3)
2	4.4	3-5	4-5	3
3	15	12-18	14-16	10
4	44	35-50	38-46	30
5	17	12-22	14-21	3
6	58	45-65	46-60	10
7	175	150-200	165-190	30

6.3.3.2. Aerosol Particle Size Determination

The particle size distribution was determined once each exposure day for the first two weeks and once weekly thereafter for each exposure group. The samples were collected with a cascade impactor (Andersen Samplers Incorporated, Atlanta, GA) operated at a flow rate 28.3 L/minute for an appropriate duration. Glass fiber filter material cut to fit the impactor was used as the impaction substrate. The net weight on each filter pad was determined. Cumulative percentages, by weight, of particles with aerodynamic diameters smaller than the effective cutoff diameters of the individual impactor stages were derived and plotted by computer. Mass median aerodynamic diameters (MMAD) and geometric standard deviations (GSD) were determined by a method similar to that of Raabe (Environ Sci. Technol., 12: 1162-1167, 1978).

6.3.3.3. Real-Time Aerosol Concentration Monitoring

Four light-scattering aerosol monitors were used to provide a close approximation of the real-time chamber concentrations during the exposure. One aerosol monitor was dedicated to Group 2 and provided continuous monitoring. A second monitor was shared between Groups 3 and 4. A third monitor was dedicated to Group 5 and the fourth monitor shared between Groups 6 and 7.

Monitoring with the shared system was controlled with a timer/valve system so that each chamber was sampled at least three times each hour. The timer controlled a series of pneumatically operated ball valves which allowed the aerosol monitor to alternately monitor both concentrations. Fresh sample was maintained in the sample line at all times by a purge pump.

The response of each aerosol monitor was displayed on a strip chart recorder. Calibration curves were developed relating recorder response (in chartlines) to gravimetrically determined actual concentrations. The calibration curves were fitted to the data points using linear regression analysis.

Aerosol monitors and sampling system parameters are shown below:

Table 6.3.3.3

Sampling System	
Approximate sample flow rate	7-10 L/min
Approximate sampling duration	5 - 10 minutes every 10 minutes, continuous for groups 2 and 5
Aerosol Monitors	
Group 2	Sibata model P5 H2
Groups 3 and 4	Sibata model P5 L2
Group 5	Sibata model P5 H2
Groups 6 and 7	Sibata model P5 L2
Calibration Settings	
Group 2	819 cpm ± 5 = 80 ± 2 chartlines
Groups 3 and 4	300 cpm ± 5 = 15 ± 2 chartlines
Group 5	104 cpm ± 5 = 12 ± 2 chartlines
Groups 6 and 7	399 cpm ± 5 = 40 ± 2 chartlines
Instrument Settings	
Fan	Off
Range	X 1
Measuring Time	1 minute
Sensitivity Adjustment Switch position	Measure
Routine Cleaning and Maintenance	
Sibata Model P5	As needed
Thimble Filters	Replaced as needed
Chart Recorder	
Type	Linear, single pen
Chartspeed	4 cm/hr
Range	
Groups 2, 5, 6 and 7	10mV full scale
Groups 3 and 4	20mV full scale

6.3.3.4. Chamber Distribution Evaluations

Prior to the first day of exposure, the homogeneity of exposure concentration in each chamber was determined by simultaneously sampling five different locations within each chamber, and comparing the results to a reference location (the location used for routine sampling during the study). This test was performed for each chamber intended for the treatment groups.

Figure 3 illustrates the sampling locations in relation to the animal positions. The following table summarizes the results.

Table 6.3.3.4.

Sample Location	Group Number 2	3	4	5	6	7
1	111	99	103	102	103	97
2	104	94	96	90	103	101
3	101	96	94	86	92	93
4	98	104	100	100	96	92
5	101	105	100	99	96	94

Tabled values are means of the 3 replicates expressed as percent of the reference location.

Homogeneity of exposure concentrations was considered acceptable for the purposes of this study. In addition, each animal was rotated to a new location on the exposure system each week. The rotation schedule was set up such that each animal would occupy every available position within the system over the course of the study.

6.4. CHEMICAL ANALYSIS

6.4.1. Analysis for Chromium (VI)

Determination of the chromium (VI) content of the chromic oxide was performed based on a Sponsor-supplied colorimetric analytical method using Diphenylcarbazide. Details of the analytical method are presented in Appendix H.

6.4.1.1. Chromic Oxide Exposure Samples

An individual filter pad was transferred from the storage container by removing the pad, via forceps, and washing the dish with 50 ml distilled water. The filter pad and the washings were collected into a 250 ml beaker. A stirring bar was added to the beaker. The solution was stirred at room temperature for 20 minutes on a magnetic stir plate. The solids were allowed to settle for 30 minutes after being agitated. The supernatant solution was filtered through a 0.45 micron nylon filter and was collected in a 100 ml volumetric flask. To this flask 1.5 g of sulfuric acid solution and 1.8 g of 1,5-diphenylcarbazide solution was added and distilled water added to Q.S. to 100 ml. The color was allowed to develop for 10 minutes. The absorbance of the final solution was measured at 540 nm. The concentration of chromium (VI) was determined by comparison to a previously prepared calibration graph.

6.4.1.2. Chromic Oxide Neat Test Material Analysis

To a 400 ml beaker, 10 g of test material were added and made up to a total weight of 250 g with distilled water. To this a magnetic stir bar was added and stirred for approximately 20 minutes. The solids were then allowed to settle. The supernatant solution was prefiltered through a Whatman No. 54 paper filter and collected in a 250 ml beaker. Sixty ml of the filtrate was further filtered through a 0.1 micron Acrodisk filter.

Fifty g of this final filtrate was transferred into a tared 250 ml beaker. 1.5 g of 50% (v/v) sulfuric acid and 1.8 g of 1% (w/v) 1,5-dihenylcarbazide solution were also added and the solution was gently swirled. Ten minutes were allowed for the color to fully develop. The absorbance of the solution versus distilled water was measured at 540 nm in a 1 cm cuvette.

6.4.1.3. Basic Chrome Sulfate Exposure Samples

The filter pad was transferred from the storage container by removing the pad, via forceps, and washing the container with distilled water. The filter pad and the washings were collected in a 250 ml beaker and the total volume was brought up to approximately 50 ml with distilled water. The contents were heated for 30 minutes to insure complete dissolution and then cooled to room temperature. Two ml of sodium hydroxide were added and the contents boiled for about 1 minute. All solids were removed by filtration through a 15 cm Whatman No. 54 filter paper and collected into a 100 ml volumetric flask. The filter was washed with hot distilled water to insure complete transfer of all soluble material. It was acidified with 2 ml of 50% sulfuric acid. Five ml of diphenylcarbazide solution was added and the mixture was diluted to the mark with distilled water. The complexation was allowed 10 minutes to develop. The solution was analyzed by visible spectrophotometric methods in a 1 cm cell vs. distilled water at 540 nm.

6.4.1.4. Basic Chrome Sulfate Neat Test Article Analysis

One g of test material was transferred to a 250 ml beaker and 100 ml of distilled water was added. The mixture was heated for 30 minutes to insure total dissolution. Five ml of sodium hydroxide solution was added and the mixture was boiled for approximately 1 minute. The solids were removed by filtration through a 15 cm Whatman No. 54 filter paper into a 250 ml volumetric flask. The filtrate was washed with approximately 100 ml of hot distilled water and then acidified to approximately pH = 1.0 with 2 ml of 50% sulfuric acid solution. Five ml of 1% diphenylcarbazide solution was added. The mixture was diluted to the mark with distilled water, mixed thoroughly, and allowed to stand for 10 minutes prior to the absorbance being measured. The blank was prepared in a similar fashion. The absorbance of the sample versus distilled water was made in a 1 cm cell at 540 nm.

6.4.2. Analysis for Chromium (III)

Determination of the chromium (III) content of the chromic oxide was performed based on Sponsor-supplied atomic absorption spectrophotometric analytical methods. Details of the analytical method are presented in Appendix G.

6.4.2.1. Chromic Oxide Exposure Samples

Immediately after obtaining the post-sampling filter weight, the glass fiber filters were placed into individual zirconium crucibles. Preliminary experiments indicated that it was very difficult to store chromic oxide chamber samples without losses. To each crucible, 3 g of sodium peroxide were added and the crucible swirled in a lean, blue oxy-acetylene flame until fusion was complete. The crucibles were allowed to cool prior to transferring

them to 400 ml beakers. Approximately 100 ml of distilled water was added and then heated to degrade any unreacted peroxides remaining. This took approximately 15 minutes. The crucibles were then washed with distilled water and removed from the beaker. The final mixture was brought to a boil for an additional 15 minutes. Each extract was filtered hot through a No. 54 hardened Whatman filter paper into a 500 ml volumetric flask. The filters were washed three times with room temperature distilled water. The filtrate was allowed to cool prior to being brought up to volume with distilled water. An aliquot was transferred to make the final dilution prior to analysis. This dilution was also done with distilled water. A filter blank sample was processed in a similar fashion. The samples were analyzed versus the blank prepared by diluting an equivalent volume of the digested blank solution to a similar final volume as the sample's final volume.

6.4.2.2. Basic Chrome Sulfate Exposure Samples

Each sample container was recorded with the sample identification and the net sample weight. To each container 50 ml of distilled water was added and was sonicated for fifteen minutes. The 50 ml of distilled water was used to wash the top and sides of the container also. An aliquot was removed and filtered through a 0.45 micron nylon assembly and then diluted to final analytical volume. The volume of the aliquot removed was based on the recorded net sample weight such that after dilution the chromium concentration would be between 2 and 4 ppm. A blank filter was run with each set of sample filters.

6.4.3. Client Samples

Of the 6 samples collected during study weeks 1, 4, 8 and 12, 2 were analyzed for Chromium III and Chromium VI by this facility, 2 were sent to the Sponsor for analysis and 2 were retained at this facility in the event additional analyses are required. The analyses, results, reporting and any regulatory requirements are the responsibility of the Sponsor.

6.5. IN-LIFE EXAMINATIONS

6.5.1. Mortality

Observations for mortality and moribund animals were conducted twice daily throughout the study.

6.5.2. Clinical Signs

Each animal was observed in detail once each week for clinical signs.

6.5.3. Body Weights

Individual body weights were determined prior to exposure and at weekly intervals throughout the study.

6.5.4. Food Consumption

At the time of the weekly detailed observations the animal's feed jar was assessed for any apparent decrease in the amount of feed consumed. If an apparent reduction in food consumption was observed, this was to be noted on the detailed observation record.

6.6. OPHTHALMOLOGY

All animals received an indirect ophthalmoscopic examination of the cornea, conjunctiva, sclera, iris and fundus, during the acclimation period. Any animal showing a lesion at this time was excluded from the randomization process. All surviving animals were again evaluated prior to the terminal necropsy. These examinations were conducted by a veterinary ophthalmologist.

6.7. CLINICAL PATHOLOGY

6.7.1. Hematological, Biochemical and Urological Analysis

Clinical laboratory studies were conducted on 10 animals/sex/group at 13 weeks of study. Blood samples were obtained from the orbital sinus plexus following an overnight fasting period in which water was available. Urine was collected during the fasting period in containers where thymol had been added as a bacteriostatic agent. The hematological, biochemical and urological parameters are listed in Appendix M with specific instrument usage and reference information.

6.7.2. Urine Samples

Following urinalysis testing, the remaining urine was aliquoted into samples of approximately 0.5 ml and 2.0 ml. The 0.5 ml samples from 5 animals/sex from Groups 1, 4 and 7 were shipped to Dr. Claude Viau, The University of Montreal, Montreal, Canada, for β_2-microglobulin analysis. The remaining 0.5 ml samples and the 2.0 ml samples are being held frozen at -70°C for possible future evaluation.

6.7.3. Whole Blood Samples

At the 13 week interval whole blood samples of approximately 0.5 ml were collected from 10 animals/sex/group and are being held frozen at -70°C pending further instructions.

6.8. BRONCHOALVEOLAR LAVAGE EVALUATIONS

The initial set of animals allotted for bronchoalveolar lavage evaluations were not exposed for 5 consecutive days. These animals were euthanized and discarded without further evaluations. A second shipment of animals was received on November 11, 1994. After a 2 week acclimation period, these animals were randomized into the 1 control and 6 treatment groups and were exposed for 5 consecutive days.

Bronchoalveolar lavage fluid (BALF) was collected from 5 animals/sex/group which were anesthetized with intraperitoneal sodium pentobarbital.

The abdominal cavity was opened and the animal exsanguinated via the abdominal aorta. The lungs, heart, trachea, larynx and tongue were removed en-block, in order to decrease the time between euthanasia and the beginning of the lavage procedure. A 14 g teflon catheter was inserted into the trachea approximately 1/4" above the bifurcation to the level of the carina. A 10 ml syringe, containing 30 ml of sterile physiological (0.9%) saline

warmed to 37°C in a water bath, per gram of animal body weight was attached to the catheter. The saline was slowly instilled into the lungs and after a 5-10 second wait, the lavage fluid was slowly aspirated back into the syringe.

The syringe was removed from the catheter and the fluid was carefully expelled into a labeled tube (Baxter dispo® Centrifuge tube) maintained in an ice bath. The lavage process was repeated two more times and the resulting BALF was pooled.

The body weight, time of euthanasia, volume of BALF recovered, time lavage began and ended were recorded for each animal. The BALF was transferred to the Clinical Pathology Laboratory for analysis.

Since only a limited number of animals could be evaluated during 1 day, the exposures were conducted sequentially over the course of 5 days. One male and 1 female from each group were exposed on study days 44 through 48. Collection of BALF occurred on the day following the fifth day of exposure.

Bronchoalveolar fluid was evaluated as follows:

A record of the total volume of sample obtained and the volume aliquoted for cellular chemistry analysis was made.

A manual nucleated cell count was performed using a Neubauer Hemacytometer counting chamber. A Cyto-smear was prepared using the Shandon Cytospin 3 Centrifuge and stained with Wright-Giemsa stain. A cell differential was performed using an Olympus microscope.

The chemistry analysis was performed spectrophotometrically on the Coulter Optichem and included Lactate Dehydrogenase (LDH), Total Protein, Beta-Glucuronidase and Glutathione Reductase. LDH determination was based on the reduction of pyruvate to lactate with concurrent oxidation of NADH to NAD, measured by a decrease in absorbance at 340 nm. Total protein was measured by the increased absorbance at 600 nm associated with pyrogallol red-molybdate complexed with basic amino acids. Beta-gluronidase activity was determined by enzymatic conversion of Beta-D-glucuronide to alcohol, D-glucuronate and p-nitrophenol, which was measured at 405 nm. Glutathione reductase activity was determined from the enzymatic reduction of oxidized glutathione and concurrent oxidation of NADPH to NADH, which was measured at 340 nm.

The bronchalveolar lavage fluid parameters are listed in Appendix M with specific instrument usage and reference information.

6.9. SPERM EVALUATIONS

After 13 weeks of exposure, 10 males from each group were euthanized and necropsied. A sperm sample from the left cauda epididymis was used for automated evaluation of sperm motility, count and morphology. The concentration and morphology of the sperm were evaluated using visual methods.

The following table presents the operational parameters of the Cell-Soft System:

Table 6.9.

No. of Frames to Analyze:	15
No. of Frames/Second:	30
Video Standard:	American
Minimum Sampling:	
Motility	2
Velocity	3
Maximum Velocity:	20u/second
Threshold Grey Level:	45
Cell Color:	White
Pixel Scale:	3.400 u/pixel
Cell Size Range (pixels):	20-200
Lateral Head Displacement	
Minimum No. of Points:	7
Minimum Velocity:	20.00 u/second
Maximum Radius:	100.00 microns

Assessment of sperm motility, morphology, epididymal concentration and spermatid head count was conducted on approximately one-half of the males exposed for 13 weeks. The evaluation of the sperm morphology slides was conducted initially by observer number 1, who evaluated the slides as per our Standard Operating Procedure. The Reproductive Toxicologist requested the morphology slides be reevaluated based on the observation of an excessive number of broken and disarticulated sperm noted in some samples during evaluation of sperm motility and concentration. This was done by observer number 2. The results of the evaluation by observer number 2 indicated significant increases in the number of abnormal sperm in two of the treated groups. At the Sponsor's request, the sperm morphology slides were evaluated a third time. The third evaluator was a department supervisor and trained the technicians involved in the previous evaluations. The results of the second and third evaluations were similar, however, the mean number of abnormal sperm observed in the control group by the third observer was higher than either of the previous reads and there were no statistical differences noted for any of the treated groups as compared with the control group.

Because of the inconsistencies between the above counts and following consultations with the Sponsor's representatives and an expert in the field of male reproductive toxicology, additional evaluations were performed to complete the sperm morphology assessment. The sperm slides from each animal received 3 separate evaluations in which 200 intact sperm were evaluated each time, twice the number evaluated in the earlier reads. This was done to reduce variation which may have been introduced by the procedure. All 3 evaluations were performed by the same technician who was observer number 2 for the initial analysis. The evaluations were performed "blind" with the slide sequence and numbering reordered between each of the readings to minimize reader bias. Slides were observed in random order. Each field was evaluated by counting all intact sperm in the field and each intact sperm was evaluated as normal or abnormal and the results

recorded. In addition, each field was assessed for disarticulated sperm and the number of disarticulated sperm was recorded for each field evaluated. Consequently, the total number of sperm assessed for morphology was 200 intact sperm and the total count after inclusion of the disarticulated sperm could represent a number greater than 200. The percent of disarticulated sperm was calculated by dividing the total number of disarticulated sperm by the total intact and disarticulated sperm. For the evaluation to be considered valid, it was determined that a coefficient of variation between the readings for each group had to be less than 5%.

6.10. ANATOMIC PATHOLOGY

6.10.1. Macroscopic

All animals of the terminal and recovery sacrifices received a complete postmortem examination under the direct supervision of a pathologist. One male animal died on study before the terminal sacrifice; all remaining animals survived. Euthanasia was by intraperitoneal sodium pentobarbital administration followed by exsanguination.

The animals were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision, taking care not to open the thoracic cavity, and any subcutaneous abnormalities identified and correlated with antemortem findings. The trachea was exposed and clamped, the thoracic cavity opened, and the lungs were removed and examined while inflated. The heart was then removed. The left bronchus was ligated such that the left lung could be removed with bronchus, afterward, while the remaining lung lobes were deflated and then reinflated via the trachea with formalin. The abdominal, thoracic and cranial cavities were examined for abnormalities *in situ* and the organs removed and examined, and weighed where appropriate. All abnormalities were recorded. The left cauda epididymis was harvested and transferred to the Reproductive Toxicology Laboratory in warm medium. After obtaining sperm from the cauda, the tissues were returned to the necropsy laboratory for fixation.

Representative samples of protocol-designated organs and tissues were collected and placed in phosphate-buffered neutral formalin where appropriate. The pituitary was fixed *in situ*. A full complement of organs and tissues was collected from all animals.

6.10.2. Organ Weights

Protocol-designated organs and tissues were trimmed free of fat and connective tissue and weighed. Absolute organ weights from all animals surviving until the scheduled sacrifice were recorded along with postmortem body weights and appropriate weight ratios were calculated (relative to body and brain weights). The thyroid/parathyroid gland was weighed after fixation.

A list of organs and tissues weighed is presented in Appendix S.

6.10.3. Microscopic

Representative samples of protocol-designated organs and tissues were processed for the preparation and microscopic examination of hematoxylin-eosin stained paraffin sections. A full complement of organs and tissues was prepared and microscopically examined for all animals in Groups 1, 4 and 7 that died on study (DOS) or were euthanized at the terminal sacrifice. Target organs of larynx, lung, mandibular and mediastinal lymph nodes, nasal tissue and trachea with bifurcation and the potential target organs of kidney and liver, were examined for all animals in Groups 2, 3, 5 and 6 of the terminal sacrifice. Gross lesions were examined for all DOS and terminally sacrificed animals in all groups. In addition, for the recovery sacrifice animals, sections were prepared for microscopic examination of larynx, lung, mandibular and mediastinal lymph nodes and trachea with bifurcation for all animals in all groups, and of nasal tissue for all animals in Groups 1, 5, 6 and 7.

A four-step grading system of trace, mild, moderate and severe was used to define gradable lesions for comparison between dosage groups.

Microscopic examination of the tissues of the DOS and terminal sacrifice animals was performed by Dr. Roger B. Thompson, except for the nasal tissues. Dr. Donald N. Kitchen examined the nasal tissues of the terminal sacrifice and all target organs of the terminal and recovery sacrifice animals. Microscopic peer review was conducted by Dr. Jerry F. Hardisty, Experimental Pathology Laboratories, Inc.

A formal peer review of the histopathologic findings was performed and consisted of an examination of the target organs (except mandibular lymph nodes) of all animals from all groups at the terminal and recovery sacrifices and of all tissues from 20% of the Group 1 (control) animals and 60% of Groups 4 and 7 animals (the high-dose groups for chromic oxide and basic chrome sulfate, respectively) at the terminal sacrifice.

A glossary of macroscopic and microscopic terms as used in this study is included in this report. A full list of organs and tissues is presented in Appendix S.

6.11. STATISTICS

Analysis of body weights, clinical pathology laboratory tests, BALF data and organ weights (absolute and relative to both body and brain weight) were performed using the methods indicated below.

For each parameter, by test material, a one-way analysis of variance ($p \leq 0.05$) was performed. If the result was non-significant, no additional analysis was performed. If the result was significant, Bartlett's test for homogeneity of variances was performed ($p \leq 0.05$). If Bartlett's test was non-significant, Dunnett's t-test was used for the pairwise comparisons. If Bartlett's test was significant, the Welch t-test with Bonferroni correction was used for the pairwise comparisons. Non-parametric analysis, Kruskal-Wallis analysis of variance ($p \leq 0.05$) followed where appropriate by the Mann-Whitney U test ($p \leq 0.05$), was used for those parameters where parametric analysis was inappropriate.

The following are the applicable references:

Snedecor, G.W. and Cochran, W.G., *Statistical Methods*, 6th edition, Iowa University Press (1967).

Analysis of Variance	pp. 277-279
Bartlett's test	pp. 296-298
Mann Whitney U-test	pp. 130-132

Dunnett, C.W. (1964). New tables for multiple comparisons with a control, *Biometrics*, 20:482-491.

6.12. DATA RETENTION

All raw data, documentation, records, protocols, test article retention samples, and final reports generated as a result of this study are retained at MPI Research and are available for inspection upon request by authorized personnel of the sponsor for a period of 10 years following the completion of the study (final report issue date). Study specimens will be retained by MPI Research for a minimum period of 1 year to a maximum of 10 years, following the completion of the study (final report issue date). Samples collected for chromium analysis will be saved for 2 years.

7. RESULTS

7.1. ENVIRONMENTAL CONDITIONS

7.1.1. Colony Room Conditions During Acclimation and Recovery

During the acclimation period, the mean temperature was 22 ± 1.1°C and ranged from 21 to 24°C and the mean relative humidity was 45 ± 6.0% and ranged from 36 to 59%. The mean temperature during the recovery period was 22 ± 0.9°C and ranged from 18 to 24°C. The relative humidity during the recovery period had a mean and standard deviation of 47 ± 9.3% with a range of 30 to 66%. The post-exposure environment summary is presented in Appendix D.

7.1.2. Colony Room Conditions During the Non-Exposure Periods

The mean colony room temperature was 21 ± 0.8°C and ranged from 19 to 23°C and the mean relative humidity was 43 ± 10.7% and ranged from 26 to 70%.

7.2. EXPOSURE ATMOSPHERE CHARACTERIZATION

During each day's exposure, the temperature, relative humidity and chamber airflow rates were recorded during the first and last hours of exposure. The group mean temperatures ranged from 22 to 23°C. The relative humidity in the exposure chambers for both test materials was lower than that in the control chamber, especially for the chromic oxide. This was due to the dry compressed air required for the generation system and dilution air to maintain a stable aerosol concentration due to the hydroscopic nature of the test materials. The difference in humidity is not believed to have affected the results of this study. The 13 week means of environmental exposure conditions are shown below.

Table 7.2.

Group Number	Number of Days	Temperature (°C)	Relative Humidity (%)	Chamber Airflow (L/min)
1	62	23 ± 0.8	21 ± 5.5	15 ± 0.0
2	62	22 ± 0.8	4 ± 2.4	96 ± 19.2
3	62	22 ± 0.6	4 ± 2.1	71 ± 18.1
4	62	22 ± 0.8	6 ± 2.3	75 ± 19.8
5	62	23 ± 0.9	11 ± 3.5	132 ± 31.1
6	62	23 ± 1.0	11 ± 2.8	108 ± 13.2
7	62	23 ± 0.9	9 ± 1.7	157 ± 20.9

The table values represent a mean of the daily mean values from the measurements at hours 1 and 6. Weekly exposure atmosphere characterization data are presented in Table 1b. Daily exposure atmosphere characterization data are presented in Appendix B.

7.2.1. Test Material Concentrations

Appendix C lists the daily mean exposure concentration data by group for the 13 week study. Table 1a presents the weekly mean concentrations by group. Figure 4 shows, in graph form, the daily mean exposure concentrations for each group.

The following table presents the 13 week means of the actual concentrations for each group.

Table 7.2.1.

Group Number	Number of Weeks	Desired Concentration (mg/m^3)	Actual (mg/m3) Mean	Actual (mg/m3) S.D.	Desired Chrome Equivalent Concentrations (mg/m^3)
2	13	4.4	4.4	0.23	3
3	13	15	15	1.2	10
4	13	44	44	3.7	30
5	13	17	17	4.3	3
6	13	58	54	4.2	10
7	13	175	168	25.3	30

S.D. - Standard Deviation

7.2.2. Particle Size Distribution

Typical particle size distribution data obtained for each test material during this study are graphed in Figure 5. Appendices E and F contain the weekly particle size distribution data and a list of the particle size distribution data by selected cutoff sizes, respectively. The following table summarizes the means of the particle size data:

Table 7.2.2.

Group Number	Number of Samples	Mean Particle Size MMAD	Mean Particle Size GSD
2	21	1.8	1.93
3	22	1.9	1.84
4	21	1.9	1.78
5	21	4.2	2.48
6	21	4.2	2.37
7	21	4.5	2.50

MMAD - Mass Median Aerodynamic Diameter
GSD - Geometric Standard Deviation

7.3. CHEMICAL ANALYSIS

7.3.1. Chromium (III) Analysis of Exposure Samples

Table 7.3.1

Group Number	% of Cr(III) found in Exposure Samples*
2	123
3	111
4	123
5	92
6	98
7	96

* Compared to the neat test article.

Table 3a contains individual sample analytical results for weeks 2, 4, 8 and 12.

7.3.2. Chromium (VI) Analysis of Exposure Samples

Table 7.3.2

Group Number	% of Cr(VI) found in Exposure Samples
2	*
3	*
4	*
5	*
6	*
7	*

*Samples below the limit of detection for analysis (10.0 ng/ml)

Table 3b contains individual sample analytical results for weeks 1, 4, 8 and 12.

7.4. IN-LIFE EXAMINATIONS

7.4.1. Mortality

One male from Group 7 (animal no. 80652) was found dead immediately following exposure on study day 4. Refer to Appendix I for the Record of Fate and Disposition. Six animals died on exposure day 1 as a direct result of the restraint tubes. These 6 animals were replaced with animals of similar weight from the same purchase order shipment.

7.4.2. Clinical Signs

Results from the weekly detailed clinical examinations are summarized in Table 2. Appendix J presents the findings for individual animals.

For Chromic Oxide, the treatment groups (Groups 2, 3 and 4) were judged to be very similar to the control group throughout the exposure and recovery periods. The only major difference was the presence and incidence of test material staining on the body surface and material around the eyes in the treatment groups.

For Basic Chrome Sulfate, the low and mid-level exposure groups (Groups 5 and 6) were judged to be very similar to the control group throughout the exposure and recovery periods. The incidence of material around the eyes was at a moderate level in the treatment groups.

During the exposure, the high level exposure group (Group 7) exhibited the following significant signs: labored breathing in 8 females and 1 male, rapid respiration in 1 female, and test material staining of the body surface in 9 females and 15 males. The clinical signs observed (except test material staining) were very sporadic in nature and frequently occurred for only 1 or 2 observations. These signs were not observed during the recovery period.

All observations were incidental and of no toxicological significance.

7.4.3. Body Weights

Figure 6 graphically presents weekly male and female body weights by treatment group. Body weight data are summarized in Table 4. Individual animal body weight data is presented in Appendix K.

After 13 weeks of exposure and 13 weeks of recovery, the Group 2, 3 and 4 (Chromic Oxide) male and female mean body weights were not statistically different from the control group body weights in any week. However, Figure 6 shows a trend for the Group 4 males. The Group 4 male mean body weight is lower than the control group males for each week beginning with exposure week 13 through recovery week 26. After 13 weeks of exposure the mean body weights of animals exposed to chromic oxide were comparable to the control group with the males gaining about 50% in each group and the females gaining 35 - 38%. During the recovery period, the body weight gains continued to be similar to the control group. Group 2, 3 and 4 males gained 27 - 29% compared to 26% for the control group males and the females gained 20 - 21% compared to 20% for the control group females.

For Basic Chrome Sulfate, Group 6 and 7 male mean body weights demonstrated a statistically significant decrease from the control group males during each week of the exposure period (except for Group 6, week two) and remained statistically significant during each week of the recovery period. The significance level for both groups was .01 for all recovery weeks except Group 7, week 21. Group 7 female reduced mean body weight gains were statistically significant at the $p < .01$ level for most weeks during the exposure period. During the recovery period, the Group 7 female mean body weights were within normal limits. Group 5 and 6 female mean body weights were not significantly different from the control group during any week of the exposure and recovery period.

At terminal sacrifice, the control group males had gained approximately 51% in mean body weight, while the Group 5, 6, and 7 males gained approximately 50%, 46%, 39%, respectively. The Group 7 females gained 33% compared to a 38% weight gain in the control group females. At the recovery sacrifice the Group 6 and 7 males continued to exhibit a mean body weight that was significantly lower than the control group but the approximate weight gains for the recovery period were slightly greater than the control group males (26% for control group, 29 - 32% for Groups 5, 6 and 7). The female mean body weights and body weight gains in Group 5, 6 and 7 were comparable to the control group at the recovery sacrifice.

On November 29, 1994 and November 30, 1994, two Group 4 animals (80523 M and 80525 M) and two Group 6 animals (80611 M and 80621 F) were not exposed due to an atypical weight loss attributed to a malfunction of the auto-watering system. The 2 exposure days were made up on December 3, 1994 and December 4, 1994. This rest period permitted the animals to recover lost body weight.

7.4.4. Food Consumption

No quantitative food consumption data was collected for this study. No observable decreases in food consumption were noted during the exposure or recovery periods.

7.5. OPHTHALMOLOGY

Individual animal ophthalmoscopic findings are presented in Appendix L. No test material-related ophthalmoscopic abnormalities were detected. Observations noted during the examinations were considered representative of pathology that would be expected for this group of animals considering age, sex and strain. These were not abnormal findings, nor were they exposure-related and occurred in only a few animals. The observations included conjunctivitis.

7.6. CLINICAL PATHOLOGY

7.6.1. Hematologic Evaluations

A summary of hematological values is presented in Table 5. Individual hemotological values are presented in Appendix N.

7.6.1.1. Chromic Oxide

After 13 weeks of exposure, none of the treatment groups, for either sex, exhibited a statistically significant difference from the control group for any parameter.

7.6.1.2. Basic Chrome Sulfate

After 13 weeks of exposure, most treatment group parameters were similar to the control group values. Groups 6 and 7, males and females, had increased leukocytes with statistically significant increases in the Group 6 males and Group 7 males and females. The segmented neutrophil values exhibited a similar pattern, Groups 6 and 7, males and females, had elevated levels and statistical significance increases in Groups 6 and 7, males and females. The Group 7 females demonstrated a statistically significant MCV decrease which was considered incidental and not associated with test article administration.

7.6.2. Serum Biochemical Evaluations

A summary of biochemical values is presented in Table 6. Individual biochemical values are presented in Appendix O.

7.6.2.1. Chromic Oxide

After 13 weeks of exposure, none of the treatment group parameters demonstrated a statistically significant difference from the control group.

7.6.2.2. Basic Chrome Sulfate

With the exception of slightly increased alkaline phosphatase in the Group 7 females and slightly decreased cholesterol in the Group 6 and 7 females, all other parameters for both sexes were similar to the control group values. Other changes were considered incidental.

7.6.3. Urinalysis Evaluations

A summary of urinalysis values is presented in Table 7. Individual Urinalysis values are presented in Appendix P.

No statistically significant differences or treatment-related effects were exhibited in any group, males or females, in the urinalysis values for either test material, chromic oxide or basic chrome sulfate.

7.7. BRONCHOALVEOLAR LAVAGE EVALUATIONS

A summary of bronchoalveolar lavage fluid evaluations is presented in Table 8. Individual bronchoalveolar lavage fluid data are presented in Appendix Q.

7.7.1. Chromic Oxide

None of the treatment groups demonstrated a statistically significant difference from the control group for any parameter.

Yellow intracytoplasmic crystalline material was present within the mononuclear cells in Groups 2, 3 and 4. The amount of material and percentage of affected cells increased progressively with increased exposure to the test article (chromic oxide), such that small amounts of crystals were present in >90% of cells in most Group 2 animals and moderate to large amounts of crystalline materal were noted in >99% of cells in all Group 4 animals. Group 3 animals were intermediate to Groups 2 and 4.

More clusters of epithelial cells were observed in treated groups (2 - 7) when compared to the control group.

7.7.2. Basic Chrome Sulfate

The results from five parameters demonstrated the same pattern for both sexes. Males and females from Groups 5, 6 and 7 had a statistically significantly decreased total nucleated cell count. Mononuclear cells decreased in Groups 6 and 7 males and Groups 5, 6 and 7 females with the Group 7 males statistically significant. Segmented neutrophils increased in Group 5, 6 and 7 males and females with Group 7 males statistically significant.

Increased protein and lactate dehydrogenase activity in Groups 6 and 7 were considered to be exposure-related, although these alterations were not statistically significant. Increased amounts of cell debris and lysed cells were observed in Groups 5, 6 and 7 and were considered exposure-related.

More clusters of epithelial cells were observed in treated groups (2 - 7) when compared to the control group.

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Table 7.7.a.

MALES
INCIDENCE TABLE OF BALF VALUES

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Number Examined	5	5	5	5	5	5	5
Intracellular Crystalline Material							
Small	0	5	0	0	0	0	0
Moderate	0	0	5	3	0	0	0
Large	0	0	0	2	0	0	0
Epithelial Cell Clusters							
1 - 4	0	1	1	2	2	2	3
5 - 7	0	0	0	0	0	1	1
10 - 14	0	0	1	0	0	0	0

Table 7.7.b.

FEMALES
INCIDENCE TABLE OF BALF VALUES

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Number Examined	5	4	5	5	5	5	5
Intracellular Crystalline Material							
Small	0	4	0	0	0	0	0
Moderate	0	0	5	1	0	0	0
Large	0	0	0	4	0	0	0
Epithelial Cell Clusters							
1 - 4	2	1	3	2	3	3	3
5 - 7	0	1	0	1	0	2	0
10 - 14	0	0	0	1	1	0	1

7.8. SPERM EVALUATIONS

A summary of male spermatogenesis data is presented in Table 9. Individual spermatogenesis data are presented in Appendix R.

Evaluations of sperm motility, morphology and epididymal concentrations were conducted on 10 males per group. Sperm motility ranged from 49.0 to 62.2 percent. Group 1 had a mean sperm motility value of 60.5% and Group 5 was 49.0%. There were no apparent treatment related effects for Group 5 or any other treated group for sperm motility compared to the control group.

Sperm concentrations (per gram of caudal tissue) ranged from 751 x 10^6 for Group 5 to a high of 913 x 10^6 for Group 4. Mean sperm concentration in the control group (Group 1) was 863 x 10^6 and mean sperm concentrations for the treated groups were comparable with the control group.

Due to the inconsistencies between the three initial evaluations of sperm morphology, the data was considered invalid. The results are not presented in this report but will be retained in the study file.

The mean coefficient of variations between the results of the repeat sperm morphology evaluations was less than 5% meeting the criteria established for a valid analysis. The results of the three readings per rat (repetitions 1, 2, and 3) which comprised the repeat evaluation are presented below as mean percent normal sperm for each exposure group. There were no statistical differences in the number of abnormal sperm for any of the test material-exposed groups as compared to the controls.

Table 7.8.

