Chemical Industry Institute of Toxicology

CIIT

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FYI-0294-000969

January 18, 1994

[redacted]

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Contains No CBI

FYI-94-000969
INIT 02/03/94

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RECD
OFFICE OF POLLUTION
PREVENTION AND TOXICS

Ms. Linda A. Travers, Director
Information Management Division
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Ms. Travers:

The Chemical Industry Institute of Toxicology has released to the public the final report of "A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats." Announcement of the availability of the final report, including a summary of the report, is included in the November-December issue of CIIT ACTIVITIES which is currently being printed. CIIT ACTIVITIES is distributed to over 4,000 individuals including 170 at EPA.

The results of this study were presented in preliminary form at the Institute's Annual Scientific Open House on October 20, 1992 and at the Society of Toxicology meeting on March 15-18, 1993 with an abstract published in the TOXICOLOGIST 13, 150 (abstract #513), 1993. A manuscript summarizing the results of the study has been submitted to a peer-reviewed journal and is now undergoing review. As soon as it has been accepted for publication, copies will be available to interested parties.

We are, therefore, confident that responsible agency officials will be fully aware of the existence and general content of the final report of our chlorine study and are enclosing a copy for your records.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.
President

ROM:eam
Enclosure
cc: Dr. Kevin Morgan
Dr. Doug Wolf
Ms. Willanna Griffin
Ms. Patricia O'Brien Pomerleau

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9/20/94

863 pgs.

Chemical Industry Institute of Toxicology

CIIT

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President

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~~FYI-0294-12885~~

~~8SHQ 0294-12885~~

88940000127/2

July 13, 1994

TSCA Public Docket Office
Room G-0004
North East Mall
401 M Street, S.W.
Washington, DC 20460

To Whom It May Concern:

In response to a suggestion recently received by phone from Mr. Bo Reiley, Office of Pollution Prevention and Toxics (a Chemicals Testing and Information Service) at EPA, we are pleased to re-send to the **TSCA Public Docket Office**, by registered mail, the following final CIIT Chemical Study Reports:

A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats, two vols., 1993 88940000127 rec'd 2/3/94

A Chronic Inhalation Toxicity Study of Nitrobenzene in B6C3F1 Mice and Fischer 344 Rats and Sprague-Dawley (CD) Rats, two vols., 1992.

As you will note from the attached correspondence, copies of these study reports were previously provided to Ms. Linda Travers of EPA. However, Mr. Reiley of EPA said, in a conversation with Willanna Griffin, Information Services at CIIT, that they were not entered into the official docket and thus may be difficult for users to locate at EPA.

CIIT provides these reports voluntarily, and FOR INFORMATION PURPOSES ONLY, to the U. S. EPA, without prejudice to CIIT's continuing position that by virtue of its charter and operations, it is not subject to EPA jurisdiction.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.
President and CEO

ROM:eam
Enclosures
cc: Mr. B. Reiley

Chemical Industry Institute of Toxicology

CIIT

Roger O. McClellan, D.V.M.
President

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January 18, 1994

94 JUL 20 AM 7:52
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Ms. Linda A. Travers, Director
Information Management Division
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Ms. Travers:

The Chemical Industry Institute of Toxicology has released to the public the final report of "A Chronic Inhalation Toxicity Study of Chlorine in Female and Male $B_6C_3F_1$ Mice and Fischer 344 Rats." Announcement of the availability of the final report, including a summary of the report, is included in the November-December issue of CIIT ACTIVITIES which is currently being printed. CIIT ACTIVITIES is distributed to over 4,000 individuals including 170 at EPA.

The results of this study were presented in preliminary form at the Institute's Annual Scientific Open House on October 20, 1992 and at the Society of Toxicology meeting on March 15-18, 1993 with an abstract published in the TOXICOLOGIST 13, 150 (abstract #513), 1993. A manuscript summarizing the results of the study has been submitted to a peer-reviewed journal and is now undergoing review. As soon as it has been accepted for publication, copies will be available to interested parties.

We are, therefore, confident that responsible agency officials will be fully aware of the existence and general content of the final report of our chlorine study and are enclosing a copy for your records.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.
President

ROM:eam
Enclosure
cc: Dr. Kevin Morgan
Dr. Doug Wolf
Ms. Willanna Griffin
Ms. Patricia O'Brien Pomerleau

Chemical Industry Institute of Toxicology

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February 19, 1993

FILE

94 JUL 20 AM 7:52

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Ms. Linda A. Travers, Director
Information Management Division
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Ms. Travers:

Several days ago, on February 22, 1993, the Chemical Industry Institute of Toxicology (CIIT) released to the public the final report of "A Chronic Inhalation Toxicity Study of Nitrobenzene in B6C3F1 Mice, Fischer 344 Rats and Sprague-Dawley (CD) Rats," which was completed just a few days previously. In accordance with CIIT policy, the announcement of the availability of this report was provided to all persons outside the Institute, including member companies, at the same time.

The announcement was made by including a summary of the report with the December 1992 issue of CIIT ACTIVITIES mailed on January 20, 1993. CIIT ACTIVITIES is distributed to over 4,000 individuals, including 170 at EPA. Copies of the full report have been provided to Dr. Jeff Gift, Hazardous Pollutant Assessment Branch, Environmental Criteria and Assessment Office, Research Triangle Park, NC, and, Dr. Cheryl Siegel-Scott, Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, D.C.

We are, therefore, confident that responsible agency officials are fully aware of the existence and general content of the final report of our nitrobenzene study. But, we also want to be sure that the report is available to the EPA office responsible under TSCA for receiving reports of completed toxicological studies, and we, therefore, are enclosing a third copy for your records.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.
President

ROM:eam

cc: Dr. Jeff Gift
Dr. Cheryl Seigel-Scott

FYI-0294-00969

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A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats

Volume 1 of 2

Contains No CBI

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
P. O. BOX 12137
RESEARCH TRIANGLE PARK, NC 27709

A CHRONIC INHALATION TOXICITY STUDY OF CHLORINE IN FEMALE AND MALE B6C3F1 MICE AND FISCHER 344 RATS

Report Issued:

December 31, 1993

8321 - Male F344 Rats
Protocol Signed: 3-30-83
First Exposure: 4-11-83
Final Exposure: 4-10-85

8436 - Female F344 Rats
Protocol Signed: 4-6-84
First Exposure: 4-16-84
Final Exposure: 4-28-86

8437 - Female and Male B6C3F1 Mice
Protocol Signed: 4-6-84
First Exposure: 4-16-84
Final Exposure: 4-17-86

James A. Popp

James A. Popp, D.V.M., Ph.D.
Study Director
CIIT

Date Dec 31, 1993

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A CHRONIC INHALATION TOXICITY STUDY OF CHLORINE IN FEMALE AND MALE B6C3F1 MICE AND FISCHER 344 RATS

PERSONNEL

Study #8321; Rats

Craig Barrow, Ph.D.	Study Director 3-30-83 to 11-12-84
James A. Popp, D.V.M., Ph.D.	Study Director 11-12-84 to 1-24-85
King Lit Wong, Ph.D.	Study Director 1-24-85 to 3-22-88
James A. Popp, D.V.M., Ph.D.	Study Director 3-22-88 to report completion
Timothy H. Raynor, B.S.	Animal Care Supervisor (3-30-83 to 2-21-85)
Paul Ross, B.S.	Animal Care Supervisor (2-21-85 to present)

Study #8437; Mice
Study #8436; Rats

Craig Barrow, Ph.D.	Study Director 4-6-84 to 1-24-85
King Lit Wong, Ph.D.	Study Director 1-24-85 to 3-22-88
James A. Popp, D.V.M., Ph.D.	Study Director 3-22-88 to report completion
Timothy H. Raynor, B.S.	Animal Care Supervisor (4-6-84 to 2-21-85)
Paul Ross, B.S.	Animal Care Supervisor (2-21-85 to present)

A CHRONIC INHALATION TOXICITY STUDY OF CHLORINE IN FEMALE AND MALE B6C3F1 MICE AND FISCHER 344 RATS

PERSONNEL (cont'd)

General

Kevin T. Morgan, B.V.Sc., Ph.D.	Necropsy Supervisor Report Pathologist (CIIT)
Douglas Wolf, D.V.M. Ph.D.	Report Pathologist (CIIT) (From 6/91)
Owen Moss, Ph.D.	Report Inhalation Toxicologist (From 10/1/90)
Derek Janszen, Ph.D.	Report Statistician (CIIT) (From 1/92)
Garris D. Parker, Jr., M.M.Sc.	Quality Assurance Officer (11/83 to 12/30/87)
Patricia O'Brien Pomerleau, M.S.	Report Quality Assurance Coordinator (From 12/1/90)
Gary I. Riley, M.V.Sc., Ph.D.	*Study Pathologist (EPL)
Marilyn Wolfe, D.V.M., Ph.D.	*Study Pathologist (EPL)
Jim E. Proctor, D.V.M., Ph.D.	*Study Pathologist (EPL)
Steve Seilkop, M.S.	**Statistician (ASI) (From 1-5-93)
Thomas M. Monticello, D.V.M., Ph.D.	***Quality Assurance Pathologist (PAI)

*Experimental Pathology Laboratories.

**Analytical Sciences Inc.

***Pathology Associates

SUMMARY

The objective of this study was to determine the toxicity and carcinogenicity of chlorine resulting from long-term inhalation exposure of female and male B6C3F1 mice and F344 rats. This study was conducted at the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, North Carolina. Male and female B6C3F1 mice and F344 rats were exposed to chlorine gas for up to 2 years to determine the chronic toxicity and carcinogenicity associated with exposure to this irritant. Groups of approximately 70 each of female and male mice and rats were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine gas for 6 hours/day, 5 days/week (mice and male rats) or 3 alternate days/week (female rats) for 2 years, with an interim necropsy of rats at 12 months (10 rats per/sex/concentration group). A complete necropsy was performed on all animals. Histopathological examination was performed on all organs from high-concentration and control animals and selected target organs from mid- and low-concentration groups. Exposure-dependent lesions were confined to the nasal passages in all sex and species groups. Chlorine-induced lesions, which were most severe in the anterior nasal cavity, included respiratory and olfactory epithelial degeneration, septal fenestration, mucosal inflammation, respiratory epithelial hyperplasia, squamous metaplasia and goblet cell hypertrophy and hyperplasia, and secretory metaplasia of the transitional epithelium of the lateral meatus. Intracellular accumulation of eosinophilic proteinaceous material was also a

prominent response involving the respiratory, transitional, and olfactory epithelia, and in some cases the squamous epithelium of the nasal vestibule. Many of these nasal lesions exhibited an increase in incidence and/or severity that was related to chlorine exposure concentration and were statistically-significantly increased at all chlorine concentrations studied. The incidence of neoplasia was not increased by exposure, indicating that inhaled chlorine is an upper respiratory tract toxicant but not a carcinogen.

INTRODUCTION

Chlorine is the most abundant naturally occurring halogen and is a highly reactive, moderately water-soluble element. The high density of chlorine relative to air causes accumulations in low areas and dissipates slowly (Barrow et al., 1977; Frank, 1986; Givan et al., 1989; Witorsch, 1987). Because of chlorine's reactivity, it is commonly employed in many industrial processes, in addition to its use as a household cleaner and disinfectant (Frank, 1986). Chlorine gas was used as a chemical warfare agent during World War I. Many soldiers who survived chlorine exposures developed respiratory symptoms and were considered severely impaired at five years after exposure (Meakins and Priestly, 1919).

Since the initial observations of chlorine toxicity in humans following wartime exposures, several human epidemiological surveys have documented the respiratory tract effects of chlorine after short-term high-concentration exposure. Accidental exposure of humans to high concentrations of chlorine for short periods can result in bronchoconstriction, cough, dyspnea and respiratory tract ulceration, edema and hemorrhage (Moore and Sherman, 1991; Schwartz et al., 1990; Shroff et al., 1988; Ramachandran et al., 1990; Wood et al., 1987). Studies in humans of possible long-term effects of acute high concentration or chronic low concentration exposure have yielded inconsistent results. There is little information on the long-term effects of transient chlorine exposure. One individual exposed to high concentrations of airborne chlorine developed bronchiolitis obliterans and organizing pneumonia one month after exposure and chronic inflammation and fibrosis associated with obstructive pulmonary disease seven months post-exposure (Maortua et al., 1991).

There is anecdotal evidence that long-term exposure to chlorine gas from mixing two cleaning agents caused respiratory embarrassment and heart enlargement which resolved after exposures ceased (Rafferty, 1980). The effects of long-term exposure to chlorine may include chronic bronchitis and decreased lung function (Charan et al., 1985; Donnelly and Fitzgerald, 1990; Enarson et al., 1984; Ferris et al., 1979; Grenquist-Norden, 1983; Hasan et al., 1983; Jones et al., 1986; Kennedy et al., 1991; Ploysongsang et al., 1982). The effects of short-term exposure to chlorine have been studied in human volunteers. Four hours of exposure to 1 but not 0.5 ppm chlorine had adverse effects on pulmonary function tests which returned to normal 24 hours after exposure ceased (Rotman et al., 1983).

Most animal studies have primarily focused on acute or subchronic exposure to chlorine over a wide range of concentrations. Mice and rats developed pulmonary edema, inflammatory cell infiltrate and tracheal epithelial hyperplasia within two days after exposure to the LC_{50} (concentration that elicits 50% mortality) of chlorine (Zwart and Woutersen, 1988). Mice and rats exposed to the RD_{50} concentration (the concentration that elicits a 50% reduction in respiratory rate) of chlorine (9.5 ppm) for 6 hours/day for 5 days developed inflammation of the lung and site-specific nasal lesions, including respiratory epithelial degeneration, ulceration, inflammation and squamous metaplasia, and necrosis of olfactory epithelium (Jiang et al., 1983). Rats exposed to 1, 5 or 10 ppm of chlorine developed concentration-dependent tolerance to sensory irritation and site-specific nasal lesions (Barrow and Steinhagen, 1982; Jiang et al., 1983).

Female and male F344 rats exposed to 1, 3, or 9 ppm chlorine, 6 hours/day, 5 days/week for 6 weeks developed concentration-dependent inflammation and necrosis in the

respiratory tract, hepatocyte vacuolation at the two highest concentrations, and renal proximal tubular degeneration in rats exposed to 9 ppm (Barrow et al., 1979). Female rats had lesions at lower exposure concentrations (1.0 ppm) than the males, indicating greater sensitivity to chlorine exposure compared to males. Female and male rhesus monkeys exposed to 0.1, 0.5, or 2.3 ppm chlorine for one year exhibited ocular irritation at the highest concentration only. In addition, a concentration-dependent focal mild hyperplasia of the respiratory epithelium was seen in the nose and trachea (Klonne et al., 1987). Similar to the increased incidence of lesions in female rats, female monkeys developed lesions at lower concentrations than males.

With the few exceptions noted above, studies on chlorine-exposed animals have been confined to lethal or high exposure concentrations. Additional information is needed on the effects of prolonged and repeated exposure to low concentrations of chlorine on the respiratory system (Frank, 1986). The present investigation was conducted in order to determine the systemic effects of prolonged exposure to lower concentrations of chlorine in rodents. This study demonstrated that treatment-induced effects were confined to the nasal passages, with clear concentration, species, and sex differences for specific lesions.

STUDY DESIGN AND SELECTION OF EXPOSURE CONCENTRATIONS

The present investigation was conducted to determine the systemic effects of chronic exposure to toxic sub-lethal and environmentally relevant concentrations of chlorine in rodents. The rodents used in this work were selected because of their wide use in cancer bioassays. The protocols developed for this work are shown in Appendix A (p. 97). Details of specific endpoints and procedures are presented in Appendices B to Z (p. 259). Studies considered directly related to this work, and not available in the published literature, are provided in Appendices Z (p. 779), AA (p. 795), BB (p. 811) and CC (p. 831) along with supplementary research conducted subsequent to completion of the basic components of the bioassay.

Study Design[1]

	Number of Animals Assigned to Interim Necropsy (12 mo)[2]	Number of Animals Assigned to Terminal Necropsy (24 mo)[2]
Treatment (ppm)[3]	0 0.4 1.0 2.5	0 0.4 1.0 2.5
8437 - B6C3F1 Female Mice	10 10 10 10	50 50 50 50
8437 - B6C3F1 Male Mice	10 10 10 10	50 50 50 50
8436 - F344 Female Rats	10 10 10 10	50 50 50 50
8321 - F344 Male Rats	10 10 10 10	50 50 50 50

[1]Ten additional animals/sex/concentration were assigned to the study, except in control male mice, where seven additional animals were assigned, to compensate for concurrent mortality

[2]Hematology and serum chemistry determinations were proposed for both scheduled necropsies.

[3]ppm chlorine exposures 6 hr/d, 5 d/wk except in female rats (6 hr/d, 3 d/wk)

The chlorine concentrations and exposure regimens used in this study were selected on the basis of published (Barrow et al., 1979) and unpublished research at CIIT (Appendices Z (p. 779) and AA (p. 795)). A published study (Appendix Z) of chlorine toxicity in F344 rats and B6C3F1 mice, using 2 to 5 ppm, 6 hr/d, 5 d/wk for 2 weeks, demonstrated only minimal changes confined to the nasal mucosa of the highest exposure concentration group. An estimated maximum concentration, one that would induce toxicity with minimal deaths during the two year period, was determined to be 2.5 ppm. Female rats were placed on a 3 d/wk exposure regimen due to the results of previous studies (Appendix AA (p. 795)) showing female rats to be more sensitive than males to chlorine toxicity. The lowest exposure concentration was selected on the basis of analytical constraints combined with concern about the proportion of free chlorine that might be converted to chloramines (Barrow and Dodd, 1979; Barrow and Steinhagen, 1980). The intermediate concentration was selected as the mid-concentration on a log base 10 scale from 0.4 to 2.5 ppm, giving final study concentrations of 0.0, 0.4, 1.0, and 2.5 ppm.

MATERIALS AND METHODS

EXPERIMENTAL ANIMAL STUDY PROCEDURES

Female and male B6C3F1 mice and F344 rats were exposed to chlorine at concentrations of 0, 0.4, 1.0, or 2.5 ppm for up to two years. The exposure schedule, which excluded holidays, was 6 hr/day, 5 days/week, with the exception of female rats which, due to their sensitivity, were exposed 3 d/wk to chlorine (see Appendix AA (p. 795)). This modification, combined with constraints imposed by the available computer software, lead to the need for 3 protocols each of which was generated by the PATH/TOX System (Xybion, Cedar Knolls, NJ). A preliminary study in female rats (Appendix AA (p. 795)) was also generated using an identical study number to that used for the present male rat study, and in the appendix this study is referred to as 8321PRELIM, and is confined to female rats exposed for up to 12 months. The importance of study 8321PRELIM lies in its use for justification of a modified exposure protocol for female rats in study 8436. The core studies of the present bioassay are outlined below. The protocols with amendments are presented in Appendix A (p. 97).

Study 8437 - female and male B6C3F1 mice. These animals were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine for 6 hr/day, 5 days/week for 2 years. No interim necropsy was carried out in mice.

Study 8436 - female F344 rats. These animals were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine for 6 hr/day, 3 days/week (Monday, Wednesday, Friday) for 12 months (interim necropsy of 10 animals per group) or 2 years.

Study 8321 - male F344 rats. These animals were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine for 6 hr/day, 5 days/week for up to 2 years. Ten animals from each of the four treatment groups of each sex were necropsied after 12 months into the study. The remaining male rats were continued through to 2 years of exposure for the final necropsy.

On March 20, 1984 three hundred and twenty female and three hundred and twenty male B6C3F1 mice (C57Bl/6NCrlBR x C3H/HeNCrlBR) and three hundred and twenty female inbred Fischer 344 rats (CDF[F344]/CrlBR) (F-344) were received from Charles River Breeding Laboratories, Stoneridge Plant, Kingston, New York to be used on the chronic chlorine studies (PATH/TOX #8437 and 8436). These animals, 36 days of age, were placed in CIIT animal facility quarantine rooms and moved to Rms 308, 309, 310, and 311 prior to the initiation of chlorine exposures on April 16, 1984.

On March 16, 1983 three hundred and twenty male inbred Fischer 344 rats (CDF[F344]/CrlBR) (F-344) were received from Charles River Breeding Laboratories, Stoneridge Plant, Kingston, New York to be used on the chronic chlorine study (PATH/TOX #8321). These rats, 36 days of age, were placed in the CIIT animal facility quarantine room and moved to Rms 308, 309, 310 and 311 prior to the initiation of chlorine exposures on April 11, 1983.

Experimental Animals

During the acclimation period all animals were observed, weighed, randomized, and identified by eartag. All mice and rats were fed NIH-07 pelleted diet (Ziegler Bros., Gardners, PA) and were given filtered, deionized water (Raynor et al., 1984) ad libitum. During this period 2 rats were removed for a comprehensive health screen (Microbiological Associates, Bethesda, MD) which consisted of a physical examination, parasitology, viral and mycoplasmal serology, oropharyngeal and intestinal bacterial culture, and histopathology of major organs. Results of the serological screen are presented in Appendix B (p. 259). No significant murine pathogens were detected. A genetic screen was conducted on B6C3F1 mice and F344 rats using biochemical and immunological markers (Charles River Biotechnical Services, Wilmington, MA). Immunological and biochemical results were compatible with the strains submitted, with a 98.4% confidence that all 4 mice were of the B6C3F1 strain, and a 93.8-99.6 confidence that the 2 rats were of the F344/N strain.

Group Assignment

Female and male rodents of each species were weighed and randomized to treatment groups separately by weight (70 per group, 280/sex/species, except male mice which had 67 animals in the control group giving a total of 277 animals for this study) using a computer-generated group assignment (CIIT SOP-TAC-164-2). All animals were individually identified with eartags (CIIT SOP-TAC-161-2). The computer-generated randomization procedure (PATH/TOX System, Xybion, Cedar Knolls, NJ) allowed each animal an equal probability of being assigned to

any group, and also assured approximately equal mean group body weights (Table 1 (p. 71)). The disposition of extra animals is not documented in the study record.

Animal Husbandry

All animals on study were housed in suspended stainless steel wire cages (Hazleton Inc., Aberdeen, MD). Mouse cages were 10 x 14.5 x 4.75 inches and were equally divided into three compartments. Female mice were housed five animals per compartment. Male mice were housed one per compartment. Rat cages were 10 x 14.5 x 7.5 inches and were equally divided into three compartments. Male and female rats were housed one per compartment. All cages were maintained on stainless steel racks kept within stainless steel and glass inhalation chambers except for removal for animal husbandry in the anteroom located outside each chamber. Rack and cage servicing was conducted according to SOP TAC-142-3. Chambers were maintained at 68-76° Fahrenheit and 40-60% relative humidity with excursions outside these ranges. Animal room lights were maintained on a 12-hour light/dark cycle with lights on from 7:00 to 19:00 hours. During periods of non-exposure, the animals were provided food (NIH-07 open formula pelleted diet, Ziegler Bros., Gardners, PA) which was monitored for chemical and microbial contaminants (Lancaster Labs., Lancaster, PA). An example of the feed analysis report with the limits of detection are listed in Appendix C. All certified NIH-07 pelleted food for the 24 month study (8321, 8436, 8437) was found to comply with the National Toxicology Program (NTP) recommendations (Rao and Knapka, 1987). Filtered, deionized tap water (Raynor et al., 1984) was provided via an automatic watering system. Racks and cages were serviced twice per day, prior to and after completion of exposures.

TEST CHEMICAL

Pure chlorine was obtained from Diamond-Shamrock Corporation, (Deer Park, TX) and shipped to Matheson Gas Products (Morrow, GA). Sufficient quantity was purchased from the same production lot to ensure adequate supplies for the duration of the study. The chlorine was blended, at Matheson Gas Products, with nitrogen (99.7% minimum purity) and shipped to CIIT in metal gas cylinders loaded at 2.3-2.5% chlorine with the balance nitrogen. Prior to each shipment, the chlorine-to-nitrogen ratio was verified by gas chromatography at Matheson Gas Products.

Chemical Analysis

Purity analyses of samples, from the single source of chlorine set aside for this study, were performed by Diamond Shamrock Corporation (Deer Park, TX). The gas phase of each sample was analyzed for chlorine and for the presence of carbon dioxide, oxygen, and nitrogen. Chlorine was analyzed using gas displacement according to method ASTM E-412-70. A calibration gas containing 0.64% carbon dioxide, 0.06% oxygen, and 0.06% nitrogen (Matheson Gas Products, Morrow, GA) was used to analyze for these gases by gas chromatography.

The liquid phase of each sample was analyzed for carbon tetrachloride and chloroform, according to gas chromatograph method ASTM E-806.

Purity analysis was reported three times during the study (18 April 1983, 15 December 1983, and 12 October 1984). In all cases, the gas phase contained (by volume) 99.95% chlorine, 0.02% carbon dioxide, and less than 0.01% nitrogen. The liquid phase contained less

than 0.003% by weight, of both carbon tetrachloride and chloroform (see Appendix D - Table D1 (p. 268)).

On-line Analysis

During exposures, 6 hours per day, 5 days per week, samples were taken from the 0, 0.4, 1.0, and 2.5 ppm chlorine exposure chambers and drawn sequentially through an Interscan Chlorine Analyzer (Interscan Corp., Chatesworth, CA). The Interscan was calibrated weekly, using a Dynacalibrator (Metronics Dynacalibrator Model 340, Metronics Associates, Inc., Santa Clara, CA) that was equipped with a chlorine permeation tube. The permeation rate of chlorine in the Dynacalibrator was determined using the methyl-orange method of chlorine analysis (Lodge, 1989; see Appendix F - Table F3 (p. 290)). A Bausch and Lomb Spectronic 21 UV-D Spectrophomotometer was used to measure the color change in the solutions.

Since chlorine could combine with airborne ammonia, forming chloramines, an additional assay to measure free chlorine was performed for 102 weeks out of the 159 week study in all chambers. This analysis was based on the complete reaction of free chlorine in solution with 2,6-dimethylphenol (2,6-DMP) to form 4-chloro-2,6-dimethylphenol (4-Cl-2,6-DMP). The amount of chlorine reacting with 2,6-DMP was measured using a 4-bromo-2,6-dimethylphenol (4-Br-2,6-DMP) tracer (Ellis and Brown, 1981). The 4-chloro-2,6-DMP was extracted with hexane and analyzed by gas chromatography (see Appendix F - Table F4 and Figure F1). Tables F1 and F2 list the GC parameters for the 2,6-DMP analysis. The on-line analysis of total chlorine by the Interscan Analyzer was accomplished by continually drawing exposure atmosphere at 0.8 l/min from the center of each 8 m^3 inhalation chamber through 0.25 inch teflon tubing with a Gast

rotary vane vacuum pump. A solenoid controlled sampling valve system was used to switch each Interscan Chlorine Analyzer between two of the four exposure chambers and room air.

Post-study ammonia levels in a loaded chamber were determined with a Wescan Ammonia Analyzer Model 360 (Alltech Associates, Inc., Deerfield, IL; see Appendix F - Table F5 (p. 293)).

EXPOSURES

Chamber Configuration and Operation

Exposures of animals to chlorine were accomplished in 8 m^3 stainless steel and glass inhalation chambers manufactured by Hazleton systems and patterned after those reported by Hinners et al. (1968). These chambers were operated in the "dynamic" flow mode with exposure air continuously entering and exiting. A supply fan, an exhaust fan, and two butterfly valves were used to control flows. Intake and exhaust air for each chamber was filtered through a series of three charcoal canisters. Four inhalation chambers were used: one each for exposure to 0.0, 0.4, 1.0, or 2.5 ppm chlorine. Total flow through each chamber was held to 2.2 m^3/min (approximately 16 air changes per hour). The theoretical half time for buildup and clearance of chlorine is 2.5 minutes for this amount of total flow and for completely mixed conditions inside the chamber (Moss, 1989). The target concentration was expected to be within 10% of the final steady state value in less than 9 minutes, based on theoretical calculations and practical measurements on these and similar chambers.

Chamber Uniformity

Under normal operating conditions of 2.2 m^3/min total flow these exposure chambers present thoroughly mixed, uniform exposure atmospheres to animals (Hinners et al., 1968). Measurements of uniformity of exposure atmospheres were made in each of the chambers using a concentration of 2.5 ppm prior to the start of exposures by calculating the coefficient of variation of concentrations measured in selected locations in the chamber as recommended (Decker et al., 1985; Cheng and Moss, 1989). In each of the three chlorine chambers, the concentration at the center of the chamber was measured followed by sequential samples from the four upper and lower corners that could be occupied by animals during exposures and at the center of the chamber again. No animals or cage units were present during these measurements in order to evaluate the worse case for mixing. The mean and standard deviation calculated from nine data points from the ten samples taken from each chamber were used to assess the between point sampling location concentration variability and the stability of generator. Repeat measures at the center point of the chamber were averaged and included in the calculations.

Generation System and Operation

The exposure atmosphere was produced by connecting a tank of chlorine to the inlet airflow line of each chamber and controlling the flow rate of chlorine gas from the tank with a rotameter and a CME flow monitor (CME Inc., Manassas, VA). The concentration in each exposure chamber was fine-tuned by adjusting chlorine flow through the rotameter.

Temperature and Relative Humidity

Wet and dry bulb temperatures were measured to estimate chamber relative humidity and to monitor chamber temperature. The dry bulb was mounted in the middle of the inhalation chamber. The wet bulb probe and associated water reservoir were mounted in a horizontal section of the exhaust duct location at the bottom of the 8 m^3 exposure chamber. Water used to moisten the wet bulb sock was drawn by capillary action from a refillable water pan mounted below the duct. Relative humidity was calculated from the equations used to generate standard psychrometric tables.

CLINICAL OBSERVATIONS AND BODY WEIGHTS

Animals were weighed and observed for clinical abnormalities weekly during the first thirteen weeks and biweekly thereafter (Appendices G and H (p. 295)). Some minor deviations from this schedule are noted in the study record.

POSTMORTEM PROCEDURES

Hematology Determinations

Hematology was performed on all ten rats/group at interim necropsy and all surviving animals/sex/concentration group (mice and rats) at the final necropsy. Animals were chosen randomly by the PATH/TOX System from each group. Three milliliters of blood were collected by cardiac puncture of rats using a Vacutainer^R holder (Becton Dickinson and Company, Rutherford, NJ) and a 64 X 10.25 mm Vacutainer^R glass tube containing 0.06 ml EDTA (K_3) as an anticoagulant. Two hundred microliters of blood were collected by cardiac puncture from the

mice using Microtainers^{R} containing EDTA (Becton Dickinson and Company, Rutherford, NJ). Blood aliquots from mice were put into calibrated capillary tubes and immediately diluted in Isoton^{R} (Coulter Electronics, Inc., Hialeah, FL), while rats had one milliliter of blood directly aliquotted into capillary tubes with no dilution. Each sample was analyzed using a Coulter S Plus II analyzer (Coulter Electronics, Inc., Hialeah, FL). The following hematology parameters were measured: white blood count (WBC), red blood count (RBC), hemoglobin (HGB), hematocrit (HCT), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets - thromobocytes (PLT), platelet "hematocrit" (PCT), mean platelet volume (MPV), and platelet distribution width (PDW). References for techniques used in hematology determinations are found in Appendix T (p. 739). Blood films were obtained using a Uni-smear spinner (Perkin-Elmer, Coleman Instruments Division, Oak Brook, IL). Dried smears were stained using a Hema-tek^{R} stainer (Miles Laboratories, Ames Division, Elkhart, IN). Differential counts were performed on 100 cells and absolute differential leukocyte counts were calculated using WBC and relative differential count results.

Clinical Chemistry Determinations

Clinical chemistry was performed (see protocol in Appendix A (p. 97)), on animals randomly selected for the interim necropsy (10 rats/group) and final necropsy (all surviving animals/group). Two milliliters of blood were collected via cardiac puncture of rats using a Vacutainer^{R} holder (Becton Dickinson and Company, Rutherford, NJ) and a 64 x 10.25 mm Vacutainer^{R} glass tube without anticoagulant. Two hundred microliters of blood were collected from mice using Microtainers^{R} without anticoagulants. Samples were then allowed to clot and serum prepared according to each test protocol. Clinical chemistry tests were performed using

commercial reagents in an Abbott VP Autoanalyzer (Abbott Laboratories, North Chicago, IL). The following clinical chemistry parameters were measured: glucose (GLU), blood urea nitrogen (BUN), alkaline phosphatase (ALK), albumin (ALB), bilirubin total (BILI), serum glutamic-oxaloacetic transaminase (AST), serum glutamic-pyruvic transaminase (ALT), calcium (CA), phosphorous inorganic (PHOS), γ-glutamyl transpeptidase (GGT) and total protein (TP). Sodium and potassium determinations were performed with a Flame Photometer 343 (Instrument Lab, Lexington, MA) and chloride analyses with a Corning Chloride 920 M Meter (Corning Scientific Instruments, Medfield, MA). Literature references for clinical chemistry methodologies are found in Appendix U (p. 741).

Necropsy Procedures

Scheduled Necropsy Animals

Ten animals from each sex/species/concentration group were scheduled for the interim necropsy and 50 animals from each sex/species/concentration group were scheduled for the final necropsy. Percent survival for female mice at one year ranged from 87.1% in the control group to 89.4 to 95.6% in chlorine exposed mice (Figure 2a (p. 93)). Percent survival for male mice at one year ranged from 78.5% in the control group to 79.5 to 85.5% in chlorine exposed mice (Figure 2b (p. 94)). While survival to one year was not affected by chlorine exposure, concern about overall survival rates led to cancellation of the interim necropsy of mice.

Animals were weighed just prior to necropsy. After anesthetization by i.p. injection of pentobarbital, blood was drawn from the heart for hematology and serum chemistry analyses. Each animal was examined for gross abnormalities, and the liver, kidneys, and brain were

weighed. Tissues collected for microscopic examination (Appendix A (p. 97)) were placed in 10% buffered formalin. The nasal passages were flushed, the lungs inflated, and the lumen of the gastrointestinal tract infused with the same fixative. Tissues containing bone were placed in 10% buffered formalin for 48 hours, decalcified in Cal-ex^R solution (Fisher Scientific, Raleigh, NC) for 48 hours, then rinsed with tap water for at least 4 hours, and replaced in formalin. In keeping with the protocols (Appendix A, section 14.0 (p. 110)), all tissues from the high concentration and control groups were processed for light microscopy. Tissues were trimmed, dehydrated in graded alcohols, cleared with xylene, and embedded in paraffin wax. Sections (5 µm) were cut and stained with hematoxylin and eosin (HE) for light microscopic examination. The section levels used for routine examination of nasal passages are depicted in Figure 1. Based upon a review of the completed microscopic evaluation of control and highest exposure group tissues, target tissues were designated by the study director and the pathologists. These designated target tissues (see Table 3 (p. 79)) and gross lesions were trimmed and processed for microscopic evaluation in both the middle and low exposure concentration groups.

Unscheduled Animals

Animals that died or were found moribund over the course of the study were necropsied according to the same procedure used for scheduled necropsy animals with the following exception:

Animals determined by the pathologist to be in an advanced autolytic state were not examined or evaluated histologically.

For complete details of animals that were unscheduled (found dead, accidental trauma, moribund), see Table 2 (p. 72).

PATHOLOGY

Fixed tissues were submitted to Experimental Pathology Laboratories, Inc. (EPL), Research Triangle Park, NC for histopathological evaluation. Following completion of microscopic examination, incidence tables for all diagnoses were prepared. A written narrative of the findings was submitted by EPL and appears as Appendix Q (p. 451). Complete microscopic pathology reports have been placed in the study file and are available from CIIT Information Services Department (CIIT, P.O. Box 12137, Research Triangle Park, NC 27709). Specimens and incidence tables were then submitted to Pathology Associates, Inc. (PAI, Research Triangle Park, NC) for independent pathology review to assure quality and consistency of diagnoses.

PATHOLOGY QUALITY ASSESSMENT

A pathology quality assessment review was conducted which consisted of a complete review of all tissues from a 20% sample selected randomly from the 70 animals in each of the control and highest concentration groups. Specified lesions from designated target organs were reviewed for all animals in all concentration groups. Not all of the specified lesions reviewed were reported as compound related. The PAI pathology reports were issued as follows: 8437 - May 28, 1992, 8436 - June 17, 1992, and 8321 - June 17, 1992. The entire report of this independent pathology review (PAI, RTP, NC) was placed in the study file and is available from CIIT Information Services Department (CIIT, P.O. Box 12137, Research Triangle Park, NC 27709). The PAI report summaries appear in Appendix X (p. 755).

Subsequent studies of selected lesions in the nasal passages were examined by a CIIT pathologist, and details of this work are presented in Appendix CC (p. 831).

STATISTICS

Chlorine Data Analysis

Hardware

The analyses were performed on an IBM-compatible 486/33 Mhz computer.

Software

The SAS System, Version 6.07 (Cary, NC), was used for most analyses. Where possible, SAS System procedures (e.g. PROC MEANS, PROC FREQ) were utilized. However, many of the statistical methods that were used in the analysis were not directly available in SAS (e.g. Shirley's and Dunn's tests, the life-table test with continuity corrections, and the logistic regression score test). Apart from the logistic regression score test, which was written for the Microsoft (Redmond, WA) FORTRAN compiler, statistical procedures were developed through SAS DATA step programs.

Survival Analysis

The probability of survival was estimated using the product-limit procedure of Kaplan and Meier (1958). Assessments of treatment-related effects on survival were based on Cox's method (1972) for pairwise comparisons, and Tarone's (1975) life table test for dose-related trends. Animals which were found dead of other than natural causes (e.g., accidental deaths) or were found missing were censored from the analyses. All reported p-values are one-sided.

Body Weight Analyses

Weekly averages of body weights were computed by treatment group and displayed in graphical form. Evaluation of treatment effects on growth was based on maximum individual body weights attained during the course of the study. Differences between control and treated groups were assessed with Dunnett's multiple comparison test. To avoid the potential impact of differences in survival on the analysis, the test was applied to means that had been adjusted via analysis of covariance for the time at which the maximum weight value was attained. In addition, an analysis of unadjusted mean values was performed.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and terminal body weight data, which are approximately normally distributed, were analyzed using the parametric multiple comparisons procedures of Williams (1971, 1972) and Dunnett (1955).

Clinical chemistry and hematology data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparisons methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose-response (Dunnett, Dunn). If the p-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test. To avoid the potential impact of differences in survival on the analysis, the test was applied to means that had been adjusted via analysis of covariance for the time at which the maximum weight value was attained. In addition, an analysis of unadjusted mean values was performed.

Calculation of Incidence

The incidence of neoplastic and non-neoplastic lesions was calculated as the ratio of the number of animals bearing lesions at a site to the number of animals that were examined histologically. For non-target tissues, animals in intermediate dose groups were examined histologically only if a macroscopic examination detected a lesion. Because calculated incidences in these groups could be misleading, they are reported without supporting p-values.

Analysis of Neoplastic and Nonneoplastic Lesion Incidence

Logistic regression analysis was the primary statistical method used to assess the significance of differences in lesion incidence among treated and control groups. This method assumes that the diagnosed tumor (or non-neoplastic lesion) was discovered as the result of death from an unrelated cause, and did not contribute to the risk of death. It was utilized since most of the tumors and lesions in this study were considered to be incidental or not rapidly lethal. In applying the method, tumor (or non-neoplastic lesion incidence) was modeled as a logistic function of exposure and time. Linear and quadratic temporal terms were included in the model initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. Assessments of significance were based on the likelihood score test for the regression coefficient on dose. This approach is the prevalence analysis of Dinse and Lagakos (1983), as further described by Dinse and Haseman (1986).

In addition to logistic regression, alternative statistical analyses were utilized. The life table test (Cox, 1972; Tarone, 1975) was applied to provide an appropriate approach for

analyzing the incidence of rapidly lethal lesions. The results of the Fisher exact test and Cochran-Armitage trend test (Armitage 1971; Gart et al., 1979), procedures which did not adjust for intercurrent mortality, are also reported.

Continuity-corrected tests were used in the analysis of tumor and non-neoplastic lesion incidence. All reported p-values are one-sided under the alternative hypothesis of a treatment related increase in tumor (or lesion) incidence.

Histopathology

The effect of treatment on nasal lesion severity was evaluated using mean severity scores in lesion-bearing animals. For lesions that did not occur in control animals, severity was compared among treated groups. Analysis of covariance was performed to adjust for the effects of time on nasal lesion severity. Initially, separate temporal covariates were utilized for controls and treated groups. The equality of the coefficients on these terms for treated groups and controls was assessed with an F test in order to ascertain whether the rate at which lesion severity progressed was treatment related. Where there were no differences between control and treated groups with respect to lesion severity progression rate, time-adjusted severity was evaluated using Dunnett's multiple comparisons test (Dunnett, 1955). In addition, an analysis of unadjusted mean values was performed.

Identification of Statistical Significance

The text indicates that exposure related effects are significant when $p < 0.05$, unless otherwise noted.

LOCATION OF SPECIMENS, RAW DATA, AND REPORTS

All specimens, raw data, and reports are stored in the archives of the Chemical Industry Institute of Toxicology, 6 Davis Drive, Research Triangle Park, NC 27709.

RESULTS

TIME COURSE FOR STUDY

Mice (8437)

The in-life portion of the study was begun on April 16, 1984 with onset of inhalation exposure of the animals. The study progressed according to schedule with the exception that the interim necropsy was cancelled. Final necropsies occurred over the period April 10, 1986 to April 18, 1986.

Female Rats (8436)

The in-life portion of the study was begun on April 16, 1984 with onset of inhalation exposures of the animals. The study progressed according to schedule with an interim necropsy on April 16, 1985. Final necropsies occurred over the period April 23, 1986 through April 30, 1986.

Male Rats (8321)

The in-life portion of the study was begun on April 11, 1983 with onset of inhalation exposures of the animals. The study progressed according to schedule with an interim necropsy on April 11, 1984. Final necropsies occurred over the period of April 3 through April 11, 1985.

In mid 1992, pathology review by PAI was initiated. A draft of the report of the chlorine study was completed by CIIT staff in June 1993 and submitted to Research Triangle Institute (RTI; Research Triangle Park, NC) for third party audit. Comments were received on December 15, 1993. The CIIT staff addressed the questions and comments made by RTI during the summer of 1993 with completion in December 1993. The Chlorine Study Report was completed and released in December 1993 following RTI review of the improvements made in the study report and the study record based on the initial review.

EXPERIMENTAL ANIMAL STUDY PROCEDURES

Three hundred twenty animals/sex/species were received and from these 280 were randomly chosen (with the exception of male mice where 277 animals were available). The PATH/TOX randomization procedure excluded the heaviest and lightest animals from each group to give even ranges with almost identical group mean body weights at the start of the study. Because the groups were randomized prior to the start of the study, the PATH/TOX program assigns animals to necropsy time points in numerical order.

The interim necropsy for female rats was conducted on April 16, 1985 and the interim necropsy for male rats was conducted on April 11, 1984 and table titles state "Interim Necropsy".

Mice final necropsies were conducted on days 725-733 of study. Female rat final necropsies were conducted on days 738-745 of study and male rat final necropsies were conducted on days 724-732 of study. While this time frame encompasses a number of weeks, table titles state "Final Necropsy" as the time point.

EXPOSURES

Chamber Concentrations

The means (± standard error) of the daily mean chlorine concentrations were 0.40 ± 0.01, 1.00 ± 0.06, and 2.50 ± 0.11 ppm for the female and male mice; 0.40 ± 0.01, 1.00 ± 0.06, and 2.48 ± 0.11 ppm for the female rats; 0.40 ± 0.01, 1.01 ± 0.04, and 2.48 ± 0.09 ppm for the male rats.

The average (± standard deviation) of the total chlorine concentrations made in conjunction with free chlorine concentration measurements were 0.40 ± 0.03, 1.01 ± 0.09, and 2.53 ± 0.16 ppm and the corresponding average free chlorine concentrations 0.20 ± 0.14, 0.79 ± 0.18, and 2.19 ± 0.32 ppm (see Appendix E - Table E3 (p. 276)).

In separate experiments, ammonia buildup was measured in chambers that housed approximately 200 rats and mice, immediately following cleaning. Between the first three to five hours, following the closing of the chamber doors the ammonia concentration was between 0.13 and 0.17 ppm (see Appendix E - Table E4 (p. 277)) as measured at the center of the chamber between 2 animal racks with urine catch pans in place. Ammonia concentration in the same chamber, 24 hours following closure of the doors, was approximately 0.75 ppm.

Chamber Uniformity

The coefficient of variations of chlorine concentrations measured in different locations in a single chamber (the between port variability) were 8.5%, 12.8%, and 5.1% for the 0.4, 1.0, and 2.5 ppm chambers, respectively (see Appendix E - Table E2 (p. 275)).

Temperature and Relative Humidity

The temperatures in the four exposure chambers, control 0.4, 1.0 and 2.5 ppm, were held to an overall mean and standard error of 72.1 ± 1.1, 72.2 ± 1.4, 72.0 ± 1.4, 72.4 ± 1.6°F for female and male mice; 72.1 ± 1.1, 72.3 ± 1.4, 72.0 ± 1.4, 72.4 ± 1.6°F for female rats; and 72.3 ± 1.0, 71.7 ± 1.4, 71.7 ± 1.2, 71.8 ± 1.3°F for male rats. The relative humidities were held to 48.0 ± 5.4, 45.8 ± 5.1, 46.0 ± 7.1, 46.0 ± 8.1% RH for female and male mice; 47.8 ± 4.8, 45.7 ± 4.5, 46.3 ± 7.3, 46.2 ± 8.0% for female rats; and 48.1 ± 3.6, 47.5 ± 4.9, 48.0 ± 5.7, 49.4 ± 7.3% for male rats (see Appendix E - Table E1 (p. 272)).

CLINICAL OBSERVATIONS AND BODY WEIGHTS

Serologic, examinations for mouse pathogens of viral and bacterial origin were consistently negative (see Appendix B (p. 259)). Rats were positive for LCM & RCV/SDA. These positive titers should not impact on the validity of the study. A summary of the incidence of clinical findings is recorded for mice and rats in Appendix H (p. 301). Exposure-related recorded clinical observations were not present in female or male mice. Twice as many male rats were observed to be dehydrated in the high concentration group compared to each of the other three groups. Treatment-related dehydration was not recorded in the female rats.

Figures G1 to G2 (p. 298) present weekly mean body weights for treated and control groups. The results of statistical analyses of maximum body weight are provided in Tables G1 to G2 (p. 299). A concentration-related body weight-gain depression was seen in female mice, female and male rats (Tables G1 and G2, Figures G1 and G2, Appendix G (p. 295)). The results indicate that chlorine exposure resulted in depressed body weight, relative to controls, for both species. Female mice exhibited significant depression in body weight only at 2.5 ppm relative to controls. Male mice exposed to chlorine at 1.0 and 2.5 ppm attained significantly ($p < 0.01$) smaller body weights than controls. Female rats exposed for 3 days per week exhibited significant ($p < 0.01$) effects at 1.0 and 2.5 ppm, but not at 0.4 ppm. There was evidence of reduced body weight in male rats at all levels of chlorine exposure.

SURVIVAL

Survival curves for mice and rats are depicted in Figures 2 and 3 (p. 93), respectively. Statistical analyses of survival data are presented in Table 4 (p. 80). Survival analyses indicated no significant chlorine exposure-related decreases in survival for female or male mice (trend test, p=0.599N and p=0.863, respectively) or for female or male rats (trend test, p=0.518 and p=0.828N, respectively). Overall survival for female mice (Kaplan-Meier, 53.1%, 56.8%, 61.3% and 60.0% respectively) was higher than for male mice (Kaplan-Meier, 38.6%, 47.0%, 39.1% and 40.3% for 0, 0.4, 1.0, and 2.5 ppm chlorine exposure, respectively). Survival rates were better for rats than for mice (Kaplan-Meier, 85.2%, 83.1%, 81.4% and 80.2% for female rats and 72.9%, 80.4%, 73.3% and 78.0% for male rats for 0, 0.4, 1.0 and 2.5 ppm chlorine exposure, respectively). It is important when making these comparisons to remember that female rats were exposed on a 3 d/wk schedule, and all other animals were exposed 5 d/wk.

POSTMORTEM EVALUATIONS

Hematology - B6C3F1 Mice

Complete hematology summary data for the B6C3F1 mice are presented in Appendix M, Tables M1-M41 (p. 359). Because there was no interim necropsy for mice, only final necropsy data are presented. Although individual values were statistically different from controls, all values were within normal ranges for historical control animals (Bannerman, 1983).

Hematology - F344 Rats

Complete hematology summary data for the F344 rats are presented in Appendix N, Tables N1-N75 (p. 383). Although individual values were statistically different from controls, all values were within normal ranges for historical control animals (Ringler and Dabich, 1979).

Clinical Chemistry - B6C3F1 Mice

Complete summary tables of clinical chemistry results are found in Appendix O, Tables O1-O14 (p. 425). Because there was no interim necropsy in the mice, final necropsy data only are presented. Although individual values were statistically different from controls, all values were within normal ranges for historical control animals (Everett and Harrison, 1983).

Clinical Chemistry - F344 Rats

Complete summary tables of clinical chemistry results are found in Appendix P, Tables P1-P28 (p. 435). Although individual values were statistically different from controls, all values were within normal ranges for historical control animals (Ringler and Dabich, 1979).

Gross Necropsy - B6C3F1 Mice

The terminal body and organ weight data are summarized in Appendix J, Tables J1-J4 (p. 311). Gross findings are presented as summary data in Appendix L, Table L1 (p. 332). There were no biologically significant treatment-related changes in gross observations at necropsy or in brain, liver or kidney weights, but in female mice the liver weights were statistically significantly reduced. Terminal body weight changes over the course of the study were significantly lower than controls in the 1 and 2.5 ppm chlorine exposed female mice.

Gross Necropsy - F344 Rats

The terminal body and organ weight data are summarized in Appendices I and J, Tables I1 to I4, and J5 and J8 (p. 316). Gross findings are presented in Appendix K, Table K1 and K2, and Appendix L, Table L2 and L3 (p. 347). There were no biologically significant treatment-related changes in brain, liver or kidney weights in female or male rats or macroscopic findings in male rats at necropsy. Terminal body weight was decreased in male rats at the interim necropsy and in both sexes at the final necropsy. High concentration exposed female rats had the macroscopic observation of cataract which was not seen in any other treatment group. However, following microscopic examination, the eye was not considered a target organ.

HISTOPATHOLOGY

Histopathology data related to this bioassay are included in original study reports by the EPL study pathologists, of which the summary reports are presented in Appendix Q (p. 451) for the mice and Appendix R (p. 467) for rats. Summary incidence data of microscopic observations for both mice and rats are presented in Appendix S (p. 499). Data tables are presented for lesions that were diagnosed at an incidence of more than one in any treatment group. Appendix X (p. 749) contains reports covering: 1) a pathology group peer review (PGPR) assessment for the histopathology, 2) resolution of discrepancies between the original pathology report and the pathology quality assessment, and 3) the summary reports of the pathology quality assessment. Addendum reports resulting from reviews of selected reproductive tract (Appendix BB (p. 811)) and nasal lesions (Appendix CC (p. 831)) by CIIT pathologists are also attached. Statistical analyses of the histopathology data are presented in Appendix S (p. 499). No significant treatment-related increases in neoplastic responses were observed.

The original EPL study pathologists commented that in general all tissues specified in the protocol were represented in the sections, autolysis was encountered in some animals, and nasal section levels varied between animals. However, it was stated that these factors did not affect the interpretation of the treatment-related lesions. The PGPR supported these

comments, and made no major changes except for the addition of one lesion (septal fenestration). An additional review (by CIIT pathologists) of this lesion and a background lesion in the nasal vestibule resulted in additional tabular data on the incidence (septal fenestration) and severity (background vestibular inflammation) of vestibular changes (Appendix CC (p. 831)). The results of all of these reports are summarized briefly below.

Lesions attributable, directly or indirectly, to chlorine exposure were confined to the nasal passages of female and male mice and rats, and to the reproductive tract of female mice. In all tissues examined a range of non-neoplastic and neoplastic 'spontaneous', 'background', or aging lesions occurred. These lesions were of the type and frequency commonly diagnosed in B6C3F1 mice (Goodman et al., 1985) and F344 rats (Boorman et al., 1990; Moore et al., 1992) in chronic bioassays.

B6C3F1 Mice (8437) - Final Necropsy and Unscheduled Deaths

Necropsies of early deaths and moribund animals occurred with more or less equal frequency among control and chlorine-exposed mice of each sex, and chlorine exposure did not appear to contribute to the mortality. Survival to the terminal necropsy was greater in females than males for all groups including the controls. No neoplastic responses associated with chlorine exposure were noted.

Nasal Lesions

Chlorine exposure resulted in a number of non-neoplastic responses that were confined to the nasal passages, and many of these lesions occurred in all chlorine treatment groups. Lesions were recorded by section level, from 1 to 5 (levels shown in Figure 1 (p. 92)) (Appendix S, Tables S1b (p. 512)), and selected data containing treatment related lesions were extracted for tabulation (Table 5 and 6). The principal changes at each level were:

Nasal Level 1: Epithelial hyperplasia, microabscesses, and eosinophilic material, involving in each case, the squamous epithelium. The overall incidence of treatment-related lesions at this level was similar for both sexes (Appendix S, Table S1 (p. 500)). Squamous epithelial hyperplasia and microabscessation occurred in control groups of both sexes but with lower frequency and severity than that observed in chlorine-exposed animals. The region of

the nose present in level 1 (nasal vestibule) has rarely been examined in toxicology studies (Morgan, 1991). Furthermore, since the time that these slides were examined by the EPL pathologists recent work has revealed a number of important responses in this site that are attributable to environmental cage contaminants for rats (Bolon et al., 1991) and mice (Morgan, unpublished observations). Re-examination of the nasal vestibule of all mice (see report, Appendix CC (p. 831)) confirmed the presence of lesions in the squamous epithelium that were potentially attributable to cage contaminants, including epithelial hyperplasia and inflammatory cell infiltration by neutrophils and mononuclear cells. The hyperplasia was frequently associated with epithelial folding. Subjective scoring of the severity of this lesion revealed a fairly high frequency in female (52%) and male (31%) control mice. The lesion was increased in both severity and frequency in all chlorine exposed groups, with no apparent concentration-response relationship. The fact that the severity of this lesion was modified by chlorine exposure in mice, in contrast to rats, indicates that it was not distinguishable from chlorine-induced lesions and should be interpreted with caution.

Septal perforation or fenestration was characterized by the presence of a hole in the anterior nasal septum resulting in an airway connecting the left and right nasal cavities. These fenestrations ranged in size from small punctures to almost complete loss of the anterior nasal septum in the first and/or second sections. The margins of the septal perforation were either eroded, ulcerated, or more usually completely covered by squamous or respiratory epithelium. The lesion was absent in control male mice and present with a low frequency (5.2%) in female control mice (Appendix CC (p. 831)). In chlorine-exposed animals, the frequency of septal fenestration ranged from 26.3 to 40.7 in male mice with no evident concentration-response relationship or no-effect concentration. In contrast to male mice, female mice had a clear association between exposure concentration and frequency of the lesion with a no-effect concentration of 0.4 ppm.

Nasal Level 2: This level of the nose contained treatment-related lesions in areas of ciliated and non-ciliated respiratory epithelium. [Note: the non-ciliated respiratory epithelium of the anterior nose is currently referred to as transitional epithelium (Harkema, 1991), and this terminology has been adopted for this report. However, in the original EPL reports (Appendix S (p. 554)) the term non-ciliated respiratory epithelium is used for this site.]

The treatment-associated lesions included eosinophilic material, 'transitional metaplasia', squamous metaplasia, and inflammation (Appendix S, Table S1b (p. 554)). Eosinophilic material which has been previously described (Buckley et al., 1984 and Popp et al., 1986) is an accumulation of proteinaceous material within respiratory epithelial cells and other sites. The eosinophilic character of these accumulations gives them a bright red appearance in HE stained sections. In place of the term transitional metaplasia, proposed by the EPL pathologist for certain responses in the respiratory/transitional epithelial regions of the anterior nose, the PGPR pathologists considered the term epithelial hyperplasia more appropriate (Appendix X (p. 755)); the text and tables of this report have been modified to reflect this change. Epithelial hyperplasia was characterized by thickening of the respiratory and/or transitional epithelia due to an increase in cell number. The affected epithelia had a disorganized appearance, and sometimes exhibited evidence of early squamous metaplasia in the form of nuclear rotation at the surface, with the long axis of affected nuclei lying parallel to the epithelial basement membrane.

In areas of respiratory epithelium, eosinophilic material and epithelial hyperplasia were confined to chlorine exposed male mice, with a concentration-related trend for severity. However, in female mice, this treatment-relationship was less clear (Appendix S, Table S1b (p. 552)). In areas of transitional epithelium the incidences of eosinophilic material, epithelial hyperplasia, squamous metaplasia, and inflammation, were increased by chlorine exposure with some concentration-related trends in both males and females (Appendix S, Table S1b (p. 554)).

Nasal Level 3: In section 3, treatment-related incidence trends were present in both sexes for respiratory epithelial eosinophilic material, respiratory epithelial hyperplasia, and atrophy of olfactory epithelium (Appendix S, Table S1b (p. 558)). Olfactory epithelial atrophy was characterized by accumulations of eosinophilic material in sustentacular cells, with crystalline inclusions in some areas, and an associated loss of sensory cells. In females, luminal exudate and eosinophilic material in the submucosal mucous glands in areas of ciliated respiratory epithelium occurred more frequently in chlorine treated groups (Appendix S, Table S1b).

Nasal Level 4: In section 4 a similar range of lesions was observed to those reported for section 3 (Appendix S, Table S1b (p. 569)). Eosinophilic material in ciliated respiratory and olfactory epithelia, in addition to olfactory epithelial atrophy, was prevalent in both sexes. Luminal exudate and eosinophilic material in submucosal glands occurred at elevated frequency in female mice but not in males.