Group	1	2	3	4	5	6	7
Reading		(% Normal ± standard deviation and coefficient of variation)					
Repetition							
1(%N)	96.8±2.5	95.5±3.3	97.8±2.6	96.5±3.5	95.7±3.5	96.5±3.0	97.4±2.2
(CV)	2.6	3.5	2.7	3.6	3.7	3.1	2.3
2(%N)	97.5±1.9	96.0±2.6	97.6±1.3	97.0±2.0	96.8±3.2	96.7±2.0	97.0±2.6
(CV)	1.9	2.7	1.3	2.1	3.3	2.1	2.7
3(%N)	97.6±2.3	94.5±2.6	98.0±1.9	96.9±1.5	94.9±2.4	95.8±1.9	95.9±3.4
(CV)	2.4	2.8	1.9	1.5	2.6	2.0	3.6
Mean CV	2.3	3.0	1.3	2.4	3.2	2.4	2.9

7.9. ANATOMIC PATHOLOGY

7.9.1. Macroscopic

Macroscopic observations are summarized in Table 10. Individual macroscopic observations are presented in Appendix U.

Test article-related macroscopic findings at the terminal and recovery sacrifices were observed in lung and mediastinal lymph node of animals in this study. The incidence of these findings was as follows:

Table 7.9.1.a.
Incidence of Test Article-Related Macroscopic Lesions
In The Lung and Mediastinal Lymph Node
Male and Female - Terminal Sacrifice

Group	1		2		3		4		5		6		7	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10	10	10	10	10	11*	10
Lung,														
Discoloration, green			10	10	10	10	10	10						
Discoloration, gray											10	8	10	10
Lymph node, Mediastinal,														
Discoloration, green					1	1	10	9						

*Includes one animal that died during the course of the study

Table 7.9.1.b.
Incidence of Test Article-Related Macroscopic Lesions
In The Lung and Mediastinal Lymph Node
Male and Female - Recovery Sacrifice

Group	1		2		3		4		5		6		7	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Number Examined	5	5	5	5	5	5	5	5	5	5	5	5	4	5
Lung,														
Discoloration, green			5	5	5	5	5	5						
Discoloration, gray									1		1		1	3
Focus/foci, tan			1						1		5	5	4	5
Lymph node, Mediastinal,														
Discoloration, green					3	4	5	5						
Discoloration, gray									2	1	4	4	3	3
Enlarged,							2	1	2		2	4	2	2

The control group (Group 1) had no macroscopic observations in the lung or mediastinal lymph node. Green discoloration was observed primarily in the animals exposed to chromic oxide (Groups 2, 3 and 4) whereas gray discoloration and tan focus/foci were most commonly observed in animals exposed to the basic chrome sulfate (Groups 5, 6 and 7). Mediastinal lymph node enlargement was also most commonly observed in the animals exposed to the basic chrome sulfate. Tan focus/foci of the lung and enlargement of the mediastinal lymph node were only present in the recovery sacrifice animals. The tan focus/foci correlated well with the presence of alveolar macrophages, and enlarged mediastinal lymph node correlated well with histiocytosis.

Additional macroscopic findings observed in the animals of this study were few in number and were considered incidental in rats of this strain and age.

7.9.2. Organ Weights

Absolute and relative organ weights are summarized in Table 11. Individual organ weight data are presented in Appendix T.

7.9.2.1. Terminal Sacrifice

At the terminal sacrifice, significant increases ($p \leq 0.01$) were observed in mean absolute and relative lung/trachea weights of both males and females of Groups 5, 6 and 7 (basic chrome sulfate). Mean absolute and relative lung/trachea weights were also significantly increased ($p \leq 0.01$) in males of Group 4 (chromic oxide). Histologic tissue alterations were present to explain these increased weights. These tissue alterations were test article-related.

Group 7 male mean absolute body and brain weights were significantly decreased ($p \leq 0.01$ and $p \leq 0.05$, respectively) and mean relative brain/body weights were significantly increased ($p \leq 0.01$). Group 7 male mean absolute kidney weights were significantly decreased ($p \leq 0.01$) as were the mean relative kidney/brain weights. However, the mean relative kidney/body weights were significantly increased ($p \leq 0.01$). The lack of an overall weight gain would explain this aberration. No histologic tissue alterations were present to explain these organ weight changes.

Significant mean absolute and relative increases ($p \leq 0.01$) in the thyroid/parathyroid weights were observed in Groups 3 and 7 females and in mean relative thyroid/parathyroid/body weights in Group 4 females. In the males, there was only a significant increase ($p \leq 0.05$) observed in the Group 7 animals mean relative thyroid/parathyroid/body weights.

Other terminal sacrifice observations included: decreased Group 7 female mean absolute body weights; decreased mean absolute liver weight and mean relative liver/brain weights in the Group 7 males; decreased mean absolute and relative spleen weights in Group 7 males, and decreased mean absolute spleen weight in the Group 7 females; and increased mean relative testis/body weights in Group 7 males.

With the exception of the lung/trachea weights, most of the organ weight changes are very small, ranging in tenths of a gram absolute weight. And although these are statistically significant, the biological importance of these changes cannot be determined from the data in this study.

7.9.2.2. Recovery Sacrifice

At the recovery sacrifice, both mean absolute and relative (to body and brain weights) lung/trachea weights were increased ($p \leq 0.01$) in the male and female animals in Groups 6 and 7. Only the mean relative lung/trachea/body weights were increased in the Group 5 animals (males at $p \leq 0.01$ and females at $p \leq 0.05$). Group 6 and 7 male absolute lung/trachea weights were 34 - 47% greater than the control values at the terminal necropsy and 32 - 50% greater after the recovery period. Histologic alterations were present to explain the pulmonary weight increases.

Mean absolute body weights were decreased ($p \leq 0.01$) in males of Groups 6 and 7 as were the mean absolute and relative kidney/brain weights ($p \leq 0.01$ and $p \leq 0.05$, respectively). The mean relative brain/body weights were increased ($p \leq 0.05$) in males of Groups 6 and 7. The Group 7 male absolute kidney weight at the terminal necropsy was 18% less than the control value and 9% less at the recovery sacrifice. No histologic changes were present to explain the renal weight decreases.

7.9.3. Microscopic

Microscopic observations are summarized in Table 12. Individual microscopic observations are presented in Appendix U. Results of the peer review are presented in Appendix V.

7.9.3.1. Terminal Sacrifice

7.9.3.1.1. Chromic Oxide

Test article-related changes were observed in the lungs, mediastinal lymph node, and lymphoid tissue around the bronchi of the lungs and at the tracheal bifurcation of all groups of both males and females exposed to chromic oxide (Table 7.9.3.1.1.). These changes ranged in severity from trace to mild and varied from focal to multifocal in distribution.

Pulmonary changes associated with chromic oxide exposure included chronic interstitial inflammation, septal cell hyperplasia (Type II pneumocytes), multifocal aggregates of black pigment in macrophages within the alveolar spaces and the presence of black pigment in the peribronchial lymphoid tissue. The pigment observed in the lung, peribronchial lymphoid tissue and mediastinal lymph node stained black with hematoxylin and eosin stain and was presumed to represent the test article. These findings corresponded to the increased lung weight observed for the Group 4 males.

Trace to mild chronic interstitial inflammation of the lung characterized by an infiltration of inflammatory cells was observed in alveolar septa surrounding aggregates of pigmented macrophages in some Group 3 and all Group 4 males and females. Chronic interstitial inflammation was accompanied by septal cell hyperplasia (Type II pneumocytes) in some Group 3 females and all Group 3 and 4 males.

Trace to mild deposition of black pigment within macrophages in the lungs was present in both males and females from all 3 chromic oxide treated groups at the terminal sacrifice. Randomly distributed foci or aggregates of pigmented macrophages filled with dense black pigment were observed within alveolar spaces adjacent to the junctions of terminal bronchioles and alveolar ducts. In most instances, pigmented macrophages filled the alveolar spaces (usually 9 to 12 per alveoli). Foci of pigmented macrophages were also seen subjacent to the pleura. Similar black pigment was also observed in the peribronchial lymphoid tissue.

Within the mediastinal lymph node, black pigment was observed in all 3 chromic oxide treated groups and was similar to the pigment seen in the peribronchial lymphoid tissue in the lungs and at the tracheal bifurcation. The presence of the pigment corresponded to the green discoloration seen macroscopically. Lymphoid hyperplasia of the node was also present in all 3 treated groups.

The changes observed in the lungs, peribronchial lymphoid tissue and mediastinal lymph node are similar to those previously reported for other inhaled inert particles (Lee, et al., 1986; Muhle, et al., 1991).

No test article-related lesions were seen in the nasal cavities of animals exposed to chromic oxide in treatment Groups 2, 3 or 4.

7.9.3.1.2. Basic Chrome Sulfate

Test article-related changes were observed in the lungs, larynx, mediastinal lymph node and nasal cavity of all treated groups of males and females exposed to basic chrome sulfate (Table 7.9.3.1.2.). These changes ranged from trace to severe and varied from focal or multifocal to diffuse in distribution.

For animals exposed to basic chrome sulfate, pulmonary changes were generally more extensive and more severe than those observed in animals exposed to chromic oxide. Changes which were observed included chronic alveolar inflammation, chronic interstitial inflammation, granulomatous inflammation, septal cell hyperplasia, multifocal to diffuse alveolar macrophages, multifocal foreign material deposition and peribronchial histiocytosis. They were seen in the lungs of all 3 treated groups (Groups 5, 6 and 7) at the terminal sacrifice except for peribronchial histocytosis, which was only seen in Groups 5 and 6. These changes corresponded to the increased lung weights observed in all groups of males and females treated with basic chrome sulfate, and were considered to be test article-related lesions.

Chronic inflammation, involving the alveoli of animals from Groups 5, 6 and 7, consisted of alveolar spaces filled with macrophages, neutrophils, lymphocytes and cellular debris. Some foci exhibited quite intense inflammation and thickening of the alveolar walls.

Chronic interstitial inflammation was usually multifocally distributed and consisted of thickened alveolar septa caused by inflammatory cell infiltration and hyperplasia of alveolar septal cells (Type II pneumocytes).

Multifocal areas of granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells and deposition of foreign material, were observed in Groups 5, 6 and 7. These lesions were most frequently seen near the junction of the terminal bronchioles and alveolar ducts. The foreign material observed in the lung and larynx was closely associated with granulomatous inflammation and was presumed to be the test article.

There was multifocal to diffuse pulmonary infiltration of alveolar macrophages with foamy or granular appearing acidophilic cytoplasm. Severity of such lesions ranged from trace to severe. Alveolar macrophages were usually located within the alveolar lumens and ranged in numbers from 2 or 3 cells per alveoli up to 12 or 14 cells per alveoli. The presence of numerous large foamy alveolar macrophages in the alveolar spaces corresponded to the gray discoloration of the lungs that was observed grossly.

Foreign material and granulomatous inflammation were observed in the lamina propria of the larynx of animals exposed to basic chrome sulfate (Groups 5, 6 and 7). Green refractile foreign material was present in the lamina propria and submucosa and was associated with an infiltration of macrophages and multinucleated giant cells (granulomatous inflammation).

Changes observed in the mediastinal lymph node in the basic chrome sulfate study consisted of multifocal histiocytosis and lymphoid hyperplasia. Histiocytosis consisted of macrophages or histiocytes with abundant foamy cytoplasm in the peribronchial lymphoid tissue and mediastinal lymph node. The lymphoid hyperplasia and histiocytosis correlated with the lymph node enlargement observed at necropsy.

Changes in the nasal tissues, which were considered to be test article-related in both males and females treated with basic chrome sulfate, included acute inflammation, suppurative exudate and mucoid exudate. One or more of these changes were seen in all 4 examined levels of the nasal cavity but were slightly more prevalent in the mid-posterior portion of the nasal cavity (Level C). Suppurative and/or mucoid exudate occurred in all 3 basic chrome sulfate treated groups, while acute inflammation occurred only in the 2 highest dose groups (Groups 6 and 7).

All other microscopic findings were incidental and/or spontaneous and unrelated to the test articles. Such lesions are considered normal for animals of this species and age. Infectious diseases were not observed in this study.

7.9.3.2. Recovery Sacrifice

7.9.3.2.1. Chromic Oxide

Microscopic changes persisted in the lung, mediastinal lymph node, and peribronchial lymphoid tissue in the lung and at the tracheal bifurcation of recovery sacrifice animals (Table 7.9.3.2.1.).

In the lung, trace to mild pigmented macrophages and black pigment in the peribronchial lymphoid tissue, persisted in all treated groups of males and females, at approximately equal incidences and severities as seen in

the terminal sacrifice animals. Trace to mild septal cell hyperplasia and trace to mild chronic interstitial inflammation persisted in Group 2 through 4 males and Group 3 and 4 females. These lesions were decreased in severity as compared to the terminal sacrifice groups. In Group 2 males multifocal aggregates of pigmented macrophages were associated with chronic interstitial inflammation and septal cell hyperplasia in 1 of 5 males and with chronic interstitial inflammation alone in a second Group 2 male. These lesions consisted only of 1 or 2 foci per lung and were only of trace severity. Pigment accumulation was not associated with pathologic changes in the other 3 Group 2 males or in any of the Group 2 females. The low incidence and minimal severity of these pathologic changes (chronic interstitial inflammation and septal cell hyperplasia) indicate that this dose is near the No Observable Adverse Effect Level (NOAEL) for subchronic exposure to chromic oxide.

In the mediastinal lymph node, lymphoid hyperplasia was observed with approximately equal incidence and severity in all treated groups. Trace to mild black pigment also persisted in all treated groups. An apparent increase in incidence in Group 2 and 3 males as compared to the terminal sacrifice suggested pulmonary clearance via the lymphatic system.

7.9.3.2.2. Basic Chrome Sulfate

In the recovery group animals, test article-related changes persisted in the lung, larynx, nasal tissues, and mediastinal lymph node (Table 7.9.3.2.2.).

In the lung, trace to moderate chronic inflammation of the alveoli persisted in Group 6 and 7 males and females, at approximately equal incidence and severity as that seen in the terminal sacrifice animals in these groups. Trace to moderate chronic interstitial inflammation was observed with approximately equal incidence and severity in all treated recovery and terminal sacrifice groups of males and females. There was an increase in the incidence and severity of septal cell hyperplasia in all treated groups of males and females at the recovery sacrifice. The incidence and severity of alveolar macrophages was approximately equal in all treated groups of males and females at the recovery sacrifice, as compared to the terminal sacrifice.

Peribronchial histiocytosis was not observed at this level in Group 5 females at the recovery sacrifice. In Group 6 males and females, peribronchial histiocytosis persisted at approximately equal incidence and severity to those same sex groups at the terminal sacrifice. The incidence of peribronchial histiocytosis increased in Group 7 males and females at the recovery sacrifice. This change suggested the clearing of the test article via the reticuloendothelial system.

Trace to mild foreign material persisted in Group 5, 6 and 7 females and 6 and 7 males; but was decreased in incidence in Group 6 and 7 males and 5 and 6 females. Granulomatous inflammation of the lung was decreased in incidence and severity in Group 5 and 6 females, and Group 6 males. However, in Group 7 males and females, the incidence of granulomatous inflammation was approximately equal to that seen in these groups at the terminal sacrifice.

In the larynx, foreign material was not detected in Group 5 males and females and in Group 6 males. The incidence and severity of foreign material in the larynx was markedly decreased in the Group 6 females and Group 7 males and females. Additionally, granulomatous inflammation in the larynx decreased in severity in all treated groups of males and females.

The incidence and severity of histiocytosis and lymphoid hyperplasia of the mediastinal lymph node remained at a similar level in both males and females of all treated groups in both the terminal and recovery sacrifices.

In the recovery sacrifice animals, nasal cavity findings were seldom observed with the exception of trace suppurative exudate seen in the most anterior section of the nasal cavity (Level A) in one Group 5 male, two Group 6 females and one Group 7 female. Suppurative exudate was also seen in the mid-anterior level of the nasal cavity (Level B) in one Group 6 female.

7.9.3.3. Summary

The rats of this study were exposed to chromic oxide and basic chrome sulfate via nose-only inhalation for 13 weeks, followed by a 13 week recovery period. There were significant differences observed in the histologic findings in the respiratory system of the animals exposed to these two compounds. Chromic oxide caused multifocal lesions in the lungs characterized by the accumulation of pigmented macrophages scattered throughout the lung parenchyma. Pigment was also present in the mediastinal lymph nodes and peribronchial lymphoid tissue. The trachea and nasal cavities were generally unaffected in the chromic oxide phase of the study.

In contrast, the basic chrome sulfate caused a diffuse lesion in the lungs characterized by the presence of alveolar macrophages, septal cell hyperplasia, foreign material deposition, granulomatous inflammation and chronic inflammation involving primarily the alveoli and septal cells. The larynx and nasal cavities were also affected by the basic chrome sulfate. Histiocytosis and lymphoid hyperplasia were commonly observed in the mediastinal lymph node.

In the recovery sacrifice animals, the nasal findings were not detected, except for trace suppurative lesions in nasal Levels A and B, seen in a few basic chrome sulfate treated animals. The lesions observed in the larynx, lungs and mediastinal lymph nodes were reduced in severity, especially in the lower dose (Group 5) with basic chromic sulfate. Changes present in the lungs and mediastinal lymph node with chromic oxide were also reduced in severity in the lowest dose group (Group 2).

All other microscopic findings were incidental and/or spontaneous and unrelated to the test articles. Such lesions are considered normal for animals of this species and age. Infectious diseases were not observed in this study.

A peer review of the unaudited draft of histopathology data was conducted by Dr. Jerry F. Hardisty of Experimental Pathology laboratories, Inc. (EPL). Even though there were some variations on individual animal observations, the study pathologist's conclusions were upheld.

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Table 7.9.3.1.1.
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
TERMINAL SACRIFICE
CHROMIC OXIDE

Group	1		2		3		4	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LUNG								
Hyperplasia, septal cell, multifocal						5	10	10
-trace						4	3	2
-mild						1	7	8
Inflammation interstitial, chronic, multifocal					4	6	10	10
-trace					2	5	7	10
-mild						1	3	
focal, trace					2			
Macrophages, pigmented, alveolar, multifocal			10	10	10	10	10	10
-trace			10	10	4	7		
-mild					6	3	10	10
Pigment, black, peribronchial, multifocal			10	9	9	10	3	10
-trace			10	9	7	9	1	9
-mild					2	1	2	1
LYMPH NODE, MEDIASTINAL								
Hyperplasia, lymphoid, diffuse				3	3	9	8	9
-trace				3	3	9	1	3
-mild							7	6
Pigment, black, multifocal			2	2	5	10	10	10
-trace			2	2	3	9	1	
-mild					2	1	9	10
TRACHEA BIFURCATION								
Pigment, black, multifocal, trace			3	4	6	2	5	1
			3	4	6	2	5	1

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Table 7.9.3.1.2.
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
TERMINAL SACRIFICE
BASIC CHROME SULFATE

Group	1		5		6		7	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LUNG								
Inflammation, chronic, alveoli, multifocal			10	10	10	10	10	10
-trace			1	4		4	1	
-mild			9	6	10	5	5	8
-moderate						1	4	2
Foreign material, multifocal				4	9	8	10	10
-trace				4	8	6	8	6
-mild					1	2	2	4
Histiocytosis, peribronchial, multifocal				4	7	6		
-trace				3	6	6		
-mild				1	1			
Hyperplasia, septal cell, multifocal			10	10	8	5	10	10
-trace			4	2		3	2	1
-mild			6	8	8	2	6	8
-moderate							2	1
Inflammation, granulomatous, multifocal				4	9	7	10	10
-trace				4	8	6	4	2
-mild					1	1	6	8
Inflammation, interstitial, chronic, multifocal			10	10	10	10	11	10
-trace			10	7	2	3	1	1
-mild				3	8	7	8	9
-moderate							2	
Macrophages, alveolar, multifocal			10	10	10	10	11	10
-mild			10	9	5	4		
-moderate				1	1	2		
diffuse								
-trace							1	
-mild					1	1	1	2
-moderate					3	3	8	6
-severe							1	

MPI RESEARCH

Table 7.9.3.1.2. (continued)
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
TERMINAL SACRIFICE
BASIC CHROME SULFATE

Group	1		5		6		7	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LARYNX								
Foreign material, multifocal			2	2	8	5	9	8
-trace			1	1	6	4	9	7
-mild				1	2	1		1
focal, mild			1					
Inflammation, granulomatous, multifocal			3	6	10	10	10	10
-trace			3	3	1	5	3	2
-mild				3	6	3	5	8
-moderate					3	2	1	
focal, mild							1	
LYMPH NODE, MEDIASTINAL								
Histiocytosis, multifocal			7	9	10	8	10	9
-trace			2	1	1	1	1	2
-mild			5	8	8	5	9	7
-moderate					1	2		
Hyperplasia, lymphoid, diffuse			5	9	9	7	10	9
-trace			5	7	6		6	1
-mild				2	3	7	4	8
NASAL TISSUE A								
Exudate, suppurative, multifocal				1	1	2	4	7
-trace				1	1	2	4	5
-mild								2
Exudate, mucoid, multifocal			2	2	1	2	4	8
-trace			1	2	1	2	4	5
-mild								2
focal, trace			1					1
NASAL TISSUE B								
Exudate, suppurative, multifocal			1	1	3	1	7	9
-trace			1	1	2	1	4	3
-mild					1		2	6
-moderate							1	
Exudate, mucoid, multifocal			6	5	5	4	8	9
-trace			6	5	3	4	5	3
-mild					2		2	6
-moderate							1	
Inflammation, acute, multifocal					1		3	5
-trace					1		1	5
-mild							2	

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Table 7.9.3.1.2. (continued)
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
TERMINAL SACRIFICE
BASIC CHROME SULFATE

Group	1		5		6		7	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
NASAL TISSUE C								
Inflammation, acute,					2	1	1	6
multifocal, trace					2	1	1	6
Exudate, suppurative,					9	4	10	10
multifocal								
-trace					4	3	6	3
-mild					5	1	4	7
Exudate, mucoid,			10	7	10	9	10	10
multifocal								
-trace			10	7	2	8	5	3
-mild					8	1	5	7
NASAL TISSUE D								
Exudate, suppurative,			1		4	2	5	8
multifocal								
-trace			1		4	1	5	5
-mild						1		3
Exudate, mucoid,			5	7	6	6	6	8
multifocal								
-trace			5	7	5	5	6	5
-mild					1	1		3
Inflammation, acute,						1		2
multifocal								
-trace						1		1
-mild								1

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Table 7.9.3.2.1.
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
RECOVERY SACRIFICE
CHROMIC OXIDE

Group	1		2		3		4	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LUNG								
Hyperplasia, septal cell, multifocal			1		5	5	4	5
-trace			1		5	3		
-mild						2	4	5
Inflammation, interstitial, chronic, multifocal			2		5	5	5	5
-trace			2		5	3		
-mild						2	5	5
Macrophages, pigmented, alveolar, multifocal			5	5	5	5	5	5
-trace			5	5	5	3		
-mild						2	5	5
Pigment, black, peribronchial, multifocal			5	5	5	5	3	5
-trace			5	5	5	5	2	5
-mild							1	
LYMPH NODE, MEDIASTINAL								
Hyperplasia, lymphoid, diffuse		1	3	1	3	4	5	5
-trace		1	3	1	3	4		4
-mild							5	1
Pigment, black, multifocal			4	2	5	5	5	5
-trace			4	2	4	5		
-mild					1		5	5
TRACHEA BIFURCATION								
Pigment, black,				1	1		2	1
multifocal, trace				1	1		2	1

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Table 7.9.3.2.2.
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
RECOVERY SACRIFICE
BASIC CHROME SULFATE

Group	1		5		6		7	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LUNG								
Inflammation, chronic,								
alveoli,					4	5	4	5
multifocal								
-trace					2	2		
-mild					2	3	3	4
-moderate							1	1
Foreign material,				1	1	1	4	5
multifocal								
-trace					1	1	2	4
-mild							2	1
focal, trace				1				
Histiocytosis,								
peribronchial,					2	2	2	1
multifocal, trace					2	2	2	1
Hyperplasia,								
septal cell,			5	5	5	5	4	5
multifocal								
-trace			5	5	5			
-mild						5	4	4
-moderate								1
Inflammation,								
granulomatous,				1	2	2	4	5
multifocal								
-trace					1	2	1	3
-mild					1		3	2
focal, trace				1				
Inflammation,								
interstitial, chronic,			5	5	5	5	4	5
multifocal								
-trace			4	5	2			
-mild			1		3	5	3	4
-moderate							1	1
Macrophages,								
alveolar,			5	5	5	5	4	5
multifocal								
-trace			2					
-mild			3	5			2	
-moderate						1		
diffuse								
-trace					1			
-mild					4	3	2	
-moderate						1		4
-severe								1

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Table 7.9.3.2.2. (continued)
INCIDENCE OF SELECTED TREATMENT-RELATED MICROSCOPIC LESIONS
RECOVERY SACRIFICE
BASIC CHROME SULFATE

Group	1		5		6		7	
Sex	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
LARYNX								
Foreign material						1	3	1
multifocal, trace						1	3	1
Inflammation, granulomatous			1	1	3	5	4	5
multifocal								
-trace			1	1	2	4		2
-mild					1	1	4	3
LYMPH NODE, MEDIASTINAL								
Histiocytosis			5	5	5	5	4	5
multifocal								
-trace			3	4				2
-mild			2	1	5	5	4	3
Hyperplasia, lymphoid			4	4	4	5	4	5
diffuse								
-trace			4	3		1		
-mild				1	4	4	4	5
NASAL TISSUE A								
Exudate, suppurative			1			2		1
multifocal, trace			1			2		1
NASAL TISSUE B								
Exudate, suppurative						1		
multifocal, trace						1		

Note: Nasal Tissues C and D were within normal limits for the recovery sacrifice males and females.

8. DISCUSSION

Three groups of male and female rats were exposed for 6 hours per days, 5 days per week for 13 consecutive weeks to mean concentrations of 4.4, 15 and 44 mg/m^3 of chromic oxide. Three different groups of male and female rats were exposed according to the same schedule to mean concentrations of 17, 54 and 168 mg/m^3 of basic chrome sulfate. Some animals from each group were maintained for a 13 week post-exposure recovery period.

These test articles were selected as representative of various families of chromium compounds. The desired exposure levels were selected by the Sponsor to be multiples of the threshold limit value for trivalent chrome and set at chrome equivalents of 3, 10 and 30 mg/m^3 for each test article. A single control group was used for both test articles. Mean particle size (MMAD) ranged from 1.8-1.9 for chromic oxide to 4.2-4.5 for basic chrome sulfate.

Another 6 groups of male and females plus appropriate controls were exposed to each of the test articles at the above concentrations for 5 consecutive days. After 5 days of exposure, these animals were used for the bronchoalveolar lavage fluid (BALF) evaluations.

8.1. CHROMIC OXIDE

No mortalities occurred during the conduct of this study in animals exposed to chromic oxide at mean concentrations of 4.4, 15, and 44 mg/m^3, Groups 2, 3 and 4 respectively. No significant exposure-related effects were noted in the ophthalmologic evaluations, clinical signs and body weights. None of the hematologic, serum biochemical, or urinalysis parameters demonstrated a statistically signficant difference from the control group after 13 weeks of exposure. There were no apparent exposure-related effects on sperm motility, morphology and concentration.

None of the BALF parameters demonstrated a statistically significant difference after 5 days of exposure. Yellow crystalline material was observed in the mononuclear cells from all treated groups. This crystalline material was believed to be the test material deposited in the trachea and lungs but changed color during the slide preparation procedure.

Macroscopic examination at the terminal sacrifice revealed an exposure related green discoloration in the lungs and mediastinal lymph nodes in all treatment groups that increased in severity as exposure concentration increased (the test material was green in color). The green lungs and lymph node discoloration were observed macroscopically at the recovery sacrifice with slightly decreased incidence and severity.

Statistically significant increases in the high level (44 mg/m^3) male mean, absolute and relative lung weights were observed at the terminal sacrifice. This corresponded with exposure related histologic tissue alterations. There were no other organ weight changes that could be clearly considered a direct effect of the chromic oxide.

Black pigment within macrophages and in the peribronchial lymphoid tissue and mediastinal lymph nodes was observed microscopically in all treated groups, males and females. The pigment observed in stained hematoxylin and eosin tissues slides was presumed to be the test article. The presence of the pigment corresponded to the green discoloration seen macroscopically. Associated with this pigment were trace to moderate exposure-related microscopic changes in the lungs and mediastinal lymph nodes. These included interstitial inflammation, septal cell hyperplasia and lymphoid hyperplasia (the effects at the low level were limited to lymphoid hyperplasia). The changes observed are similar to those previously reported for other insoluble, respirable particles (Lee, et al., 1986; Muhle, et al., 1991). The trachea and nasal cavity were generally unaffected from exposure to chromic oxide.

At the recovery sacrifice, black pigment observed at the terminal sacrifice persisted with approximately the same incidence and severity. At the low level (4.4 mg/m^3), 2 of the males had septal cell hyperplasia and/or chronic interstitial inflammation associated with aggregates of pigmented macrophages. However, pigment accumulation was not associated with pathological effects in 3 of the 5 males and all of the females exposed previously to chromic oxide. Microscopic observations in these animals found only scattered macrophages containing intracytoplasmic pigment and accumulation of similar pigment in the peribronchial and mediastinal lymph tissue. Septal cell hyperplasia and chronic interstitial inflammation persisted in rats exposed at the mid and high levels but the severity of the lesions was decreased as compared to the terminal sacrifice rats at these levels. The presence of pigment in the lymphoid tissue suggests pulmonary clearance of the pigment via the lymphatic system.

8.2. BASIC CHROME SULFATE

One mortality occurred to a Group 7 male which was exposed to the high level of basic chrome sulfate (168 mg/m^3) for four days. This was an unusual situation because no other mortalities or severe clinical signs occurred during the conduct of this study for any other animal exposed to basic chrome sulfate either at the time of this animal's death or during the remaining 12 weeks of exposure. Although no abnormalities were observed at necropsy, the cause of this death may have been related to stress induced by the exposure procedure early in the study. Six other animals not from Group 7 died on exposure day 1 as a result of stress induced by the restraint tubes and had to be replaced. For these reasons it does not seem appropriate to consider this mortality as a test material-related death because the cause cannot be clearly established. No mortalities occurred to animals from Groups 5 and 6 exposed to low and mid levels of 17 and 54 mg/m^3. Labored breathing and rapid respiration in several high level females and 1 high level male (not the animal which died) were the significant clinical signs noted during the exposure and recovery periods. The significant clinical signs observed were very sporadic and frequently occurred for only 1 to 2 observations. No exposure related effects were noted in the ophthalmologic evaluations. There were no apparent exposure related effects on sperm motility, morphology and concentration.

Exposure-related reductions in mean body weight gains, some statistically significant, occurred in mid and high level males and high level females during the 13 week

exposure period. The mid and high level male mean body weights remained statistically lower during the recovery period. However, the weight gains for these males were slightly greater than the control group during the recovery period (29-32% compared to 26%). Body weight values for low level males and females and mid level females were comparable to the control values at the terminal and recovery sacrifices.

At the terminal necropsy, an exposure-related gray discoloration of the lungs in mid and high level males and females was observed. The incidence of lung discoloration decreased at the recovery sacrifice while tan foci developed in the lungs and the incidence of enlarged, gray discolored mediastinal lymph nodes increased. The test material was green in color.

At the terminal sacrifice, significant increases were observed in mean absolute and relative lung/trachea weights in both sexes at all exposure levels. These corresponded to microscopic changes and were considered test-article related. Small weight changes occurred in several other organs but did not correlate with any microscopic pathology. These changes could not be directly related to a direct effect of the test article.

After 13 weeks of exposure to basic chrome sulfate, trace to severe exposure-related changes were observed microscopically in the nasal cavity, larynx, lungs and mediastinal lymph node in all groups and both sexes. The changes noted include interstitial and granulomatous inflammation, septal cell hyperplasia, foreign material deposition, intraalveolar accumulation of macrophages with foamy/granular- appearing acidophilic cytoplasm and histiocytosis. Some of these effects may be related to the acidity of the basic chrome sulfate which readily forms acidic solutions (pH of approximately 2.8) presumably with the sulfate group.

At the recovery sacrifice, the exposure-related changes continued in the larynx, lungs and mediastinal lymph node. The incidence and severity remained approximately equal to the terminal sacrifice animals for most changes observed. Decreased or resolved changes included peribronchial histiocytosis in low level females, and foreign material and granulomatous inflammation in the lungs of low and mid level males and females. Foreign material was not observed in the larynx of low level males and females, and mid level males. Nasal cavity findings were resolved in all animals with the exception of trace suppurative exudate randomly seen in a few rats.

9. CONCLUSION

The results of this study demonstrate that rats exposed 5 days/week, 6 hours/day for 13 weeks to chromic oxide via inhalation at levels of 4.4, 15 and 44 mg/m^3 of chromic oxide (equivalent to 3, 10, and 30 mg/m^3 of trivalent chrome) developed pathological changes in the bronchial and mediastinal lymphatic tissue and the lungs consisting of lymphoid and septal cell hyperplasia and interstitial inflammation which are commonly reported in response to the presence of insoluble, respirable particles. The effects following inhalation of chromic oxide were limited to the respiratory tissue and associated lymph nodes. No other systemic effects which could be directly related to chromic oxide were observed. Signs of recovery were observed following cessation of exposure. Due to the microscopic effects observed in some of the animals exposed to the low level of chromic oxide a No Observable Adverse Effect Level (NOAEL) was

not established. However, the low incidence and minimal severity of the pathological effects in the low level animals suggest that a level of 44 mg/m^3 is very near a NOAEL for subchronic exposure to chromic oxide.

The results also demonstrate that rats exposed similarly for 13 weeks to basic chrome sulfate at levels of 17, 54 and 168 mg/m^3 (also equivalent to 3, 10 and 30 mg/m^3 of trivalent chrome) developed diffuse lesions in the lungs characterized by the accumulation of foreign material, infiltration of alveolar macrophages, septal cell hyperplasia, and granulomatous and chronic inflammation. Histiocytosis and lymphoid hyperplasia occurred in the mediastinal lymph node. Effects also occurred in the nasal cavities and larynx. The effects of exposure to basic chrome sulfate were generally localized to the respiratory tract and associated lymph nodes. Other than general effects on body weight, no other systemic effects were identified which could be directly related to exposure to the test article. Some signs of recovery occurred following cessation of exposure. A No Observable Adverse Effect Level (NOAEL) was not established for basic chrome sulfate in this study.

This study indicates that there are significant differences in toxicity between insoluble chromic oxide and soluble basic chrome sulfate with subchronic inhalation in rats. The effects seen with chromic oxide appear to be pathological response to the accumulation of insoluble, respirable particles in the lung and lymphatic tissue. In contrast, the effects of basic chrome sulfate are relatively more severe and in part may be related to the acidic nature of this material. The effects of both materials are limited to the respiratory tract and for chromic oxide generally appear to be reversible under the exposure conditions of this study. While the effects seen with basic chrome sulfate may be reversible, the length of the recovery period in this study was insufficient to make a definitive determination.

This study was conducted in conformance with the Good Laboratory Practice Standards with the exception of the β_2-microglobulin analysis performed on the urine by Dr. Claude Viau, at the University of Montreal, Montreal, Canada. This laboratory was not GLP-compliant but was selected because of the established expertise of this laboratory to conduct this specialized evaluation and the ability to conduct the analysis within the time constraints imposed by the study design. Comments on Study Data are presented in Appendix X. This report accurately reflects the raw data obtained during the performance of the study.

Roger Hilaski

Roger J. Hilaski, M.A.
Associate Director
Inhalation Toxicology
Study Director

8-2-96
Date

The following are the applicable references:

Lee, K. P., Henry, Norman W. III, Trochimowicz, H. J., and Reinhardt, C. F., (1986). Pulmonary Response to Impaired Lung Clearance in Rats following Excessive TiO_2 Dust Deposition. *Environmental Research*, 41; 144-167.

Muhle, H., Bellmann, B., Creutzenberg, O., Dasenbrock, C., Ernst, H., Kilpper, R., MacKenzie, J. C., Morrow, P., Mohr, U., Takenaka, S., and Mermelstein, R., (1991). Pulmonary Response to Toner upon Chronic Inhalation Exposure in Rats. *Fundamental and Applied Toxicology*, 17; 280-299.

MPI RESEARCH

10. SIGNATURES

Kevin H. Denny, M.S., D.A.B.T.
Associate Director, Developmental
and Reproductive Toxicology

7/25/96
Date

Gail L. Walter, D.V.M., M.T. (ASCP)
A.C.V.P. Diplomate
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Roger B. Thompson, D.V.M., Ph.D,
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7/24/96
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Johnnie J. Eighmy, D.V.M., M.S.,
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Director of Pathology

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Date

GLOSSARY

Absent, portion - Missing a part of the whole.

Acanthosis - A thickening of the epidermis due to hypertrophy and/or hyperplasia of the prickle cell layer (stratum spinosum or malpighian layer) of the skin.

Altered foci, clear cell - In the liver, groups of hepatocytes occurring randomly and which may slightly compress adjacent parenchyma; generally consisting of hepatocytes with vacuolated cytoplasm. Thus, the focus of cells appears clear compared with adjacent non-affected hepatocytes.

Atrophy - A wasting away or decrease in the size of a cell, tissue, organ, or part.

Cardiomyopathy - A general diagnostic term designating primary degenerative myocardial disease, often of obscure or unknown etiology.

Congestion - The excessive or abnormal accumulation of blood within the vessels of an organ or tissue.

Cyst - Any closed cavity or sac lined by epithelium; usually contains a liquid or semi-solid material.

Cyst, ultimobranchial - Any closed cavity or sac lined by squamous or stratified squamous epithelium and containing degenerating squamous epithelial cells; considered to be rudiments of the fifth pharyngeal pouch or thyroid primordia.

Degeneration, tubular - The deterioration of epithelial cells lining the renal tubules.

Deviation - An abnormality; a turning away from the regular standard or course.

Dilatation - An increase in size of a tissue or organ due to an expansion of a lumen, or other such space or chamber.

Discoloration, gray - A change in color from normal or from surrounding tissue to a grayish hue.

Discoloration, green - A change in color from normal or from surrounding tissue to a greenish hue.

Discoloration, red - A change in color from normal or from surrounding tissue to a reddish hue.

Ectopic tissue - Morphologically normal tissue in a location where the tissue is not normally found.

Enlarged - Of bigger than normal size. Considered to be a diffuse change, affecting the entire organ or tissue, unless otherwise indicated.

Erythrophagocytosis - The consumption of erythrocytes by other cells, especially macrophages.

Exudate, mucoid - The presence of mucus or a mucus-like material which has been deposited in lumens or cavities or on tissue surfaces, usually as a result of inflammation.

Exudate, suppurative - Inflammatory material which has been deposited on internal or external surfaces of an organ or tissue consisting chiefly of neutrophils (pus).

Focus/foci, black - One or more discrete areas exhibiting a black coloration which is/are different from the color of the surrounding tissue and which is/are flush with or depressed relative to the surrounding tissue.

Focus/foci, tan - One or more discrete areas exhibiting a yellowish-brown coloration which is/are different from the color of the surrounding tissue and which is/are flush with or depressed relative to the surrounding tissue.

Foreign body, plant material - A mass or particle of material of plant origin which is not normal to the place where it is found.

Foreign material - Any material not made by the cells or tissues which is not usually found in the location in question.

Hemorrhage - The presence of blood outside the vascular system.

Histiocytosis - The presence of macrophages or histiocytes with abundant foamy cytoplasm.

Hyperkeratosis - Excessive thickening of the keratin layer of a keratinized stratified squamous epithelium-covered surface.

Hyperplasia, epithelial - A non-neoplastic proliferation of the epithelial cell components of a tissue or organ.

Hyperplasia, lymphoid - A non-neoplastic proliferation of germinal centers and/or an increase in the number or density of lymphocytes in a lymphoid organ.

Hyperplasia, septal cell - A non-neoplastic proliferation of the cells populating the alveolar walls of the lung.

Infiltration, lymphocytic - The presence of increased numbers of lymphocytes within a tissue.

Infiltration, lymphoid, peribronchial - The presence of increased numbers of lymphocytes, generally in the form of aggregates, within the lamina propria, submucosa and/or adventitia of the bronchi or bronchioles of the lung and/or the adjacent connective tissue.

Infiltration, mononuclear cell - The presence of increased numbers of cells with nonsegmented nuclei, particularly lymphocytes, plasma cells and/or macrophages, within an organ or tissue.

Inflammation, acute - A tissue reaction characterized by a prominent accumulation of neutrophils, with or without exudate and possibly a few lymphocytes or other inflammatory cells as typically seen early in the inflammatory process. It is not pathognomonic for a specific etiology and may or may not be of toxicologic and/or pathologic significance, depending on the context in which it occurs.

Inflammation, chronic - A tissue reaction characterized by a prominent accumulation of lymphocytes, plasma cells, macrophages and/or fibroblasts, usually with the formation of collagenous connective tissue as typically seen late in the inflammatory process. It is not pathognomonic for a specific etiology, and may or may not be of toxicologic and/or pathologic significance, depending on the context in which it occurs.

Inflammation, granulomatous - A subacute to chronic tissue response characterized by a predominance of macrophages in the inflammatory cell population. The inflammatory response may include multinucleated giant cells and connective tissue.

Inflammation, interstitial, chronic - A tissue reaction, particularly of the area between parts or in the interspaces of a tissue, characterized by a prominent accumulation of lymphocytes, plasma cells, macrophages and/or fibroblasts, usually with the formation of collagenous connective tissue as typically seen late in the inflammatory process. It is not pathognomonic for a specific etiology and may or may not be of toxicologic and/or pathologic significance, depending on the context in which it occurs.

Inflammation, subacute - A tissue reaction characterized by a mixture of neutrophils, lymphocytes and occasionally macrophages and/or plasma cells as typically seen subsequent to the early stages of the inflammatory process. It is not pathognomonic for a specific etiology and may or may not be of toxicologic and/or pathologic significance, depending on the context in which it occurs.

Inflammation, suppurative - A tissue reaction characterized by the presence of neutrophils as a predominant inflammatory cell component.

Lumenal debris, cellular - Material recognizable as of cellular origin, such as nuclear or cytoplasmic fragments, within the lumen of a hollow structure.

Macrophages, alveolar - A large mononuclear cell with abundant cytoplasm normally located within the air spaces (alveoli) of the lung and which is capable of phagocytosis. The cytoplasm may be vacuolated, or may contain foreign debris or pigments. Use of this diagnosis may indicate an alteration in number present and/or a morphological change.

Macrophages, pigmented - Large mononuclear cells capable of phagocytosis and the degradation of dead cells and other debris and containing pigmented material within their cytoplasm of otherwise unspecified color.

Metaplasia, osseous - Formation of bone in an extraskeletal site through a non-neoplastic alteration in cellular differentiation.

Microconcretion - The formation of small microscopic mineralized debris or particles within or associated with the renal tubules and/or urinary bladder.

Mineralization - The formation or deposit of mineral matter in an organ or tissue.

Mineralization, vascular - The presence of mineral deposits within the tunica intima, tunica media and/or tunica adventitia of blood vessels.

Necrosis - Death of tissue, usually as individual cells, groups of cells, or in localized areas in a living animal.

Necrosis, lymphoid - Death of lymphocytes or lymphoid tissue in a living animal.

Pigment, black - The presence of any material, black in color, within a tissue; may be located within the cytoplasm of cells or free in the intercellular space.

Plasmacytosis, medullary - The presence of plasma cells within the medullary cords and sinuses of lymph nodes.

Regeneration, tubular - The formation of a renewed epithelial lining of tubules in the kidney that have undergone prior damage; characterized by deeper hematoxylin staining of the cytoplasm and nucleus as compared with mature renal epithelium.

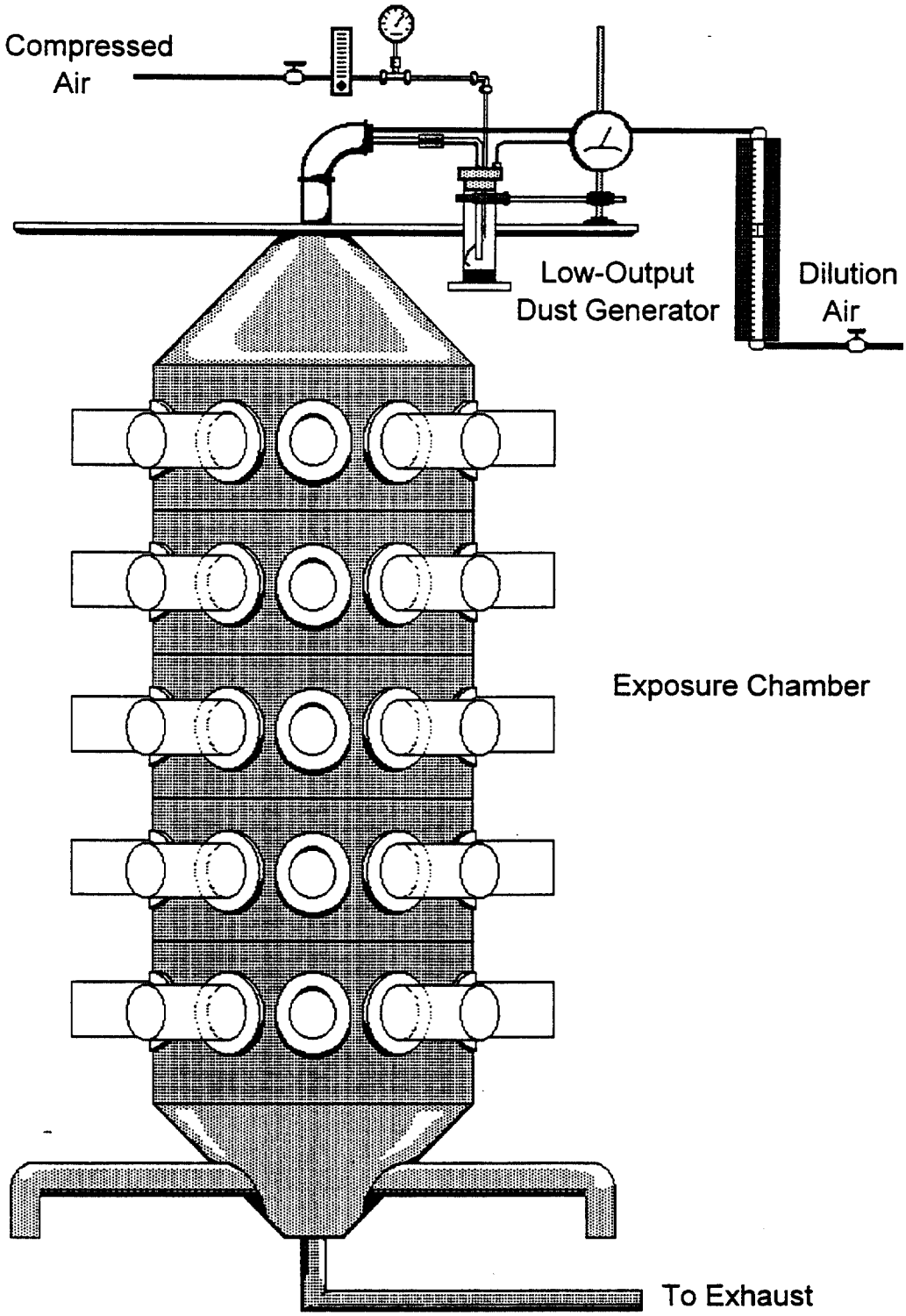
Scab - A covering or crust formed by drying of exudate mixed with cellular debris on a superficial surface, usually secondary to the healing process of injured tissue.

Small - Comparatively little in size or dimension; not as large as normally expected.

Ulcer - A loss of epithelial cells from a cutaneous or mucous surface, extending to or through the basement membrane, resulting in exposure of the dermis or lamina propria.

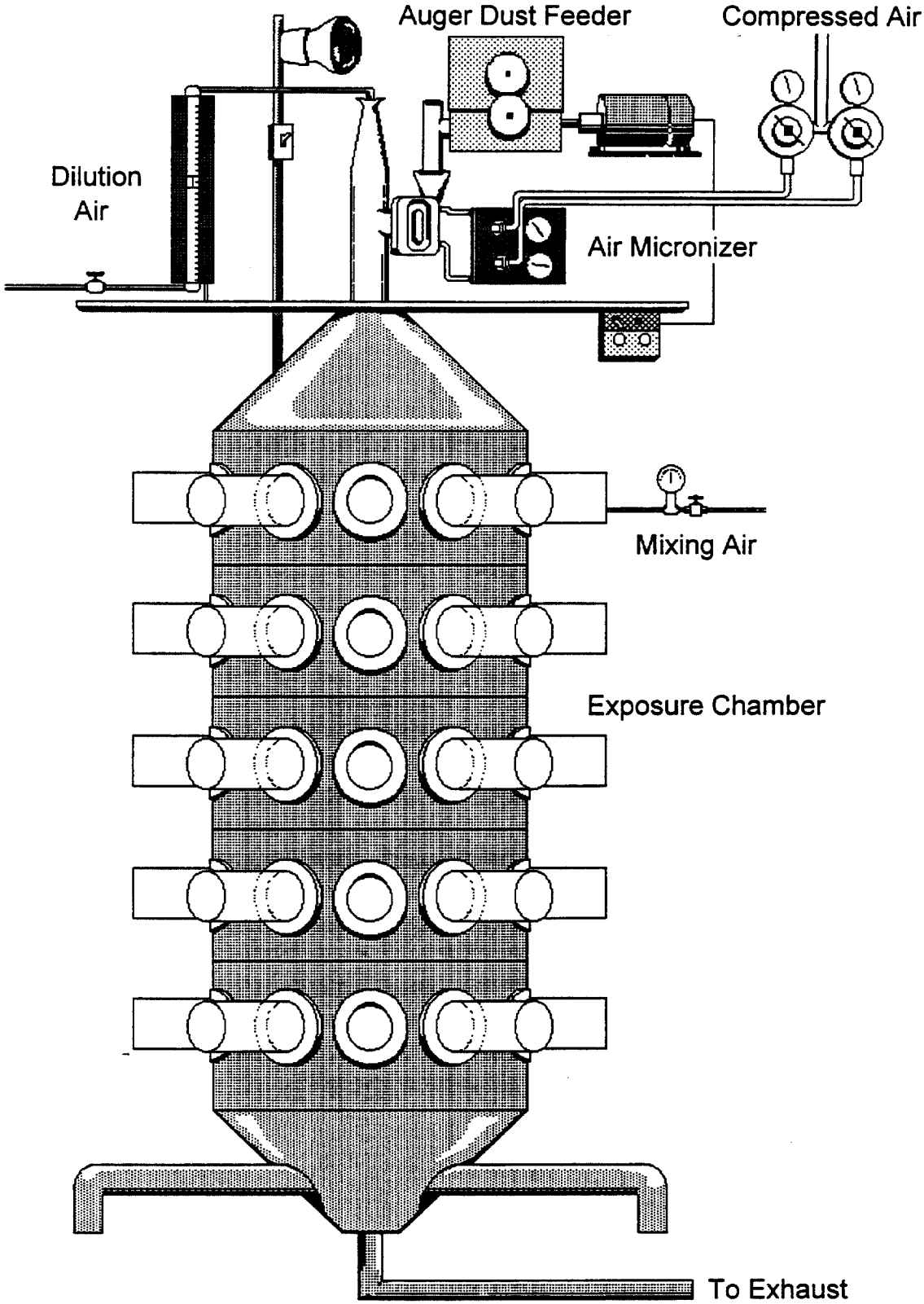
Within normal limits - Tissue considered to be normal, under the conditions of the study and considering the age, sex and strain of the animal concerned. Alterations may be present which, under other circumstances, would be considered deviations from normal.

Figure 1 Chromic Oxide Generation and Exposure System



683-002

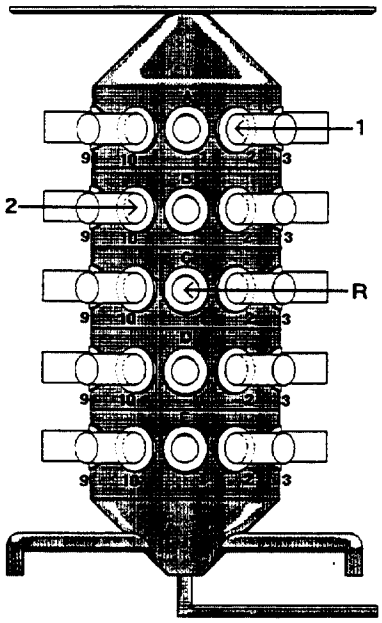
Figure 2 Basic Chrome Sulfate Generation and Exposure System



683-002

Figure 3 Sample Location Diagram for Chamber Distribution Evaluation

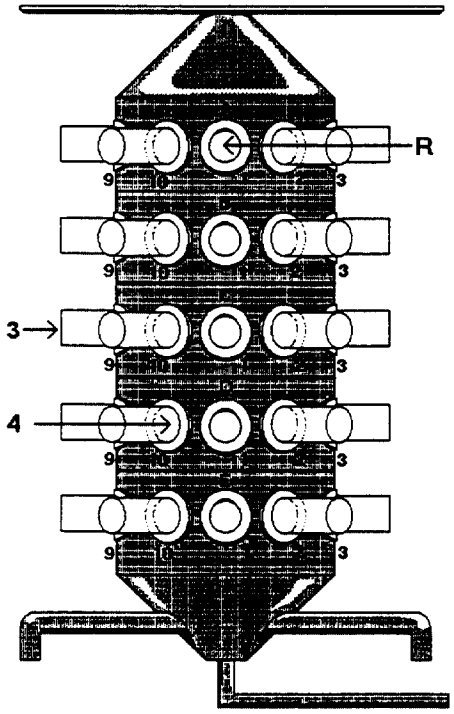
Chromic Oxide System



Large numbers indicate sample location.

R = Reference
Sample 1 collected from A2
Sample 2 collected from B10
Sample 3 collected from C6
Sample 4 collected from D8
Sample 5 collected from E4

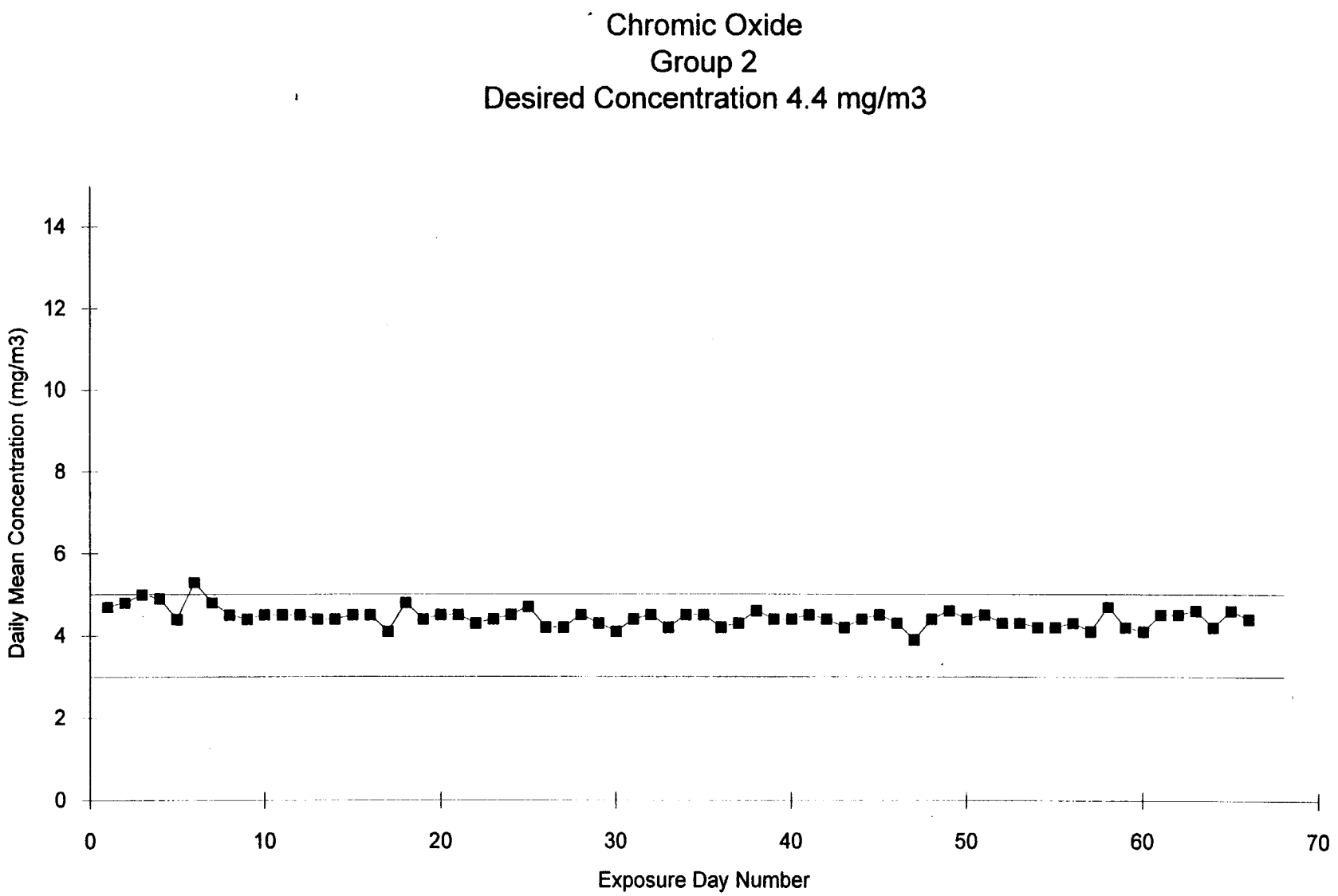
Basic Chrome Sulfate System



Large numbers indicate sample location.

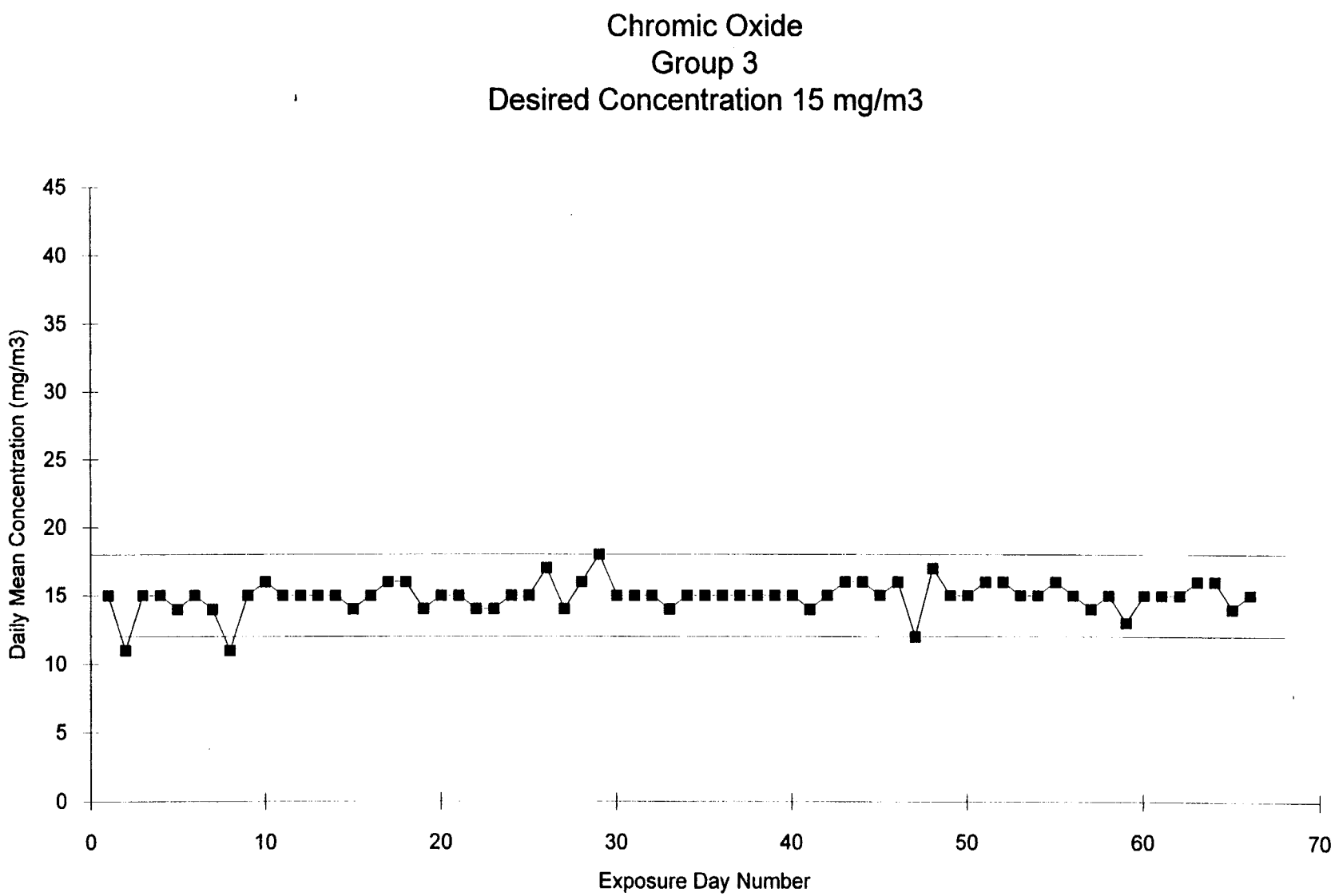
R = Reference
Sample 1 collected from A4
Sample 2 collected from B7
Sample 3 collected from C9
Sample 4 collected from D10
Sample 5 collected from E8

Figure 4 Graph of the Daily Actual Exposure Concentrations



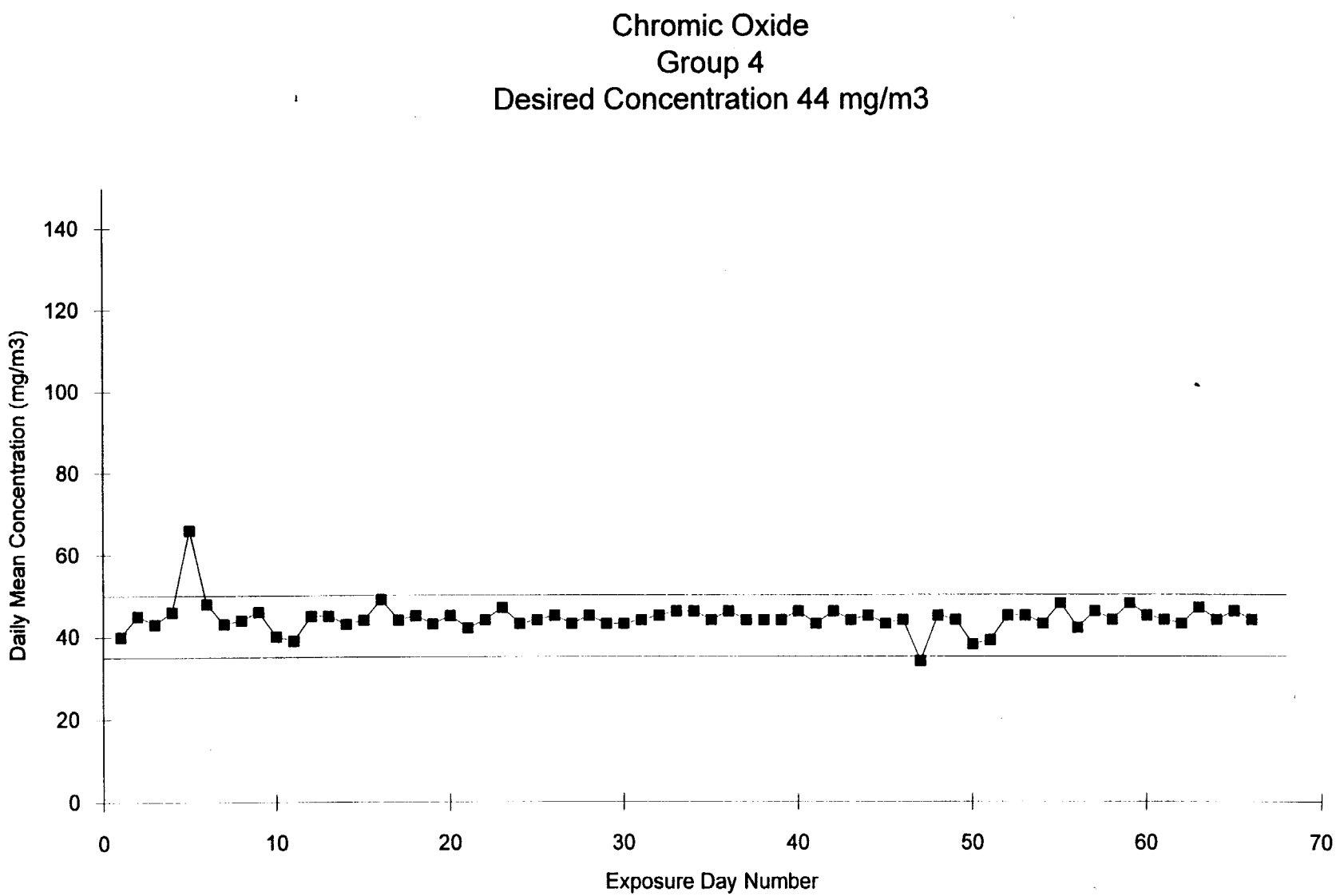
683-002

Figure 4 Graph of the Daily Actual Exposure Concentrations



683-002

Figure 4 Graph of the Daily Actual Exposure Concentrations



683-002

Figure 4 Graph of the Daily Actual Exposure Concentrations

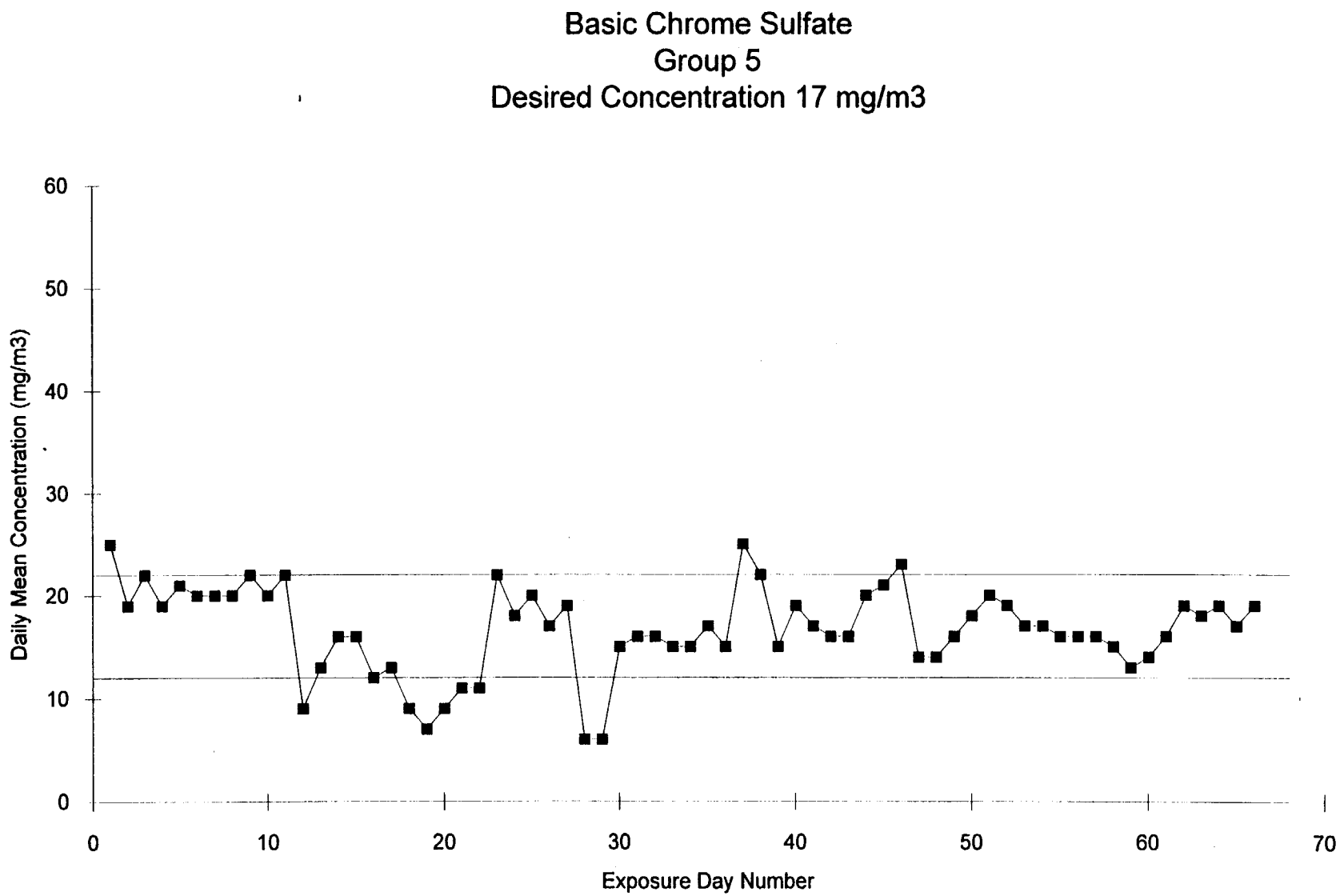


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Figure 4 Graph of the Actual Daily Exposure Concentrations