Nasal Level 5: In section 5, atrophy of the olfactory epithelium and accumulation of eosinophilic material occurred at a low, but with a treatment-related increase, in female mice (Appendix S, Table S1b (p. 579)). In males, however, the incidence of olfactory epithelial atrophy and eosinophilic globule accumulation decreased sharply between levels 4 and 5. Cystic degeneration of Bowman's glands occurred adjacent to sites of olfactory epithelial atrophy, and the highest incidence of this change (39%) occurred in females exposed to 2.5 ppm chlorine.

Reproductive Tract

A review of reproductive tract lesions was carried out for female mice (Appendix BB (p. 811)). Ovarian abscesses and suppurative inflammation of the uterus occurred at an incidence of 47% and 44%, respectively, in the 2.5 ppm group. A smaller proportion of the low and mid-concentration animals were affected with this lesion. In the control group, 21% of the animals were diagnosed with suppurative inflammation of the uterus, but only 4% had ovarian abscesses. These lesions were attributed to the infectious condition described by Rao et al. (1987).

F344 Rats - Interim Necropsy and Unscheduled Deaths

Pathology results from animals that died during the study are provided in Appendix R (p. 467). In both the 12 months and final necropsy, and for unscheduled deaths where histopathology was performed, treatment-related lesions were confined to the nasal passages.

Background lesions, including squamous epithelial hyperplasia and inflammation of the nasal vestibule were observed in control male and female rats. These lesions, which were attributable to exposure of the animals to environmental contaminants (Bolon et al., 1991), were reviewed by a CIIT pathologist and found to affect all groups of treated and untreated

rats, with a similar incidence and severity (Appendix CC (p. 831)). The mean severity scores of these lesions ranged from absent (score of 0) to minimal (score of 2). Females were generally less affected than males. (Appendix CC (p. 831)).

Female F344 Rats (8436)

One early death occurred in each of the control and the group 4 females, and cause of death was not attributed to chlorine exposure. Treatment-related lesions were confined to the nasal passages (Appendix S, Tables S2b (p. 686)).

Nasal Lesions

Selected data containing treatment-related lesions were extracted for tabulation (Table 7).

Nasal Levels 1 and 2: Increased numbers of goblet cells and neutrophils (subacute inflammation) were observed in chlorine-exposed rats. The nasal vestibule of female rats had background lesions in all groups and these lesions were of similar severity and incidence to those found in males (Appendix CC (p. 831)). No septal fenestrations were observed in female rats.

Nasal Levels 3, 4, and 5: Goblet cell hyperplasia was increased in chlorine-exposed animals. A treatment-related increase in incidence and severity of eosinophilic material was observed in respiratory and olfactory epithelial cells. The olfactory epithelium was most severely affected.

Incidental Nasal Lesions: No treatment related lesions were noted.

Male F344 Rats (8321)

There were a few early deaths (4) in male rats that were not considered chlorine-related. Treatment-induced lesions, which were confined to the nasal passages, are summarized in Appendix S, Tables S2b (p. 686).

Nasal Lesions

Selected data containing treatment-related lesions were extracted for tabulation (Table 8).

Nasal Levels 1 and 2: Treatment-related lesions were the most pronounced in levels 3 and 4. Septal fenestration was detected in section level 1 of one male rat exposed to 2.5 ppm chlorine. One male rat in the 1.0 ppm group exhibited atrophy of the atrioturbinate. These findings indicate that treatment-related effects were present in section levels 1 and 2, but were probably obscured by the background lesions present in this site (Appendix CC (p. 831)).

Nasal Level 3: Goblet cell hyperplasia was recorded and scored for this level of the nose. The scores for this lesion (Table 8 (p. 91)) indicated a clear treatment-induced response; however, a clear concentration-response relationship was less clear (Appendix X (p. 755)). There was an increased incidence of eosinophilic material in the olfactory epithelium of the dorsal medial meatus in treated rats. The severity of this lesion was minimal in controls and varied from minimal to moderately severe in the chlorine-exposed animals.

Nasal Level 4: Chlorine-induced responses were present in respiratory epithelium, underlying glands, and olfactory epithelium. Goblet cell hyperplasia (see comments above) was present to a minimal extent in one control rat and was present with increased incidence and severity in treated rats. Eosinophilic material were present in the respiratory epithelium of control rats, and this lesion exhibited an increased incidence in 1.0 and 2.5 ppm group animals. Eosinophilic material were also present in glandular epithelium in treated animals but not in controls. There was a concentration-related increase in the incidence of olfactory epithelial eosinophilic material in chlorine exposed animals.

Nasal Level 5: No treatment related lesions were noted.

Incidental Nasal Lesions: A few incidental lesions occurred in the nasal cavity, including epithelial microabscesses and mineralization. One nasal adenocarcinoma was found in a group 3 animal. The PGPR agreed that this was an incidental finding, unrelated to chlorine exposure.

F344 Rats - Final Necropsy and Unscheduled Deaths

Female F344 Rats (8436)

Early deaths occurred with essentially equal frequency in control and chlorine-exposed female rats, and these deaths were not attributed to chlorine exposure. In a number of the animals that died vascular thrombi were observed in the anterior nasal passages (Appendix CC (p. 831)), and one animal exhibited ulceration of the nasal mucosa. In the final necropsy animals, treatment-related lesions were confined to the nasal passages (Appendix S, Table S2b (p. 686)).

Nasal Lesions

Nasal Level 1: Subacute inflammation and goblet cell hyperplasia were observed with equal frequency in control and treated animals.

Nasal Level 2: Goblet cell hyperplasia was most prominent in chlorine-exposed animals, and occurred with increased frequency compared to controls (Appendix S, Table S2b (p. 692)), with a concentration-related trend for severity. Eosinophilic material occurred in the glandular epithelium of some 0.4 and 1.0 ppm group animals. Subacute inflammation was increased in 2.5 ppm group animals.

Nasal Level 3: Concentration-related increases in severity and incidence of goblet cell hyperplasia and eosinophilic material were observed. The eosinophilic material was most extensive in the olfactory epithelium. Mucopurulent exudate was present in two 2.5 ppm group animals.

Nasal Levels 4 and 5: Treatment-related increases were observed in incidence and severity of goblet cell hyperplasia and eosinophilic deposits in the respiratory, glandular, and olfactory epithelia, with the olfactory epithelium being most severely affected.

Male F344 Rats (8321)

Early deaths, which occurred with similar frequency in control and chlorine-exposed male rats, were not attributed to treatment. In the final necropsy animals, treatment-related lesions were observed in the nasal passages at all treatment concentrations. These changes are presented in Appendix S, Table S2b (p. 686).

Nasal Lesions

Nasal Level 1: Squamous epithelial microabscesses and hyperplasia occurred with greater frequency in chlorine-exposed animals.

Nasal Level 2: Goblet cell hyperplasia was most severe in 0.4 ppm group animals, compared to controls and 1.0 and 2.5 ppm groups.

Nasal Levels 3, 4, and 5: The major lesion was eosinophilic material in olfactory, respiratory, and glandular epithelium, goblet cell hyperplasia, and subacute inflammation of the lamina propria. The hyperplastic glandular epithelium was derived from infolding of the surface respiratory epithelium (glandularization), which was most pronounced in treated animals. Inflammation was present in controls, but was more pronounced in treated animals. In level 5, subepithelial mineralization occurred in a substantial number of both control and treated animals, but the incidence was decreased in the two highest concentration groups.

Incidental Nasal Lesions: A number of other lesions occurred sporadically in control and treated male rats, including mineralized concentrations, mucopurulent exudate, and inspissated mucus. A fibrosarcoma of the hard palate occurred in one control rat, and an adenocarcinoma in the nasal epithelium in a single 1.0 ppm group rat that died early.

Statistical Analysis of Nasal Histopathology Data

For nasal toxicity many of the endpoints graded were statistically significantly increased for both incidence and severity score. The majority of these nasal responses exhibited a statistically significantly increased incidence at all exposure concentrations (Tables 5-8 (p. 88)).

However, for the severity score, the majority of statistically significant lesions were largely confined to the 2.5 and 1.0 ppm exposure groups. Lesions which were found on the basis of statistical analysis to be increased for both incidence and severity at all three exposure concentrations (i.e., no no-effect concentration observed) were:

(a) Squamous epithelial hyperplasia (female mice)
(b) Respiratory epithelial hyperplasia (male mice)
(C) Eosinophilic material in the olfactory epithelium (male rats)

No nasal neoplasms attributable to chlorine exposure were observed in mice or rats.

In both control and chlorine-exposed animals, a wide range of neoplastic and non-neoplastic lesions were observed in many organs by light microscopy, as would be expected in aging rodents (Burek, 1978; Mohr et al., 1992). Chlorine-associated responses were restricted to the nasal passages (male and female, rats and mice) and reproductive tract (female mice). The nasal lesions were generally site-specific within the nose, but their severity and/or incidence was not always related to chlorine exposure concentration. The majority of these nasal responses exhibited a clear anterior-to-posterior severity gradient, being most severe in the anterior nose, and only rarely extending to the nasopharyngeal meatus. The majority of these responses were statistically significantly increased at all chlorine concentrations studied. There were no biologically or statistically significant chlorine exposure-related increases in neoplasms in the nasal mucosa or other tissues in mice or rats.

F344 Rat Eye Lesions

A wide range of degenerative ocular lesions were observed in both female and male rats. Statistical analysis of the incidence of unilateral eye lesions, including retinal degeneration, indicated potential treatment relationship for these lesions. However, combination of unilateral with bilateral eye lesions for statistics resulted in loss of statistical significance. Given the lack of a clear concentration relationship for these lesions, their location in largely intra-orbital locations, and their diverse nature, it was concluded that these lesions were probably not attributable to chlorine exposure.

Principal Observations from Histopathology

Chlorine-induced toxicity is apparently confined to the reproductive tract of female mice and the nasal passages of female and male, mice and rats. Female rats are sensitive to chlorine exposure, which resulted in considerable losses in an initial study (8321) and a modified exposure schedule for female rats. However, histopathologic examination failed to demonstrate the cause of these deaths. In the anterior nose (section levels 1 and 2) interpretation of treatment-related responses was made more difficult because of background lesions which were not present in the posterior nose (section levels 3, 4 and 5). These background lesions are probably attributable to environmental cage contaminants, such as ammonia (Bolon et al., 1991; Inhalation Report Appendix E, Table E4 (p. 277)). The major chlorine-induced or augmented responses were: squamous epithelial hyperplasia of the vestibule (mice); inflammation of the epithelium and lamina propria of the anterior nose (mice and rats); perforation (fenestration) of the anterior nasal septum (mice, one rat); transitional epithelial hyperplasia and mucous metaplasia (mice and rats); respiratory epithelial hyperplasia and glandularization (mice and rats); accumulations of eosinophilic material in respiratory, glandular, and olfactory epithelia (mice and rats), and; olfactory epithelial sensory cell loss (mice and rats). A number (but not all) of these changes exhibited a concentration-relationship for incidence and severity. For a number of responses, no no-effect concentration was observed. No evidence of chlorine-induced cancer was observed in the nasal passages or any other sites.

DISCUSSION

The present investigation has demonstrated that airborne chlorine is not a carcinogen in mice or rats. There is no evidence from published studies that chlorine is carcinogenic. In one epidemiological survey of a group of pulp mill workers exposed to chlorine and chlorine byproducts, an increased incidence of lung tumors was reported (Jäppinen and Pukkala, 1991). Seven lung tumors were observed compared to the 2.3 expected; however, 6/7 of these lung tumors were in cigarette smokers. The authors suggested that the increased incidence may have been associated with workplace exposure to chlorinated compounds, but confounding variables in this study render that conclusion questionable. Although chlorine is not carcinogenic in rodents, in the present study it was clearly a nasal irritant that affected all airway epithelial types in the nose, but no effect was observed in the larynx or lower respiratory tract.

Female mice had an apparent concentration-dependent reproductive tract inflammatory response to chlorine treatment. However, it was unlikely that chlorine caused this inflammatory lesion. Metritis and ovarian abscessation had been reported in a series of chronic bioassays in which Klebsiella sp. bacteria were isolated (Rao et al., 1987). The incidence of infection was not treatment related, 8.9% in treated and 9.2% in controls (Rao et al., 1987). Factors such as microbial status of the animals, age, reproductive tract function, and management procedures were consistently related to the presence of endometritis and ovarian abscesses (Rao et al., 1987).

In the present study, the production of chloramines may have had an impact on the actual chamber chlorine concentrations. In each of the 0.4, 1.0, and 2.5 ppm chambers, there was, on the average, a total of 0.25 ppm of chlorine unaccounted for, between measurements for total and free chlorine. This reduction of free chlorine may have been due to the presence of ammonia in the chamber during the six hours of exposure. In equivalently loaded, clean control chambers, the mean ammonia concentration was 0.15 ppm, between the first three to five hours following closure of the chamber doors. The ammonia content in the expired air of rodents (0.073 ppm; Barrow and Steinhagen, 1980) would have little effect on these measured concentrations because the animal load represented less than 5% of the total volume of the

chamber. The major source of ammonia in the chambers was most likely the urine produced by the animals. The large variances in the free chlorine data (70%, 23% and 15%, respectively, for the 0.4, 1.0 and 2.5 ppm chambers) are an indication of the variation in the analysis method and actual chamber ammonia concentration during the six-hour exposure day each week that these measurements were taken, and may reflect the amount of excrement in the chambers as a function of time. Other than the free chlorine measurements, no measurements were regularly taken during the course of the study to indicate the range of ammonia concentrations before and after removal of urine and feces catch pans. Although ammonia combining with chlorine does produce chloramine, the contribution that chloramines made to the toxicity is questionable.

Chlorine-induced cellular injury is believed to be a result of oxidation of functional groups in cell components after reaction of chlorine with water, forming HCl and HOCl (McNulty et al., 1983). The spontaneous breakdown of HOCl to HCl and free O results in generation of oxygen radicals and causes the major cytotoxic effects by this nascent oxygen (Barrow et al., 1977; Givan et al., 1989; Schraufstätter et al., 1990). The hydrochloric acid formed may also act as a secondary irritant (Wood et al., 1987). These mechanisms would be consistent with the nasal tissue damage and inflammation observed in mice and rats in the present study.

Accumulation of eosinophilic, presumably proteinaceous, deposits in the nose, reported and described previously as a common background lesion in untreated control rats, increase in frequency with age and exposure to gaseous irritants (St. Clair and Morgan, 1992). The significance of intracytoplasmic eosinophilic proteinaceous accumulation is uncertain, although it has been described with several other respiratory irritant gases and may serve as an indicator of toxicity (Buckley et al., 1984; Morgan, 1991; Popp et al., 1986). In the present study, development of eosinophilic proteinaceous accumulation was associated with varying degrees of mucous cell metaplasia and hyperplasia. This observation is consistent with the proposal that eosinophilic proteinaceous accumulations are composed of a protein associated with aberrant or excessive mucus synthesis. Recent studies demonstrated that, in rats exposed to pyridine vapors, these deposits stained positive by immunohistochemistry for

naphthyl butyrate esterase (Lewis et al., 1993). However, the toxicologic significance of this response is unknown.

An interesting finding from this study and previous studies is the sex difference in response to chlorine gas exposure. Female rats and monkeys were more sensitive than males (Barrow et al., 1979; Klonne et al., 1987). In the present study, mice exhibited sex differences in response to comparable concentrations of chlorine. Male mice had equivalent incidence of septal fenestration at all exposure concentrations, whereas female mice only had increased incidences at the mid and high concentrations, suggesting that male mice are more sensitive than females to chorine exposure. Female rats were markedly more sensitive to chlorine exposure than male rats and would have suffered severely decreased survival if exposed 5 days/week (Appendix AA), instead of 3 days/week at the same concentrations as the male rats. The reasons for these sex differences are unknown but warrant further investigation.

The range of treatment-induced non-neoplastic responses observed in the nasal lining of rodents in the present study are of value for determining human disease risk associated with inhaled chlorine. The specific localization of the rodent lesions in the upper respiratory tract, as has been reported for other water soluble reactive gases (Jiang et al.1986; Witorsch, 1987), may reflect regional airway dosimetry, regional tissue susceptibility, or a combination of these factors (Morgan and Monticello, 1990). Recent studies of another highly water soluble gas, formaldehyde, indicate some similarities in the distribution of nasal lesions in rodents for these two toxicants, in both cases the lateral meatus is the most severely affected region of the nose following acute (Monticello et al., 1991) and chronic (Morgan et al., 1986) exposures. The distribution of formaldehyde-induced nasal lesions in the anterior nose is probably attributable to airflow-driven regional gas dosimetry (Kimbell et al., 1993). A similar mechanism could account for the chlorine-induced anterior nasal lesions observed in mice and rats in the present study.

In rhesus monkeys exposed to chlorine, nasal lesions principally occurred on the margins of the middle turbinate and adjacent lateral wall and nasal septum (Klonne et al., 1987), which was similar to that reported for formaldehyde in this species (Monticello et al.,

1989). Formaldehyde-induced nasal lesions in monkeys were also considered to be attributable to airflow-driven dosimetry on the basis of inspiratory airflow patterns (Morgan et al., 1991). In addition to nasal lesions, both formaldehyde (6 ppm) and chlorine (2.3 ppm) induced mild lesions in the trachea in rhesus monkeys following inhalation exposure. No evidence of damage to the respiratory tract distal to the nasopharyngeal meatus was observed in rodents exposed to chlorine in the present study . These data suggest that regional dosimetry plays a major role in the distribution of lesions induced by chlorine in rodents and rhesus monkeys.

It is unlikely that regional dosimetry accounts for the diffuse olfactory epithelial lesions observed in the ethmoturbinates in the present study. The transitional secretory (mucous) metaplasia in rats and mice exposed to chlorine is similar to the nasal lesions reported in ozone exposed rats (Hotchkiss et al., 1990). The airway epithelium acts as a protective barrier between inspired air and the underlying tissues and is provided with a number of defenses, including the mucus epiphase that contains a number of antioxidants (Koren et al., 1990). Modification of surface mucus could play an important role in chlorine toxicity, as has been proposed for ozone (Pryor, 1992). Recent studies of nasal dosimetry of ozone in the rat using computational fluid dynamics indicated that airflow-driven dosimetry is probably not the major factor accounting for the distribution of nasal lesions (Kimbell et al., 1993). This observation indicates that site specific tissue susceptibility may combine with local tissue factors to account for the distribution and nature of the toxic responses observed in rats and mice exposed to chlorine gas.

Studies such as these always lead to a critical question in toxicology, Does rodent upper respiratory tract toxicity indicate human risk of respiratory tract toxicity? Humans exposed to toxic levels of chlorine (66 ppm) develop basal cell and goblet cell hyperplasia and inflammation in the bronchi (Shroff et al., 1988). These lesions were similar in character, but different in location, to those noted in rodents exposed to chlorine in the present study. Any attempt to use data derived from rodents exposed to chlorine, for assessment of human health risks, should take into account the potential influence of interspecies differences in regional dosimetry, site-specific tissue susceptibility, and the role of airway defenses, such as the

mucociliary apparatus. This work might also benefit from consideration of the large data base available for other reactive gases, including formaldehyde and ozone.

CIRCUMSTANCES THAT MAY HAVE AFFECTED THE QUALITY AND INTEGRITY OF THE STUDY

Several items have been identified that may be interpreted to have potentially impacted the quality and integrity of these studies. On evaluation of each item, CIIT deems that no single item nor the combination of all items seriously impacted the study. The following items are noted with individual evaluations.

Study #8436 - Female F344 rats were exposed on Tuesday, May 1, 1984 which is a deviation from their Monday, Wednesday, Friday protocol schedule. This single additional exposure during a 2 year period of exposure is unlikely to alter the results of the study.

Drinking water was not analyzed during the course of the study for the presence of chlorine or impurities. However, a water filtration system was in place during the course of this study. This system would have reduced water impurities in the water supplied from a local municipal water source.

Rust was removed from some of the chambers April 30, 1984 using naval jelly as approved by the Testing Program Steering Committee. Since the contents of naval jelly are readily water soluble, no residual material would be expected after routine cage and chamber sanitation.

There were no animal room notebooks maintained for study 8321 prior to June 15, 1983. Clinical observations and body weights were recorded in AOLOG the PATH/TOX system electronic study notebook during the period from April 4, 1983 through June 15, 1983 as specified in the protocol. The AOLOG record provides documentation of proper animal care even though the animal room notebooks are incomplete.

Four mice on study 8437 (4 high concentration exposed male mice and one control female mouse) died during the first two weeks of exposure and were not replaced as specified in the protocol.

The quality of the in-life clinical observations and body weights were variable in detail and consistency apparently due to the differences between animal care technicians assigned to the various experimental groups. Body weights have been reviewed for each study. The decision was made by the study director to edit out body weights recorded to be less than 1 gram in study 8437. This decision affected the record of 5 B6C3F1 mice and 1 rat. Animals were not weighed according to protocol in several instances (8321 - week 14 and week 53; 8436 - week 31, 41, and 91; 8437 - week 21 and 27). While the deficiencies preclude detailed comparison of clinical observations and body weight across treatment groups and at different times within a treatment group, the toxicologic endpoints evaluated by histopathology examination of tissues from animals in the study were not affected.

One male mouse was missexed in study 8437. Twenty-three notations in animal room notebooks indicated the presence of pregnant animals or pups in the chambers. Postpartum female rats or mice were not removed from the study. The impact of breeding can not be absolutely ascertained.

Over the course of the studies there were multiple notations in animal room notebooks of animals dehydrated due to the watering system malfunctions or systems disconnected when the animals were scheduled for water or inadequate food supply.

Documentation is missing in the study record concerning receipt of 5 cylinders of chlorine gas used in these studies. While the documentation of receipt of the cylinders is not available, analysis of the contents of the cylinders provide verification of the exposure.

Inconsistencies were noted in the recording of clinical pathology results from the raw data into the PATH/TOX data base. Since all clinical pathology data has been QC checked, the inclusion or exclusion of specific values has been consistently entered into the final study record. Therefore, the reported data are accurate.

During the course of the study, there was concern for possible heavy metal exposure from caging since chlorine damage was noted. However, several analyses of tissues from

exposed animals did not demonstrate increased levels of iron, nickel or chromium after four months of exposure to chlorine gas damaged metal caging.

The production of chloramines may have had an impact on the actual chamber chlorine concentrations. In each of the 0.4, 1.0, and 2.5 ppm chambers, there was, on the average, a total of 0.25 ppm of chlorine unaccounted for, between measurements for total and free chlorine (see Appendix E - Table E3 (p. 276)). This reduction of free chlorine may have been due to the presence of ammonia in the chamber during the six hours of exposure. In equivalently loaded, clean control chambers, the mean ammonia concentration was 0.15 ppm, between the first three to five hours following closure of the chamber doors (see Appendix E - Table E4 (p. 277)). The ammonia content in the expired air of rodents (0.073 ppm; Barrow and Steinhagen, 1980) would have little effect on these measured concentrations because the animal load represented less than 5% of the total volume of the chamber. The major source of ammonia in the chambers was most likely the urine produced by the animals. The large variances in the free chlorine data (70%, 23% and 15%, respectively, for the 0.4, 1.0 and 2.5 ppm chambers) are an indication of the variation in the analysis method and actual chamber ammonia concentration during the six-hour exposure day each week that these measurements were taken, and may reflect the amount of excrement in the chambers as a function of time. Other than the free chlorine measurements, no measurements were regularly taken during the course of the study to indicate the range of ammonia concentrations before and after removal of urine and feces catch pans. Although ammonia combining with chlorine does produce chloramine, the contribution that chloramines made to the toxicity is questionable.

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Table 1

Mean Body Weight of Each Animal Group Following Randomization[a]

B6C3F1 Mice and F344 Rats

Sex/Species	Treatment Groups[b] 1	2	3	4
Female B6C3F1 Mice 4-9-84	21.38 ± 1.16	21.37 ± 1.14	21.38 ± 1.13	21.37 ± 1.12
Male B6C3F1 Mice 4-9-84	24.41 ± 6.37	24.51 ± 6.22	24.45 ± 6.25	24.49 ± 6.23
Female F344 Rats 4-9-84	115.10 ± 4.33	115.08 ± 4.31	115.09 ± 4.31	115.07 ± 4.35
Male F344 Rats 4-4-83	159.69 ± 8.06	159.67 ± 8.06	159.65 ± 8.09	159.63 ± 8.05

[a]Body weights (g) are expressed ± S.D.
[b]For # per group see Table 2

Table 2a

Animal Accounting

B6C3F1 Mice - 8437

	Males				Females			
Dose (ppm)	0	0.4	1.0	2.5	0	0.4	1.0	2.5
Interim Necropsy	0	0	0	0	0	0	0	0
Final Necropsy	23	30	26	26	33	39	34	36
Found Dead	31	28	32	33	24	22*	17	21
Left Study as Missing	3	4	1	3	4	2	11	9
Accidental Trauma	3	1	2	1	2	1	2	0
Found Moribund	7	7	9	7	7	6	6	4
Removed for Research	0	0	0	0	0	0	0	0
Total	67	70	70	70	70	69	70	70

*One animal, #354, was a male and is not included in the total count. Its pathology results have been removed from the study record. Because data from this animal in areas other than pathology was not removed from the data base a difference in total group number may be noticed in data tables that include all animals or unscheduled animals. This small discrepancy does not effect the statistical analysis or interpretation of this study.

Table 2b
CHLORINE STUDY
in B6C3F1 Mice
Unscheduled Deaths

STUDY # 8437
SPECIES B6C3F1 Mice
SEX Female

Dose (ppm)	0	0.4	1.0	2.5
Found Dead	282,284,285, 288,290,292, 295,297,298, 300,302,304, 305,307,316, 318,319,320, 322,327,330, 333,335,347	354*,356,357, 360,366,369, 370,371,372, 373,375,379, 382,384,387, 389,390,392, 397,402,405, 414,417	418,423,429, 430,431,433, 441,447,448, 455,462,463, 464,470,477, 480,485	491,495,498, 506,508,512, 514,516,519, 525,526,532, 536,539,544, 545,548,550, 551,553,554
Total	24	22	17	21

Dose (ppm)	0	0.4	1.0	2.5
Left Study as Missing	281,293, 294,339	383,401	420,427,437, 442,446,449, 451,467,471, 473,481	490,497,500, 513,523,534, 543,549,556
Total	4	2	11	9

Dose (ppm)	0	0.4	1.0	2.5
Found Moribund, Necropsied	283,291,301, 317,326,331, 345	348,367,388, 398,404,415	424,438,458, 468,475,483	494,507,511, 546
Total	7	6	6	4

Dose (ppm)	0	0.4	1.0	2.5
Accidental Trauma, Necropsied	314,337	395	422,445	---
Total	2	1	2	0

Total	37	31	36	34

*Not included in total count because this animal was mistakenly sexed as female when it was assigned to the study.

Table 2c
CHLORINE STUDY
in B6C3F1 Mice
Unscheduled Deaths

STUDY # 8437
SPECIES B6C3F1 Mice
SEX Male

Dose (ppm)	0	0.4	1.0	2.5
Found Dead	2,5,7,8,9,10, 11,13,20,22,23, 24,26,27,31,32, 33,34,36,38,40, 43,48,49,53,54, 55,56,59,64,65	68,70,75,76,85, 89,91,97,99, 101,103,104, 105,110,114, 115,120,121, 122,125,128, 130,131,132, 133,134,136 137	139,142,144, 145,146,147, 153,157,159, 161,162,164, 167,169,174, 175,177,179, 182,186,187, 193,194,195, 196,197,198, 202,203,204, 206,207	209,211,212, 214,215,218, 219,222,223, 225,227,229, 230,236,238, 240,245,246, 248,250,252, 253,255,256, 259,260,264, 266,267,268, 270,275,277
Total	31	28	32	33

Dose (ppm)	0	0.4	1.0	2.5
Left Study as Missing	29,58,67	69,80,88,94	166	239,254,276
Total	3	4	1	3

Dose (ppm)	0	0.4	1.0	2.5
Found Moribund, Necropsied	12,18,19,21, 25,35,46	81,87,102,107, 117,119,126	138,154,155, 180,181,184, 188,190,191	213,235,237, 247,249,265, 272
Total	7	7	9	7

Dose (ppm)	0	0.4	1.0	2.5
Accidental Trauma, Necropsied	3,63,66	129	171,201	217
Total	3	1	2	1

Total	44	40	44	44

Table 2d

Animal Accounting

F344 Rats - 8436 (Restart)

	Female			
Dose (ppm)	0	0.4	1.0	2.5
Interim Necropsy	10	10	10	10
Final Necropsy	50	49	48	48
Found Dead	5	3	3	2
Left Study as Missing	1	1	1	0
Accidental Trauma	0	0	0	0
Found Moribund	4	7	8	10
Removed for Research	0	0	0	0
Total	70	70	70	70

Table 2e
CHLORINE STUDY
in F344 Rats
Unscheduled Deaths

STUDY # 8436
SPECIES F344 Rat
SEX Female

Dose (ppm)	0	0.4	1.0	2.5
Found Dead	6,14,26,45,51	87,131,136	157,166,178	228,241
Total	5	3	3	2

Dose (ppm)	0	0.4	1.0	2.5
Left Study as Missing	70	127	158	---
Total	1	1	1	0

Dose (ppm)	0	0.4	1.0	2.5
Found Moribund, Necropsied	13,22,39,54	82,83,84,134, 135,137,139	174,175,180, 182,189,197, 201,202	239,245,247, 253,259,261, 263,264,271, 278
Total	4	7	8	10

Dose (ppm)	0	0.4	1.0	2.5
Accidental Trauma, Necropsied	---	---	---	---
Total	0	0	0	0

Total	10	11	12	12

Table 2f

Animal Accounting 8321

F344 Rats

	Males			
Dose (ppm)	0	0.4	1.0	2.5
Interim Necropsy	10	10	10	10
Final Necropsy	43*	48	43	46
Found Dead	7*	5	10	8
Left Study as Missing	0	0	0	0
Accidental Trauma	0	0	1	0
Found Moribund	9	7	6	5
Removed for Research	1	0	0	1
Total	70	70	70	70

* One animal (#60, Group 1 - Male) was found dead during the final necropsy period and is included in the final necropsy group. Body weight data, organ weight data and pathology data are included with the final necropsy group.

Table 2g
CHLORINE STUDY
in F344 Rats
Unscheduled Deaths

STUDY # 8321
SPECIES F344 Rats
SEX Male

Dose (ppm)	0	0.4	1.0	2.5
Found Dead	17,25,26,32,47, 49,60*,64	101,105,111, 136,140	148,155,156, 167,172,183, 189,194,195, 206	223,224,225, 229,236,238, 247,279
Total	7	5	10	8

Dose (ppm)	0	0.4	1.0	2.5
Left Study as Missing	---	---	---	---
Total	0	0	0	0

Dose (ppm)	0	0.4	1.0	2.5
Found Moribund, Necropsied	15,20,22,29, 39,43,44,55, 58	91,95,110,116, 125,127,134	152,154,162, 174,193,197	245,246,258, 261,274
Total	9	7	6	5

Dose (ppm)	0	0.4	1.0	2.5
Accidental Trauma, Necropsied	---	---	205	---
Total	0	0	1	0

Dose (ppm)	0	0.4	1.0	2.5
Removed for Research	2	---	---	211
Total	1	0	0	1

Total	17	12	17	14

*Not included in total count because animals that are found dead during the final necropsy are included with that group.

Table 3

Target Organs for Chlorine

	8437 (B6C3F1)		8436 (F344)	8321 (F344)
	M	F	F	M
Nasal Cavity	X	X	X	X
Reproductive Tract		X		

Table 4a Statistical Analysis of Survival data - Female mice

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
FEMALE MICE
FIRST TERMINAL SACRIFICE AT 731 DAYS

INDIVIDUAL SURVIVAL TIMES (DAYS)

DOSE = 0 PPM

TOTAL 70 UNCENSORED DEATHS 31 CENSORED DEATHS 6 TERMINAL 33

UNCENSORED DEATHS

5	25	126	176	176	180	268	297	302	396
421	462	494	510	542	552	555	557	559	562
569	590	631	652	654	670	674	710	714	716
721									

CENSORED DEATHS

352	374	519	561	561	617

DOSE = 0.4 PPM

TOTAL 70 UNCENSORED DEATHS 29 CENSORED DEATHS 3 TERMINAL 38

UNCENSORED DEATHS

25	60	102	485	488	509	513	539	541	543
570	572	598	603	607	607	610	613	614	627
645	652	659	668	673	700	709	714	725	

CENSORED DEATHS

23	51	520

DOSE = 1.0 PPM

TOTAL 70 UNCENSORED DEATHS 23 CENSORED DEATHS 13 TERMINAL 34

UNCENSORED DEATHS

24	54	208	247	268	393	444	444	545	570
604	607	618	663	670	672	680	683	684	707
710	711	714							

CENSORED DEATHS

165	170	239	243	243	267	267	295	351	410
479	590	718							

DOSE = 2.5 PPM

TOTAL 70 UNCENSORED DEATHS 25 CENSORED DEATHS 9 TERMINAL 36

UNCENSORED DEATHS

33	75	95	160	166	239	294	411	417	422
439	446	467	470	506	515	569	610	637	683
691	696	707	717	723					

CENSORED DEATHS

31	31	31	46	295	397	455	466	537

Table 4a cont

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
FEMALE MICE
FIRST TERMINAL SACRIFICE AT 731 DAYS

KAPLAN-MEIER SURVIVAL PROBABILITY ESTIMATES (%)

DOSE	TIME (DAYS) 90	180	270	365	425	485	545	605	665	731 (A)
0 PPM	97.1	91.4	90.0	87.1	84.2	82.7	78.3	67.5	62.7	53.1
0.4 PPM	97.1	95.6	95.6	95.6	95.6	94.1	85.2	79.3	65.8	56.8
1.0 PPM	97.1	97.1	92.5	92.5	90.9	87.5	85.8	82.3	77.1	61.3
2.5 PPM	97.0	92.4	90.9	89.4	84.7	78.3	75.0	73.4	70.0	60.0

SURVIVAL SUMMARY STATISTICS

	DOSE 0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
SURVIVAL AT END OF STUDY (KAPLAN-MEIER)	53.1%	56.8%	61.3%	60.0%
SIGNIFICANCE (B) (LIFE TABLE)	P=0.599N	P=0.571N	P=0.305N	P=0.573N
MEAN DAY OF NATURAL DEATHS (C) (STANDARD ERROR)	466.6 (38.5)	550.7 (33.7)	518.3 (45.4)	447.5 (43.7)
MEAN LIFE SPAN (D) (STANDARD ERROR)	593.9 (23.3)	633.5 (21.4)	588.7 (24.8)	568.5 (27.8)

(A) FIRST TERMINAL SACRIFICE
(B) THE FIRST ENTRY IS THE TREND TEST (TARONE, 1975) RESULT. SUBSEQUENT ENTRIES ARE THE RESULTS OF PAIRWISE TESTS (COX,1972). NEGATIVE TRENDS ARE INDICATED BY "N".
(C) MEAN OF ALL UNCENSORED DEATHS PRIOR TO TERMINAL SACRIFICE
(D) MEAN OF ALL DEATHS (UNCENSORED, CENSORED, TERMINAL SACRIFICE)

Table 4b Statistical Analyses of Survival Data - Male mice

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
MALE MICE
FIRST TERMINAL SACRIFICE AT 725 DAYS

INDIVIDUAL SURVIVAL TIMES (DAYS)

DOSE = 0 PPM

TOTAL 67 UNCENSORED DEATHS 38 CENSORED DEATHS 6 TERMINAL 23

UNCENSORED DEATHS

44	44	45	79	106	106	107	107	114	233
289	292	303	359	378	379	451	470	474	525
526	526	552	553	587	590	597	603	607	625
636	652	654	667	702	704	713	718		

CENSORED DEATHS

12	145	285	372	372	547

DOSE = 0.4 PPM

TOTAL 70 UNCENSORED DEATHS 35 CENSORED DEATHS 5 TERMINAL 30

UNCENSORED DEATHS

16	18	25	38	38	73	79	79	100	103
235	263	270	341	381	387	402	402	421	450
467	499	506	563	589	596	610	628	649	652
674	684	687	688	693					

CENSORED DEATHS

57	73	227	295	604

DOSE = 1.0 PPM

TOTAL 70 UNCENSORED DEATHS 41 CENSORED DEATHS 3 TERMINAL 26

UNCENSORED DEATHS

17	18	18	19	72	74	82	108	143	198
204	206	312	324	327	421	438	441	442	448
500	513	522	533	536	552	579	598	615	645
652	672	673	680	680	704	706	711	718	718
722									

CENSORED DEATHS

58	240	284

DOSE = 2.5 PPM

TOTAL 70 UNCENSORED DEATHS 40 CENSORED DEATHS 4 TERMINAL 26

UNCENSORED DEATHS

5	5	5	37	39	44	99	194	242	345
372	374	379	380	380	442	443	443	444	446
446	449	450	516	516	522	541	560	579	603
645	645	646	655	662	671	683	683	703	705

CENSORED DEATHS

31	101	466	607

Table 4b cont

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
MALE MICE
FIRST TERMINAL SACRIFICE AT 725 DAYS

KAPLAN-MEIER SURVIVAL PROBABILITY ESTIMATES (%)

DOSE	TIME (DAYS) 90	180	270	365	425	485	545	605	665	725 (A)
0 PPM	93.9	86.4	84.8	78.5	75.3	70.4	65.4	55.4	47.0	38.6
0.4 PPM	88.5	85.5	81.0	79.5	71.8	68.8	65.7	61.1	54.9	47.0
1.0 PPM	89.9	87.0	82.7	78.2	76.7	70.7	63.1	58.6	54.1	39.1
2.5 PPM	91.4	89.9	87.0	85.5	78.1	66.3	60.3	55.8	48.0	40.3

SURVIVAL SUMMARY STATISTICS

	DOSE 0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
SURVIVAL AT END OF STUDY (KAPLAN-MEIER)	38.6%	47.0%	39.1%	40.3%
SIGNIFICANCE (B) (LIFE TABLE)	P=0.863	P=0.574N	P=1.000N	P=1.000N
MEAN DAY OF NATURAL DEATHS (C) (STANDARD ERROR)	424.1 (37.1)	380.2 (41.0)	427.8 (38.2)	425.0 (34.9)
MEAN LIFE SPAN (D) (STANDARD ERROR)	515.3 (29.1)	518.7 (30.5)	528.2 (29.4)	529.3 (28.0)

(A) FIRST TERMINAL SACRIFICE
(B) THE FIRST ENTRY IS THE TREND TEST (TARONE, 1975) RESULT. SUBSEQUENT ENTRIES ARE THE RESULTS OF PAIRWISE TESTS (COX,1972). NEGATIVE TRENDS ARE INDICATED BY "N".
(C) MEAN OF ALL UNCENSORED DEATHS PRIOR TO TERMINAL SACRIFICE
(D) MEAN OF ALL DEATHS (UNCENSORED, CENSORED, TERMINAL SACRIFICE)

Table 4c Statistical Analyses of Survival Data - Female Rats

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
FEMALE RATS
FIRST TERMINAL SACRIFICE AT 730 DAYS

INDIVIDUAL SURVIVAL TIMES (DAYS)

DOSE = 0 PPM

TOTAL 70 UNCENSORED DEATHS 9 CENSORED DEATHS 11 TERMINAL 50

UNCENSORED DEATHS
261 464 589 635 655 696 707 709 712
CENSORED DEATHS
366 366 366 366 366 366 366 366 366 366
719

DOSE = 0.4 PPM

TOTAL 70 UNCENSORED DEATHS 10 CENSORED DEATHS 11 TERMINAL 49

UNCENSORED DEATHS
507 536 598 626 635 642 680 697 703 725
CENSORED DEATHS
366 366 366 366 366 366 366 366 366 366
604

DOSE = 1.0 PPM

TOTAL 70 UNCENSORED DEATHS 11 CENSORED DEATHS 11 TERMINAL 48

UNCENSORED DEATHS
494 528 598 598 624 655 660 682 696 702
729
CENSORED DEATHS
366 366 366 366 366 366 366 366 366 366
590

DOSE = 2.5 PPM

TOTAL 70 UNCENSORED DEATHS 12 CENSORED DEATHS 10 TERMINAL 48

UNCENSORED DEATHS
24 442 500 614 614 617 624 661 670 677
697 703
CENSORED DEATHS
366 366 366 366 366 366 366 366 366 366

Table 4c cont

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
FEMALE RATS
FIRST TERMINAL SACRIFICE AT 738 DAYS

KAPLAN-MEIER SURVIVAL PROBABILITY ESTIMATES (%)

DOSE	TIME (DAYS) 90	180	270	365	425	485	545	605	665	738 (A)
0 PPM	100.0	100.0	98.6	98.6	98.6	96.9	96.9	95.2	91.9	85.2
0.4 PPM	100.0	100.0	100.0	100.0	100.0	100.0	96.7	95.0	89.9	83.1
1.0 PPM	100.0	100.0	100.0	100.0	100.0	100.0	96.7	93.3	88.2	81.4
2.5 PPM	98.6	98.6	98.6	98.6	98.6	96.9	95.2	95.2	86.9	80.2

SURVIVAL SUMMARY STATISTICS

	DOSE 0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
SURVIVAL AT END OF STUDY (KAPLAN-MEIER)	85.2%	83.1%	81.4%	80.2%
SIGNIFICANCE (B) (LIFE TABLE)	P=0.518	P=0.958	P=0.765	P=0.585
MEAN DAY OF NATURAL DEATHS (C) (STANDARD ERROR)	603.1 (50.4)	634.9 (22.7)	633.3 (22.2)	570.3 (54.5)
MEAN LIFE SPAN (D) (STANDARD ERROR)	667.2 (16.9)	668.2 (15.9)	666.3 (15.9)	656.1 (18.4)

(A) FIRST TERMINAL SACRIFICE
(B) THE FIRST ENTRY IS THE TREND TEST (TARONE, 1975) RESULT. SUBSEQUENT ENTRIES ARE THE RESULTS OF PAIRWISE TESTS (COX,1972). NEGATIVE TRENDS ARE INDICATED BY 'N'.
(C) MEAN OF ALL UNCENSORED DEATHS PRIOR TO TERMINAL SACRIFICE
(D) MEAN OF ALL DEATHS (UNCENSORED, CENSORED, TERMINAL SACRIFICE)

Table 4d Statistical Analyses of Survival Data - Male Rats

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
MALE RATS
FIRST TERMINAL SACRIFICE AT 724 DAYS

INDIVIDUAL SURVIVAL TIMES (DAYS)

DOSE = 0 PPM

TOTAL 70 UNCENSORED DEATHS 16 CENSORED DEATHS 11 TERMINAL 43

UNCENSORED DEATHS
422 519 550 557 579 600 610 620 659 690
701 701 702 712 712 717
CENSORED DEATHS
291 367 367 367 367 367 367 367 367 367
367

DOSE = 0.4 PPM

TOTAL 70 UNCENSORED DEATHS 12 CENSORED DEATHS 10 TERMINAL 48

UNCENSORED DEATHS
344 358 460 506 578 633 641 656 669 680
680 715
CENSORED DEATHS
367 367 367 367 367 367 367 367 367 367

DOSE = 1.0 PPM

TOTAL 70 UNCENSORED DEATHS 16 CENSORED DEATHS 11 TERMINAL 43

UNCENSORED DEATHS
22 150 417 523 533 549 617 623 633 635
648 660 660 710 716 717
CENSORED DEATHS
367 367 367 367 367 367 367 367 367 367
473

DOSE = 2.5 PPM

TOTAL 70 UNCENSORED DEATHS 13 CENSORED DEATHS 11 TERMINAL 46

UNCENSORED DEATHS
371 548 572 583 596 628 628 635 674 675
678 695 721
CENSORED DEATHS
291 367 367 367 367 367 367 367 367 367
367

Table 4d cont

CHLORINE

STATISTICAL ANALYSIS OF SURVIVAL DATA
MALE RATS
FIRST TERMINAL SACRIFICE AT 724 DAYS

KAPLAN-MEIER SURVIVAL PROBABILITY ESTIMATES (%)

DOSE	TIME (DAYS) 90	180	270	365	425	485	545	605	665	724 (A)
0 PPM	100.0	100.0	100.0	100.0	98.3	98.3	96.6	89.8	84.7	72.9
0.4 PPM	100.0	100.0	100.0	97.1	97.1	95.5	93.8	92.1	87.1	80.4
1.0 PPM	98.6	97.1	97.1	97.1	95.5	95.5	92.1	90.4	78.4	73.3
2.5 PPM	100.0	100.0	100.0	100.0	98.3	98.3	98.3	91.5	86.4	78.0

SURVIVAL SUMMARY STATISTICS

	DOSE 0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
SURVIVAL AT END OF STUDY (KAPLAN-MEIER)	72.9%	80.4%	73.3%	78.0%
SIGNIFICANCE (B) (LIFE TABLE)	P=0.828N	P=0.528N	P=1.000	P=0.685N
MEAN DAY OF NATURAL DEATHS (C) (STANDARD ERROR)	628.2 (21.6)	576.7 (37.3)	550.8 (49.8)	615.7 (24.9)
MEAN LIFE SPAN (D) (STANDARD ERROR)	644.9 (16.3)	647.7 (16.5)	629.8 (19.3)	646.7 (16.4)

(A) FIRST TERMINAL SACRIFICE
(B) THE FIRST ENTRY IS THE TREND TEST (TARONE, 1975) RESULT. SUBSEQUENT ENTRIES ARE THE RESULTS OF PAIRWISE TESTS (COX,1972). NEGATIVE TRENDS ARE INDICATED BY "N".
(C) MEAN OF ALL UNCENSORED DEATHS PRIOR TO TERMINAL SACRIFICE
(D) MEAN OF ALL DEATHS (UNCENSORED, CENSORED, TERMINAL SACRIFICE)

Table 5. Major Nasal Lesions in Female Mice Exposed to Chlorine for up to 104 Weeks

	Chlorine Concentration, PPM							
	0		0.4		1.0		2.5	
Lesion Tissue	I (%)	S	I (%)	S	I (%)	S	I (%)	S
Septal Fenestration (Level 1 and 2)	5[a]	N	5	N	25[a,b]	N	36[a,b]	N
Squamous Epithelium Hyperplasia (Level 1)	50[a]	1.7	88[a,b]	2.4[c]	91[a,b]	2.3[c]	81[a,b]	2.4[c]
Squamous Epithelium Eosinophilic Material (Level 1)	2[a]	0.9	17[a,b]	1.1	9	1.4	26[a,b]	2.4
Respiratory Epithelium Hyperplasia (Level 2)	8[a]	1.8	47[a,b]	2.2	87[a,b]	2.7[c]	39[a,b]	3.3[c]
Respiratory Epithelium Eosinophilic Material (Level 2)	13[a]	1.7	56[a,b]	2.1	89[a,b]	2.8[c]	75[a,b]	3.0[c]
Squamous Metaplasia (Level 2)	0[a]	----	6	2.8	2	4.0	42[a,b]	3.0
Olfactory Epithelium Atrophy (Level 3)	3[a]	2.0	20[a,b]	2.2	21[a,b]	2.3	39[a,b]	2.8
Olfactory Epithelium Eosinophilic Material (Level 4)	16[a]	1.9	14	1.8	50[a,b]	2.1	77[a,b]	3.0[c]

I (%) - Incidence as Percent - the denominator for this calculation included all animals for which the nasal passages were considered adequate for microscopic examination.

S - Mean Severity Score

N - Not evaluated for lesion severity

Level # - Nose Section Level, refer to Figure 3

[a]-Logistic Regression, $p < 0.05$

[b]-Fischer's exact, $p < 0.05$

[c]-Dunnett's test, $p < 0.05$

Table 6. Major Nasal Lesions in Male Mice Exposed to Chlorine for up to 104 Weeks

	Chlorine Concentration, PPM							
	0		0.4		1.0		2.5	
Lesion Tissue	I (%)	S	I (%)	S	I (%)	S	I (%)	S
Septal Fenestration (Level 1 and 2)	0	N	27[a,b]	N	41[a,b]	N	26[a,b]	N
Squamous Epithelium Hyperplasia (Level 1)	28[a]	1.3	78[a,b]	2.4[c]	84[a,b]	2.5[c]	78[a,b]	1.7
Squamous Epithelium Eosinophilic Material (Level 1)	0[a]	----	9[a,b]	1.5	12[a,b]	1.8	16[a,b]	1.6
Respiratory Epithelium Hyperplasia (Level 2)	17[a]	1.7	44[a,b]	2.2[c]	48[a,b]	2.7[c]	61[a,b]	2.7[c]
Respiratory Epithelium Eosinophilic Material (Level 2)	2[a]	2.0	6	1.8	40[a,b]	2.5	63[a,b]	2.6
Squamous Metaplasia (Level 2)	20	2.0	16	2.5[c]	34	2.9[c]	23	2.5[c]
Olfactory Epithelium Atrophy (Level 3)	13[a]	1.5	12	1.5	28[a,b]	2.7[c]	42[a,b]	2.2[c]
Olfactory Epithelium Eosinophilic Material (Level 4)	2[a]	1.0	2	2.0	13[a,b]	1.9	49[a,b]	2.4

I (%) - Incidence as Percent - the denominator for this calculation included all animals for which the nasal passages were considered adequate for microscopic examination.

S - Mean Severity Score

N - Not evaluated for lesion severity

Level # - Nose Section Level, refer to Figure 3

[a]-Logistic Regression, $p < 0.05$

[b]-Fischer's exact, $p < 0.05$

[c]-Dunnett's test, $p < 0.05$

Table 7. Major Nasal Lesions in Female Rats Exposed to Chlorine for up to 104 Weeks

	Chlorine Concentration, PPM							
	0		0.4		1.0		2.5	
Lesion Tissue	I (%)	S	I (%)	S	I (%)	S	I (%)	S
Goblet Cell Hyperplasia (Level 3)	4[a]	1.0	71[a,b]	1.3	90[a,b]	2.0[c]	91[a,b]	2.5[c]
Respiratory Epithelium Eosinophilic Material (Level 3)	70[a]	1.2	85[a,b]	1.2	84[a,b]	1.3	93[a,b]	2.0[c]
Glandular Epithelium Eosinophilic Material (Level 3)	23[a]	1.1	40[a,b]	1.1	75[a,b]	1.4	76[a,b]	1.5[c]
Olfactory Epithelium Eosinophilic Material (Level 3)	52[a]	1.9	91[a,b]	2.0	99[a,b]	2.8[c]	99[a,b]	2.9[c]

I (%) - Incidence as Percent - the denominator for this calculation included all animals for which the nasal passages were considered adequate for microscopic examination.

S - Mean Severity Score

Level # - Nose Section Level, refer to Figure 3

[a]-Logistic Regression, $p < 0.05$

[b]-Fischer's exact, $p < 0.05$

[c]-Dunnett's test, $p < 0.05$

Table 8. Major Nasal Lesions in Male Rats Exposed to Chlorine for up to 104 Weeks

	Chlorine Concentration, PPM							
	0		0.4		1.0		2.5	
Lesion Tissue	I (%)	S	I (%)	S	I (%)	S	I (%)	S
Subacute Inflammation (Level 5)	12[a]	1.7	41[a,b]	1.3	39[a,b]	1.3	56[a,b]	1.4
Squamous Epithelial Hyperplasia (Level 2)	7[a]	1.6	25[a]	1.9	27[a,b]	1.9	27[a,b]	1.6
Goblet Cell Hyperplasia (Level 3)	12[a]	1.6	81[a,b]	1.8	87[a,b]	2.2[c]	93[a,b]	2.7[c]
Respiratory Epithelium Eosinophilic Material (Level 3)	3[a]	1.4	33[a,b]	1.5	51[a,b]	1.6	73[a,b]	1.6
Grandular Epithelium Eosinophilic Material (Level 3)	1[a]	1.9	42[a,b]	2.1	49[a,b]	2.1	70[a,b]	2.2
Olfactory Epithelium Eosinophilic Material (Level 3)	12[a,b]	1.4	83[a,b]	2.2[c]	80[a,b]	2.6[c]	82[a,b]	3.0[c]

I (%) - Incidence as Percent - the denominator for this calculation included all animals for which the nasal passages were considered adequate for microscopic examination.

S - Mean Severity Score

Level # - Nose Section Level, refer to Figure 3

[a]-Logistic Regression, $p < 0.05$

[b]-Fischer's exact, $p < 0.05$

[c]-Dunnett's test, $p < 0.05$

Figure 1

Diagram of Rodent Nasal Cavity with Section Levels Indicated

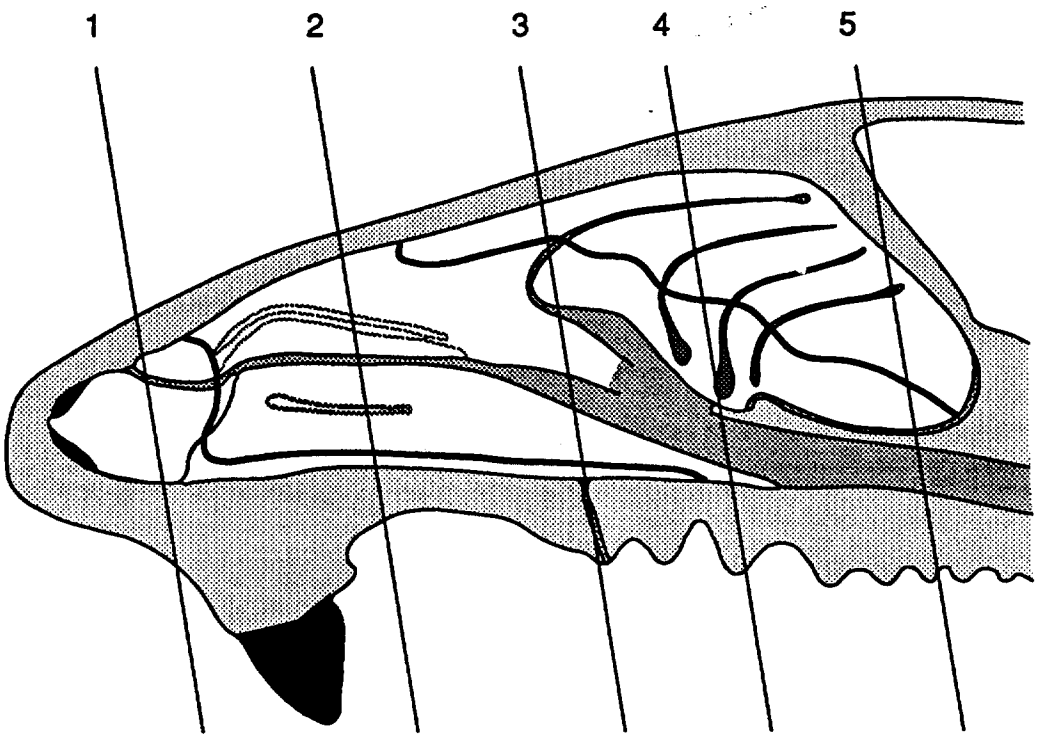
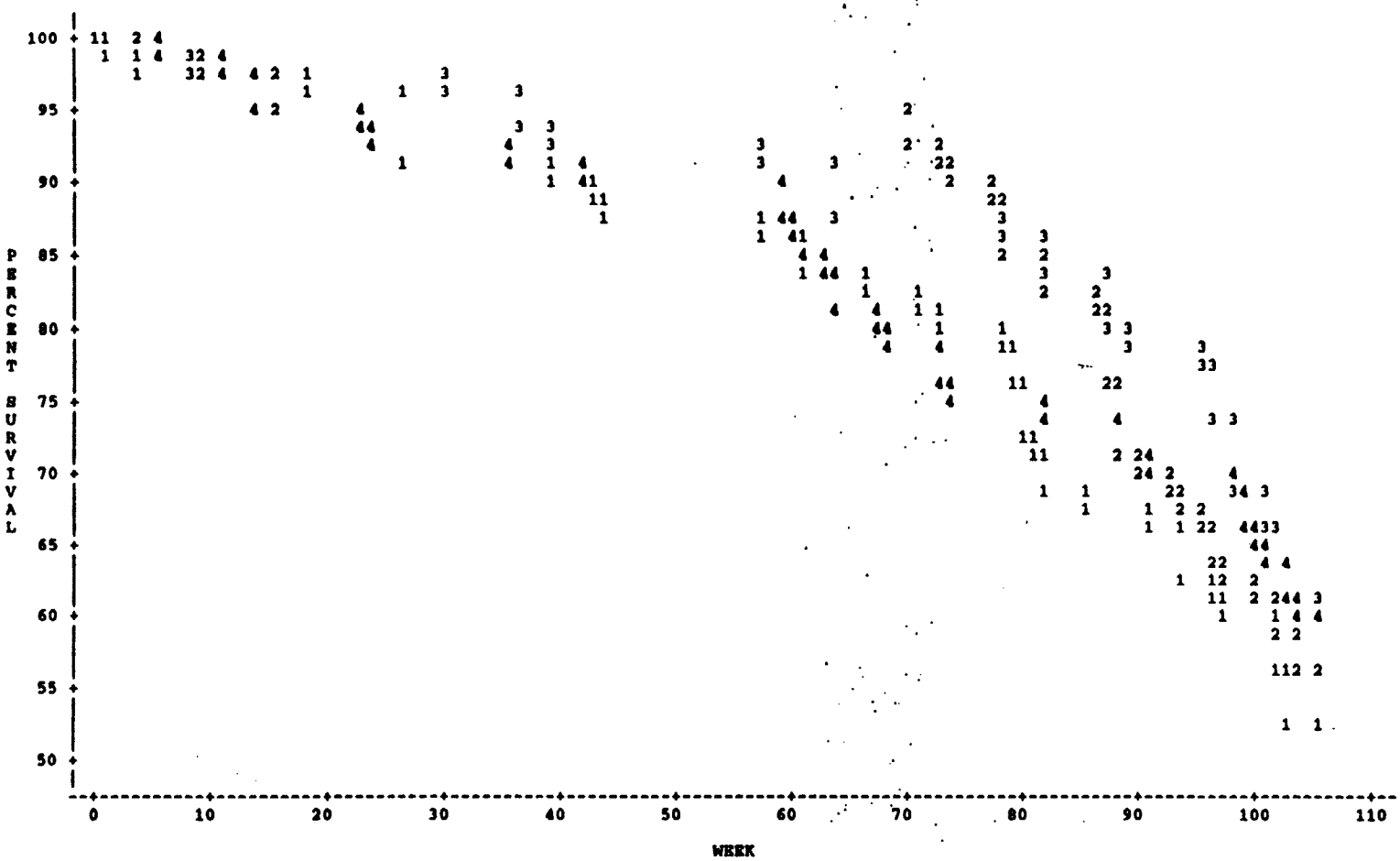


Figure 2a

CHLORINE
KAPLAN-MEIER SURVIVAL CURVES
0 PPM = 1
0.4 PPM = 2
1.0 PPM = 3
2.5 PPM = 4

SPECIES=MICE SEX=FEMALE

Plot of SURVIVAL*WEEK. Symbol is value of DOSE.