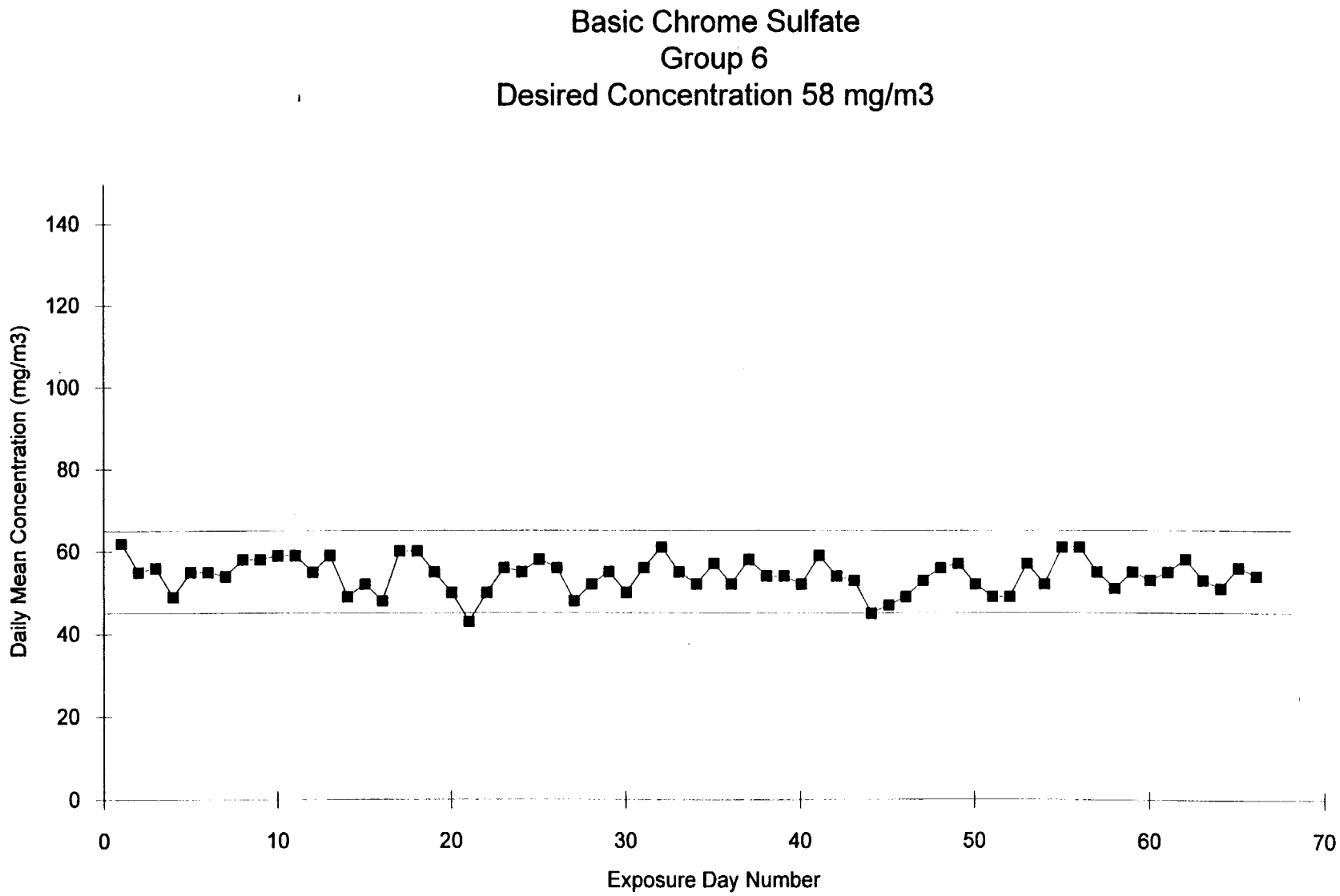

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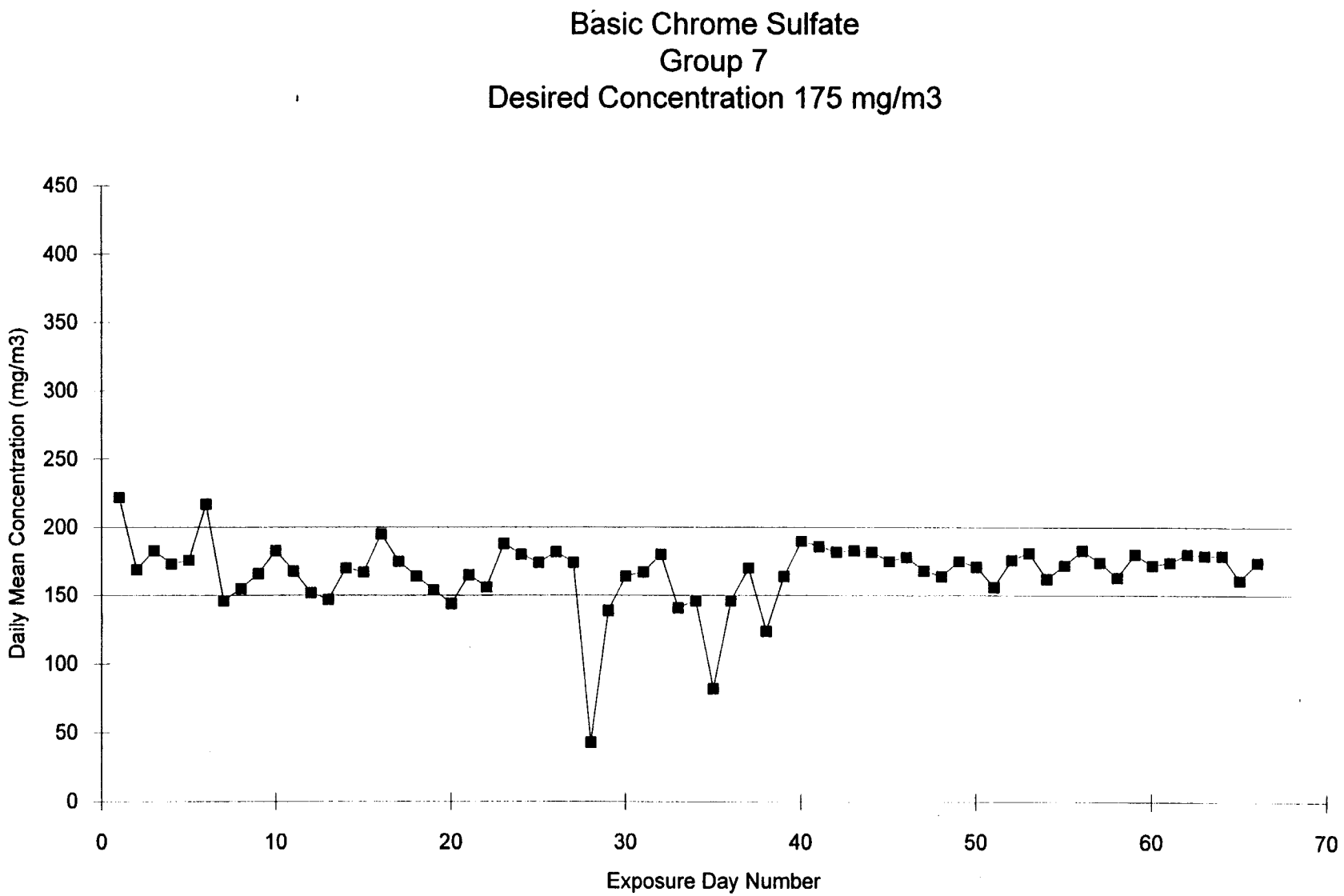
Figure 4 Graph of the Actual Daily Exposure Concentrations



683-002

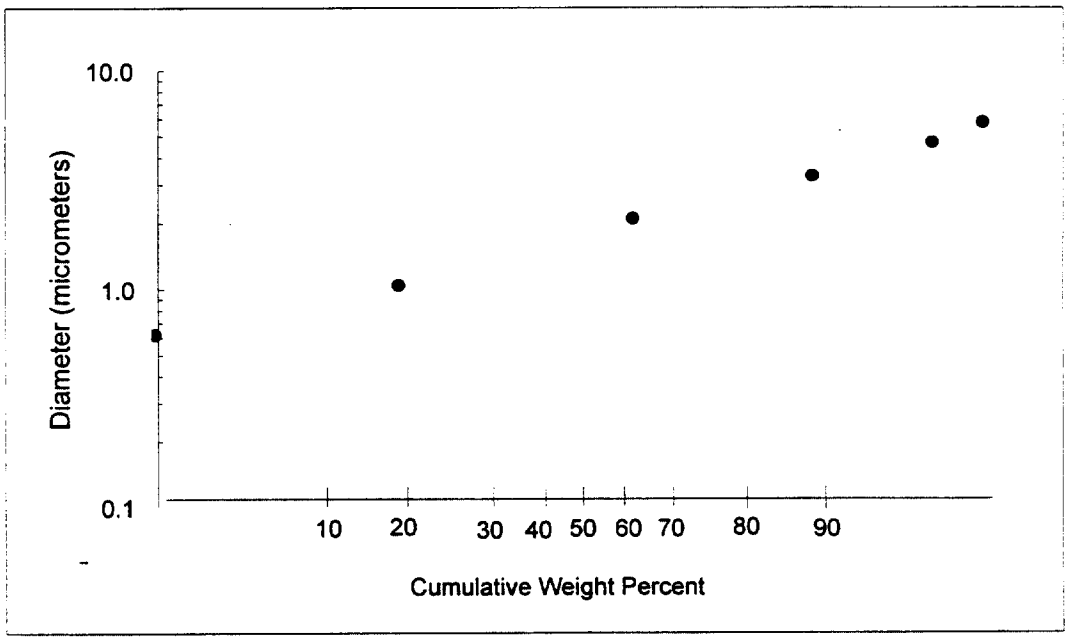
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 2

Particle Size Distribution for Chromic Oxide

Sample Collected on 1/3/95 8:42 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	0.2	99.8
1	5.8	2.2	97.5
2	4.7	1.7	95.8
3	3.3	8.1	87.7
4	2.1	26.0	61.7
5	1.05	41.5	20.1
6	0.62	17.9	2.2
7	0.44	1.7	0.5
Filter	<0.44	0.5	0.0



The mass median aerodynamic diameter is 1.8 micrometers
The geometric standard deviation is 1.76

ECD = Effective Cutoff Diameter

683-002

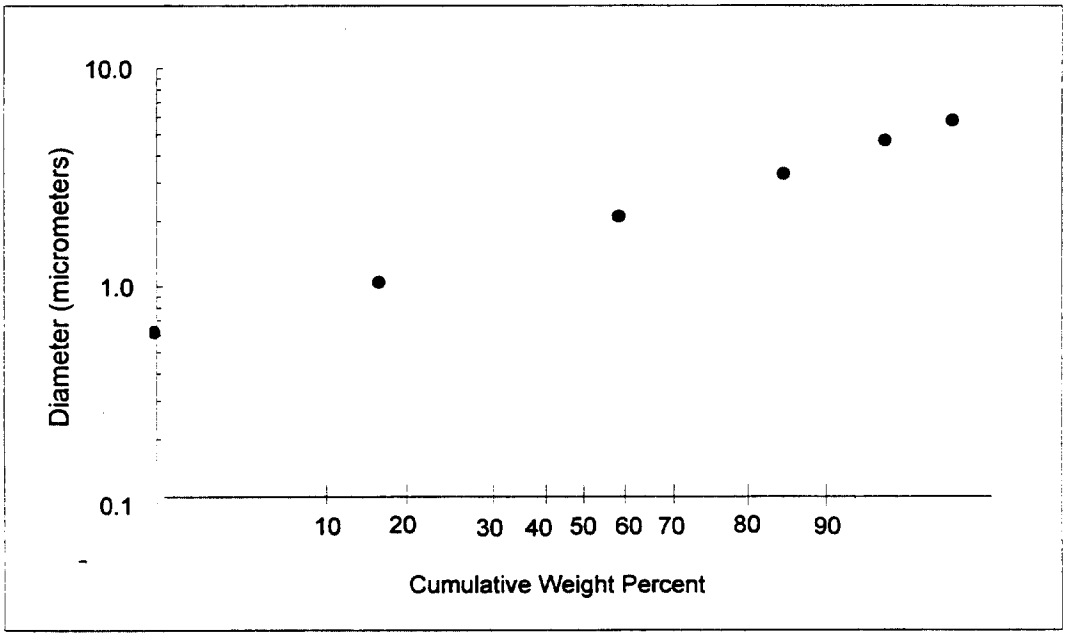
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 3

Particle Size Distribution for Chromic Oxide

Sample Collected on 12/27/94 9:26 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	1.2	98.8
1	5.8	2.2	96.6
2	4.7	3.2	93.4
3	3.3	8.8	84.6
4	2.1	25.6	58.9
5	1.05	41.3	17.7
6	0.62	15.4	2.2
7	0.44	2.2	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 1.9 micrometers
The geometric standard deviation is 1.84

ECD = Effective Cutoff Diameter

683-002

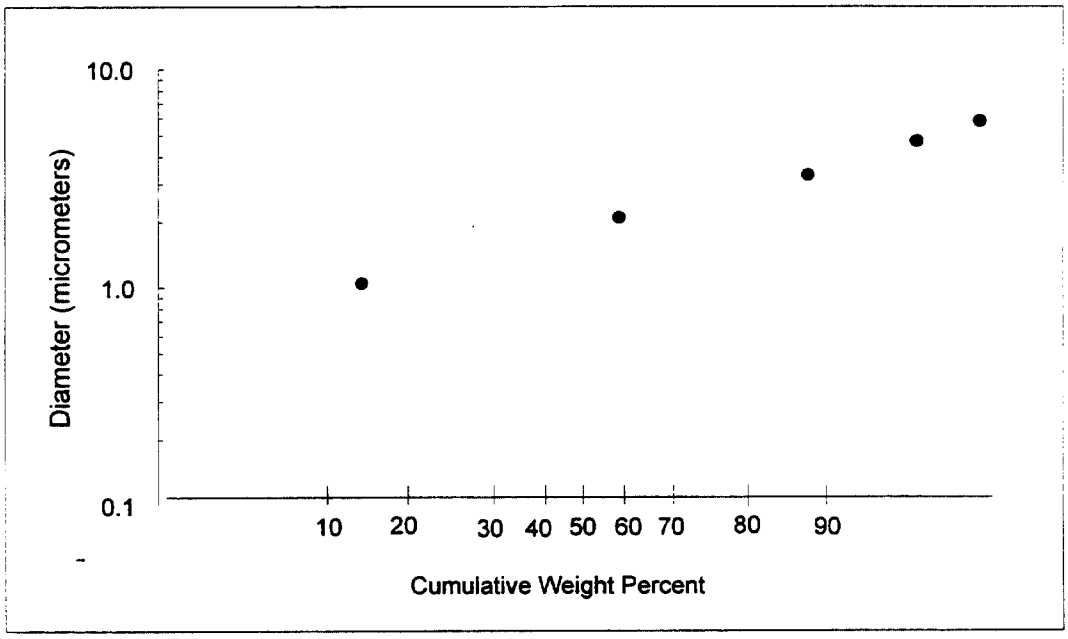
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 4

Particle Size Distribution for Chromic Oxide

Sample Collected on 1/3/95 10:01 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	1.0	99.0
1	5.8	1.5	97.5
2	4.7	2.4	95.1
3	3.3	7.9	87.2
4	2.1	28.2	59.0
5	1.05	43.5	15.5
6	0.62	14.3	1.2
7	0.44	1.2	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 1.9 micrometers
The geometric standard deviation is 1.75

ECD = Effective Cutoff Diameter

683-002

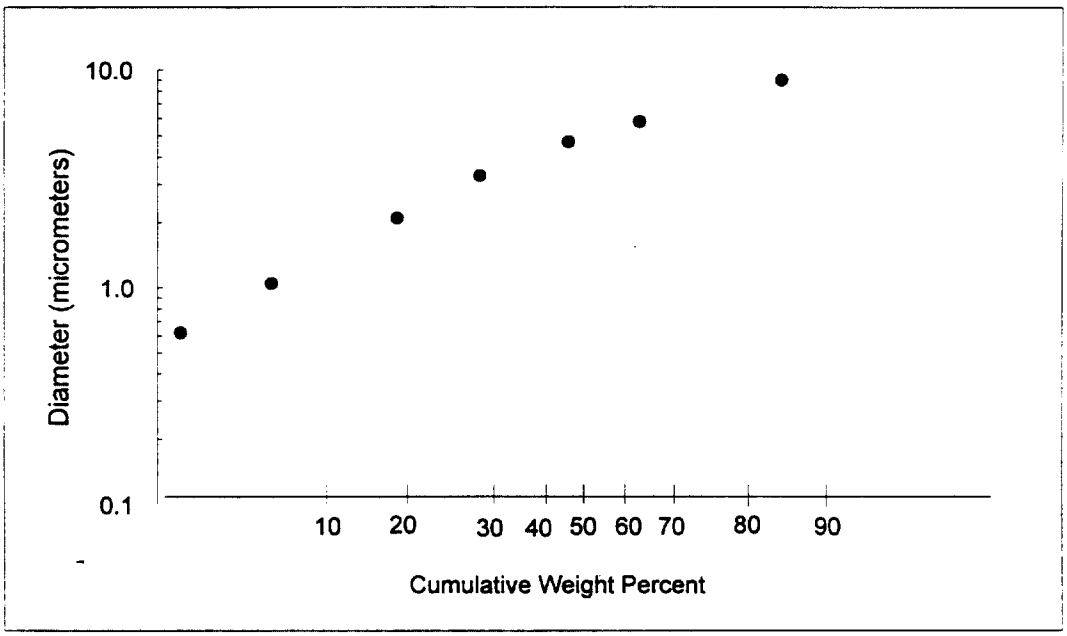
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 5

Particle Size Distribution for Basic Chrome Sulfate

Sample Collected on 1/3/95 9:10 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	15.8	84.2
1	5.8	21.6	62.6
2	4.7	13.4	49.2
3	3.3	16.4	32.8
4	2.1	12.9	19.9
5	1.05	12.6	7.4
6	0.62	4.4	3.0
7	0.44	2.1	0.9
Filter	<0.44	0.9	0.0



The mass median aerodynamic diameter is 4.3 micrometers
The geometric standard deviation is 2.51

ECD = Effective Cutoff Diameter

683-002

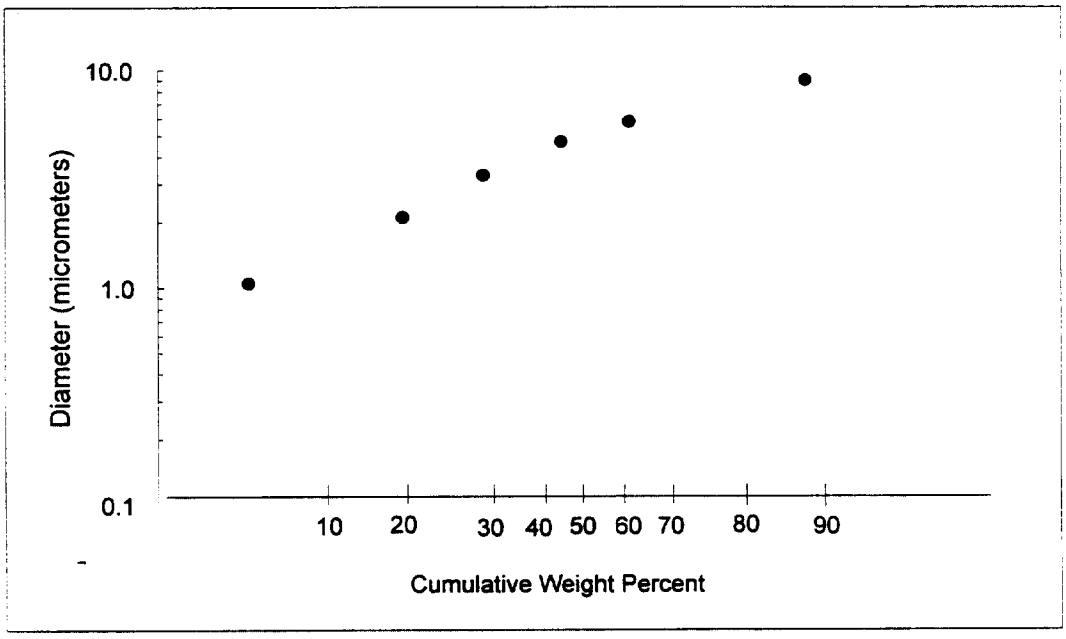
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 6

Particle Size Distribution for Basic Chrome Sulfate

Sample Collected on 12/20/94 9:20 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	13.0	87.0
1	5.8	26.0	61.0
2	4.7	13.0	48.0
3	3.3	14.5	33.5
4	2.1	12.8	20.7
5	1.05	14.8	5.9
6	0.62	5.1	0.9
7	0.44	0.9	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 4.3 micrometers
The geometric standard deviation is 2.25

ECD = Effective Cutoff Diameter

683-002

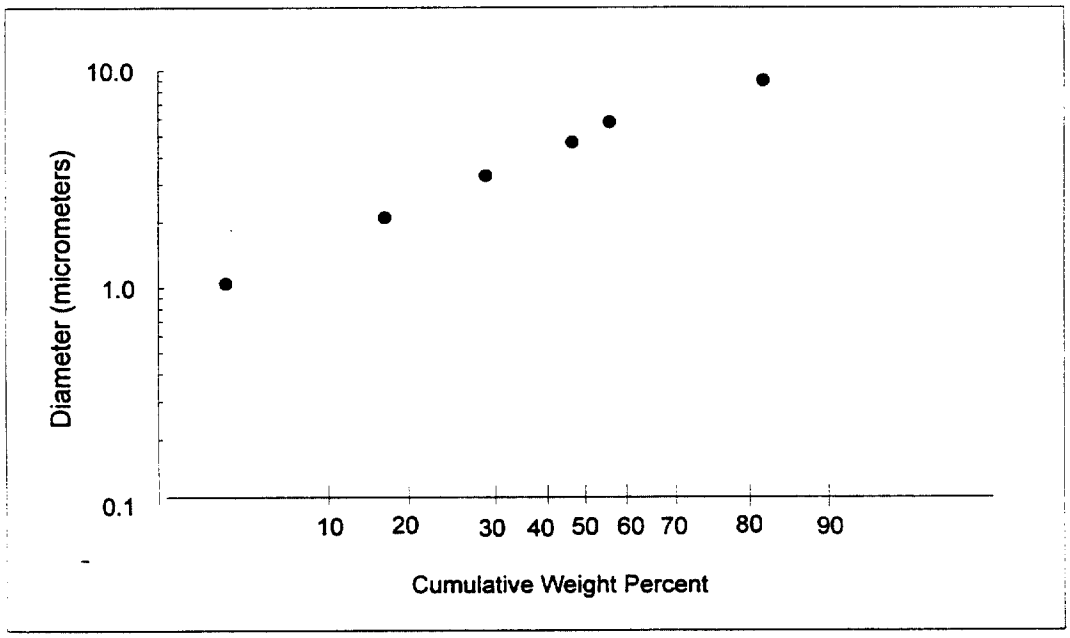
Figure 5 Numerical Data and Graph of Particle Size Distribution

Study Number: 683-002 Group 7

Particle Size Distribution for Basic Chrome Sulfate

Sample Collected on 1/10/95 8:50 AM

Stage Number	ECD (micro-meters)	Weight Percent	Cumulative Weight Percent
0	9	18.1	81.9
1	5.8	25.0	56.9
2	4.7	7.1	49.7
3	3.3	16.2	33.6
4	2.1	15.5	18.1
5	1.05	13.4	4.7
6	0.62	4.5	0.2
7	0.44	0.2	0.0
Filter	<0.44	0.0	0.0



The mass median aerodynamic diameter is 4.6 micrometers
The geometric standard deviation is 2.26

ECD = Effective Cutoff Diameter

683-002

Figure 6. Mean Body Weight
Male

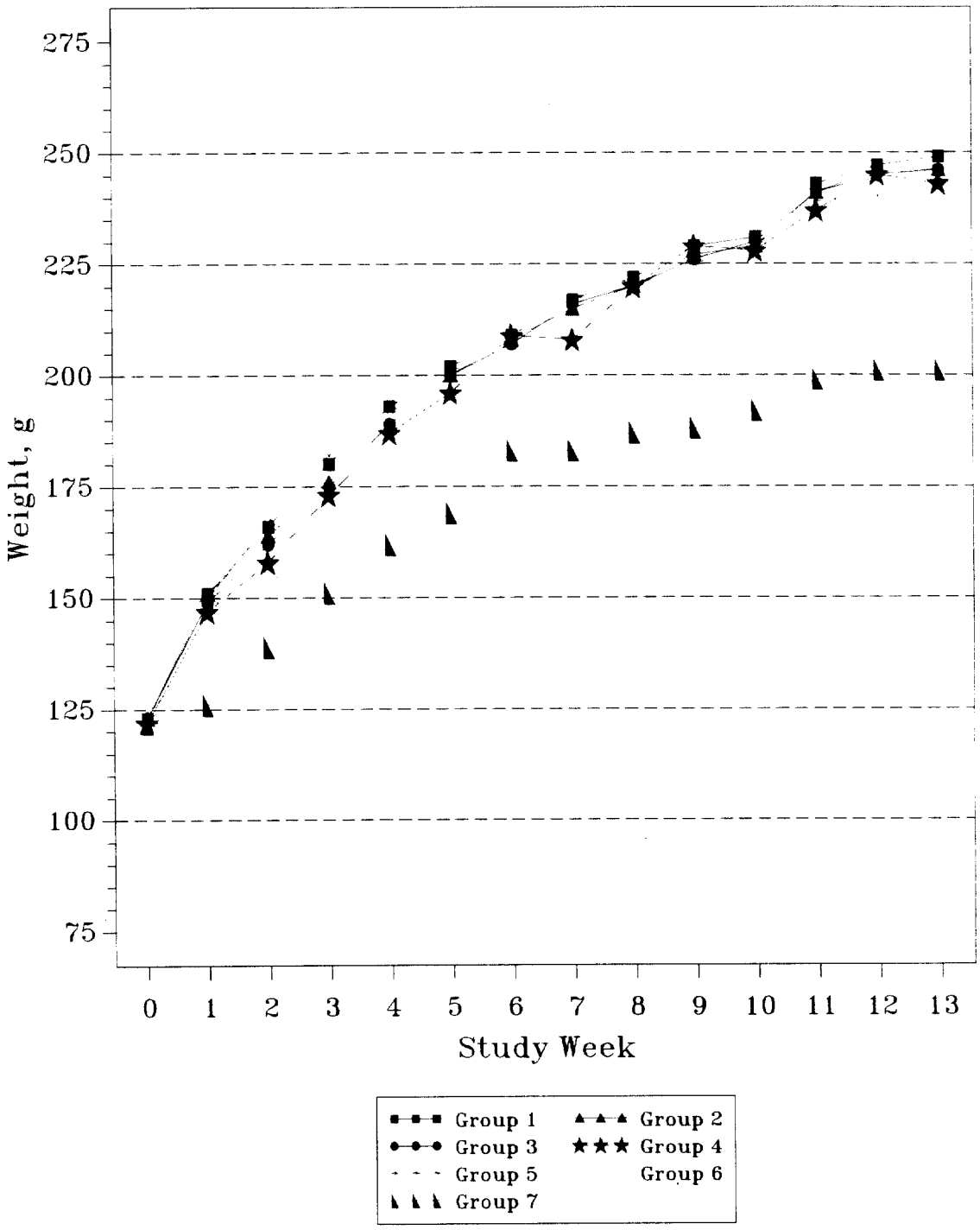


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Figure 6. Cont.

Mean Body Weight
Female

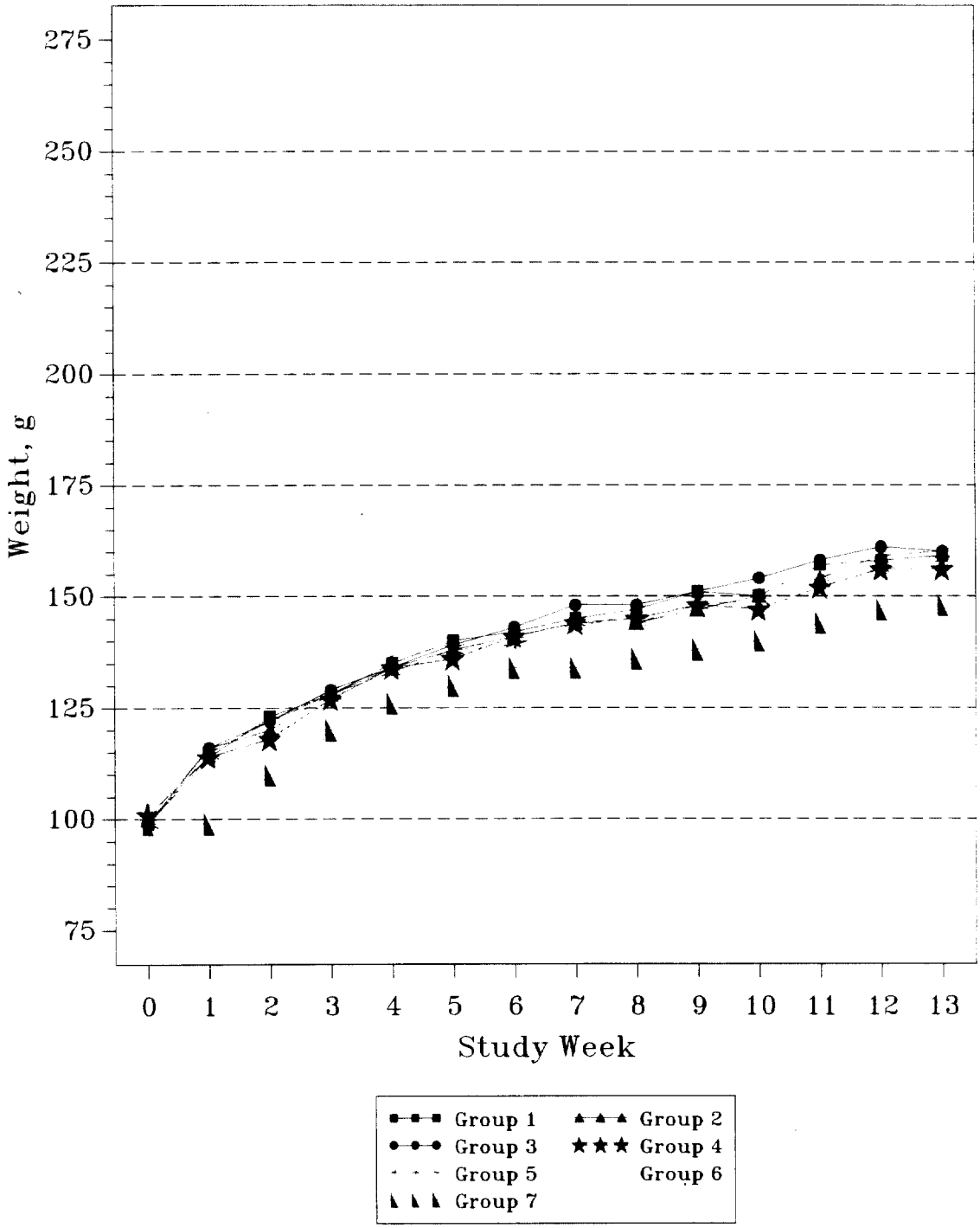

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Figure 6. Cont.

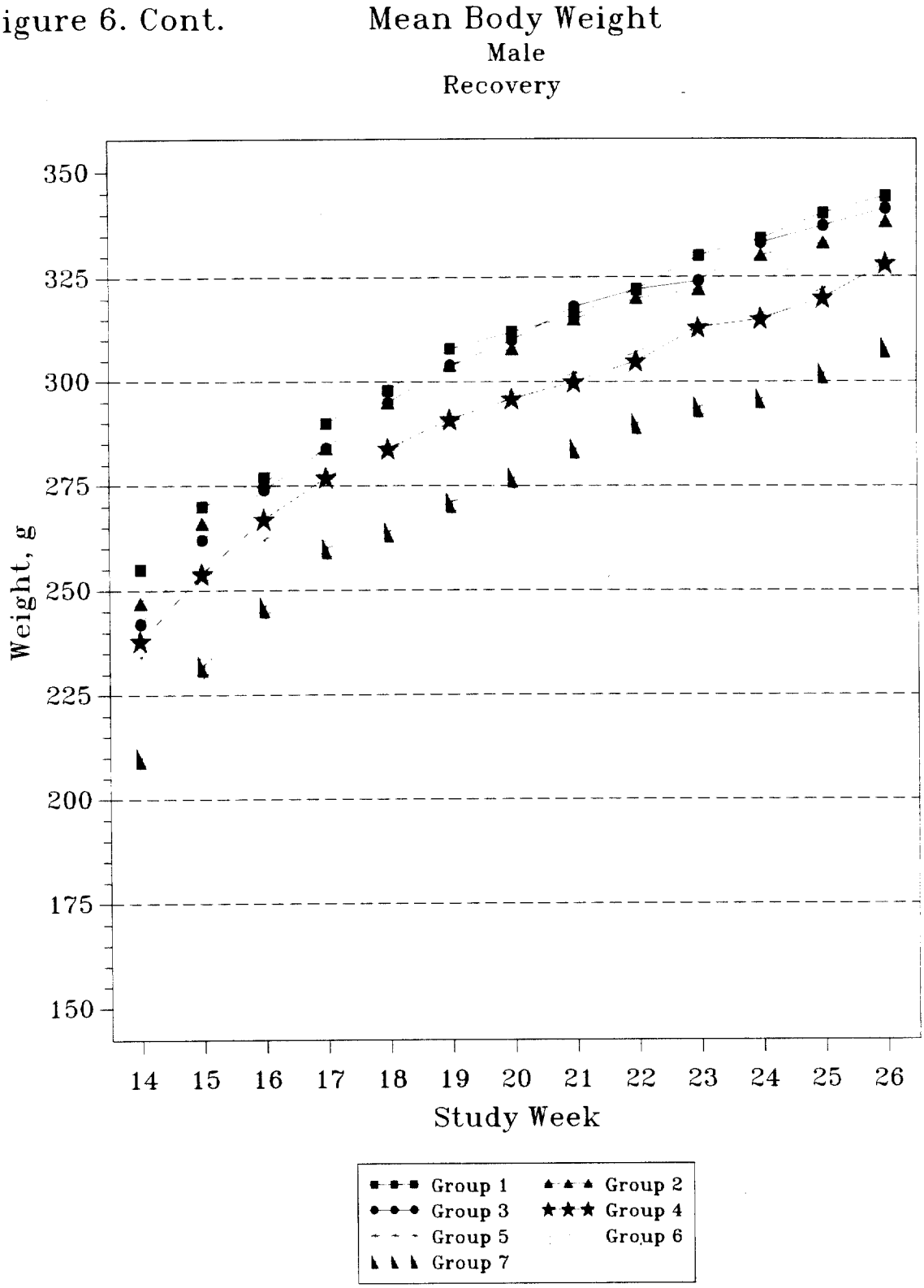

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Figure 6. Cont.

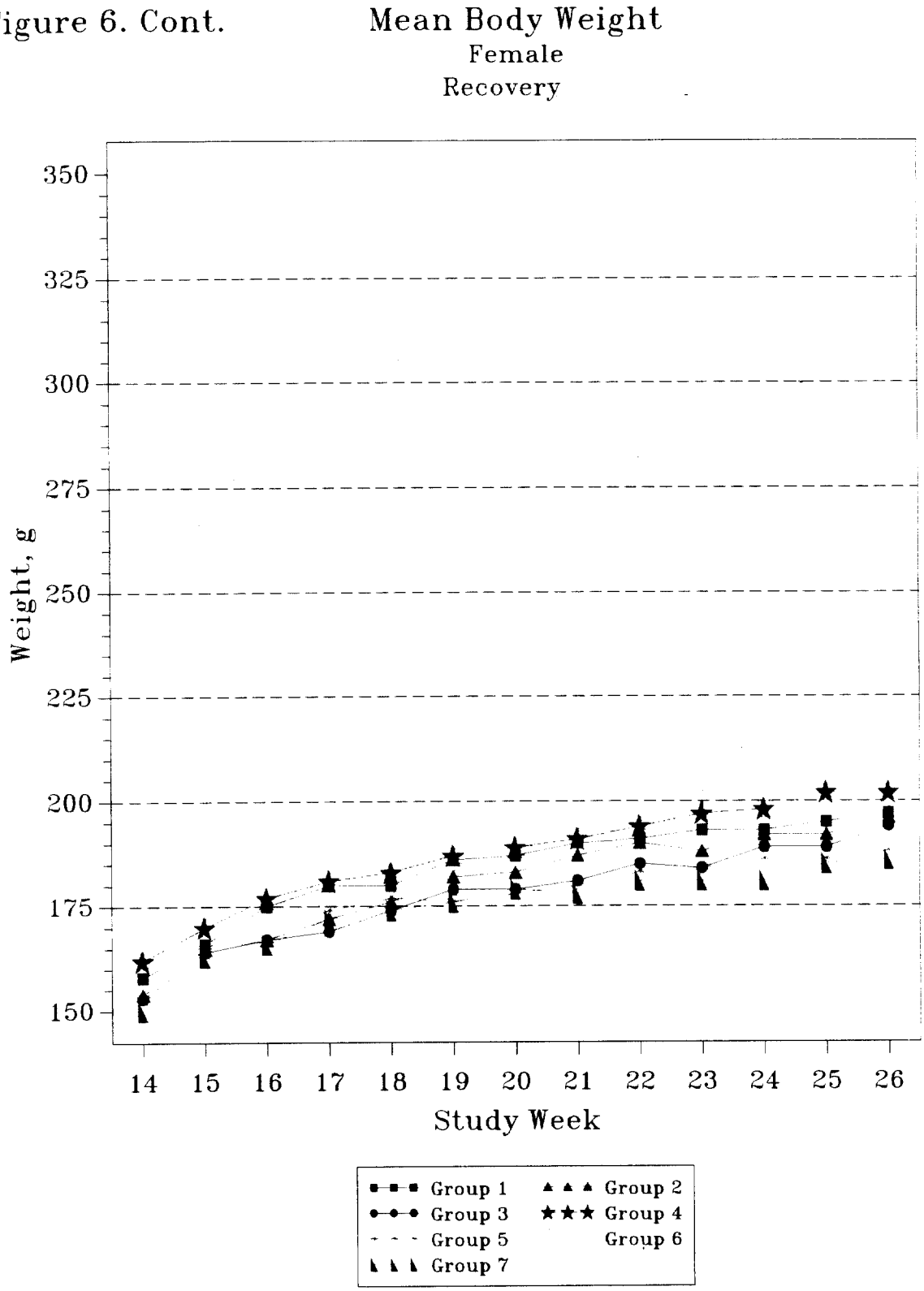

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Table 1a Gravimetric Exposure Concentration Data (Weekly)

Weekly Mean Actual Exposure Concentration (mg/m^3)

Exposure Week Number	Group 2		Group 3		Group 4		Group 5		Group 6		Group 7	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1	4.8	0.23	14	1.7	48	10.3	21	2.5	55	4.6	185	21.5
2	4.7	0.37	14	1.9	44	3.0	20	0.9	57	2.2	173	28.0
3	4.5	0.05	15	0.7	43	2.5	15	4.8	55	4.4	161	10.5
4	4.5	0.25	15	0.8	45	2.3	10	2.4	55	5.5	166	19.7
5	4.5	0.15	15	0.5	44	1.9	16	5.1	52	6.0	173	12.5
6	4.3	0.14	16	1.7	44	1.2	12	7.0	53	3.6	135	63.8
7	4.3	0.16	15	0.0	44	1.1	16	0.8	55	4.3	148	38.7
8	4.4	0.11	15	0.4	44	1.1	20	4.0	55	3.0	167	26.3
9	4.4	0.11	16	0.5	44	1.1	19	3.1	50	3.8	180	3.4
10	4.3	0.30	15	2.1	40	5.2	16	1.9	55	2.4	170	4.7
11	4.3	0.13	16	0.6	43	2.8	18	1.5	52	3.8	169	11.7
12	4.3	0.23	15	1.1	46	2.6	15	1.3	57	4.3	174	7.8
13	4.4	0.22	15	0.5	45	1.5	17	2.2	54	2.6	177	3.6

Exposure week number 14 contained 2 exposure days and was therefore considered inappropriate to include in this table.