NOTE: 10 obs hidden.

Figure 2b

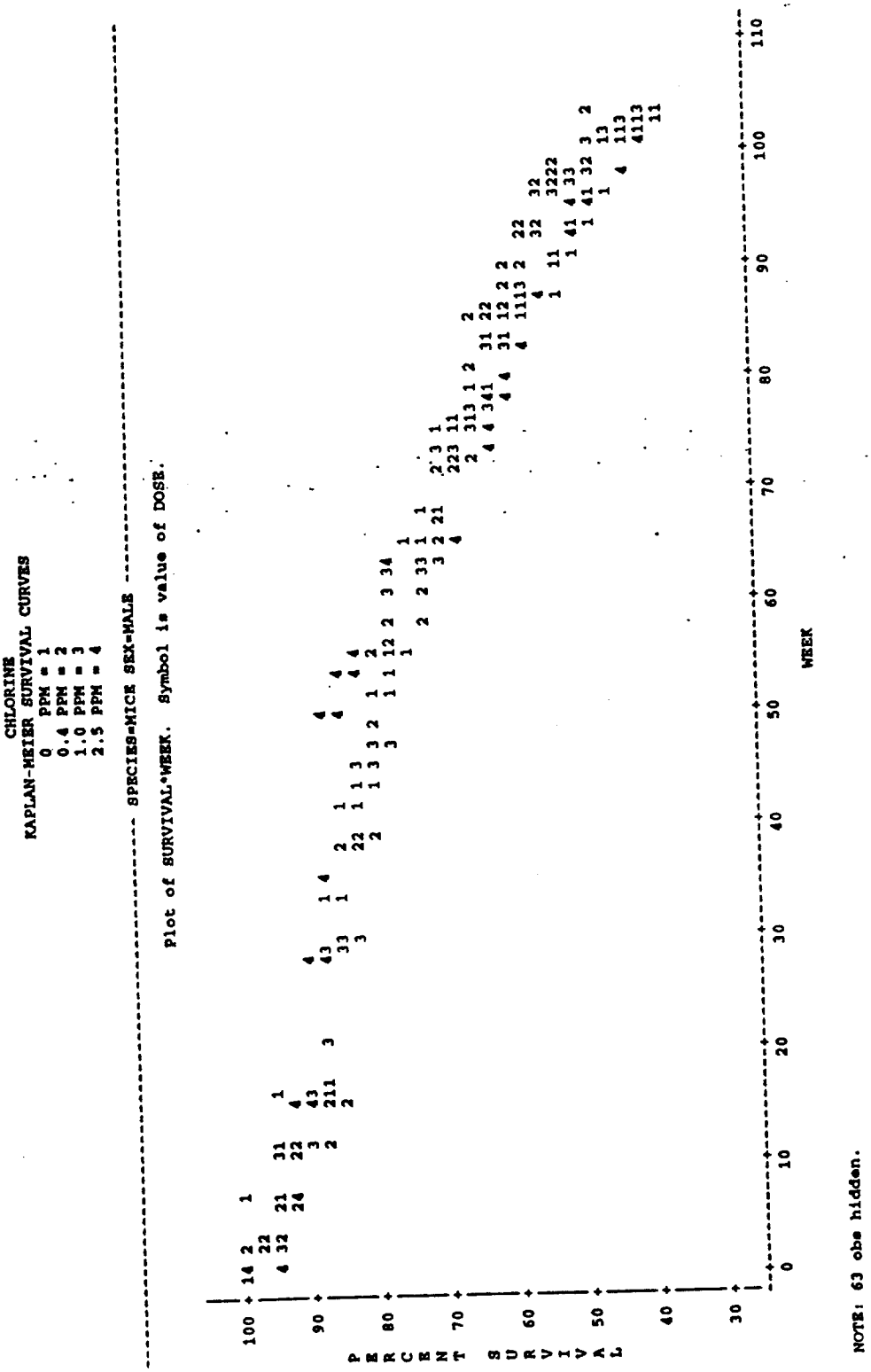

CHLORINE
KAPLAN-MEIER SURVIVAL CURVES
0 PPM = 1
0.4 PPM = 2
1.0 PPM = 3
2.5 PPM = 4
SPECIES=MICE SEX=MALE
Plot of SURVIVAL*WEEK. Symbol is value of DOSE.
PERCENT SURVIVAL
WEEK
NOTE: 63 obs hidden.

Figure 3a

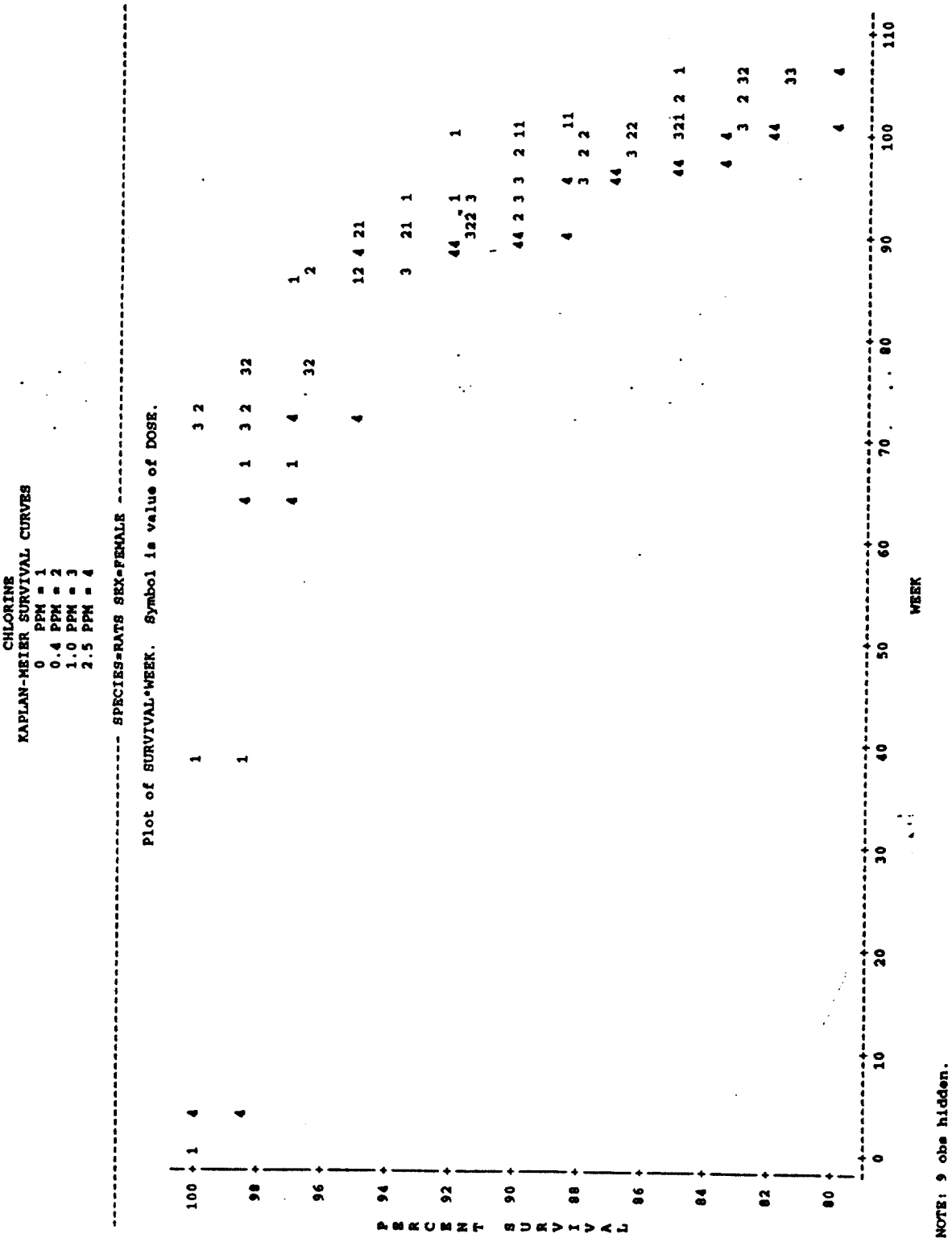
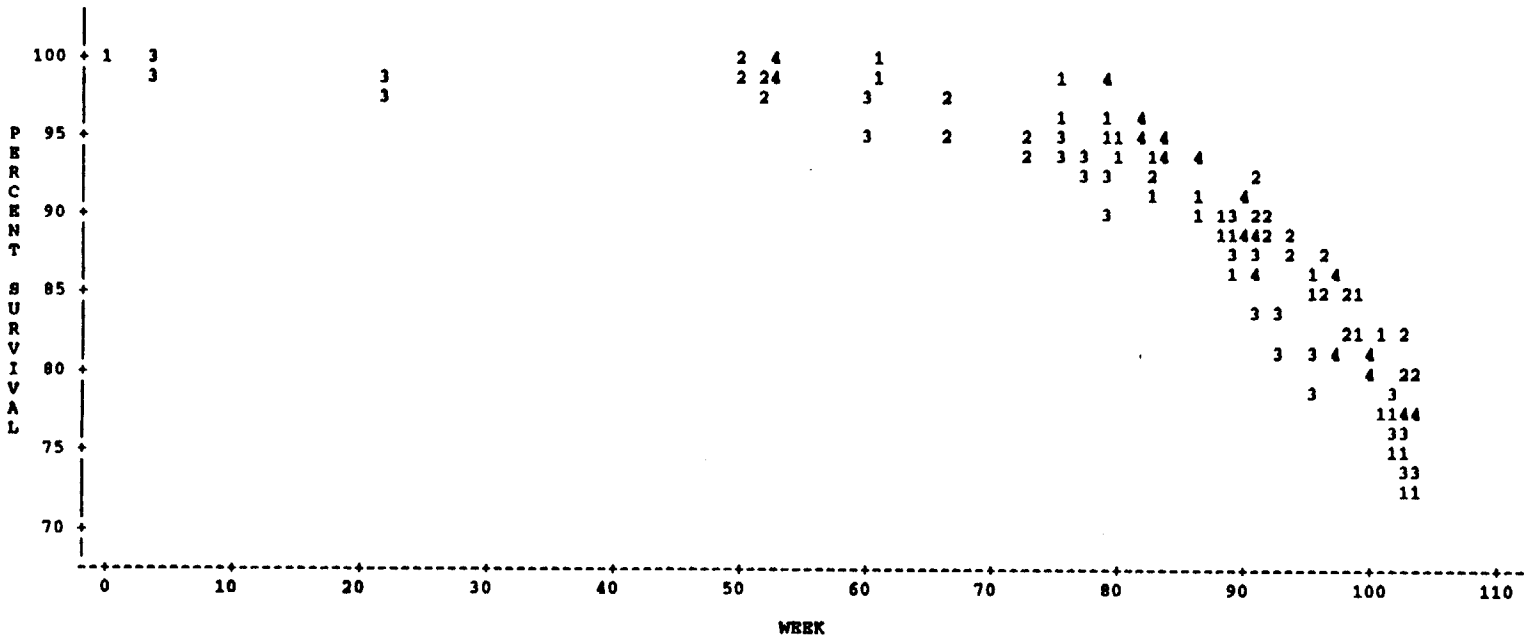

CHLORINE
KAPLAN-MEIER SURVIVAL CURVES
0 PPM = 1
0.4 PPM = 2
1.0 PPM = 3
2.5 PPM = 4
SPECIES=RATS SEX=FEMALE
Plot of SURVIVAL*WEEK. Symbol is value of DOSE.
PERCENT SURVIVAL
WEEK
NOTE: 9 obs hidden.

Figure 3b

CHLORINE
KAPLAN-MEIER SURVIVAL CURVES
0 PPM = 1
0.4 PPM = 2
1.0 PPM = 3
2.5 PPM = 4

SPECIES=RATS SEX=MALE

Plot of SURVIVAL*WEEK. Symbol is value of DOSE.



NOTE: 7 obs hidden.

APPENDIX A PROTOCOL: RISK ASSESSMENT STUDY OF CHLORINE IN B6C3F1 MICE AND F344 RATS

8437 - Female and Male Mice

8436 - Female Rats

8321 - Male Rats

1.0 STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS AND MICE

1.1 PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

1.2 SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

1.3 TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
6 DAVIS DRIVE
RESEARCH TRIANGLE PARK, N.C.

2.0 SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

2.1 STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

2.2 STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
ANIMAL CARE TECHNICIAN:	S. DENNIS
STUDY PATHOLOGIST:	J. POPP
INHALATION SUPERVISOR:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	K. MORGAN
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER

3.0 PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - MON. 16-APR-84
COMPLETION DATE: - - - - - - - - - - - - - - WED. 16-APR-86
FINAL REPORT DATE: - - - - - - - - - - - - - WED. 1-APR-87
TISSUE SLIDE COMPLETION DATE: - - - - - - - WED. 31-DEC-86
FINAL SACRIFICE DATE: - - - - - - - - - - - WED. 16-APR-86
INTERIM SACRIFICE DATES: - - - - - - - - - - TUE. 16-APR-85
INTERIM REPORT DATES: - - - - - - - - - - - TUE. 31-DEC-85

4.0 STUDY TYPE: INHALATION CHRONIC

4.1 SPECIES: - - - - - - - - - - - - - - - - - - - MOUSE
STRAIN: - B6C3F1
AGE: - 4 TO 8 WEEKS
WEIGHT: - 10 TO 30 GRAMS
METHOD OF IDENTIFICATION: - - - - - - - - - - EAR TAG (SOP # TAC-161-1)

4.2 SUPPLIER: CHARLES RIVER LABORATORIES - KINGSTON

4.3 REASON FOR SELECTION OF SPECIES: THE SPONSER HAS A SIGNIFIGANT PAST HISTORY WITH THIS SPECIES.

5.0 NUMBER OF ANIMALS ON STUDY:

PRETEST: 620 # MALES: 310 # FEMALES: 310
STUDY: 560 # MALES: 280 # FEMALES: 280

5.1 METHOD OF ASSIGNMENT TO GROUPS TO PREVENT BIAS: (SOP # TAC-164-2)

6.0 TEST ARTICLES:

6.1 NAME: CHLORINE

ID: CL2
DENSITY OF TEST ARTICLE (MG/ML): - - - - - - 3.214
MOLECULAR WEIGHT OF TEST ARTICLE: - - - - - 70.906
AMOUNT REQUIRED: - - - - - - - - - - - - - - - 5000 LITERS
DESCRIPTION: - - - - - - - - - - - - - - - - - GAS
RESPONSIBLE DEPARTMENT: - - - - - - - - - - - GENERAL AND BIOCHEMICAL TOX.
CONDITIONS TO MAINTAIN STABILITY: NONE
SAFETY PRECAUTIONS AND PROCEDURES: PURE CHLORINE IS GREENISH-YELLOW, ABOUT 2.5 TIMES AS HEAVY AS AIR. CHLORINE HAS A DISAGREEABLE AND SUFFOCATING ODOR WITH AN IRRITATING EFFECT ON THE NOSE AND THROAT. RESPIRATORY PROTECTION IS NECESSARY. CONCENTRATIONS ABOVE 1 PPM ARE IRRITATING. EXPOSURE TO 500-1000 PPM IS VERY DANGEROUS. SEE HAZARDOUS AGENT PROTOCOL #8308.
STABILITY: ANALYZE PRIOR TO START OF STUDY AND AT 6 MONTH INTERVALS UNTIL THE STUDY ENDS.

6.11 ADMINISTRATION

ROUTE: - INHALATION
METHOD: - INHALATION
REASON FOR ROUTE SELECTION: INHALATION IS THE USUAL ROUTE OF EXPOSURE FOR A GAS.
VEHICLE OR CARRIER: HEPA FILTERED AIR

6.12 TEST ARTICLE-CARRIER MIXTURE

METHOD OF PREPARATION: METERED CONTINUOUSLY AS A CHLORINE-NITROGEN MIXTURE INTO AN 8 CUBIC METER INHALATION CHAMBER OPERATED WITH DYNAMIC AIR FLOW.
PHYSICAL STATE OF MIXTURE: GAS

7.0 CONTROL ARTICLES:

7.1 NAME (VEHICLE): HEPA FILTERED AIR

7.11 ADMININSTRATION

ROUTE: - INHALATION
METHOD: - INHALATION

8.0 TREATMENT GROUPS AND DOSAGES:

DOSE GROUP	NUMBER ANIMALS	SEX	TARGET CONCENTRATION, PPM * ARTICLES A	B
1	70	MALE	------	------
2	70	MALE	------	0.400
3	70	MALE	------	1.000
4	70	MALE	------	2.500
1	70	FEMALE	------	------
2	70	FEMALE	------	0.400
3	70	FEMALE	------	1.000
4	70	FEMALE	------	2.500

* ARTICLE CODES: A=HEPA FILTERED AIR
B=CHLORINE

9.0 DIET INFORMATION:

BRAND OF DIET: - - - - - - - - - - - - - - - - NIH OPEN FORMULA
PHYSICAL FORM OF DIET: - - - - - - - - - - - - PELLETS
SOURCE OF DRINKING WATER: - - - - - - - - - - PURIFIED WATER
WATER DISTRIBUTION SYSTEM: - - - - - - - - - - AUTO WATERING SYSTEM
AVAILABILITY OF WATER: - - - - - - - - - - - - SEE 9.1

9.1 FEEDING TIME IN RELATION TO DOSING: FEED AND WATER GIVEN AD LIBITUM EXCEPT DURING EXPOSURE.

10.0 ENVIRONMENTAL CONDITIONS:

10.1 PRE-TEST CONDITIONS:

CONDITIONING PERIOD IN DAYS (MINIMUM): - - - 14
CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1

10.2 TEST CONDITIONS:

CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1
BEDDING: - - - - - - - - - - - - - - - - - - - NONE
ROOM TEMPERATURE: - - - - - - - - - - - - - - 68.0 TO 76.0 DEGREES F
RELATIVE HUMIDITY: - - - - - - - - - - - - - - 40.0 TO 65.0 PERCENT
ROOM LIGHTS ON: - - - - - - - - - - - - - - - 7:00 TO 19:00 HOURS
ANIMAL ROOM NUMBERS: - - - - - - - - - - - - - 308 309 310 311

10.3 CONTAMINANTS EXPECTED IN DIET, DRINKING WATER, BEDDING, ECT.: NONE

11.0 LABORATORY DETERMINATIONS AND SCHEDULES:

11.1 SM. ANIMAL WTS./FEED/CLIN. OBS.

11.11 BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	10.00	50.00	10.00	50.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-1

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 1,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 1,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

11.2 INHALATIION MONIORING & CONTROL

11.21 INHALATION CHAMBER MEASUREMENTS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
DBT	DRY BULB TEMPERATURE	DEGS. F	68.00	78.00	68.00	78.00	TIN-014-3
WBT	WET BULB TEMPERATURE	DEGS. F	50.00	78.00	50.00	78.00	TIN-014-3
RH	RELATIVE HUMIDITY	PERCENT	40.00	65.00	40.00	65.00	TIN-014-3
AF	CHAMBER AIR FLOW	L/MIN.	1300.	2900.	1300.	2900.	TIN-004-1
CFR	CONTAMINANT FLOW RATE	ML/MIN.	1.00	1000.	1.00	1000.	TIN-003-2
ACC	ANALYTIC CHAMBER CONCENT.	PPM	-----	-----	-----	-----	TIN-006-1
NCC	NOMINAL CHAMBER CONCENT.	PPM	-----	-----	-----	-----	---------
RAN	RATIO ANALYTIC/NOMINAL	PERCENT	80.00	110.00	80.00	110.00	---------
CFC	CONTAMINANT FLOW CHECK	------	-----	-----	-----	-----	---------

EXPOSURE SCHEDULE: DURATION 104 WEEKS
HOURS/DAY 6
DAYS/WEEK 5

DATA SAMPLING: ANALYTIC CHAMBER CONCENTRATION 1 TIMES/HOUR
ALL OTHER CHAMBER PARAMETERS 1 TIMES/HOUR

11.3 COMPUTER GENERATED LABELS

11.31 LABEL PRODUCTION SOP # ---------

11.4 HEMATOLOGY LABORATORY DATA

11.41 WBC DIFFERENTIAL COUNTS SOP # PHE-200-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
SEG	SEGMENTED NEUTROPHILS	1000/CMM	20.00	32.00	20.00	32.00	PHE-200-2
BAN	BAND NEUTROPHILS	------	-----	2.00	-----	2.00	PHE-200-2
LYM	LYMPHOCYTES	------	64.00	76.00	64.00	76.00	PHE-200-2
MON	MONOCYTES	------	-----	4.00	-----	4.00	PHE-200-2
EOS	EOSINOPHILS	------	-----	5.00	-----	5.00	PHE-200-2
BAS	BASOPHILS	------	-----	2.00	-----	2.00	PHE-200-2

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.42 COULTER VALUES SOP # PHE-100-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
WBC	WHITE BLOOD CELL COUNT	1000/CMM	4.30	6.50	4.00	6.10	PHE-101-1
RBC	RED BLOOD CELL COUNT	1000/CMM	8.07	8.55	8.00	8.45	PHE-102-1
HGB	HEMOGLOBIN	GR/DL	15.00	15.80	15.00	15.80	PHE-103-1
HCT	HEMATOCRIT	PERCENT	42.00	44.40	41.00	43.00	PHE-104-1
MCV	MEAN RBC CELL VOLUME	CU.MIC.	51.60	53.40	51.60	53.40	PHE-105-1
MCH	MEAN RBC CORPUS. HEMOGLOBIN	PICOGRAM	18.10	18.90	18.10	18.90	PHE-106-1
MCHC	MEAN CORPUS. HEMO. CONC.	PERCENT	35.30	36.10	35.30	36.10	PHE-107-1
RDW	RED CELL DISTRIBUTION WIDTH	PERCENT	9.90	10.90	9.90	10.90	PHE-108-1
PLT	PLATELETS, THROMBOCYTES	1000/CMM	824.00	916.00	824.00	916.00	PHE-109-1
PCT	PLATELET "HEMATOCRIT"	PERCENT	0.59	0.64	0.59	0.64	PHE-110-1
MPV	MEAN PLATELET VOLUME	CU.MIC.	6.70	7.10	6.70	7.10	PHE-111-1
PDW	PLATELET DISTRIBUTION WIDTH	PERCENT	15.30	15.70	15.30	15.70	PHE-112-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.43 BLOOD COLLECTION PROCEDURES:

11.431 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.432 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.5 SERUM CHEMISTRY DATA COLLECTION

11.51 ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-1
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-1
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-1
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.52 MANUAL SOP # PCC-203-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.53 BLOOD COLLECTION PROCEDURES:

11.531 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.532 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.6 NECROPSY PROCEDURES

11.61 SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+14]
METHOD OF SACRIFICE: - - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

11.62 NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/GROUP/SAC. 1	10	10	10	10	10	10	10	10

11.63 NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	50	50	50	50

11.64 COMMENTS ON SACRIFICES: NONE

11.65 ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

11.66 TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

11.7 TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 40
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 200

11.71 TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	SEMINAL VESICLE
PROSTATE	TESTES	EPIDIDYMIS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3

NOSE 4 NOSE 5 GROSS LESION

12.0 STATISTICAL TABLES AND REPORTS:

12.1 BODY WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.2 CLINICAL CHEMISTRIES

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.3 COULTER AND DIFFERENTIAL WBC PARAMETERS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.4 CLINICAL SIGNS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.5 GROSS NECROPSY FINDINGS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.6 HISTOPATHOLOGIC LESIONS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.7 TUMOR INCIDENCE

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX
MEAN TUMOR LATENCY TABLES

12.8 ORGAN WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX

12.9 TEMPERATURE OF CHAMBER

MANN-WHITNEY TEST (NON-PARAMETRIC) BY GROUP BY SEX

13.0 RECORDS TO BE MAINTAINED: ALL RECORDS, SPECIMENS, AND SAMPLES REQUIRED TO ASSURE COMPLIANCE WITH GOOD LABORATORY PRACTICE REGULATIONS WILL BE MAINTAINED FOR AT LEAST THE TIME PERIODS SPECIFIED IN THE REGULATIONS. THESE WILL INCLUDE, BUT NOT BE LIMITED TO, ALL RAW DATA, DOCUMENTATION, PROTOCOLS, INTERIM AND FINAL REPORTS, SUMMARIES OF TRAINING AND EXPERIENCE OF PERSONNEL, JOB DESCRIPTIONS, RECORDS AND REPORTS OF THE MAINTENANCE, CALIBRATION, AND INSPECTION OF EQUIPMENT.

14.0 SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8436, 8437

1. THE CHLORINE STUDY IS MANAGED BY THREE PROTOCOLS:
   #8321 - MALE RATS
   #8436 - FEMALE RATS
   #8437 - MALE AND FEMALE MICE

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

5. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

6. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

7. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. FOR SCHEDULED SACRIFICES, ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS.
   FOR UNSCHEDULED DEATHS PRIOR TO 21 MONTHS INTO THE STUDY, THE FOLLOWING TISSUES WILL BE PROCESSED FOR HISTOLOGIC EVALUATION:
   A. ALL TARGET ORGANS
   B. ALL TISSUES FROM ANIMALS IN GROUP 4.
   C. ALL TISSUES FROM ANIMALS IN GROUP 1, WITH THE EXCEPTION OF THOSE WITH MODERATE TO SEVERE AUTOLYSIS.
   D. GROUPS 2 AND 3: TISSUES, OTHER THAN THE TARGET ORGANS, TO BE SELECTED BY THE STUDY PATHOLOGIST IN ORDER TO DETERMINE THE CAUSE OF DEATH. IF CAUSE OF DEATH WAS DIAGNOSED GROSSLY, E.G. HEAD CRUSH, THEN ONLY THE TARGET ORGANS WILL BE PROCESSED.
   ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARC

PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

13. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

14.0 PROTOCOL AMENDMENTS:

14.1 DATE: 11-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
DURING THE CONDITIONING PERIOD SOME OF THE MALE MICE WERE UNABLE TO ADJUST TO THE STAINLESS STEEL RACKS AND DIED. THIS RESULTED IN A SIGNIFICANT LOSS OF ANIMALS WHICH NECESSITATED CHANGING THE NUMBERS IN THE CONTROL GROUP.

AMENDMENT:

o NUMBER OF ANIMALS ON STUDY:

PRETEST:	620	# MALES:	310	# FEMALES:	310
STUDY:	557	# MALES:	277	# FEMALES:	280

o METHOD OF ASSIGNMENT TO GROUPS TO PREVENT BIAS: (SOP # TAC-164-2)

14.2 DATE: 11-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE NUMBER OF ANIMALS IN THE MALE CONTROL GROUP HAS BEEN AMENDED.

AMENDMENT:
o TREATMENT GROUPS AND DOSAGES:

DOSE GROUP	NUMBER ANIMALS	SEX	TARGET CONCENTRATION, PPM * ARTICLES A	B
1	67	MALE	------	------
2	70	MALE	------	0.400
3	70	MALE	------	1.000
4	70	MALE	------	2.500
1	70	FEMALE	------	------
2	70	FEMALE	------	0.400
3	70	FEMALE	------	1.000
4	70	FEMALE	------	2.500

* ARTICLE CODES: A=HEPA FILTERED AIR
B=CHLORINE

14.3 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:

o STUDY TYPE: INHALATION CHRONIC

o SPECIES: - MOUSE
STRAIN: - B6C3F1
AGE: - 4 TO 8 WEEKS
WEIGHT: - 10 TO 30 GRAMS
METHOD OF IDENTIFICATION: - - - - - - - - - - EAR TAG (SOP # TAC-161-2)

o SUPPLIER: CHARLES RIVER LABORATORIES - KINGSTON

o REASON FOR SELECTION OF SPECIES: THE SPONSER HAS A SIGNIFIGANT PAST HISTORY WITH THIS SPECIES.

14.4 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:
o SW. ANIMAL WTS./FEED/CLIN. OBS.

o BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	10.00	50.00	10.00	50.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-3

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 1,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 1,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

14.5 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:
o SERUM CHEMISTRY DATA COLLECTION

o ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-2
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-2
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-2
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o MANUAL SOP # PCC-203-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.6 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CORRECTED THE NUMBERS OF ANIMALS TO READ AT INTERIM AND FINAL SACRIFICE BECAUSE INCORRECT NUMBERS WERE ENTERED WHEN THE PROTOCOL WAS GENERATED.

AMENDMENT:

o TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 80
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 400

o TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	SEMINAL VESICLE
PROSTATE	TESTES	EPIDIDYMIS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3
NOSE 4	NOSE 5	GROSS LESION	

14.7 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
SPECIAL INSTRUCTIONS HAVE BEEN UPDATED FOR SOP NUMBERS AND CHANGES INCURRED BECAUSE OF THE REDUCED NUMBER OF MALE CONTROL MICE (ITEMS 2, 3, 12).

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8436, 8437

1. THE CHLORINE STUDY IS MANAGED BY THREE PROTOCOLS:
   #8321 - MALE RATS
   #8436 - FEMALE RATS
   #8437 - MALE AND FEMALE MICE

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION, EXCEPT THE MALE CONTROL GROUP WHICH WILL HAVE 7, WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE ADDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-3

4. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

5. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-2.

6. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

7. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. FOR SCHEDULED SACRIFICES, ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS.

FOR UNSCHEDULED DEATHS PRIOR TO 21 MONTHS INTO THE STUDY, THE FOLLOWING TISSUES WILL BE PROCESSED FOR HISTOLOGIC EVALUATION:

A. ALL TARGET ORGANS
B. ALL TISSUES FROM ANIMALS IN GROUP 4.
C. ALL TISSUES FROM ANIMALS IN GROUP 1, WITH THE EXCEPTION OF THOSE WITH MODERATE TO SEVERE AUTOLYSIS.
D. GROUPS 2 AND 3: TISSUES, OTHER THAN THE TARGET ORGANS, TO BE SELECTED BY THE STUDY PATHOLOGIST IN ORDER TO DETERMINE THE CAUSE OF DEATH. IF CAUSE OF DEATH WAS DIAGNOSED GROSSLY, E.G. HEAD CRUSH, THEN ONLY THE TARGET ORGANS WILL BE PROCESSED.

ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARC PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

14.8 DATE: 20-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
ANIMAL CARE TECHNICIAN:	S. DENNIS
STUDY PATHOLOGIST:	J. POPP
INHALATION SUPERVISOR:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
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ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	K. MORGAN
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER

14.9 DATE: 16-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	J. POPP
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
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HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.10 DATE: 18-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	J. POPP
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
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ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.11 DATE: 10-JUL-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

- STUDY DIRECTOR: C. BARROW DATE: FRI. 6-APR-84

- STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	J. POPP
INHALATION TECHNICIAN:	A. JAMES
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ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS

14.12 DATE: 11-OCT-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	J. POPP
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
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ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS

14.13 DATE: 24-JAN-85 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	J. POPP
INHALATION TECHNICIAN:	A. JAMES
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ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS

14.14 DATE: 21-FEB-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

INHALATION SUPERVISOR:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	J. POPP
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
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ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON

14.15 DATE: 22-FEB-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  K. WONG

- STUDY STAFF:

INHALATION SUPERVISOR:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	J. POPP
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	B. BROWN

14.16 DATE: 4-MAR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

INHALATION SUPERVISOR:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	J. POPP
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ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI

14.17 DATE: 25-APR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	J. POPP
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
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ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER

14.18 DATE: 25-APR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
THE 12-MONTH INTERIM SACRIFICE OF MICE WAS CANCELLED DUE TO INSUFFICIENT NUMBER OF SURVIVORS IN ALL EXPOSURE GROUPS.

AMENDMENT:

o NECROPSY PROCEDURES

o SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+14]
METHOD OF SACRIFICE: - - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

o NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE: NONE

o NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	50	50	50	50

o COMMENTS ON SACRIFICES: NONE

o ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

o TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

14.19 DATE: 21-MAY-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	J. POPP
HEMATOLOGIST:	D. WILLIAMS
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INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN

14.20 DATE: 28-MAY-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
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INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD

14.21 DATE: 22-JUL-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  K. WONG

- STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
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INHALATION SUPERVISOR:	K. WONG
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ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND

14.22 DATE: 22-JUL-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
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INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND

14.23 DATE: 9-AUG-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
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ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND
INHALATION TECHNICIAN:	K. COUNCIL
	K. COUNCIL
ANIMAL CARE TECHNICIAN:	J. MCNEIL

14.24 DATE: 12-AUG-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

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ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	J. MCNEIL

14.25 DATE: 17-DEC-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

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ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
ANIMAL CARE TECHNICIAN:	K. COUCH
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.26 DATE: 26-FEB-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

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ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.27 DATE: 8-APR-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EXTENDED GRACE DAYS

AMENDMENT:

- HEMATOLOGY LABORATORY DATA

  - WBC DIFFERENTIAL COUNTS SOP # PHE-200-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
SEG	SEGMENTED NEUTROPHILS	1000/CMM	20.00	32.00	20.00	32.00	PHE-200-2
BAN	BAND NEUTROPHILS	------	-----	2.00	-----	2.00	PHE-200-2
LYM	LYMPHOCYTES	------	64.00	76.00	64.00	76.00	PHE-200-2
MON	MONOCYTES	------	-----	4.00	-----	4.00	PHE-200-2
EOS	EOSINOPHILS	------	-----	5.00	-----	5.00	PHE-200-2
BAS	BASOPHILS	------	-----	2.00	-----	2.00	PHE-200-2

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [-10,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

  - COULTER VALUES SOP # PHE-100-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
WBC	WHITE BLOOD CELL COUNT	1000/CMM	4.30	6.50	4.00	6.10	PHE-101-1
RBC	RED BLOOD CELL COUNT	1000/CMM	8.07	8.55	8.00	8.45	PHE-102-1
HGB	HEMOGLOBIN	GR/DL	15.00	15.80	15.00	15.80	PHE-103-1
HCT	HEMATOCRIT	PERCENT	42.00	44.40	41.00	43.00	PHE-104-1
MCV	MEAN RBC CELL VOLUME	CU.MIC.	51.60	53.40	51.60	53.40	PHE-105-1
MCH	MEAN RBC CORPUS. HEMOGLOBIN	PICOGRAM	18.10	18.90	18.10	18.90	PHE-106-1
MCHC	MEAN CORPUS. HEMO. CONC.	PERCENT	35.30	36.10	35.30	36.10	PHE-107-1
RDW	RED CELL DISTRIBUTION WIDTH	PERCENT	9.90	10.90	9.90	10.90	PHE-108-1
PLT	PLATELETS, THROMBOCYTES	1000/CMM	824.00	916.00	824.00	916.00	PHE-109-1
PCT	PLATELET "HEMATOCRIT"	PERCENT	0.59	0.64	0.59	0.64	PHE-110-1
MPV	MEAN PLATELET VOLUME	CU.MIC.	6.70	7.10	6.70	7.10	PHE-111-1
PDW	PLATELET DISTRIBUTION WIDTH	PERCENT	15.30	15.70	15.30	15.70	PHE-112-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [-10,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.28 DATE: 8-APR-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EXTENDED GRACE DAYS

AMENDMENT:

o NECROPSY PROCEDURES

o SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+14]
METHOD OF SACRIFICE: - - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

o NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE: NONE

o NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	50	50	50	50

o COMMENTS ON SACRIFICES: NONE

o ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

o TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

14.29 DATE: 8-APR-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EXTENDED GRACE DAYS

AMENDMENT:
o SERUM CHEMISTRY DATA COLLECTION

o ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-2
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-2
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-2
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [-10,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o MANUAL SOP # PCC-203-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [-10,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.30 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
12 MONTH SAC CANCELED

AMENDMENT:

o PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - MON. 16-APR-84
COMPLETION DATE: - - - - - - - - - - - - - - WED. 16-APR-86
FINAL REPORT DATE: - - - - - - - - - - - - - WED. 1-APR-87
TISSUE SLIDE COMPLETION DATE: - - - - - - - WED. 31-DEC-86
FINAL SACRIFICE DATE: - - - - - - - - - - - WED. 16-APR-86

14.31 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
MORE DETAIL

AMENDMENT:

o STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS AND MICE (8321 - F-344 RATS; 8436 - FEMALE RATS RESTART; 8437 - B6C3F1 MICE RESTART)

o PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

o SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

o TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
6 DAVIS DRIVE
RESEARCH TRIANGLE PARK, N.C.

14.32 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
COMBINING SPECIAL INSTRUCTIONS FOR CHLORINE STUDIES

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

*
10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.33 DATE: 10-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
ADDITIONAL SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

*
10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL

BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*

6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
   26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
   BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.34 DATE: 19-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
AMENDING SP. INST.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*

1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*

9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. THE LARYNX WILL BE EXAMINED IN ALL CONTROL AND HIGH DOSE ANIMALS; MALES AND FEMALES, SCHEDULED AND UNSCHEDULED DEATHS INCLUDING 12 MO SAC. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*

10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*

11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*

8321 ONLY!

*

1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*

2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*

6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:

26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.35 DATE: 24-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DELETING REDUNDANT INFO

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*

1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*

9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*

10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*

11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*

8321 ONLY!

*

1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE

WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.36 DATE: 5-OCT-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EDIT SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.
*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.
*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.
*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.
*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.
*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.
*
8321 ONLY!
*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE
*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.
*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.
*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.
*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL AND STORED.

*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 12-APR-84 = 60 FEMALES

14.37 DATE: 22-MAR-88 APPROVED BY: J. GIBSON

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
J. POPP

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	J. POPP
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.38 DATE: 22-MAR-88 APPROVED BY: J. GIBSON

REASON FOR AMENDMENT:
INTERIM SAC CANCELED DUE TO HIGH MORTALITY RATE.

AMENDMENT:

o TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 0
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 400

o TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	SEMINAL VESICLE
PROSTATE	TESTES	EPIDIDYMIS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3
NOSE 4	NOSE 5	GROSS LESION	

14.39 DATE: 30-NOV-88 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
D PASCHAL CORRECTING PROBLEM DUE TO EARLIER AMENDMENT TO DELETE THE INTERIM SACRIFICE. INTERIM SAC SCHEDULE RESTORED.

AMENDMENT:

o PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - - MON. 16-APR-84
COMPLETION DATE: - - - - - - - - - - - - - - - WED. 16-APR-86
FINAL REPORT DATE: - - - - - - - - - - - - - - WED. 1-APR-87
TISSUE SLIDE COMPLETION DATE: - - - - - - - - WED. 31-DEC-86
FINAL SACRIFICE DATE: - - - - - - - - - - - - WED. 16-APR-86
INTERIM SACRIFICE DATES: - - - - - - - - - - TUE. 16-APR-85
INTERIM REPORT DATES: - - - - - - - - - - - - TUE. 31-DEC-85

14.40 DATE: 26-MAY-93 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
IN THE COURSE OF ASSEMBLING THE STUDY RECORD AND PREPARING THE REPORT, SEVERAL STUDY DEFICIENCIES WERE IDENTIFIED. IN MY OPINION, THESE DEFICIENCES INDICATE THAT THE RECORDS AND CONDUCT OF THIS STUDY IS NOT IN COMPLETE COMPLIANCE WITH GOOD LABORATORY PRACTICE.

AMENDMENT:

- ADDITIONAL RECORDS TO BE MAINTAINED: APPROPRIATE RECORDS, SPECIMENS AND SAMPLES WILL BE MAINTAINED ACCORDING TO CIIT PROCEDURES. THESE WILL INCLUDE, BUT NOT BE LIMITED TO ALL RAW DATA, DOCUMENTATION, PROTOCOLS, AND FINAL REPORT.

1.0 STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS AND MICE

1.1 PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

1.2 SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

1.3 TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
6 DAVIS DRIVE
RESEARCH TRIANGLE PARK, N.C.

2.0 SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

2.1 STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

2.2 STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
ANIMAL CARE TECHNICIAN:	S. DENNIS
STUDY PATHOLOGIST:	K. MORGAN
INHALATION SUPERVISOR:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
ANIMAL CARE TECHNICIAN:	D. JOYNER
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE

3.0 PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - - MON. 16-APR-84
COMPLETION DATE: - - - - - - - - - - - - - - - WED. 16-APR-86
FINAL REPORT DATE: - - - - - - - - - - - - - - WED. 1-APR-87
TISSUE SLIDE COMPLETION DATE: - - - - - - - - WED. 31-DEC-86
FINAL SACRIFICE DATE: - - - - - - - - - - - - WED. 16-APR-86
INTERIM SACRIFICE DATES: - - - - - - - - - - TUE. 16-APR-85
INTERIM REPORT DATES: - - - - - - - - - - - - TUE. 31-DEC-85

4.0 STUDY TYPE: INHALATION CHRONIC

4.1 SPECIES: - RAT
STRAIN: - F344
AGE: - 4 TO 8 WEEKS
WEIGHT: - 50 TO 150 GRAMS
METHOD OF IDENTIFICATION: - - - - - - - - - - EAR TAG (SOP # TAC-161-1)

4.2 SUPPLIER: CHARLES RIVER LABORATORIES - KINGSTON

4.3 REASON FOR SELECTION OF SPECIES:

5.0 NUMBER OF ANIMALS ON STUDY:

PRETEST: 310 # MALES: # FEMALES: 310
STUDY: 280 # MALES: # FEMALES: 280

5.1 METHOD OF ASSIGNMENT TO GROUPS TO PREVENT BIAS: (SOP # TAC-164-2)

6.0 TEST ARTICLES:

6.1 NAME: CHLORINE

ID: CL2
DENSITY OF TEST ARTICLE (MG/ML): - - - - - - - 3.214
MOLECULAR WEIGHT OF TEST ARTICLE: - - - - - - 70.906
AMOUNT REQUIRED: - - - - - - - - - - - - - - - 5000 LITERS
DESCRIPTION: - - - - - - - - - - - - - - - - - GAS
RESPONSIBLE DEPARTMENT: - - - - - - - - - - - GENERAL AND BIOCHEMICAL TOX.
CONDITIONS TO MAINTAIN STABILITY: NONE
SAFETY PRECAUTIONS AND PROCEDURES: PURE CHLORINE IS GREENISH-YELLOW, ABOUT 2.5 TIMES AS HEAVY AS AIR. CHLORINE HAS A DISAGREEABLE AND SUFFOCATING ODOR WITH AN IRRITATING EFFECT ON THE NOSE AND THROAT. RESPIRATORY PROTECTION IS NECESSARY. CONCENTRATIONS ABOVE 1 PPM ARE IRRITATING. EXPOSURE TO 500-1000 PPM IS VERY DANGEROUS. SEE HAZARDOUS AGENT PROTOCOL #8308.
STABILITY: ANALYZE PRIOR TO START OF STUDY AND AT 6 MONTH INTERVALS UNTIL THE STUDY ENDS.

6.11 ADMINISTRATION

ROUTE: - INHALATION
METHOD: - INHALATION
REASON FOR ROUTE SELECTION: INHALATION IS THE USUAL ROUTE OF EXPOSURE FOR A GAS.
VEHICLE OR CARRIER: HEPA FILTERED AIR

6.12 TEST ARTICLE-CARRIER MIXTURE

METHOD OF PREPARATION: METERED CONTINUOUSLY AS A CHLORINE-NITROGEN MIXTURE INTO AN 8 CUBIC METER INHALATION CHAMBER OPERATED WITH DYNAMIC AIR FLOW.
PHYSICAL STATE OF MIXTURE: GAS

7.0 CONTROL ARTICLES:

7.1 NAME (VEHICLE): HEPA FILTERED AIR

7.11 ADMININSTRATION

ROUTE: - INHALATION
METHOD: - INHALATION

8.0 TREATMENT GROUPS AND DOSAGES:

DOSE GROUP	NUMBER ANIMALS	SEX	TARGET CONCENTRATION, PPM * ARTICLES A	B
1	70	FEMALE	------	------
2	70	FEMALE	------	0.400
3	70	FEMALE	------	1.000
4	70	FEMALE	------	2.500

* ARTICLE CODES: A=HEPA FILTERED AIR
B=CHLORINE

9.0 DIET INFORMATION:

BRAND OF DIET: - - - - - - - - - - - - - - - - NIH OPEN FORMULA
PHYSICAL FORM OF DIET: - - - - - - - - - - - - PELLETS
SOURCE OF DRINKING WATER: - - - - - - - - - - PURIFIED WATER
WATER DISTRIBUTION SYSTEM: - - - - - - - - - - AUTO WATERING SYSTEM
AVAILABILITY OF WATER: - - - - - - - - - - - - SEE 9.1

9.1 FEEDING TIME IN RELATION TO DOSING: FEED AND WATER GIVEN AD LIBITUM EXCEPT DURING EXPOSURE.

10.0 ENVIRONMENTAL CONDITIONS:

10.1 PRE-TEST CONDITIONS:

CONDITIONING PERIOD IN DAYS (MINIMUM): - - - 14
CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1

10.2 TEST CONDITIONS:

CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1
BEDDING: - - - - - - - - - - - - - - - - - - - NONE
ROOM TEMPERATURE: - - - - - - - - - - - - - - 68.0 TO 76.0 DEGREES F
RELATIVE HUMIDITY: - - - - - - - - - - - - - - 40.0 TO 65.0 PERCENT
ROOM LIGHTS ON: - - - - - - - - - - - - - - - 7:00 TO 19:00 HOURS
ANIMAL ROOM NUMBERS: - - - - - - - - - - - - - 308 309 310 311

10.3 CONTAMINANTS EXPECTED IN DIET, DRINKING WATER, BEDDING, ECT.: NONE

11.0 LABORATORY DETERMINATIONS AND SCHEDULES:

11.1 SM. ANIMAL WTS./FEED/CLIN. OBS.

11.11 BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	50.00	450.00	50.00	400.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-1

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 1,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 1,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

11.2 INHALATIION MONIORING & CONTROL

11.21 INHALATION CHAMBER MEASUREMENTS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
DBT	DRY BULB TEMPERATURE	DEGS. F	68.00	78.00	68.00	78.00	TIN-014-3
WBT	WET BULB TEMPERATURE	DEGS. F	50.00	78.00	50.00	78.00	TIN-014-3
RH	RELATIVE HUMIDITY	PERCENT	40.00	65.00	40.00	65.00	TIN-014-3
AF	CHAMBER AIR FLOW	L/MIN.	1300.	2900.	1300.	2900.	TIN-004-1
CFR	CONTAMINANT FLOW RATE	ML/MIN.	1.00	1000.	1.00	1000.	TIN-003-2
ACC	ANALYTIC CHAMBER CONCENT.	PPM	-----	-----	-----	-----	TIN-006-1
NCC	NOMINAL CHAMBER CONCENT.	PPM	-----	-----	-----	-----	---------
RAN	RATIO ANALYTIC/NOMINAL	PERCENT	30.00	110.00	30.00	110.00	---------
CFC	CONTAMINANT FLOW CHECK	------	-----	-----	-----	-----	---------

EXPOSURE SCHEDULE: DURATION 104 WEEKS
HOURS/DAY 6
DAYS/WEEK 3

DATA SAMPLING: ANALYTIC CHAMBER CONCENTRATION 1 TIMES/HOUR
ALL OTHER CHAMBER PARAMETERS 1 TIMES/HOUR

11.3 COMPUTER GENERATED LABELS

11.31 LABEL PRODUCTION

SOP # ---------

11.4 HEMATOLOGY LABORATORY DATA

11.41 WBC DIFFERENTIAL COUNTS

SOP # PHE-200-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
SEG	SEGMENTED NEUTROPHILS	1000/CMM	20.00	32.00	20.00	32.00	PHE-200-2
BAN	BAND NEUTROPHILS	------	-----	2.00	-----	2.00	PHE-200-2
LYM	LYMPHOCYTES	------	64.00	76.00	64.00	76.00	PHE-200-2
MON	MONOCYTES	------	-----	4.00	-----	4.00	PHE-200-2
EOS	EOSINOPHILS	------	-----	5.00	-----	5.00	PHE-200-2
BAS	BASOPHILS	------	-----	2.00	-----	2.00	PHE-200-2

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.42 COULTER VALUES

SOP # PHE-100-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
WBC	WHITE BLOOD CELL COUNT	1000/CMM	4.30	6.50	4.00	6.10	PHE-101-1
RBC	RED BLOOD CELL COUNT	1000/CMM	8.07	8.55	8.00	8.45	PHE-102-1
HGB	HEMOGLOBIN	GR/DL	15.00	15.80	15.00	15.80	PHE-103-1
HCT	HEMATOCRIT	PERCENT	42.00	44.40	41.00	43.00	PHE-104-1
MCV	MEAN RBC CELL VOLUME	CU.MIC.	51.60	53.40	51.60	53.40	PHE-105-1
MCH	MEAN RBC CORPUS. HEMOGLOBIN	PICOGRAM	18.10	18.90	18.10	18.90	PHE-106-1
MCHC	MEAN CORPUS. HEMO. CONC.	PERCENT	35.30	36.10	35.30	36.10	PHE-107-1
RDW	RED CELL DISTRIBUTION WIDTH	PERCENT	9.90	10.90	9.90	10.90	PHE-108-1
PLT	PLATELETS, THROMBOCYTES	1000/CMM	824.00	916.00	824.00	916.00	PHE-109-1
PCT	PLATELET "HEMATOCRIT"	PERCENT	0.59	0.64	0.59	0.64	PHE-110-1
MPV	MEAN PLATELET VOLUME	CU.MIC.	6.70	7.10	6.70	7.10	PHE-111-1
PDW	PLATELET DISTRIBUTION WIDTH	PERCENT	15.30	15.70	15.30	15.70	PHE-112-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+99]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.43 BLOOD COLLECTION PROCEDURES:

11.431 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.432 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.5 SERUM CHEMISTRY DATA COLLECTION

11.51 ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-1
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-1
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-1
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.52 MANUAL SOP # PCC-203-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

11.53 BLOOD COLLECTION PROCEDURES:

11.531 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.532 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.6 NECROPSY PROCEDURES

11.61 SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+14]
METHOD OF SACRIFICE: - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

11.62 NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	FEMALE			
DOSE GROUP	1	2	3	4
#/GROUP/SAC. 1	10	10	10	10

11.63 NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	FEMALE			
DOSE GROUP	1	2	3	4
#/DOSE GROUP	50	50	50	50

11.64 COMMENTS ON SACRIFICES: NONE

11.65 ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

11.66 TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

11.7 TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 40
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 200

11.71 TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	SEMINAL VESICLE
PROSTATE	TESTES	EPIDIDYMIS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3

NOSE 4 NOSE 5 GROSS LESION

12.0 STATISTICAL TABLES AND REPORTS:

12.1 BODY WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.2 CLINICAL CHEMISTRIES

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.3 COULTER AND DIFFERENTIAL WBC PARAMETERS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.4 CLINICAL SIGNS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.5 GROSS NECROPSY FINDINGS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.6 HISTOPATHOLOGIC LESIONS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.7 TUMOR INCIDENCE

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX
MEAN TUMOR LATENCY TABLES

12.8 ORGAN WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX

12.9 TEMPERATURE OF CHAMBER

MANN-WHITNEY TEST (NON-PARAMETRIC) BY GROUP BY SEX

13.0 RECORDS TO BE MAINTAINED: ALL RECORDS, SPECIMENS, AND SAMPLES REQUIRED TO ASSURE COMPLIANCE WITH GOOD LABORATORY PRACTICE REGULATIONS WILL BE MAINTAINED FOR AT LEAST THE TIME PERIODS SPECIFIED IN THE REGULATIONS. THESE WILL INCLUDE, BUT NOT BE LIMITED TO, ALL RAW DATA, DOCUMENTATION, PROTOCOLS, INTERIM AND FINAL REPORTS, SUMMARIES OF TRAINING AND EXPERIENCE OF PERSONNEL, JOB DESCRIPTIONS, RECORDS AND REPORTS OF THE MAINTENANCE, CALIBRATION, AND INSPECTION OF EQUIPMENT.

14.0 SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8436, 8437

1. THE CHLORINE STUDY IS MANAGED BY THREE PROTOCOLS:
   #8321 - MALE RATS
   #8436 - FEMALE RATS
   #8437 - MALE AND FEMALE MICE

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

5. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

6. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

7. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. FOR SCHEDULED SACRIFICES, ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS.
   FOR UNSCHEDULED DEATHS PRIOR TO 21 MONTHS INTO THE STUDY, THE FOLLOWING TISSUES WILL BE PROCESSED FOR HISTOLOGIC EVALUATION:
   A. ALL TARGET ORGANS
   B. ALL TISSUES FROM ANIMALS IN GROUP 4.
   C. ALL TISSUES FROM ANIMALS IN GROUP 1, WITH THE EXCEPTION OF THOSE WITH MODERATE TO SEVERE AUTOLYSIS.
   D. GROUPS 2 AND 3: TISSUES, OTHER THAN THE TARGET ORGANS, TO BE SELECTED BY THE STUDY PATHOLOGIST IN ORDER TO DETERMINE THE CAUSE OF DEATH. IF CAUSE OF DEATH WAS DIAGNOSED GROSSLY, E.G. HEAD CRUSH, THEN ONLY THE TARGET ORGANS WILL BE PROCESSED.

   ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH

PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

13. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

14.0 PROTOCOL AMENDMENTS:

14.1 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:

o STUDY TYPE: INHALATION CHRONIC

o SPECIES: - RAT
STRAIN: - F344
AGE: - 4 TO 8 WEEKS
WEIGHT: - 50 TO 150 GRAMS
METHOD OF IDENTIFICATION: - - - - - - - - - - EAR TAG (SOP # TAC-161-2)

o SUPPLIER: CHARLES RIVER LABORATORIES - KINGSTON

o REASON FOR SELECTION OF SPECIES:

14.2 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:
o SM. ANIMAL WTS./FEED/CLIN. OBS.

o BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	50.00	450.00	50.00	400.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-3

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 1,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 1,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

14.3 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:
o INHALATIION MONIORING & CONTROL

o INHALATION CHAMBER MEASUREMENTS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
DBT	DRY BULB TEMPERATURE	DEGS. F	68.00	78.00	68.00	78.00	TIN-014-3
WBT	WET BULB TEMPERATURE	DEGS. F	50.00	78.00	50.00	78.00	TIN-014-3
RH	RELATIVE HUMIDITY	PERCENT	40.00	65.00	40.00	65.00	TIN-014-3
AF	CHAMBER AIR FLOW	L/MIN.	1300.	2900.	1300.	2900.	TIN-004-2
CFR	CONTAMINANT FLOW RATE	ML/MIN.	1.00	1000.	1.00	1000.	TIN-003-2
ACC	ANALYTIC CHAMBER CONCENT.	PPM	-----	-----	-----	-----	TIN-006-1
NCC	NOMINAL CHAMBER CONCENT.	PPM	-----	-----	-----	-----	---------
RAN	RATIO ANALYTIC/NOMINAL	PERCENT	30.00	110.00	30.00	110.00	---------
CFC	CONTAMINANT FLOW CHECK	------	-----	-----	-----	-----	---------

EXPOSURE SCHEDULE: DURATION 104 WEEKS
HOURS/DAY 6
DAYS/WEEK 3

DATA SAMPLING: ANALYTIC CHAMBER CONCENTRATION 1 TIMES/HOUR
ALL OTHER CHAMBER PARAMETERS 1 TIMES/HOUR

14.4 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
CHANGE IN SOP FOR EVENT

AMENDMENT:
o SERUM CHEMISTRY DATA COLLECTION

o ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-2
AST SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-2
BILI BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-2
CA CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o MANUAL SOP # PCC-2C3-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+40]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.5 DATE: 12-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE SPECIAL INSTRUCTIONS HAVE BEEN UPDATED FOR SOP NUMBERS AND CHANGES INCURRED BECAUSE OF THE REDUCED NUMBER OF MALE CONTROL MICE (ITEMS 2,3,12).

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8436, 8437

1. THE CHLORINE STUDY IS MANAGED BY THREE PROTOCOLS:
   #8321 - MALE RATS
   #8436 - FEMALE RATS
   #8437 - MALE AND FEMALE MICE

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION, EXCEPT THE MALE CONTROL GROUP WHICH WILL HAVE 7, WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE ADDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-3

4. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

5. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-2.

6. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

7. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. FOR SCHEDULED SACRIFICES, ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS.
   FOR UNSCHEDULED DEATHS PRIOR TO 21 MONTHS INTO THE STUDY, THE

FOLLOWING TISSUES WILL BE PROCESSED FOR HISTOLOGIC EVALUATION:

A. ALL TARGET ORGANS
B. ALL TISSUES FROM ANIMALS IN GROUP 4.
C. ALL TISSUES FROM ANIMALS IN GROUP 1, WITH THE EXCEPTION OF THOSE WITH MODERATE TO SEVERE AUTOLYSIS.
D. GROUPS 2 AND 3: TISSUES, OTHER THAN THE TARGET ORGANS, TO BE SELECTED BY THE STUDY PATHOLOGIST IN ORDER TO DETERMINE THE CAUSE OF DEATH. IF CAUSE OF DEATH WAS DIAGNOSED GROSSLY, E.G. HEAD CRUSH, THEN ONLY THE TARGET ORGANS WILL BE PROCESSED.

ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARC PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

14.6 DATE: 20-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
ANIMAL CARE TECHNICIAN:	S. DENNIS
STUDY PATHOLOGIST:	K. MORGAN
INHALATION SUPERVISOR:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
ANIMAL CARE TECHNICIAN:	D. JOYNER
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE

14.7 DATE: 16-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: C. BARROW DATE: FRI. 6-APR-84

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
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ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.8 DATE: 18-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
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PATHOLOGIST:	R. IRONS
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.9 DATE: 10-JUL-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  C. BARROW

- STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS

14.10 DATE: 11-OCT-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
C. BARROW

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	R. IRONS
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS

14.11 DATE: 12-NOV-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
J. POPP

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	D. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	S. FREEMAN
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	K. WOLLARD

14.12 DATE: 24-JAN-85 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION SUPERVISOR:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	S. FREEMAN
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	K. WOLLARD

14.13 DATE: 21-FEB-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

INHALATION SUPERVISOR:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	D. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN

14.14 DATE: 4-MAR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

INHALATION SUPERVISOR:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI

14.15 DATE: 25-APR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER

14.16 DATE: 25-APR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DELETED MALE REPRODUCTIVE ORGANS AS THIS PROTOCOL HAS FEMALE RATS ONLY.

AMENDMENT:

o NECROPSY PROCEDURES

o SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - [-7 ,+14]
METHOD OF SACRIFICE: - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - PENTOBARBITAL

o NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	FEMALE			
DOSE GROUP	1	2	3	4
#/GROUP/SAC. 1	10	10	10	10

o NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	FEMALE			
DOSE GROUP	1	2	3	4
#/DOSE GROUP	50	50	50	50

o COMMENTS ON SACRIFICES: NONE

o ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

o TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	ESOPHAGUS
EYES & OPTIC N.	HARDERIAN GLAND	HEART	ILEUM
JEJUNUM	KIDNEY	LIVER	MAND. LYMPH NDS.
MESE. LYMPH NDS.	LUNGS	LARYNX	MAMMARY GLANDS
NOSE/TURBINATES	OVIDUCTS	OVARIES	PANCREAS
PITUITARY GLAND	PARATHYROID	SPINAL CORD	SALIVARY GLAND
SKIN	SKELETAL MUSCLE	SCIATIC NERVE	SPLEEN
STOMACH	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

14.17 DATE: 25-APR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DELETED MALE REPRODUCTIVE ORGANS AS THIS PROTOCOL HAS FEMALE RATS ONLY.

AMENDMENT:

o TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 40
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 200

o TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3
NOSE 4	NOSE 5	GROSS LESION	

14.18 DATE: 21-MAY-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS

ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN

14.19 DATE: 23-MAY-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	B. SUTTON
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD

14.20 DATE: 22-JUL-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	B. SUTTON
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND

14.21 DATE: 22-JUL-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  K. WONG

- STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND

14.22 DATE: 9-AUG-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
K. WONG

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
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ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION SUPERVISOR:	K. WONG
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
ANIMAL CARE TECHNICIAN:	DARNELLA ROWLAND
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	J. MCNEIL

14.23 DATE: 17-DEC-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  K. WONG

- STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
ANIMAL CARE TECHNICIAN:	K. COUCH
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.24 DATE: 26-FEB-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: FRI. 6-APR-84
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
  K. WONG

- STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.25 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
MORE DETAIL

AMENDMENT:

- STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS AND MICE (8321 - F-344 RATS; 8436 - FEMALE RATS RESTART; 8437 - B6C3F1 MICE RESTART)

- PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

- SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

- TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
  6 DAVIS DRIVE
  RESEARCH TRIANGLE PARK, N.C.

14.26 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
COMBINING SPECIAL INSTRUCTIONS IN CHLORINE STUDIES

AMENDMENT:

- SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.27 DATE: 10-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
ADDITIONAL SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND

USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*

9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

*

10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*

8321 ONLY!

*

1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*

2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE

METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.28 DATE: 19-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
AMENDING SP. INST.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. THE LARYNX WILL BE EXAMINED IN ALL CONTROL AND HIGH DOSE ANIMALS; MALES AND FEMALES, SCHEDULED AND UNSCHEDULED DEATHS INCLUDING 12 MO SAC. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!
*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE
*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.
*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.
*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.
*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.
*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.29 DATE: 24-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DELETING REDUNDANT INFO

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS

ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*

6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
   26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
   BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.30 DATE: 5-OCT-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EDIT SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*

1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE

CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL AND STORED.

*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 12-APR-84 = 60 FEMALES

14.31 DATE: 22-MAR-88 APPROVED BY: J. GIBSON

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: FRI. 6-APR-84
J. GIBSON

o STUDY DIRECTOR: _____ DATE: FRI. 6-APR-84
J. POPP

o STUDY STAFF:

CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	D. LYGHT
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE SUPERVISOR:	P. ROSS
INHALATION TECHNICIAN:	M. HIGUCHI
INHALATION TECHNICIAN:	W. HARRINGTON
ANIMAL CARE TECHNICIAN:	A. BYNUM
ANIMAL CARE TECHNICIAN:	K. WASHINGTON
ANIMAL CARE TECHNICIAN:	L. PARKER
INHALATION TECHNICIAN:	B. STEINHAGEN
ANIMAL CARE TECHNICIAN:	T. SHEPARD
INHALATION TECHNICIAN:	K. COUNCIL
ANIMAL CARE TECHNICIAN:	K. BELZER
INHALATION TECHNICIAN:	R. MYATICH
INHALATION TECHNICIAN:	C. MICOR

14.32 DATE: 26-MAY-93 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
IN THE COURSE OF ASSEMBLING THE STUDY RECORD AND PREPARING THE REPORT, SEVERAL STUDY DEFICIENCIES WERE IDENTIFIED. IN MY OPINION, THESE DEFICIENCIES INDICATE THAT THE RECORDS AND CONDUCT OF THIS STUDY IS NOT IN COMPLETE COMPLIANCE WITH GOOD LABORATORY PRACTICE.

AMENDMENT:

- ADDITIONAL RECORDS TO BE MAINTAINED: APPROPRIATE RECORDS, SPECIMENS AND SAMPLES WILL BE MAINTAINED ACCORDING TO CIIT PROCEDURES. THESE WILL INCLUDE, BUT NOT BE LIMITED TO ALL RAW DATA, DOCUMENTATION, PROTOCOLS, AND FINAL REPORT.

1.0 STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS

1.1 PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

1.2 SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

1.3 TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
6 DAVIS DRIVE
RESEARCH TRIANGLE PARK, N.C.

2.0 SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

2.1 STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

2.2 STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
PROJECT RECORDS COORDINATOR:	A. MCCARTHY
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS

3.0 PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - MON. 11-APR-83
COMPLETION DATE: - - - - - - - - - - - - - - MON. 8-APR-85
FINAL REPORT DATE: - - - - - - - - - - - - - TUE. 1-APR-86
TISSUE SLIDE COMPLETION DATE: - - - - - - - TUE. 31-DEC-85
FINAL SACRIFICE DATE: - - - - - - - - - - - MON. 8-APR-85
INTERIM SACRIFICE DATES: - - - - - - - - - - MON. 9-JUL-84
INTERIM REPORT DATES: - - - - - - - - - - - MON. 31-DEC-84

4.0 STUDY TYPE: INHALATION CHRONIC

4.1 SPECIES: - - - - - - - - - - - - - - - - - - - RAT
STRAIN: - F344
AGE: - 4 TO 8 WEEKS
WEIGHT: - 50 TO 150 GRAMS
METHOD OF IDENTIFICATION: - - - - - - - - - - EAR TAG (SOP # TAC-161-1)

4.2 SUPPLIER: CHARLES RIVER LABORATORIES - KINGSTON

4.3 REASON FOR SELECTION OF SPECIES: THE SPONSOR HAS A SIGNIFICANT PAST HISTORY WITH THIS SPECIES. A SIGNIFICANT AMOUNT OF THE EXISTING DATA BASE FOR ANIMAL TOXICITY OF CHLORINE IS FROM STUDIES IN RATS. THE F-344 RAT HAS A WELL ESTABLISHED INCIDENCE OF NATURALLY OCCURRING TUMORS AND A LONG LIFE SPAN.

5.0 NUMBER OF ANIMALS ON STUDY:

PRETEST: 620 # MALES: 310 # FEMALES: 310
STUDY: 560 # MALES: 280 # FEMALES: 280

5.1 METHOD OF ASSIGNMENT TO GROUPS TO PREVENT BIAS: (SOP # TAC-164-2)

6.0 TEST ARTICLES:

6.1 NAME: CHLORINE

ID: CL2
DENSITY OF TEST ARTICLE (MG/ML): - - - - - - 3.214
MOLECULAR WEIGHT OF TEST ARTICLE: - - - - - 70.906
AMOUNT REQUIRED: - - - - - - - - - - - - - - 5000 LITERS
DESCRIPTION: - - - - - - - - - - - - - - - - GAS
RESPONSIBLE DEPARTMENT: - - - - - - - - - - - GENERAL AND BIOCHEMICAL TOX.
CONDITIONS TO MAINTAIN STABILITY: NONE
SAFETY PRECAUTIONS AND PROCEDURES: PURE CHLORINE IS GREENISH-YELLOW, ABOUT 2.5 TIMES AS HEAVY AS AIR. CHLORINE HAS A DISAGREEABLE AND SUFFOCATING ODOR WITH AN IRRITATING EFFECT ON THE NOSE AND THROAT. RESPIRATORY PROTECTION IS NECESSARY. CONCENTRATIONS ABOVE 1 PPM ARE IRRITATING. EXPOSURE TO 500-1000 PPM IS VERY DANGEROUS. SEE HAZARDOUS AGENT PROTOCOL #8308.

STABILITY: ANALYZE PRIOR TO START OF STUDY AND AT 6 MONTH INTERVALS UNTIL THE STUDY ENDS.

6.11 ADMINISTRATION

ROUTE: - INHALATION
METHOD: - INHALATION
REASON FOR ROUTE SELECTION: INHALATION IS THE USUAL ROUTE OF EXPOSURE FOR A GAS.
VEHICLE OR CARRIER: HEPA FILTERED AIR

6.12 TEST ARTICLE-CARRIER MIXTURE

METHOD OF PREPARATION: METERED CONTINUOUSLY AS A CHLORINE-NITROGEN MIXTURE INTO AN 8 CUBIC METER INHALATION CHAMBER OPERATED WITH DYNAMIC AIR FLOW.
PHYSICAL STATE OF MIXTURE: GAS

7.0 CONTROL ARTICLES:

7.1 NAME (VEHICLE): HEPA FILTERED AIR

7.11 ADMININSTRATION

ROUTE: - INHALATION
METHOD: - INHALATION

8.0 TREATMENT GROUPS AND DOSAGES:

DOSE GROUP	NUMBER ANIMALS	SEX	TARGET CONCENTRATION, PPM * ARTICLES A	B
1	70	MALE	------	------
2	70	MALE	------	0.400
3	70	MALE	------	1.000
4	70	MALE	------	2.500
1	70	FEMALE	------	------
2	70	FEMALE	------	0.400
3	70	FEMALE	------	1.000
4	70	FEMALE	------	2.500

* ARTICLE CODES: A=HEPA FILTERED AIR
B=CHLORINE

9.0 DIET INFORMATION:

BRAND OF DIET: - - - - - - - - - - - - - - - - NIH OPEN FORMULA
PHYSICAL FORM OF DIET: - - - - - - - - - - - - PELLETS
SOURCE OF DRINKING WATER: - - - - - - - - - - PURIFIED WATER
WATER DISTRIBUTION SYSTEM: - - - - - - - - - - AUTO WATERING SYSTEM
AVAILABILITY OF WATER: - - - - - - - - - - - - SEE 9.1

9.1 FEEDING TIME IN RELATION TO DOSING: FEED AND WATER GIVEN AD LIBITUM EXCEPT DURING EXPOSURE.

10.0 ENVIRONMENTAL CONDITIONS:

10.1 PRE-TEST CONDITIONS:

CONDITIONING PERIOD IN DAYS (MINIMUM): - - - 14
CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1

10.2 TEST CONDITIONS:

CAGE TYPE AND SIZE: - - - - - - - - - - - - - HANGING STAINLESS STEEL (11X15 CM)
NUMBER ANIMALS/CAGE: - - - - - - - - - - - - - 1
BEDDING: - - - - - - - - - - - - - - - - - - - NONE
ROOM TEMPERATURE: - - - - - - - - - - - - - - 68.0 TO 76.0 DEGREES F
RELATIVE HUMIDITY: - - - - - - - - - - - - - - 40.0 TO 65.0 PERCENT
ROOM LIGHTS ON: - - - - - - - - - - - - - - - 7:00 TO 19:00 HOURS
ANIMAL ROOM NUMBERS: - - - - - - - - - - - - - 308 309 310 311

10.3 CONTAMINANTS EXPECTED IN DIET, DRINKING WATER, BEDDING, ECT.: NONE

11.0 LABORATORY DETERMINATIONS AND SCHEDULES:

11.1 SM. ANIMAL WTS./FEED/CLIN. OBS.

11.11 BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	50.00	450.00	50.00	400.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-1

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 0,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 0,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

11.2 INHALATIION MONIORING & CONTROL

11.21 INHALATION CHAMBER MEASUREMENTS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
DBT	DRY BULB TEMPERATURE	DEGS. F	68.00	78.00	68.00	78.00	TIN-014-3
WBT	WET BULB TEMPERATURE	DEGS. F	50.00	78.00	50.00	78.00	TIN-014-3
RH	RELATIVE HUMIDITY	PERCENT	40.00	65.00	40.00	65.00	TIN-014-3
AF	CHAMBER AIR FLOW	L/MIN.	1300.	2900.	1300.	2900.	TIN-004-1
CFR	CONTAMINANT FLOW RATE	ML/MIN.	1.00	1000.	1.00	1000.	TIN-003-2
ACC	ANALYTIC CHAMBER CONCENT.	PPM	-----	-----	-----	-----	TIN-006-1
NCC	NOMINAL CHAMBER CONCENT.	PPM	-----	-----	-----	-----	---------
RAN	RATIO ANALYTIC/NOMINAL	PERCENT	40.00	110.00	40.00	110.00	---------
CFC	CONTAMINANT FLOW CHECK	------	-----	-----	-----	-----	---------

EXPOSURE SCHEDULE: DURATION 104 WEEKS
HOURS/DAY 6
DAYS/WEEK 5

DATA SAMPLING: ANALYTIC CHAMBER CONCENTRATION 1 TIMES/HOUR
ALL OTHER CHAMBER PARAMETERS 1 TIMES/HOUR

11.3 COMPUTER GENERATED LABELS

11.31 LABEL PRODUCTION

SOP # ---------

11.4 HEMATOLOGY LABORATORY DATA

11.41 WBC DIFFERENTIAL COUNTS

SOP # PHE-200-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
SEG	SEGMENTED NEUTROPHILS	1000/CMM	20.00	32.00	20.00	32.00	PHE-200-2
BAN	BAND NEUTROPHILS	------	-----	2.00	-----	2.00	PHE-200-2
LYM	LYMPHOCYTES	------	64.00	76.00	64.00	76.00	PHE-200-2
MON	MONOCYTES	------	-----	4.00	-----	4.00	PHE-200-2
EOS	EOSINOPHILS	------	-----	5.00	-----	5.00	PHE-200-2
BAS	BASOPHILS	------	-----	2.00	-----	2.00	PHE-200-2

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 66, EVERY 39 WEEKS THROUGH WEEK 105

11.42 COULTER VALUES

SOP # PHE-100-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
WBC	WHITE BLOOD CELL COUNT	1000/CMM	4.30	6.50	4.00	6.10	PHE-101-1
RBC	RED BLOOD CELL COUNT	1000/CMM	8.07	8.55	8.00	8.45	PHE-102-1
HGB	HEMOGLOBIN	GR/DL	15.00	15.80	15.00	15.80	PHE-103-1
HCT	HEMATOCRIT	PERCENT	42.00	44.40	41.00	43.00	PHE-104-1
MCV	MEAN RBC CELL VOLUME	CU.MIC.	51.60	53.40	51.60	53.40	PHE-105-1
MCH	MEAN RBC CORPUS. HEMOGLOBIN	PICOGRAM	18.10	18.90	18.10	18.90	PHE-106-1
MCHC	MEAN CORPUS. HEMO. CONC.	PERCENT	35.30	36.10	35.30	36.10	PHE-107-1
RDW	RED CELL DISTRIBUTION WIDTH	PERCENT	9.90	10.90	9.90	10.90	PHE-108-1
PLT	PLATELETS, THROMBOCYTES	1000/CMM	824.00	916.00	824.00	916.00	PHE-109-1
PCT	PLATELET "HEMATOCRIT"	PERCENT	0.59	0.64	0.59	0.64	PHE-110-1
MPV	MEAN PLATELET VOLUME	CU.MIC.	6.70	7.10	6.70	7.10	PHE-111-1
PDW	PLATELET DISTRIBUTION WIDTH	PERCENT	15.30	15.70	15.30	15.70	PHE-112-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 66, EVERY 39 WEEKS THROUGH WEEK 105

11.43 BLOOD COLLECTION PROCEDURES:

11.431 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.432 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.5 SERUM CHEMISTRY DATA COLLECTION

11.51 ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-1
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-1
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-1
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 66, EVERY 39 WEEKS THROUGH WEEK 105

11.52 MANUAL SOP # PCC-203-1

PARAMETER	UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 66, EVERY 39 WEEKS THROUGH WEEK 105

11.53 BLOOD COLLECTION PROCEDURES:

11.531 PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

11.532 TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

11.6 NECROPSY PROCEDURES

11.61 SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+30]
METHOD OF SACRIFICE: - - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

11.62 NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/GROUP/SAC. 1	10	10	10	10	10	10	10	10

11.63 NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	50	50	50	50

11.64 COMMENTS ON SACRIFICES: NONE

11.65 ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

11.66 TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

11.7 TISSUES FOR MICROSCOPIC EXAMINATION

NUMBER ANIMALS TO READ AT INTERIM SACRIFICE: 80
NUMBER ANIMALS TO READ AT FINAL SACRIFICE: 400

11.71 TISSUE LIST (SOP # PHP-001-1)

BRAIN	SPINAL CORD	PITUITARY GLAND	THYROID GLANDS
PARATHYROID	LARYNX	TRACHEA	ESOPHAGUS
STOMACH	DUODENUM	JEJUNUM	ILEUM
CECUM	COLON	PANCREAS	SALIVARY GLAND
MAND. LYMPH NDS.	MESE. LYMPH NDS.	THYMUS	SPLEEN
HEART	AORTA	TONGUE	LIVER
KIDNEY	ADRENAL GLANDS	LUNGS	SEMINAL VESICLE
PROSTATE	TESTES	EPIDIDYMIS	OVARIES
OVIDUCTS	UTERUS	URINARY BLADDER	EYES & OPTIC N.
HARDERIAN GLAND	SKIN	MAMMARY GLANDS	SKELETAL MUSCLE
SCIATIC NERVE	BONE, FEMUR	BONE, STERNUM	BONE MARROW
EAR CANAL	NOSE 1	NOSE 2	NOSE 3

NOSE 4 NOSE 5 GROSS LESION

12.0 STATISTICAL TABLES AND REPORTS:

12.1 BODY WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.2 CLINICAL CHEMISTRIES

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.3 COULTER AND DIFFERENTIAL WBC PARAMETERS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX
ONE-WAY ANALYSIS OF VARIANCE BY GROUP BY SEX

12.4 CLINICAL SIGNS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.5 GROSS NECROPSY FINDINGS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.6 HISTOPATHOLOGIC LESIONS

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX

12.7 TUMOR INCIDENCE

RAW DATA TABLES BY GROUP BY SEX
SUMMARY TABLES BY GROUP BY SEX
MEAN TUMOR LATENCY TABLES

12.8 ORGAN WEIGHTS

RAW DATA TABLES BY GROUP BY SEX
MEAN AND STANDARD DEVIATION BY GROUP BY SEX

12.9 TEMPERATURE OF CHAMBER

MANN-WHITNEY TEST (NON-PARAMETRIC) BY GROUP BY SEX

13.0 RECORDS TO BE MAINTAINED: ALL RECORDS, SPECIMENS, AND SAMPLES REQUIRED TO ASSURE COMPLIANCE WITH GOOD LABORATORY PRACTICE REGULATIONS WILL BE MAINTAINED FOR AT LEAST THE TIME PERIODS SPECIFIED IN THE REGULATIONS. THESE WILL INCLUDE, BUT NOT BE LIMITED TO, ALL RAW DATA, DOCUMENTATION, PROTOCOLS, INTERIM AND FINAL REPORTS, SUMMARIES OF TRAINING AND EXPERIENCE OF PERSONNEL, JOB DESCRIPTIONS, RECORDS AND REPORTS OF THE MAINTENANCE, CALIBRATION, AND INSPECTION OF EQUIPMENT.

14.0 SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-168-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS,

TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

14.0 PROTOCOL AMENDMENTS:

14.1 DATE: 19-APR-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE USE OF ZERO AIR TO ZERO THE ANALYZERS HAS RESULTED IN A POSITIVE INTERFERENCE WHEN READING THE CONTROL CHAMBER. THIS IS AN INCORRECT READING BECAUSE THE RESULTS FROM THE 2,6 DMP ASSAY HAVE INDICATED NO CHLORINE IS PRESENT IN THE CONTROL CHAMBER. THIS ERROR IS ALSO ADDITIVE TO THE THREE TEST CHAMBERS AND WILL RESULT IN UNDER-EXPOSURE OF THE TREATED GROUPS. AS A RESULT, THE USE OF ZERO AIR IS NOT JUSTIFIED.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS,

TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

14.2 DATE: 25-APR-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  C. BARROW

- STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
PROJECT RECORDS COORDINATOR:	A. MCCARTHY

INHALATION TECHNICIAN: D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST: M. MORRIS

14.3 DATE: 25-APR-88 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
A STATEMENT REGARDING THE REPLACEMENT OF DEAD ANIMALS WAS ADDED TO THE SPECIAL INSTRUCTIONS TO EXPLAIN WHY ANIMALS CONTINUE TO HAVE BODY WEIGHTS AFTER RECORDED AS DEAD.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14.4 DATE: 27-APR-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE RAT WEIGHT SCHEDULE WAS CHANGED AFTER DAY 85 SO THAT THE WEIGHING SCHEDULE IS ON OPPOSITE WEEKS OF THE MICE.

AMENDMENT:
o SM. ANIMAL WTS./FEED/CLIN. OBS.

o BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	50.00	450.00	50.00	400.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-1

SCHEDULED PRETEST DAYS: GRACE PERIOD DAYS [- 0,+ 5]
-7

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 0,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	92	106	120
134	148	162	176	190	204	218	232	246	260	274	288	302	316	330	344
358	372	386	400	414	428	442	456	470	484	498	512	526	540	554	568
582	596	610	624	638	652	666	680	694	708	722					

14.5 DATE: 18-MAY-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
ITEM #14 WAS ADDED TO THE SPECIAL INSTRUCTIONS TO OUTLINE THE NEW EXPOSURE SCHEDULE FOR FEMALE RATS. THIS CHANGE IS BEING INITIATED TO PRESERVE THE HEALTH OF THESE RATS. AFTER 5 WEEKS ON TEST THE FEMALE RATS EXPOSED TO 1.0 AND 2.5 PPM CHLORINE HAVE GREATER THAN A 20% DECREASE IN BODY WEIGHT GAIN, COMPARED TO CONTROLS.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1988 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE

ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

14.6 DATE: 18-MAY-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
PROJECT RECORDS COORDINATOR:	A. MCCARTHY
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER

14.7 DATE: 3-JUN-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE EXPOSURE SCHEDULE FOR THE 0.4 PPM GROUP WAS CHANGED TO COINCIDE WITH THE EXPOSURE REGIMEN FOR THE 1.0 AND 2.5 PPM GROUPS. THIS WILL MAKE EVALUATION OF FINDINGS BETWEEN GROUPS MORE MEANINGFUL.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

15. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

14.8 DATE: 17-JUN-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL

HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
PROJECT RECORDS COORDINATOR:	A. MCCARTHY
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER
PATHOLOGY TECHNOLOGIST:	J. MARTIN

14.9 DATE: 12-JUL-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE SCHEDULE WAS ALTERED TO CORRECT AN ERROR IN WEIGHING.
DAY 92 WAS DELETED AND DAY 99 SUBSTITUTED.

AMENDMENT:
o SW. ANIMAL WTS./FEED/CLIN. OBS.

o BODY WTS. & CLINICAL SIGNS SOP # ---------

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
BW	BODY WEIGHTS	GRAMS	50.00	450.00	50.00	400.00	TAC-162-1
CO	CLINICAL OBSERVATIONS	------	-----	-----	-----	-----	TAC-128-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY DAYS: GRACE PERIOD DAYS [- 0,+ 5]

1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	127
141	155	169	183	197	211	225	239	253	267	281	295	309	323	337	351
365	379	393	407	421	435	449	463	477	491	505	519	533	547	561	575
589	603	617	631	645	659	673	687	701	715	729					

14.10 DATE: 25-JUL-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
R. IRONS, J. POPP AND J. SWENBERG WERE ADDED TO PERSONNEL LIST
TO ALLOW DATA ENTRY WHEN THEY ARE RESPONSIBLE FOR WEEKEND AND
HOLIDAY NECROPSY COVERAGE.

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  C. BARROW

- STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	D. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
PROJECT RECORDS COORDINATOR:	A. MCCARTHY
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER
PATHOLOGY TECHNOLOGIST:	J. MARTIN
PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP

14.11 DATE: 3-AUG-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THIS SPECIAL SACRIFICE OF ANIMALS IS BEING PERFORMED TO DETERMINE WHETHER CHLORINE TREATED ANIMALS ARE BEING AFFECTED BY METAL TOXICITY RESULTING FROM CHLORINE REACTING WITH THE STAINLESS STEEL CAGES.

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
   #8321 FOR RATS
   #8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1988 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE

ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

15. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

16. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.12 DATE: 12-SEP-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THIS SPECIAL SACRIFICE OF ANIMALS IF BEING PERFORMED TO DETERMINE WHETHER CHLORINE TREATED ANIMALS ARE BEING AFFECTED BY METAL TOXICITY RESULTING FROM CHLORINE REACTING WITH THE STAINLESS STEEL CAGES.

AMENDMENT:

o PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - - MON. 11-APR-83
COMPLETION DATE: - - - - - - - - - - - - - - - MON. 8-APR-85
FINAL REPORT DATE: - - - - - - - - - - - - - - TUE. 1-APR-86
TISSUE SLIDE COMPLETION DATE: - - - - - - - - TUE. 31-DEC-85
FINAL SACRIFICE DATE: - - - - - - - - - - - - MON. 8-APR-85
INTERIM SACRIFICE DATES: - - - - - - - - - - MON. 8-AUG-83 MON. 9-JUL-84
INTERIM REPORT DATES: - - - - - - - - - - - - MON. 31-DEC-84

14.13 DATE: 21-OCT-83 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  C. BARROW

- STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
ANIMAL CARE TECHNICIAN:	D. JOYNER
PATHOLOGY TECHNOLOGIST:	J. MARTIN
PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON

14.14 DATE: 16-JAN-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  C. BARROW

- STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	L. BUCKLEY
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
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HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
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HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
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ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGY TECHNOLOGIST:	J. MARTIN
PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE

14.15 DATE: 12-MAR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE INTERIM SACRIFICE DATE WAS CHANGED FROM 9-JUL-84 TO 11-APR-84 TO CONFORM TO THE RECOMMENDATIONS REACHED AT THE 11-14-83 CHLORINE ADVISORY COMMITTEE MEETING. IT WAS CONCLUDED THAT THE FEMALE RATS ON TEST AT 2.5 PPM HAD EXCEEDED THE MAXIMUM TOLERATED DOSE. NEW FEMALE RATS WILL START A NEW EXPOSURE SCHEDULE OF 6 HR/DAY, 3 DAY/WEEK FOR 24 MONTHS SHORTLY AFTER THE 12 MONTH SACRIFICE. A NEW PROTOCOL WILL BE WRITTEN FOR THIS STUDY.

AMENDMENT:

o PROPOSED DATES:

START DATE: - - - - - - - - - - - - - - - - - - MON. 11-APR-83
COMPLETION DATE: - - - - - - - - - - - - - - - MON. 8-APR-85
FINAL REPORT DATE: - - - - - - - - - - - - - - TUE. 1-APR-86
TISSUE SLIDE COMPLETION DATE: - - - - - - - - TUE. 31-DEC-85
FINAL SACRIFICE DATE: - - - - - - - - - - - - MON. 8-APR-85
INTERIM SACRIFICE DATES: - - - - - - - - - - MON. 8-AUG-83 WED. 11-APR-84
INTERIM REPORT DATES: - - - - - - - - - - - - MON. 31-DEC-84

14.16 DATE: 29-MAR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE INTERIM SACRIFICE WAS CHANGED FROM 15 MONTHS TO 12 MONTHS.
THE HEMATOLOGY SCHEDULE HAS BEEN CHANGED TO ACCOMMODATE THE
SCHEDULE.

AMENDMENT:
o HEMATOLOGY LABORATORY DATA

o WBC DIFFERENTIAL COUNTS SOP # PHE-200-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
SEG	SEGMENTED NEUTROPHILS	1000/CMM	20.00	32.00	20.00	32.00	PHE-200-2
BAN	BAND NEUTROPHILS	------	-----	2.00	-----	2.00	PHE-200-2
LYM	LYMPHOCYTES	------	64.00	76.00	64.00	76.00	PHE-200-2
MON	MONOCYTES	------	-----	4.00	-----	4.00	PHE-200-2
EOS	EOSINOPHILS	------	-----	5.00	-----	5.00	PHE-200-2
BAS	BASOPHILS	------	-----	2.00	-----	2.00	PHE-200-2

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o COULTER VALUES SOP # PHE-100-2

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
WBC	WHITE BLOOD CELL COUNT	1000/CMM	4.30	6.50	4.00	6.10	PHE-101-1
RBC	RED BLOOD CELL COUNT	1000/CMM	8.07	8.55	8.00	8.45	PHE-102-1
HGB	HEMOGLOBIN	GR/DL	15.00	15.80	15.00	15.80	PHE-103-1
HCT	HEMATOCRIT	PERCENT	42.00	44.40	41.00	43.00	PHE-104-1
MCV	MEAN RBC CELL VOLUME	CU.MIC.	51.60	53.40	51.60	53.40	PHE-105-1
MCH	MEAN RBC CORPUS. HEMOGLOBIN	PICOGRAM	18.10	18.90	18.10	18.90	PHE-106-1
MCHC	MEAN CORPUS. HEMO. CONC.	PERCENT	35.30	36.10	35.30	36.10	PHE-107-1
RDW	RED CELL DISTRIBUTION WIDTH	PERCENT	9.90	10.90	9.90	10.90	PHE-108-1
PLT	PLATELETS, THROMBOCYTES	1000/CMM	824.00	916.00	824.00	916.00	PHE-109-1
PCT	PLATELET "HEMATOCRIT"	PERCENT	0.59	0.64	0.59	0.64	PHE-110-1
MPV	MEAN PLATELET VOLUME	CU.MIC.	6.70	7.10	6.70	7.10	PHE-111-1
PDW	PLATELET DISTRIBUTION WIDTH	PERCENT	15.30	15.70	15.30	15.70	PHE-112-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.17 DATE: 29-MAR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE INTERIM SACRIFICE WAS CHANGED FROM 15 MONTHS TO 12 MONTHS.
THE SERUM CHEMISTRY SCHEDULE HAS BEEN CHANGED TO ACCOMMODATE
THE NEW SCHEDULE.

AMENDMENT:

o SERUM CHEMISTRY DATA COLLECTION

o ABBOT VP & FL. PH. SOP # PCC-100-3

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
ALB	ALBUMIN	G/DL	3.50	4.80	3.50	4.80	PCC-101-1
ALK	ALKALINE PHOSPHATASE	IU/L	400.00	800.00	400.00	800.00	PCC-102-1
ALT	SGPT	IU/L	20.00	40.00	20.00	40.00	PCC-103-1
AST	SGOT	IU/L	70.00	120.00	70.00	120.00	PCC-104-1
BILI	BILIRUBIN TOTAL	MG/DL	-----	0.40	-----	0.40	PCC-105-1
BUN	BLOOD UREA NITROGEN	MG/DL	10.00	30.00	10.00	30.00	PCC-106-1
CA	CALCIUM	MG/DL	10.00	12.00	10.00	12.00	PCC-107-1
GLU	GLUCOSE	MG/DL	140.00	200.00	140.00	200.00	PCC-110-1
GGTP	GGTP	IU/L	-----	1.00	-----	1.00	PCC-111-2
PHOS	PHOSPHOROUS INORGANIC	MG/DL	7.00	12.00	7.00	12.00	PCC-115-2
TP	PROTEIN TOTAL	G/DL	5.00	7.30	5.00	7.30	PCC-116-1
NA	SODIUM	MEQ/L	140.00	150.00	140.00	150.00	PCC-200-1
K	POTASSIUM	MEQ/L	3.50	6.20	3.50	6.20	PCC-200-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o MANUAL SOP # PCC-203-1

PARAMETER		UNITS	PARAMETER RANGE VALUES MALE LOW	MALE HIGH	FEMALE LOW	FEMALE HIGH	SOP #
CL	CHLORIDE	MEQ/L	95.00	105.00	95.00	105.00	PCC-203-1

SCHEDULED PRETEST DAYS: NONE

SCHEDULED STUDY WEEKS: GRACE PERIOD DAYS [- 7,+30]

STARTING ON WEEK 53, EVERY 52 WEEKS THROUGH WEEK 105

o BLOOD COLLECTION PROCEDURES:

o PRE-TEST:

FAST OVER NIGHT: - - - - - - - - - - - - - - - NO

o TEST: (SOP # PTH-001-1)

FAST OVER NIGHT: - - - - - - - - - - - - - - - YES
METHOD OF COLLECTION: - - - - - - - - - - - - CARDIAC BLEEDING
TIME OF COLLECTION: - - - - - - - - - - - - - PRIOR TO NECROPSY

BLEED ANIMALS SCHEDULED FOR SACRIFICE

14.18 DATE: 9-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
SPECIFIED INTERIM SAC NUMBER OF ANIMALS TO ACCOMMODATE REVISED STUDY SCHEDULE.

AMENDMENT:

o NECROPSY PROCEDURES

o SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - - [-7 ,+30]
METHOD OF SACRIFICE: - - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - - PENTOBARBITAL

o NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/GROUP/SAC. 1	0	0	0	0	5	0	0	5
#/GROUP/SAC. 2	10	10	10	10	10	10	10	10

o NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	50	50	50	50

o COMMENTS ON SACRIFICES: NONE

o ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

o TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

14.19 DATE: 9-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
THE FEMALES HAVE BEEN ELIMINATED FROM THE FINAL SAC. DUE TO THE RESPONSE OF THE FEMALES.

AMENDMENT:

o NECROPSY PROCEDURES

o SACRIFICE DATA (SOP # PNE-001-1)
GRACE DAYS: - - - - - - - - - - - - - - - - [-7 ,+30]
METHOD OF SACRIFICE: - - - - - - - - - - - - EXSANGUINATION
ANESTHETIC: - - - - - - - - - - - - - - - - PENTOBARBITAL

- NUMBER ANIMALS/DOSE GROUP/INTERIM SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/GROUP/SAC. 1	0	0	0	0	5	0	0	5
#/GROUP/SAC. 2	10	10	10	10	10	10	10	10

- NUMBER ANIMALS/DOSE GROUP/FINAL SACRIFICE

	MALE				FEMALE			
DOSE GROUP	1	2	3	4	1	2	3	4
#/DOSE GROUP	50	50	50	50	0	0	0	0

- COMMENTS ON SACRIFICES: NONE

- ORGANS TO WEIGH (SOP # PNE-001-1)

ORGAN	SEX	EXPECTED % OF BODY WEIGHT LOW RANGE	HIGH RANGE
LIVER		2.2000	5.9000
BRAIN		0.5300	2.1000
KIDNEY		0.6000	2.5000

- TISSUES TO COLLECT (SOP # PNE-001-1)

ADRENAL GLANDS	AORTA	BONE, FEMUR	BONE MARROW
BRAIN	BONE, STERNUM	CECUM	COLON
CERVIX	DUODENUM	EAR CANAL	EPIDIDYMIS
ESOPHAGUS	EYES & OPTIC N.	HARDERIAN GLAND	HEART
ILEUM	JEJUNUM	KIDNEY	LIVER
MAND. LYMPH NDS.	MESE. LYMPH NDS.	LUNGS	LARYNX
MAMMARY GLANDS	NOSE/TURBINATES	OVIDUCTS	OVARIES
PANCREAS	PITUITARY GLAND	PROSTATE	PARATHYROID
SPINAL CORD	SALIVARY GLAND	SKIN	SKELETAL MUSCLE
SCIATIC NERVE	SPLEEN	STOMACH	SEMINAL VESICLE
TESTES	THYROID GLANDS	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA
GROSS LESION	ZYMBALS GLAND		

14.20 DATE: 20-APR-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
ANIMAL CARE TECHNICIAN:	S. DENNIS
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
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PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE

14.21 DATE: 16-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
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HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
HISTOPATHOLOGY TECHNOLOGIST:	K. BILLINGS
HISTOPATHOLOGY TECHNOLOGIST:	B. GROSS
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGY TECHNOLOGIST:	J. MARTIN
PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON

14.22 DATE: 16-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	M. PHELPS
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
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ANIMAL CARE TECHNICIAN:	S. MCKINNEY
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
HISTOPATHOLOGY TECHNOLOGIST:	L. CARTER
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	R. IRONS
PATHOLOGIST:	J. SWENBERG
PATHOLOGIST:	J. POPP
HISTOPATHOLOGY TECHNOLOGIST:	J. BOUCHERON
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.28 DATE: 18-MAY-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
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INHALATION TECHNICIAN:	A. JAMES
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER

14.24 DATE: 10-JUL-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS

14.25 DATE: 11-OCT-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
C. BARROW

o STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	A. JAMES
CLINICAL CHEMIST:	D. NEPTUN
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS

14.26 DATE: 11-OCT-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  C. BARROW

- STUDY STAFF:

STUDY PATHOLOGIST:	K. MORGAN
ANIMAL CARE SUPERVISOR:	T. RAYNOR
STUDY TOXICOLOGIST:	T. HAMM
INHALATION TECHNICIAN:	B. STEINHAGEN
INHALATION TECHNICIAN:	A. JAMES
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS

14.27 DATE: 12-NOV-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION TECHNICIAN:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
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ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
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HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. POPP
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER

14.28 DATE: 12-NOV-84 APPROVED BY: C. BARROW

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
J. POPP

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION TECHNICIAN:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
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HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
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ANIMAL CARE TECHNICIAN:	G. JONES
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ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. POPP
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER

14.29 DATE: 12-NOV-84 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
J. POPP

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION TECHNICIAN:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
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QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
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PATHOLOGIST:	J. POPP
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	S. FREEMAN
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	K. WOLLARD

14.30 DATE: 24-JAN-85 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
K. WONG

o STUDY STAFF:

ANIMAL CARE SUPERVISOR:	T. RAYNOR
INHALATION TECHNICIAN:	B. STEINHAGEN
STUDY PATHOLOGIST:	K. MORGAN
CLINICAL CHEMIST:	D. NEPTUN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
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QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
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INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	S. FREEMAN
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE TECHNICIAN:	K. WOLLARD

14.31 DATE: 21-FEB-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
K. WONG

o STUDY STAFF:

INHALATION TECHNICIAN:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
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INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN

14.32 DATE: 4-MAR-85 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
K. WONG

o STUDY STAFF:

INHALATION TECHNICIAN:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
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ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI

14.33 DATE: 4-SEP-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DATES TAKEN FROM CL2 ADVISORY MEET. MINUTES OF 11-14-83
AMENDEMENTS WERE NOT MADE AT TIME OF TERMINATION OF STUDIES

AMENDMENT:

o NOTE: ALL MICE (8322) WERE TAKEN OFF STUDY ON OCTOBER 8, 1983 DUE TO A MOUSE HEPATITUS VIRAL INFECTION.
THE FEMALE RATS WERE TAKEN OFF STUDY ON APRIL 11, 1984 SINCE THEY HAD EXCEEDED THE MAXIMUM TOLERATED DOSE WHEN EXPOSED TO 2.5 PPM CHLORINE BASED ON BODY WEIGHT DEPRESSION.

14.34 DATE: 4-SEP-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
ERROR

AMENDMENT:

o

14.35 DATE: 4-SEP-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DIFFICULTIES AMENDING PROTOCOL TO REFLECT TERMINATION DATES
RESTORING TO PREVIOUS AMENDMENTS

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
#8321 FOR RATS
#8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

15. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

16. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.36 DATE: 4-SEP-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
ERROR

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
#8321 FOR RATS
#8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

15. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY,

RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

16. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

NOTE: ALL MICE (8322) WERE TAKEN OFF STUDY ON OCTOBER 8, 1983 DUE TO A MOUSE HEPATITUS VIRAL INFECTION.
THE FEMALE RATS WERE TAKEN OFF STUDY ON APRIL 11, 1984 SINCE THEY HAD EXCEEDED THE MAXIMUM TOLERATED DOSE WHEN EXPOSED TO 2.5 PPM CHLORINE BASED ON BODY WEIGHT DEPRESSION.

14.37 DATE: 4-SEP-86 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
RESTORING PROTOCOL TO LAST VERSION, AMENDMENTS UNECESSARY

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322

1. THE CHLORINE STUDY IS MANAGED BY TWO PROTOCOLS:
#8321 FOR RATS
#8322 FOR MICE.

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS.

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. FREE CL2 ANALYSIS WILL BE MADE AT THE END OF EACH DAY'S EXPOSURE. LESS FREQUENT ANALYSIS OF CHLORAMINE CONCENTRATIONS MAY BE MADE AS THE STUDY PROGRESSES AND SUPPORTING DATA IS AVAILABLE. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. ALL TISSUES IN THE HIGH DOSE AND CONTROL GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND

LOW DOSE GROUPS. ALL TISSUES WILL BE EXAMINED IN ANIMALS DYING UNSCHEDULED DEATHS LESS THAN 21 MONTHS INTO THE STUDY. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.

10. HISTOPATHOLOGY ON ALL HIGH DOSE AND CONTROL ANIMALS KILLED OR DYING AFTER 21 MONTHS WILL BE DONE ON LIVER, KIDNEY, LUNG, BRAIN, PITUITARY, PANCREAS, HEART, STOMACH, URINARY BLADDER, SPLEEN, THYROID AND PARATHYROID GLANDS, ADRENAL GLAND, OVARY AND UTERUS, TESTIS AND EPIDIDYMIS, PROSTATE, SEMINAL VESICLE, MANDIBULAR LYMPH NODE, LARYNX, TRACHEA AND NASOTURBINATE 1-5. ADDITIONAL TISSUES MAY BE SELECTED AFTER THE INTERIM SACRIFICE.

11. HISTOPATHOLOGY ON LOW AND INTERMEDIATE EXPOSURE ANIMALS WILL INCLUDE NASOTURBINATE 1-5, LARYNX, TRACHEA AND LUNG. ADDITIONAL TISSUES MAY BE ADDED AFTER THE INTERIM SACRIFICE.

12. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

13. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

14. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANIT-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

15. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

16. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.38 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
COMBINING ALL CHLORINE SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE PROTOCOLS #8321, 8322, 8436, 8437

1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

14.39 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
COMBINING SPECIAL INSTRUCTIONS FOR CHLORINE STUDIES

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
   #8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
   #8436 FEMALE RAT RESTART
   #8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND

USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*

6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*

7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*

8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*

9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

*

10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*

8321 ONLY!

*

1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*

2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE

METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

14.40 DATE: 7-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
MORE DETAIL

AMENDMENT:

o STUDY TITLE: RISK ASSESSMENT STUDY OF CHLORINE IN RATS AND MICE (8321 - F-344 RATS; 8436 - FEMALE RAT RESTART; 8437 - B6C3F1 MICE RESTART)

o PURPOSE OF STUDY: THE PURPOSE OF THIS INVESTIGATION IS TO ESTABLISH THE HEALTH RISK, INCLUDING CARCINOGENICITY, ASSOCIATED WITH THE CHRONIC INHALATION OF CHLORINE IN F-344 RATS AND B6C3F1 MICE.

o SPONSOR: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

o TEST FACILITY: CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
6 DAVIS DRIVE
RESEARCH TRIANGLE PARK, N.C.

14.41 DATE: 10-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
ADDITIONAL SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE

CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*

9. HISTOPATHOLOGY WILL BE COMPLETED ON ALL TISSUES LISTED IN THE TISSUE LIST (ITEM 11.71 OF THE PROTOCOL) IN ALL ANIMALS OF THE CONTROL AND HIGH DOSE GROUPS. HISTOPATHOLOGY WILL BE COMPLETED ON TARGET TISSUES AND GROSS LESIONS FROM ALL OF THE ANIMALS IN THE MID AND LOW DOSE GROUPS.

*

10. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*

8321 ONLY!

*

1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*

2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*

6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.42 DATE: 19-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
AMENDING SP INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. THE LARYNX WILL BE EXAMINED IN ALL CONTROL AND HIGH DOSE ANIMALS; MALES AND FEMALES, SCHEDULED AND UNSCHEDULED DEATHS INCLUDING 12 MO SAC. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE

WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*

2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*

3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*

4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*

5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*

6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.43 DATE: 24-AUG-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
DELETING REDUNDANT INFO

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437

*

1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART

*

2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)

*

3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1

*

4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1

*

5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1

*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.

*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.

*
8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.

*
9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.

*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR FINAL RESEARCH PURPOSES.

*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.

*
8321 ONLY!

*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

*
2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

*
3. BEGINNING ON MAY 19, 1983 THE FEMALE RATS IN THE 1.0 AND 2.5 PPM GROUPS WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY. ON TUESDAYS AND THURSDAYS, THESE FEMALE RATS WILL REMAIN IN THE CHAMBER ANTI-ROOM IN A SEPARATE RACK WITHOUT FOOD AND WATER UNTIL THE EXPOSURES ARE OVER FOR THE DAY. EXPOSURES WILL CONTINUE AS USUAL FOR THE 0.4 PPM GROUP AND CONTROLS.

*
4. BEGINNING ON JUNE 6, 1983 THE FEMALE RATS IN THE 0.4 PPM CHAMBER WILL BE EXPOSED TO CHLORINE ON MONDAY, WEDNESDAY AND FRIDAYS ONLY, RATHER THAN THE ORIGINAL MONDAY THROUGH FRIDAY SCHEDULE.

*
5. FIVE CONTROL FEMALE RATS AND FIVE RATS FROM THE 2.5 PPM CHAMBER WILL BE SACRIFICED ON AUGUST 8, 1983 USING CARBON DIOXIDE. LIVER, KIDNEYS, LUNG AND GUT WILL BE TAKEN USING NON-METAL SURGICAL INSTRUMENTS. LIVER AND KIDNEYS WILL BE SENT TO THE NUCLEAR ENGINEERING DEPARTMENT OF NORTH CAROLINA STATE UNIVERSITY. THESE TISSUES WILL BE ANALYZED FOR NICKEL, CHROMIUM AND IRON BY THE METHOD OF NEUTRON ACTIVATION. LUNGS AND GUT WILL BE SAVED FOR FUTURE ANALYSIS, IF NECESSARY. THE REMAINING CARCASS WILL BE SUBJECTED TO TISSUE COLLECTION AS PER PROTOCOL.

*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 2-APR-84 = 24 FEMALES

14.44 DATE: 5-OCT-87 APPROVED BY: K. WONG

REASON FOR AMENDMENT:
EDIT SPEC INST

AMENDMENT:

o SPECIAL INSTRUCTIONS: CHLORINE STUDY #8321, 8322, 8436, 8437
*
1. #8321 RATS (FEMALE RATS TERMINATED AT 12 MO)
#8322 MICE (ALL MICE TERMINATED 8-OCT-83 DUE TO VIRUS)
#8436 FEMALE RAT RESTART
#8437 MICE RESTART
*
2. 10 ADDITIONAL ANIMALS/SEX/CONCENTRATION WILL BE EXPOSED TO COMPENSATE FOR UNSCHEDULED DEATHS. (EXCEPTION: 8437 MALE MICE WILL HAVE 7 ADD'L ANIMALS)
*
3. 8 (4/SEX/CONCENTRATION) SENTINEL ANIMALS WILL BE INCLUDED AND USED FOR VIRAL SEROLOGY ONLY. SOP TAC-128-1
*
4. CHAMBER DISTRIBUTION PRIOR TO EXPOSURE: SOP TIN-009-1
*
5. CAGE ROTATION OF ANIMALS: SOP TAC-163-1
*
6. STUDY WILL BE MONITORED BY THE QUALITY ASSURANCE OFFICER IN ACCORDANCE WITH SOP QAI-001-1.
*
7. SERA FROM ANIMALS AT SACRIFICE WILL BE FROZEN AND STORED FOR FUTURE ANALYSIS IF NEEDED.
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8. FREE CL2 WILL BE MEASURED BY A GC TECHNIQUE BASED UPON THE CHLORINATION OF 2,6 DIMETHYLPHENOL. UNDER NO CIRCUMSTANCES WILL FREE CHLORINE BE MEASURED LESS THAN ONCE/WEEK/CHAMBER.
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9. ALL TISSUES IN THE CONTROL AND HIGH DOSE GROUPS WILL BE EXAMINED. TARGET TISSUES AND GROSS LESIONS WILL BE EXAMINED IN THE MID AND LOW DOSE GROUPS. TARGET ORGANS WILL BE SELECTED AFTER EVALUATION OF THE CONTROL AND HIGH DOSE GROUPS.
*
10. ANY ANIMALS REMAINING AFTER THE FINAL SACRIFICE WILL BE USED FOR RESEARCH PURPOSES.
*
11. MALE MICE WILL BE HOUSED ONE PER CAGE; FEMALE MICE WILL BE HOUSED FIVE PER CAGE.
*
8321 ONLY!
*
1. BEGINNING ON APRIL 18, 1983 THE INTERSCAN ANALYZERS WHICH MEASURE CHAMBER CHLORINE LEVELS WILL BE ZEROED WITH CONTROL CHAMBER AIR

INSTEAD OF ZERO AIR. ANALYSIS OF CHLORINE IN THE CONTROL CHAMBER WILL BE ACCOMPLISHED WITH THE 2,6 DIMETHYLPHENOL ASSAY. THIS CHANGE WILL REMAIN AS THE STANDARD OPERATING PROCEDURE FOR ZEROING THE ANALYZERS THROUGHOUT THE STUDY, UNLESS ANOTHER TECHNIQUE IS DEVELOPE

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2. DURING THE FIRST TWO WEEKS OF THE STUDY, ANY ANIMAL FOUND DEAD WILL BE REPLACED WITH ANOTHER ANIMAL AND MAINTAIN THE SAME ANIMAL NUMBER.

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*
6. ANIMALS REMOVED FOR RESEARCH PRIOR TO 12 MONTH SAC FOR K. MORGAN:
26-JAN-84 = 2 MALES (#2 & 211) AND 2 FEMALES (#307 & 500)
BETWEEN 19-MAR-84 AND 12-APR-84 = 60 FEMALES

14.45 DATE: 22-MAR-88 APPROVED BY: J. GIBSON

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: J. POPP DATE: WED. 30-MAR-83

o STUDY STAFF:

INHALATION TECHNICIAN:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. POPP
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI

14.46 DATE: 8-DEC-88 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
UPDATING STUDY STAFF LIST

AMENDMENT:

- SPONSOR: _____ DATE: WED. 30-MAR-83
  J. GIBSON

- STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
  J. POPP

- STUDY STAFF:

INHALATION TECHNICIAN:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. POPP
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ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI
TECHNOLOGIST, INHALATION:	K. ROBERTS

14.47 DATE: 12-DEC-88 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
KAY ROBERTS NEEDS I MOD EDIT PRIV TO COMPLETE DATA EDITS

AMENDMENT:

o SPONSOR: _____ DATE: WED. 30-MAR-83
J. GIBSON

o STUDY DIRECTOR: _____ DATE: WED. 30-MAR-83
J. POPP

o STUDY STAFF:

INHALATION TECHNICIAN:	B. STEINHAGEN
CLINICAL CHEMIST:	D. NEPTUN
STUDY PATHOLOGIST:	K. MORGAN
HEMATOLOGIST:	C. SMITH
HEMATOLOGIST:	D. WILLIAMS
HISTOPATHOLOGY TECHNOLOGIST:	D. PATTERSON
HISTOPATHOLOGY TECHNOLOGIST:	H. RANDALL
HISTOPATHOLOGY TECHNOLOGIST:	O. LYGHT
QUALITY ASSURANCE OFFICER:	G. PARKER
ANIMAL CARE TECHNICIAN:	G. JONES
ANIMAL CARE TECHNICIAN:	E. ALLEN
ANIMAL CARE TECHNICIAN:	C. PARKINSON
INHALATION TECHNICIAN:	D. AUMAN
HISTOPATHOLOGY TECHNOLOGIST:	M. MORRIS
PATHOLOGIST:	J. POPP
ANIMAL CARE TECHNICIAN:	J. JOHNSTONE
ANIMAL CARE TECHNICIAN:	B. PARKER
ANIMAL CARE TECHNICIAN:	C. BRANNON
ANIMAL CARE TECHNICIAN:	H. HUNTER
INHALATION TECHNICIAN:	B. DAVIS
ANIMAL CARE TECHNICIAN:	S. DENNIS
ANIMAL CARE TECHNICIAN:	A. MILLER
ANIMAL CARE TECHNICIAN:	J. KNIGHT
ANIMAL CARE SUPERVISOR:	P. ROSS
ANIMAL CARE TECHNICIAN:	J. PARKER
ANIMAL CARE TECHNICIAN:	D. DODY
ANIMAL CARE TECHNICIAN:	B. SUTTON
ANIMAL CARE TECHNICIAN:	B. BROWN
INHALATION TECHNICIAN:	M. HIGUCHI
TECHNOLOGIST, INHALATION:	K. ROBERTS

14.48 DATE: 26-MAY-93 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
IN THE COURSE OF ASSEMBLING THE STUDY RECORD AND PREPARING THE ON, THESE DEFICIENCIES INDICATE THAT THE RECORDS AND CONDUCT OF THIS STUDY IS NOT IN COMPLETE COMPLIANCE WITH GOOD LABORATORY PRACTICES.

AMENDMENT:

- ADDITIONAL RECORDS TO BE MAINTAINED: APPROPRIATE RECORDS, SPECIMENS AND SAMPLES WILL BE MAINTAINED ACCORDING TO CIIT PROCEDURES. THESE WILL INCLUDE, BUT NOT BE LIMITED TO ALL RAW DATA, DOCUMENTATION, PROTOCOLS, AND FINAL REPORT.

14.49 DATE: 26-MAY-93 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
IN THE COURSE OF ASSEMBLING THE STUDY RECORD AND PREPARING THE REPORT, SEVERAL STUDY DEFICIENCIES WERE IDENTIFIED. IN MY OPINIO

AMENDMENT:

- ADDITIONAL RECORDS TO BE MAINTAINED: APPROPRIATE RECORDS SPECIMENS AND SAMPLES WILL BE MAINTAINED ACCORDING TO CIIT PROCEDURES. THESE WILL INCLUDE BUT NOT BE LIMITED TO ALL RAW DATA, DOCUMENTATION, PROTOCOLS AND FINAL REPORT.

14.50 DATE: 27-MAY-93 APPROVED BY: J. POPP

REASON FOR AMENDMENT:
IN THE COURSE OF ASSEMBLING THE STUDY RECORD AND PREPARING THE REPORT, SEVERAL STUDY DEFICIENCIES WERE IDENTIFIED. IN MY OPINION, THESE DEFICIENCIES INDICATE THAT THE RECORDS AND CONDUCT OF THIS STUDY IS NOT IN COMPLETE COMPLIANCE WITH GOOD LABORATORY PRACTICE.

AMENDMENT:

- ADDITIONAL RECORDS TO BE MAINTAINED: APPROPRIATE RECORDS, SPECIMENS AND SAMPLES WILL BE MAINTAINED ACCORDING TO CIIT PROCEDURES. THESE WILL INCLUDE, BUT NOT BE LIMITED TO ALL RAW DATA, DOCUMENTATION, PROTOCOLS, AND FINAL REPORT.