Table 1b Weekly Exposure Atmosphere Characterization

	Study Week	Temperature (°C) Mean	Temperature (°C) S.D.	Relative Humidity (%) Mean	Relative Humidity (%) S.D.	Airflow (L/min) Mean	Airflow (L/min) S.D.
Group 1	1	24	0.8	24	11.7	15	0.0
	2	24	0.4	16	1.3	15	0.0
	3	24	0.5	21	5.0	15	0.0
	4	24	0.8	21	1.1	15	0.0
	5	23	0.9	23	2.1	15	0.0
	6	23	0.5	20	2.2	15	0.0
	7	23	1.5	18	6.4	15	0.0
	8	25	0.9	16	2.4	15	0.0
	9	23	0.9	27	8.6	15	0.0
	10	24	0.5	21	2.1	15	0.0
	11	24	1.0	21	6.3	15	0.0
	12	24	1.3	24	4.4	15	0.0
	13	24	0.5	21	4.9	15	0.0
Group 2	1	23	0.7	4	1.8	93	4.5
	2	23	0.7	3	1.5	91	15.4
	3	22	0.7	7	5.9	92	13.9
	4	22	0.9	4	1.5	83	18.8
	5	22	0.4	7	2.8	85	21.3
	6	22	0.0	3	0.8	101	6.3
	7	21	1.6	4	1.3	104	26.9
	8	23	0.4	3	1.1	97	15.2
	9	22	0.8	4	0.8	82	22.2
	10	22	0.5	5	1.3	105	32.4
	11	22	0.8	3	1.9	105	10.0
	12	22	1.0	5	1.5	103	18.8
	13	22	1.5	4	1.6	101	19.2
Group 3	1	23	0.4	4	1.5	60	10.8
	2	23	0.4	3	0.4	73	16.0
	3	22	0.9	6	5.2	66	7.9
	4	23	0.4	4	0.8	67	11.8
	5	22	0.4	4	0.9	58	8.9
	6	23	0.6	4	1.0	83	12.5
	7	22	1.8	4	1.6	76	22.2
	8	23	0.7	4	1.6	70	11.2
	9	23	0.5	4	1.1	76	26.6
	10	22	0.5	4	0.6	77	10.3
	11	23	0.6	3	1.0	79	18.0
	12	23	0.8	5	1.5	70	33.7
	13	23	1.1	5	4.0	76	20.2
Group 4	1	23	0.7	7	3.4	72	15.5
	2	23	0.9	4	1.1	65	8.4
	3	22	1.1	6	3.8	70	10.0
	4	22	1.1	5	2.2	88	22.0
	5	22	0.4	6	1.6	80	12.2
	6	22	0.0	5	1.7	74	24.6
	7	21	1.4	7	2.9	84	28.3

S.D. - Standard deviation

Table 1b Weekly Exposure Atmosphere Characterization

	Study Week	Temperature (°C) Mean	Temperature (°C) S.D.	Relative Humidity (%) Mean	Relative Humidity (%) S.D.	Airflow (L/min) Mean	Airflow (L/min) S.D.
	8	22	0.5	6	0.9	82	25.2
	9	22	0.0	7	1.7	70	19.4
	10	22	1.0	8	1.0	65	22.3
	11	22	0.5	7	2.2	64	14.9
	12	22	1.0	7	3.0	75	22.3
	13	21	0.8	7	1.7	89	23.5
Group 5	1	23	1.1	17	4.9	154	10.8
	2	23	0.4	9	0.8	177	13.4
	3	23	0.7	10	0.9	146	21.7
	4	23	0.8	10	1.3	128	11.2
	5	23	0.4	10	1.1	129	43.2
	6	23	0.5	13	5.6	146	29.0
	7	23	1.2	11	1.5	90	9.7
	8	24	0.5	9	1.3	133	23.3
	9	23	0.4	10	0.9	123	27.1
	10	24	0.6	10	0.8	98	21.7
	11	23	0.0	10	1.0	155	8.4
	12	23	2.1	12	6.2	122	30.7
	13	23	1.8	14	4.7	118	23.6
Group 6	1	24	0.8	16	4.0	108	12.5
	2	23	0.4	11	2.8	114	12.0
	3	23	0.4	12	1.5	105	14.1
	4	23	0.4	12	5.3	103	17.5
	5	24	0.9	12	3.4	104	10.8
	6	24	1.4	11	2.2	103	20.2
	7	23	0.8	11	1.3	105	14.9
	8	24	1.1	9	1.5	118	4.0
	9	23	1.2	9	0.4	103	13.6
	10	23	1.0	9	0.5	108	13.2
	11	23	0.5	10	1.3	105	14.7
	12	23	1.3	10	0.5	118	2.6
	13	23	2.0	10	1.7	112	12.3
Group 7	1	23	0.9	13	3.0	172	10.2
	2	23	0.7	9	1.1	175	5.9
	3	23	0.9	9	0.9	163	8.4
	4	23	0.8	9	0.5	168	6.3
	5	23	0.4	9	0.9	173	12.6
	6	23	0.5	9	0.6	175	25.7
	7	22	0.5	10	0.9	159	21.7
	8	24	0.4	8	0.4	140	17.7
	9	23	0.4	9	1.1	144	24.7
	10	23	0.0	10	1.0	128	6.5
	11	23	1.0	9	0.6	141	10.5
	12	24	1.8	9	0.5	140	15.6
	13	22	1.9	10	1.6	150	22.5

S.D. - Standard deviation

683-002

Table 2 Summary of Weekly Detailed Clinical Examinations

Interval: -2 - 14 Weeks Group Number Observation	Males 1 (15)		2 (15)		3 (15)		4 (15)		5 (15)		6 (15)		7 (15)	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Normal														
Normal/no visible abnormalities	15	15.1	15	15.0	15	14.3	15	13.3	15	15.0	15	15.1	15	6.7
Appearance and condition														
Tail/portion of tail missing	0	0.0	0	0.0	1	6.0	0	0.0	0	0.0	0	0.0	0	0.0
Body surface														
Body surface stained	0	0.0	0	0.0	1	1.0	1	1.0	2	1.5	0	0.0	2	1.0
Hair loss	0	0.0	1	4.0	0	0.0	1	3.0	0	0.0	0	0.0	0	0.0
Scabbed area	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
Test Material Staining	0	0.0	0	0.0	1	1.0	11	2.5	0	0.0	0	0.0	15	7.6
Respiration														
Labored breathing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Eyes														
Excessive lacrimation	0	0.0	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0
Material around eye	3	1.0	0	0.0	2	3.5	1	2.0	2	1.0	2	1.5	1	2.0

Key: () = Number of animals alive at start of interval
a = Number animals affected
b = Mean number of animal weeks with clinical sign

Table 2 Cont. Summary of Weekly Detailed Clinical Examinations

Interval: -2 - 14 Weeks

Group Number	Females 1 (15)		2 (15)		3 (15)		4 (15)		5 (15)		6 (15)		7 (15)	
Observation	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Normal														
Normal/no visible abnormalities	15	13.7	15	14.1	15	12.7	15	10.8	15	14.7	15	14.4	15	13.0
Appearance and condition														
Tail bent	0	0.0	1	5.0	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0
Tail/portion of tail missing	1	6.0	0	0.0	1	7.0	0	0.0	0	0.0	1	5.0	0	0.0
Behavior/activity														
Sneezing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Body surface														
Abrasion	0	0.0	0	0.0	1	9.0	0	0.0	0	0.0	0	0.0	0	0.0
Body surface stained	4	2.5	0	0.0	1	1.0	4	2.0	0	0.0	2	1.5	1	2.0
Hair loss	0	0.0	2	5.5	0	0.0	0	0.0	0	0.0	1	3.0	0	0.0
Scabbed area	0	0.0	0	0.0	1	3.0	0	0.0	0	0.0	0	0.0	0	0.0
Test Material Staining	0	0.0	1	1.0	6	1.7	11	3.0	0	0.0	0	0.0	9	2.3
Respiration														
Labored breathing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	8	1.8
Rapid Respiration	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Oral/nasal														
Staining around mouth	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Eyes														
Area around eye/eyelids red	1	1.0	0	0.0	0	0.0	2	2.5	0	0.0	0	0.0	0	0.0
Excessive lacrimation	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Material around eye	2	3.0	1	1.0	6	2.0	10	2.7	5	2.0	4	1.0	1	1.0

Key: () = Number of animals alive at start of interval
a = Number animals affected
b = Mean number of animal weeks with clinical sign

Table 2 Cont. Summary of Weekly Detailed Clinical Examinations

Interval: 15 - 26 Weeks Group Number Observation	Males 1 (5)		2 (5)		3 (5)		4 (5)		5 (5)		6 (5)		7 (4)	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Normal														
Normal/no visible abnormalities	5	11.8	5	10.4	5	11.4	5	12.0	5	11.6	5	11.8	4	12.0
Body surface														
Body surface stained	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	0	0.0	0	0.0
Oral/nasal														
Red/brown material around nose	0	0.0	2	1.0	2	1.0	0	0.0	0	0.0	1	1.0	0	0.0
Staining around mouth	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Nasal Discharge	0	0.0	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Red/brown material mouth	0	0.0	0	0.0	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0
Eyes														
Material around eye	1	1.0	1	5.0	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0

Key: () = Number of animals alive at start of interval
a = Number animals affected
b = Mean number of animal weeks with clinical sign

Table 2 Cont. Summary of Weekly Detailed Clinical Examinations

Interval: 15 - 26 Weeks

Group Number	Females 1 (5)		2 (5)		3 (5)		4 (5)		5 (5)		6 (5)		7 (5)	
Observation	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Normal														
Normal/no visible abnormalities	4	10.3	5	8.0	5	8.0	5	9.6	5	10.2	5	11.8	5	11.8
Appearance and condition														
Tail bent	0	0.0	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0
Tail/portion of tail missing	1	12.0	0	0.0	1	8.0	0	0.0	0	0.0	0	0.0	0	0.0
Eyes														
Area around eye/eyelids red	1	4.0	1	1.0	0	0.0	1	1.0	1	2.0	0	0.0	1	1.0
Excessive lacrimation	1	1.0	1	4.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Material around eye	4	1.5	3	6.3	2	5.5	3	3.7	2	3.5	1	1.0	0	0.0

Key: () = Number of animals alive at start of interval
a = Number animals affected
b = Mean number of animal weeks with clinical sign

Table 3a Results of Chromium (III) Analysis on Exposure Atmosphere Sample

Chromic Oxide

Group No.	Study Week	Exposure Day	Milligrams of Salt Gravimetric	Milligrams of Salt Analytical	% of Gravimetric Concentration
2	2*	8	2.9	3.18	110
	4	16	4.1	4.00	98
	8	37	3.8	3.35	88
	12	60	3.5	6.38	182
3	2*	8	5.2	5.63	108
	4	16	8.8	9.03	103
	8	37	8.1	7.60	94
	12	60	8.1	9.43	116
4	2*	8	11.6	12.80	110
	4	16	11.7	9.43	81
	8	37	11.7	11.50	98
	12	59	11.0	21.4	195
				Mean	110

Basic Chrome Sulfate

Group No.	Study Week	Exposure Day	Milligrams of Salt Gravimetric	Milligrams of Salt Analytical	% of Gravimetric Concentration
5	1	2	11.9	10.00	84
	4	16	7.6	7.23	95
	8	37	10.9	10.30	95
	12	59	8.8	10.60	120
6	1	2	13.0	11.20	86
	4	16	10.5	9.90	94
	8	37	13.7	13.30	97
	12	59	14.6	20.20	138
7	1	2	15.9	13.90	87
	4	16	17.2	17.10	99
	8	37	19.6	17.90	91
	12	59	21.2	26.40	125
				Mean	95

* Due to an oversight, samples from Groups 2, 3, and 4 were not retained during study week 1.

Table 3b Results of Chromium (VI) Analysis on Exposure Atmosphere Sample

Chromic Oxide

Group No.	Study Week	Exposure Day	Milligrams of Salt Gravimetric	Milligrams of Salt Analytical	% of Gravimetric Concentration
2	1	2	4.0	*	*
	4	16	3.4	*	*
	8	37	3.5	*	*
	12	59	3.9	*	*
3	1	2	6.2	*	*
	4	16	6.3	*	*
	8	37	8.3	*	*
	12	59	7.0	*	*
4	1	2	9.8	*	*
	4	16	10.6	*	*
	8	37	10.8	*	*
	12	59	12.5	*	*

Basic Chrome Sulfate

Group No.	Study Week	Exposure Day	Milligrams of Salt Gravimetric	Milligrams of Salt Analytical	% of Gravimetric Concentration
5	1	2	14.5	*	*
	4	16	4.2	*	*
	8	37	8.4	*	*
	12	59	4.2	*	*
6	1	2	14.8	*	*
	4	16	7.0	*	*
	8	37	8.7	*	*
	12	59	7.4	*	*
7	1	2	17.0	*	*
	4	16	10.4	*	*
	8	37	19.6	*	*
	12	59	12.4	*	*

* Samples below the limit of detection for analysis(10.0 ng/ml)

Table 3c. Cr(VI) Analysis on Neat Chromic Oxide and Basic Chrome Sulfate

Chromic Oxide

Sample Number		mg of Cr(VI)	% Cr(VI)
7-29-94-2		0.0865	0.00863
7-29-94-3		0.0834	0.00807
	Mean	0.0850	0.00835

Basic Chrome Sulfate

Sample Number		mg of Cr(VI)	% Cr(VI)
7-29-94-4		0.0890	0.00889
7-29-94-5		0.0896	0.00895
7-29-94-6		0.0964	0.00960
	Mean	0.0917	0.00915

Sample 7-29-94-1 was not reported due to technical problems during processing.

Neat test material was analysed using sponsor-supplied method AM-8.2.8.

Table 4

Males: Summary of Body Weight Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Body Weight g	Pretest	123	6.2	15	123	7.6	15	123	7.4	15	122	6.0	15
	1	151	6.1	15	151	9.7	15	149	9.6	15	147	9.0	15
	2	166	5.8	15	164	10.5	15	162	9.3	15	158	9.1	15
	3	180	7.0	15	176	10.8	15	175	10.1	15	173	10.3	15
	4	193	8.0	15	189	11.6	15	189	9.8	15	187	11.1	15
	5	202	10.9	15	200	10.7	15	200	8.7	15	196	11.0	15
	6	209	12.4	15	208	10.7	15	207	8.8	15	209	12.3	15
	7	217	12.4	15	215	11.1	15	216	8.5	15	208	25.7	15
	8	222	13.3	15	220	12.4	15	220	8.2	15	220	14.3	15
	9	229	12.4	15	227	12.4	15	226	7.3	15	229	13.6	15
	10	231	12.2	15	229	13.8	15	230	7.9	15	228	13.2	15
	11	243	11.7	15	241	14.4	15	241	8.3	15	237	11.9	15
	12	247	11.6	15	246	13.2	15	245	10.3	15	245	13.1	15
	13	249	11.1	15	246	14.3	15	246	10.9	15	243	15.5	15

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Note: Though animals were exposed for two days during study week 14, this week is not presented here.

Table 4 Cont.

Males: Summary of Body Weight Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Body Weight g	Pretest	123	6.5	15	124	9.6	15	122	6.4	15
	1	150	9.6	15	140[1]	13.5	15	126	8.3	15
	2	167	10.3	15	153	14.9	15	139	8.0	14
	3	182	11.0	15	167[1]	14.9	15	151	10.3	14
	4	193	12.0	15	178	14.0	15	162	11.6	14
	5	202	13.4	15	187	14.3	15	169	10.2	14
	6	209	13.2	15	193[1]	16.3	15	183	9.5	14
	7	217	13.5	15	199	18.0	15	183	7.9	14
	8	220	14.6	15	203	17.8	15	187	10.0	14
	9	225	13.4	15	211	16.9	15	188	10.5	14
	10	229	13.5	15	212	16.5	15	192	9.4	14
	11	239	15.0	15	220	16.3	15	199	10.1	14
	12	240	15.7	15	224	16.0	15	201	9.6	14
	13	244	15.4	15	228	17.0	15	201	9.1	14

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Note: Though animals were exposed for two days during study week 14, this week is not presented here.

Table 4 Cont.

Females: Summary of Body Weight Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Body Weight g	Pretest	99	3.4	15	100	4.1	15	99	3.6	15	101	3.8	15
	1	114	3.6	15	116	5.6	15	116	4.7	15	114	4.0	15
	2	123	4.0	15	120	5.9	15	122	5.8	15	118	4.7	15
	3	128	4.0	15	128	5.9	15	129	5.6	15	127	5.7	15
	4	135	4.9	15	134	6.2	15	134	6.3	15	134	6.7	15
	5	140	5.9	15	138	6.6	15	139	6.5	15	136	5.8	15
	6	142	5.7	15	141	8.3	15	143	6.8	15	141	5.9	15
	7	145	6.6	15	144	7.8	15	148	6.6	15	144	6.2	15
	8	147	6.0	15	144	7.6	15	148	6.5	15	145	7.1	15
	9	151	6.3	15	147	7.8	15	151	6.4	15	148	7.1	15
	10	150	6.9	15	150	7.5	15	154	7.0	15	147	6.8	15
	11	157	6.3	15	154	6.8	15	158	6.9	15	152	6.8	15
	12	158	6.2	15	159	7.6	15	161	6.6	15	156	7.0	15
	13	159	6.2	15	160	5.7	15	160	5.2	15	156	7.1	15

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Note: Though animals were exposed for two days during study week 14, this week is not presented here.

Table 4 Cont.

Females: Summary of Body Weight Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Body Weight g	Pretest	99	3.5	15	100	6.3	15	99	3.4	15
	1	115	4.7	15	112	7.2	15	99[2]	6.7	15
	2	122	6.8	15	121	7.7	15	110[2]	6.8	15
	3	128	7.2	15	129	7.5	15	120[2]	6.6	15
	4	133	8.6	15	136	8.7	15	126[2]	6.1	15
	5	138	9.3	15	139	8.6	15	130[1]	6.9	15
	6	139	9.3	15	139	9.2	15	134[2]	6.8	15
	7	144	10.2	15	143	9.6	15	134[2]	6.2	15
	8	144	10.1	15	146	9.3	15	136[2]	7.3	15
	9	148	9.5	15	149	9.6	15	138[2]	7.7	15
	10	149	9.8	15	150	8.4	15	140[2]	6.8	15
	11	153	10.7	15	154	9.4	15	144[2]	7.5	15
	12	156	10.5	15	157	9.8	15	147[2]	7.7	15
	13	158	10.6	15	159	9.5	15	148[2]	7.4	15

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Note: Though animals were exposed for two days during study week 14, this week is not presented here.

Table 4 Cont.

Males: Summary of Body Weight Values - Recovery*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	14	255	9.8	5	247	4.7	5	242	9.0	5	238	11.5	5
	15	270	8.7	5	266	6.9	5	262	7.4	5	254	11.8	5
	16	277	9.7	5	276	7.4	5	274	6.5	5	267	11.2	5
	17	290	11.0	5	284	8.3	5	284	6.3	5	277	9.5	5
	18	298	12.7	5	295	7.8	5	295	6.2	5	284	7.9	5
	19	308	12.8	5	304	7.4	5	304	8.6	5	291	8.5	5
	20	312	15.8	5	308	9.6	5	310	7.3	5	296	10.6	5
	21	316	18.1	5	315	10.7	5	318	8.9	5	300	10.5	5
	22	322	18.2	5	320	9.9	5	322	9.7	5	305	10.0	5
	23	330	18.5	5	322	10.0	5	324	6.7	5	313	7.7	5
	24	334	20.2	5	330	9.8	5	333	10.1	5	315	8.0	5
	25	340	19.7	5	333	10.0	5	337	11.4	5	320	10.1	5
	26	344	19.9	5	338	10.6	5	341	11.7	5	328	6.9	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 4 Cont.

Males: Summary of Body Weight Values - Recovery

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Body Weight g	14	234	20.2	5	212[2]	14.6	5	210[2]	1.3	4
	15	253	18.7	5	232[2]	15.2	5	232[2]	2.5	4
	16	262	17.0	5	243[2]	15.8	5	246[2]	5.6	4
	17	277	14.9	5	260[2]	15.6	5	260[2]	5.9	4
	18	284	14.7	5	266[2]	17.8	5	264[2]	7.7	4
	19	290	12.6	5	271[2]	17.5	5	271[2]	7.0	4
	20	296	15.2	5	275[2]	21.2	5	277[1]	8.9	4
	21	302	14.3	5	282[2]	19.8	5	284[2]	8.3	4
	22	307	15.3	5	288[2]	19.6	5	290[2]	8.0	4
	23	313	16.9	5	294[2]	18.4	5	294[2]	9.5	4
	24	316	15.9	5	298[2]	17.1	5	296[2]	7.2	4
	25	322	16.4	5	304[2]	18.4	5	302[2]	8.0	4
	26	328	16.6	5	307[2]	16.5	5	308[2]	8.0	4

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 4 Cont.

Females: Summary of Body Weight Values - Recovery*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	14	158	6.8	5	154	6.4	5	153	7.0	5	162	5.9	5
	15	166	6.9	5	165	9.3	5	164	8.8	5	170	5.2	5
	16	175	5.8	5	167	8.3	5	167	8.3	5	177	7.6	5
	17	180	6.6	5	172	9.9	5	169	8.2	5	181	6.8	5
	18	180	7.1	5	176	9.5	5	174	8.4	5	183	8.3	5
	19	186	7.8	5	182	10.2	5	179	8.4	5	187	8.9	5
	20	187	7.9	5	183	12.3	5	179	7.5	5	189	8.4	5
	21	190	6.3	5	187	11.7	5	181	6.0	5	191	10.3	5
	22	191	7.2	5	190	11.6	5	185	8.9	5	194	9.5	5
	23	193	8.1	5	188	10.8	5	184	8.1	5	197	11.7	5
	24	193	8.5	5	192	10.8	5	189	9.2	5	198	11.1	5
	25	195	8.5	5	192	9.9	5	189	6.8	5	202	10.7	5
	26	197	10.1	5	196	10.2	5	194	7.0	5	202	9.3	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 4 Cont. Females: Summary of Body Weight Values - Recovery*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Body Weight g	14	154	13.2	5	161	14.6	5	150	5.6	5
	15	165	15.3	5	170	12.9	5	163	2.3	5
	16	167	14.4	5	174	12.9	5	166	4.4	5
	17	174	15.5	5	182	12.6	5	172	5.1	5
	18	177	16.4	5	184	12.7	5	174	5.4	5
	19	176	15.4	5	187	13.5	5	176	5.6	5
	20	178	13.8	5	189	11.9	5	179	6.5	5
	21	180	15.3	5	190	11.7	5	178	3.3	5
	22	183	15.5	5	195	9.7	5	181	5.2	5
	23	184	13.6	5	199	9.1	5	181	4.2	5
	24	186	14.3	5	198	9.3	5	181	5.1	5
	25	186	15.6	5	202	10.9	5	185	5.3	5
	26	188	13.1	5	202	10.8	5	186	5.2	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 5 Males: Summary of Hematological Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Leukocytes $x10^3$/cumm	13	5.7	1.32	10	5.9	1.00	10	6.0	0.74	10	6.4	1.08	10
Erythrocytes $x10^6$/cumm	13	9.42	0.768	10	9.34	0.453	10	9.14	0.492	10	8.82	0.660	10
Hemoglobin g/dl	13	16.4	0.98	10	16.2	0.56	10	15.9	0.68	10	15.5	0.93	10
Hematocrit %	13	49.6	4.00	10	49.4	2.53	10	48.5	2.23	10	46.5	3.32	10
MCV $microns^3$	13	52.6	0.66	10	52.9	0.52	10	53.1	0.77	10	52.7	0.54	10
MCH Picograms	13	17.4	0.50	10	17.4	0.43	10	17.4	0.37	10	17.5	0.48	10
MCHC %	13	33.1	0.89	10	32.8	0.76	10	32.8	0.44	10	33.3	0.84	10
Platelets $x10^3$/cumm	13	606	72.4	10	628	37.3	10	630	52.7	10	616	46.2	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 5 Cont. Males: Summary of Hematological Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Leukocytes $x10^3$/cumm	13	6.1	1.97	10	7.4[1]	1.70	10	8.5[2]	1.60	10
Erythrocytes $x10^6$/cumm	13	9.48	0.644	10	9.30	0.891	10	9.60	0.476	10
Hemoglobin g/dl	13	16.2	0.89	10	16.2	1.13	10	16.4	0.70	10
Hematocrit %	13	49.4	3.32	10	48.6	4.58	10	49.9	2.67	10
MCV $microns^3$	13	52.1	0.29	10	52.3	0.42	10	52.0	0.52	10
MCH Picograms	13	17.1	0.31	10	17.4	0.67	10	17.1	0.34	10
MCHC %	13	32.8	0.56	10	33.3	1.29	10	33.0	0.90	10
Platelets $x10^3$/cumm	13	600	61.0	10	633	55.8	10	626	75.6	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 5 Cont. Males: Summary of Hematological Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Reticulocytes /100 RBC	13	2.9	1.39	10	3.9	2.65	10	4.0	1.75	10	3.6	1.70	10
Segmented Neutrophils $x10^3$/cumm	13	1.5	0.54	10	1.6	0.23	10	1.6	0.32	10	2.0	0.86	10
Band Neutrophils $x10^3$/cumm	13	0.0[a]	0.03	10	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10
Lymphocytes $x10^3$/cumm	13	4.0	1.21	10	4.2	1.00	10	4.2	0.86	10	4.3	1.14	10
Eosinophils $x10^3$/cumm	13	0.1[a]	0.05	10	0.0[a]	0.07	10	0.1[a]	0.07	10	0.1[a]	0.06	10
Monocytes $x10^3$/cumm	13	0.1[a]	0.08	10	0.1[a]	0.04	10	0.1[a]	0.05	10	0.1[a]	0.06	10
Basophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10
Other Cells $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[a]This mean includes value(s) of <0.1

Table 5 Cont. Males: Summary of Hematological Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Reticulocytes /100 RBC	13	3.2	1.37	10	3.7	1.58	10	3.8	1.89	10
Segmented Neutrophils $x10^3$/cumm	13	1.9	0.59	10	2.7[2]	0.70	10	3.7[2]	0.92	10
Band Neutrophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10
Lymphocytes $x10^3$/cumm	13	4.1	1.51	10	4.5	1.27	10	4.6	1.01	10
Eosinophils $x10^3$/cumm	13	0.1[a]	0.05	10	0.1	0.09	10	0.1[a]	0.13	10
Monocytes $x10^3$/cumm	13	0.1[a]	0.06	10	0.1[a]	0.09	10	0.1[a]	0.07	10
Basophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10
Other Cells $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	10	0.0	0.00	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different Group 1; $p<0.01$
[a]This mean includes value(s) of <0.1

Table 5 Cont. Females: Summary of Hematological Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Leukocytes $x10^3$/cumm	13	5.6	0.85	10	5.3	0.52	9	5.4	0.88	10	5.2	0.85	10
Erythrocytes $x10^6$/cumm	13	8.47	0.781	10	8.62	0.381	9	8.46	0.468	10	8.52	0.213	10
Hemoglobin g/dl	13	15.8	1.12	10	16.1	0.54	9	15.9	0.70	10	15.9	0.43	10
Hematocrit %	13	47.7	4.21	10	48.6	2.36	9	48.0	2.71	10	48.3	1.21	10
MCV microns^3	13	56.3	0.34	10	56.4	0.42	9	56.7	0.30	10	56.7	0.22	10
MCH Picograms	13	18.6	0.48	10	18.7	0.37	9	18.8	0.47	10	18.7	0.40	10
MCHC %	13	33.1	0.75	10	33.2	0.68	9	33.2	0.86	10	33.1	0.69	10
Platelets $x10^3$/cumm	13	632	57.0	10	639	44.8	9	665	45.2	10	640	38.0	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 5 Cont. Females: Summary of Hematological Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Leukocytes $x10^3$/cumm	13	6.1	0.78	10	6.7	1.48	9	8.5[2]	1.38	10
Erythrocytes $x10^6$/cumm	13	8.53	0.283	10	8.31	0.533	9	9.04	0.430	10
Hemoglobin g/dl	13	16.1	0.41	10	15.5	1.02	9	16.6	0.67	10
Hematocrit %	13	48.3	1.53	10	47.0	2.94	9	50.4	2.35	10
MCV microns^3	13	56.6	0.25	10	56.6	0.33	9	55.7[2]	0.40	10
MCH Picograms	13	18.8	0.31	10	18.6	0.30	9	18.4	0.33	10
MCHC %	13	33.2	0.47	10	32.9	0.50	9	33.0	0.57	10
Platelets $x10^3$/cumm	13	633	57.6	10	625	58.9	9	657	53.3	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 5 Cont. Females: Summary of Hematological Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Reticulocytes /100 RBC	13	3.4	1.17	10	3.3	1.29	9	3.6	1.09	10	3.4	1.22	10
Segmented Neutrophils $x10^3$/cumm	13	1.4	0.34	10	1.2	0.50	9	1.4	0.54	10	1.4	0.43	10
Band Neutrophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10	0.0	0.00	10
Lymphocytes $x10^3$/cumm	13	4.1	0.60	10	3.9	0.58	9	3.9	0.81	10	3.7	0.66	10
Eosinophils $x10^3$/cumm	13	0.1[a]	0.05	10	0.1[a]	0.03	9	0.1[a]	0.06	10	0.1[a]	0.07	10
Monocytes $x10^3$/cumm	13	0.1[a]	0.07	10	0.1[a]	0.07	9	0.1[a]	0.06	10	0.1[a]	0.05	10
Basophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10	0.0	0.00	10
Other Cells $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10	0.0	0.00	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[a]This mean includes value(s) of <0.1

Table 5 Cont. Females: Summary of Hematological Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Reticulocytes /100 RBC	13	3.4	1.85	10	3.2	1.53	9	3.6	1.76	10
Segmented Neutrophils $x10^3$/cumm	13	1.8	0.40	10	2.6[2]	0.66	9	3.6[2]	0.80	10
Band Neutrophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10
Lymphocytes $x10^3$/cumm	13	4.1	1.05	10	3.9	1.12	9	4.7	0.75	10
Eosinophils $x10^3$/cumm	13	0.1[a]	0.10	10	0.1[a]	0.07	9	0.2[1,a]	0.13	10
Monocytes $x10^3$/cumm	13	0.1[a]	0.06	10	0.1[a]	0.07	9	0.1[a]	0.09	10
Basophils $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10
Other Cells $x10^3$/cumm	13	0.0	0.00	10	0.0	0.00	9	0.0	0.00	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$
[a]This mean includes value(s) of <0.1

[2]Significantly different from Group 1; $p \leq 0.01$

Table 6 Males: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Sodium mEq/l	13	150	2.9	10	148	1.6	10	148	2.4	10	146	1.9	10
Potassium mEq/l	13	6.3	0.51	10	5.9	0.45	10	6.1	0.39	10	6.0	0.55	10
Chloride mEq/l	13	106	1.7	10	105	2.6	10	105	2.9	10	105	1.9	10
Calcium mg/dl	13	10.8	0.51	10	10.5	0.37	10	10.4	0.32	10	10.3	0.33	10
Phosphorus mg/dl	13	9.6	1.27	10	9.2	0.92	10	9.1	0.82	10	8.8	0.92	10
Alkaline Phosphatase U/L	13	134	15.7	10	125	10.0	10	124	13.3	10	116	15.5	10

683-002

S.D. - Standard Deviation *No statistical significance observed
N - Number of Animals

Table 6 Cont. Males: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Sodium mEq/l	13	149	3.6	10	148	2.0	10	147	3.7	10
Potassium mEq/l	13	6.8	0.89	10	6.3	0.58	10	6.5	0.85	10
Chloride mEq/l	13	106	2.5	10	105	2.1	10	105	2.8	10
Calcium mg/dl	13	10.5	0.57	10	10.5	0.36	10	10.4	0.49	10
Phosphorus mg/dl	13	9.8	1.23	10	9.6	1.25	10	9.8	1.99	10
Alkaline Phosphatase U/L	13	129	17.9	10	135	17.6	10	154	27.0	10

683-002

S.D. - Standard Deviation *No statistical significance observed
N - Number of Animals

Table 6 Cont.

Males: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Total Bilirubin mg/dl	13	0.3	0.09	10	0.3	0.09	10	0.3	0.14	10	0.3	0.10	10
Gamma Glutamyl-transpeptidase U/L	13	1[b]	0.0	10	1[b]	0.0	10	1[b]	0.0	10	2[b]	1.6	10
Aspartate Aminotransferase U/L	13	109	13.0	10	113	17.1	10	113	15.8	10	106	10.7	10
Alanine Aminotransferase U/L	13	51	4.1	10	52	7.5	10	54	4.4	10	50	7.2	10
Creatine Phosphokinase U/L	13	537	196.5	10	535	213.9	10	505	181.5	10	470	163.7	10
Urea Nitrogen mg/dl	13	16	2.8	10	15	2.1	10	15	1.9	10	16	3.2	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 6 Cont.

Males: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Total Bilirubin mg/dl	13	0.4	0.15	10	0.3	0.10	10	0.4[a]	0.18	10
Gamma Glutamyl-transpeptidase U/L	13	1[b]	0.3	10	2[b]	1.6	10	1[b]	1.3	10
Aspartate Aminotransferase U/L	13	126	22.6	10	117	15.4	10	153	78.0	10
Alanine Aminotransferase U/L	13	57	11.2	10	54	6.8	10	60	25.6	10
Creatine Phosphokinase U/L	13	581	190.9	10	470	176.7	10	539	424.8	10
Urea Nitrogen mg/dl	13	15	3.6	10	15	2.0	10	17	3.5	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[a]This mean includes value(s) of <0.1

[b]This mean includes value(s) of <1

Table 6 Cont.

Males: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Creatinine mg/dl	13	0.7	0.08	10	0.6	0.08	10	0.6	0.11	10	0.6	0.13	10
Total Protein g/dl	13	7.0	0.58	10	6.7	0.47	10	6.7	0.46	10	6.5	0.45	10
Albumin g/dl	13	3.7	0.29	10	3.6	0.24	10	3.5	0.21	10	3.4	0.19	10
Globulin g/dl	13	3.2	0.34	10	3.1	0.29	10	3.1	0.28	10	3.1	0.29	10
A/G Ratio	13	1.2	0.08	10	1.2	0.10	10	1.1	0.07	10	1.1	0.07	10
Cholesterol mg/dl	13	54	5.3	10	52	6.9	10	52	7.6	10	54	9.3	10
Glucose mg/dl	13	83	11.4	10	82	11.5	10	80	9.3	10	84	9.8	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 6 Cont. Males: Summary of Biochemical Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Creatinine mg/dl	13	0.7	0.09	10	0.6	0.08	10	0.6[1]	0.12	10
Total Protein g/dl	13	7.0	0.63	10	6.8	0.59	10	6.8	0.74	10
Albumin g/dl	13	3.7	0.25	10	3.6	0.31	10	3.6	0.41	10
Globulin g/dl	13	3.3	0.42	10	3.2	0.30	10	3.2	0.35	10
A/G Ratio	13	1.1	0.10	10	1.1	0.06	10	1.1	0.07	10
Cholesterol mg/dl	13	51	9.5	10	53	7.7	10	53	6.8	10
Glucose mg/dl	13	79	6.2	10	84	7.5	10	91	24.6	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

Table 6 Cont. Females: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Sodium mEq/l	13	149	3.0	10	148	2.4	10	148	4.3	10	148	3.6	10
Potassium mEq/l	13	6.3	0.50	10	6.4	0.62	10	6.2	0.69	10	6.1	0.69	10
Chloride mEq/l	13	108	2.4	10	108	2.5	10	107	3.7	10	108	2.7	10
Calcium mg/dl	13	10.6	0.40	10	10.5	0.35	10	10.5	0.32	10	10.3	0.25	10
Phosphorus mg/dl	13	9.9	2.18	10	9.9	2.61	10	9.0	1.17	10	9.2	1.29	10
Alkaline Phosphatase U/L	13	121	19.4	10	124	18.8	10	120	15.7	10	123	14.3	10

683-002

S.D. - Standard Deviation *No statistical significance observed
N - Number of Animals

Table 6 Cont. Females: Summary of Biochemical Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Sodium mEq/l	13	148	2.5	10	147	2.3	10	147	3.4	10
Potassium mEq/l	13	6.6	0.40	10	6.4	0.64	10	6.1	0.69	10
Chloride mEq/l	13	108	2.7	10	107	1.7	10	106	2.7	10
Calcium mg/dl	13	10.4	0.40	10	10.3	0.32	10	10.3	0.40	10
Phosphorus mg/dl	13	9.7	0.93	10	10.2	2.27	10	9.8	1.99	10
Alkaline Phosphatase U/L	13	119	16.7	10	129	9.6	10	152[2]	15.6	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 6 Cont.

Females: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Total Bilirubin mg/dl	13	0.4	0.14	10	0.4	0.08	10	0.3	0.14	10	0.3	0.09	10
Gamma Glutamyl-transpeptidase U/L	13	2[b]	1.9	10	2[b]	0.7	10	2[b]	0.5	10	2[b]	0.8	10
Aspartate Aminotransferase U/L	13	121	17.0	10	136	38.3	10	116	22.6	10	117	8.6	10
Alanine Aminotransferase U/L	13	47	5.5	10	51	8.1	10	47	7.0	10	49	2.4	10
Creatine Phosphokinase U/L	13	514	175.8	10	678[c]	515.2	10	489	207.3	10	466	149.0	10
Urea Nitrogen mg/dl	13	18	2.3	10	18	1.5	10	17	3.4	10	17	1.9	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

[c]This mean includes value(s) of >2000

Table 6 Cont. Females: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Total Bilirubin mg/dl	13	0.4	0.16	10	0.3	0.07	10	0.3	0.13	10
Gamma Glutamyl-transpeptidase U/L	13	1[b]	0.7	10	2[b]	0.7	10	2[b]	0.9	10
Aspartate Aminotransferase U/L	13	123	30.9	10	137	28.3	10	145	25.2	10
Alanine Aminotransferase U/L	13	48	9.9	10	51	10.1	10	51	7.0	10
Creatine Phosphokinase U/L	13	554	230.7	10	569	211.7	10	474	207.9	10
Urea Nitrogen mg/dl	13	17	2.9	10	16	2.8	10	18	2.2	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 6 Cont.

Females: Summary of Biochemical Values*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Creatinine mg/dl	13	0.7	0.07	10	0.7	0.10	10	0.7	0.13	10	0.7	0.07	10
Total Protein g/dl	13	6.6	0.49	10	6.6	0.48	10	6.7	0.56	10	6.4	0.48	10
Albumin g/dl	13	3.6	0.25	10	3.5	0.27	10	3.5	0.29	10	3.4	0.19	10
Globulin g/dl	13	3.1	0.26	10	3.1	0.25	10	3.2	0.35	10	3.0	0.32	10
A/G Ratio	13	1.2	0.05	10	1.1	0.08	10	1.1	0.10	10	1.2	0.10	10
Cholesterol mg/dl	13	76	8.2	10	76	3.7	10	77	7.7	10	73	13.6	10
Glucose mg/dl	13	76	11.8	10	71	14.8	10	75	10.9	10	74	9.6	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 6 Cont. Females: Summary of Biochemical Values

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Creatinine mg/dl	13	0.7	0.08	10	0.7	0.11	10	0.7	0.09	10
Total Protein g/dl	13	6.6	0.33	10	6.6	0.41	10	6.6	0.53	10
Albumin g/dl	13	3.5	0.16	10	3.4	0.26	10	3.4	0.28	10
Globulin g/dl	13	3.1	0.21	10	3.2	0.21	10	3.2	0.29	10
A/G Ratio	13	1.1	0.08	10	1.1	0.09	10	1.1	0.07	10
Cholesterol mg/dl	13	71	7.2	10	63[1]	8.6	10	63[2]	6.8	10
Glucose mg/dl	13	76	15.8	10	79	21.2	10	72	15.1	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 7 Males: Summary of Urinalysis Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Volume ml	13	6.8	4.02	10	7.3	8.15	10	7.3	5.10	10	9.3	6.43	10
Specific Gravity	13	1.027[d]	0.0111	10	1.026	0.0136	8	1.026[d]	0.0112	10	1.023[d,e]	0.0136	10
pH	13	6.2	0.47	10	6.2	0.59	8	6.4	0.52	10	6.1[f]	0.64	10
Creatinine mg/16hr	13	3.6	0.45	9	3.7	0.38	8	3.7	0.36	9	3.6	0.50	9
Urinary Beta$_2$ Microglobulin µg/16hr	13	1.5	0.47	5	NA	NA	NA	NA	NA	NA	2.7	2.21	5

683-002

S.D. - Standard Deviation
N - Number of Animals
NA - Not Applicable

*No statistical significance observed
[d]This mean includes value(s) of >1.050
[f]This mean includes value(s) of ≤5.0

[e]This mean includes value(s) of ≤1.005

Table 7 Cont.

Males: Summary of Urinalysis Values*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Volume ml	13	10.0	7.24	10	13.3	21.08	10	6.3	4.71	10
Specific Gravity	13	1.020	0.0127	9	1.023	0.0112	9	1.029[d]	0.0150	10
pH	13	6.6	0.49	9	6.3[f]	0.83	9	6.2[f]	0.53	10
Creatinine mg/16hr	13	3.7	0.55	9	2.8[a]	1.35	9	2.9	0.35	8
Urinary Beta$_2$ Microglobulin µg/16hr	13	NA	NA	NA	NA	NA	NA	1.5	0.83	5

683-002

S.D. - Standard Deviation
N - Number of Animals
NA - Not Applicable

*No statistical significance observed
[a]This mean includes value(s) of <0.1
[d]This mean includes value(s) of >1.050
[f]This mean includes value(s) of ≤5.0

Table 7 Cont. Females: Summary of Urinalysis Values*

Parameters Measured	Week of Study	Group 1 Mean	Group 1 S.D.	Group 1 N	Group 2 Mean	Group 2 S.D.	Group 2 N	Group 3 Mean	Group 3 S.D.	Group 3 N	Group 4 Mean	Group 4 S.D.	Group 4 N
Volume ml	13	11.8	9.91	10	6.5	3.99	10	7.0	3.62	10	9.0	5.47	10
Specific Gravity	13	1.017	0.0079	10	1.027[d]	0.0122	10	1.024[d]	0.0115	10	1.020[d,e]	0.0131	10
pH	13	6.2[f]	0.58	10	6.2[f]	0.71	10	5.9[f]	0.67	10	6.0[f]	0.64	10
Creatinine mg/16hr	13	2.6	0.33	10	2.6	0.52	9	2.7	0.21	9	2.5	0.41	10
Urinary Beta$_2$ Microglobulin µg/16hr	13	0.3	0.11	5	NA	NA	NA	NA	NA	NA	0.2	0.06	4

683-002

S.D. - Standard Deviation
N - Number of Animals
NA - Not Applicable

*No statistical significance observed
[d]This mean includes value(s) of >1.050
[f]This mean includes value(s) of ≤5.0
[e]This mean includes value(s) of ≤1.005

Table 7 Cont.

Females: Summary of Urinalysis Values*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Volume ml	13	6.5	2.89	10	8.5	6.36	10	8.8	7.00	10
Specific Gravity	13	1.025	0.0120	10	1.023[d,e]	0.0149	10	1.026[d]	0.0146	10
pH	13	6.0	0.37	10	5.9[f]	0.77	10	6.1[f]	0.60	10
Creatinine mg/16hr	13	2.6	0.55	10	2.5	0.36	9	2.4	0.30	9
Urinary Beta$_2$ Microglobulin µg/16hr	13	NA	NA	NA	NA	NA	NA	0.2	0.08	4

683-002

S.D. - Standard Deviation
N - Number of Animals
NA - Not Applicable

*No statistical significance observed
[e]This mean includes value(s) of ≤1.005
[f]This mean includes value(s) of ≤5.0

[d]This mean includes value(s) of >1.050

Table 8 Males: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Volume (BALF) mL		12.8	2.03	5	14.4	0.70	5	12.6	3.96	5	13.4	2.46	5
Nucleated Cell Count (BALF) /cmm		157	41.4	5	160	29.8	5	153	49.0	5	126	39.4	5
Segmented Neutrophils %		1	1.8	5	1	0.5	5	0	0.4	5	2	3.8	5
Eosinophils %		0	0.0	5	0	0.0	5	0	0.0	5	0	0.0	5
Lymphocytes %		3	6.2	5	0	0.4	5	0	0.4	5	1	0.8	5
Mononuclear Cells %		96	7.8	5	99	0.8	5	100	0.5	5	97	4.1	5

683-002

S.D. - Standard Deviation *No statistical significance observed
N - Number of Animals

Table 8 Cont. Males: Summary of Bronchoalveolar Lavage Fluid

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Volume (BALF) mL		13.8	1.10	5	13.9	1.58	4	12.2	1.23	5
Nucleated Cell Count (BALF) /cmm		49[2]	11.3	5	76[2]	13.7	4	86[1]	34.9	5
Segmented Neutrophils %		7	4.8	5	21	6.3	4	48[2]	11.4	5
Eosinophils %		0	0.0	5	0	0.5	4	0	0.4	5
Lymphocytes %		1	1.1	5	0	0.0	4	3	3.9	5
Mononuclear Cells %		92	4.9	5	79	6.1	4	48[2]	13.8	5

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 8 Cont. Males: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Beta-Glucuronidase (BALF) mU/L		1[b]	0.0	5	1[b]	0.4	5	1[b]	0.0	5	2	1.3	5
Protein (BALF) mg/dl		3.7	0.87	5	3.6	2.71	5	3.6	2.07	5	2.5	0.88	5
Lactic Dehydrogenase (BALF) U/L		29	20.2	5	22	6.3	5	36	33.2	5	22	6.7	5
Glutathione Reductase (BALF) U/L		4	1.8	5	5	1.9	5	5	1.9	5	5	1.2	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 8 Cont. Males: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Beta-Glucuronidase (BALF) mU/L		1[b]	0.0	5	1[b]	0.5	4	1[b]	0.9	5
Protein (BALF) mg/dL		4.0	0.74	5	4.6	1.40	4	8.2	3.30	5
Lactic Dehydrogenase (BALF) U/L		25	5.7	5	44	12.61	4	88	36.6	5
Glutathione Reductase (BALF) U/L		5	0.7	5	5	1.3	4	6	1.4	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 8 Cont. Females: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Volume (BALF) mL		8.3	2.88	5	10.0	0.52	4	9.9	0.88	5	9.2	1.36	5
Nucleated Cell Count (BALF) /cmm		142	38.1	5	133	24.4	4	133	50.8	5	93	22.4	5
Segmented Neutrophils %		0	0.0	5	1	0.6	4	0	0.5	5	1	1.3	5
Eosinophils %		0	0.0	5	0	0.0	4	0	0.0	5	0	0.0	5
Lymphocytes %		0	0.4	5	1	2.5	4	0	0.9	5	1	0.8	5
Mononuclear Cells %		100	0.4	5	98	2.2	4	99	1.3	5	98	1.9	5

683-002

S.D. - Standard Deviation *No statistical significance observed
N - Number of Animals

Table 8 Cont. Females: Summary of Bronchoalveolar Lavage Fluid

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Volume (BALF) mL		9.9	1.00	5	9.3	0.64	5	8.8	0.97	5
Nucleated Cell Count (BALF) /cmm		46[2]	11.2	5	51[2]	14.1	5	64[2]	26.5	5
Segmented Neutrophils %		10	5.0	5	47	18.8	5	45	17.6	5
Eosinophils %		0	0.0	5	0	0.9	5	1	0.9	5
Lymphocytes %		1	0.8	5	2	1.8	5	3	3.1	5
Mononuclear Cells %		89	5.4	5	50	19.9	5	51	18.5	5

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 8 Cont. Females: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 1			Group 2			Group 3			Group 4		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Beta-Glucuronidase (BALF) mU/L		2[b]	0.9	5	1[b]	0.5	4	1[b]	0.4	5	1[b]	0.5	5
Protein (BALF) mg/dL		3.3	0.81	5	3.0	1.21	4	2.9	1.52	5	3.8	1.45	5
Lactic Dehydrogenase (BALF) U/L		30	8.2	5	25	2.1	4	23	8.9	5	32	9.7	5
Glutathione Reductase (BALF) U/L		4	1.5	5	5	0.5	4	5	1.2	5	5	0.8	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 8 Cont.

Females: Summary of Bronchoalveolar Lavage Fluid*

Parameters Measured	Week of Study	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Beta-Glucuronidase (BALF) mU/L		1[b]	0.4	5	3[b]	2.5	5	2[b]	0.9	5
Protein (BALF) mg/dL		4.6	0.48	5	7.7	3.01	5	9.5	3.18	5
Lactic Dehydrogenase (BALF) U/L		35	15.2	5	71	28.6	5	115	36.5	5
Glutathione Reductase (BALF) U/L		6	1.6	5	5	0.7	5	7	2.3	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed
[b]This mean includes value(s) of <1

Table 9

Summary of Male Spermatogenesis Data *

	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Sperm Motility %	60.5	12.88	10	55.9	16.41	10	55.9	16.07	10	62.2	14.05	10
Sperm Concentration X 10^6 Per g Caudal Tissue	863.0	308.37	10	897.5	212.27	10	904.0	251.55	10	913.1	320.74	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont.

Summary of Male Spermatogenesis Data*

	Group 5			Group 6			Group 7		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Sperm Motility %	49.0	9.42	10	59.1	17.55	10	61.2	16.09	10
Sperm Concentration X 10^6 Per g Caudal Tissue	751.0	172.41	10	830.9	388.54	10	707.9	219.07	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont.

Summary of Male Spermatogenesis Data (Read 1)

	Group I			Group II			Group III			Group IV		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	3.2	2.49	10	4.5	3.31	10	2.2	2.57	10	3.5	2.57	10
Number Disarticulated	31.2	14.20	10	46.3	18.10	10	24.0	7.32	10	26.4	15.46	10
Percent Disarticulated	13.0	5.58	10	18.6[1]	5.80	10	10.7	2.95	10	11.2	5.88	10

683-002

S.D. - Standard deviation
N - Number of animals

[1]Significantly different from Group I; $p \leq 0.05$

Table 9 Cont.

Summary of Male Spermatogenesis Data* (Read 1)

	Group V			Group VI			Group VII		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	4.3	3.49	10	3.5	3.01	10	2.6	2.02	10
Number Disarticulated	41.2	31.94	10	53.4	58.14	10	45.7	35.32	10
Percent Disarticulated	15.9	9.90	10	18.3	13.82	10	17.3	10.44	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont.

Summary of Male Spermatogenesis Data* (Read 2)

	Group I			Group II			Group III			Group IV		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	2.5	1.89	10	4.0	2.59	10	2.4	1.31	10	3.0	1.97	10
Number Disarticulated	42.8	25.05	10	59.1	20.78	10	39.0	15.36	10	33.3	19.73	10
Percent Disarticulated	16.9	9.10	10	22.3	6.34	10	16.1	5.36	10	13.8	7.16	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont. Summary of Male Spermatogenesis Data* (Read 2)

	Group V			Group VI			Group VII		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	3.2	3.15	10	3.3	2.03	9	3.0	2.58	10
Number Disarticulated	46.1	30.80	10	57.8	52.37	10	55.3	39.06	10
Percent Disarticulated	17.6	9.34	10	20.2	13.01	10	20.3	10.44	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont.

Summary of Male Spermatogenesis Data* (Read 3)

	Group I			Group II			Group III			Group IV		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	2.4	2.25	10	4.6	2.57	10	2.0	1.90	10	3.1	1.54	10
Number Disarticulated	49.5	29.57	10	65.2	26.32	10	44.2	20.42	10	59.3	33.49	10
Percent Disarticulated	18.8	9.51	10	24.0	6.93	10	17.6	6.79	10	21.7	10.68	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 9 Cont.

Summary of Male Spermatogenesis Data* (Read 3)

	Group V			Group VI			Group VII		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Percent Abnormal	4.1	2.41	10	4.2	1.87	10	4.1	3.41	10
Number Disarticulated	67.2	31.50	10	70.8	46.39	10	61.7	30.00	10
Percent Disarticulated	24.5	9.14	10	24.5	11.14	10	22.7	8.59	10

683-002

S.D. - Standard deviation
N - Number of animals

*No statistical significance observed

Table 10

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
NUMBER OF ANIMALS EXAMINED		0	10	0	10	0	10	0	10	0	10	0	10
NUMBER WITHIN NORMAL LIMITS		0	9	0	0	0	0	0	0	0	10	0	0
Eye		(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Discoloration, red, trace		0	0	0	0	0	1	0	0	0	0	0	0
Lung		(0)	(0)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(0)	(0)	(10)
Discoloration, green,		0	0	0	10	0	10	0	10	0	0	0	0
	-trace	0	0	0	9	0	2	0	0	0	0	0	0
	-mild	0	0	0	1	0	7	0	4	0	0	0	0
	-moderate	0	0	0	0	0	1	0	6	0	0	0	0
Discoloration, gray,		0	0	0	0	0	0	0	0	0	0	0	10
	-trace	0	0	0	0	0	0	0	0	0	0	0	7
	-mild	0	0	0	0	0	0	0	0	0	0	0	3
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Lymph Node, Mandibular		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Enlarged, mild		0	0	0	0	0	0	0	1	0	0	0	0
Lymph Node, Mediastinal		(0)	(0)	(0)	(0)	(0)	(1)	(0)	(10)	(0)	(0)	(0)	(0)
Discoloration, green,		0	0	0	0	0	1	0	10	0	0	0	0
	-trace	0	0	0	0	0	1	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	3	0	0	0	0
	-moderate	0	0	0	0	0	0	0	7	0	0	0	0
Nasal Tissues		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	10	0	10	0	10	0	10

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
NUMBER OF ANIMALS EXAMINED		1	10
NUMBER WITHIN NORMAL LIMITS		0	0
Eye		(0)	(0)
Discoloration, red, trace		0	0
Lung		(0)	(10)
Discoloration, green,		0	0
	-trace	0	0
	-mild	0	0
	-moderate	0	0
Discoloration, gray,		0	10
	-trace	0	0
	-mild	0	7
	-moderate	0	3
Lymph Node, Mandibular		(0)	(0)
Enlarged, mild		0	0
Lymph Node, Mediastinal		(0)	(0)
Discoloration, green,		0	0
	-trace	0	0
	-mild	0	0
	-moderate	0	0
Nasal Tissues		(1)	(10)
Within normal limits		1	10

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Skin	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Discoloration, green, moderate	0	0	0	0	0	0	0	0	0	0	0	0
Stomach, Glandular	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Focus/foci, black, trace	0	0	0	1	0	0	0	0	0	0	0	0
Tail	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Absent, portion, no grade	0	0	0	0	0	1	0	0	0	0	0	0
Scab, trace	0	0	0	0	0	0	0	0	0	0	0	0
Testis	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Small, mild	0	1	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 7 DOS	 SAC
Skin	(1)	(0)
Discoloration, green, moderate	1	0
Stomach, Glandular	(0)	(0)
Focus/foci, black, trace	0	0
Tail	(0)	(1)
Absent, portion, no grade	0	0
Scab, trace	0	1
Testis	(0)	(0)
Small, mild	0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE / OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
NUMBER OF ANIMALS EXAMINED		0	10	0	10	0	10	0	10	0	10	0	10
NUMBER WITHIN NORMAL LIMITS		0	10	0	0	0	0	0	0	0	10	0	1
Eye		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
Within normal limits		0	0	0	0	0	0	0	0	0	1	0	0
Lung		(0)	(0)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(0)	(0)	(8)
Discoloration, green,		0	0	0	10	0	10	0	10	0	0	0	0
	-trace	0	0	0	10	0	1	0	0	0	0	0	0
	-mild	0	0	0	0	0	9	0	6	0	0	0	0
	-moderate	0	0	0	0	0	0	0	4	0	0	0	0
Discoloration, gray,		0	0	0	0	0	0	0	0	0	0	0	8
	-trace	0	0	0	0	0	0	0	0	0	0	0	8
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Lymph Node, Mediastinal		(0)	(0)	(0)	(0)	(0)	(1)	(0)	(9)	(0)	(0)	(0)	(0)
Discoloration, green,		0	0	0	0	0	1	0	9	0	0	0	0
	-trace	0	0	0	0	0	1	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	2	0	0	0	0
	-moderate	0	0	0	0	0	0	0	7	0	0	0	0
Nasal Tissues		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	10	0	10	0	10	0	10
Ovary		(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Cyst, mild		0	0	0	0	0	0	0	0	0	0	0	1
Enlarged, trace		0	0	0	0	0	0	0	0	0	0	0	0
Tail		(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Absent, portion, no grade		0	0	0	0	0	0	0	0	0	0	0	1
Deviation, no grade		0	0	0	1	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	 SAC
NUMBER OF ANIMALS EXAMINED		0	10
NUMBER WITHIN NORMAL LIMITS		0	0
Eye		(0)	(0)
Within normal limits		0	0
Lung		(0)	(10)
Discoloration, green,		0	0
	-trace	0	0
	-mild	0	0
	-moderate	0	0
Discoloration, gray,		0	10
	-trace	0	2
	-mild	0	5
	-moderate	0	3
Lymph Node, Mediastinal		(0)	(0)
Discoloration, green,		0	0
	-trace	0	0
	-mild	0	0
	-moderate	0	0
Nasal Tissues		(0)	(10)
Within normal limits		0	10
Ovary		(0)	(1)
Cyst, mild		0	0
Enlarged, trace		0	1
Tail		(0)	(0)
Absent, portion, no grade		0	0
Deviation, no grade		0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
NUMBER OF ANIMALS EXAMINED		5	5	5	5	5	5
NUMBER WITHIN NORMAL LIMITS		4	0	0	0	2	0
Liver		(0)	(0)	(0)	(0)	(0)	(1)
Focus/foci, tan, trace		0	0	0	0	0	1
Lung		(0)	(5)	(5)	(5)	(2)	(5)
Discoloration, green,		0	5	5	5	0	0
	-trace	0	5	0	0	0	0
	-mild	0	0	5	3	0	0
	-moderate	0	0	0	2	0	0
Focus/foci, tan,		0	1	0	0	1	5
	-trace	0	1	0	0	1	2
	-mild	0	0	0	0	0	3
	-moderate	0	0	0	0	0	0
Discoloration, gray,		0	0	0	0	1	1
	-trace	0	0	0	0	1	0
	-mild	0	0	0	0	0	1
Lymph Node, Mediastinal		(0)	(0)	(3)	(5)	(2)	(4)
Enlarged,		0	0	0	2	2	2
	-trace	0	0	0	0	2	0
	-mild	0	0	0	2	0	2
	-moderate	0	0	0	0	0	0
Discoloration, green,		0	0	3	5	0	0
	-mild	0	0	3	0	0	0
	-moderate	0	0	0	5	0	0
Discoloration, gray,		0	0	0	0	2	4
	-trace	0	0	0	0	0	1
	-mild	0	0	0	0	2	3
	-moderate	0	0	0	0	0	0
Nasal Tissues		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		4	0	0	0	5	5
Discoloration, red, mild		1	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7
NUMBER OF ANIMALS EXAMINED		4
NUMBER WITHIN NORMAL LIMITS		0
Liver		(0)
Focus/foci, tan, trace		0
Lung		(4)
Discoloration, green,		0
	-trace	0
	-mild	0
	-moderate	0
Focus/foci, tan,		4
	-trace	0
	-mild	0
	-moderate	4
Discoloration, gray,		1
	-trace	0
	-mild	1
Lymph Node, Mediastinal		(3)
Enlarged,		2
	-trace	0
	-mild	0
	-moderate	2
Discoloration, green,		0
	-mild	0
	-moderate	0
Discoloration, gray,		3
	-trace	1
	-mild	0
	-moderate	2
Nasal Tissues		(4)
Within normal limits		4
Discoloration, red, mild		0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
NUMBER OF ANIMALS EXAMINED		5	5	5	5	5	5
NUMBER WITHIN NORMAL LIMITS		5	0	0	0	4	0
Lung		(0)	(5)	(5)	(5)	(0)	(5)
Discoloration, green,		0	5	5	5	0	0
	-trace	0	5	2	0	0	0
	-mild	0	0	3	0	0	0
	-moderate	0	0	0	5	0	0
Focus/foci, tan,		0	0	0	0	0	5
	-trace	0	0	0	0	0	1
	-mild	0	0	0	0	0	0
	-moderate	0	0	0	0	0	4
	-severe	0	0	0	0	0	0
Discoloration, gray,		0	0	0	0	0	0
	-moderate	0	0	0	0	0	0
	-severe	0	0	0	0	0	0
Lymph Node, Mediastinal		(0)	(0)	(4)	(5)	(1)	(4)
Enlarged,		0	0	0	1	0	4
	-mild	0	0	0	1	0	3
	-moderate	0	0	0	0	0	1
Discoloration, green,		0	0	4	5	0	0
	-mild	0	0	4	1	0	0
	-moderate	0	0	0	3	0	0
	-severe	0	0	0	1	0	0
Discoloration, gray,		0	0	0	0	1	4
	-mild	0	0	0	0	1	1
	-moderate	0	0	0	0	0	3
Nasal Tissues		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	5	5
Ovary		(0)	(0)	(0)	(0)	(0)	(1)
Cyst, mild		0	0	0	0	0	1
Tail		(1)	(0)	(0)	(0)	(0)	(0)
Within normal limits		1	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 10 Cont.

Incidence of Macroscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7
NUMBER OF ANIMALS EXAMINED		5
NUMBER WITHIN NORMAL LIMITS		0
Lung		(5)
Discoloration, green,		0
	-trace	0
	-mild	0
	-moderate	0
Focus/foci, tan,		5
	-trace	0
	-mild	1
	-moderate	3
	-severe	1
Discoloration, gray,		3
	-moderate	1
	-severe	2
Lymph Node, Mediastinal		(3)
Enlarged,		2
	-mild	2
	-moderate	0
Discoloration, green,		0
	-mild	0
	-moderate	0
	-severe	0
Discoloration, gray,		3
	-mild	1
	-moderate	2
Nasal Tissues		(5)
Within normal limits		5
Ovary		(0)
Cyst, mild		0
Tail		(0)
Within normal limits		0

683-002 CODE: () = NUMBER OF ANIMALS WITH MACROSCOPIC OBSERVATIONS

Table 11 Males: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	224	11.7	10	218	14.8	10	222	11.3	10	222	14.5	10
Brain g	1.79	0.087	10	1.77	0.041	10	1.81	0.073	10	1.79	0.046	10
Brain/Body Weight %x10	8.02	0.380	10	8.14	0.490	10	8.14	0.403	10	8.11	0.576	10
Adrenal mg	55	8.9	10	61	7.6	10	64	15.6	10	64	13.0	10
Adrenal/Body Weight $\%x10^{3}$	24.9	4.98	10	28.1	4.48	10	28.6	6.19	10	28.9	6.35	10
Adrenal/Brain Weight %	3.11	0.637	10	3.44	0.467	10	3.53	0.844	10	3.55	0.688	10
Heart g	0.78	0.068	10	0.76	0.085	10	0.75	0.073	10	0.81	0.117	10
Heart/Body Weight %x10	3.48	0.337	10	3.48	0.372	10	3.39	0.257	10	3.65	0.520	10
Heart/Brain Weight $\%x10^{-1}$	4.34	0.454	10	4.29	0.504	10	4.17	0.360	10	4.52	0.622	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont.

Males: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5			Group 6			Group 7		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	225	10.2	10	211	13.6	10	174[2]	9.3	10
Brain g	1.82	0.055	10	1.76	0.061	10	1.71[1]	0.069	10
Brain/Body Weight %x10	8.12	0.374	10	8.38	0.473	10	9.83[2]	0.518	10
Adrenal mg	64	6.5	10	63	11.9	10	57	12.4	10
Adrenal/Body Weight $\%x10^{3}$	28.3	3.71	10	29.9	4.95	10	32.3	5.69	10
Adrenal/Brain Weight %	3.49	0.434	10	3.58	0.711	10	3.30	0.669	10
Heart g	0.84	0.080	10	0.73	0.076	10	0.70	0.126	10
Heart/Body Weight %x10	3.75	0.489	10	3.50	0.465	10	4.03	0.767	10
Heart/Brain Weight $\%x10^{-1}$	4.61	0.488	10	4.17	0.461	10	4.10	0.729	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont. Males: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Kidney g	1.62	0.085	10	1.64	0.102	10	1.65	0.118	10	1.62	0.090	10
Kidney/Body Weight %x10	7.26	0.300	10	7.53	0.400	10	7.42	0.398	10	7.32	0.311	10
Kidney/Brain Weight %x10^{-2}	0.91	0.045	10	0.93	0.057	10	0.91	0.061	10	0.91	0.050	10
Liver g	5.48	0.367	10	5.46	0.440	10	5.51	0.323	10	5.46	0.332	10
Liver/Body Weight %	2.45	0.070	10	2.51	0.155	10	2.48	0.070	10	2.46	0.055	10
Liver/Brain Weight %x10^{-2}	3.06	0.205	10	3.09	0.257	10	3.05	0.148	10	3.05	0.194	10
Lung/Trachea g	0.99	0.070	10	0.98	0.055	10	1.00	0.077	10	1.11[2]	0.050	9
Lung/Trachea/ Body Weight %x10	4.42	0.187	10	4.52	0.273	10	4.49	0.396	10	4.98[2]	0.228	9
Lung/Trachea/ Brain Weight %x10^{-1}	5.52	0.349	10	5.56	0.308	10	5.52	0.501	10	6.23[2]	0.269	9

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont. Males: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Kidney g	1.64	0.082	10	1.54	0.106	10	1.35[2]	0.049	10
Kidney/Body Weight %x10	7.28	0.207	10	7.30	0.283	10	7.78[2]	0.350	10
Kidney/Brain Weight $\%x10^{-2}$	0.90	0.056	10	0.87	0.060	10	0.79[2]	0.041	10
Liver g	5.63	0.271	10	5.17	0.459	10	4.39[2]	0.146	10
Liver/Body Weight %	2.50	0.050	10	2.45	0.091	10	2.53	0.120	10
Liver/Brain Weight $\%x10^{-2}$	3.09	0.130	10	2.93	0.249	10	2.58[2]	0.142	10
Lung/Trachea g	1.26[2]	0.071	10	1.51[2]	0.088	10	1.86[2]	0.089	10
Lung/Trachea/ Body Weight %x10	5.60[2]	0.271	10	7.15[2]	0.252	10	10.69[2]	0.688	10
Lung/Trachea/ Brain Weight $\%x10^{-1}$	6.91[2]	0.411	10	8.55[2]	0.478	10	10.90[2]	0.836	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont.

Males: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Spleen g	0.45	0.038	10	0.43	0.038	10	0.44	0.027	10	0.44	0.039	10
Spleen/Body Weight %x10	1.99	0.149	10	1.96	0.089	10	1.96	0.089	10	1.97	0.160	10
Spleen/Brain Weight %x10^{-1}	2.49	0.198	10	2.42	0.201	10	2.41	0.131	10	2.43	0.213	10
Testis g	2.36	0.356	10	2.30	0.220	10	2.43	0.246	10	2.25	0.248	10
Testis/Body Weight %x10	10.54	1.315	10	10.57	0.914	10	10.91	0.896	10	10.15	1.193	10
Testis/Brain Weight %x10^{-2}	1.32	0.188	10	1.30	0.125	10	1.34	0.144	10	1.25	0.123	10
Thyroid/Parathyroid mg	14	2.5	10	16	2.2	10	15	1.7	10	15	2.7	10
Thyroid/Parathyroid/ Body Weight %x10^{3}	6.21	1.052	10	7.49	0.755	10	6.76	0.854	10	6.67	1.421	10
Thyroid/Parathyroid/ Brain Weight %x10	7.8	1.41	10	9.2	1.22	10	8.3	0.89	10	8.2	1.44	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Males: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5			Group 6			Group 7		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Spleen g	0.43	0.036	10	0.40[1]	0.040	10	0.32[2]	0.035	10
Spleen/Body Weight %x10	1.91	0.132	10	1.89	0.125	10	1.84	0.151	10
Spleen/Brain Weight %x10^{-1}	2.36	0.210	10	2.26[1]	0.196	10	1.88[2]	0.186	10
Testis g	2.39	0.261	10	2.22	0.286	10	2.18	0.215	10
Testis/Body Weight %x10	10.65	1.098	10	10.52	1.049	10	12.53[2]	1.238	10
Testis/Brain Weight %x10^{-2}	1.31	0.118	10	1.26	0.155	10	1.28	0.161	10
Thyroid/Parathyroid mg	15	2.9	10	14	1.8	10	15	3.5	10
Thyroid/Parathyroid/ Body Weight %x10^{3}	6.64	1.475	10	6.74	1.021	10	8.76[1]	2.074	10
Thyroid/Parathyroid/ Brain Weight %x10	8.2	1.63	10	8.1	1.18	10	8.9	2.07	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont.

Females: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	143	6.6	10	141	5.7	10	147	4.1	10	137	6.6	10
Brain g	1.61	0.092	10	1.60	0.092	10	1.60	0.113	10	1.60	0.068	10
Brain/Body Weight %x10	11.26	0.562	10	11.32	0.627	10	10.85	0.830	10	11.65	0.664	10
Adrenal mg	60	10.7	10	62	10.7	10	62	10.5	10	63	6.6	10
Adrenal/Body Weight $\%x10^{3}$	41.7	7.11	10	44.2	7.09	10	41.8	7.66	10	45.7	4.85	10
Adrenal/Brain Weight %	3.70	0.516	10	3.90	0.570	10	3.84	0.555	10	3.92	0.381	10
Heart g	0.56	0.086	10	0.55	0.052	10	0.56	0.040	10	0.53	0.035	10
Heart/Body Weight %x10	3.92	0.533	10	3.92	0.356	10	3.77	0.307	10	3.90	0.313	10
Heart/Brain Weight $\%x10^{-1}$	3.48	0.453	10	3.47	0.245	10	3.48	0.254	10	3.35	0.179	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Body Weight g	141	9.5	10	139	8.3	10	129[2]	7.9	10
Brain g	1.59	0.062	10	1.61	0.070	10	1.55	0.103	10
Brain/Body Weight %x10	11.29	0.587	10	11.58	0.655	10	12.00	0.769	10
Adrenal mg	63	8.8	10	68	11.3	10	62	14.1	10
Adrenal/Body Weight %x10^{3}	44.7	4.56	10	48.5	7.58	10	48.4	11.06	10
Adrenal/Brain Weight %	3.97	0.438	10	4.19	0.614	10	4.01	0.761	10
Heart g	0.55	0.070	10	0.55	0.077	10	0.53	0.025	10
Heart/Body Weight %x10	3.92	0.461	10	3.93	0.515	10	4.16	0.308	10
Heart/Brain Weight %x10^{-1}	3.48	0.461	10	3.39	0.387	10	3.47	0.253	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different Group 1; $p \leq 0.01$

Table 11 Cont.