APPENDIX B

SEROLOGICAL TEST RESULTS

Serology Summary for Studies 8321, 8436, 8437

Serology Viral Agents	Test Methods†
Pneumonia Virus of Mice (PVM)	ELISA
Reovirus Type 3 (REO3)	HI
Minute Virus of Mice (MVM)	HI
Mouse Encephalomyelitis (GD VII)	ELISA & HI
K-Virus (K)- Mice only	HI
Polyoma (POLY)- Mice only	HI
Sendai (SEND)	ELISA & HI
Kilham Rat Virus (KRV)- Rats only	HI
Ectromelia (ECTRO)- Mice only	ELISA
Toolan H1 Virus (H-1)	HI
Mouse Adenovirus (MAD)	CF
Lymphocytic Choriomeningitis Virus (LCM)	CF
Mouse Hepatitis Virus (MHV)- Mice only	ELISA
Rat Coronavirus (RCV)- Rats only	ELISA
Sialodacryoadenitis (SDA)- Rats only	ELISA
Mycoplasma pulmonis	ELISA

†Test Methods

- HI- Hemagglutination Inhibition
- ELISA- Enzyme Linked Immunosorbant Assay
- CF- Compliment Fixation

Summary of Chlorine Serology Results for F344 Rats

Date	Positive for Virus(es)	Significant Titers	Number Positive/ Number Tested
03/17/83	none	NS	0/2
03/18/83	none	NS	0/2
04/01/83	none	NS	0/2
04/07/83	none	NS	0/2
05/19/83	none	NS	0/4
06/16/83	PVM*, LCM*	(PVM -20, 20 LCM)	0/4
07/14/83	LCM*	LCM-40, 40	2/4
08/11/83	none	NS	0/4
09/16/83	none	NS	0/4
10/13/83	RCV/SDA**	.57	1/4
10/25/83	RCV/SDA	≥1.77, 1.35, 1.05, 1.03, .71, .59, .78, .55, .75, 1.20, .17, .90, .66, 1.21, .86, .20, .27, .60	18/24
11/29/83	RCV/SDA	.91, 1.78	2/4
12/15/83	RCV/SDA	1.46, 1.30, 1.04, .50	4/4
01/19/84	RCV/SDA	.33, 1.50, .54	3/4
02/17/84	RCV/SDA	1.45, .43, 1.88, .70	4/4
03/16/84	RCV/SDA	.33, .26	2/4
04/19/84	none	NS	0/4
05/10/84	RCV/SDA	.28	1/8
06/14/84	RCV/SDA	.38, .24, 1.60, .85	4/8
07/12/84	RCV/SDA	.42, 1.02, .55.50, .19, .53, 1.82, .51, .35	9/25
08/16/84	none	NS	0/4
09/20/84	RCV/SDA	.25, .54	2/4
10/11/84	RCV/SDA	.52, .71	2/4
11/15/84	RCV/SDA	.31	1/4
12/13/84	none	NS	0/4
01/17/85	none	NS	0/3
02/21/85	RCV/SDA	1.15	1/4
03/21/85	RCV/SDA	.26	1/4
05/16/85	none	NS	0/4
06/20/85	none	NS	0/4
07/18/85	none	NS	0/5
08/15/85	none	NS	0/5
09/12/85	none	NS	0/5
10/10/85	none	NS	0/4
11/07/85	none	NS	0/4
12/05/85	none	NS	0/4
01/23/86	none	NS	0/4
02/21/86	none	NS	0/4
03/20/86	none	NS	0/4
04/24/86	none	NS	0/4

*significant titer 20 for PVM, 10 for LCM, unreadable at dilution indicated. Negative at two-fold higher dilution

**significant titer = ≥0.17

NS - not significant

Summary of Chlorine Serology Results for B6C3F1 Mice

Date	Positive for Virus(es)	Significant Titers	Number Positive/Number Tested
04/19/84	none	NS	0/4
05/10/84	none	NS	0/3
06/14/84	none	NS	0/3
07/12/84	none	NS	0/3
08/16/84	none	NS	0/3
09/20/84	none	NS	0/1
10/11/84	none	NS	0/2
11/15/84	none	NS	0/3
12/13/84	none	NS	0/4
01/17/85	none	NS	0/3
02/21/85	none	NS	0/1
05/16/85	none	NS	0/2
06/20/85	none	NS	0/2
07/18/85	none	NS	0/2
08/15/85	none	NS	0/3
09/12/85	none	N S	0/1
10/10/85	none	NS	0/1
11/07/85	none	NS	0/3
12/05/85	none	NS	0/3
01/23/86	none	NS	0/3
02/21/86	none	NS	0/3
03/20/86	none	NS	0/3

NS - not significant

APPENDIX C

FEED ANALYSIS

14:35:06- 51232 - 3 - 2 Y M N01 069

ANALYSIS REPORT

Lancaster Laboratories INCORPORATED

DC # 10058
L-HC 24834

LLI Sample No F 238745

Zeigler Bros. Inc.
P. O. Box 95
Gardners PA 17324

Date Reported 6/16/83
Date Submitted 5/27/83
Discard Date 9/14/83
P. O. No. none

NIH-07 553
P-5-24-83P

BASIC ASSAY #2

ANALYSIS	AS RECEIVED		LAB CODE
Protein	22.4	% by wt.	104-38
Fat	3.3	% by wt.	109-11
Fiber	3.8	% by wt.	110-14
Ash	6.78	% by wt.	112-38
Phosphorous	1.0	% by wt.	113-18
Aflatoxin	< 5.	ppb	114-38
Thiamine	1.2	mg/100g	131-12
Vitamin A	2300.	IU/100g	134-12
Carotene NC	230.	mcg/100g	135-12
Arsenic	0.77	ppm	145-40
Cadmium	< 0.1	ppm	149-40
Calcium	1.44	% by wt.	150-40
Lead	0.46	ppm	155-53
Mercury	< 0.05	ppm	159-40
Selenium	0.32	ppm	164-53
Pesticide screen I;II;III		attached	179-43
Nitrate Nitrogen	13.	ppm	190-18
Nitrite Nitrogen	2.5	ppm	191-18
Standard Plate Count	80000.	/gram	321-60
Coliforms	< 3.	/gm by MPN	325-60
E. coli	< 3.	/gm by MPN	326-60
BHA	< 2.	ppm	343-18
BHT	1.	ppm	344-18

2 COPIES TO Zeigler Brothers Inc. Attn: Tim Markey

SEE REVERSE SIDE FOR EXPLANATION OF SYMBOLS AND ABBREVIATIONS

The American Association for Laboratory Accreditation Chemical & Biological fields of testing

MAIN LABORATORY.
2425 New Holland Pike, Lancaster Pa 17601 • (717) 656-2301

FRANKLIN DIVISION

Respectfully submitted
Lancaster Laboratories, Inc.
David V. Schumacher

ANALYSIS REPORT

Lancaster Laboratories INCORPORATED

LLI Sample No F 238745

Date Reported 6/16/83
Date Submitted 5/27/83
Discard Date 9/14/83

Zeigler Bros. Inc.

NIH-07 553
P-5-24-83P

BASIC ASSAY #2

Pesticide screen I;II;III	AS RECEIVED			FAT WT. BASIS
Alpha BHC	<	0.01	ppm	
Beta BHC	<	0.01	ppm	
Gamma BHC - Lindane	<	0.01	ppm	
Delta BHC	<	0.01	ppm	
Heptachlor	<	0.01	ppm	
Aldrin	<	0.01	ppm	
Heptachlor Epoxide	<	0.01	ppm	
DDE	<	0.01	ppm	
DDD	<	0.01	ppm	
DDT	<	0.01	ppm	
HCB	<	0.01	ppm	
Mirex	<	0.01	ppm	
Methoxychlor	<	0.05	ppm	
Dieldrin	<	0.01	ppm	
Endrin	<	0.01	ppm	
Telodrin	<	0.01	ppm	
Chlordane	<	0.05	ppm	
Toxaphene	<	0.1	ppm	
Estimated PCB's	<	0.2	ppm	
Ronnel	<	0.01	ppm	
Ethion	<	0.02	ppm	
Trithion	<	0.05	ppm	
Diazinon	<	0.1	ppm	
Methyl Parathion	<	0.02	ppm	
Ethyl Parathion	<	0.02	ppm	
Malathion	<	0.05	ppm	
Endosulfan I	<	0.01	ppm	
Endosulfan II	<	0.01	ppm	
Endosulfan Sulfate	<	0.03	ppm	

SEE REVERSE SIDE FOR EXPLANATION OF SYMBOLS AND ABBREVIATIONS

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Respectfully submitted,
Lancaster Laboratories, Inc.

SUMMARY OF RESULTS

Date Received	Customer Sample #	TECO Lab.#	NDMA[1] ppb	NDEA[1] ppb	NDPA[1] ppb	NDBA[1] ppb	NPIP[1] ppb	NPYR[1] ppb	NMOR[1] ppb	% Rec.[2] NDPA	Corrected ppb[3] NDMA	NPYR
5/31/83	P-5-24-83P	5536	2.0	-[4]	-	-	-	1.2	-	92	2.2	1.3
	NIH-07 Pellets											

1. N-nitroso compounds in parts-per-billion (ng/g), uncorrected for recovery.
2. N-nitrosodipropylamine added as an internal standard.
3. N-nitroso compounds in parts-per-billion (ng/g), corrected for recovery
4. - : Not detected
   Limit of detection (LLD): 0.4 ppb for NDBA, 0.3 ppb for the rest.
5. Trace is less than 3 x LLD

Method of Analysis: GC-TEA

Date of Analysis: 6/6/83

Analyst: Linda Cantor

Thermo Electron CORPORATION

Analytical Services Laboratory

APPENDIX D

CHLORINE PURITY ANALYSIS

Table D1. Summation of Purity Analysis Measurements for Chlorine.

Study No.'s :8321, 8436, 8437

Date	Component	Concentration	Phase Tested	Test Method
April 18, 1983	Chlorine	99.95% by volume	Gas	ASTM E-412 70
	Carbon Dioxide	0.02% by volume	Gas	Gas Chromatograph
	Oxygen	<0.01% by volume	Gas	Gas Chromatograph
	Nitrogen	<0.01% by volume	Gas	Gas Chromatograph
	Carbon Tetrachloride	<0.003% by weight	Liquid	ASTM E-806
	Chloroform	<0.003% by weight	Liquid	ASTM E-806
December 15, 1983	Chlorine	99.95% by volume	Gas	ASTM E-412 70
	Carbon Dioxide	0.02% by volume	Gas	Gas Chromatograph
	Oxygen	<0.01% by volume	Gas	Gas Chromatograph
	Nitrogen	<0.01% by volume	Gas	Gas Chromatograph
	Carbon Tetrachloride	<0.003% by weight	Liquid	ASTM E-806
	Chloroform	<0.003% by weight	Liquid	ASTM E-806
October 12, 1984	Chlorine	99.95% by volume	Gas	ASTM E-412 70
	Carbon Dioxide	0.02% by volume	Gas	Gas Chromatograph
	Oxygen	<0.01% by volume	Gas	Gas Chromatograph
	Nitrogen	<0.01% by volume	Gas	Gas Chromatograph
	Carbon Tetrachloride	<0.003% by weight	Liquid	ASTM E-806
	Chloroform	<0.003% by weight	Liquid	ASTM E-806

Assay of Chlorine in Cylinder #BF14414

Diamond Shamrock

January 27, 1981

Dr. Craig Barrow
C.I.I.T.
P. O. Box 12137
Research Triangle Park, NC 27709

Dear Dr. Barrow:

SUBJECT: ASSAY OF CHLORINE IN CYLINDER #BF14414

The subject cylinder of liquid chlorine loaded by Jones Chemical has been analyzed using accepted analytical methods. We hereby certify the following as the best expression of results of replicate tests performed in our Deer Park laboratory:

COMPONENT	CONCENTRATION	PHASE TESTED	TEST METHOD
Chlorine	99.7 % by volume	Gas	ASTM E-412 70
Carbon Dioxide	0.24% by volume	Gas	Gas Chromatography*
Oxygen	0.04% by volume	Gas	Gas Chromatography*
Nitrogen	0.02% by volume	Gas	Gas Chromatography*
Carbon Tetrachloride	less than 0.003% by weight	Liquid	ASTM E-806+
Chloroform	less than 0.003% by weight	Liquid	ASTM E-806+

*Carle Model AGC-111H, using calibration mixture supplied by Matheson (Oxygen 0.06%, Nitrogen 0.06%, Carbon Dioxide 0.64%)
+Hewlett-Packard 5840A, using calibration mixture described in the ASTM method

In order to provide subsequent analyses of this material, we have retained a small sample in our laboratory. The analysis of the small cylinder (tabulated below) differs from the analysis of the 150# cylinder (above) for the following reasons:

1. The 150# cylinder contained air when loaded, most of which remains in the gas phase of the cylinder. We purged 10 to 15# of chlorine vapor from the cylinder attempting to remove this air. The smaller cylinder was evacuated before loading.

2. The chlorine loaded into the 150# cylinder contained the normal amount of carbon dioxide, which is relatively soluble in cold chlorine. As the liquid chlorine warmed after loading, the carbon dioxide moved into the vapor phase of the cylinder and was reduced by our purging procedure.

RECEIVED
P. R. C.
FEB 4 1981
CIIT

Diamond Shamrock Corporation P.O. Box 500, Deer Park, Texas 77536 Phone: 713 476-2000

3. The small, evacuated cylinder was loaded from the liquid phase of the 150# cylinder; therefore, the small cylinder should not be expected to contain either oxygen, nitrogen, or carbon dioxide in appreciable amounts.

We propose to reanalyze this material on a per request basis.

Our analysis of the small cylinder is as follows:

COMPONENT	CONCENTRATION	PHASE TESTED	TEST METHOD
Chlorine	greater than 99.95% by volume	Gas	ASTM E-412 70
Carbon Dioxide	less than 0.004% by volume	Gas	Gas Chromatography*
Nitrogen	less than 0.001% by volume	Gas	Gas Chromatography*
Oxygen	less than 0.001% by volume	Gas	Gas Chromatography*
Carbon Tetrachloride	less than 0.003% by weight	Liquid	ASTM E-806+
Chloroform	less than 0.003% by weight	Liquid	ASTM E-806+

Please feel free to call me (713-476-2416) or my associate, Ted Lorfing (713-476-2196) if you need further information or need clarification of some point in the report.

Sincerely,

Clifford L Payne

Clifford L. Payne
Laboratory Supervisor

cs

cc: Bert Rabbe/Don Wilson
Jerel Stafford
Ed Freeh

APPENDIX E

CONCENTRATION, TEMPERATURE AND RELATIVE HUMIDITY DATA

Table E1. Summation of Data for Chamber Parameters

Study No. 8321

Parameter *	2.50 PPM	1.00 PPM	0.40 PPM	0.00 PPM
ACC (PPM)				
MEAN	2.48	1.01	0.40	0.00
SEM	0.09	0.04	0.01	0.00
MIN	2.12	0.84	0.37	0.00
MAX	2.86	1.15	0.44	0.00
n**	499	499	499	499
CFR (ml/min)				
MEAN	537	218	101	-
SEM	94	45	23	-
MIN	263	92	54	-
MAX	801	377	182	-
n**	499	499	499	499
AF (L/min)				
MEAN	2184	2177	2190	2209
SEM	68	56	58	33
MIN	2046	2052	2039	2110
MAX	2346	2346	2316	2296
n**	499	499	499	499
NCC (PPM)				
MEAN	6.0	2.4	1.1	-
SEM	1.0	0.5	0.2	-
MIN	3.0	1.0	0.6	-
MAX	9.2	3.9	1.9	-
n**	499	499	499	499
RAN				
MEAN	43	44	39	-
SEM	9	9	9	-
MIN	24	24	20	-
MAX	84	94	69	-
n**	499	499	499	499
DBT °F				
MEAN	71.8	71.7	71.7	72.3
SEM	1.3	1.2	1.4	1.0
MIN	68.2	68.4	68.7	69.8
MAX	76.2	75.0	75.8	75.0
n**	499	499	499	499
WBT °F				
MEAN	60.0	59.5	59.4	60.1
SEM	1.8	1.6	1.4	1.2
MIN	53.8	54.4	55.1	57.3
MAX	70.5	65.9	69.9	64.9
n**	499	499	499	499
RH %				
MEAN	49.4	48.0	47.5	48.1
SEM	7.3	5.7	4.9	3.6
MIN	29.7	32.1	35.1	39.2
MAX	91.6	69.7	96.0	65.8
n**	499	499	499	499

*The following are definitions of the acronyms used to describe the Parameters

DBT = Dry Bulb Temperature
WBT = Wet Bulb Temperature
RH = Relative Humidity
AF = Air Flow
**= The values are based on daily means from at least 4 readings for each exposure parameter per chamber per day

CFR = Chlorine Flow Rate through Rotameter
ACC = Analytical Chamber Concentration
NCC = Nominal Chamber Concentration
RAN = Analytical Conc./ Nominal Conc. x 100

Table E1 (Continuation) Summation of Data for Chamber Parameters

Study No. 8436

Parameter *	2.50PPM	1.00 PPM	0.40 PPM	0.00 PPM
ACC (PPM)				
MEAN	2.48	1.00	0.40	0.00
SEM	0.11	0.06	0.01	0.00
MIN	1.86	0.78	0.33	0.00
MAX	2.84	1.16	0.50	0.00
n**	303	303	303	303
CFR (ml/min)				
MEAN	430	210	83	-
SEM	121	48	31	-
MIN	251	132	41	-
MAX	762	377	182	-
n**	303	303	303	303
AF (L/min)				
MEAN	2143	2190	2146	2160
SEM	74	66	50	83
MIN	1654	2068	2046	1965
MAX	2346	2554	2288	2282
n**	303	303	303	303
NCC (PPM)				
MEAN	4.9	2.3	0.9	-
SEM	1.3	0.5	0.3	-
MIN	2.7	1.4	0.4	-
MAX	9.0	3.9	1.9	-
n**	303	303	303	303
RAN				
MEAN	54	46	51	-
SEM	13	10	17	-
MIN	26	26	20	-
MAX	88	76	96	-
n**	303	303	303	303
DBT °F				
MEAN	72.4	72.0	72.3	72.1
SEM	1.6	1.4	1.4	1.1
MIN	68.2	68.7	68.9	68.6
MAX	76.6	76.0	76.2	75.0
n**	303	303	303	303
WBT °F				
MEAN	59.6	59.3	59.4	59.8
SEM	1.7	1.8	1.1	1.3
MIN	54.5	54.4	55.5	57.3
MAX	68.7	69.7	62.6	69.3
n**	303	303	303	303
RH %				
MEAN	46.2	46.3	45.7	47.8
SEM	8.0	7.3	4.5	4.8
MIN	26.9	31.4	35.3	39.5
MAX	82.2	89.9	56.0	85.6
n**	303	303	303	303

*The following are definitions of the acronyms used to describe the Parameters

DBT = Dry Bulb Temperature
WBT = Wet Bulb Temperature
RH = Relative Humidity
AF = Air Flow
**= The values are based on daily means from at least 4 readings for each exposure parameter per chamber per day

CFR = Chlorine Flow Rate through Rotameter
ACC = Analytical Chamber Concentration
NCC = Nominal Chamber Concentration
RAN = Analytical Conc./ Nominal Conc. x 100

Table E1 (Continuation). Summation of Data for Chamber Parameters

Study No. 8437

Parameter *	2.50PPM	1.00 PPM	0.40 PPM	0.00 PPM
ACC (PPM)				
MEAN	2.50	1.00	0.40	0.00
SEM	0.11	0.06	0.01	0.00
MIN	1.86	0.78	0.33	0.00
MAX	2.86	1.19	0.50	0.00
n**	501	501	501	501
CFR (ml/min)				
MEAN	424	207	83	-
SEM	119	48	32	-
MIN	251	92	40	-
MAX	801	377	182	-
n**	501	501	501	501
AF (L/min)				
MEAN	2144	2188	2146	2161
SEM	74	66	50	81
MIN	1654	2052	2039	1955
MAX	2346	2554	2288	2282
n**	501	501	501	501
NCC (PPM)				
MEAN	4.8	2.3	0.9	-
SEM	1.3	0.5	0.4	-
MIN	2.7	1.0	0.4	-
MAX	9.2	3.9	1.9	-
n**	501	501	501	501
RAN				
MEAN	56	47	51	-
SEM	13	11	17	-
MIN	24	24	20	-
MAX	99	94	93	-
n**	501	501	501	501
DBT °F				
MEAN	72.4	72.0	72.2	72.1
SEM	1.6	1.4	1.4	1.1
MIN	68.1	68.7	69	68.6
MAX	76.6	76.0	76.2	75.0
n**	501	501	501	501
WBT °F				
MEAN	59.5	59.2	59.3	59.8
SEM	1.9	1.8	1.2	1.5
MIN	53.8	54.4	55.1	56.9
MAX	70.5	69.7	69.9	70.6
n**	501	501	501	501
RH %				
MEAN	46.0	46.0	45.8	48.0
SEM	8.1	7.1	5.1	5.4
MIN	25.4	31.4	35.3	39.2
MAX	91.6	89.9	96.0	85.6
n**	501	501	501	501

*The following are definitions of the acronyms used to describe the Parameters

DBT = Dry Bulb Temperature
WBT = Wet Bulb Temperature
RH = Relative Humidity
AF = Air Flow
**= The values are based on daily means from at least 4 readings for each exposure parameter per chamber per day

CFR = Chlorine Flow Rate through Rotameter
ACC = Analytical Chamber Concentration
NCC = Nominal Chamber Concentration
RAN = Analytical Conc./ Nominal Conc. x 100

TABLE E2

Concentration Distribution within 8 M^3 Exposure Chambers 308, 309, 310, 311

Sample Location Number	Chamber 308 Concentration (PPM)	Chamber 309 Concentration (PPM)	Chamber 310 Concentration (PPM)	Chamber 311 Concentration (PPM)
1 (Center)	2.30	2.70	2.65	2.55
2*	3.00	2.75	2.67	2.75
3	2.65	2.57	1.95	2.50
4	2.95	2.40	2.65	2.67
5	1.95	2.50	1.95	2.32
6	2.80	2.50	2.80	2.65
7	2.20	2.05	2.35	2.45
8	2.75	2.65	2.57	2.45
9	2.05	2.38	2.55	2.55
1 (Center)	2.50	2.77	2.70	2.50
Total Port Variability (%)	15.48	8.61	12.80	5.20
Within Port Variability (%)	4.17	1.28	0.93	1.00
Between Port Variability (%)	14.91	8.52	12.76	5.10

*These #s correspond to the following different locations in the chamber:

1 = Center
2 = Top left front
3 = Top right front
4 = Bottom left front
5 = Bottom right front
6 = Top left back
7 = Top right back
8 = Bottom left back
9 = Bottom right back

Table E3 Total and Free Chlorine Concentrations.

Target Chlorine Concentration (ppm)		Free Chlorine[1] Concentration (ppm)	Total Chlorine[2] Concentration (ppm)
0.0	mean	-------	0.0
	STDEV	-------	± 0.0
	n		149
0.40	mean	0.20	0.40
	STDEV	± 0.14	± 0.03
	n	148	148
1.00	mean	0.79	1.01
	STDEV	± 0.18	± 0.09
	n	149	149
2.50	mean	2.19	2.53
	STDEV	± 0.32	± 0.16
	n	149	149

[1]Free Chlorine concentration is the mean of all results from free chlorine assays for each particular chamber. A standard deviation is calculated.

[2]The most representative chamber total chlorine concentration present during the free chlorine sampling period was taken to be the mean total chlorine concentration as measured by the Interscan in the chamber for the day that the free chlorine sample was collected. These representative total chlorine values for the different days were averaged (and a standard deviation calculated).

Study No.'s: 8321, 8436, 8437

Table E4 Ammonia Concentrations. [1]

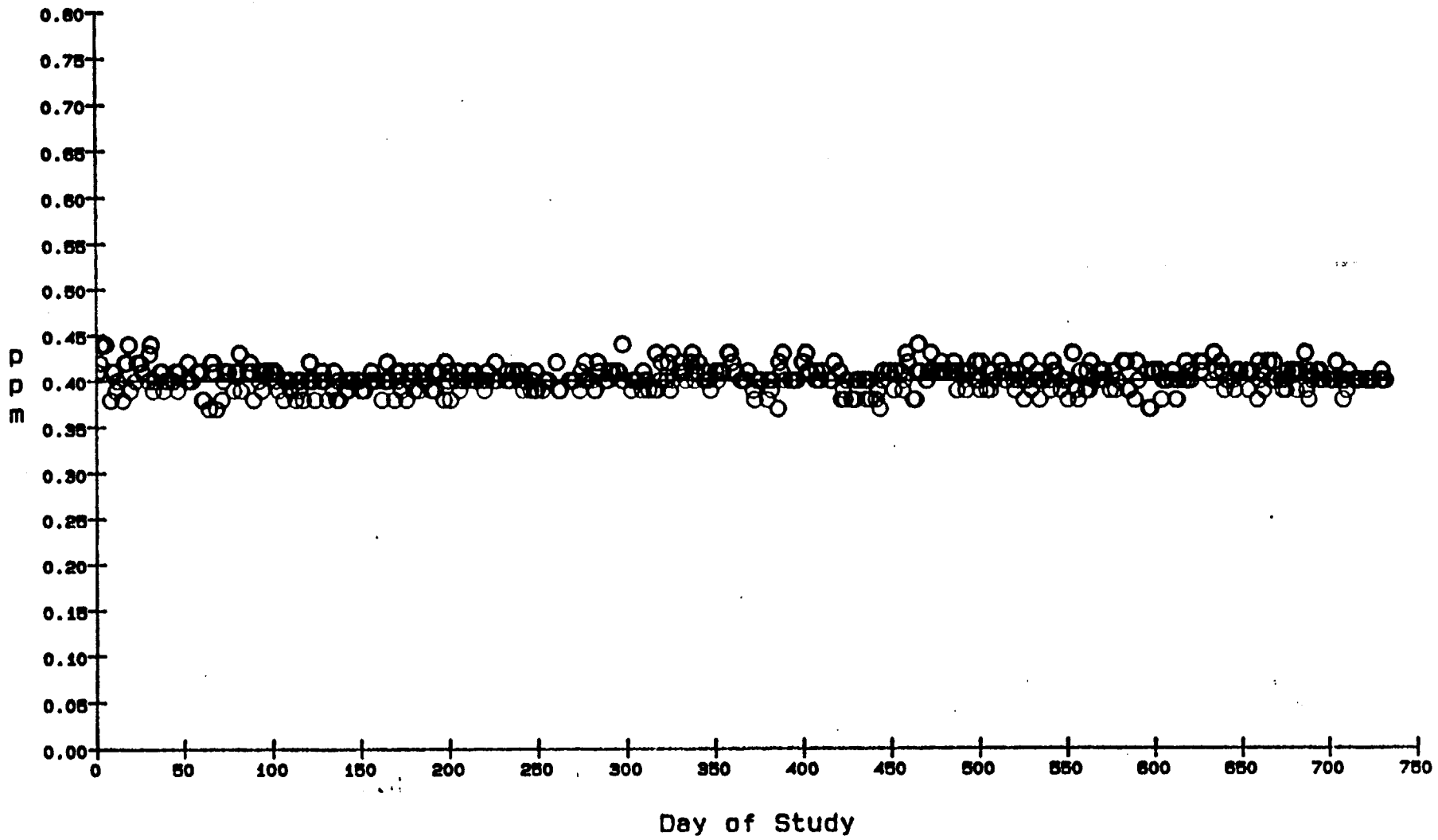
Event	Date	Sample Start	Time Stop	Duration - Time from Closing of Doors (Hr:Min)	Concentration of Ammonia 20 to 24 hrs following cleaning (ppm)	Duration - Time from Closing of Doors (Hr:Min)	Concentration of Ammonia 3 to 5 hrs following cleaning (ppm)
Chamber Closed	3/2/93	11:05 AM					
Sample S1	3/3/93	9:55 AM	10:10 AM	23:05	0.91		
Chamber Opened	3/3/93	10:15 AM					
Chamber Closed	3/3/93	2:30 PM					
Sample S7	3/4/93	10:18 AM	10:31 AM	20:01	0.61		
Chamber Opened	3/4/93	10:31 AM					
Chamber Closed	3/4/93	10:45 AM					
Sample S9	3/4/93	2:45 PM	3:15 PM			4:30	0.17
Chamber opened	3/4/93	10:31 AM					
Chamber Closed	3/4/93	10:45 AM					
Sample S5	3/5/93	10:09 AM	10:24 AM	23:39	0.74		
Chamber Opened	3/5/93	10:25 AM					
Chamber Closed	3/5/93	10:40 AM					
Sample S11	3/5/93	1:30 PM	2:00 PM			3:20	0.13

Average concentration from 20 to 24 hours =	0.75
St Dev=	0.15
Count =	3

Average concentration from 3 to 5 hours =	0.15
St Dev=	0.03
Count =	2

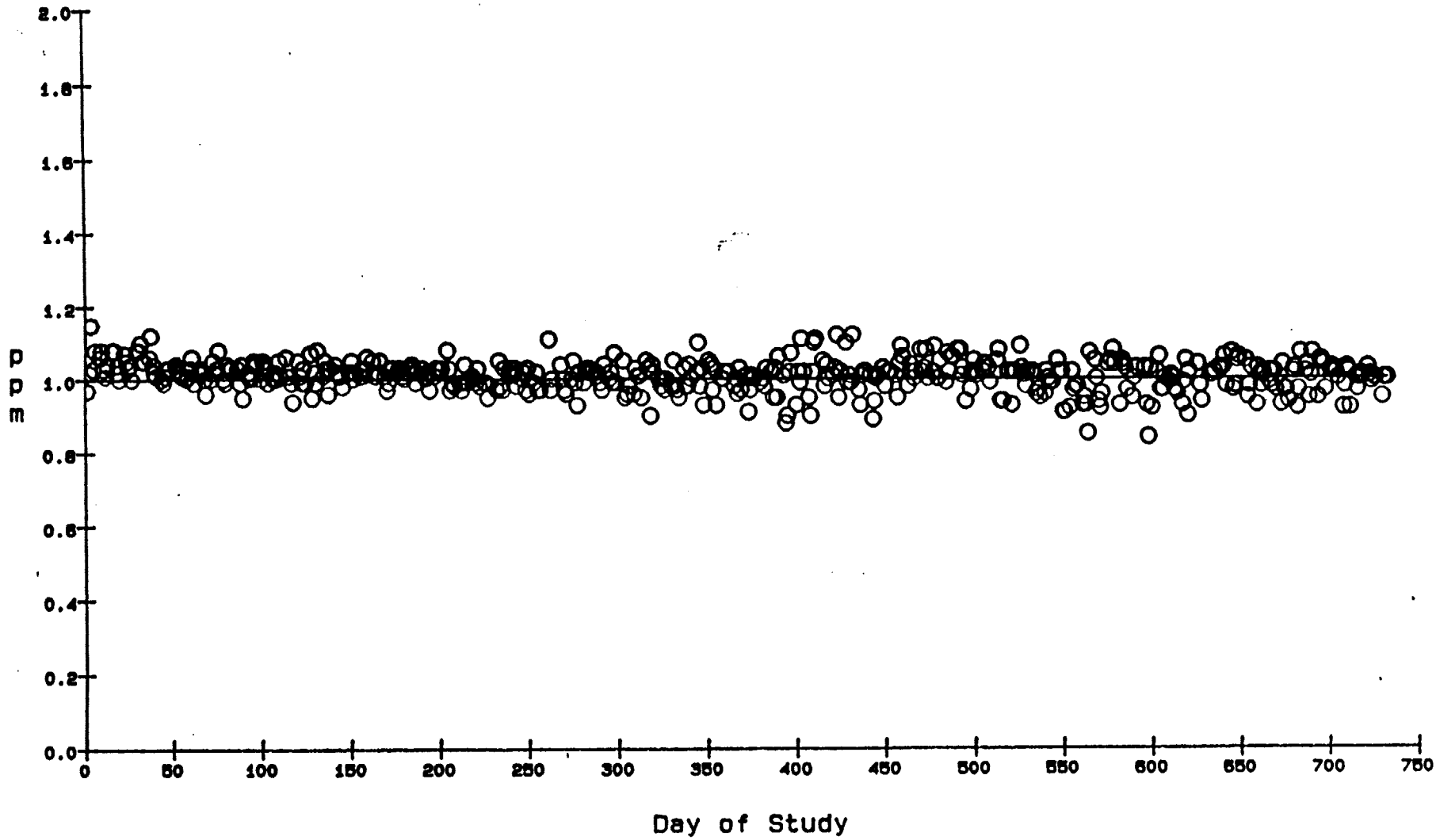
[1] Ammonia levels measured at the center of the chamber with two animal racks with urine catch pans in place. Chambers loaded with 111 mice and 63 rats.

STUDY NO. 8321
Total Chlorine Concentration
Chamber 309



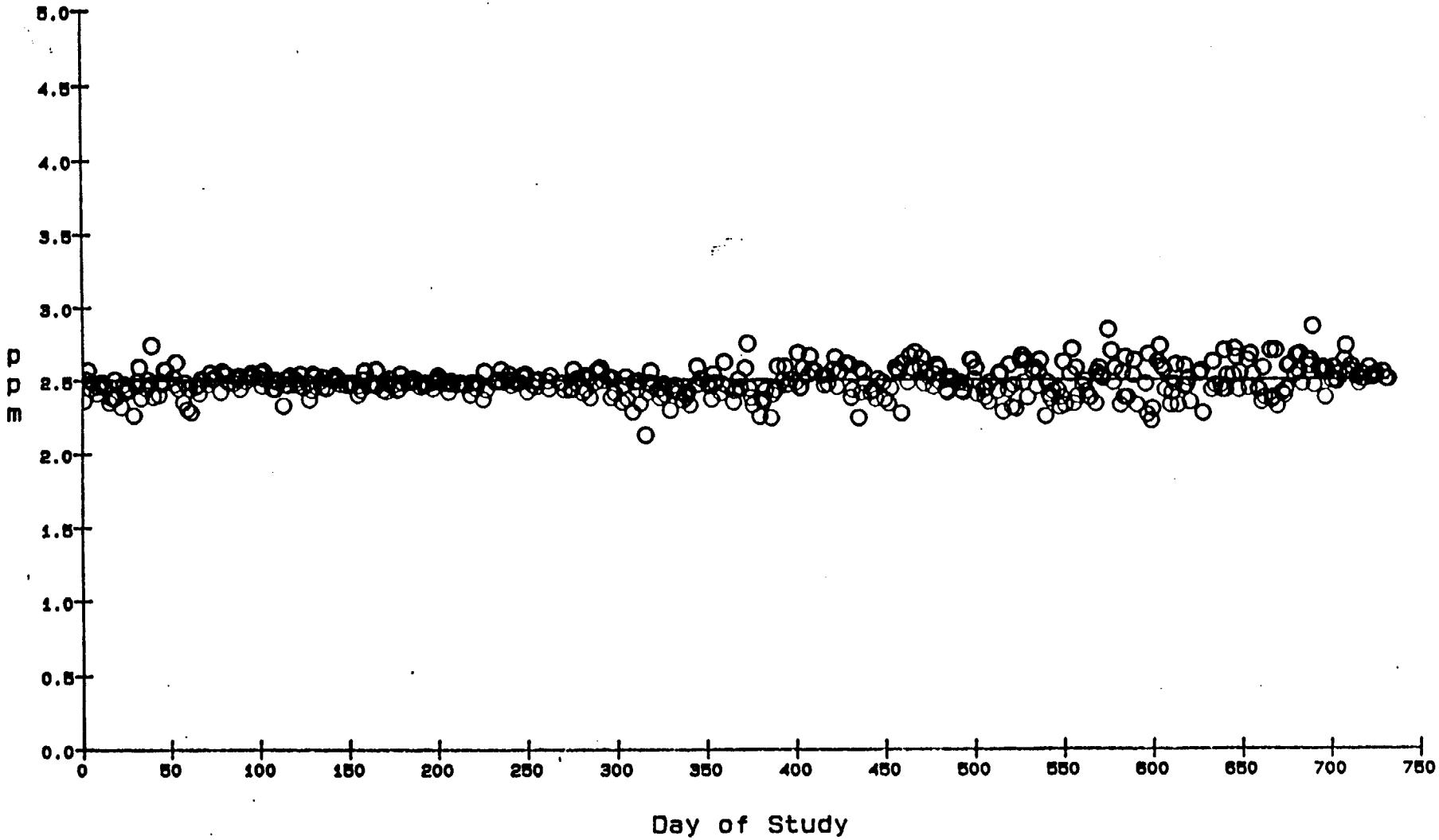
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8321
Total Chlorine Concentration
Chamber 310



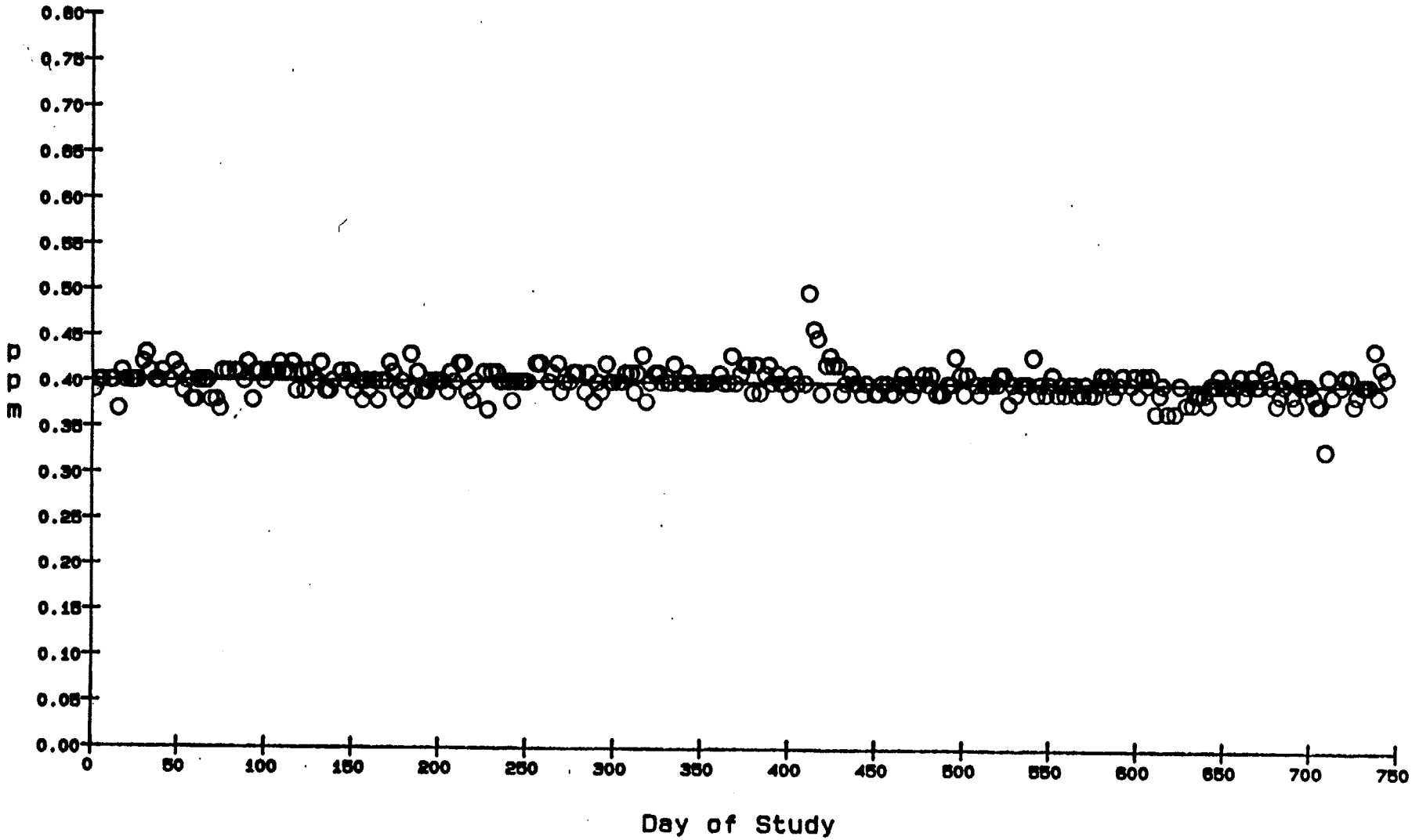
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8321
Total Chlorine Concentration
Chamber 311



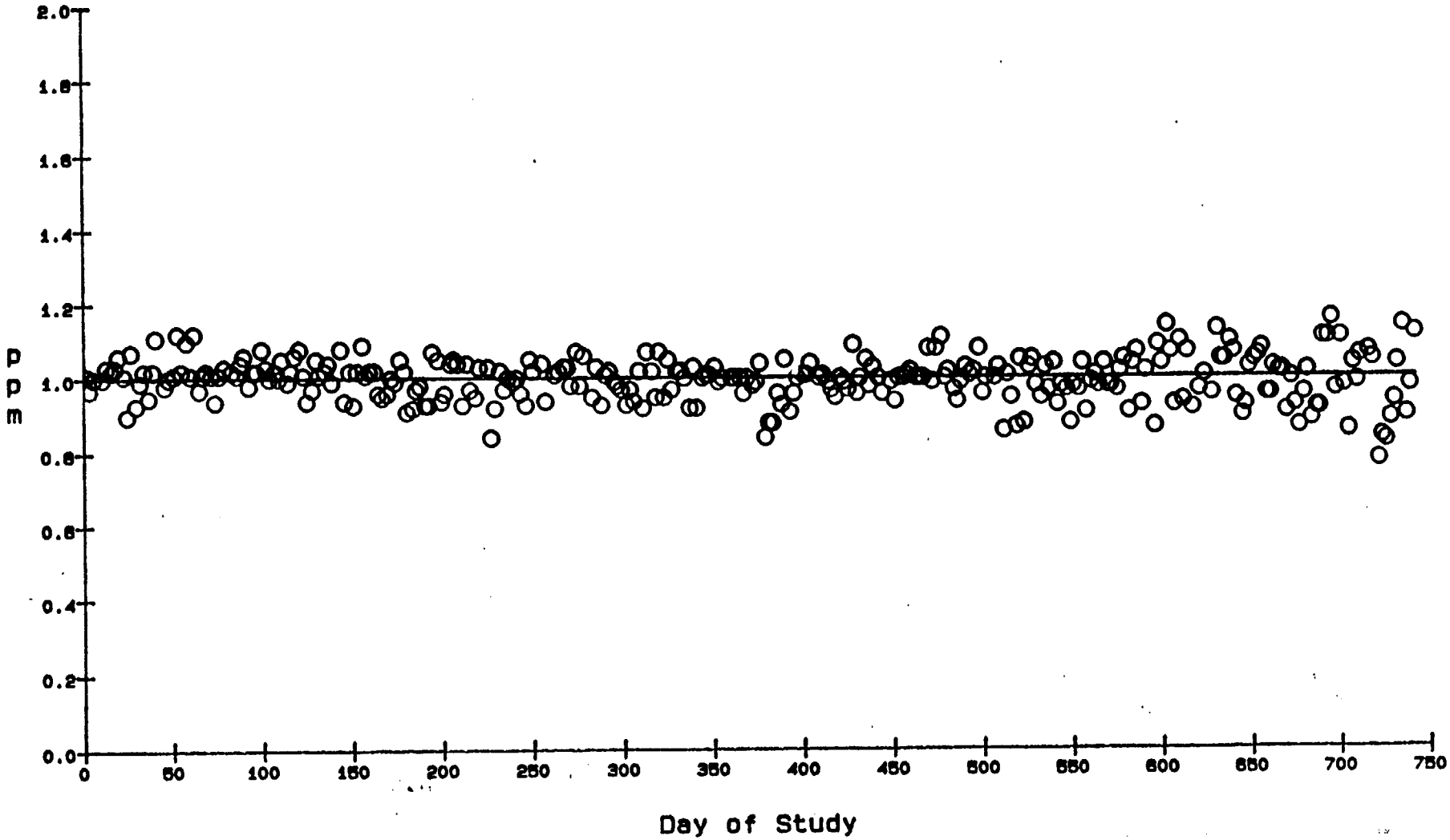
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8436
Total Chlorine Concentration
Chamber 309



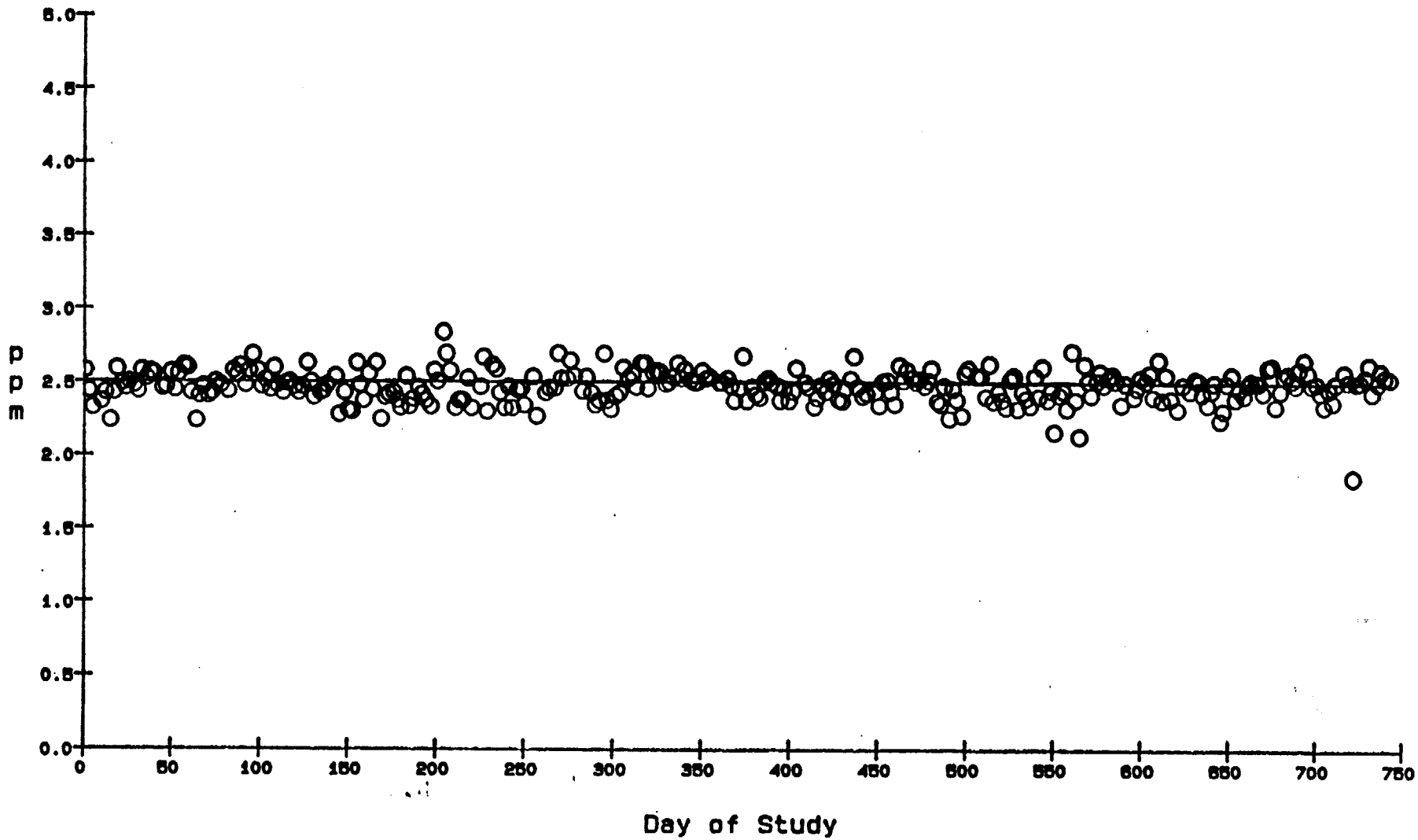
O MEAN
—— TARGET CONCENTRATION

STUDY NO. 8436
Total Chlorine Concentration
Chamber 310



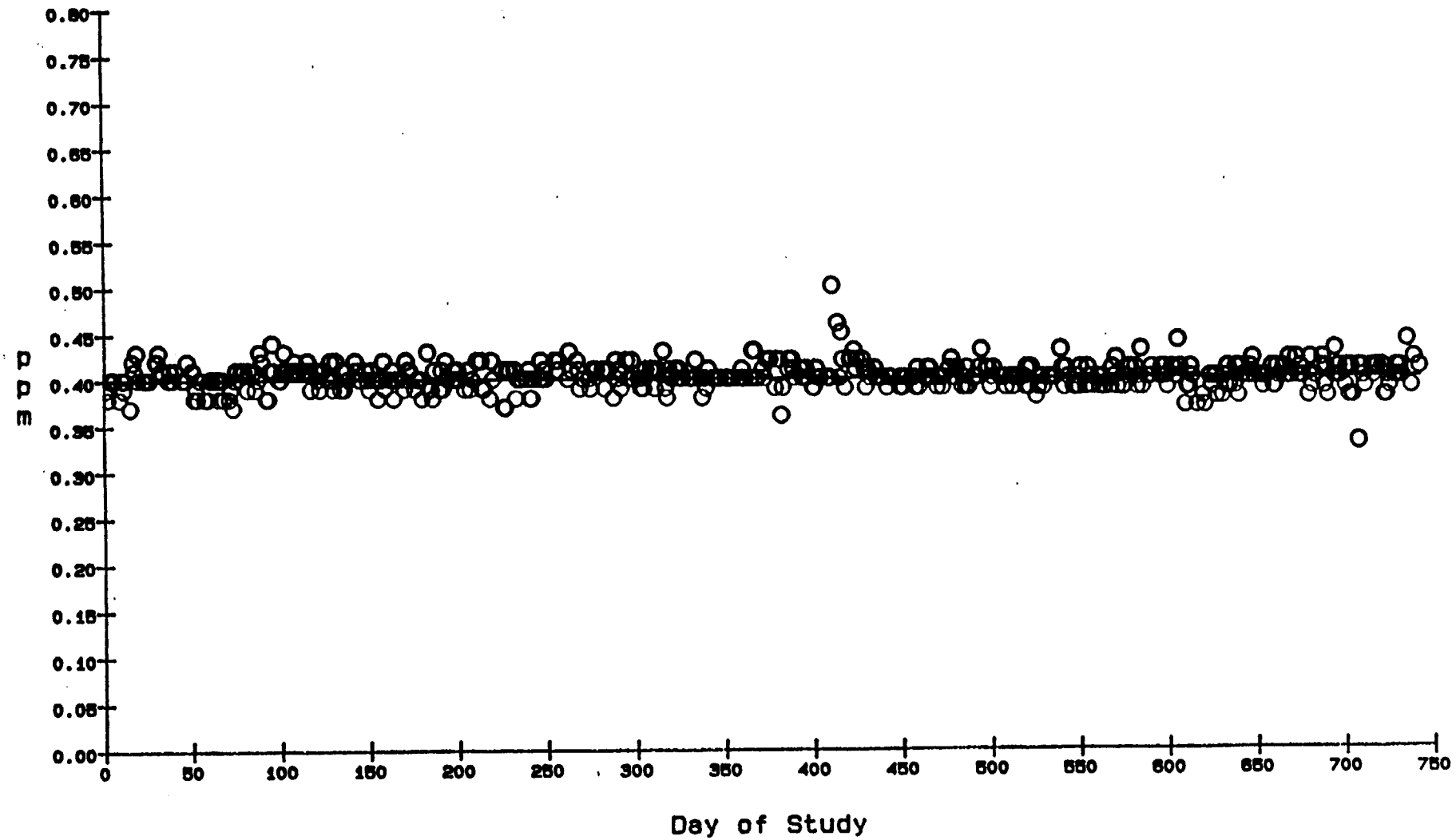
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8436
Total Chlorine Concentration
Chamber 311



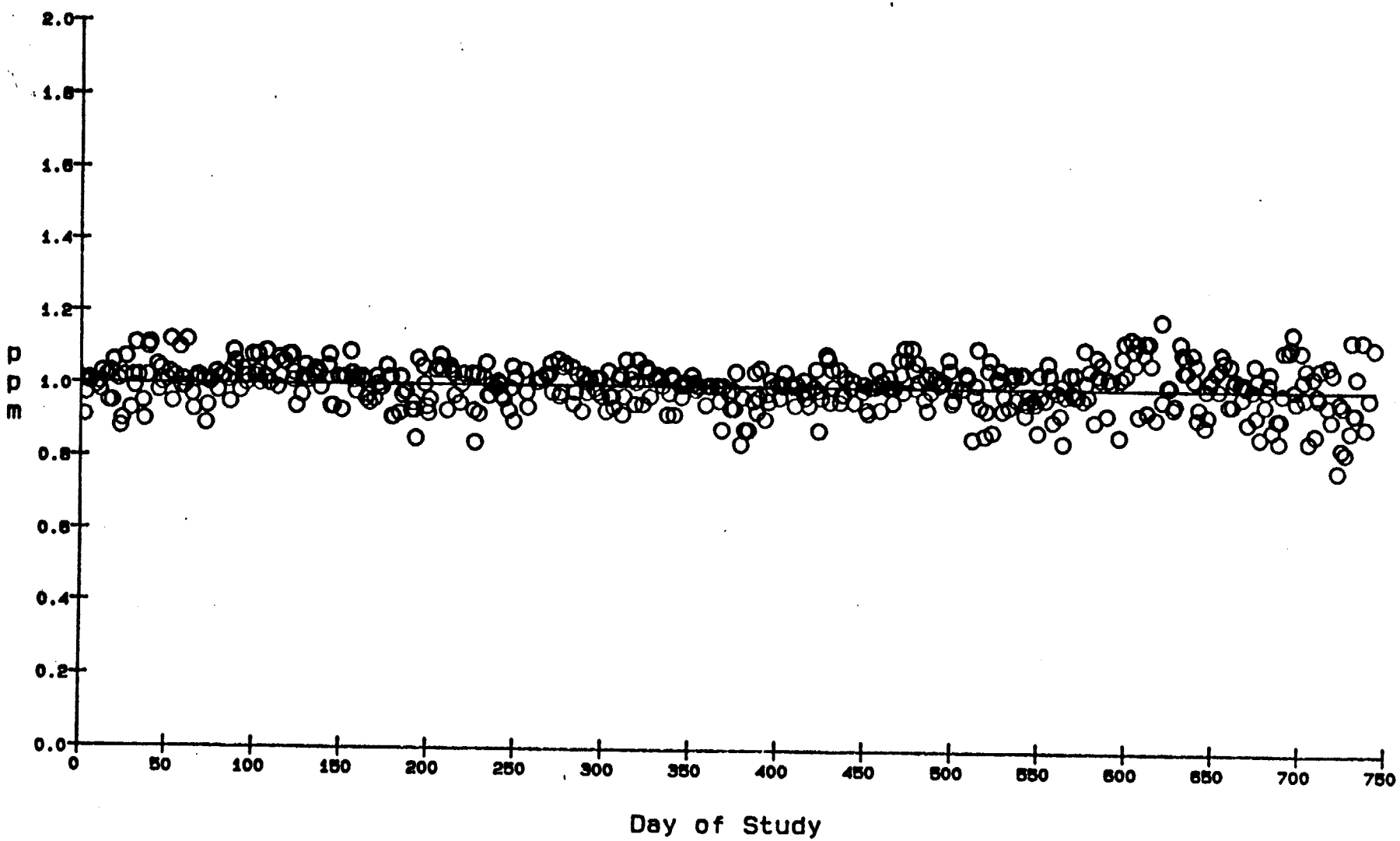
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8437
Total Chlorine Concentration
Chamber 309



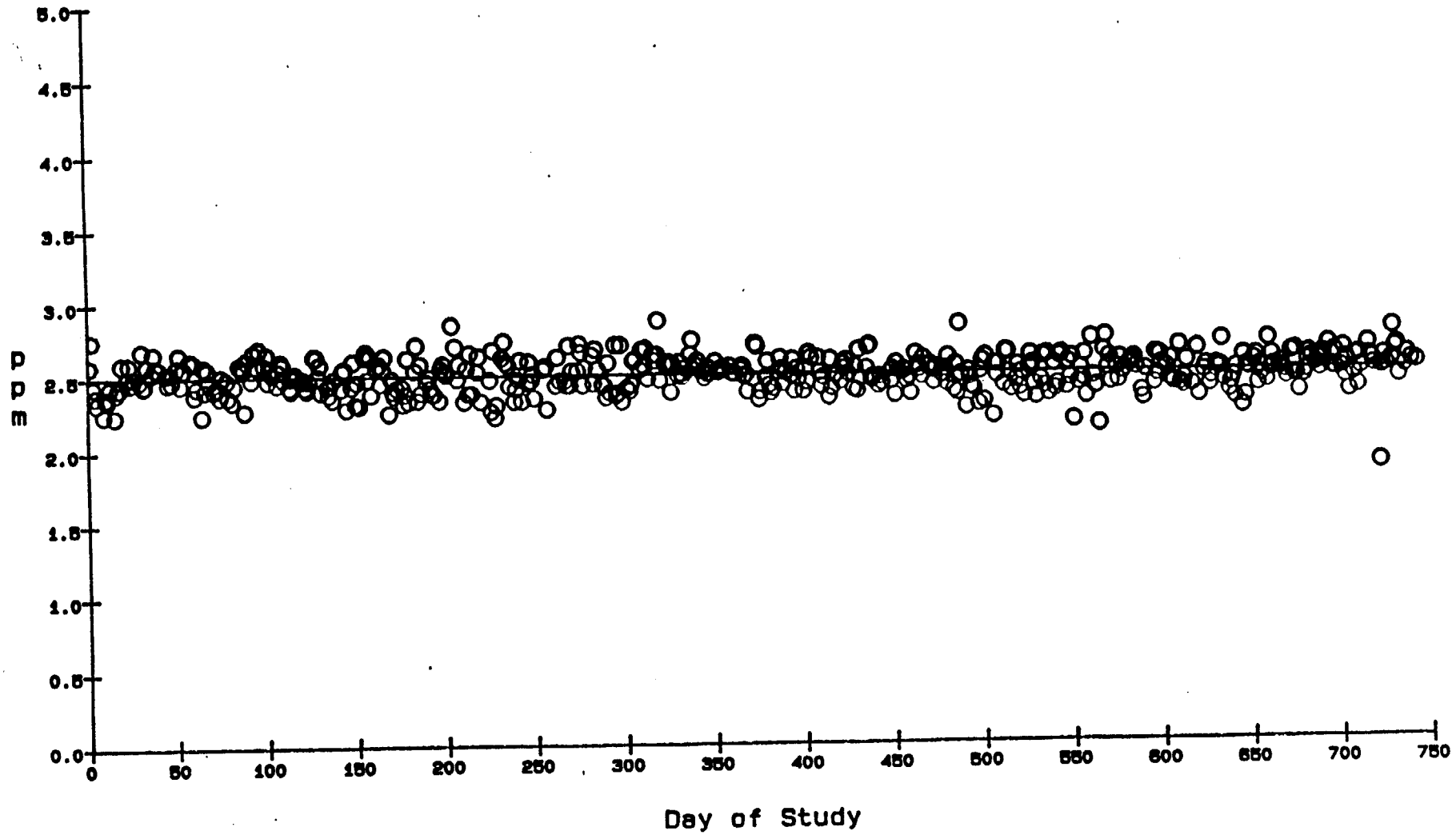
O MEAN
——— TARGET CONCENTRATION

STUDY NO. 8437
Total Chlorine Concentration
Chamber 310



O MEAN
—— TARGET CONCENTRATION

STUDY NO. 8437
Total Chlorine Concentration
Chamber 311



O MEAN
——— TARGET CONCENTRATION

APPENDIX F

CHLORINE GAS CHROMATOGRAPHY CALIBRATION CURVES

Table F1 Standard Hewlett Packard 5840A Gas Chromatograph Operating Conditions[1] for 4-Cl-2,6-DMP and 4-Br-2,6-DMP.