Females: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Kidney g	1.07	0.058	10	1.10	0.113	10	1.08	0.068	10	1.05	0.049	10
Kidney/Body Weight %x10	7.49	0.398	10	7.82	0.837	10	7.31	0.490	10	7.65	0.272	10
Kidney/Brain Weight %x10^{-2}	0.67	0.040	10	0.69	0.060	10	0.68	0.051	10	0.66	0.037	10
Liver g	3.70	0.308	10	3.79	0.235	10	3.87	0.233	10	3.58	0.205	10
Liver/Body Weight %	2.58	0.152	10	2.69	0.186	10	2.63	0.146	10	2.61	0.072	10
Liver/Brain Weight %x10^{-2}	2.29	0.135	10	2.38	0.173	10	2.43	0.173	10	2.24	0.122	10
Lung/Trachea g	0.81	0.081	10	0.81	0.080	10	0.85	0.084	10	0.88	0.068	10
Lung/Trachea/ Body Weight %x10	5.65	0.418	10	5.78	0.577	10	5.77	0.629	10	6.40	0.618	10
Lung/Trachea/ Brain Weight %x10^{-1}	5.02	0.304	10	5.11	0.387	10	5.32	0.395	10	5.49	0.339	10

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Kidney g	1.07	0.089	10	1.10	0.075	10	1.03	0.048	10
Kidney/Body Weight %x10	7.57	0.521	10	7.92	0.301	10	7.98	0.428	10
Kidney/Brain Weight %x10^{-2}	0.67	0.050	10	0.69	0.042	10	0.67	0.056	10
Liver g	3.74	0.270	10	3.76	0.287	10	3.41	0.230	10
Liver/Body Weight %	2.66	0.119	10	2.70	0.121	10	2.65	0.068	10
Liver/Brain Weight %x10^{-2}	2.36	0.147	10	2.34	0.146	10	2.22	0.172	10
Lung/Trachea g	0.98[2]	0.094	10	1.29[2]	0.164	10	1.66[2]	0.084	10
Lung/Trachea/ Body Weight %x10	6.99[2]	0.619	10	9.24[2]	1.036	10	12.89[2]	1.134	10
Lung/Trachea/ Brain Weight %x10^{-1}	6.19[2]	0.416	10	7.98[2]	0.787	10	10.76[2]	1.002	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Ovary mg	94	11.1	10	98	18.1	10	97	6.6	10	94	9.1	10
Ovary/Body Weight %x10^{2}	6.56	0.782	10	6.92	1.081	10	6.58	0.418	10	6.88	0.608	10
Ovary/Brain Weight %	5.83	0.735	10	6.14	1.083	10	6.11	0.740	10	5.93	0.649	10
Spleen g	0.33	0.037	10	0.33	0.027	10	0.32	0.031	10	0.30	0.031	10
Spleen/Body Weight %x10	2.32	0.268	10	2.31	0.214	10	2.17	0.213	10	2.22	0.274	10
Spleen/Brain Weight %x10^{-1}	2.06	0.251	10	2.04	0.123	10	2.01	0.214	10	1.91	0.218	10
Thyroid/Parathyroid mg	12	1.9	10	13	1.3	10	15[2]	1.5	10	14	2.3	10
Thyroid/Parathyroid/ Body Weight %x10^{3}	8.26	1.493	10	8.89	0.880	10	10.10[1]	1.147	10	10.04[1]	1.346	10
Thyroid/Parathyroid/ Brain Weight %x10	7.3	1.25	10	7.9	1.00	10	9.3[2]	1.02	10	8.7	1.53	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Ovary mg	97	15.1	10	106	30.8	10	85	13.2	10
Ovary/Body Weight %x10^{2}	6.86	0.901	10	7.53	1.846	10	6.58	0.846	10
Ovary/Brain Weight %	6.10	0.857	10	6.60	2.099	10	5.49	0.641	10
Spleen g	0.31	0.033	10	0.30	0.033	10	0.28[2]	0.033	10
Spleen/Body Weight %x10	2.19	0.212	10	2.17	0.162	10	2.19	0.273	10
Spleen/Brain Weight %x10^{-1}	1.95	0.209	10	1.88	0.185	10	1.83	0.252	10
Thyroid/Parathyroid mg	11	1.3	10	12	1.8	10	14[1]	2.1	10
Thyroid/Parathyroid/ Body Weight %x10^{3}	7.96	1.154	10	8.63	1.265	10	10.77[2]	1.522	10
Thyroid/Parathyroid/ Brain Weight %x10	7.0	0.78	10	7.4	0.92	10	9.0[1]	1.57	10

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from Group 1; $p \leq 0.05$

[2]Significantly different from Group 1; $p \leq 0.01$

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	340	20.2	5	336	12.7	5	338	10.6	5	321	7.7	5
Brain g	1.85	0.090	5	1.84	0.037	5	1.85	0.018	5	1.86	0.079	5
Brain/Body Weight %x10	5.45	0.410	5	5.49	0.280	5	5.49	0.219	5	5.80	0.377	5
Adrenal mg	52	9.1	5	51	4.2	5	55	11.0	5	50	4.4	5
Adrenal/Body Weight $\%x10^{3}$	15.4	2.62	5	15.1	1.30	5	16.2	2.94	5	15.7	1.17	5
Adrenal/Brain Weight %	2.81	0.376	5	2.76	0.253	5	2.96	0.620	5	2.72	0.321	5
Heart g	0.98	0.083	5	0.98	0.050	5	0.98	0.033	5	0.90	0.041	5
Heart/Body Weight %x10	2.88	0.225	5	2.93	0.106	5	2.91	0.066	5	2.81	0.135	5
Heart/Brain Weight $\%x10^{-1}$	5.29	0.273	5	5.36	0.313	5	5.30	0.213	5	4.86	0.344	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice

Parameters Measured	Group 5			Group 6			Group 7		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	326	18.3	5	306[2]	18.1	5	305[2]	7.2	4
Brain g	1.84	0.048	5	1.84	0.035	5	1.87	0.015	4
Brain/Body Weight %x10	5.67	0.203	5	6.04[1]	0.397	5	6.15[1]	0.161	4
Adrenal mg	64	16.5	5	46	11.0	5	55	7.6	4
Adrenal/Body Weight %x10^{3}	19.5	4.44	5	15.1	3.33	5	18.2	2.86	4
Adrenal/Brain Weight %	3.45	0.836	5	2.51	0.575	5	2.95	0.418	4
Heart g	1.02	0.288	5	0.99	0.227	5	0.89	0.041	4
Heart/Body Weight %x10	3.11	0.702	5	3.22	0.539	5	2.93	0.202	4
Heart/Brain Weight %x10^{-1}	5.52	1.459	5	5.39	1.314	5	4.76	0.224	4

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the control group; $p \leq 0.05$

[2]Significantly different from the control group; $p \leq 0.01$

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Kidney g	2.13	0.137	5	2.11	0.113	5	2.09	0.054	5	2.06	0.079	5
Kidney/Body Weight %x10	6.26	0.148	5	6.30	0.268	5	6.19	0.205	5	6.40	0.202	5
Kidney/Brain Weight $\%x10^{-2}$	1.15	0.101	5	1.15	0.075	5	1.13	0.032	5	1.11	0.069	5
Liver g	10.62	0.876	5	10.44	0.963	5	10.63	0.275	5	10.10	0.370	5
Liver/Body Weight %	3.12	0.151	5	3.11	0.182	5	3.14	0.062	5	3.14	0.090	5
Liver/Brain Weight $\%x10^{-2}$	5.77	0.652	5	5.68	0.575	5	5.74	0.196	5	5.44	0.375	5
Lung/Trachea g	1.32	0.113	5	1.36	0.116	5	1.36	0.127	5	1.37	0.089	5
Lung/Trachea/ Body Weight %x10	3.89	0.214	5	4.06	0.261	5	4.02	0.308	5	4.26	0.254	5
Lung/Trachea/ Brain Weight $\%x10^{-1}$	7.16	0.601	5	7.42	0.724	5	7.35	0.723	5	7.38	0.759	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Kidney g	2.06	0.127	5	1.91[2]	0.089	5	1.90[2]	0.035	4
Kidney/Body Weight %x10	6.34	0.281	5	6.25	0.355	5	6.24	0.085	4
Kidney/Brain Weight %x10^{-2}	1.12	0.061	5	1.04[1]	0.055	5	1.01[1]	0.020	4
Liver g	10.58	1.027	5	9.83	0.652	5	9.31	0.339	4
Liver/Body Weight %	3.25	0.181	5	3.21	0.115	5	3.06	0.076	4
Liver/Brain Weight %x10^{-2}	5.74	0.502	5	5.34	0.432	5	4.97	0.191	4
Lung/Trachea g	1.52	0.132	5	1.95[2]	0.068	5	2.67[2]	0.144	4
Lung/Trachea/ Body Weight %x10	4.66[2]	0.373	5	6.37[2]	0.298	5	8.77[2]	0.274	4
Lung/Trachea/ Brain Weight %x10^{-1}	8.23	0.758	5	10.57[2]	0.391	5	14.28[2]	0.793	4

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the control group; $p \leq 0.05$

[2]Significantly different from the control group; $p \leq 0.01$

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Spleen g	0.73	0.062	5	0.73	0.075	5	0.70	0.033	5	0.72	0.049	5
Spleen/Body Weight %x10	2.14	0.113	5	2.18	0.143	5	2.07	0.097	5	2.23	0.197	5
Spleen/Brain Weight $\%x10^{-1}$	3.94	0.362	5	3.99	0.463	5	3.78	0.181	5	3.85	0.130	5
Testis g	2.94	0.201	5	3.03	0.177	5	2.91	0.280	5	2.83	0.137	5
Testis/Body Weight %x10	8.67	0.639	5	9.03	0.688	5	8.60	0.885	5	8.79	0.452	5
Testis/Brain Weight $\%x10^{-2}$	1.59	0.080	5	1.65	0.080	5	1.57	0.150	5	1.52	0.106	5
Thyroid/Parathyroid mg	15	1.5	5	18	1.9	5	21	2.1	5	17	4.7	5
Thyroid/Parathyroid/ Body Weight $\%x10^{3}$	4.46	0.380	5	5.36	0.661	5	6.09	0.607	5	5.27	1.423	5
Thyroid/Parathyroid/ Brain Weight %x10	8.2	1.01	5	9.8	0.99	5	11.1	1.16	5	9.1	2.62	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Males: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Spleen g	0.73	0.078	5	0.68	0.034	5	0.66	0.055	4
Spleen/Body Weight %x10	2.24	0.196	5	2.23	0.196	5	2.18	0.192	4
Spleen/Brain Weight $\%x10^{-1}$	3.96	0.419	5	3.68	0.139	5	3.55	0.310	4
Testis g	2.94	0.153	5	2.72	0.374	5	2.82	0.244	4
Testis/Body Weight %x10	9.06	0.783	5	8.94	1.352	5	9.26	0.982	4
Testis/Brain Weight $\%x10^{-2}$	1.60	0.088	5	1.48	0.183	5	1.51	0.132	4
Thyroid/Parathyroid mg	18	1.7	5	17	1.2	5	18	2.1	4
Thyroid/Parathyroid/ Body Weight $\%x10^{3}$	5.41	0.814	5	5.46	0.231	5	5.97	0.765	4
Thyroid/Parathyroid/ Brain Weight %x10	9.5	1.16	5	9.1	0.72	5	9.7	1.07	4

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	195	8.2	5	194	12.3	5	188	8.4	5	199	10.5	5
Brain g	1.78	0.039	5	1.73	0.072	5	1.76	0.076	5	1.75	0.035	5
Brain/Body Weight %x10	9.15	0.402	5	8.97	0.565	5	9.36	0.812	5	8.84	0.485	5
Adrenal mg	62	5.3	5	67	8.0	5	68	11.8	5	62	9.2	5
Adrenal/Body Weight %x10^{3}	32.0	3.49	5	34.7	5.71	5	36.3	7.35	5	31.4	4.98	5
Adrenal/Brain Weight %	3.50	0.352	5	3.87	0.554	5	3.88	0.688	5	3.54	0.489	5
Heart g	0.66	0.034	5	0.65	0.034	5	0.68	0.098	5	0.71	0.083	5
Heart/Body Weight %x10	3.39	0.108	5	3.35	0.133	5	3.60	0.646	5	3.55	0.363	5
Heart/Brain Weight %x10^{-1}	3.71	0.201	5	3.74	0.241	5	3.84	0.485	5	4.03	0.466	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 5			Group 6			Group 7		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Body Weight g	187	11.9	5	199	11.9	5	183	2.5	5
Brain g	1.75	0.050	5	1.78	0.084	5	1.73	0.033	5
Brain/Body Weight %x10	9.40	0.501	5	8.97	0.806	5	9.42	0.203	5
Adrenal mg	62	9.1	5	57	17.3	5	59	12.3	5
Adrenal/Body Weight %x10^{3}	33.4	6.82	5	28.5	8.33	5	32.2	6.83	5
Adrenal/Brain Weight %	3.54	0.606	5	3.21	0.998	5	3.43	0.769	5
Heart g	0.65	0.045	5	0.71	0.100	5	0.70	0.148	5
Heart/Body Weight %x10	3.50	0.269	5	3.56	0.437	5	3.80	0.819	5
Heart/Brain Weight %x10^{-1}	3.73	0.252	5	3.98	0.482	5	4.03	0.796	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont.

Females: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Kidney g	1.33	0.091	5	1.35	0.125	5	1.25	0.082	5	1.15	0.441	5
Kidney/Body Weight %x10	6.81	0.190	5	6.95	0.399	5	6.65	0.205	5	5.71	2.133	5
Kidney/Brain Weight %x10^{-2}	0.75	0.053	5	0.78	0.077	5	0.72	0.075	5	0.65	0.248	5
Liver g	6.20	0.329	5	6.08	0.679	5	5.87	0.323	5	6.14	0.507	5
Liver/Body Weight %	3.18	0.183	5	3.14	0.176	5	3.12	0.114	5	3.08	0.126	5
Liver/Brain Weight %x10^{-2}	3.48	0.153	5	3.51	0.400	5	3.35	0.267	5	3.50	0.288	5
Lung/Trachea g	0.93	0.079	5	0.96	0.042	5	0.98	0.106	5	1.00	0.129	5
Lung/Trachea/ Body Weight %x10	4.74	0.384	5	4.97	0.515	5	5.22	0.468	5	5.05	0.585	5
Lung/Trachea/ Brain Weight %x10^{-1}	5.19	0.479	5	5.53	0.406	5	5.63	0.806	5	5.72	0.641	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Recovery Sacrifice

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Kidney g	1.31	0.166	5	1.33	0.089	5	1.27	0.020	5
Kidney/Body Weight %x10	6.98	0.499	5	6.69	0.345	5	6.92	0.056	5
Kidney/Brain Weight $\%x10^{-2}$	0.75	0.079	5	0.75	0.050	5	0.74	0.014	5
Liver g	5.84	0.640	5	6.18	0.801	5	5.70	0.305	5
Liver/Body Weight %	3.12	0.226	5	3.10	0.233	5	3.11	0.163	5
Liver/Brain Weight $\%x10^{-2}$	3.33	0.386	5	3.49	0.520	5	3.30	0.128	5
Lung/Trachea g	1.08	0.120	5	1.59[2]	0.127	5	2.45[2]	0.120	5
Lung/Trachea/ Body Weight %x10	5.75[1]	0.315	5	8.02[2]	0.750	5	13.34[2]	0.614	5
Lung/Trachea/ Brain Weight $\%x10^{-1}$	6.15	0.664	5	8.96[2]	0.751	5	14.16[2]	0.534	5

683-002

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the control group; $p \leq 0.05$ [2]Significantly different from the control group; $p \leq 0.01$

Table 11 Cont. Females: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 1			Group 2			Group 3			Group 4		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
Ovary mg	124	10.4	5	129	20.0	5	132	19.3	5	118	15.9	5
Ovary/Body Weight $\%x10^{2}$	6.36	0.767	5	6.67	1.100	5	7.00	0.946	5	5.95	0.742	5
Ovary/Brain Weight %	6.95	0.626	5	7.46	1.338	5	7.51	1.089	5	6.74	0.918	5
Spleen g	0.51	0.025	5	0.49	0.016	5	0.54	0.061	5	0.51	0.061	5
Spleen/Body Weight %x10	2.61	0.077	5	2.52	0.176	5	2.87	0.220	5	2.59	0.230	5
Spleen/Brain Weight $\%x10^{-1}$	2.86	0.175	5	2.81	0.144	5	3.09	0.450	5	2.93	0.323	5
Thyroid/Parathyroid mg	16	2.3	5	15	1.6	5	16	2.6	5	15	2.9	5
Thyroid/Parathyroid/ Body Weight $\%x10^{3}$	8.33	1.080	5	7.74	0.598	5	8.45	1.433	5	7.32	1.506	5
Thyroid/Parathyroid/ Brain Weight %x10	9.1	1.13	5	8.7	1.02	5	9.1	1.56	5	8.3	1.75	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 11 Cont. Females: Summary of Organ Weight Values - Recovery Sacrifice*

Parameters Measured	Group 5 Mean	Group 5 S.D.	Group 5 N	Group 6 Mean	Group 6 S.D.	Group 6 N	Group 7 Mean	Group 7 S.D.	Group 7 N
Ovary mg	114	11.4	5	188	139.3	5	122	23.3	5
Ovary/Body Weight %x10^{2}	6.10	0.431	5	9.37	6.671	5	6.64	1.343	5
Ovary/Brain Weight %	6.50	0.619	5	10.80	8.506	5	7.05	1.397	5
Spleen g	0.50	0.085	5	0.52	0.039	5	0.52	0.052	5
Spleen/Body Weight %x10	2.67	0.308	5	2.60	0.128	5	2.84	0.267	5
Spleen/Brain Weight %x10^{-1}	2.86	0.473	5	2.91	0.222	5	3.02	0.269	5
Thyroid/Parathyroid mg	14	2.2	5	13	2.8	5	15	1.1	5
Thyroid/Parathyroid/ Body Weight %x10^{3}	7.32	1.050	5	6.69	1.547	5	8.11	0.530	5
Thyroid/Parathyroid/ Brain Weight %x10	7.8	1.27	5	7.4	1.54	5	8.6	0.57	5

683-002

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

Table 12

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
NUMBER OF ANIMALS EXAMINED	0	10	0	10	0	10	0	10	0	10	0	10
NUMBER WITHIN NORMAL LIMITS	0	0	0	0	0	0	0	0	0	0	0	0
Adrenal Gland, Cortex	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Adrenal Gland, Medulla	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Artery, Aorta	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Bone Marrow, Femur	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Bone, Femur	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Brain	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Epididymis	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	9	0	0	0	0	0	10	0	0	0	0
Lumenal debris, cellular, mild	0	1	0	0	0	0	0	0	0	0	0	0
Esophagus	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 7 DOS	 SAC
NUMBER OF ANIMALS EXAMINED	1	10
NUMBER WITHIN NORMAL LIMITS	0	0
Adrenal Gland, Cortex	(1)	(10)
Within normal limits	1	10
Adrenal Gland, Medulla	(1)	(10)
Within normal limits	1	10
Artery, Aorta	(1)	(10)
Within normal limits	1	10
Bone Marrow, Femur	(1)	(10)
Within normal limits	1	10
Bone, Femur	(1)	(10)
Within normal limits	1	10
Brain	(1)	(10)
Within normal limits	1	10
Epididymis	(1)	(10)
Within normal limits	1	10
Lumenal debris, cellular, mild	0	0
Esophagus	(1)	(10)
Within normal limits	1	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Eye		(0)	(10)	(0)	(0)	(0)	(1)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	1	0	10	0	0	0	0
Eye, Optic Nerve		(0)	(10)	(0)	(0)	(0)	(1)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	1	0	10	0	0	0	0
Harderian Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	10	0	0	0	0
Hemorrhage,		0	1	0	0	0	0	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
	-moderate	0	1	0	0	0	0	0	0	0	0	0	0
Heart		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	5	0	0	0	0	0	6	0	0	0	0
Cardiomyopathy, trace		0	5	0	0	0	0	0	4	0	0	0	0
Kidney		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	0	0	0	0	1	0	0	0	0	0	1
Microconcretion,		0	10	0	10	0	9	0	10	0	10	0	9
	-trace	0	7	0	8	0	9	0	8	0	10	0	9
	-mild	0	3	0	2	0	0	0	2	0	0	0	0
Regeneration, tubular, trace		0	3	0	4	0	0	0	4	0	0	0	0
Lacrimal Gland, Exorbital		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Eye		(1)	(10)
Within normal limits		1	10
Eye, Optic Nerve		(1)	(10)
Within normal limits		1	10
Harderian Gland		(1)	(10)
Within normal limits		1	9
Hemorrhage,		0	1
	-mild	0	1
	-moderate	0	0
Heart		(1)	(10)
Within normal limits		1	8
Cardiomyopathy, trace		0	2
Kidney		(1)	(10)
Within normal limits		0	0
Microconcretion,		1	10
	-trace	0	10
	-mild	1	0
Regeneration, tubular, trace		0	1
Lacrimal Gland, Exorbital		(1)	(10)
Within normal limits		1	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Large Intestine, Cecum		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Inflammation, acute, mild		0	0	0	0	0	0	0	0	0	0	0	0
Large Intestine, Colon		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Large Intestine, Rectum		(0)	(9)	(0)	(0)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	9	0	0	0	0
Larynx		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	3	0	3	0	1	0	3	0	3	0	0
Inflammation, chronic,		0	3	0	3	0	5	0	4	0	0	0	0
	-trace	0	3	0	3	0	4	0	4	0	0	0	0
	-mild	0	0	0	0	0	1	0	0	0	0	0	0
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Mineralization,		0	6	0	6	0	8	0	7	0	7	0	7
	-trace	0	2	0	5	0	5	0	7	0	5	0	2
	-mild	0	4	0	1	0	3	0	0	0	2	0	5
Exudate, mucoid, mild		0	0	0	0	0	0	0	0	0	0	0	0
Foreign material,		0	0	0	0	0	0	0	0	0	2	0	8
	-trace	0	0	0	0	0	0	0	0	0	1	0	6
	-mild	0	0	0	0	0	0	0	0	0	1	0	2
Hyperplasia, epithelial, mild		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	0	0	0	0	0	3	0	10
	-trace	0	0	0	0	0	0	0	0	0	3	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	6
	-moderate	0	0	0	0	0	0	0	0	0	0	0	3
Inflammation, suppurative, mild		0	0	0	0	0	1	0	0	0	1	0	1
Lumenal debris, cellular, moderate		0	0	0	0	0	0	0	0	0	0	0	0
Ulcer, mild		0	0	0	0	0	0	0	0	0	0	0	0
Foreign material, lumen, moderate		0	0	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Large Intestine, Cecum		(1)	(10)
Within normal limits		1	9
Inflammation, acute, mild		0	1
Large Intestine, Colon		(1)	(10)
Within normal limits		1	10
Large Intestine, Rectum		(1)	(10)
Within normal limits		1	10
Larynx		(1)	(10)
Within normal limits		0	0
Inflammation, chronic,		1	0
	-trace	0	0
	-mild	0	0
	-moderate	1	0
Mineralization,		0	4
	-trace	0	4
	-mild	0	0
Exudate, mucoid, mild		0	1
Foreign material,		0	9
	-trace	0	9
	-mild	0	0
Hyperplasia, epithelial, mild		1	0
Inflammation, granulomatous,		0	10
	-trace	0	3
	-mild	0	6
	-moderate	0	1
Inflammation, suppurative, mild		0	0
Lumenal debris, cellular, moderate		1	0
Ulcer, mild		0	1
Foreign material, lumen, moderate		1	0

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1 DOS	Group 1 SAC	Group 2 DOS	Group 2 SAC	Group 3 DOS	Group 3 SAC	Group 4 DOS	Group 4 SAC	Group 5 DOS	Group 5 SAC	Group 6 DOS	Group 6 SAC
Liver		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	9	0	10	0	10	0	10	0	10	0	10
Infiltration, mononuclear cell, trace		0	1	0	0	0	0	0	0	0	0	0	0
Lung		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Infiltration, lymphocytic,		0	10	0	10	0	9	0	10	0	10	0	9
	-trace	0	5	0	2	0	1	0	0	0	2	0	1
	-mild	0	5	0	8	0	8	0	10	0	8	0	8
Inflammation, chronic,		0	0	0	0	0	0	0	0	0	10	0	10
	-trace	0	0	0	0	0	0	0	0	0	1	0	0
	-mild	0	0	0	0	0	0	0	0	0	9	0	10
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Foreign material,		0	0	0	0	0	0	0	0	0	0	0	9
	-trace	0	0	0	0	0	0	0	0	0	0	0	8
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Histiocytosis,		0	0	0	0	0	0	0	0	0	0	0	7
	-trace	0	0	0	0	0	0	0	0	0	0	0	6
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Hyperplasia, septal cell,		0	0	0	0	0	0	0	10	0	10	0	8
	-trace	0	0	0	0	0	0	0	3	0	4	0	0
	-mild	0	0	0	0	0	0	0	7	0	6	0	8
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	0	0	0	0	0	0	0	9
	-trace	0	0	0	0	0	0	0	0	0	0	0	8
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Inflammation, interstitial, chronic,		0	0	0	0	0	4	0	10	0	10	0	10
	-trace	0	0	0	0	0	4	0	7	0	10	0	2
	-mild	0	0	0	0	0	0	0	3	0	0	0	8
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Lumenal debris, cellular, mild		0	0	0	0	0	1	0	0	0	0	0	0
Macrophages, alveolar,		0	0	0	0	0	0	0	0	0	10	0	10
	-trace	0	0	0	0	0	0	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	0	0	10	0	6
	-moderate	0	0	0	0	0	0	0	0	0	0	0	4
	-severe	0	0	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Liver		(1)	(10)
Within normal limits		1	10
Infiltration, mononuclear cell, trace		0	0
Lung		(1)	(10)
Infiltration, lymphocytic,		1	9
	-trace	0	3
	-mild	1	6
Inflammation, chronic,		1	10
	-trace	0	1
	-mild	1	5
	-moderate	0	4
Foreign material,		1	9
	-trace	1	7
	-mild	0	2
Histiocytosis,		0	0
	-trace	0	0
	-mild	0	0
Hyperplasia, septal cell,		0	10
	-trace	0	2
	-mild	0	6
	-moderate	0	2
Inflammation, granulomatous,		1	9
	-trace	0	4
	-mild	1	5
Inflammation, interstitial, chronic,		1	10
	-trace	0	1
	-mild	1	7
	-moderate	0	2
Lumenal debris, cellular, mild		0	0
Macrophages, alveolar,		1	10
	-trace	1	0
	-mild	0	1
	-moderate	0	8
	-severe	0	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Lung (Continued)		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Macrophages, pigmented,		0	0	0	10	0	10	0	10	0	0	0	0
	-trace	0	0	0	10	0	4	0	0	0	0	0	0
	-mild	0	0	0	0	0	6	0	10	0	0	0	0
Metaplasia, osseous, trace		0	0	0	0	0	0	0	1	0	0	0	0
Mineralization, vascular,		0	10	0	8	0	6	0	5	0	7	0	8
	-trace	0	10	0	7	0	5	0	5	0	5	0	6
	-mild	0	0	0	1	0	1	0	0	0	2	0	2
Pigment, black,		0	0	0	10	0	9	0	3	0	0	0	0
	-trace	0	0	0	10	0	7	0	1	0	0	0	0
	-mild	0	0	0	0	0	2	0	2	0	0	0	0
Lymph Node, Mandibular		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	8	0	6	0	6	0	5	0	4	0	6
Hemorrhage,		0	0	0	0	0	0	0	0	0	0	0	0
	-trace	0	0	0	0	0	0	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Erythrophagocytosis, mild		0	0	0	1	0	1	0	1	0	0	0	0
Hyperplasia, lymphoid, mild		0	0	0	0	0	1	0	0	0	0	0	0
Plasmacytosis, medullary,		0	2	0	3	0	2	0	4	0	6	0	4
	-trace	0	0	0	2	0	0	0	0	0	0	0	0
	-mild	0	2	0	1	0	0	0	3	0	4	0	3
	-moderate	0	0	0	0	0	2	0	1	0	2	0	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Lung (Continued)		(1)	(10)
Macrophages, pigmented,		0	0
	-trace	0	0
	-mild	0	0
Metaplasia, osseous, trace		0	0
Mineralization, vascular,		0	3
	-trace	0	2
	-mild	0	1
Pigment, black,		0	0
	-trace	0	0
	-mild	0	0
Lymph Node, Mandibular		(1)	(10)
Within normal limits		1	3
Hemorrhage,		0	4
	-trace	0	1
	-mild	0	3
Erythrophagocytosis, mild		0	0
Hyperplasia, lymphoid, mild		0	0
Plasmacytosis, medullary,		0	4
	-trace	0	0
	-mild	0	3
	-moderate	0	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Lymph Node, Mediastinal		(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	8	0	8	0	5	0	0	0	3	0	0
Hemorrhage, mild		0	1	0	0	0	0	0	0	0	0	0	0
Histiocytosis,		0	0	0	0	0	0	0	0	0	7	0	10
	-trace	0	0	0	0	0	0	0	0	0	2	0	1
	-mild	0	0	0	0	0	0	0	0	0	5	0	8
	-moderate	0	0	0	0	0	0	0	0	0	0	0	1
Hyperplasia, lymphoid,		0	0	0	0	0	3	0	8	0	5	0	9
	-trace	0	0	0	0	0	3	0	1	0	5	0	6
	-mild	0	0	0	0	0	0	0	7	0	0	0	3
Pigment, black,		0	0	0	2	0	5	0	10	0	0	0	0
	-trace	0	0	0	2	0	3	0	1	0	0	0	0
	-mild	0	0	0	0	0	2	0	9	0	0	0	0
Lymph Node, Mesenteric		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Nasal Tissue A		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	8	0	9
Exudate, suppurative, trace		0	0	0	0	0	0	0	0	0	0	0	1
Exudate, mucoid, trace		0	0	0	0	0	0	0	0	0	2	0	1
Nasal Tissue B		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	4	0	5
Inflammation, acute,		0	0	0	0	0	0	0	0	0	0	0	1
	-trace	0	0	0	0	0	0	0	0	0	0	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	1	0	3
	-trace	0	0	0	0	0	0	0	0	0	1	0	2
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	6	0	5
	-trace	0	0	0	0	0	0	0	0	0	6	0	3
	-mild	0	0	0	0	0	0	0	0	0	0	0	2
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Lymph Node, Mediastinal		(1)	(10)
Within normal limits		1	0
Hemorrhage, mild		0	0
Histiocytosis,		0	10
	-trace	0	1
	-mild	0	9
	-moderate	0	0
Hyperplasia, lymphoid,		0	10
	-trace	0	6
	-mild	0	4
Pigment, black,		0	0
	-trace	0	0
	-mild	0	0
Lymph Node, Mesenteric		(1)	(10)
Within normal limits		1	10
Nasal Tissue A		(1)	(10)
Within normal limits		1	6
Exudate, suppurative, trace		0	4
Exudate, mucoid, trace		0	4
Nasal Tissue B		(1)	(10)
Within normal limits		0	3
Inflammation, acute,		0	3
	-trace	0	1
	-mild	0	2
Exudate, suppurative,		0	7
	-trace	0	4
	-mild	0	2
	-moderate	0	1
Exudate, mucoid,		1	7
	-trace	1	4
	-mild	0	2
	-moderate	0	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Nasal Tissue C		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	0	0	0
Inflammation, acute, trace		0	0	0	0	0	0	0	0	0	0	0	2
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	0	0	9
	-trace	0	0	0	0	0	0	0	0	0	0	0	4
	-mild	0	0	0	0	0	0	0	0	0	0	0	5
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	10	0	10
	-trace	0	0	0	0	0	0	0	0	0	10	0	2
	-mild	0	0	0	0	0	0	0	0	0	0	0	8
Nasal Tissue D		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	5	0	4
Exudate, suppurative, trace		0	0	0	0	0	0	0	0	0	1	0	4
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	5	0	6
	-trace	0	0	0	0	0	0	0	0	0	5	0	5
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Nerve, Sciatic		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Pancreas		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	9	0	0	0	0
Atrophy, mild		0	0	0	0	0	0	0	1	0	0	0	0
Parathyroid Gland		(0)	(8)	(0)	(0)	(0)	(0)	(0)	(8)	(0)	(0)	(0)	(0)
Within normal limits		0	8	0	0	0	0	0	8	0	0	0	0
Pituitary Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Nasal Tissue C		(1)	(10)
Within normal limits		1	0
Inflammation, acute, trace		0	1
Exudate, suppurative,		0	10
	-trace	0	6
	-mild	0	4
Exudate, mucoid,		0	10
	-trace	0	5
	-mild	0	5
Nasal Tissue D		(1)	(10)
Within normal limits		1	4
Exudate, suppurative, trace		0	5
Exudate, mucoid,		0	6
	-trace	0	6
	-mild	0	0
Nerve, Sciatic		(1)	(10)
Within normal limits		1	10
Pancreas		(1)	(10)
Within normal limits		1	10
Atrophy, mild		0	0
Parathyroid Gland		(1)	(5)
Within normal limits		1	5
Pituitary Gland		(1)	(10)
Within normal limits		1	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Prostate Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	8	0	0	0	0
Inflammation, chronic,		0	1	0	0	0	0	0	1	0	0	0	0
	-mild	0	1	0	0	0	0	0	0	0	0	0	0
	-moderate	0	0	0	0	0	0	0	1	0	0	0	0
Inflammation, subacute, mild		0	0	0	0	0	0	0	1	0	0	0	0
Salivary Gland, Mandibular		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Salivary Gland, Sublingual		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Seminal Vesicle		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Skeletal Muscle, Thigh		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Skin		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Small Intestine, Duodenum		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Small Intestine, Ileum		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Prostate Gland		(1)	(10)
Within normal limits		1	10
Inflammation, chronic,		0	0
	-mild	0	0
	-moderate	0	0
Inflammation, subacute, mild		0	0
Salivary Gland, Mandibular		(1)	(10)
Within normal limits		1	10
Salivary Gland, Sublingual		(1)	(10)
Within normal limits		1	10
Seminal Vesicle		(1)	(10)
Within normal limits		1	10
Skeletal Muscle, Thigh		(1)	(10)
Within normal limits		1	10
Skin		(1)	(10)
Within normal limits		1	10
Small Intestine, Duodenum		(1)	(10)
Within normal limits		1	10
Small Intestine, Ileum		(1)	(10)
Within normal limits		1	10

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Small Intestine, Jejunum	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Cervical	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Lumbar	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Thoracic	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spleen	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Stomach, Glandular	(0)	(10)	(0)	(1)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	9	0	0	0	0
Mineralization, trace	0	0	0	0	0	0	0	1	0	0	0	0
Ulcer, mild	0	0	0	1	0	0	0	0	0	0	0	0
Stomach, Nonglandular	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Tail	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Acanthosis, mild	0	0	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis, mild	0	0	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION	Group 7 DOS	 SAC
Small Intestine, Jejunum	(1)	(10)
Within normal limits	1	10
Spinal Cord, Cervical	(1)	(10)
Within normal limits	1	10
Spinal Cord, Lumbar	(1)	(10)
Within normal limits	1	10
Spinal Cord, Thoracic	(1)	(10)
Within normal limits	1	10
Spleen	(1)	(10)
Within normal limits	1	10
Stomach, Glandular	(1)	(10)
Within normal limits	1	9
Mineralization, trace	0	1
Ulcer, mild	0	0
Stomach, Nonglandular	(1)	(10)
Within normal limits	1	10
Tail	(0)	(1)
Acanthosis, mild	0	1
Hyperkeratosis, mild	0	1