CIIT Study #: 8321,8436,8437

Instrument: Hewlett Packard 5840A Detector: FID

Location: Room 230

COLUMN	Type: capillary	Length: 25 meter	Phase/Packing: N/A
	Film/Material: fused silicia	Diameter: not available	Head Pressure: 15 psi
	Supplier: Supelco	Preconditioned: not available	

TEMPERATURE (°C)	Injector: 275	Sample Loop: N/A	Detector: 300
	Oven (initial): 40	Oven (final): 240	Ramp Rate: 10/min.

FLOWS@ 40°C	Carrier: 30 ml/min	
	H_2: 30 ml/min	
	Air: 240 ml/min	

PARAMETERS	Attenuation: 2↑4	Peak Width: not available	Threshold: not available
	Run Time: not available	Chart Speed: 0.75	% Offset: not available

INJECTIONS:	Manual: yes	Amount: 2 µl	
	Valve: N/A	Loop Size: N/A	

PRESSURE GUAGE:	CARRIER: (psi)	HYDROGEN: (psi)	AIR: (psi)
	not available	not available	not available

[1]Refer to SOP TIN-018-2 (10 Apr 84) for operating conditions.

N/A = Not Applicable

Table F2 Standard Shimadzu 8AGC Gas Chromatograph Operating Conditions[1] for 4-Cl-2,6-DMP and 4-Br-2,6-DMP.

CIIT Study #:8321,8436,8437

Instrument:Shimadzu 8AGC Detector: FID

Location: Room 200W

COLUMN	Type: packed	Length: 6 feet	Phase/Packing: 20% SP2100
	Film/Material: 80/100 Supelcoport	Diameter: 1/8 "	Head Pressure: not available
	Supplier: Supelco	Preconditioned: 230 ° overnight	

TEMPERATURE (°C)	Injector: 250	Sample Loop: N/A	Detector: 250
	Oven (initial): 40	Oven (final): 230	Ramp Rate: 10/min.

FLOWS@ 40°C	Carrier: 1 = 1 2 = 1.5	Primary = 6 Gauge Setpoints
	H_2: 1 = 0.72 2 = 0.72	
	Air: 0.33	

PARAMETERS	Attenuation: * 2 ↑ 1	Peak Width: not available	Threshold: not available
	Run Time: 30 min.	Chart Speed: 3	% Offset: not available

*Integrator Attentuation = 10

INJECTIONS:	Manual: yes Amount:1 µl	
	Valve:N/A Loop Size:N/A	

PRESSURE GUAGE:	CARRIER: (psi)	HYDROGEN: (psi)	AIR: (psi)
	100	22	95-100

[1]Refer to SOP TIN-018-2 (06 Mar 85) for operating conditions.

N/A = Not Applicable

Table F3 Calibration of the methylene-orange chlorine analysis method.

Date	Equation of Line	R^2
09-Feb-83	Y = -0.0057x + 0.599	----
15-Apr-83	Y = -0.0060x + 0.599	0.9992
11-Jan-84	Y = -0.0058x + 0.609	0.998
20-Mar-85	Y = -0.0060x + 0.600	0.9988

where:

x = μg chlorine

Y = Optical Density (O.D.)

Table F4. Gas Chromatograph (GC) Calibration for µMoles of 4-Cl-2,6-DMP.

Date	µg 4-Cl-2,6DMP	µMoles/102 mL 4-Cl-2,6 DMP	% Cl:Br	Slope	Y Int	r2
2/4/83	12.31	0.0743	4.40	55.81	-0.081	0.9998
	49.24	0.2973	17.57			
0.2462 µg/µL	86.17	0.5203	30.76			
4-Cl-2,6,DMP	123.1	0.7433	42.81			
	160.03	0.9663	57.59			
	2.46	0.0149	0.82			
	6.15	0.0371	2.09			
4/26/83		0.0153	0.87	53.83	0.232	0.9998
		0.1530	8.29			
.2400 µg/µL		0.3060	16.70			
4-Cl-2,6,DMP		0.5360	29.88			
		0.7660	41.34			
		0.9960	53.54			
8/8/83		0.0153	1.62	63.90	2.810	0.9970
		0.1530	12.85			
.2400 µg/µL		0.3060	24.39			
4-Cl-2,6,DMP		0.5360	37.38			
		0.7660	53.26			
		0.9960	64.49			
8/31/83		0.0153	0.93	52.66	0.516	0.9998
		0.1530	8.92			
.2400 µg/µL		0.3060	16.67			
4-Cl-2,6,DMP		0.5360	29.20			
		0.7660	40.25			
		0.9960	53.13			
3/1/84		0.0153	0.85	52.12	0.079	0.9999
		0.1530	8.14			
.2400 µg/µL		0.3060	16.04			
4-Cl-2,6,DMP		0.5360	27.85			
		0.7660	40.10			
11/30/84		0.0306	1.42	55.74	0.949	0.9970
		0.1530	9.49			
.2400 µg/µL		0.3060	19.42			
4-Cl-2,6,DMP		0.5360	31.90			
		0.7660	42.37			
2/11/85		0.3060	16.46	54.42	-1.200	0.9930
		0.1530	6.31			
.2400 µg/µL		0.0306	1.45		Shimadzu GC	
4-Cl-2,6,DMP		0.7660	42.31			
		0.5360	24.95			
10/2/85		0.0296	0.45	27.85	-0.403	1.0000
		0.1478	3.74			
0.2315 µg/µL		0.2956	7.76		Shimadzu GC	
4-Cl-2,6,DMP		0.5174	13.98			
		0.7391	20.22			

Figure F1. Calibration of Hewlett Packard 5840 GC for 4-Chloro-2,6-Dimethylphenol

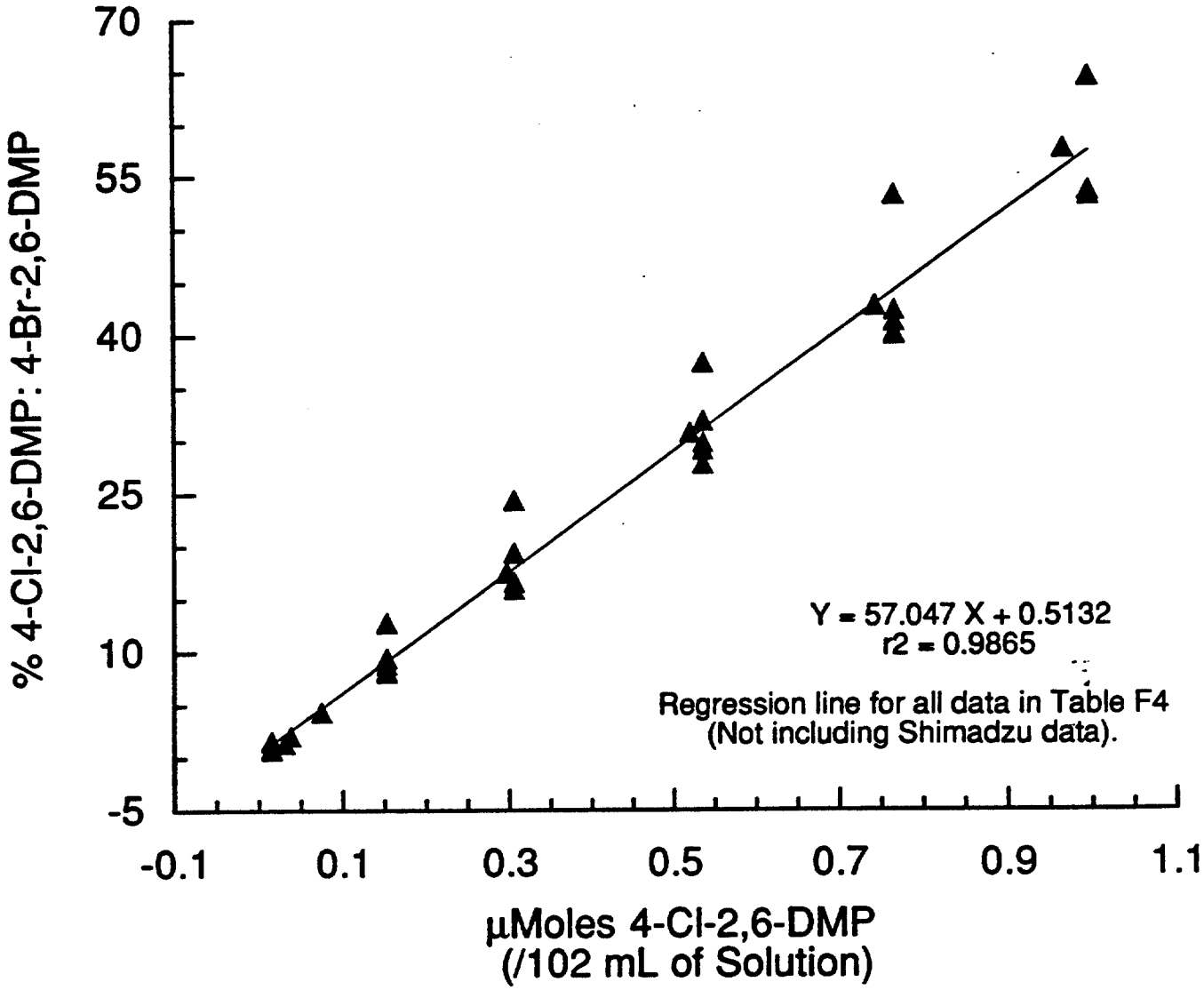


Table F5: Calibration of Wescan Model 360 Ammonia Analyzer

	3/4/93 Trial 1	3/5/93 Trial 2	3/5/93 Trial 3	Mean	StDev	n
X Values	Y Values	Y Values	Y Values	Y Values	Y Values	Y Values
µg NH3 per mL	Δ Chart Divisions	Δ Chart Divisions	Δ Chart Divisions	Δ Chart Divisions	Δ Chart Divisions	Δ Chart Divisions
1	8.3	7.3	7.4	7.7	0.6	3
2	15.7	14.8	15.7	15.4	0.5	3
3		23.9	23.7	23.8	0.1	2
5	37.4	38.7	38	38.0	0.7	3
10	77.8	79.3	78	78.4	0.8	3

Final regression line from X values and Mean Y values:

Slope =	7.84
Y Int =	-0.25
r2=	0.9998

APPENDIX G

BODY WEIGHT DATA

Table G1

Statistical Analyses of Maximum Body Weight - B6C3F1 Mice

Dose	Adjusted Mean	Female Mice Unadjusted Mean	S.E.	N
0	39.13	38.64	0.89	70
0.4	37.70	37.84	0.59	70
1.0	36.91	37.08	0.65	70
2.5	34.33**	34.52**	0.66	70

Dose	Adjusted Mean	Male Mice Unadjusted Mean	S.E.	N
0	41.32	40.79	0.67	67
0.4	39.31	39.14	0.61	70
1.0	37.59**	37.89**	0.57	70
2.5	38.03**	38.43**	0.59	67

* $p<0.05$
** $p<0.01$

Table G2

Statistical Analyses of Maximum Body Weight - F344 Rats

Male Rats, Exposed 5 days/week				
Dose	Adjusted Mean	Unadjusted Mean	S.E.	N
0	410.0	410.8	3.4	70
0.4	398.2*	396.6**	3.0	70
1.0	388.8**	387.2**	4.7	70
2.5	359.2**	361.5**	3.1	70

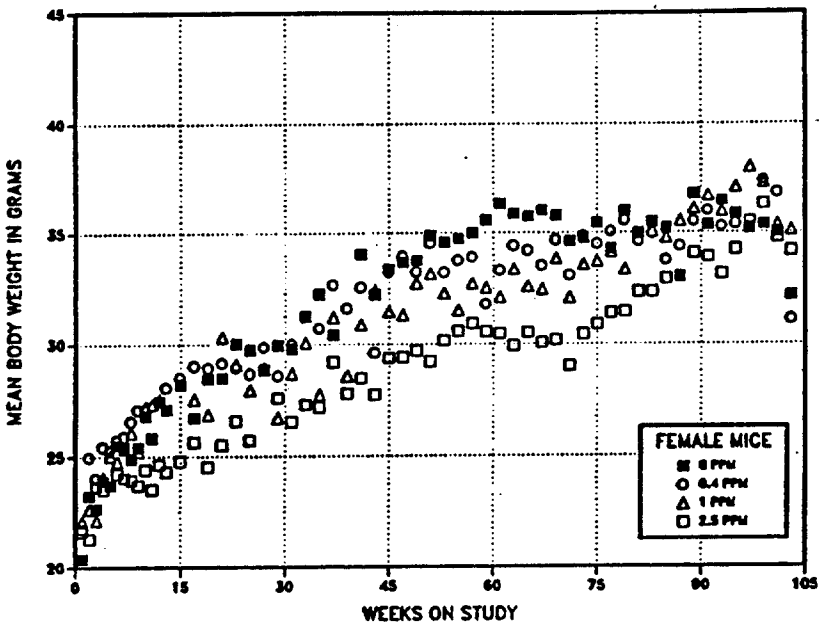
Female Rats, Exposed 3 days/week				
Dose	Adjusted Mean	Unadjusted Mean	S.E.	N
0	270.6	270.0	3.6	70
0.4	275.9	277.5	4.9	70
1.0	259.9*	259.9	3.6	70
2.5	240.8**	239.8**	3.7	70

* $p<0.05$
** $p<0.01$

Figure G1a and G1b

Body Weight Curves - B6C3F1 Mice

CHLORINE



CHLORINE

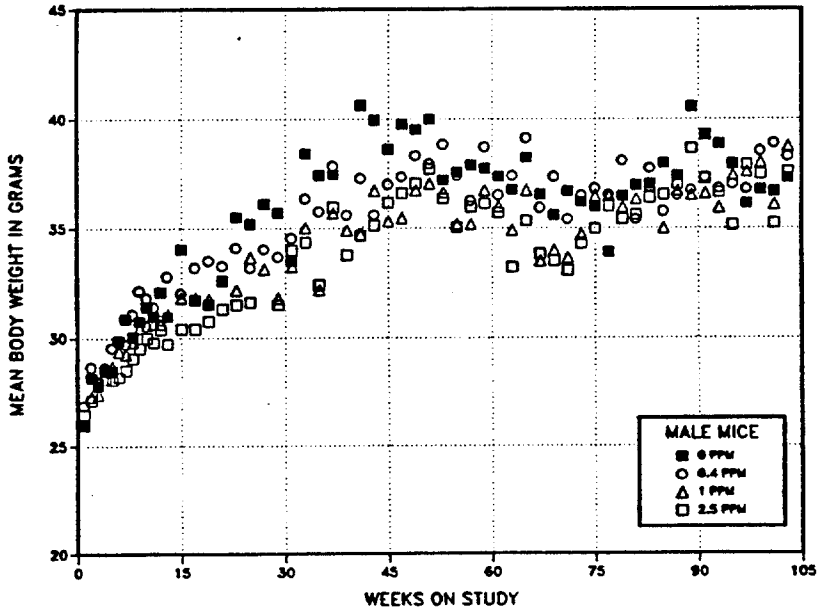
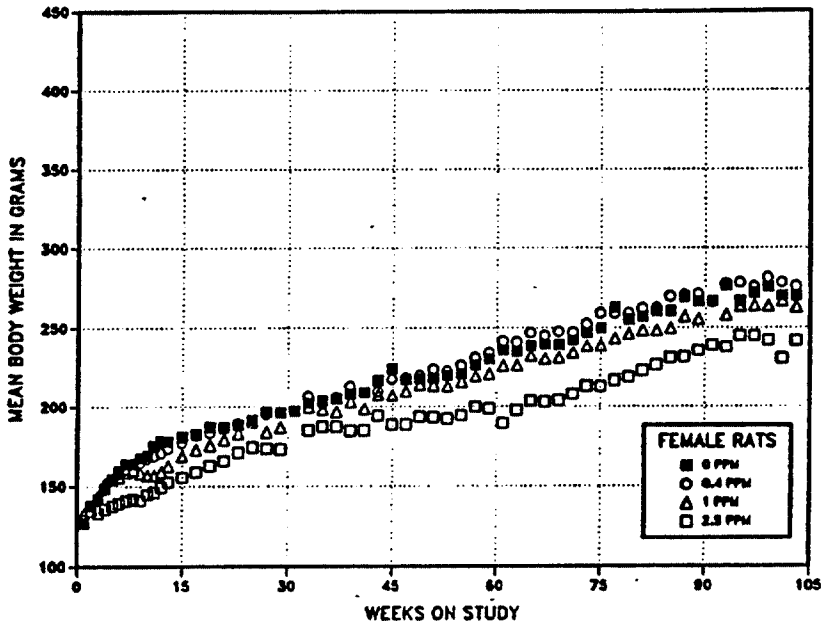


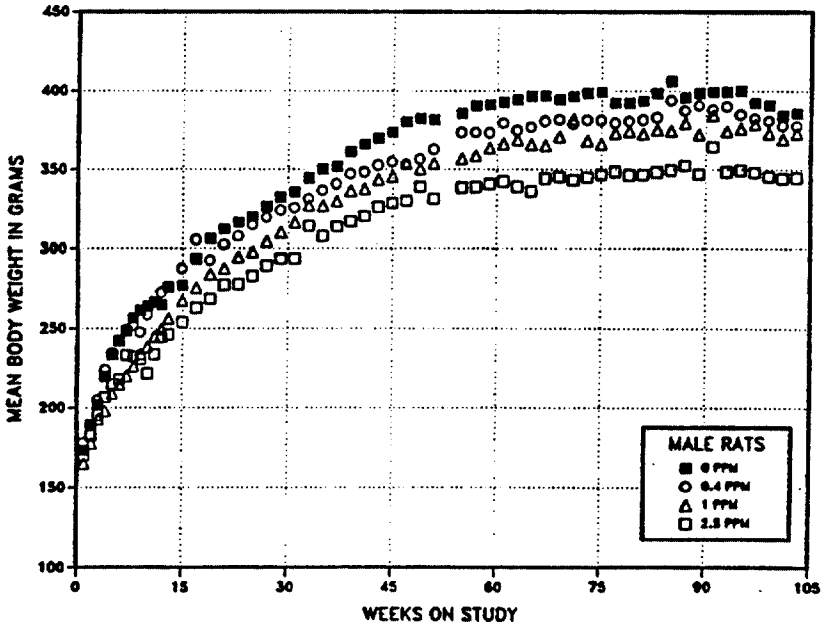
Figure G2a and G2b

Body Weight Curves - F344 Rats

CHLORINE (exposed 3 days/week)



CHLORINE (exposed 5 days/week)



APPENDIX H

CLINICAL OBSERVATIONS SUMMARY DATA

Table H1a
Incidence of Clinical Observations
for Female Mice Over the Course of the Study*

Clinical Observation	Dose Group No. in Group	1 70	2 70	3 70	4 70
Superficial Palpable Masses		1	2	2	-
Subcutaneous Palpable Masses		-	1	1	1
Alopecia		67	68	65	63

*Only observations that were present in > 5% of the animals in any dose group and all masses found are reported here. The time frame for clinical observations was 16-Apr-84 to 31-Mar-86.

Table H1b
Incidence of Clinical Observations
for Male Mice Over the Course of the Study*

Clinical Observation	Dose Group No. in Group	1 67	2 70	3 70	4 70
Superficial Palpable Masses		2	9	8	2
Subcutaneous Palpable Masses		2	3	1	-
Total Body Emaciated		6	4	1	2
Total Body Dehydrated		5	7	3	3
Alopecia		7	5	5	3

*Only observations that were present in > 5% of the animals in any dose group and all masses found are reported here. The time frame for clinical observations was 16-Apr-84 to 31-Mar-86.

Table H2a
Incidence of Clinical Observations
for Female Rats Over the Course of the Study*

Clinical Observation	Dose Group No. in Group	1 70	2 70	3 70	4 70
Overgrown Teeth		-	-	-	4
Superficial Palpable Masses		3	1	3	1
Subcutaneous Palpable Masses		5	3	-	1
Total Body Emaciated		1	2	4	3
Alopecia		-	-	1	4
Eyes Squinted		-	-	-	4
Eyes Closed (Shut)		-	-	-	7

*Only observations that were present in > 5% of the animals in any dose group and all masses found are reported here. The time frame for clinical observations was 16-Apr-84 to 31-Mar-86.

Table H2b
Incidence of Clinical Observations
for Male Rats Over the Course of the Study*

Clinical Observation	Dose Group No. in Group	1 70	2 70	3 70	4 70
Superficial Palpable Masses		2	3	4	3
Subcutaneous Palpable Masses		6	-	2	2
Total Body Emaciated		6	2	2	6
Total Body Dehydrated		9	10	8	21
Alopecia		-	2	7	-
Corneal Opacity		2	4	4	1

*Only observations that were present in > 5% of the animals in any dose group and all masses found are reported here. The time frame for clinical observations was 11-Apr-83 to 25-Mar-85.

APPENDIX I

TERMINAL BODY AND ORGAN WEIGHT SUMMARY DATA: INTERIM NECROPSY

TABLE I1 ANALYSIS OF INITIAL AND FINAL BODY WEIGHTS OF RATS AT INTERIM NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	11 (10)	167.1	5.0	364.9	6.1	-	197.8	6.9	-
0.4	10 (10)	176.9	2.5	343.9	6.3	-5.75	*167.0	7.5	-15.61
1	11 (10)	158.2	2.9	352.2	9.1	-3.49	192.1	7.3	-2.89
2.5	11 (10)	166.6	3.4	**327.4	6.3	-10.27	**165.3	7.4	-16.46
TREND(d)		- (P=0.041)		- (P=0.003)			- (P=0.052)		
TEST USED(e)		Dunnett		Williams			Dunnett		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	10 (10)	125.7	1.9	211.7	3.7	-	85.50	2.92	-
0.4	10 (10)	130.4	1.2	210.0	2.4	-0.80	79.57	2.95	-6.94
1	10 (10)	*133.2	1.7	204.9	3.1	-3.21	71.68	3.32	-16.16
2.5	10 (10)	130.5	2.0	199.2	7.7	-5.87	*68.76	7.45	-19.58
TREND(d)		+ (P=0.018)		- (P=0.151)			- (P=0.014)		
TEST USED(e)		Dunnett		Dunnett			Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals per dose group (Number surviving at interim necropsy).
(b) Mean weight change of the animals in each dose group.
(c) [(Dosed group mean - Control group mean)/Control group mean] X 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE I2 ANALYSIS OF BRAIN WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT INTERIM NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	1.975	0.011	364.9	6.1	5.43	0.10	-
0.4	10	1.946	0.024	343.9	6.3	5.67	0.09	104
1	10	1.982	0.011	352.2	9.1	5.66	0.16	104
2.5	10	1.949	0.016	**327.4	6.3	**5.97	0.11	110
TREND(d)		- (P=0.655)		- (P=0.003)		+ (P=0.003)		
TEST USED(e)		Dunnett		Williams		Williams		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	1.841	0.017	211.7	3.7	8.73	0.21	-
0.4	10	1.844	0.021	210.0	2.4	8.80	0.16	101
1	10	1.835	0.020	204.9	3.1	8.97	0.14	103
2.5	10	1.845	0.018	199.2	7.7	9.39	0.39	108
TREND(d)		- (P=0.981)		- (P=0.151)		+ (P=0.237)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Brain and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE I3 ANALYSIS OF KIDNEY WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT INTERIM NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	2.280	0.039	364.9	6.1	6.27	0.18	-
0.4	10	2.333	0.051	343.9	6.3	*6.78	0.10	108
1	10	2.396	0.043	352.2	9.1	*6.86	0.27	109
2.5	10	2.347	0.033	**327.4	6.3	**7.18	0.11	115
TREND(d)		+ (P=0.093)		- (P=0.003)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	1.441	0.076	211.7	3.7	6.81	0.35	-
0.4	10	1.558	0.014	210.0	2.4	7.42	0.09	109
1	10	1.556	0.034	204.9	3.1	*7.60	0.16	112
2.5	10	1.521	0.033	199.2	7.7	*7.70	0.22	113
TREND(d)		+ (P=0.673)		- (P=0.151)		+ (P=0.015)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Kidney and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE I4 ANALYSIS OF LIVER WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT INTERIM NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	9.255	0.149	364.9	6.1	25.43	0.62	-
0.4	10	8.854	0.214	343.9	6.3	25.76	0.44	101
1	10	9.088	0.206	352.2	9.1	25.91	0.69	102
2.5	10	8.704	0.140	**327.4	6.3	26.61	0.28	105
TREND(d)		- (P=0.026)		- (P=0.003)		+ (P=0.019)		
TEST USED(e)		Dunnett		Williams		Dunnett		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	5.964	0.134	211.7	3.7	28.20	0.53	-
0.4	10	5.918	0.128	210.0	2.4	28.20	0.60	100
1	10	5.916	0.136	204.9	3.1	28.88	0.51	102
2.5	10	5.726	0.300	199.2	7.7	28.68	0.74	102
TREND(d)		- (P=0.412)		- (P=0.151)		+ (P=0.629)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Liver and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

APPENDIX J

TERMINAL BODY AND ORGAN WEIGHT SUMMARY DATA: FINAL NECROPSY

TABLE J1 ANALYSIS OF INITIAL AND FINAL BODY WEIGHTS OF MICE AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

MALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	67 (24)	25.96	0.39	32.95	0.64	-	6.53	0.52	-
0.4	69 (30)	26.89	0.31	33.09	0.72	0.41	5.66	0.50	-13.38
1	68 (29)	26.01	0.26	33.50	0.85	1.67	7.42	0.51	13.64
2.5	66 (26)	26.50	0.23	32.36	0.59	-1.81	5.72	0.41	-12.39
TREND (d)		- (P=0.550)		- (P=0.488)			- (P=0.775)		
TEST USED (e)		Dunnett		Dunnett			Dunnett		

FEMALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	70 (35)	20.38	0.22	30.54	0.82	-	10.87	0.66	-
0.4	69 (38)	**21.75	0.15	31.21	0.47	2.21	9.48	0.36	-12.73
1	70 (34)	**22.11	0.16	30.96	0.64	1.40	**8.69	0.47	-20.02
2.5	70 (38)	**21.62	0.16	30.37	0.54	-0.55	**8.37	0.45	-22.99
TREND (d)		+ (P<0.001)		- (P=0.418)			- (P<0.001)		
TEST USED (e)		Williams		Dunnett			Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals per dose group (Number surviving at final necropsy).
(b) Mean weight change of the animals in each dose group.
(c) [(Dosed group mean - Control group mean)/Control group mean] X 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J2 ANALYSIS OF BRAIN WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN MICE AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

MALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	24	0.458	0.006	32.95	0.64	14.00	0.31	-
0.4	30	0.453	0.004	33.09	0.72	13.85	0.29	99
1	28	0.444	0.004	33.50	0.85	13.26	0.27	95
2.5	26	0.454	0.004	32.36	0.59	14.11	0.22	101
TREND(d)		- (P=0.536)		- (P=0.488)		+ (P=0.913)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

FEMALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	34	0.472	0.004	30.54	0.82	15.60	0.36	-
0.4	38	0.466	0.004	31.21	0.47	15.03	0.23	96
1	34	0.468	0.004	30.96	0.64	15.27	0.29	98
2.5	37	0.471	0.004	30.37	0.54	15.52	0.26	99
TREND(d)		- (P=0.957)		- (P=0.418)		+ (P=0.386)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Brain and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J3 ANALYSIS OF KIDNEY WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN MICE AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

MALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	24	0.828	0.021	32.95	0.64	25.23	0.62	-
0.4	30	0.819	0.017	33.09	0.72	24.88	0.41	99
1	29	0.822	0.024	33.50	0.85	24.64	0.48	98
2.5	26	0.804	0.012	32.36	0.59	24.94	0.35	99
TREND(d)		- (P=0.389)		- (P=0.488)		- (P=0.837)		
TEST USED(e)		Dunnett		Dunnett		Dunnett		

FEMALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	35	0.591	0.035	30.54	0.82	19.40	0.91	-
0.4	38	0.550	0.016	31.21	0.47	17.62	0.49	91
1	34	0.617	0.104	30.96	0.64	20.13	3.44	104
2.5	38	0.508	0.007	30.37	0.54	16.86	0.34	87
TREND(d)		- (P=0.002)		- (P=0.418)		- (P=0.005)		
TEST USED(e)		Williams		Dunnett		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Kidney and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J4 ANALYSIS OF LIVER WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN MICE AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

MALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	24	2.280	0.205	32.95	0.64	69.79	6.32	-
0.4	30	1.870	0.102	33.09	0.72	57.77	4.11	83
1	29	2.230	0.191	33.50	0.85	69.62	8.34	100
2.5	26	1.862	0.097	32.36	0.59	57.88	3.25	83
TREND (d)		- (P=0.229)		- (P=0.488)		- (P=0.580)		
TEST USED (e)		Dunnett		Dunnett		Dunnett		

FEMALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	35	1.914	0.143	30.54	0.82	62.88	4.10	-
0.4	38	1.778	0.054	31.21	0.47	56.81	1.19	90
1	34	*1.627	0.028	30.96	0.64	**52.91	0.95	84
2.5	38	*1.647	0.029	30.37	0.54	*54.62	1.12	87
TREND (d)		- (P=0.129)		- (P=0.418)		- (P=0.157)		
TEST USED (e)		Dunnett		Dunnett		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Liver and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J5 ANALYSIS OF INITIAL AND FINAL BODY WEIGHTS OF RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	59 (43)	174.8	1.5	377.3	5.2	-	204.8	4.4	-
0.4	60 (48)	178.6	1.2	371.7	4.0	-1.50	194.3	3.6	-5.10
1	59 (43)	**166.4	1.6	364.4	5.6	-3.44	198.3	3.9	-3.18
2.5	59 (46)	**171.0	1.6	**344.9	4.0	-8.59	**177.3	3.5	-13.40
TREND(d)		- (P=0.001)		- (P<0.001)			- (P<0.001)		
TEST USED(e)		Williams		Williams			Williams		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	57 (51)	127.1	0.7	254.9	4.0	-	129.4	3.6	-
0.4	60 (49)	129.3	0.8	266.2	3.0	4.40	137.5	2.6	6.22
1	57 (48)	**133.2	0.6	253.5	3.5	-0.57	*118.8	3.1	-8.22
2.5	60 (48)	127.2	0.9	**233.0	4.0	-8.62	**104.7	3.3	-19.11
TREND(d)		+ (P=0.171)		- (P<0.001)			- (P<0.001)		
TEST USED(e)		Dunnett		Williams			Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals per dose group (Number surviving at final necropsy).
(b) Mean weight change of the animals in each dose group.
(c) [(Dosed group mean - Control group mean)/Control group mean] X 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J6 ANALYSIS OF BRAIN WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	43	2.035	0.010	377.3	5.2	5.44	0.09	-
0.4	48	2.025	0.013	371.7	4.0	5.48	0.07	101
1	43	2.042	0.023	364.4	5.6	5.68	0.13	104
2.5	46	2.018	0.011	**344.9	4.0	**5.88	0.07	108
TREND(d)		- (P=0.375)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	50	1.791	0.011	254.9	4.0	7.03	0.11	-
0.4	49	*1.835	0.008	266.2	3.0	6.93	0.08	99
1	48	1.804	0.012	253.5	3.5	7.19	0.13	102
2.5	47	1.819	0.011	**233.0	4.0	**7.92	0.16	113
TREND(d)		+ (P=0.631)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Brain and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J7 ANALYSIS OF KIDNEY WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	43	2.974	0.104	377.3	5.2	7.92	0.27	-
0.4	48	2.851	0.042	371.7	4.0	7.70	0.12	97
1	43	2.802	0.051	364.4	5.6	7.74	0.14	98
2.5	46	2.790	0.063	**344.9	4.0	8.14	0.23	103
TREND(d)		- (P=0.026)		- (P<0.001)		+ (P=0.042)		
TEST USED(e)		Dunnett		Williams		Dunnett		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	KIDNEY (grams) MEAN	KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	50	1.863	0.038	254.9	4.0	7.32	0.20	-
0.4	49	1.883	0.024	266.2	3.0	7.11	0.12	97
1	48	1.912	0.042	253.5	3.5	7.62	0.22	104
2.5	48	1.780	0.021	**233.0	4.0	7.70	0.10	105
TREND(d)		- (P=0.051)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Kidney and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE J8 ANALYSIS OF LIVER WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

MALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	43	12.275	0.254	377.3	5.2	32.72	0.74	-
0.4	48	11.876	0.269	371.7	4.0	31.98	0.66	98
1	43	11.449	0.326	364.4	5.6	31.40	0.74	96
2.5	46	**11.087	0.275	**344.9	4.0	32.28	0.88	99
TREND(d)		- (P<0.001)		- (P<0.001)		- (P=0.274)		
TEST USED(e)		Williams		Williams		Dunnett		

3 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	50	7.008	0.126	254.9	4.0	27.49	0.65	-
0.4	49	7.198	0.101	266.2	3.0	27.11	0.36	99
1	48	6.898	0.143	253.5	3.5	27.17	0.65	99
2.5	48	*6.548	0.141	**233.0	4.0	28.27	0.61	103
TREND(d)		- (P=0.001)		- (P<0.001)		+ (P=0.098)		
TEST USED(e)		Williams		Williams		Dunnett		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Liver and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

APPENDIX K

GROSS NECROPSY SUMMARY DATA: INTERIM NECROPSY

TABLE K1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS
CHLORINE: #8436 Female F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN CECUM

	GROUP	
	1	4
	N	N
FINDING		
ABNORMAL COLOR	1	1

ORGAN LIVER

	GROUP		
	1	3	4
	N	N	N
FINDING			
ABNORMAL COLOR	.	1	.
DIAPHRAGMATIC HERNIA	1	1	.
GROWTH(S)/MASS(ES)	1	.	1

ORGAN MAND. LYMPH NDS.

	GROUP	
	1	3
	N	N
FINDING		
ABNORMAL COLOR	1	1

TABLE K1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8438 Female F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN MESE. LYMPH NDS.

	GROUP
	4
	N
FINDING	
ABNORMAL SIZE	2

ORGAN OVARIES

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
PARA-OVARIAN CYST(S)	1	3	2	1

ORGAN PITUITARY GLAND

	GROUP		
	2	3	4
	N	N	N
FINDING			
ABNORMAL COLOR	1	3	1

TABLE K1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN SPLEEN

	GROUP
	2
	N
FINDING	
ACCESSORY SPLEEN	1

ORGAN STOMACH

	GROUP
	1
	N
FINDING	
ABNORMAL LUMINAL CONTENTS	1

ORGAN UT

	GROUP		
	1	2	4
	N	N	N
FINDING			
ENLARGED	1	2	2
GROWTH(S)/MASS(ES)	.	1	1

TABLE K2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS
CHLORINE: #8321 Male F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN BRAIN

	GROUP
	4
	N
FINDING	
ABNORMAL COLOR	1

ORGAN COLON

	GROUP
	4
	N
FINDING	
GROWTH(S)/MASS(ES)	1

ORGAN EPIDIDYMIS

	GROUP
	4
	N
FINDING	
GROWTH (S)/MASS (ES)	1

TABLE K2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN EYES & OPTIC N.

	GROUP 3 N
FINDING	
ABNORMAL COLOR	1
ABNORMAL SIZE	1

ORGAN GROSS LESION

	GROUP 1 N	GROUP 3 N
FINDING		
DEEP CERV. NODE REDDISH	.	1
GROWTH(S)/MASS(ES)	1	1

ORGAN KIDNEY

	GROUP 3 N	GROUP 4 N
FINDING		
ABNORMAL COLOR	1	1

TABLE K2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN LIVER

	GROUP	
	1	3
	N	N
FINDING		
ABNORMAL COLOR	.	1
DIAPHRAGMATIC HERNIA	1	.

ORGAN LUNGS

	GROUP		
	1	2	3
	N	N	N
FINDING			
ABNORMAL COLOR	.	1	2
GROWTH(S)/MASS(ES)	1	.	.

ORGAN MAND. LYMPH NDS.

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	1	2	3	3
ENLARGED	.	.	.	2

TABLE K2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN NOSE/TURBINATES

	GROUP
	3
	N
FINDING	
RECEDING	1

ORGAN PITUITARY GLAND

	GROUP	
	2	3
	N	N
FINDING		
ENLARGED	.	1
GROWTH(S)/MASS(ES)	1	.

ORGAN PROSTATE

	GROUP
	4
	N
FINDING	
GROWTH(S)/MASS(ES)	2

TABLE K2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Interim - Incidence Summary, Gross Findings

ORGAN SEMINAL VESICLES

	GROUP
	4
	N
FINDING	
GROWTH(S)/MASS(ES)	1

ORGAN TESTES

	GROUP		
	1	2	4
	N	N	N
FINDING			
ABNORMAL COLOR	1	1	.
ABNORMAL SIZE	1	.	.
VAS DEFERENS FILLED WITH BLOOD	.	.	1

ORGAN URINARY BLADDER

	GROUP
	4
	N
FINDING	
GROWTH(S)/MASS(ES)	1

APPENDIX L

GROSS NECROPSY SUMMARY DATA: ALL ANIMALS

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN **WHOLE BODY**

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
GROWTH(S)/MASS(ES)	.	7	4	.	.	.	4	.
HEAD CRUSH	.	.	3	6	.	5	.	.
MISSING-PRESUMED DEAD	4	.	10	9	.	4	.	.

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN ADRENAL GLANDS

	SEX
	MALE
	GROUP
	2
	N
FINDING	
ABNORMAL COLOR	5

ORGAN BRAIN

	SEX				
	FEMALE	MALE			
	GROUP	GROUP			
	4	1	2	3	4
	N	N	N	N	N
FINDING					
SOFT	4	5	7	7	6

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN DUODENUM

	SEX	
	MALE	
	GROUP	
	3	4
	N	N
FINDING		
ABNORMAL LUMINAL CONTENTS	9	6

ORGAN EYES & OPTIC N.

	SEX
	FEMALE
	GROUP
	2
	N
FINDING	
OPACITY	4

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN GROSS LESION

	SEX
	FEMALE
	GROUP
	2
	N
FINDING	
GROWTH(S)/MASS(ES)	4

ORGAN HARDERIAN GLAND

	SEX
	FEMALE
	GROUP
	2
	N
FINDING	
MASS	4

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN HEART

	SEX	
	MALE	
	GROUP	
	1	4
	N	N
FINDING		
ENLARGED	8	7

ORGAN JEJUNUM

	SEX
	MALE
	GROUP
	4
	N
FINDING	
AUTOLYSIS	4

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN KIDNEY

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL COLOR	6	6	3	7	6	8	6	4
ABNORMAL SIZE	.	.	3	.	.	11	12	.
CYST(S)	.	.	.	.	4	.	4	.
DILATED PELVIS (HYDRONEPHROSIS)	.	.	.	.	5	7	.	5

ORGAN LIVER

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL COLOR	17	11	18	10	4	6	4	5
ENLARGED	5	8	5	.	.	.	6	.
FOCI	.	5	5	4	4	.	4	.
GROWTH(S)/MASS(ES)	7	13	4	9	22	18	22	27

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN LUNGS

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL COLOR	6	23	9	12	8	20	26	10
GROWTH(S)/MASS(ES)	.	6	.	.	7	5	.	.

ORGAN LYMPH NODES

	SEX					
	FEMALE				MALE	
	GROUP				GROUP	
	1	2	3	4	1	2
	N	N	N	N	N	N
FINDING						
ENLARGED	11	10	7	13	4	7

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN MAND. LYMPH NDS.

	SEX		
	FEMALE		
	GROUP		
	1	2	4
	N	N	N
FINDING			
ABNORMAL COLOR	5	7	.
ENLARGED	8	9	5

ORGAN MESE. LYMPH NDS.

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL COLOR	11	14	10	8	11	17	16	18
ABNORMAL SIZE	12	14	7	13	8	10	12	11

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN OVARIES

	SEX			
	FEMALE			
	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
CYST(S) WITHIN OVARY	4	6	5	6
GROWTH(S)/MASS(ES)	.	6	5	18
PARA-OVARIAN CYST(S)	9	8	10	4

ORGAN PANCREAS

	SEX
	FEMALE
	GROUP
	3
	N
FINDING	
CYST	4
GROWTH(S)/MASS(ES)	3

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN PENIS

	SEX			
	MALE			
	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
PARAPHIMOSIS	9	10	11	8

ORGAN PERITONEAL CAV.

	SEX
	MALE
	GROUP
	3
	N
FINDING	
ABNORMAL CONTENTS	8

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN PITUITARY GLAND

	SEX	
	FEMALE	MALE
	GROUP	GROUP
	2	4
	N	N
FINDING		
ABNORMAL COLOR	5	4

ORGAN PLEURAL CAVITY

	SEX
	FEMALE
	GROUP
	3
	N
FINDING	
ABNORMAL CONTENTS	3

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN SEMINAL VESICLES

	SEX			
	MALE			
	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	.	5	.	.
ABNORMAL SIZE	9	10	8	12

ORGAN SKIN

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL CONDITIONS	30	42	21	31	10	10	9	9

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN SPLEEN

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL COLOR	8	5	5	.	4	.	.	.
ABNORMAL SIZE	24	27	12	12	6	8	20	7

ORGAN STOMACH

	SEX							
	FEMALE				MALE			
	GROUP				GROUP			
	1	2	3	4	1	2	3	4
	N	N	N	N	N	N	N	N
FINDING								
ABNORMAL CONTENT	4	.	.	.	.	.	10	7
GROWTH(S)/MASS(ES)	21	32	15	17	14	9	.	8

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN THYMUS

	SEX					
	FEMALE				MALE	
	GROUP				GROUP	
	1	2	3	4	1	4
	N	N	N	N	N	N
FINDING						
ENLARGED	7	5	3	5	.	.
INVOLUTED	13	.	.	12	4	21

ORGAN URINARY BLADDER

	SEX						
	FEMALE			MALE			
	GROUP			GROUP			
	1	3	4	1	2	3	4
	N	N	N	N	N	N	N
FINDING							
ENLARGED/DILATED	4	5	9	19	16	22	17
THICKENED WALL	.	.	.	.	4	.	.

TABLE L1 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MICE (cont'd)
CHLORINE: #8437 Male & Female Mice - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN UT

	SEX			
	FEMALE			
	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	.	.	8	5
ATROPHIC/SMALL	4	.	.	.
CYST(S)	.	6	20	.
ENLARGED	23	24	18	21
GROWTH(S)/MASS(ES)	.	10	.	9

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN **WHOLE BODY**

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
GROWTH(S)/MASS(ES)	.	5	5	.

ORGAN ADRENAL GLANDS

	GROUP
	1
	N
FINDING	
ABNORMAL COLOR	6

ORGAN EYES & OPTIC N.

	GROUP
	4
	N
FINDING	
LENS CATARACT	4

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN GROSS LESION

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
GROWTH(S)/MASS(ES)	8	12	6	8

ORGAN KIDNEY

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	11	13	10	9

ORGAN LIVER

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	23	18	20	18
DIAPHRAGMATIC HERNIA	5	4	8	.
GROWTH(S)/MASS(ES)	6	6	8	5

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN LUNGS

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	5	19	11	5

ORGAN LYMPH NODES

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	4	8	5	6
ENLARGED	6	.	.	5

ORGAN MAMMARY GLANDS

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
GROWTH(S)/MASS(ES)	16	6	.	8
PROMINENT	5	11	8	6

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN MAND. LYMPH NDS.

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	6	5	9	10
ENLARGED	4	9	4	7

ORGAN MESE. LYMPH NDS.

	GROUP		
	1	2	4
	N	N	N
FINDING			
ABNORMAL SIZE	7	7	6

ORGAN OVARIES

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
PARA-OVARIAN CYST(S)	14	8	11	15

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN PITUITARY GLAND

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	15	20	16	13
GROWTH(S)/MASS(ES)	13	15	14	13

ORGAN SPLEEN

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	.	.	4	.
ABNORMAL SIZE	9	9	8	10

ORGAN THYMUS

	GROUP
	3
	N
FINDING	
ENLARGED	5

TABLE L2 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - FEMALE F344 RATS (cont'd)
CHLORINE: #8436 Female F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN THYROID GLANDS

	GROUP	
	1	3
	N	N
FINDING		
ENLARGED	4	4

ORGAN UT

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ENLARGED	11	10	10	9
GROWTH(S)/MASS(ES)	4	7	.	6

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS
CHLORINE: #8321 Male F344 Rats - Overall -Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN **WHOLE BODY**

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
DISCHARGE	6	7	.	8
GROWTH(S)/MASS(ES)	5	.	4	.

ORGAN ADRENAL GLANDS

	GROUP
	1
	N
FINDING	
ABNORMAL COLOR	6

ORGAN EYES & OPTIC N.

	GROUP	
	2	3
	N	N
FINDING		
ABNORMAL COLOR	7	5

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN GROSS LESION

	GROUP		
	1	2	3
	N	N	N
FINDING			
GROWTH(S)/MASS(ES)	8	5	7

ORGAN KIDNEY

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	23	21	21	15
GRANULAR/PITTED/ROUGH SURFACE	16	22	15	10

ORGAN LIVER

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	10	19	10	17
ABNORMAL SIZE	.	4	.	.
DIAPHRAGMATIC HERNIA	4	.	.	.
FOCAL AREAS	5	.	.	.
GROWTH(S)/MASS(ES)	6	.	.	.

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN LUNGS

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	11	12	11	7
FOCI	5	.	.	.

ORGAN LYMPH NODES

	GROUP		
	1	2	3
	N	N	N
FINDING			
ABNORMAL COLOR	8	4	5
ENLARGED	6	5	.

ORGAN MAND. LYMPH NDS.

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	12	14	10	9
ENLARGED	11	5	5	4

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN MESE. LYMPH NDS.

	GROUP	
	1	2
	N	N
FINDING		
ENLARGED	5	4

ORGAN PITUITARY GLAND

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	9	10	4	12
ENLARGED	4	.	.	.
GROWTH(S)/MASS(ES)	6	12	7	8

ORGAN SEMINAL VESICLES

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL SIZE	33	37	25	22

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN SKIN

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
GROWTH(S)/MASS(ES)	8	5	5	4

ORGAN SPLEEN

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	4	5	.	5
ABNORMAL SIZE	11	14	18	11

ORGAN STOMACH

	GROUP
	4
	N
FINDING	
ABNORMAL LUMINAL CONTENTS	4

TABLE L3 - GROSS NECROPSY INCIDENCE SUMMARY REPORT - MALE F344 RATS (cont'd)
CHLORINE: #8321 Male F344 Rats - Overall - Incidence Summary, Gross Findings
Only Findings with =>5% incidence

ORGAN TESTES

	GROUP			
	1	2	3	4
	N	N	N	N
FINDING				
ABNORMAL COLOR	50	54	42	48
ABNORMAL SIZE	15	11	7	5

ORGAN THYMUS

	GROUP
	1
	N
FINDING	
ENLARGED	4

ORGAN URINARY BLADDER

	GROUP	
	1	3
	N	N
FINDING		
DISTENDED	4	4

APPENDIX M

HEMATOLOGY SUMMARY DATA

B6C3F1 MICE

APPENDIX M

HEMATOLOGY--B6C3F1 MICE

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TABLE M1 WBC (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

WBC IN MALE MICE					WBC IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	3.63	0.40	-	0	30	2.47	0.18	-
0.4	28	**2.75	0.32	76	0.4	37	3.63	1.12	147
1	22	*2.58	0.21	71	1	33	3.39	0.65	137
2.5	26	**2.72	0.30	75	2.5	31	2.91	0.28	118
TREND(b)		- (P=0.027)			TREND(b)		+ (P=0.225)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

TABLE M2 LYMPHOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

LYMPHOCYTES IN MALE MICE					LYMPHOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	1.62	0.17	-	0	30	1.46	0.14	-
0.4	28	*1.18	0.12	73	0.4	37	2.43	1.11	166
1	22	1.30	0.16	80	1	33	1.82	0.51	125
2.5	26	1.50	0.29	92	2.5	31	1.50	0.26	103
TREND(b)		- (P=0.127)			TREND(b)		- (P=0.523)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M3 SEGMENTED NEUTROPHILS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

SEGMENTED NEUTROPHILS IN MALE MICE					SEGMENTED NEUTROPHILS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	1.84	0.22	-	0	30	0.923	0.069	-
0.4	28	*1.53	0.29	83	0.4	37	1.107	0.071	120
1	22	*1.21	0.14	66	1	33	1.493	0.296	162
2.5	26	**1.18	0.13	64	2.5	31	**1.276	0.078	138
TREND(b)		- (P=0.010)			TREND(b)		+ (P=0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE M4 MONOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MONOCYTES IN MALE MICE					MONOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.087	0.015	-	0	30	0.079	0.016	-
0.4	28	**0.035	0.009	41	0.4	37	0.091	0.016	116
1	22	0.064	0.017	74	1	33	0.065	0.013	82
2.5	26	0.044	0.009	51	2.5	31	0.127	0.022	160
TREND(b)		- (P=0.119)			TREND(b)		+ (P=0.110)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M5 EOSINOPHILS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

EOSINOPHILS IN MALE MICE					EOSINOPHILS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.003	0.002	-	0	30	0.002	0.001	-
0.4	28	0.000	0.000	0	0.4	37	0.004	0.002	205
1	22	0.003	0.002	103	1	33	0.001	0.001	67
2.5	26	0.000	0.000	0	2.5	31	0.001	0.001	48
TREND(b)		- (P=0.349)			TREND(b)		- (P=0.411)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE M6 BANDS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

BANDS IN MALE MICE					BANDS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.004	0.004	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	0	0.4	37	0.001	0.001	.
1	22	0.000	0.000	0	1	33	0.006	0.005	.
2.5	26	0.000	0.000	0	2.5	31	0.000	0.000	.
TREND(b)		- (P=0.169)			TREND(b)		+ (P=0.763)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M7 BASOPHILS IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

BASOPHILS IN MALE MICE					BASOPHILS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	.	0.4	37	0.000	0.000	.
1	22	0.001	0.001	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.000	0.000	.
TREND(b)		+ (P=0.651)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE M8 HEMATOCRIT (%) IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

HEMATOCRIT IN MALE MICE					HEMATOCRIT IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	44.24	2.03	-	0	30	45.07	1.05	-
0.4	28	44.86	0.86	101	0.4	37	44.32	0.63	98
1	22	45.28	0.90	102	1	33	43.83	0.58	97
2.5	26	46.06	1.28	104	2.5	31	**42.11	0.55	93
TREND(b)		+ (P=0.280)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M9 HEMOGLOBIN (g/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

HEMOGLOBIN IN MALE MICE					HEMOGLOBIN IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	14.60	0.69	-	0	30	15.09	0.37	-
0.4	28	14.65	0.27	100	0.4	37	14.78	0.20	98
1	22	14.76	0.27	101	1	33	14.64	0.22	97
2.5	26	15.08	0.41	103	2.5	31	**14.09	0.20	93
TREND(b)		+ (P=0.381)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE M10 MCH (pg) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MCH IN MALE MICE					MCH IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	16.33	0.36	-	0	30	16.44	0.15	-
0.4	28	15.80	0.10	97	0.4	37	16.38	0.10	100
1	22	15.69	0.11	96	1	33	16.10	0.13	98
2.5	26	15.80	0.17	97	2.5	31	*15.99	0.12	97
TREND(b)		- (P=0.247)			TREND(b)		- (P=0.004)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M11 MCHC (g/dl) IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MCHC IN MALE MICE					MCHC IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	32.97	0.16	-	0	30	33.45	0.17	-
0.4	28	32.70	0.12	99	0.4	37	33.37	0.14	100
1	22	32.67	0.13	99	1	33	33.39	0.15	100
2.5	26	32.76	0.13	99	2.5	31	33.45	0.13	100
TREND(b)		- (P=0.271)			TREND(b)		- (P=0.885)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE M12 MCV (fl) IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MCV IN MALE MICE					MCV IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	49.55	1.21	-	0	30	49.08	0.53	-
0.4	28	48.28	0.26	97	0.4	37	49.02	0.24	100
1	22	48.02	0.29	97	1	33	48.15	0.29	98
2.5	26	48.20	0.50	97	2.5	31	*47.74	0.23	97
TREND(b)		- (P=0.389)			TREND(b)		- (P=0.002)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M13 RBC (1,000,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

RBC IN MALE MICE					RBC IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	9.08	0.46	-	0	30	9.23	0.26	-
0.4	28	9.28	0.20	102	0.4	37	9.04	0.14	98
1	22	9.42	0.20	104	1	33	9.09	0.11	99
2.5	26	9.58	0.31	106	2.5	31	**8.81	0.11	95
TREND(b)		+ (P=0.206)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE M14 NRBC (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

NRBC IN MALE MICE					NRBC IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.067	0.063	-	0	30	0.003	0.002	-
0.4	28	0.000	0.000	0	0.4	37	0.001	0.001	26
1	22	0.000	0.000	0	1	33	0.000	0.000	0
2.5	26	0.004	0.002	5	2.5	31	0.002	0.001	69
TREND(b)		- (P=0.892)			TREND(b)		+ (P=0.737)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M15 PLATELETS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

PLATELETS IN MALE MICE					PLATELETS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	1637	113	-	0	30	1017	67	-
0.4	28	1765	42	108	0.4	37	1120	55	110
1	22	1755	77	107	1	33	1089	41	107
2.5	26	1620	72	99	2.5	31	1149	40	113
TREND(b)		- (P=0.250)			TREND(b)		+ (P=0.350)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE M16 ATYPICAL LYMPHOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

ATYPICAL LYMPHOCYTES IN MALE MICE					ATYPICAL LYMPHOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	.	0.4	37	0.001	0.001	.
1	22	0.000	0.000	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.001	0.001	.
TREND(b)		- (P<0.001)			TREND(b)		+ (P=0.528)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M17 METAMYELOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

METAMYELOCYTES IN MALE MICE					METAMYELOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.002	0.002	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	0	0.4	37	0.000	0.000	.
1	22	0.001	0.001	50	1	33	0.000	0.000	.
2.5	26	0.000	0.000	0	2.5	31	0.001	0.001	.
TREND(b)		- (P=0.504)			TREND(b)		+ (P=0.172)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE M18 MYELOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MYELOCYTES IN MALE MICE					MYELOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.004	0.004	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	0	0.4	37	0.000	0.000	.
1	22	0.000	0.000	0	1	33	0.000	0.000	.
2.5	26	0.000	0.000	0	2.5	31	0.000	0.000	.
TREND(b)		- (P=0.169)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M19 PROMYELOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

PROMYELOCYTES IN MALE MICE					PROMYELOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	.	0.4	37	0.000	0.000	.
1	22	0.000	0.000	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE M20 BLAST CELLS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

BLAST CELLS IN MALE MICE					BLAST CELLS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	.	0.4	37	0.000	0.000	.
1	22	0.000	0.000	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M21 MAST CELLS (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MAST CELLS IN MALE MICE					MAST CELLS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.001	0.001	.	0.4	37	0.000	0.000	.
1	22	0.000	0.000	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.000	0.000	.
TREND (b)		- (P=0.651)			TREND (b)		- (P<0.001)		
TEST USED (c)		Dunn			TEST USED (c)		Shirley		

TABLE M22 LARGE GRANULAR LEUKOCYTES (1,000/microliter) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

LARGE GRANULAR LEUKOCYTES IN MALE MICE					LARGE GRANULAR LEUKOCYTES IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	0.000	0.000	-	0	30	0.000	0.000	-
0.4	28	0.000	0.000	.	0.4	37	0.000	0.000	.
1	22	0.000	0.000	.	1	33	0.000	0.000	.
2.5	26	0.000	0.000	.	2.5	31	0.000	0.000	.
TREND (b)		- (P<0.001)			TREND (b)		- (P<0.001)		
TEST USED (c)		Shirley			TEST USED (c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M23 TOTAL CELL COUNT IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

TOTAL CELL COUNT IN MALE MICE					TOTAL CELL COUNT IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	100.00	0.00	-	0	30	90.70	3.56	-
0.4	28	94.57	2.62	95	0.4	37	96.73	1.57	107
1	22	96.05	2.17	96	1	33	94.61	2.40	104
2.5	26	94.88	3.12	95	2.5	31	97.81	1.10	108
TREND(b)		- (P=0.200)			TREND(b)		+ (P=0.158)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE M24 MEAN PLATELET VOLUME (cubic microns) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

MEAN PLATELET VOLUME IN MALE MICE					MEAN PLATELET VOLUME IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	22	5.05	0.13	-	0	28	5.03	0.11	-
0.4	28	4.81	0.06	95	0.4	37	5.02	0.08	100
1	21	4.82	0.06	95	1	33	5.02	0.09	100
2.5	24	4.91	0.10	97	2.5	30	4.95	0.09	98
TREND(b)		- (P=0.467)			TREND(b)		- (P=0.678)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M25 RED CELL DISTRIBUTION WIDTH (%) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

RED CELL DISTRIBUTION WIDTH IN MALE MICE					RED CELL DISTRIBUTION WIDTH IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	23	15.42	0.73	-	0	30	13.65	0.42	-
0.4	28	*13.96	0.57	91	0.4	37	**14.08	0.17	103
1	22	*13.87	0.28	90	1	33	13.40	0.26	98
2.5	26	*13.90	0.37	90	2.5	31	13.36	0.19	98
TREND(b)		- (P=0.063)			TREND(b)		- (P=0.377)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

TABLE M26 PLATELETS IN HEMATOCRIT (%) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

PLATELETS IN HEMATOCRIT IN MALE MICE					PLATELETS IN HEMATOCRIT IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	22	0.848	0.044	-	0	28	0.529	0.024	-
0.4	28	0.844	0.018	100	0.4	37	0.550	0.023	104
1	21	0.858	0.040	101	1	33	0.538	0.018	102
2.5	24	0.780	0.033	92	2.5	30	0.563	0.017	106
TREND(b)		- (P=0.151)			TREND(b)		+ (P=0.612)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M27 PLATELET DISTRIBUTION WIDTH (%) IN MICE
AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

PLATELET DISTRIBUTION WIDTH IN MALE MICE					PLATELET DISTRIBUTION WIDTH IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	22	17.10	0.15	-	0	28	17.06	0.10	-
0.4	28	17.16	0.09	100	0.4	36	17.20	0.09	101
1	21	17.01	0.09	100	1	33	17.35	0.12	102
2.5	24	17.28	0.13	101	2.5	30	17.16	0.09	101
TREND(b)		+ (P=0.330)			TREND(b)		+ (P=0.324)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE M28 PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
FEMALE B6C3F1 MICE

TIME = FINAL NECROPSY

5 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	24	33	31	31	119
PLD	6	3	2	0	11
PLI	0	1	0	0	1
Total	30	37	33	31	131

STATISTICS FOR TABLE OF PARM BY DOSE

Statistic	DF	Value	Prob
Chi-Square	6	10.892	0.092
Likelihood Ratio Chi-Square	6	12.156	0.059
Mantel-Haenszel Chi-Square	1	5.979	0.014
Phi Coefficient		0.288	
Contingency Coefficient		0.277	
Cramer's V		0.204	

Sample Size = 131
WARNING: 67% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

TABLE M29

PROPORTION OF FEMALE MICE WITH ANISOCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	4/33	4/38	2/34	1/35
COCHRAN-ARMITAGE	P=0.098			
FISHER'S EXACT TEST		P=0.562	P=0.322	P=0.160

TABLE M30

PROPORTION OF FEMALE MICE WITH HOWELL-JOLLY BODIES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	30/33	37/38	33/34	31/35
COCHRAN-ARMITAGE	P=0.249			
FISHER'S EXACT TEST		P=0.255	P=0.295	P=0.534

TABLE M31

PROPORTION OF FEMALE MICE WITH MACROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	6/33	8/38	2/34	1/35
COCHRAN-ARMITAGE	P=0.013			
FISHER'S EXACT TEST		P=0.500	P=0.120	P=0.044

TABLE M32

PROPORTION OF FEMALE MICE WITH MICROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	5/33	5/38	2/34	1/35
COCHRAN-ARMITAGE	P=0.047			
FISHER'S EXACT TEST		P=0.538	P=0.201	P=0.086

TABLE M33

PROPORTION OF FEMALE MICE WITH POLYCHROMASIA PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	6/33	7/38	4/34	6/35
COCHRAN-ARMITAGE	P=0.509			
FISHER'S EXACT TEST		P=0.612	P=0.347	P=0.580

TABLE M34 PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
MALE B6C3F1 MICE

TIME = FINAL NECROPSY

5 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	10	16	12	17	55
PLD	2	0	0	1	3
PLI	11	12	10	8	41
Total	23	28	22	26	99

STATISTICS FOR TABLE OF PARM BY DOSE

Statistic	DF	Value	Prob
Chi-Square	6	6.122	0.410
Likelihood Ratio Chi-Square	6	6.888	0.331
Mantel-Haenszel Chi-Square	1	1.698	0.193
Phi Coefficient		0.249	
Contingency Coefficient		0.241	
Cramer's V		0.176	

Sample Size = 99
WARNING: 33% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

TABLE M35

PROPORTION OF MALE MICE WITH ANISOCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	7/23	3/29	4/24	5/26
COCHRAN-ARMITAGE	P=0.469			
FISHER'S EXACT TEST		P=0.071	P=0.221	P=0.282

TABLE M36

PROPORTION OF MALE MICE WITH HOWELL-JOLLY BODIES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	23/23	28/29	22/24	26/26
COCHRAN-ARMITAGE	P=0.547			
FISHER'S EXACT TEST		P=0.558	P=0.255	P=1.000

TABLE M37

PROPORTION OF MALE MICE WITH HYPOCHROMASIA PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	1/23	0/29	0/24	0/26
COCHRAN-ARMITAGE	P=0.401			
FISHER'S EXACT TEST		P=0.442	P=0.489	P=0.469

TABLE M38

PROPORTION OF MALE MICE WITH MACROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	9/23	3/29	3/24	6/26
COCHRAN-ARMITAGE	P=0.422			
FISHER'S EXACT TEST		P=0.017	P=0.038	P=0.182

TABLE M39

PROPORTION OF MALE MICE WITH MICROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	7/23	2/29	2/24	6/26
COCHRAN-ARMITAGE	P=0.468			
FISHER'S EXACT TEST		P=0.031	P=0.059	P=0.397

TABLE M40

PROPORTION OF MALE MICE WITH POIKILOCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	1/23	0/29	0/24	0/26
COCHRAN-ARMITAGE	P=0.401			
FISHER'S EXACT TEST		P=0.442	P=0.489	P=0.469

TABLE M41

PROPORTION OF MALE MICE WITH POLYCHROMASIA PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	13/23	9/29	7/24	10/26
COCHRAN-ARMITAGE	P=0.325			
FISHER'S EXACT TEST		P=0.059	P=0.054	P=0.164

APPENDIX N

HEMATOLOGY SUMMARY DATA

F344 RATS

APPENDIX N

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TABLE N1 WBC (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
WBC IN MALE RATS					WBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	3.27	0.38	-	0	9	1.82	0.22	-
0.4	10	3.21	0.27	98	0.4	10	1.78	0.16	98
1	10	2.88	0.23	88	1	10	1.68	0.23	92
2.5	10	2.98	0.25	91	2.5	9	1.90	0.13	104
TREND(b)		- (P=0.717)			TREND(b)		+ (P=0.638)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N2 LYMPHOCYTES (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
LYMPHOCYTES IN MALE RATS					LYMPHOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	1.72	0.17	-	0	9	1.31	0.16	-
0.4	10	1.82	0.17	106	0.4	10	1.18	0.10	90
1	10	1.74	0.18	101	1	10	1.17	0.18	89
2.5	10	1.76	0.18	102	2.5	9	1.34	0.10	102
TREND(b)		+ (P=0.847)			TREND(b)		+ (P=0.866)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N3 WBC (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
WBC IN MALE RATS					WBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	4.96	0.96	-	0	50	11.56	5.32	-
0.4	48	3.90	0.36	79	0.4	49	2.55	0.24	22
1	42	4.24	0.53	85	1	47	2.24	0.15	19
2.5	46	10.10	4.38	204	2.5	47	3.59	1.10	31
TREND(b)		- (P=0.787)			TREND(b)		- (P=0.428)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N4 LYMPHOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
LYMPHOCYTES IN MALE RATS					LYMPHOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	2.14	0.40	-	0	50	1.97	0.60	-
0.4	48	1.83	0.29	85	0.4	49	1.27	0.10	65
1	42	1.94	0.23	91	1	47	1.17	0.08	59
2.5	46	1.60	0.21	75	2.5	47	1.59	0.30	81
TREND(b)		- (P=0.363)			TREND(b)		- (P=0.782)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N5 SEGMENTED NEUTROPHILS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SEGMENTED NEUTROPHILS IN MALE RATS					SEGMENTED NEUTROPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	1.374	0.247	-	0	9	0.407	0.063	-
0.4	10	1.235	0.131	90	0.4	10	0.477	0.049	117
1	10	0.993	0.092	72	1	10	0.419	0.044	103
2.5	10	1.075	0.112	78	2.5	9	0.429	0.049	105
TREND(b)		- (P=0.283)			TREND(b)		+ (P=0.938)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N6 MONOCYTES (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MONOCYTES IN MALE RATS					MONOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.038	0.013	-	0	9	0.036	0.012	-
0.4	10	0.028	0.005	73	0.4	10	0.037	0.009	104
1	10	0.021	0.008	56	1	10	0.056	0.010	156
2.5	10	0.039	0.013	104	2.5	9	0.051	0.011	141
TREND(b)		- (P=0.844)			TREND(b)		+ (P=0.178)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N7 SEGMENTED NEUTROPHILS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SEGMENTED NEUTROPHILS IN MALE RATS					SEGMENTED NEUTROPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	1.95	0.23	-	0	50	1.306	0.209	-
0.4	48	1.61	0.08	82	0.4	49	1.100	0.133	84
1	42	1.75	0.13	89	1	47	0.846	0.054	65
2.5	46	2.00	0.20	103	2.5	47	0.946	0.077	72
TREND(b)		+ (P=0.569)			TREND(b)		- (P=0.338)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N8 MONOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MONOCYTES IN MALE RATS					MONOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.213	0.074	-	0	50	0.076	0.013	-
0.4	48	0.144	0.014	67	0.4	49	0.095	0.016	126
1	42	0.168	0.029	79	1	47	0.086	0.010	114
2.5	46	0.185	0.068	87	2.5	47	0.092	0.016	122
TREND(b)		- (P=0.146)			TREND(b)		+ (P=0.325)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N9 EOSINOPHILS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
EOSINOPHILS IN MALE RATS					EOSINOPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.048	0.009	-	0	9	0.036	0.011	-
0.4	10	0.054	0.015	113	0.4	10	0.041	0.010	116
1	10	0.047	0.012	97	1	10	0.024	0.014	68
2.5	10	0.039	0.013	82	2.5	9	0.049	0.015	137
TREND(b)		- (P=0.488)			TREND(b)		- (P=0.958)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N10 BANDS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BANDS IN MALE RATS					BANDS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	.	0.4	10	0.000	0.000	.
1	10	0.000	0.000	.	1	10	0.000	0.000	.
2.5	10	0.000	0.000	.	2.5	9	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N11 EOSINOPHILS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
EOSINOPHILS IN MALE RATS					EOSINOPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.057	0.008	-	0	50	0.026	0.007	-
0.4	48	0.065	0.008	113	0.4	49	0.018	0.004	69
1	42	0.070	0.012	123	1	47	0.019	0.003	71
2.5	46	0.055	0.008	96	2.5	47	0.025	0.004	95
TREND(b)		- (P=0.777)			TREND(b)		+ (P=0.135)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N12 BANDS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BANDS IN MALE RATS					BANDS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.000	0.000	-	0	50	0.000	0.000	-
0.4	48	0.000	0.000	.	0.4	49	0.000	0.000	0
1	42	0.000	0.000	.	1	47	0.000	0.000	0
2.5	46	0.011	0.011	.	2.5	47	0.000	0.000	0
TREND(b)		+ (P=0.185)			TREND(b)		- (P=0.185)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N13 BASOPHILS IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BASOPHILS IN MALE RATS					BASOPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	.	0.4	10	0.000	0.000	.
1	10	0.000	0.000	.	1	10	0.000	0.000	.
2.5	10	0.000	0.000	.	2.5	9	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N14 HEMATOCRIT (%) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
HEMATOCRIT IN MALE RATS					HEMATOCRIT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	47.68	0.31	-	0	9	45.22	0.58	-
0.4	10	47.99	0.38	101	0.4	10	45.92	0.33	102
1	10	46.36	1.43	97	1	10	*46.88	0.41	104
2.5	10	47.40	0.26	99	2.5	9	45.19	0.63	100
TREND(b)		- (P=0.506)			TREND(b)		+ (P=0.725)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N15 BASOPHILS IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BASOPHILS IN MALE RATS					BASOPHILS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.000	0.000	-	0	50	0.000	0.000	-
0.4	48	0.000	0.000	.	0.4	49	0.000	0.000	.
1	42	0.000	0.000	.	1	47	0.000	0.000	.
2.5	46	0.000	0.000	.	2.5	47	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N16 HEMATOCRIT (%) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
HEMATOCRIT IN MALE RATS					HEMATOCRIT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	46.18	0.96	-	0	50	43.84	0.91	-
0.4	48	46.83	0.67	101	0.4	49	44.03	0.82	100
1	42	45.31	0.74	98	1	47	45.29	0.46	103
2.5	46	46.37	1.04	100	2.5	47	43.69	1.01	100
TREND(b)		+ (P=0.478)			TREND(b)		+ (P=0.983)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N17 HEMOGLOBIN (g/dl) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
HEMOGLOBIN IN MALE RATS					HEMOGLOBIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	16.30	0.14	-	0	9	15.91	0.18	-
0.4	10	16.21	0.06	99	0.4	10	16.09	0.06	101
1	10	15.62	0.47	96	1	10	16.29	0.12	102
2.5	10	15.98	0.11	98	2.5	9	15.79	0.15	99
TREND(b)		- (P=0.063)			TREND(b)		- (P=0.917)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N18 MCH (pg) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCH IN MALE RATS					MCH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	17.08	0.06	-	0	9	18.99	0.15	-
0.4	10	17.09	0.13	100	0.4	10	19.04	0.10	100
1	10	17.26	0.15	101	1	10	18.94	0.11	100
2.5	10	17.12	0.07	100	2.5	9	19.12	0.17	101
TREND(b)		+ (P=0.661)			TREND(b)		+ (P=0.752)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N19 HEMOGLOBIN (g/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
HEMOGLOBIN IN MALE RATS					HEMOGLOBIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	15.80	0.35	-	0	50	15.25	0.28	-
0.4	48	15.90	0.23	101	0.4	49	15.25	0.29	100
1	42	15.39	0.28	97	1	47	15.70	0.15	103
2.5	46	15.88	0.35	101	2.5	47	15.16	0.34	99
TREND(b)		+ (P=0.517)			TREND(b)		- (P=0.984)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N20 MCH (pg) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCH IN MALE RATS					MCH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	18.08	0.12	-	0	50	20.15	0.53	-
0.4	48	18.01	0.13	100	0.4	49	19.45	0.15	97
1	42	18.26	0.25	101	1	47	19.54	0.16	97
2.5	46	18.72	0.42	104	2.5	47	19.93	0.49	99
TREND(b)		+ (P=0.932)			TREND(b)		- (P=0.570)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N21 MCHC (g/dl) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCHC IN MALE RATS					MCHC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	34.15	0.15	-	0	9	35.18	0.24	-
0.4	10	33.78	0.21	99	0.4	10	35.00	0.15	99
1	10	33.73	0.09	99	1	10	34.74	0.10	99
2.5	10	33.73	0.20	99	2.5	9	34.98	0.25	99
TREND(b)		- (P=0.050)			TREND(b)		- (P=0.142)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N22 MCV (fl) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCV IN MALE RATS					MCV IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	49.94	0.12	-	0	9	53.94	0.22	-
0.4	10	50.54	0.28	101	0.4	10	54.32	0.11	101
1	10	**51.12	0.45	102	1	10	54.43	0.27	101
2.5	10	*50.72	0.25	102	2.5	9	*54.57	0.15	101
TREND(b)		+ (P=0.017)			TREND(b)		+ (P=0.019)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N23 MCHC (g/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCHC IN MALE RATS					MCHC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	34.15	0.23	-	0	50	34.99	0.28	-
0.4	48	33.99	0.20	100	0.4	49	34.63	0.15	99
1	42	33.95	0.31	99	1	47	34.68	0.18	99
2.5	46	34.30	0.26	100	2.5	47	34.74	0.14	99
TREND(b)		- (P=0.728)			TREND(b)		+ (P=0.818)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N24 MCV (fl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MCV IN MALE RATS					MCV IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	52.90	0.22	-	0	50	57.26	1.00	-
0.4	48	52.90	0.21	100	0.4	49	56.12	0.45	98
1	42	53.76	0.73	102	1	47	56.28	0.38	98
2.5	46	54.57	1.26	103	2.5	47	57.22	1.27	100
TREND(b)		- (P=0.681)			TREND(b)		- (P=0.116)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N25 PLATELETS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELETS IN MALE RATS					PLATELETS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	687.0	20.0	-	0	9	672.8	13.8	-
0.4	10	741.6	21.8	108	0.4	10	655.0	17.5	97
1	10	732.0	20.6	107	1	10	641.7	15.7	95
2.5	10	725.7	27.7	106	2.5	9	669.0	23.2	99
TREND(b)		+ (P=0.311)			TREND(b)		- (P=0.474)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N26 ATYPICAL LYMPHOCYTES (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ATYPICAL LYMPHOCYTES IN MALE RATS					ATYPICAL LYMPHOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	.	0.4	10	0.003	0.003	.
1	10	0.000	0.000	.	1	10	0.000	0.000	.
2.5	10	0.000	0.000	.	2.5	9	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P=0.638)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N27 PLATELETS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELETS IN MALE RATS					PLATELETS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	760.4	17.2	-	0	50	720.9	21.1	-
0.4	48	760.1	17.9	100	0.4	49	754.0	16.1	105
1	42	818.7	24.6	108	1	47	724.0	17.6	100
2.5	46	726.1	21.5	95	2.5	47	698.9	22.1	97
TREND(b)		+ (P=0.916)			TREND(b)		- (P=0.464)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N28 ATYPICAL LYMPHOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ATYPICAL LYMPHOCYTES IN MALE RATS					ATYPICAL LYMPHOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.002	0.001	-	0	50	0.000	0.000	-
0.4	48	0.000	0.000	0	0.4	49	0.000	0.000	.
1	42	0.022	0.017	1E3	1	47	0.002	0.002	.
2.5	46	0.000	0.000	0	2.5	47	0.000	0.000	.
TREND(b)		- (P=0.865)			TREND(b)		+ (P=0.591)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N29 ATYPICAL MONONUCLEAR CELLS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ATYPICAL MONONUCLEAR CELLS IN MALE RATS					ATYPICAL MONONUCLEAR CELLS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.025	0.011	-	0	9	0.006	0.004	-
0.4	10	0.022	0.007	88	0.4	10	0.002	0.002	35
1	10	0.033	0.010	129	1	10	0.000	0.000	0
2.5	10	0.023	0.006	90	2.5	9	0.004	0.002	61
TREND (b)		+ (P=0.773)			TREND (b)		- (P=0.689)		
TEST USED (c)		Shirley			TEST USED (c)		Shirley		

TABLE N30 BODY WEIGHT (grams) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BODY WEIGHT IN MALE RATS					BODY WEIGHT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.027	0.015	-	0	9	0.003	0.003	-
0.4	10	0.013	0.006	49	0.4	10	0.000	0.000	0
1	10	0.023	0.010	86	1	10	0.000	0.000	0
2.5	10	0.010	0.005	38	2.5	9	0.003	0.003	87
TREND (b)		- (P=0.629)			TREND (b)		- (P=0.973)		
TEST USED (c)		Shirley			TEST USED (c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N31 METAMYELOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
METAMYELOCTYES IN MALE RATS					METAMYELOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.136	0.132	-	0	50	0.000	0.000	-
0.4	48	0.060	0.044	44	0.4	49	0.000	0.000	.
1	42	0.050	0.044	37	1	47	0.000	0.000	.
2.5	46	*2.868	2.524	2E3	2.5	47	0.000	0.000	.
TREND(b)		+ (P=0.073)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N32 MYELOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MYELOCYTES IN MALE RATS					MYELOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.271	0.265	-	0	50	0.000	0.000	-
0.4	48	0.107	0.094	39	0.4	49	0.000	0.000	.
1	42	0.092	0.083	34	1	47	0.000	0.000	.
2.5	46	1.690	1.215	623	2.5	47	0.000	0.000	.
TREND(b)		+ (P=0.350)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N33 RBC (1,000,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
RBC IN MALE RATS					RBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	9.54	0.07	-	0	9	8.37	0.11	-
0.4	10	9.48	0.08	99	0.4	10	8.45	0.07	101
1	10	9.07	0.32	95	1	10	8.60	0.09	103
2.5	10	*9.34	0.05	98	2.5	9	8.28	0.13	99
TREND(b)		- (P=0.049)			TREND(b)		+ (P=0.990)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N34 NRBC (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
NRBC IN MALE RATS					NRBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.039	0.011	-	0	9	0.023	0.009	-
0.4	10	0.036	0.008	93	0.4	10	0.039	0.014	170
1	10	0.026	0.011	66	1	10	0.016	0.005	71
2.5	10	0.035	0.009	90	2.5	9	0.024	0.007	106
TREND(b)		- (P=0.712)			TREND(b)		+ (P=0.989)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N35 RBC (1,000,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
RBC IN MALE RATS					RBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	8.74	0.20	-	0	50	7.79	0.19	-
0.4	48	8.86	0.15	101	0.4	49	7.88	0.16	101
1	42	8.50	0.19	97	1	47	8.06	0.10	103
2.5	46	8.71	0.26	100	2.5	47	7.83	0.21	101
TREND(b)		+ (P=0.440)			TREND(b)		+ (P=0.487)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N36 NRBC (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
NRBC IN MALE RATS					NRBC IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.140	0.059	-	0	50	0.657	0.448	-
0.4	48	0.090	0.014	64	0.4	49	0.064	0.015	10
1	42	0.139	0.066	99	1	47	0.086	0.047	13
2.5	46	1.271	0.912	906	2.5	47	0.110	0.058	17
TREND(b)		+ (P=0.717)			TREND(b)		- (P=0.062)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N37 PROMYELOCYTES (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PROMYELOCYTES IN MALE RATS					PROMYELOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	•	0.4	10	0.000	0.000	•
1	10	0.000	0.000	•	1	10	0.000	0.000	•
2.5	10	0.000	0.000	•	2.5	9	0.000	0.000	•
TREND(b)		- (P=0.049)			TREND(b)		+ (P=0.990)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N38 BLAST CELLS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BLAST CELLS IN MALE RATS					BLAST CELLS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	•	0.4	10	0.000	0.000	•
1	10	0.000	0.000	•	1	10	0.000	0.000	•
2.5	10	0.000	0.000	•	2.5	9	0.000	0.000	•
TREND(b)		- (P=0.712)			TREND(b)		+ (P=0.989)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N39 PROMYELOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PROMYELOCYTES IN MALE RATS					PROMYELOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.032	0.028	-	0	50	0.000	0.000	-
0.4	48	0.003	0.003	8	0.4	49	0.000	0.000	.
1	42	0.006	0.006	17	1	47	0.000	0.000	.
2.5	46	0.254	0.172	795	2.5	47	0.000	0.000	.
TREND(b)		+ (P=0.348)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE N40 BLAST CELLS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
BLAST CELLS IN MALE RATS					BLAST CELLS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.017	0.012	-	0	50	0.000	0.000	-
0.4	48	0.001	0.001	5	0.4	49	0.000	0.000	.
1	42	0.006	0.006	34	1	47	0.000	0.000	.
2.5	46	0.166	0.126	999	2.5	47	0.000	0.000	.
TREND(b)		+ (P=0.629)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N41 MAST CELLS (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MAST CELLS IN MALE RATS					MAST CELLS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	•	0.4	10	0.000	0.000	•
1	10	0.000	0.000	•	1	10	0.000	0.000	•
2.5	10	0.000	0.000	•	2.5	9	0.000	0.000	•
TREND(b)		- (P=0.049)			TREND(b)		+ (P=0.990)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N42 LARGE GRANULAR LEUKOCYTES (1,000/microliter) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
LARGE GRANULAR LEUKOCYTES IN MALE RATS					LARGE GRANULAR LEUKOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.000	0.000	-	0	9	0.000	0.000	-
0.4	10	0.000	0.000	•	0.4	10	0.000	0.000	•
1	10	0.000	0.000	•	1	10	0.000	0.000	•
2.5	10	0.000	0.000	•	2.5	9	0.000	0.000	•
TREND(b)		- (P=0.712)			TREND(b)		+ (P=0.989)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N43 MAST CELLS (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MAST CELLS IN MALE RATS					MAST CELLS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.000	0.000	-	0	50	0.000	0.000	-
0.4	48	0.000	0.000	.	0.4	49	0.000	0.000	.
1	42	0.000	0.000	.	1	47	0.000	0.000	.
2.5	46	0.000	0.000	.	2.5	47	0.000	0.000	.
TREND(b)		- (P<0.001)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N44 LARGE GRANULAR LEUKOCYTES (1,000/microliter) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
LARGE GRANULAR LEUKOCYTES IN MALE RATS					LARGE GRANULAR LEUKOCYTES IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.000	0.000	-	0	50	7.524	4.514	-
0.4	48	0.000	0.000	.	0.4	49	**0.000	0.000	0
1	42	0.000	0.000	.	1	47	*0.032	0.031	0
2.5	46	0.000	0.000	.	2.5	47	*0.825	0.685	11
TREND(b)		- (P<0.001)			TREND(b)		- (P=0.086)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N45 TOTAL CELL COUNT IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL CELL COUNT IN MALE RATS					TOTAL CELL COUNT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	94.00	4.90	-	0	9	56.67	5.51	-
0.4	10	100.00	0.00	106	0.4	10	*78.40	6.93	138
1	10	99.30	0.70	106	1	10	**84.40	6.92	149
2.5	10	98.70	1.30	105	2.5	9	**97.33	2.67	172
TREND(b)		- (P=0.049)			TREND(b)		+ (P=0.990)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N46 MEAN PLATELET VOLUME (cubic microns) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MEAN PLATELET VOLUME IN MALE RATS					MEAN PLATELET VOLUME IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	6.91	0.03	-	0	9	6.36	0.05	-
0.4	10	6.90	0.05	100	0.4	10	6.38	0.06	100
1	10	6.70	0.09	97	1	10	6.27	0.07	99
2.5	10	6.80	0.04	98	2.5	9	6.21	0.08	98
TREND(b)		- (P=0.712)			TREND(b)		+ (P=0.989)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N47 TOTAL CELL COUNT IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL CELL COUNT IN MALE RATS					TOTAL CELL COUNT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	99.74	0.26	-	0	50	97.60	1.13	-
0.4	48	99.58	0.31	100	0.4	49	95.24	1.79	98
1	42	99.69	0.31	100	1	47	98.19	0.80	101
2.5	46	99.37	0.48	100	2.5	47	97.28	1.57	100
TREND(b)		- (P=0.730)			TREND(b)		+ (P=0.254)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE N48 MEAN PLATELET VOLUME (cubic microns) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
MEAN PLATELET VOLUME IN MALE RATS					MEAN PLATELET VOLUME IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	6.65	0.05	-	0	48	6.73	0.06	-
0.4	48	6.58	0.04	99	0.4	49	6.81	0.06	101
1	42	6.57	0.06	99	1	47	6.73	0.05	100
2.5	46	6.60	0.05	99	2.5	45	6.65	0.07	99
TREND(b)		- (P=0.417)			TREND(b)		- (P=0.413)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N49 RED CELL DISTRIBUTION WIDTH (%) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
RED CELL DISTRIBUTION WIDTH IN MALE RATS					RED CELL DISTRIBUTION WIDTH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	12.52	0.11	-	0	9	12.03	0.14	-
0.4	10	**13.17	0.13	105	0.4	10	*11.64	0.06	97
1	10	**14.06	0.64	112	1	10	*11.59	0.07	96
2.5	10	*12.76	0.19	102	2.5	9	*11.67	0.15	97
TREND(b)		+ (P=0.345)			TREND(b)		- (P=0.023)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N50 PLATELETS IN HEMATOCRIT (%) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELETS IN HEMATOCRIT IN MALE RATS					PLATELETS IN HEMATOCRIT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	0.476	0.015	-	0	9	0.428	0.008	-
0.4	10	0.511	0.013	107	0.4	10	0.418	0.012	98
1	10	0.491	0.015	103	1	10	0.402	0.011	94
2.5	10	0.494	0.018	104	2.5	9	0.416	0.013	97
TREND(b)		+ (P=0.654)			TREND(b)		- (P=0.219)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N51 RED CELL DISTRIBUTION WIDTH (%) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
RED CELL DISTRIBUTION WIDTH IN MALE RATS					RED CELL DISTRIBUTION WIDTH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	14.57	0.32	-	0	50	13.51	0.43	-
0.4	48	14.44	0.18	99	0.4	49	13.63	0.56	101
1	42	14.82	0.56	102	1	47	*12.79	0.20	95
2.5	46	*14.50	0.44	100	2.5	47	**13.04	0.40	97
TREND(b)		- (P=0.014)			TREND(b)		- (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE N52 PLATELETS IN HEMATOCRIT (%) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELETS IN HEMATOCRIT IN MALE RATS					PLATELETS IN HEMATOCRIT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.505	0.010	-	0	48	0.495	0.011	-
0.4	48	0.500	0.012	99	0.4	49	0.512	0.010	103
1	42	0.535	0.016	106	1	47	0.486	0.012	98
2.5	46	0.476	0.013	94	2.5	45	0.482	0.008	97
TREND(b)		- (P=0.628)			TREND(b)		- (P=0.330)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N53 PLATELET DISTRIBUTION WIDTH (%) IN RATS AT INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELET DISTRIBUTION WIDTH IN MALE RATS					PLATELET DISTRIBUTION WIDTH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	15.47	0.12	-	0	9	15.63	0.09	-
0.4	10	15.32	0.06	99	0.4	10	15.76	0.11	101
1	10	15.42	0.10	100	1	10	15.68	0.12	100
2.5	10	15.39	0.08	99	2.5	9	15.80	0.15	101
TREND(b)		+ (P=0.874)			TREND(b)		- (P=0.990)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N54 PLATELET DISTRIBUTION WIDTH (%) IN RATS
AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PLATELET DISTRIBUTION WIDTH IN MALE RATS					PLATELET DISTRIBUTION WIDTH IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	15.76	0.06	-	0	48	15.89	0.07	-
0.4	48	15.68	0.05	100	0.4	49	15.95	0.08	100
1	42	15.76	0.06	100	1	47	15.86	0.08	100
2.5	46	15.82	0.08	100	2.5	45	15.83	0.06	100
TREND(b)		+ (P=0.810)			TREND(b)		- (P=0.437)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE N55

PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
FEMALE F344 RATS
TIME = INTERIM NECROPSY

3 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	9	10	10	9	38
Total	9	10	10	9	38

TABLE N56

PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
MALE F344 RATS
TIME = INTERIM NECROPSY

5 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	10	10	10	10	40
Total	10	10	10	10	40

TABLE N57

PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
FEMALE F344 RATS
TIME = FINAL NECROPSY

3 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	47	49	46	45	187
PLD	3	0	1	2	6
Total	50	49	47	47	193

STATISTICS FOR TABLE OF PARM BY DOSE

Statistic	DF	Value	Prob
Chi-Square	3	3.315	0.346
Likelihood Ratio Chi-Square	3	4.545	0.208
Mantel-Haenszel Chi-Square	1	0.015	0.904
Phi Coefficient		0.131	
Contingency Coefficient		0.130	
Cramer's V		0.131	

Sample Size = 193
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

TABLE N58

PLATELET - ADEQUATE (PLA)/INCREASE (PLI)/DECREASE (PLD)
MALE F344 RATS
TIME = FINAL NECROPSY

5 DAY EXPOSURE

TABLE OF PARM BY DOSE

PARM	DOSE				
Frequency	0	0.4	1	2.5	Total
PLA	41	46	41	42	170
PLD	1	2	1	4	8
Total	42	48	42	46	178

STATISTICS FOR TABLE OF PARM BY DOSE

Statistic	DF	Value	Prob
Chi-Square	3	2.778	0.427
Likelihood Ratio Chi-Square	3	2.562	0.464
Mantel-Haenszel Chi-Square	1	2.144	0.143
Phi Coefficient		0.125	
Contingency Coefficient		0.124	
Cramer's V		0.125	

Sample Size = 178
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

TABLE N59

PROPORTION OF FEMALE RATS WITH MACROCYTES PRESENT
INTERIM NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/10	0/10	0/10	2/9
COCHRAN-ARMITAGE	P=0.032			
FISHER'S EXACT TEST		P=1.000	P=1.000	P=0.211

TABLE N60

PROPORTION OF FEMALE RATS WITH POLYCHROMASIA PRESENT
INTERIM NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/10	0/10	0/10	2/9
COCHRAN-ARMITAGE	P=0.032			
FISHER'S EXACT TEST		P=1.000	P=1.000	P=0.211

TABLE N61

PROPORTION OF MALE RATS WITH HOWELL-JOLLY BODIES PRESENT
INTERIM NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	1/10	0/10	1/10	1/10
COCHRAN-ARMITAGE	P=0.544			
FISHER'S EXACT TEST		P=0.500	P=0.763	P=0.763

TABLE N62

PROPORTION OF MALE RATS WITH POLYCHROMASIA PRESENT
INTERIM NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/10	0/10	1/10	0/10
COCHRAN-ARMITAGE	P=0.780			
FISHER'S EXACT TEST		P=1.000	P=0.500	P=1.000

TABLE N63

PROPORTION OF FEMALE RATS WITH ANISOCYTES PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	6/50	3/49	1/47	5/47
COCHRAN-ARMITAGE	P=0.541			
FISHER'S EXACT TEST		P=0.254	P=0.066	P=0.544

TABLE N64

PROPORTION OF FEMALE RATS WITH BASOPHILIC STIPPING PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/50	0/49	0/47	1/47
COCHRAN-ARMITAGE	P=0.200			
FISHER'S EXACT TEST		P=1.000	P=1.000	P=0.485

TABLE N65

PROPORTION OF FEMALE RATS WITH HOWELL-JOLLY BODIES PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	3/50	2/49	0/47	1/47
COCHRAN-ARMITAGE	P=0.232			
FISHER'S EXACT TEST		P=0.510	P=0.133	P=0.332

TABLE N66

PROPORTION OF FEMALE RATS WITH MACROCYTES PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	10/50	6/49	7/47	7/47
COCHRAN-ARMITAGE	P=0.420			
FISHER'S EXACT TEST		P=0.220	P=0.348	P=0.348

TABLE N67

PROPORTION OF FEMALE RATS WITH MICROCYTES PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	5/50	3/49	1/47	5/47
COCHRAN-ARMITAGE	P=0.431			
FISHER'S EXACT TEST		P=0.369	P=0.117	P=0.590

TABLE N68

PROPORTION OF FEMALE RATS WITH POLYCHROMASIA PRESENT
FINAL NECROPSY
3 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	6/50	3/49	2/47	5/47
COCHRAN-ARMITAGE	P=0.534			
FISHER'S EXACT TEST		P=0.254	P=0.155	P=0.544

TABLE N69

PROPORTION OF MALE RATS WITH ANISOCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	3/42	4/48	8/42	4/46
COCHRAN-ARMITAGE	P=0.496			
FISHER'S EXACT TEST		P=0.575	P=0.097	P=0.551

TABLE N70

PROPORTION OF MALE RATS WITH BASOPHILIC STIPPING PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/42	0/48	0/42	1/46
COCHRAN-ARMITAGE	P=0.213			
FISHER'S EXACT TEST		P=1.000	P=1.000	P=0.523

TABLE N71
PROPORTION OF MALE RATS WITH HOWELL-JOLLY BODIES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	6/42	2/48	9/42	11/46
COCHRAN-ARMITAGE	P=0.029			
FISHER'S EXACT TEST		P=0.095	P=0.285	P=0.192

TABLE N72

PROPORTION OF MALE RATS WITH MACROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	9/42	12/48	15/42	8/46
COCHRAN-ARMITAGE	P=0.293			
FISHER'S EXACT TEST		P=0.442	P=0.113	P=0.417

TABLE N73

PROPORTION OF MALE RATS WITH MICROCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	3/42	5/48	6/42	4/46
COCHRAN-ARMITAGE	P=0.559			
FISHER'S EXACT TEST		P=0.435	P=0.241	P=0.551

TABLE N74

PROPORTION OF MALE RATS WITH POIKILOCYTES PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	0/42	0/48	1/42	0/46
COCHRAN-ARMITAGE	P=0.781			
FISHER'S EXACT TEST		P=1.000	P=0.500	P=1.000

TABLE N75

PROPORTION OF MALE RATS WITH POLYCHROMASIA PRESENT
FINAL NECROPSY
5 DAY EXPOSURE

	DOSE			
	0	0.4	1	2.5
RATE	22/42	31/48	31/42	39/46
COCHRAN-ARMITAGE	P=0.001			
FISHER'S EXACT TEST		P=0.169	P=0.035	P=0.001

APPENDIX O

CLINICAL CHEMISTRY SUMMARY DATA

B6C3F1 MICE

APPENDIX O

CLINICAL CHEMISTRY--B6C3F1 MICE

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TABLE 01 ALBUMIN (g/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

ALBUMIN IN MALE MICE					ALBUMIN IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	19	2.99	0.12	-	0	27	3.05	0.10	-
0.4	25	3.10	0.09	104	0.4	38	3.24	0.04	106
1	24	3.11	0.11	104	1	30	3.16	0.05	103
2.5	22	**3.29	0.10	110	2.5	30	3.05	0.04	100
TREND(b)		+ (P=0.007)			TREND(b)		- (P=0.040)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE 02 ALKALINE PHOSPHATASE (IU/L) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

ALKALINE PHOSPHATASE IN MALE MICE					ALKALINE PHOSPHATASE IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	18	51.19	6.39	-	0	18	145.9	11.2	-
0.4	25	52.06	2.11	102	0.4	32	*111.3	6.4	76
1	23	*66.34	6.54	130	1	27	145.7	8.1	100
2.5	22	**77.67	9.60	152	2.5	25	129.1	7.1	89
TREND(b)		+ (P<0.001)			TREND(b)		+ (P=0.575)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE 03 ALT (IU/L) IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

ALT IN MALE MICE					ALT IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	21	75.47	11.51	-	0	30	181.15	99.65	-
0.4	28	97.43	18.92	129	0.4	38	57.45	4.50	32
1	24	104.63	18.70	139	1	34	70.33	10.71	39
2.5	24	129.13	25.50	171	2.5	33	90.31	18.52	50
TREND(b)		+ (P=0.149)			TREND(b)		+ (P=0.869)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE 04 AST (IU/L) IN MICE AT FINAL NECROPSY
IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

AST IN MALE MICE					AST IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	21	170.5	21.4	-	0	32	408.2	169	-
0.4	28	187.8	25.1	110	0.4	38	159.6	8.2	39
1	24	200.1	22.6	117	1	34	197.2	17.1	48
2.5	24	198.6	23.4	116	2.5	32	208.8	23.6	51
TREND(b)		+ (P=0.384)			TREND(b)		- (P=0.567)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE 05 TOTAL BILIRUBIN (mg/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

TOTAL BILIRUBIN IN MALE MICE					TOTAL BILIRUBIN IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	21	0.395	0.044	-	0	28	0.318	0.032	-
0.4	27	*0.307	0.030	78	0.4	38	0.263	0.011	83
1	23	**0.274	0.019	69	1	33	0.282	0.010	89
2.5	23	**0.248	0.019	63	2.5	33	0.279	0.009	88
TREND(b)		- (P<0.001)			TREND(b)		- (P=0.868)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

TABLE 06 UREA NITROGEN (mg/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

UREA NITROGEN IN MALE MICE					UREA NITROGEN IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	22	39.46	5.25	-	0	32	24.83	3.97	-
0.4	27	37.76	5.54	96	0.4	38	19.29	1.00	78
1	24	33.02	3.36	84	1	34	18.16	1.49	73
2.5	25	31.48	1.78	80	2.5	35	20.98	1.75	84
TREND(b)		- (P=0.594)			TREND(b)		+ (P=0.462)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE 07 CALCIUM (mg/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

CALCIUM IN MALE MICE					CALCIUM IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	20	9.86	0.18	-	0	27	9.73	0.05	-
0.4	26	9.47	0.21	96	0.4	38	9.65	0.06	99
1	23	9.62	0.17	98	1	33	*9.60	0.11	99
2.5	24	9.52	0.09	97	2.5	31	*9.54	0.05	98
TREND(b)		- (P=0.491)			TREND(b)		- (P=0.004)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE 08 CHLORIDE (meq/l) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

CHLORIDE IN MALE MICE					CHLORIDE IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	10	117.2	1.9	-	0	12	117.7	1.4	-
0.4	6	118.8	1.8	101	0.4	13	113.3	1.6	96
1	5	116.8	1.5	100	1	8	118.1	1.1	100
2.5	8	117.8	0.9	100	2.5	7	118.7	1.9	101
TREND(b)		+ (P=0.582)			TREND(b)		+ (P=0.323)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE 09 GGT (U/L) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

GGT IN MALE MICE					GGT IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	18	0.644	0.231	-	0	25	2.44	0.51	-
0.4	26	1.504	0.464	233	0.4	37	1.60	0.30	66
1	22	1.018	0.263	158	1	28	1.76	0.34	72
2.5	22	0.945	0.259	147	2.5	29	1.64	0.30	67
TREND(b)		+ (P=0.584)			TREND(b)		- (P=0.411)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE 010 PHOSPHORUS (mg/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

PHOSPHORUS IN MALE MICE					PHOSPHORUS IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	21	8.28	0.37	-	0	28	6.46	0.28	-
0.4	27	7.84	0.34	95	0.4	38	5.99	0.18	93
1	23	*7.27	0.25	88	1	34	6.35	0.25	98
2.5	24	7.47	0.20	90	2.5	33	6.31	0.23	98
TREND(b)		- (P=0.043)			TREND(b)		+ (P=0.882)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE 011 POTASSIUM (meq/l) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

POTASSIUM IN MALE MICE					POTASSIUM IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	5	6.58	0.94	-	0	5	4.28	0.19	-
0.4	3	5.67	0.24	86	0.4	6	4.08	0.24	95
1	3	6.50	0.20	99	1	2	5.50	0.30	129
2.5	4	5.80	0.41	88	2.5	1	4.90	(d)	114
TREND(b)		+ (P=0.959)			TREND(b)		+ (P=0.154)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE 012 SERUM GLUCOSE (mg/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

SERUM GLUCOSE IN MALE MICE					SERUM GLUCOSE IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	22	202.8	11.7	-	0	31	181.5	9.9	-
0.4	28	207.2	11.6	102	0.4	38	207.9	5.7	115
1	24	215.8	9.8	106	1	34	194.0	7.0	107
2.5	26	192.2	13.7	95	2.5	34	173.4	6.7	96
TREND(b)		- (P=0.618)			TREND(b)		- (P=0.027)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.
(d) No means calculated because less than 2 measurements were available.

TABLE 013 SODIUM (meq/l) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

SODIUM IN MALE MICE					SODIUM IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	5	152.4	1.6	-	0	5	146.3	2.1	-
0.4	3	154.7	0.3	101	0.4	6	142.0	3.7	97
1	3	152.1	1.7	100	1	2	147.3	4.7	101
2.5	4	152.4	1.3	100	2.5	1	141.1	(d)	96
TREND (b)		+ (P=0.876)			TREND (b)		- (P=0.516)		
TEST USED (c)		Dunn			TEST USED (c)		Dunn		

TABLE 014 TOTAL PROTEIN (g/dl) IN MICE AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE

TOTAL PROTEIN IN MALE MICE					TOTAL PROTEIN IN FEMALE MICE				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	20	5.85	0.23	-	0	27	5.76	0.09	-
0.4	26	6.00	0.18	103	0.4	38	5.93	0.07	103
1	23	5.98	0.21	102	1	31	5.86	0.07	102
2.5	22	6.02	0.18	103	2.5	30	5.99	0.08	104
TREND (b)		+ (P=0.770)			TREND (b)		+ (P=0.221)		
TEST USED (c)		Dunn			TEST USED (c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.
(d) No means calculated because less than 2 measurements were available.

APPENDIX P

CLINICAL CHEMISTRY SUMMARY DATA

F344 RATS

APPENDIX P

CLINICAL CHEMISTRY--F344 RATS

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TABLE P1 ALBUMIN (g/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ALBUMIN IN MALE RATS					ALBUMIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	3.99	0.04	-	0	10	5.18	0.20	-
0.4	10	3.97	0.04	100	0.4	9	4.86	0.10	94
1	10	3.99	0.05	100	1	10	4.98	0.15	96
2.5	10	3.97	0.07	100	2.5	9	4.97	0.15	96
TREND(b)		- (P=0.528)			TREND(b)		- (P=0.647)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P2 ALKALINE PHOSPHATASE (IU/L) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ALKALINE PHOSPHATASE IN MALE RATS					ALKALINE PHOSPHATASE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	136.1	5.4	-	0	10	115.9	10.5	-
0.4	10	137.4	5.6	101	0.4	10	129.5	8.0	112
1	10	138.6	5.7	102	1	10	*138.7	5.0	120
2.5	10	149.7	6.6	110	2.5	9	126.4	11.5	109
TREND(b)		+ (P=0.109)			TREND(b)		+ (P=0.146)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P3 ALBUMIN (g/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ALBUMIN IN MALE RATS					ALBUMIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	4.11	0.06	-	0	47	4.63	0.07	-
0.4	47	4.24	0.07	103	0.4	49	4.52	0.06	98
1	42	4.33	0.10	105	1	46	4.52	0.06	98
2.5	46	4.25	0.07	103	2.5	47	**4.47	0.07	97
TREND(b)		+ (P=0.326)			TREND(b)		- (P=0.008)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE P4 ALKALINE PHOSPHATASE (IU/L) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ALKALINE PHOSPHATASE IN MALE RATS					ALKALINE PHOSPHATASE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	147.3	11.9	-	0	41	74.27	3.47	-
0.4	48	129.8	8.5	88	0.4	44	77.61	4.01	104
1	42	145.8	11.0	99	1	42	80.72	3.75	109
2.5	46	153.1	14.1	104	2.5	42	**90.31	4.69	122
TREND(b)		+ (P=0.611)			TREND(b)		+ (P=0.002)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P5 ALT (IU/L) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
ALT IN MALE RATS					ALT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	126.04	23.69	-	0	10	90.60	12.42	-
0.4	10	102.37	6.79	81	0.4	10	77.56	4.68	86
1	10	*87.09	7.19	69	1	10	93.14	9.32	103
2.5	10	87.51	6.62	69	2.5	9	68.09	5.37	75
TREND(b)		- (P=0.030)			TREND(b)		- (P=0.401)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P6 AST (IU/L) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
AST IN MALE RATS					AST IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	168.0	35.3	-	0	10	153.3	14.3	-
0.4	10	147.9	11.2	88	0.4	10	157.1	22.3	102
1	10	127.0	10.5	76	1	10	202.0	29.6	132
2.5	10	138.9	11.9	83	2.5	9	122.4	9.4	80
TREND(b)		- (P=0.415)			TREND(b)		- (P=0.523)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P9 TOTAL BILIRUBIN (mg/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL BILIRUBIN IN MALE RATS					TOTAL BILIRUBIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	0.211	0.011	-	0	10	0.330	0.026	-
0.4	10	0.200	0.000	95	0.4	10	0.310	0.028	94
1	10	0.200	0.015	95	1	10	0.310	0.028	94
2.5	10	0.210	0.010	99	2.5	9	0.256	0.018	77
TREND(b)		- (P=0.981)			TREND(b)		- (P=0.073)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P10 UREA NITROGEN (mg/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
UREA NITROGEN IN MALE RATS					UREA NITROGEN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	15.43	0.44	-	0	10	14.73	0.58	-
0.4	10	16.43	0.28	106	0.4	10	14.89	0.56	101
1	10	15.89	0.30	103	1	10	**16.92	0.28	115
2.5	10	15.87	0.38	103	2.5	9	15.38	0.63	104
TREND(b)		- (P=0.841)			TREND(b)		+ (P=0.172)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P7 ALT (IU/L) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE: ALT IN MALE RATS					3 DAY EXPOSURE: ALT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	70.88	5.67	-	0	47	88.04	16.56	-
0.4	48	73.27	9.31	103	0.4	49	69.98	4.52	79
1	42	61.95	4.39	87	1	46	65.37	2.39	74
2.5	46	81.35	13.83	115	2.5	47	102.94	21.91	117
TREND (b)		+ (P=0.656)			TREND (b)		+ (P=0.067)		
TEST USED (c)		Dunn			TEST USED (c)		Shirley		

TABLE P8 AST (IU/L) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE: AST IN MALE RATS					3 DAY EXPOSURE: AST IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	117.4	12.6	-	0	47	264.1	92.9	-
0.4	48	119.8	12.0	102	0.4	49	130.5	7.9	49
1	42	109.2	8.1	93	1	46	126.5	9.6	48
2.5	46	145.6	32.3	124	2.5	47	228.9	68.2	87
TREND (b)		+ (P=0.311)			TREND (b)		+ (P=0.935)		
TEST USED (c)		Dunn			TEST USED (c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P11 TOTAL BILIRUBIN (mg/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL BILIRUBIN IN MALE RATS					TOTAL BILIRUBIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	0.388	0.021	-	0	47	0.415	0.088	-
0.4	48	0.419	0.022	108	0.4	49	0.261	0.010	63
1	42	0.450	0.061	116	1	46	0.313	0.041	75
2.5	46	**0.407	0.064	105	2.5	47	**0.413	0.164	99
TREND(b)		- (P=0.002)			TREND(b)		- (P=0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P12 UREA NITROGEN (mg/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
UREA NITROGEN IN MALE RATS					UREA NITROGEN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	16.90	0.48	-	0	47	15.54	0.39	-
0.4	48	17.21	0.67	102	0.4	49	15.16	0.33	98
1	42	17.35	0.90	103	1	46	15.63	0.28	101
2.5	46	*16.29	0.83	96	2.5	47	**17.92	0.44	115
TREND(b)		- (P=0.047)			TREND(b)		+ (P<0.001)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P13 CALCIUM (mg/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
CALCIUM IN MALE RATS					CALCIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	10.79	0.06	-	0	10	11.43	0.43	-
0.4	10	10.63	0.08	99	0.4	10	11.18	0.14	98
1	10	*10.55	0.06	98	1	10	11.34	0.29	99
2.5	10	**10.44	0.12	97	2.5	9	11.41	0.19	100
TREND(b)		- (P=0.004)			TREND(b)		- (P=0.513)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P14 CHLORIDE (meq/l) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
CHLORIDE IN MALE RATS					CHLORIDE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	101.44	0.50	-	0	10	100.1	0.7	-
0.4	10	100.30	0.80	99	0.4	9	101.0	0.9	101
1	10	100.70	0.86	99	1	10	100.9	0.5	101
2.5	10	99.40	0.91	98	2.5	9	101.4	0.8	101
TREND(b)		- (P=0.168)			TREND(b)		+ (P=0.086)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P15 CALCIUM (mg/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
CALCIUM IN MALE RATS					CALCIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	10.73	0.15	-	0	47	11.00	0.08	-
0.4	47	11.43	0.35	106	0.4	49	10.80	0.09	98
1	42	11.13	0.21	104	1	46	10.81	0.09	98
2.5	46	10.94	0.13	102	2.5	47	*10.77	0.09	98
TREND(b)		- (P=0.964)			TREND(b)		- (P=0.035)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

TABLE P16 CHLORIDE (meq/l) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
CHLORIDE IN MALE RATS					CHLORIDE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	101.1	0.6	-	0	47	102.3	0.5	-
0.4	47	100.6	0.5	100	0.4	49	102.1	0.4	100
1	42	101.7	0.5	101	1	46	101.2	0.5	99
2.5	46	100.5	0.6	99	2.5	47	102.6	0.6	100
TREND(b)		- (P=0.661)			TREND(b)		- (P=0.676)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P17 GGT (U/L) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
GGT IN MALE RATS					GGT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	4.19	0.41	-	0	10	5.35	1.86	-
0.4	10	3.28	0.46	78	0.4	10	3.24	0.34	61
1	10	3.81	0.33	91	1	10	3.56	0.29	67
2.5	10	3.36	0.34	80	2.5	9	3.29	0.74	61
TREND(b)		- (P=0.229)			TREND(b)		- (P=0.752)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P18 PHOSPHORUS (mg/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
PHOSPHORUS IN MALE RATS					PHOSPHORUS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	5.87	0.19	-	0	10	4.61	0.40	-
0.4	10	6.24	0.26	106	0.4	10	4.23	0.32	92
1	10	6.26	0.14	107	1	10	4.65	0.30	101
2.5	10	6.33	0.23	108	2.5	9	4.28	0.40	93
TREND(b)		+ (P=0.214)			TREND(b)		- (P=0.669)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P19 GGT (U/L) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE: GGT IN MALE RATS					3 DAY EXPOSURE: GGT IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	7.24	0.97	-	0	47	5.56	0.78	-
0.4	48	*5.30	0.59	73	0.4	49	4.33	0.36	78
1	42	**4.87	0.62	67	1	46	3.67	0.31	66
2.5	46	*5.50	0.76	76	2.5	46	4.10	0.38	74
TREND(b)		- (P=0.011)			TREND(b)		- (P=0.103)		
TEST USED(c)		Shirley			TEST USED(c)		Dunn		

TABLE P20 PHOSPHORUS (mg/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE: PHOSPHORUS IN MALE RATS					3 DAY EXPOSURE: PHOSPHORUS IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	5.04	0.18	-	0	47	4.29	0.13	-
0.4	48	5.28	0.17	105	0.4	49	4.21	0.13	98
1	42	5.40	0.25	107	1	46	4.30	0.13	100
2.5	46	5.17	0.12	103	2.5	47	4.43	0.13	103
TREND(b)		+ (P=0.250)			TREND(b)		+ (P=0.398)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P21 POTASSIUM (meq/l) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
POTASSIUM IN MALE RATS					POTASSIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	5.78	0.11	-	0	10	5.18	0.12	-
0.4	10	5.98	0.17	104	0.4	9	5.34	0.13	103
1	10	5.95	0.10	103	1	10	5.78	0.28	112
2.5	10	6.23	0.34	108	2.5	9	5.41	0.37	104
TREND(b)		+ (P=0.088)			TREND(b)		+ (P=0.753)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P22 SERUM GLUCOSE (mg/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SERUM GLUCOSE IN MALE RATS					SERUM GLUCOSE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	204.6	4.7	-	0	10	174.9	3.5	-
0.4	10	188.4	5.9	92	0.4	10	183.3	5.2	105
1	10	190.7	6.0	93	1	10	177.9	6.3	102
2.5	10	185.1	7.6	90	2.5	9	171.9	6.4	98
TREND(b)		- (P=0.067)			TREND(b)		- (P=0.328)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P23 POTASSIUM (meq/l) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
POTASSIUM IN MALE RATS					POTASSIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	5.43	0.09	-	0	44	5.24	0.13	-
0.4	47	5.51	0.13	102	0.4	47	5.11	0.09	98
1	42	5.40	0.11	100	1	46	5.13	0.09	98
2.5	46	5.50	0.10	101	2.5	45	5.28	0.09	101
TREND(b)		+ (P=0.865)			TREND(b)		+ (P=0.141)		
TEST USED(c)		Dunn			TEST USED(c)		Dunn		

TABLE P24 SERUM GLUCOSE (mg/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SERUM GLUCOSE IN MALE RATS					SERUM GLUCOSE IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	194.3	2.6	-	0	47	165.4	3.9	-
0.4	48	*181.0	4.0	93	0.4	49	170.0	3.7	103
1	42	188.2	4.0	97	1	46	164.9	3.5	100
2.5	46	183.4	4.9	94	2.5	47	**146.4	3.2	88
TREND(b)		- (P=0.270)			TREND(b)		- (P<0.001)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P25 SODIUM (meq/l) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SODIUM IN MALE RATS					SODIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	144.9	0.4	-	0	10	145.4	0.4	-
0.4	10	144.5	0.5	100	0.4	9	145.7	0.7	100
1	10	145.5	0.3	100	1	10	146.0	1.6	100
2.5	10	145.1	0.4	100	2.5	9	144.0	0.3	99
TREND(b)		+ (P=0.606)			TREND(b)		- (P=0.053)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P26 TOTAL PROTEIN (g/dl) IN RATS AT THE INTERIM NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL PROTEIN IN MALE RATS					TOTAL PROTEIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	9	6.47	0.07	-	0	10	7.90	0.23	-
0.4	10	6.38	0.05	99	0.4	10	7.45	0.13	94
1	10	6.35	0.09	98	1	10	7.71	0.18	98
2.5	10	6.28	0.09	97	2.5	9	7.44	0.22	94
TREND(b)		- (P=0.051)			TREND(b)		- (P=0.223)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

TABLE P27 SODIUM (meq/l) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
SODIUM IN MALE RATS					SODIUM IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	146.0	0.2	-	0	44	144.0	0.3	-
0.4	47	147.0	0.2	101	0.4	47	144.0	0.2	100
1	42	*145.4	0.2	100	1	46	143.5	0.2	100
2.5	46	**145.1	0.2	99	2.5	45	*143.5	0.2	100
TREND(b)		- (P<0.001)			TREND(b)		- (P=0.010)		
TEST USED(c)		Shirley			TEST USED(c)		Shirley		

TABLE P28 TOTAL PROTEIN (g/dl) IN RATS AT FINAL NECROPSY IN THE CHRONIC TEST OF CHLORINE

5 DAY EXPOSURE					3 DAY EXPOSURE				
TOTAL PROTEIN IN MALE RATS					TOTAL PROTEIN IN FEMALE RATS				
DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)	DOSE PPM	NUMBER	MEAN	S.E.	RATIO (a)
0	42	6.59	0.08	-	0	47	7.45	0.09	-
0.4	47	6.85	0.10	104	0.4	49	7.30	0.08	98
1	42	6.84	0.14	104	1	46	7.34	0.08	99
2.5	46	6.66	0.09	101	2.5	47	**7.20	0.09	97
TREND(b)		- (P=0.923)			TREND(b)		- (P=0.003)		
TEST USED(c)		Dunn			TEST USED(c)		Shirley		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) (Dosed group mean / Control group mean) x 100.
(b) Direction and significance of trend (Jonckheere's test).
(c) Multiple comparisons test comparing dose group to control group.

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A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats

Volume 2 of 2

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APPENDIX Q

EPL HISTOPATHOLOGY REPORT - B6C3F1 MICE

RISK ASSESSMENT STUDY OF CHLORINE IN MICE
STUDY NUMBER 8437
EPL PROJECT NUMBER 304-338

PATHOLOGY SUMMARY

A histopathologic examination of tissues was performed to establish the health risk, including carcinogenicity, associated with the chronic inhalation of Chlorine in B6C3F1 mice. The mice were exposed for six hours a day, five days a week, for 104 weeks. The experimental design of the study is outlined as follows:

Dose Group	Number of Animals	Sex	Target Concentration (ppm) Chlorine
1	67	Male	0.000
2	70	Male	0.400
3	70	Male	1.000
4	70	Male	2.500
1	70	Female	0.000
2	70	Female	0.400
3	70	Female	1.000
4	70	Female	2.500

Two hundred and seventy-seven males and 280 females were included in the study. Surviving mice were sacrificed after 24 months. Two hundred and sixty-three males and 250 females received a necropsy examination and were available for histopathological evaluation.

According to the protocol the following tissues were examined: brain, spinal cord, pituitary gland, thyroid gland, parathyroid gland, larynx, trachea, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, salivary gland, mandibular lymph node, mesen-

teric lymph node, thymus, spleen, heart, aorta, tongue, liver, kidneys, adrenal glands, lungs, seminal vesicle, prostate, testes, epididymis, ovaries, oviducts, uterus, urinary bladder, eyes and optic nerves, Harderian gland, skin, mammary gland, skeletal muscle, sciatic nerve, bone-femur, bone-sternum, bone marrow, ear canal, nose-5 levels, gross lesions. All of the above tissues were examined in all control and Group 4 mice. Only target tissues (noses at 5 levels) and gross lesions were examined in Groups 2 and 3 mice.