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Testis		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	7	0	0	0	0	0	6	0	0	0	0
Degeneration, tubular,		0	2	0	0	0	0	0	2	0	0	0	0
	-trace	0	1	0	0	0	0	0	2	0	0	0	0
	-moderate	0	1	0	0	0	0	0	0	0	0	0	0
Mineralization, trace		0	2	0	0	0	0	0	2	0	0	0	0
Thymus Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	8	0	0	0	0
Hemorrhage,		0	0	0	0	0	0	0	2	0	0	0	0
	-trace	0	0	0	0	0	0	0	1	0	0	0	0
	-mild	0	0	0	0	0	0	0	1	0	0	0	0
Necrosis, lymphoid, trace		0	0	0	0	0	0	0	0	0	0	0	0
Thyroid Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	10	0	0	0	0
Cyst, ultimobranchial, trace		0	1	0	0	0	0	0	0	0	0	0	0
Trachea		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	9	0	8	0	9	0	7	0	9	0	6
Inflammation, chronic,		0	1	0	2	0	0	0	3	0	0	0	4
	-trace	0	1	0	2	0	0	0	3	0	0	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	3
Mineralization, trace		0	0	0	0	0	0	0	0	0	1	0	0
Lumenal debris, cellular, trace		0	0	0	0	0	1	0	0	0	0	0	0
Pigment, black, trace		0	0	0	1	0	1	0	1	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Testis		(1)	(10)
Within normal limits		1	8
Degeneration, tubular,		0	1
	-trace	0	1
	-moderate	0	0
Mineralization, trace		0	1
Thymus Gland		(1)	(10)
Within normal limits		1	9
Hemorrhage,		0	0
	-trace	0	0
	-mild	0	0
Necrosis, lymphoid, trace		0	1
Thyroid Gland		(1)	(10)
Within normal limits		1	10
Cyst, ultimobranchial, trace		0	0
Trachea		(1)	(10)
Within normal limits		0	9
Inflammation, chronic,		1	0
	-trace	1	0
	-mild	0	0
Mineralization, trace		0	0
Lumenal debris, cellular, trace		1	1
Pigment, black, trace		0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Trachea, Bifurcation		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	5	0	5	0	4	0	2	0	6	0	8
Infiltration, lymphocytic,		0	5	0	4	0	6	0	5	0	3	0	2
	-trace	0	5	0	2	0	2	0	4	0	0	0	0
	-mild	0	0	0	2	0	4	0	1	0	3	0	2
Mineralization,		0	1	0	1	0	3	0	4	0	1	0	1
	-trace	0	1	0	1	0	2	0	4	0	1	0	0
	-mild	0	0	0	0	0	1	0	0	0	0	0	1
Pigment, black, trace		0	0	0	3	0	6	0	5	0	0	0	0
Urinary Bladder		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Zymbal's Gland		(0)	(5)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	5	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Trachea, Bifurcation		(1)	(10)
Within normal limits		1	8
Infiltration, lymphocytic,		0	2
	-trace	0	2
	-mild	0	0
Mineralization,		0	0
	-trace	0	0
	-mild	0	0
Pigment, black, trace		0	0
Urinary Bladder		(1)	(10)
Within normal limits		1	10
Zymbal's Gland		(0)	(10)
Within normal limits		0	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
NUMBER OF ANIMALS EXAMINED	0	10	0	10	0	10	0	10	0	10	0	10
NUMBER WITHIN NORMAL LIMITS	0	0	0	0	0	0	0	0	0	0	0	0
Adrenal Gland, Cortex	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Adrenal Gland, Medulla	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Artery, Aorta	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Bone Marrow, Femur	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Bone, Femur	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Brain	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Esophagus	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Eye	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(1)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	1	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 7 DOS	 SAC
NUMBER OF ANIMALS EXAMINED	0	10
NUMBER WITHIN NORMAL LIMITS	0	0
Adrenal Gland, Cortex	(0)	(10)
Within normal limits	0	10
Adrenal Gland, Medulla	(0)	(10)
Within normal limits	0	10
Artery, Aorta	(0)	(10)
Within normal limits	0	10
Bone Marrow, Femur	(0)	(10)
Within normal limits	0	10
Bone, Femur	(0)	(10)
Within normal limits	0	10
Brain	(0)	(10)
Within normal limits	0	10
Esophagus	(0)	(10)
Within normal limits	0	10
Eye	(0)	(10)
Within normal limits	0	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Eye, Optic Nerve		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	9	0	0	0	0
Harderian Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Heart		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	8	0	0	0	0	0	9	0	0	0	0
Cardiomyopathy, trace		0	2	0	0	0	0	0	1	0	0	0	0
Kidney		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	1	0	0	0	1	0	0	0	1	0	0
Mineralization, trace		0	0	0	0	0	0	0	0	0	1	0	0
Microconcretion,		0	9	0	10	0	9	0	10	0	8	0	10
	-trace	0	9	0	9	0	8	0	10	0	8	0	10
	-mild	0	0	0	1	0	1	0	0	0	0	0	0
Lacrimal Gland, Exorbital		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Large Intestine, Cecum		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Large Intestine, Colon		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Eye, Optic Nerve		(0)	(9)
Within normal limits		0	9
Harderian Gland		(0)	(10)
Within normal limits		0	10
Heart		(0)	(10)
Within normal limits		0	9
Cardiomyopathy, trace		0	1
Kidney		(0)	(10)
Within normal limits		0	1
Mineralization, trace		0	0
Microconcretion,		0	9
	-trace	0	9
	-mild	0	0
Lacrimal Gland, Exorbital		(0)	(10)
Within normal limits		0	10
Large Intestine, Cecum		(0)	(10)
Within normal limits		0	10
Large Intestine, Colon		(0)	(10)
Within normal limits		0	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Large Intestine, Rectum		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Larynx		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	4	0	3	0	5	0	7	0	3	0	0
Inflammation, chronic,		0	3	0	4	0	1	0	1	0	0	0	1
	-trace	0	3	0	4	0	1	0	0	0	0	0	1
	-mild	0	0	0	0	0	0	0	1	0	0	0	0
Mineralization,		0	5	0	5	0	4	0	3	0	7	0	5
	-trace	0	4	0	3	0	4	0	3	0	6	0	4
	-mild	0	1	0	2	0	0	0	0	0	1	0	1
Necrosis, trace		0	0	0	0	0	0	0	0	0	0	0	0
Foreign material,		0	0	0	0	0	0	0	0	0	2	0	5
	-trace	0	0	0	0	0	0	0	0	0	1	0	4
	-mild	0	0	0	0	0	0	0	0	0	1	0	1
Hyperplasia, epithelial, trace		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	0	0	0	0	0	6	0	10
	-trace	0	0	0	0	0	0	0	0	0	3	0	5
	-mild	0	0	0	0	0	0	0	0	0	3	0	3
	-moderate	0	0	0	0	0	0	0	0	0	0	0	2
Inflammation, suppurative, trace		0	0	0	0	0	0	0	0	0	1	0	0
Lumenal debris, cellular,		0	0	0	0	0	0	0	1	0	1	0	1
	-trace	0	0	0	0	0	0	0	0	0	0	0	0
	-mild	0	0	0	0	0	0	0	1	0	1	0	1
Foreign material, lumen,		0	0	0	0	0	0	0	0	0	0	0	5
	-trace	0	0	0	0	0	0	0	0	0	0	0	4
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Liver		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	9	0	10	0	10	0	10	0	10
Inflammation, chronic, trace		0	0	0	1	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Large Intestine, Rectum		(0)	(10)
Within normal limits		0	10
Larynx		(0)	(10)
Within normal limits		0	0
Inflammation, chronic,		0	0
	-trace	0	0
	-mild	0	0
Mineralization,		0	4
	-trace	0	3
	-mild	0	1
Necrosis, trace		0	1
Foreign material,		0	8
	-trace	0	7
	-mild	0	1
Hyperplasia, epithelial, trace		0	1
Inflammation, granulomatous,		0	10
	-trace	0	2
	-mild	0	8
	-moderate	0	0
Inflammation, suppurative, trace		0	0
Lumenal debris, cellular,		0	1
	-trace	0	1
	-mild	0	0
Foreign material, lumen,		0	0
	-trace	0	0
	-mild	0	0
Liver		(0)	(10)
Within normal limits		0	10
Inflammation, chronic, trace		0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Lung		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Infiltration, lymphocytic,		0	10	0	9	0	10	0	10	0	10	0	10
	-trace	0	5	0	4	0	0	0	0	0	2	0	3
	-mild	0	5	0	5	0	10	0	10	0	8	0	7
Inflammation, chronic,		0	0	0	0	0	0	0	0	0	10	0	10
	-trace	0	0	0	0	0	0	0	0	0	4	0	4
	-mild	0	0	0	0	0	0	0	0	0	6	0	5
	-moderate	0	0	0	0	0	0	0	0	0	0	0	1
Foreign material,		0	0	0	0	0	0	0	0	0	4	0	8
	-trace	0	0	0	0	0	0	0	0	0	4	0	6
	-mild	0	0	0	0	0	0	0	0	0	0	0	2
Histiocytosis,		0	0	0	0	0	0	0	0	0	4	0	6
	-trace	0	0	0	0	0	0	0	0	0	3	0	6
	-mild	0	0	0	0	0	0	0	0	0	1	0	0
Hyperplasia, septal cell,		0	0	0	0	0	5	0	10	0	10	0	5
	-trace	0	0	0	0	0	4	0	2	0	2	0	3
	-mild	0	0	0	0	0	1	0	8	0	8	0	2
	-moderate	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	0	0	0	0	0	4	0	7
	-trace	0	0	0	0	0	0	0	0	0	4	0	6
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Inflammation, interstitial, chronic,		0	0	0	0	0	6	0	10	0	10	0	10
	-trace	0	0	0	0	0	5	0	10	0	7	0	3
	-mild	0	0	0	0	0	1	0	0	0	3	0	7
Lumenal debris, cellular,		0	1	0	0	0	1	0	0	0	0	0	1
	-trace	0	1	0	0	0	0	0	0	0	0	0	1
	-mild	0	0	0	0	0	1	0	0	0	0	0	0
Macrophages, alveolar,		0	0	0	0	0	0	0	0	0	10	0	10
	-mild	0	0	0	0	0	0	0	0	0	9	0	5
	-moderate	0	0	0	0	0	0	0	0	0	1	0	5
Macrophages, pigmented,		0	0	0	10	0	10	0	10	0	0	0	0
	-trace	0	0	0	10	0	7	0	0	0	0	0	0
	-mild	0	0	0	0	0	3	0	10	0	0	0	0
Metaplasia, osseous, trace		0	0	0	0	0	1	0	0	0	0	0	1
Mineralization, vascular,		0	7	0	7	0	5	0	5	0	6	0	4
	-trace	0	7	0	6	0	4	0	5	0	4	0	4
	-mild	0	0	0	1	0	1	0	0	0	2	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Lung		(0)	(10)
Infiltration, lymphocytic,		0	10
	-trace	0	4
	-mild	0	6
Inflammation, chronic,		0	10
	-trace	0	0
	-mild	0	8
	-moderate	0	2
Foreign material,		0	10
	-trace	0	6
	-mild	0	4
Histiocytosis,		0	0
	-trace	0	0
	-mild	0	0
Hyperplasia, septal cell,		0	10
	-trace	0	1
	-mild	0	8
	-moderate	0	1
Inflammation, granulomatous,		0	10
	-trace	0	2
	-mild	0	8
Inflammation, interstitial, chronic,		0	10
	-trace	0	1
	-mild	0	9
Lumenal debris, cellular,		0	0
	-trace	0	0
	-mild	0	0
Macrophages, alveolar,		0	10
	-mild	0	4
	-moderate	0	6
Macrophages, pigmented,		0	0
	-trace	0	0
	-mild	0	0
Metaplasia, osseous, trace		0	1
Mineralization, vascular,		0	8
	-trace	0	7
	-mild	0	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Lung (Continued)		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Pigment, black,		0	0	0	9	0	10	0	10	0	0	0	0
	-trace	0	0	0	9	0	9	0	9	0	0	0	0
	-mild	0	0	0	0	0	1	0	1	0	0	0	0
Lymph Node, Mandibular		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	8	0	5	0	6	0	5	0	5	0	6
Hemorrhage, mild		0	0	0	1	0	0	0	0	0	0	0	0
Erythrophagocytosis, mild		0	0	0	0	0	0	0	1	0	0	0	0
Hyperplasia, lymphoid,		0	0	0	1	0	0	0	0	0	1	0	0
	-mild	0	0	0	0	0	0	0	0	0	1	0	0
	-moderate	0	0	0	1	0	0	0	0	0	0	0	0
Plasmacytosis, medullary,		0	2	0	4	0	4	0	4	0	4	0	4
	-mild	0	2	0	4	0	2	0	4	0	3	0	3
	-moderate	0	0	0	0	0	2	0	0	0	1	0	1
Lymph Node, Mediastinal		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	5	0	0	0	0	0	0	0	1
Hemorrhage,		0	0	0	2	0	0	0	0	0	1	0	0
	-mild	0	0	0	1	0	0	0	0	0	0	0	0
	-moderate	0	0	0	1	0	0	0	0	0	1	0	0
Erythrophagocytosis, mild		0	0	0	0	0	0	0	0	0	0	0	1
Histiocytosis,		0	0	0	0	0	0	0	0	0	9	0	8
	-trace	0	0	0	0	0	0	0	0	0	1	0	1
	-mild	0	0	0	0	0	0	0	0	0	8	0	5
	-moderate	0	0	0	0	0	0	0	0	0	0	0	2
Hyperplasia, lymphoid,		0	0	0	3	0	9	0	9	0	9	0	7
	-trace	0	0	0	3	0	9	0	3	0	7	0	0
	-mild	0	0	0	0	0	0	0	6	0	2	0	7
Pigment, black,		0	0	0	2	0	10	0	10	0	0	0	0
	-trace	0	0	0	2	0	9	0	0	0	0	0	0
	-mild	0	0	0	0	0	1	0	10	0	0	0	0

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Lung (Continued)		(0)	(10)
Pigment, black,		0	0
	-trace	0	0
	-mild	0	0
Lymph Node, Mandibular		(0)	(10)
Within normal limits		0	6
Hemorrhage, mild		0	0
Erythrophagocytosis, mild		0	0
Hyperplasia, lymphoid,		0	0
	-mild	0	0
	-moderate	0	0
Plasmacytosis, medullary,		0	4
	-mild	0	3
	-moderate	0	1
Lymph Node, Mediastinal		(0)	(10)
Within normal limits		0	1
Hemorrhage,		0	0
	-mild	0	0
	-moderate	0	0
Erythrophagocytosis, mild		0	0
Histiocytosis,		0	9
	-trace	0	2
	-mild	0	7
	-moderate	0	0
Hyperplasia, lymphoid,		0	9
	-trace	0	1
	-mild	0	8
Pigment, black,		0	0
	-trace	0	0
	-mild	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Lymph Node, Mesenteric		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	9	0	0	0	0
Histiocytosis, trace		0	0	0	0	0	0	0	1	0	0	0	0
Mammary Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Nasal Tissue A		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	8	0	8
Inflammation, acute, trace		0	0	0	0	0	0	0	0	0	0	0	0
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	1	0	2
	-trace	0	0	0	0	0	0	0	0	0	1	0	2
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	2	0	2
	-trace	0	0	0	0	0	0	0	0	0	2	0	2
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Nasal Tissue B		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	5	0	6
Inflammation, acute, trace		0	0	0	0	0	0	0	0	0	0	0	0
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	1	0	1
	-trace	0	0	0	0	0	0	0	0	0	1	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	5	0	4
	-trace	0	0	0	0	0	0	0	0	0	5	0	4
	-mild	0	0	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Lymph Node, Mesenteric		(0)	(10)
Within normal limits		0	9
Histiocytosis, trace		0	1
Mammary Gland		(0)	(10)
Within normal limits		0	10
Nasal Tissue A		(0)	(10)
Within normal limits		0	2
Inflammation, acute, trace		0	2
Exudate, suppurative,		0	7
	-trace	0	5
	-mild	0	2
Exudate, mucoid,		0	8
	-trace	0	6
	-mild	0	2
Nasal Tissue B		(0)	(10)
Within normal limits		0	1
Inflammation, acute, trace		0	5
Exudate, suppurative,		0	9
	-trace	0	3
	-mild	0	6
Exudate, mucoid,		0	9
	-trace	0	3
	-mild	0	6

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Nasal Tissue C		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	3	0	1
Inflammation, acute, trace		0	0	0	0	0	0	0	0	0	0	0	1
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	0	0	4
	-trace	0	0	0	0	0	0	0	0	0	0	0	3
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	7	0	9
	-trace	0	0	0	0	0	0	0	0	0	7	0	8
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Nasal Tissue D		(0)	(10)	(0)	(10)	(0)	(9)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	10	0	10	0	9	0	10	0	3	0	4
Inflammation, acute,		0	0	0	0	0	0	0	0	0	0	0	1
	-trace	0	0	0	0	0	0	0	0	0	0	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	0
Exudate, suppurative,		0	0	0	0	0	0	0	0	0	0	0	2
	-trace	0	0	0	0	0	0	0	0	0	0	0	1
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Exudate, mucoid,		0	0	0	0	0	0	0	0	0	7	0	6
	-trace	0	0	0	0	0	0	0	0	0	7	0	5
	-mild	0	0	0	0	0	0	0	0	0	0	0	1
Nerve, Sciatic		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Ovary		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(1)
Within normal limits		0	9	0	0	0	0	0	10	0	0	0	0
Cyst, mild		0	0	0	0	0	0	0	0	0	0	0	1
Hemorrhage, mild		0	0	0	0	0	0	0	0	0	0	0	1
Mineralization, trace		0	1	0	0	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Nasal Tissue C		(0)	(10)
Within normal limits		0	0
Inflammation, acute, trace		0	6
Exudate, suppurative,		0	10
	-trace	0	3
	-mild	0	7
Exudate, mucoid,		0	10
	-trace	0	3
	-mild	0	7
Nasal Tissue D		(0)	(10)
Within normal limits		0	2
Inflammation, acute,		0	2
	-trace	0	1
	-mild	0	1
Exudate, suppurative,		0	8
	-trace	0	5
	-mild	0	3
Exudate, mucoid,		0	8
	-trace	0	5
	-mild	0	3
Nerve, Sciatic		(0)	(10)
Within normal limits		0	10
Ovary		(0)	(10)
Within normal limits		0	10
Cyst, mild		0	0
Hemorrhage, mild		0	0
Mineralization, trace		0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Pancreas	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Parathyroid Gland	(0)	(8)	(0)	(0)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(0)
Within normal limits	0	8	0	0	0	0	0	9	0	0	0	0
Pituitary Gland	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Salivary Gland, Mandibular	(0)	(10)	(0)	(1)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Plasmacytosis, medullary, mild	0	0	0	1	0	0	0	0	0	0	0	0
Salivary Gland, Sublingual	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Skeletal Muscle, Thigh	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Skin	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Small Intestine, Duodenum	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 7 DOS	 SAC
Pancreas	(0)	(10)
Within normal limits	0	10
Parathyroid Gland	(0)	(10)
Within normal limits	0	10
Pituitary Gland	(0)	(10)
Within normal limits	0	10
Salivary Gland, Mandibular	(0)	(10)
Within normal limits	0	10
Plasmacytosis, medullary, mild	0	0
Salivary Gland, Sublingual	(0)	(10)
Within normal limits	0	10
Skeletal Muscle, Thigh	(0)	(10)
Within normal limits	0	10
Skin	(0)	(10)
Within normal limits	0	10
Small Intestine, Duodenum	(0)	(10)
Within normal limits	0	10

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Small Intestine, Ileum	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Small Intestine, Jejunum	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Cervical	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Lumbar	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spinal Cord, Thoracic	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Spleen	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Stomach, Glandular	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Stomach, Nonglandular	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits	0	10	0	0	0	0	0	10	0	0	0	0
Tail	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Within normal limits	0	0	0	1	0	0	0	0	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION	Group 7 DOS	 SAC
Small Intestine, Ileum	(0)	(10)
Within normal limits	0	10
Small Intestine, Jejunum	(0)	(10)
Within normal limits	0	10
Spinal Cord, Cervical	(0)	(10)
Within normal limits	0	10
Spinal Cord, Lumbar	(0)	(10)
Within normal limits	0	10
Spinal Cord, Thoracic	(0)	(10)
Within normal limits	0	10
Spleen	(0)	(10)
Within normal limits	0	10
Stomach, Glandular	(0)	(10)
Within normal limits	0	10
Stomach, Nonglandular	(0)	(10)
Within normal limits	0	10
Tail	(0)	(0)
Within normal limits	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Thymus Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	10	0	0	0	0
Hemorrhage,		0	1	0	0	0	0	0	0	0	0	0	0
	-trace	0	0	0	0	0	0	0	0	0	0	0	0
	-mild	0	1	0	0	0	0	0	0	0	0	0	0
Necrosis, lymphoid, trace		0	0	0	0	0	0	0	0	0	0	0	0
Thyroid Gland		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	7	0	0	0	0
Cyst, ultimobranchial, trace		0	0	0	0	0	0	0	1	0	0	0	0
Ectopic tissue, mild		0	0	0	0	0	0	0	2	0	0	0	0
Trachea		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	8	0	7	0	6	0	10	0	7	0	7
Inflammation, chronic,		0	2	0	3	0	2	0	0	0	3	0	3
	-trace	0	2	0	2	0	2	0	0	0	1	0	2
	-mild	0	0	0	1	0	0	0	0	0	2	0	1
Lumenal debris, cellular, trace		0	0	0	0	0	0	0	0	0	0	0	0
Macrophages, pigmented, trace		0	0	0	0	0	2	0	0	0	0	0	0
Pigment, black, trace		0	0	0	1	0	1	0	0	0	0	0	0
Trachea, Bifurcation		(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)	(0)	(10)
Within normal limits		0	5	0	5	0	5	0	7	0	10	0	8
Infiltration, lymphocytic,		0	5	0	5	0	4	0	2	0	0	0	2
	-trace	0	4	0	4	0	4	0	1	0	0	0	0
	-mild	0	1	0	1	0	0	0	1	0	0	0	2
Mineralization, trace		0	0	0	0	0	0	0	1	0	0	0	0
Histiocytosis, trace		0	0	0	0	0	0	0	0	0	0	0	1
Macrophages, pigmented,		0	0	0	0	0	2	0	0	0	0	0	0
	-trace	0	0	0	0	0	1	0	0	0	0	0	0
	-mild	0	0	0	0	0	1	0	0	0	0	0	0
Pigment, black, trace		0	0	0	4	0	2	0	1	0	0	0	0

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	 SAC
Thymus Gland		(0)	(10)
Within normal limits		0	6
Hemorrhage,		0	1
	-trace	0	1
	-mild	0	0
Necrosis, lymphoid, trace		0	3
Thyroid Gland		(0)	(10)
Within normal limits		0	10
Cyst, ultimobranchial, trace		0	0
Ectopic tissue, mild		0	0
Trachea		(0)	(10)
Within normal limits		0	7
Inflammation, chronic,		0	2
	-trace	0	1
	-mild	0	1
Lumenal debris, cellular, trace		0	2
Macrophages, pigmented, trace		0	0
Pigment, black, trace		0	0
Trachea, Bifurcation		(0)	(10)
Within normal limits		0	8
Infiltration, lymphocytic,		0	2
	-trace	0	2
	-mild	0	0
Mineralization, trace		0	0
Histiocytosis, trace		0	0
Macrophages, pigmented,		0	0
	-trace	0	0
	-mild	0	0
Pigment, black, trace		0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
		DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Urinary Bladder		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Uterus		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	8	0	0	0	0	0	10	0	0	0	0
Dilatation,		0	2	0	0	0	0	0	0	0	0	0	0
	-trace	0	1	0	0	0	0	0	0	0	0	0	0
	-mild	0	1	0	0	0	0	0	0	0	0	0	0
Uterus, Cervix		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Vagina		(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(0)	(0)	(0)
Within normal limits		0	10	0	0	0	0	0	10	0	0	0	0
Zymbal's Gland		(0)	(9)	(0)	(0)	(0)	(0)	(0)	(9)	(0)	(0)	(0)	(0)
Within normal limits		0	9	0	0	0	0	0	9	0	0	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
0 through Terminal Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7 DOS	Group 7 SAC
Urinary Bladder		(0)	(10)
Within normal limits		0	10
Uterus		(0)	(10)
Within normal limits		0	9
Dilatation,		0	1
	-trace	0	0
	-mild	0	1
Uterus, Cervix		(0)	(10)
Within normal limits		0	10
Vagina		(0)	(10)
Within normal limits		0	10
Zymbal's Gland		(0)	(8)
Within normal limits		0	8

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
NUMBER OF ANIMALS EXAMINED		5	5	5	5	5	5
NUMBER WITHIN NORMAL LIMITS		0	0	0	0	0	0
Larynx		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		1	0	1	1	2	0
Inflammation, chronic, trace		3	3	1	2	1	0
Mineralization,		3	5	4	4	3	5
	-trace	3	5	3	3	3	5
	-mild	0	0	1	1	0	0
Foreign body, plant material, mild		0	0	0	0	0	0
Foreign material, trace		0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	1	3
	-trace	0	0	0	0	1	2
	-mild	0	0	0	0	0	1
Inflammation, suppurative, trace		1	1	1	0	0	0
Lumenal debris, cellular, mild		0	0	0	0	1	0
Foreign material, lumen, mild		0	0	0	0	0	1
Liver		(0)	(0)	(0)	(0)	(0)	(1)
Altered foci, clear cell, mild		0	0	0	0	0	1
Lung		(5)	(5)	(5)	(5)	(5)	(5)
Infiltration, lymphocytic,		5	5	5	5	5	5
	-trace	3	2	3	4	2	1
	-mild	2	3	2	1	3	4
Inflammation, chronic,		0	0	0	0	0	4
	-trace	0	0	0	0	0	2
	-mild	0	0	0	0	0	2
	-moderate	0	0	0	0	0	0
Foreign material,		0	0	0	0	0	1
	-trace	0	0	0	0	0	1
	-mild	0	0	0	0	0	0
Histiocytosis, trace		0	0	0	0	0	2
Hyperplasia, septal cell,		0	1	5	4	5	5
	-trace	0	1	5	0	5	5
	-mild	0	0	0	4	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7
NUMBER OF ANIMALS EXAMINED		4
NUMBER WITHIN NORMAL LIMITS		0
Larynx		(4)
Within normal limits		0
Inflammation, chronic, trace		0
Mineralization,		4
	-trace	0
	-mild	4
Foreign body, plant material, mild		1
Foreign material, trace		3
Inflammation, granulomatous,		4
	-trace	0
	-mild	4
Inflammation, suppurative, trace		0
Lumenal debris, cellular, mild		0
Foreign material, lumen, mild		0
Liver		(0)
Altered foci, clear cell, mild		0
Lung		(4)
Infiltration, lymphocytic,		4
	-trace	1
	-mild	3
Inflammation, chronic,		4
	-trace	0
	-mild	3
	-moderate	1
Foreign material,		4
	-trace	2
	-mild	2
Histiocytosis, trace		2
Hyperplasia, septal cell,		4
	-trace	0
	-mild	4

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Lung (Continued)		(5)	(5)	(5)	(5)	(5)	(5)
Inflammation, granulomatous,		0	0	0	0	0	2
	-trace	0	0	0	0	0	1
	-mild	0	0	0	0	0	1
Inflammation, interstitial, chronic,		0	2	5	5	5	5
	-trace	0	2	5	0	4	2
	-mild	0	0	0	5	1	3
	-moderate	0	0	0	0	0	0
Macrophages, alveolar,		0	0	0	0	5	5
	-trace	0	0	0	0	2	1
	-mild	0	0	0	0	3	4
Macrophages, pigmented,		0	5	5	5	0	0
	-trace	0	5	5	0	0	0
	-mild	0	0	0	5	0	0
Mineralization, vascular, trace		4	3	5	2	3	1
Pigment, black,		0	5	5	3	0	0
	-trace	0	5	5	2	0	0
	-mild	0	0	0	1	0	0
Lymph Node, Mandibular		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		3	5	5	5	5	5
Congestion, mild		2	0	0	0	0	0
Lymph Node, Mediastinal		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		5	1	0	0	0	0
Histiocytosis,		0	0	0	0	5	5
	-trace	0	0	0	0	3	0
	-mild	0	0	0	0	2	5
Hyperplasia, lymphoid,		0	3	4	5	4	4
	-trace	0	3	4	0	4	0
	-mild	0	0	0	5	0	4
Pigment, black,		0	4	5	5	0	0
	-trace	0	4	4	0	0	0
	-mild	0	0	1	5	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7
Lung (Continued)		(4)
Inflammation, granulomatous,		4
	-trace	1
	-mild	3
Inflammation, interstitial, chronic,		4
	-trace	0
	-mild	3
	-moderate	1
Macrophages, alveolar,		4
	-trace	0
	-mild	4
Macrophages, pigmented,		0
	-trace	0
	-mild	0
Mineralization, vascular, trace		2
Pigment, black,		0
	-trace	0
	-mild	0
Lymph Node, Mandibular		(4)
Within normal limits		4
Congestion, mild		0
Lymph Node, Mediastinal		(4)
Within normal limits		0
Histiocytosis,		4
	-trace	0
	-mild	4
Hyperplasia, lymphoid,		4
	-trace	0
	-mild	4
Pigment, black,		0
	-trace	0
	-mild	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Nasal Tissue A		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	4	5
Exudate, suppurative, trace		0	0	0	0	1	0
Nasal Tissue B		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	5	5
Nasal Tissue C		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	5	5
Nasal Tissue D		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	5	5
Trachea		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		3	3	4	4	5	4
Inflammation, chronic, trace		2	2	1	1	0	1
Trachea, Bifurcation		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		3	3	3	2	3	3
Infiltration, lymphocytic,		2	2	2	3	2	2
	-trace	2	2	1	3	2	2
	-mild	0	0	1	0	0	0
Pigment, black, trace		0	0	1	2	0	0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Male

TISSUE OBSERVATION		Group 7
Nasal Tissue A		(4)
Within normal limits		4
Exudate, suppurative, trace		0
Nasal Tissue B		(4)
Within normal limits		4
Nasal Tissue C		(4)
Within normal limits		4
Nasal Tissue D		(4)
Within normal limits		4
Trachea		(4)
Within normal limits		4
Inflammation, chronic, trace		0
Trachea, Bifurcation		(4)
Within normal limits		3
Infiltration, lymphocytic,		1
	-trace	1
	-mild	0
Pigment, black, trace		0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
NUMBER OF ANIMALS EXAMINED		5	5	5	5	5	5
NUMBER WITHIN NORMAL LIMITS		0	0	0	0	0	0
Larynx		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		4	3	2	2	2	0
Inflammation, chronic, trace		0	0	1	0	0	0
Mineralization, trace		1	2	2	3	2	3
Foreign material, trace		0	0	0	0	0	1
Inflammation, granulomatous,		0	0	0	0	1	5
	-trace	0	0	0	0	1	4
	-mild	0	0	0	0	0	1
Foreign material, lumen, mild		0	0	0	0	1	1
Lung		(5)	(5)	(5)	(5)	(5)	(5)
Infiltration, lymphocytic,		5	5	5	5	5	5
	-trace	3	1	1	5	4	2
	-mild	2	4	4	0	1	3
Inflammation, chronic,		0	0	0	0	0	5
	-trace	0	0	0	0	0	2
	-mild	0	0	0	0	0	3
	-moderate	0	0	0	0	0	0
Foreign material,		0	0	0	0	1	1
	-trace	0	0	0	0	1	1
	-mild	0	0	0	0	0	0
Histiocytosis, trace		0	0	0	0	0	2
Hyperplasia, septal cell,		0	0	5	5	5	5
	-trace	0	0	3	0	5	0
	-mild	0	0	2	5	0	5
	-moderate	0	0	0	0	0	0
Inflammation, granulomatous,		0	0	0	0	1	2
	-trace	0	0	0	0	1	2
	-mild	0	0	0	0	0	0
Inflammation, interstitial, chronic,		0	0	5	5	5	5
	-trace	0	0	3	0	5	0
	-mild	0	0	2	5	0	5
	-moderate	0	0	0	0	0	0

CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7
NUMBER OF ANIMALS EXAMINED		5
NUMBER WITHIN NORMAL LIMITS		0
Larynx		(5)
Within normal limits		0
Inflammation, chronic, trace		0
Mineralization, trace		4
Foreign material, trace		1
Inflammation, granulomatous,		5
	-trace	2
	-mild	3
Foreign material, lumen, mild		1
Lung		(5)
Infiltration, lymphocytic,		3
	-trace	1
	-mild	2
Inflammation, chronic,		5
	-trace	0
	-mild	4
	-moderate	1
Foreign material,		5
	-trace	4
	-mild	1
Histiocytosis, trace		1
Hyperplasia, septal cell,		5
	-trace	0
	-mild	4
	-moderate	1
Inflammation, granulomatous,		5
	-trace	3
	-mild	2
Inflammation, interstitial, chronic,		5
	-trace	0
	-mild	4
	-moderate	1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Lung (Continued)		(5)	(5)	(5)	(5)	(5)	(5)
Macrophages, alveolar,	-mild	0	0	0	0	5	5
	-moderate	0	0	0	0	5	3
	-severe	0	0	0	0	0	2
Macrophages, pigmented,	-trace	0	0	0	0	0	0
	-mild	0	5	5	5	0	0
Mineralization, vascular, trace		0	5	3	0	0	0
Pigment, black, trace		0	0	2	5	0	0
		4	4	4	3	4	3
		0	5	5	5	0	0
Lymph Node, Mandibular		(5)	(5)	(5)	(5)	(5)	(5)
Within normal limits		5	5	5	5	5	5
Lymph Node, Mediastinal		(4)	(5)	(5)	(5)	(5)	(5)
Within normal limits		2	3	0	0	0	0
Congestion, mild		1	0	0	0	0	0
Histiocytosis,	-trace	0	0	0	0	5	5
	-mild	0	0	0	0	4	0
Hyperplasia, lymphoid,	-trace	0	0	0	0	1	5
	-mild	1	1	3	5	4	5
Pigment, black,	-trace	1	1	3	4	3	1
	-mild	0	0	0	1	1	4
		0	2	5	5	0	0
		0	2	5	0	0	0
		0	0	0	5	0	0
Nasal Tissue A		(5)	(0)	(0)	(0)	(5)	(5)
Within normal limits		5	0	0	0	5	3
Exudate, suppurative, trace		0	0	0	0	0	2

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7
Lung (Continued)		(5)
Macrophages, alveolar,		5
	-mild	0
	-moderate	4
	-severe	1
Macrophages, pigmented,		0
	-trace	0
	-mild	0
Mineralization, vascular, trace		3
Pigment, black, trace		0
Lymph Node, Mandibular		(5)
Within normal limits		5
Lymph Node, Mediastinal		(5)
Within normal limits		0
Congestion, mild		0
Histiocytosis,		5
	-trace	2
	-mild	3
Hyperplasia, lymphoid,		5
	-trace	0
	-mild	5
Pigment, black,		0
	-trace	0
	-mild	0
Nasal Tissue A		(5)
Within normal limits		4
Exudate, suppurative, trace		1

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Nasal Tissue B							
Within normal limits		(5) 5	(0) 0	(0) 0	(0) 0	(5) 5	(5) 4
Exudate, suppurative, trace		0	0	0	0	0	1
Nasal Tissue C							
Within normal limits		(5) 5	(0) 0	(0) 0	(0) 0	(5) 5	(5) 5
Nasal Tissue D							
Within normal limits		(5) 5	(0) 0	(0) 0	(0) 0	(5) 5	(5) 5
Ovary							
Cyst, moderate		(0) 0	(0) 0	(0) 0	(0) 0	(0) 0	(1) 1
Trachea							
Within normal limits		(5) 5	(5) 5	(5) 5	(5) 5	(5) 5	(5) 5
Trachea, Bifurcation							
Within normal limits		(5) 5	(5) 3	(5) 2	(5) 4	(5) 4	(5) 4
Infiltration, lymphocytic,	-trace	0	2	3	1	1	1
	-mild	0	2	3	1	0	1
Pigment, black, trace		0 0	0 1	0 0	0 1	1 0	0 0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

Table 12 Cont.

Incidence of Microscopic Observations
Recovery Sacrifice: Rat
Female

TISSUE OBSERVATION		Group 7
Nasal Tissue B		(5)
Within normal limits		5
Exudate, suppurative, trace		0
Nasal Tissue C		(5)
Within normal limits		5
Nasal Tissue D		(5)
Within normal limits		5
Ovary		(0)
Cyst, moderate		0
Trachea		(5)
Within normal limits		5
Trachea, Bifurcation		(5)
Within normal limits		5
Infiltration, lymphocytic,		0
	-trace	0
	-mild	0
Pigment, black, trace		0

683-002 CODE: () = NUMBER OF ANIMALS EXAMINED

H

Triage of 8(e) Submissions

Date sent to triage:_____ NON-CAP CAP

Submission number: 13745 A TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 -HERD (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.):_____

Notes:

☒ This is the **original** 8(e) submission; refile after triage evaluation.

☐ This **original** submission has been **split**; rejoin after triage evaluation.

☐ Other:

Photocopies Needed for Triage Evaluation

entire document: 0 1 2 3

front section and CECATS: 0 1 2 3

Initials:_____ **Date:**_____

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0996- 13745 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME:
Industrial Health Foundation

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/12/96 OTS DATE: ~~10/7~~ 09/18/96 CSRAD DATE: 10/21/96

CHEMICAL NAME:	CAS#
chromic oxide	1308-38-9
basic chrome sulfate	unknown

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	(0241)	IMMUNO (ANIMAL)	01 (02) 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	0248	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	(0299)	OTHER	01 (02) 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
(0214)	SUB CHRONIC TOX (ANIMAL)	01 (02) 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	Rats	LOW	—	
CAS SR	NO	NO (CONTINUE)		MED		
	IN TRANSIT	REFER		[HIGH]		

COMMENTS: Rats were exposed via head-only inhalation at 4.4, 15 and 44 mg/m3 to chromic oxide (Cr_2O_3) and at 17, 58 and 175 mg/m3 to basic chromic sulfate. Both chemical produced severe effects to respiratory tract, septal cell hyperplasia, chronic interstitial inflammation was observed with Cr_2O_3. Basic chromic sulfate (soluble) produced lesions of respiratory tract. NOAEL(S) were not observed for both chemicals.