In general all tissues as specified in the protocol were represented in the sections. A few tissues were apparently inadvertently missed at the time of necropsy or lost during histologic processing. Varying degrees of autolysis were evident microscopically in tissues from a number of mice that died prior to sacrifice. In a few tissues, such as the nasal cavities and those from the gastrointestinal tract, autolysis was of such a degree that critical evaluation or identification of the tissue was difficult. These factors, however, did not affect the overall evaluation of the study. There were inconsistencies in the sectioning of the nasal cavity such that there was variability in the region of the nose examined for any given nose level. However, wide variability in the nose levels from one animal to the other occurred in relatively few animals, and did not affect the interpretation of treatment-related lesions.

Hematoxylin and eosin stained slides of the protocol-required tissues were prepared by EPL, from tissues fixed, trimmed, and decalcified where necessary, by CIIT. Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. Inflammatory, degenerative, and hyperplastic changes were graded 1 to 5 depending upon severity, neoplasms were designated as present (P) on the Histopathology Incidence Tables. Tissues that were severely autolyzed and could not be evaluated are indicated with an "A" only. All lesions are summarized by treatment group in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. All neoplasms are also listed in the same manner in the Neoplasm Summary Incidence Tables.

A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change(s), if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Worksheets prepared at the time of the necropsies: these gross lesion tables were available when tissues were trimmed for histology. Microscopic findings were generally not given for gross observations relating to nutritional condition, fluid in body cavities, or discharges from orifices.

RESULTS

Early deaths and moribund sacrifices occurred with more or less equal frequency among control mice and treated mice of each sex. Survival to the terminal sacrifice was greater in females than males for all groups including the control group.

Treatment-related histomorphologic lesions occurred only in the nasal cavities of male and female mice at all dose levels. The following tables summarize, by dose and sex, the principal nasal lesions occurring at each of the nasal levels.

In section 1 of the nasal cavity, the three most frequent treatment-related lesions were hyperplasia, microabscesses and eosinophilic globules, involving, in each case, the squamous epithelium. Hyperplasia and microabscesses occurred in the control groups of both sexes but at a lower incidence and severity. Eosinophilic globule inclusions in the cytoplasm of squamous epithelial cells were noted in only one control female and in none of the control males. The overall incidence of treatment-related lesions at this level was similar for both sexes.

Selected Treatment-Related Lesions
Nose Level 1 - Males

	Group 1	Group 2	Group 3	Group 4
No. Examined	58	65	68	55
Squamous Epithelium, Hyperplasia	16(28%)	51(78%)	57(84%)	43(78%)
Squamous Epithelium, Microabscesses	6(10%)	22(34%)	15(22%)	15(27%)
Squamous Epithelium, Eosinophilic Globules	0(0%)	6(9%)	8(12%)	9(16%)

Selected Treatment-Related Lesions
Nose Level 1 - Females

	Group 1	Group 2	Group 3	Group 4
No. Examined	60	66	58	57
Squamous Epithelium, Hyperplasia	30(50%)	58(88%)	53(91%)	46(81%)
Squamous Epithelium, Microabscesses	9(15%)	20(30%)	16(28%)	15(26%)
Squamous Epithelium, Eosinophilic Globules	1(2%)	11(17%)	5(9%)	15(26%)

Section 2 of the nasal cavity contained treatment-related lesions in areas of ciliated and nonciliated respiratory epithelium. Eosinophilic globules and transitional metaplasia were present in both epithelial areas in male and female animals. Squamous metaplasia and inflammation, both involving nonciliated respiratory epithelium, exhibited treatment-related incidence trends in females only. The diagnosis of transitional metaplasia was applied to instances of mild or early epithelial metaplasia which had not progressed to the extent of forming demonstrable squamous cells.

Selected Treatment-Related Lesions
Nose Level 2 - Males

	Group 1	Group 2	Group 3	Group 4
No. Examined	60	62	65	62
Respiratory Epithelium, Ciliated, Eosinophilic Globules	0(0%)	3(5%)	15(23%)	12(19%)
Respiratory Epithelium, Ciliated, Transitional Metaplasia	0(0%)	3(5%)	12(23%)	15(24%)
Respiratory Epithelium, Nonciliated, Eosinophilic Globules	1(2%)	4(6%)	26(40%)	39(63%)
Respiratory Epithelium, Nonciliated, Transitional Metaplasia	10(17%)	27(44%)	31(48%)	38(61%)
Respiratory Epithelium, Nonciliated, Squamous Metaplasia	12(20%)	10(16%)	22(34%)	14(23%)
Respiratory Epithelium, Nonciliated, Inflammation	1(2%)	1(2%)	3(5%)	1(2%)

Selected Treatment-Related Lesions
Nose Level 2 - Females

	Group 1	Group 2	Group 3	Group 4
No. Examined	60	63	54	57
Respiratory Epithelium, Ciliated, Eosinophilic Globules	12(20%)	9(14%)	7(13%)	21(37%)
Respiratory Epithelium, Ciliated, Transitional Metaplasia	2(3%)	3(5%)	2(4%)	8(14%)
Respiratory Epithelium, Nonciliated, Eosinophilic Globules	8(13%)	35(56%)	48(89%)	43(75%)
Respiratory Epithelium, Nonciliated, Transitional Metaplasia	5(8%)	29(46%)	47(87%)	22(39%)
Respiratory Epithelium, Nonciliated, Squamous Metaplasia	0(0%)	4(6%)	1(2%)	24(42%)
Respiratory Epithelium, Nonciliated, Inflammation	5(8%)	5(8%)	8(15%)	15(26%)

In section 3 of the nasal cavity, treatment-related incidence trends were present in both sexes in areas of olfactory epithelium. The lesions consisted of atrophy and eosinophilic globules. In areas of ciliated respiratory epithelium, eosinophilic globules and transitional metaplasia exhibited treatment-related incidence trends in both sexes. In females, luminal exudate and eosinophilic globules in the submucosal mucous glands in areas of ciliated respiratory epithelium occurred more frequently in treated groups.

Selected Treatment-Related Lesions
Nose Level 3 - Males

	Group 1	Group 2	Group 3	Group 4
No. Examined	60	66	67	62
Respiratory Epithelium, Ciliated, Eosinophilic Globules	0(0%)	6(9%)	37(55%)	50(81%)
Respiratory Epithelium, Ciliated, Transitional Metaplasia	1(2%)	3(5%)	13(19%)	30(48%)
Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules	0(0%)	1(2%)	3(4%)	0(0%)
Olfactory Epithelium, Atrophy	8(13%)	8(12%)	19(28%)	26(42%)
Olfactory Epithelium, Eosinophilic Globules	2(3%)	7(11%)	18(27%)	22(35%)
Luminal Exudate	1(2%)	3(5%)	5(7%)	4(6%)

Selected Treatment-Related Lesions
Nose Level 3 - Females

	Group 1	Group 2	Group 3	Group 4
No. Examined	63	66	58	56
Respiratory Epithelium, Ciliated, Eosinophilic Globules	27(43%)	25(38%)	47(81%)	42(75%)
Respiratory Epithelium, Ciliated, Transitional Metaplasia	1(2%)	1(2%)	4(7%)	11(20%)
Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules	2(3%)	4(6%)	19(33%)	11(20%)
Olfactory Epithelium, Atrophy	2(3%)	14(21%)	12(21%)	22(39%)
Olfactory Epithelium, Eosinophilic Globules	17(27%)	24(36%)	42(72%)	18(32%)
Luminal Exudate	3(5%)	4(6%)	7(12%)	11(20%)

Section 4 of the nasal cavity contained a similar range of lesions to those reported for section 3. Eosinophilic globules in ciliated respiratory epithelium and olfactory epithelium, in addition to olfactory epithelial atrophy, were prevalent in both sexes at level 4. Two changes - luminal exudate and eosinophilic globules in submucosal mucous glands - occurred at elevated incidences in females but not in males.

Selected Treatment-Related Lesions
Nose Level 4 - Males

	Group 1	Group 2	Group 3	Group 4
No. Examined	61	66	68	62
Respiratory Epithelium, Ciliated, Eosinophilic Globules	2(3%)	4(6%)	15(22%)	34(55%)
Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules	1(2%)	2(3%)	5(7%)	4(6%)
Olfactory Epithelium, Atrophy	0(0%)	3(5%)	11(16%)	28(44%)
Olfactory Epithelium, Eosinophilic Globules	1(2%)	1(2%)	9(13%)	31(50%)
Luminal Exudate	1(2%)	1(2%)	2(3%)	0(0%)

Selected Treatment-Related Lesions
Nose Level 4 - Females

	Group 1	Group 2	Group 3	Group 4
No. Examined	63	66	58	56
Respiratory Epithelium, Ciliated, Eosinophilic Globules	18(29%)	6(9%)	20(34%)	35(63%)
Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules	2(3%)	4(6%)	9(16%)	26(46%)
Olfactory Epithelium, Atrophy	3(5%)	10(15%)	14(24%)	19(34%)
Olfactory Epithelium, Eosinophilic Globules	10(16%)	9(14%)	29(50%)	43(77%)
Luminal Exudate	1(2%)	4(6%)	7(12%)	10(18%)

In section 5 of the nasal cavity, atrophy and eosinophilic globules occurred in both sexes. The incidences of these lesions were higher in females, being comparable to those observed at level 4. In males, however, the incidence of olfactory epithelial atrophy and eosinophilic globules decreased sharply between levels 4 and 5. Cystic degeneration of Bowman's glands occurred adjacent to lesions of olfactory epithelial atrophy. The highest incidence of this change occurred in high-dose females.

Selected Treatment-Related Lesions
Nose Level 5 - Males

	Group 1	Group 2	Group 3	Group 4
No. Examined	61	66	64	60
Respiratory Epithelium, Ciliated, Eosinophilic Globules	0(0%)	0(0%)	2(3%)	3(5%)
Olfactory Epithelium, Atrophy	1(2%)	3(5%)	9(14%)	6(10%)
Olfactory Epithelium, Eosinophilic Globules	0(0%)	0(0%)	2(3%)	5(8%)
Olfactory Epithelium, Bowman's Glands, Degeneration, Cystic	0(0%)	1(2%)	5(8%)	4(7%)
Luminal Exudate	0(0%)	4(6%)	2(3%)	7(12%)

Selected Treatment-Related Lesions
Nose Level 5 - Females

	Group 1	Group 2	Group 3	Group 4
No. Examined	62	64	58	56
Respiratory Epithelium, Ciliated, Eosinophilic Globules	4(6%)	1(2%)	1(2%)	9(16%)
Olfactory Epithelium, Atrophy	0(0%)	8(13%)	13(22%)	25(45%)
Olfactory Epithelium, Eosinophilic Globules	0(0%)	2(3%)	3(5%)	19(34%)
Olfactory Epithelium, Bowman's Glands, Degeneration, Cystic	0(0%)	2(3%)	4(7%)	22(39%)
Luminal Exudate	2(3%)	4(6%)	7(12%)	22(39%)

A number of other lesions occurred sporadically in the nasal cavity of treated and control animals. These were not considered to be treatment related. No primary neoplasms of the nasal cavity were observed in any treated or control animals.

A variety of nonneoplastic spontaneous lesions and incidental findings occurred in various organs and tissues. These lesions were of the usual number and type commonly diagnosed in B6C3F1 mice of this age, and occurred for the most part, at comparable incidences in control and treated mice.

Ovarian abscesses and suppurative inflammation of the uterus occurred at an incidence of 39% and 28%, respectively, in the high dose group. A smaller proportion of the low and mid-dose animals were

affected with these lesions. In the control group, a single animal was diagnosed with suppurative inflammation of the uterus. Ovarian abscesses were not observed in this group. These lesions of the reproductive tract were attributed to the infectious condition described by Rao et al. (1987) and frequently associated with Klebsiella sp.

Various neoplasms common in B6C3F1 mice of this age occurred at comparable incidences in control and treated rats. Those which occurred most frequently included hepatocellular adenomas and carcinomas, bronchiolar alveolar adenomas and carcinomas, thyroid adenomas and pituitary adenomas of the pars anterior.

CONCLUSION

Inhalation of Chlorine at dose levels from 0.4 to 2.5 ppm by B6C3F1 mice for two years resulted in nonneoplastic changes confined to the nasal cavity. The most significant changes were the presence of eosinophilic intracytoplasmic inclusions in squamous, respiratory and olfactory epithelium; hyperplasia of squamous epithelium (level 1), metaplasia (transitional and squamous) of ciliated and nonciliated respiratory epithelium; and atrophy of olfactory epithelium. The treatment-related lesions occurred at all levels of the nose but were most severe at levels 3 and 4 of the nasal cavity.

for Jerry F. Hardisty DVM
M. GARY I. RILEY, M.V.Sc., Ph.D.
Pathologist

April 28, 1992
Date

REFERENCE

Rao, G.N., Hickman, R.L., Seilkop, S.K. and Boorman, G.A. (1987) Utero-ovarian infection in aged B6C3F1 mice. Lab Animal Sci. 37, 153-158.

APPENDIX R

EPL HISTOPATHOLOGY REPORT - F344 RATS

APPENDIX R1a

PATHOLOGY SUMMARY

F344 RATS

FEMALES

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY STUDY NUMBER 8436

RISK ASSESSMENT STUDY OF CHLORINE IN RATS

PATHOLOGY SUMMARY

EPL PROJECT NUMBER 304-337

A histopathologic examination of tissues was performed to establish the health risk, including carcinogenicity, associated with the chronic inhalation of chlorine in female Fischer 344 rats. Rats were exposed for six hours per day, three days per week, for 104 weeks. The experimental design of the study is outlined as follows:

		Total Number of Females Examined	
Group	Concentration (ppm)	Interim Sacrifice/ Moribund Sacrifice and Deaths	Final Sacrifice/ Moribund Sacrifice and Deaths
1	Control	10/1	50/8
2	0.400	10/0	49/9
3	1.000	10/0	48/10
4	2.500	10/1	48/11

Ten animals from each of the four treatment groups were sacrificed after 12 months on the study. Tissues from these rats as well as those that died prior to 12 months were examined and tabulated together.

The surviving female rats were sacrificed after 24 months and examined microscopically. All female rats that died or were sacrificed in a moribund condition after the 12-month sacrifice and prior to the 24-month sacrifice were also evaluated.

According to the protocol the following tissues were examined: brain, spinal cord, pituitary gland, thyroid gland (2), parathyroid, larynx, trachea, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, salivary gland, mandibular lymph node, mesenteric lymph node, thymus, spleen, heart, aorta, tongue, liver (2), kidney (2), adrenal gland (2), lung (5), ovary (2), oviduct (2), uterus, urinary bladder, eye (2), optic nerve (2), harderian gland (2), skin, mammary gland, skeletal muscle, sciatic nerve, bone (femur), bone (sternum), bone marrow (femur), bone marrow (sternum), ear canal (2), nose (5 levels), and gross lesions or tissue masses with adjacent tissue. All of the above tissues were examined in all control rats and Group 4 rats. Only target tissues (noses at five levels) and gross lesions were examined in Groups 2 and 3 rats.

In general, all tissues as specified in the protocol were represented in the sections. A few tissues were apparently inadvertently missed at the time of necropsy or lost during histologic processing. Varying degrees of autolysis were evident microscopically in tissues from a number of rats that died prior to sacrifice. In a few tissues, such as the nasal cavities and those from the gastrointestinal tract, autolysis was of such a degree that critical evaluation or identification of the tissue was difficult. These factors, however, did not affect the overall evaluation of the study. There were inconsistencies in the sectioning of the nasal cavity such that there was variability in the region of the nose examined for any given nose level. However, wide variability in the nose levels from one animal to the other occurred in relatively few animals,

and these inconsistencies did not affect the interpretation of treatment-related lesions.

Hematoxylin and eosin stained slides of the protocol required tissues were prepared by Experimental Pathology Laboratories, Inc. Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. Inflammatory, degenerative, and hyperplastic changes were graded 1 to 5 depending upon severity; neoplasms, cysts, developmental anomalies, and other nongradable changes were designated as present (P) on the Histopathology Incidence Tables. Tissues that were autolyzed to a moderate degree but could be evaluated for lesions are tabulated with the diagnosis and an "A" to indicate autolysis. Those that were severely autolyzed and could not be evaluated are indicated with an "A" only. All lesions are summarized by treatment group in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. All neoplasms are also listed in the same manner in the Neoplasm Summary Incidence Tables. Lesions in the nasal cavity are presented by severity in the Summary Incidence Tables (By Severity).

A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time of the necropsies; these gross lesion tables were available when tissues were trimmed for histology. Microscopic findings were generally not given for gross observations

relating to nutritional condition, fluid in body cavities, or discharges from orifices.

RESULTS

12-Month Interim Sacrifice and Deaths

Female Rats

There was one early death among treated Group 4 female rats and one early death among the control female rats. No treatment-related neoplastic or hyperplastic lesions were observed, and the only treatment-related microscopic changes were in the nasal cavity.

Treatment-related histopathologic lesions occurred in the nasal cavities of female rats sacrificed at 12 months. An increased number of goblet cells and subacute inflammation (consisting mainly of scattered neutrophils) were noted in sections 1 and 2 of the nasal cavity when compared with controls. In sections 3, 4, and 5 of the nasal cavity, a treatment-related incidence and severity of eosinophilic (hyalinized) globules were observed in the cytoplasm of the glandular (no glandular epithelial changes in nose 5), respiratory, and olfactory epithelial cells. The olfactory epithelium appeared to be the most severely affected in most rats; however, the proportion of nasal mucosa covered by olfactory and respiratory epithelium in respective sections of the nasal cavity had some influence on overall microscopic severity evaluations. Goblet cell hyperplasia was evident when treated nasal cavities were compared with controls. Inflammation was not evident in the posterior sections of the treated nasal cavity as noted in anterior nasal sections (1 and 2).

Microscopic changes were not evident in the remainder of the respiratory tract (larynx, trachea, and lungs) when treated rats were compared with controls.

A variety of spontaneous lesions and incidental findings occurred in various organs and tissues. These occurred, for the most part, at comparable incidences in control and treated rats. They included such changes as cardiomyopathy; pigmentation of tubular epithelium and chronic nephropathy in the kidney; peribronchial/peribronchiolar mononuclear cell foci, granulomas (focal), and alveolar macrophage accumulations in the lung; ovarian cysts; bile duct hyperplasia and chronic hepatitis in the liver; increased plasma cells and reticuloendothelial hyperplasia in lymph nodes; and extramedullary hematopoiesis and pigmentation in the spleen.

Increased plasma cells in the mandibular lymph node of a number of rats probably reflected the trauma and related reaction that occurred with ear tagging.

Only a few neoplasms were found in the interim sacrificed females, and all were considered incidental findings. A glioma was noted in the brain of one Group 1 (control) female, and an endometrial stromal polyp was found in one Group 2 female uterus and in one Group 4 female uterus.

Terminal Sacrifice and Deaths

Female Rats

Early deaths and/or animals sacrificed in a moribund condition occurred with more or less equal frequency among control rats

and treated rats. Eight control (Group 1), nine Group 2, ten Group 3, and eleven Group 4 (high dose) females died or were sacrificed in a moribund condition.

Treatment-related histomorphologic lesions occurred in the nasal cavities of female rats at all dose levels sacrificed at 24 months. In section 1 of the nasal cavity, the incidence of microscopic observations (subacute inflammation and goblet cell hyperplasia) was similar in all groups; however, subacute inflammation was noted in five Group 4 females compared to two Group 1 females. The incidence of goblet cell hyperplasia was similar in controls and treated groups. Vascular thrombi were noted only in nasal cavities of females that died, and an ulcer was found in the mucosa of one Group 2 female that died.

In section 2 of the nasal cavity, goblet cell hyperplasia was the most prominent treatment-related microscopic finding. The incidence was higher in all treated groups (45 of 58 for Group 2, 52 of 57 for Group 3, and 52 of 57 for Group 4) than in controls (9 of 58), and the severity of goblet cell hyperplasia demonstrated a dose-related trend [see Summary Incidence Tables (By Severity)]. Eosinophilic globules in glandular epithelium were noted only in a few Group 2 and Group 3 rats, but a dose-relationship was not evident. A dose-related incidence or severity of eosinophilic globules also was not evident in respiratory epithelium. Subacute inflammation was evident in more Group 4 rats than in controls, and the exudate (serous or mucopurulent) in the nasal cavity was observed more frequently in Group 4

rats than in controls. The incidence and severity of other nasal cavity observations in nose 2 sections were considered incidental findings.

In section 3 of the nasal cavity, the incidence and severity of goblet cell hyperplasia and eosinophilic globules in the respiratory and olfactory epithelium suggested a dose-relationship. The severity of eosinophilic globules was greatest in the olfactory epithelium in all groups; the least difference in the severity of eosinophilic globules was in the glandular epithelium when treated and control nose 3 sections were compared [see Summary Incidence Tables (By Severity)]. Mucopurulent exudate was noted in the nasal cavities of two Group 4 females. The other nasal cavity findings (epithelial microabscesses and inflammation in the nasolacrimal duct) were considered incidental findings.

In sections 4 and 5 of the nasal cavity, goblet cell hyperplasia and eosinophilic globules in respiratory, olfactory, and glandular epithelium were treatment-related when control and treated groups were compared. This trend was evident in the incidence and severity of lesions [see Summary Incidence Tables (By Severity)]. As in nose 3 the more severe changes (eosinophilic globules) were in the cytoplasm of the olfactory epithelium.

Other lesions of the nasal cavity occurred sporadically and with some frequency among control and treated rats and were not treatment-related. A squamous cell carcinoma was present in the oral cavity of one Group 3 female and on the tongue of one Group 3 female and in the oral cavity of one Group 4 female.

A variety of non-neoplastic spontaneous lesions and incidental findings occurred in various organs and tissues. These lesions were of the usual number and type commonly diagnosed in female Fischer 344 rats of this age and occurred, for the most part, at comparable incidences in control and treated rats.

Various neoplasms common in Fischer 344 rats of this age occurred at comparable incidences in control and treated rats. Those which occurred most frequently included mononuclear cell leukemia, endometrial stromal polyps, adenomas of the pars distalis of the pituitary gland, pheochromocytomas of the adrenal medulla, and hepatocellular adenomas.

CONCLUSIONS

Inhalation of chlorine by Fischer 344 female rats for 12 months resulted in changes in the nasal cavity. The most significant lesions were goblet cell hyperplasia in sections 2-5; subacute inflammation in anterior sections; and the presence of eosinophilic globules in the cytoplasm of olfactory, respiratory, and glandular epithelium in sections 3-5. Eosinophilic globules were most pronounced in noses 3-5. Eosinophilic globules in olfactory epithelium was more severe than in respiratory and glandular epithelial cells. Neoplastic and other non-neoplastic lesions occurred randomly in various organs and tissues and were considered to be incidental and unrelated to treatment.

Inhalation of chlorine by Fischer 344 female rats for 24 months resulted in treatment-related lesions in the nasal cavity. Microscopic

changes in sections of nose 1 from treated rats were minimal when compared with controls. Goblet cell hyperplasia was the main treatment-related change in sections of nose 2. The lesions in noses 3, 4, and 5 of treated females consisted of goblet cell hyperplasia and eosinophilic globules in olfactory, respiratory, and glandular epithelium. In animals sacrificed at 24 months, these lesions were in general slightly more severe than noted in the 12-month interim sacrifice.

for Jerry F. Hardisty DVM
JIM E. PROCTOR, D.V.M., Ph.D.
Veterinary Pathologist

June 10, 1992
Date

JEP/vln

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Risk Assessment Study of Chlorine in Rats

Client Study: Study Number 8436 EPL Project Coordinator: Dr. Hardisty

EPL Project Number: 304-337 EPL Pathologist: Dr. Proctor

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	December 31, 1987; March 28, 1988; April 5, 1988	December 31, 1987; March 28, 1988; April 5, 1988
Project Setup	January 8, 1988	January 8, 1988
Histology Setup	January 8, 1988	January 8, 1988
Histology Complete	January 13, 1988	January 13, 1988
Rough Draft Report	July 12, 1988	July 12, 1988
Final Report	June 10, 1992	June 10, 1992
Other		

Date of last quarterly facility inspection April, 1992

This study is certified to have been performed in compliance with the appropriate Good Laboratory Practice regulations.

Jane Hanson
EPL Quality Assurance Unit

June 10, 1992
Date

APPENDIX R1b

PATHOLOGY SUMMARY

F344 RATS

MALES

CIIT STUDY NUMBER 8321

RISK ASSESSMENT STUDY OF CHLORINE IN RATS

PATHOLOGY SUMMARY

A histopathologic examination of tissues from male and female Fischer 344 rats was performed to establish the health risk, including carcinogenicity, associated with the chronic inhalation of chlorine. Rats were exposed for six hours per day, five days per week, for 104 weeks. The experimental design of the study is outlined as follows:

Group	Concentration (ppm)	Number of Animals Males	Females
1	0	70	70
2	0.400	70	70
3	1.000	70	70
4	2.500	70	70

At approximately six weeks into the study the female rats in the 1.000 and 2.500 ppm groups were exposed to chlorine only on Monday, Wednesday, and Friday each week for the duration of the study. At approximately eight weeks into the study the female rats in the 0.400 ppm group were exposed to chlorine only on Monday, Wednesday, and Friday for the duration of the study.

Ten animals of each sex from each of the four treatment groups were sacrificed after 12 months on the study. Tissues from these rats as well as those that died prior to 12 months were examined and tabulated together. The female rats were removed for research after the 12-month interim sacrifice.

The surviving male rats were sacrificed after 24 months and examined microscopically. All male rats that died or were sacrificed in a moribund condition after the 12-month sacrifice and prior to the 24-month sacrifice were also evaluated.

According to protocol, the following tissues were examined: brain, spinal cord, pituitary gland, thyroid gland (2), parathyroid, larynx, trachea, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, salivary gland, mandibular lymph node, mesenteric lymph node, thymus, spleen, heart, aorta, tongue, liver (2), kidney (2), adrenal gland (2), lung (5), seminal vesicle, prostate, testis (2), epididymis (2), ovary (2), oviduct (2), uterus, urinary bladder, eye (2), optic nerve (2), harderian gland (2), skin, mammary gland, skeletal muscle, sciatic nerve, bone (femur), bone (sternum), bone marrow (femur), bone marrow (sternum), ear canal (2), nose (5 levels), and gross lesions or tissue masses with adjacent tissue. All of the above tissues were examined in all control rats and Group 4 rats. Only target tissues (noses at five levels) and gross lesions were examined in Groups 2 and 3 rats.

In general, all tissues as specified in the protocol were represented in the sections. A few tissues were apparently inadvertently missed at the time of necropsy or lost during histologic processing. Varying degrees of autolysis were evident microscopically in tissues from a number of rats that died prior to sacrifice. In a few tissues, such as the nasal cavities and those from the gastrointestinal tract, it was of such a degree that critical evaluation or identification of the tissue was

difficult. Four female rats from Group 3, one male rat from Group 1, and one male rat from Group 4 were so severely autolyzed that they were discarded entirely. These factors, however, did not affect the overall evaluation of the study, as only a few of the animals that died early had generalized severe autolysis or severe autolysis in a restricted set of tissues. There were inconsistencies in the sectioning of the nasal cavity such that there was variability in the region of the nose examined for any given nose level. However, wide variability in the nose level from one animal to another occurred in relatively few animals, and these inconsistencies did not affect the interpretation of treatment-related lesions.

Hematoxylin and eosin stained slides of the protocol-required tissues were prepared by Experimental Pathology Laboratories, Inc. Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. Inflammatory, degenerative, and hyperplastic changes were graded one to five depending upon severity; neoplasms, cysts, developmental anomalies, and other nongradable changes were designated as present (P) on the Histopathology Incidence Tables. Tissues that were autolyzed to a moderate degree but could be evaluated for lesions are tabulated with the diagnosis and an "A" to indicate autolysis. Those that were severely autolyzed and could not be evaluated are indicated with an "A" only. All lesions are summarized by treatment group in the Summary Incidence Tables together with the total number of animals in each

group for which the tissues were examined. All neoplasms are also listed in the same manner in the Neoplasm Summary Incidence Tables.

A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time the necropsies were performed and the Individual Animal Worksheet - Histology prepared when the tissues were trimmed for histology. Microscopic findings were generally not given for gross observations relating to nutritional condition, fluid in body cavities, or discharges from orifices.

RESULTS

12-Month Interim Sacrifice and Deaths

Female Rats:

There were more early deaths among treated female rats (37) than among the control female rats (1), especially in Group 3 (18) and Group 4 (15). In general, female rats in Groups 3 and 4 that died early were described as dehydrated and/or emaciated with depletion of body fat.

Treatment-related histomorphologic lesions occurred in the nasal cavity of female rats sacrificed at 12 months. The most pronounced changes occurred in levels 3, 4, and 5 of the nasal cavity. In nose 3, a greater number of treated versus control rats had eosinophilic, or hyalinized, globules present in the glandular, respiratory, and olfactory epithelium.

The incidence of this lesion in respiratory epithelium was dose related. The severity of the lesion was usually mild in control rats and ranged from minimal to moderately severe in treated rats. Goblet cell hyperplasia was present in one control rat and in most of the treated rats. The severity was increased in a dose-related manner in the treated groups. Subacute inflammation characterized by variable numbers of neutrophils and mononuclear cells in the submucosa of the turbinates, septum, and lateral walls of the nasal cavity occurred more frequently in treated versus control rats. The inflammation was usually minimal except in Group 4 rats in which it was usually mild.

In nose 4, eosinophilic globules occurred more frequently in glandular, respiratory, and olfactory epithelium in treated rats versus control rats. The severity of the change ranged from minimal to mild in the few controls in which it was present and from minimal to moderately severe in treated animals. Goblet cell hyperplasia occurred in one control rat with mild severity and in most of the treated rats with a dose-related increase in severity from minimal to moderate. Subacute inflammation of the submucosa occurred in control and treated animals and was usually minimal in severity except in Group 4 rats in which it was usually mild.

In nose 5, eosinophilic globules occurred in olfactory and respiratory epithelium in both control and treated rats but with a slight increase in incidence and severity in rats of Groups 3 and 4. Goblet cell hyperplasia was increased in a dose-related manner. The severity was

minimal in control and Group 2 rats and minimal to moderate in rats of Groups 3 and 4.

In nose 2, goblet cell hyperplasia and subacute inflammation occurred in almost all rats, control and treated. There was a slight increase in severity of goblet cell hyperplasia in Groups 3 and 4. Other incidental lesions in various levels of the nasal cavity occurred with some frequency but did not appear to be treatment related. These included hyperplasia of squamous epithelium, hemorrhage, and subepithelial mineralization.

Subacute inflammation occurred in the trachea more frequently in the Group 4 rats than in control rats. However, the lesion was usually minimal and was characterized by a loosely arranged aggregate of mononuclear cells and a few neutrophils in the submucosa. There was no disruption of the surface epithelium. The lesion did not appear to be treatment related.

A variety of spontaneous lesions and incidental findings occurred in various organs and tissues. These occurred, for the most part, at comparable incidences in control and treated rats. They included such changes as subchronic myocarditis; pigmentation of tubular epithelium, proteinaceous casts, tubular regeneration, and tubular mineralization in the kidney; mineralization of blood vessels, peribronchial/peribronchiolar mononuclear cell foci, and subpleural alveolar macrophage accumulations in the lung; C-cell hyperplasia; parovarian cysts; and bile duct hyperplasia, periportal fibrosis, and microgranulomas in the liver.

Increased plasma cells in the mandibular lymph node of a number of rats probably reflected the trauma and related reaction that occurred with ear tagging.

Lymphoid depletion in the spleen was diagnosed in Group 4 female rats that died early. This lesion is frequently noted in rats in extremis due to the stress-related release of adrenal cortical hormones.

Neoplastic lesions of the reproductive tract occurred sporadically in treated groups. These neoplasms included a leiomyoma of the cervix and endometrial stromal polyps of the uterus. One control female had mononuclear cell leukemia.

12-Month Interim Sacrifice and Deaths

Male Rats:

There were only a few deaths (4) of male rats prior to the 12-month interim sacrifice and these did not appear to be treatment related.

Treatment-related histomorphologic lesions occurred in the nasal cavity of male rats sacrificed at 12 months. The most pronounced changes occurred in levels 3 and 4 of the nasal cavity. In nose 3, there was a dose-related increased incidence of eosinophilic globules in glandular and respiratory epithelium. The severity of the lesion was minimal in Group 2 rats and varied from minimal to moderate in Groups 3 and 4. There was an increased incidence of eosinophilic globules in olfactory epithelium in treated versus control rats. The severity of the lesion was minimal in the control rats and varied from minimal to moderately severe in the treated

rats. Goblet cell hyperplasia occurred with a dose-related increased incidence. Subacute inflammation of the submucosa was increased in incidence in treated versus control animals but was usually minimal in severity.

In nose 4, there was a dose-related increased incidence of eosinophilic globules in olfactory epithelium. The lesion was minimal to mild in Group 2 rats and ranged from minimal to moderately severe in Groups 3 and 4 rats. There were eosinophilic globules in glandular epithelium in treated animals and not in controls. Eosinophilic globules in respiratory epithelium occurred in both control and treated rats, but there was a greater incidence of the lesion in rats of Groups 3 and 4 versus control and Group 2 rats. Goblet cell hyperplasia occurred with increased incidence in treated versus control rats. The lesion was minimal in the one control rat in which it occurred and ranged from minimal to moderate severity in the treated rats.

In nose 5, eosinophilic globules were found in the respiratory epithelium of about one-third of the treated animals and the change was minimal to mild in severity. Eosinophilic globules in olfactory epithelium occurred in both control and treated rats with only a slightly greater severity in Group 4 rats. There were no significant treatment-related lesions in noses 1 and 2 of male rats sacrificed at 12 months.

A few incidental lesions occurred sporadically in the nasal cavity but were not treatment-related. These included epithelial microabscesses, mineralized concretions, and subepithelial mineralization.

A variety of spontaneous lesions and incidental findings occurred in various organs and tissues. These occurred, for the most part, at comparable incidences in control and treated rats. They included such changes as proteinaceous casts, tubular regeneration, pigmentation of tubular epithelium, and tubular mineralization in the kidney; subchronic myocarditis; mineralization of blood vessels and peribronchial/peribronchiolar mononuclear cell foci in the lung; bile duct hyperplasia, periportal fibrosis, and microgranulomas in the liver; and interstitial cell hyperplasia, tubular atrophy/degeneration, and tubular mineralization in the testis.

Increased plasma cells in the mandibular lymph node of a number of rats probably reflected the trauma and related reaction that occurred with ear tagging.

A variety of neoplasms occurred sporadically in control and treated rats. These included an astrocytoma (brain), mesothelioma (testis and epididymis), alveolar/bronchiolar adenoma (lung), adenoma (pars distalis of pituitary gland), pheochromocytoma (adrenal gland), and an adenomatous polyp (colon).

Summary of Nasal Cavity Lesions in Males and Females Sacrificed at 12 Months

In general, no treatment-related lesions were identified in nose 1 of male and female rats sacrificed at 12 months or in nose 2 of male rats. There was a slight increase in severity of goblet cell hyperplasia in nose 2 of female rats.

Both sexes had the most pronounced changes in nose 3 and nose 4. Nose 5 was affected more severely in females than in males. Major changes included the presence of eosinophilic or hyalinized material in olfactory, respiratory, and glandular epithelium; goblet cell hyperplasia; and inflammation of the submucosa.

In nose 3, in general, the presence of eosinophilic globules in olfactory, respiratory, and glandular epithelium increased in incidence and severity in treated versus control male and female rats. In respiratory epithelium the increased incidence was dose related in both sexes. Goblet cell hyperplasia increased in incidence in treated versus control male and female rats and the increased incidence was dose related in male rats. The lesion was usually more severe in treated females than in treated males. Subacute inflammation occurred in greater incidence in nose 3 of treated versus control male and female rats.

In nose 4, in general, the presence of eosinophilic globules in olfactory, respiratory, and glandular epithelium increased in incidence and severity in treated versus control male and female rats. An exception is that the incidence and severity of eosinophilic globules in respiratory epithelium was similar in control and Group 2 male rats. The increased incidence of eosinophilic globules in olfactory epithelium was dose related in male rats. The severity of eosinophilic globules was usually greater in Group 4 females than in Group 4 males. Goblet cell hyperplasia in nose 4 occurred with increased incidence and severity in treated versus control male and female rats.

In general, in nose 5, there was a slight increase in incidence of eosinophilic globules in olfactory and respiratory epithelium in treated versus control male and female rats. Among the female rats the severity of the lesion increased from usually minimal in controls to minimal to moderately severe in Groups 3 and 4. Among the male rats there was a slight increase in severity of the lesion in Group 4. In nose 5 there was an increased incidence of goblet cell hyperplasia in treated versus control female rats.

24-Month Terminal Sacrifice and Deaths

Male Rats:

Early deaths and animals that were sacrificed moribund occurred with more or less equal frequency among control rats and rats at all levels of treatment.

Treatment-related histomorphologic lesions occurred in the nasal cavity of male rats at all dose levels sacrificed at 24 months.

In nose 1 and nose 2, epithelial microabscesses and hyperplasia of squamous epithelium occurred in greater incidence in treated versus control rats. Epithelial microabscesses were characterized by focal aggregates of neutrophils within the squamous epithelium lining the nasal cavity. The incidence of goblet cell hyperplasia in nose 2 was greatest in Group 2 rats. Considerably fewer control rats and rats in Groups 3 and 4 were affected with this lesion. It is not known why the rats of this lowest dose group were so affected.

The major lesions in noses 3, 4, and 5 were eosinophilic globules in olfactory, respiratory, and glandular epithelium; goblet cell hyperplasia; and subacute inflammation of the submucosa. The glandular epithelium affected by the presence of eosinophilic globules was usually formed by the infoldings of respiratory epithelium into the submucosa. This infolding was pronounced in treated rats. Although the incidence of subacute inflammation was greater in treated versus controls rats in nose levels 3, 4, and 5, a substantial number of control rats had a submucosal inflammatory infiltrate in all levels of the nasal cavity.

In nose 3, eosinophilic globules occurred in olfactory epithelium in a few control rats and in almost all treated rats. The severity of the lesion was greatest in Group 4 rats. The incidence of eosinophilic globules in respiratory and glandular epithelium was not as great in treated rats as the incidence of eosinophilic globules in olfactory epithelium. Goblet cell hyperplasia occurred in a few control rats and in almost all treated rats. The severity of the lesion increased with increasing dose of chlorine.

In nose 4, eosinophilic globules occurred in olfactory, respiratory, and glandular epithelium in almost all treated rats and in a few control rats. The severity was usually minimal to mild in controls and was usually mild to moderately severe in treated rats. Goblet cell hyperplasia occurred in a few control rats and in almost all treated rats. The severity was minimal to mild in controls and usually mild to moderately severe in treated rats.

In nose 5, a substantial number of control rats had eosinophilic globules in olfactory epithelium, but the incidence and severity was greater among treated rats. Only a few control rats and most of the treated rats had eosinophilic globules in respiratory epithelium. By comparison only a small number of treated rats had eosinophilic globules in glandular epithelium. This reflects the increased infolding of respiratory epithelium to form glandular epithelium that occurred in treated rats, but this infolding was not as common in nose 5 as in noses 3 and 4. The incidence of goblet cell hyperplasia in nose 5 was increased in treated versus control rats but the number of rats affected and the severity of the lesion was not as great as for the lesion in noses 3 and 4.

Subepithelial mineralization occurred in a substantial number of both control and treated animals in nose 5. Fewer rats in all groups had the lesion in nose 4. At both levels of the nasal cavity, however, fewer rats in Groups 3 and 4 were affected than rats in Group 2 or in controls. The reason for the decreased incidence in the two highest dose groups is not known.

Other lesions of the nasal cavity occurred sporadically and with some frequency among control and treated rats and were not treatment-related. These included mineralized concretions, mucopurulent exudate, and inspissated mucus. A fibrosarcoma of the hard palate occurred in one control rat, and an adenocarcinoma of the nasal epithelium occurred in one Group 3 rat that died early.

A variety of non-neoplastic spontaneous lesions and incidental findings occurred in various organs and tissues. These lesions were of the usual number and type commonly diagnosed in male F-344 rats of this age and occurred, for the most part, at comparable incidences in control and treated rats.

Various neoplasms common in F-344 rats of this age occurred at comparable incidences in control and treated rats. Those which occurred most frequently included mononuclear cell leukemia, interstitial cell tumor of the testis, adenoma of the pars distalis of the pituitary gland, pheochromocytoma of the adrenal medulla, and hepatocellular adenoma.

CONCLUSIONS

Inhalation of chlorine by F-344 male and female rats for 12 months resulted in changes in the nasal cavity. The most significant lesions were goblet cell hyperplasia, subacute inflammation, and the presence of eosinophilic globules in the cytoplasm of olfactory, respiratory, and glandular epithelium. Lesions were most pronounced in noses 3 and 4 of both sexes. In nose 3, goblet cell hyperplasia was more severe in treated females than in treated males. In nose 4, eosinophilic globules in olfactory epithelium was more severe in treated females than in treated males. Neoplastic and other non-neoplastic lesions occurred randomly in various organs and tissues and were considered to be incidental and unrelated to treatment.

Inhalation of chlorine by F-344 male rats for 24 months resulted in treatment-related lesions in all levels of the nasal cavity. Epithelial microabscesses occurred in noses 1 and 2 with greater incidence in treated versus control rats. The lesions in noses 3, 4, and 5 were the same as those that occurred in treated male rats at the 12-month sacrifice: goblet cell hyperplasia, subacute inflammation, and eosinophilic globules in olfactory, respiratory, and glandular epithelium. In animals that were sacrificed at 24 months, these lesions were more severe in general and usually affected a greater percentage of the rats per group. Neoplastic and other non-neoplastic lesions occurred randomly in various organs and tissues and were considered to be incidental and unrelated to treatment.

Marilyn J. Wolfe

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Pathologist

June 12, 1992

MJW/sfh

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Risk Assessment Study of Chlorine in Rats

Client Study: 8321 EPL Project Coordinator: Dr. Jerry Hardisty

EPL Project Number: 304-332 EPL Pathologist: Dr. Marilyn Wolfe

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	9/18/87; 10/20/87; 11/2/87	9/18/87; 10/20/87; 11/2/87
Project Setup	10/14, 22/87; 12/29/87	10/14, 22/87; 12/29/87
Histology Setup	10/22/87	10/22/87
Histology Complete	12/10/87	12/10/87
Rough Draft Report	12/28, 29/87; 5/3-6, 9/88; 6/8, 9, 14, 15, 17, 27/88	12/28, 29/87; 5/3-6, 9/88; 6/8, 9, 14, 15, 17, 27/88
Final Report	6/12/92	6/12/92
Other	N/A	N/A

Date of last quarterly facility inspection 4/92

This study is certified to have been performed in compliance with the appropriate Good Laboratory Practice regulations.

Patricia L Runge
EPL Quality Assurance Unit

6/12/92
Date

APPENDIX S

HISTOPATHOLOGIC SUMMARY DATA: ALL ANIMALS

TABLE S1	SUMMARY INCIDENCE OF MICROSCOPIC OBSERVATIONS - B6C3F1 MICE	
TABLE S1a	NEOPLASTIC FINDINGS	500
TABLE S1b	NON-NEOPLASTIC FINDINGS	512
TABLE S2	SUMMARY INCIDENCE OF MICROSCOPIC OBSERVATIONS - F344 RAT	
TABLE S2a	NEOPLASTIC FINDINGS	616
TABLE S2b	NON-NEOPLASTIC FINDINGS	636

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

(A) NUMBER OF TUMOR-BEARING ANIMALS / NUMBER OFANIMALS EXAMINED AT SITE.
(B) KAPLAN-MEIER ESTIMATED LIFETIME TUMOR INCIDENCE AFTER ADJUSTMENT FOR INTERCURRENT MORTALITY.
(D) OBSERVED INCIDENCE AT FINAL NECROPSY.
(E) STATISTICAL EVALUATION NOT COMPUTED SINCE FULL GROUPS WERE NOT EXAMINED OR DATA DO NOT MEET CRITERIA FOR STATISTICAL TEST.
(F) BENEATH THE CONTROL INCIDENCE ARE THE P-VALUES ASSOCIATED WITH THE TREND TEST. BENEATH THE DOSED GROUP INCIDENCE ARE THE P-VALUES CORRESPONDING TO PAIRWISE COMPARISONS BETWEEN THE CONTROLS AND THAT DOSED GROUP. THE LIFE TABLE ANALYSIS REGARDS TUMORS IN ANIMALS DYING PRIOR TO FINAL NECROPSY AS BEING (DIRECTLY OR INDIRECTLY) THE CAUSE OF DEATH. THE INCIDENTAL TUMOR TEST REGARDS THESE LESIONS AS NON-FATAL. LOGISTIC REGRESSION IS AN ALTERNATIVE METHOD FOR ANALYZING THE INCIDENCE OF NON-FATAL TUMORS.THE COCHRAN-ARMITAGE AND FISHER'S EXACT TESTS COMPARE DIRECTLY THE OVERALLINCIDENCE RATES. FOR ALL TESTS, A NEGATIVE TREND IS INDICATED BY "N".
(G) DATA NOT PRESENTED DUE TO
    1) ORGAN OR LESION NOT SEX APPROPRIATE
    2) FEWER THAN TWO FINDINGS FOR ALL GROUPS
    3) INTERPATHOLOGIST VARIATION
(I) INTERIM NECROPSY
(T) FINAL NECROPSY

* TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.05).
** TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.01).

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal								
Pheochromocytoma: Benign, Malignant								
TUMOR RATES								
OVERALL (A)	1/56 (2%)	0/7 (0%)	1/4 (25%)	0/58 (0%)	1/61 (2%)	1/8 (13%)	0/3 (0%)	2/58 (3%)
ADJUSTED (B)	4.3%	0.0%	2.6%	0.0%	3.1%	1.9%	0.0%	4.8%
FINAL (D)	1/23 (4%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	1/32 (3%)	0/3 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	---	616	---	732 (T)	608	---	507
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.512
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.556
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.488
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.481
Harderian Gland								
Adenoma								
TUMOR RATES								
OVERALL (A)	1/62 (2%)	2/3 (67%)	1/1 (100%)	3/63 (5%)	5/60 (8%)	5/5 (100%)	3/3 (100%)	3/57 (5%)
ADJUSTED (B)	4.0%	51.4%	100.0%	10.0%	14.3%	100.0%	100.0%	8.6%
FINAL (D)	0/23 (0%)	1/2 (50%)	1/1 (100%)	2/26 (8%)	4/33 (12%)	4/4 (100%)	3/3 (100%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	714	675	726 (T)	561	653	669	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.340	(E)	(E)	(E)	P=0.882
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	P=0.876
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.329	(E)	(E)	(E)	P=0.876
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.316		(E)	(E)	P=0.847

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Heart								
Hemangiosarcoma								
TUMOR RATES								
OVERALL (A)	0/62 (0%)	0/3 (0%)	0/3 (0%)	2/65 (3%)	0/62 (0%)	0/0 (0%)	0/0 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	6.5%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	1/26 (4%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	646	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.274	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.293	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.254	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.260		(E)	(E)	(E)
Liver								
Hepatocellular Adenoma								
TUMOR RATES								
OVERALL (A)	10/62 (16%)	9/28 (32%)	14/34 (41%)	12/64 (19%)	2/62 (3%)	8/33 (24%)	1/26 (4%)	6/59 (10%)
ADJUSTED (B)	32.0%	52.5%	70.3%	40.0%	6.1%	47.1%	8.3%	16.7%
FINAL (D)	5/23 (22%)	7/14 (50%)	10/15 (67%)	9/26 (35%)	2/33 (6%)	8/17 (47%)	1/12 (8%)	6/36 (17%)
FIRST INCIDENCE (DAYS)	304	500	580	381	732 (T)	732 (T)	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.520	(E)	(E)	(E)	P=0.161
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.610	(E)	(E)	(E)	P=0.161
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.470	(E)	(E)	(E)	P=0.161
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.440		(E)	(E)	P=0.121

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver Hepatocellular Adenoma or Hepatocellular Carcinoma								
TUMOR RATES								
OVERALL (A)	21/62 (34%)	15/28 (54%)	21/34 (62%)	26/64 (41%)	4/62 (6%)	9/33 (27%)	1/26 (4%)	6/59 (10%)
ADJUSTED (B)	56.0%	69.5%	80.0%	63.8%	10.2%	48.2%	8.3%	16.7%
FINAL (D)	8/23 (35%)	9/14 (64%)	11/15 (73%)	12/26 (46%)	2/33 (6%)	8/17 (47%)	1/12 (8%)	6/36 (17%)
FIRST INCIDENCE (DAYS)	304	500	537	381	397	628	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.401	(E)	(E)	(E)	P=0.417
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.461	(E)	(E)	(E)	P=0.412
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.305	(E)	(E)	(E)	P=0.364
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.275		(E)	(E)	P=0.340
Liver Hepatocellular Carcinoma								
TUMOR RATES								
OVERALL (A)	12/62 (19%)	6/28 (21%)	7/34 (21%)	16/64 (25%)	2/62 (3%)	1/33 (3%)	0/26 (0%)	0/59 (0%)
ADJUSTED (B)	35.9%	23.0%	21.3%	40.2%	4.4%	2.1%	0.0%	0.0%
FINAL (D)	4/23 (17%)	2/14 (14%)	1/15 (7%)	4/26 (15%)	0/33 (0%)	0/17 (0%)	0/12 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	452	507	537	443	397	628	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.378	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.374	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.288	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.292		(E)	(E)	P=1.000

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lung Alveolar/Bronchiolar Adenoma								
TUMOR RATES								
OVERALL (A)	2/61 (3%)	0/25 (0%)	2/30 (7%)	7/65 (11%)	1/62 (2%)	2/28 (7%)	1/11 (9%)	1/59 (2%)
ADJUSTED (B)	6.6%	0.0%	22.0%	21.8%	3.0%	18.2%	2.4%	2.8%
FINAL (D)	0/23 (0%)	0/8 (0%)	1/5 (20%)	4/26 (15%)	1/33 (3%)	2/11 (18%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	598	---	599	381	732 (T)	732 (T)	684	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.121	(E)	(E)	(E)	P=0.781
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.125	(E)	(E)	(E)	P=0.781
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.105	(E)	(E)	(E)	P=0.781
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.098		(E)	(E)	P=0.740
Lung Alveolar/Bronchiolar Carcinoma								
TUMOR RATES								
OVERALL (A)	5/61 (8%)	3/25 (12%)	1/30 (3%)	3/65 (5%)	3/62 (5%)	0/28 (0%)	0/11 (0%)	1/59 (2%)
ADJUSTED (B)	21.7%	17.1%	2.7%	10.7%	8.2%	0.0%	0.0%	2.0%
FINAL (D)	5/23 (22%)	1/8 (13%)	0/5 (0%)	1/26 (4%)	1/33 (3%)	0/11 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	629	653	704	675	---	---	468
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.898	(E)	(E)	(E)	P=0.937
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.927	(E)	(E)	(E)	P=0.931
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.900	(E)	(E)	(E)	P=0.931
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.883		(E)	(E)	P=0.934

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lung Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma								
TUMOR RATES								
OVERALL (A)	7/61 (11%)	3/25 (12%)	3/30 (10%)	10/65 (15%)	4/62 (6%)	2/28 (7%)	1/11 (9%)	2/59 (3%)
ADJUSTED (B)	26.9%	17.1%	24.1%	30.6%	11.1%	18.2%	2.4%	4.7%
FINAL (D)	5/23 (22%)	1/8 (13%)	1/5 (20%)	5/26 (19%)	2/33 (6%)	2/11 (18%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	598	629	599	381	675	732 (T)	684	468
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.398	(E)	(E)	(E)	P=0.903
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.461	(E)	(E)	(E)	P=0.893
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.374	(E)	(E)	(E)	P=0.890
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.353		(E)	(E)	P=0.885
Ovary Cystadenoma								
TUMOR RATES	(G)							
OVERALL (A)					1/52 (2%)	0/64 (0%)	3/55 (5%)	0/47 (0%)
ADJUSTED (B)					3.2%	0.0%	8.1%	0.0%
FINAL (D)					1/31 (3%)	0/35 (0%)	1/32 (3%)	0/32 (0%)
FIRST INCIDENCE (DAYS)					732 (T)	---	681	---
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.816	(E)	P=0.330	(E)
INCIDENTAL TUMOR					P=0.790	(E)	P=0.437	(E)
LOGISTIC REGRESSION					P=0.795	(E)	P=0.339	(E)
COCHRAN-ARMITAGE					P=0.780			
FISHER EXACT						P=1.000	P=0.330	P=1.000

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Ovary Granulosa Cell Tumor								
TUMOR RATES	(G)							
OVERALL (A)					1/59 (2%)	1/64 (2%)	0/56 (0%)	2/54 (4%)
ADJUSTED (B)					3.0%	2.0%	0.0%	5.7%
FINAL (D)					1/33 (3%)	0/35 (0%)	0/33 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)					732 (T)	614	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.350	P=0.783	(E)	P=0.521
INCIDENTAL TUMOR					P=0.279	P=0.791	(E)	P=0.521
LOGISTIC REGRESSION					P=0.326	P=0.785	(E)	P=0.521
COCHRAN-ARMITAGE					P=0.307			
FISHER EXACT						P=0.772	P=1.000	P=0.467
Ovary Tubular Adenoma								
TUMOR RATES	(G)							
OVERALL (A)					2/59 (3%)	1/64 (2%)	0/56 (0%)	1/54 (2%)
ADJUSTED (B)					5.6%	2.9%	0.0%	2.9%
FINAL (D)					1/33 (3%)	1/35 (3%)	0/33 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)					675	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.831	P=0.890	(E)	P=0.890
INCIDENTAL TUMOR					P=0.826	P=0.907	(E)	P=0.884
LOGISTIC REGRESSION					P=0.825	P=0.901	(E)	P=0.884
COCHRAN-ARMITAGE					P=0.802			
FISHER EXACT						P=0.893	P=1.000	P=0.861

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pituitary Pars Anterior, Adenoma								
TUMOR RATES								
OVERALL (A)	0/46 (0%)	0/0 (0%)	0/2 (0%)	0/40 (0%)	3/42 (7%)	5/10 (50%)	0/1 (0%)	5/31 (16%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	12.0%	51.3%	0.0%	17.1%
FINAL (D)	0/21 (0%)	0/0	0/0	0/18 (0%)	3/25 (12%)	4/8 (50%)	0/0	4/27 (15%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	715	---	724
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.401
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.344
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.398
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.201
Pituitary Pars Intermedia, Adenoma								
TUMOR RATES								
OVERALL (A)	0/46 (0%)	0/0 (0%)	0/2 (0%)	0/40 (0%)	0/42 (0%)	3/10 (30%)	1/1 (100%)	0/31 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	37.5%	0.0%	0.0%
FINAL (D)	0/21 (0%)	0/0	0/0	0/18 (0%)	0/25 (0%)	3/8 (38%)	0/0	0/27 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	732 (T)	712	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach								
Squamous Papilloma								
TUMOR RATES								
OVERALL (A)	3/55 (5%)	2/12 (17%)	0/13 (0%)	3/64 (5%)	1/60 (2%)	0/34 (0%)	0/16 (0%)	0/58 (0%)
ADJUSTED (B)	13.0%	25.0%	0.0%	11.5%	1.9%	0.0%	0.0%	0.0%
FINAL (D)	3/23 (13%)	2/8 (25%)	0/3 (0%)	3/26 (12%)	0/33 (0%)	0/30 (0%)	0/14 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	---	726 (T)	553	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.723	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.723	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.723	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.729		(E)	(E)	P=1.000
Thyroid								
Follicular Cell Adenoma								
TUMOR RATES								
OVERALL (A)	9/59 (15%)	0/0 (0%)	0/0 (0%)	9/63 (14%)	5/61 (8%)	0/0 (0%)	0/0 (0%)	7/56 (13%)
ADJUSTED (B)	32.6%	0.0%	0.0%	31.7%	15.2%	0.0%	0.0%	19.4%
FINAL (D)	5/23 (22%)	0/0	0/0	7/26 (27%)	5/33 (15%)	0/0	0/0	7/36 (19%)
FIRST INCIDENCE (DAYS)	626	---	---	647	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.692	(E)	(E)	(E)	P=0.440
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.718	(E)	(E)	(E)	P=0.440
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.718	(E)	(E)	(E)	P=0.440
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		P=1.000	P=1.000	P=0.658		P=1.000	P=1.000	P=0.322

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thyroid								
Follicular Cell: Adenoma or Carcinoma								
TUMOR RATES								
OVERALL (A)	9/59 (15%)	0/0 (0%)	0/0 (0%)	10/63 (16%)	5/61 (8%)	0/0 (0%)	0/0 (0%)	7/56 (13%)
ADJUSTED (B)	32.6%	0.0%	0.0%	33.4%	15.2%	0.0%	0.0%	19.4%
FINAL (D)	5/23 (22%)	0/0	0/0	7/26 (27%)	5/33 (15%)	0/0	0/0	7/36 (19%)
FIRST INCIDENCE (DAYS)	626	---	---	542	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.595	(E)	(E)	(E)	P=0.440
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.643	(E)	(E)	(E)	P=0.440
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.643	(E)	(E)	(E)	P=0.440
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.562		(E)	(E)	P=0.322
Uterus								
Vaginal Squamous Cell Carcinoma								
TUMOR RATES	(G)							
OVERALL (A)					2/56 (4%)	0/66 (0%)	0/56 (0%)	1/57 (2%)
ADJUSTED (B)					6.3%	0.0%	0.0%	2.8%
FINAL (D)					2/32 (6%)	0/37 (0%)	0/33 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)					732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.776	(E)	(E)	P=0.899
INCIDENTAL TUMOR					P=0.776	(E)	(E)	P=0.899
LOGISTIC REGRESSION					P=0.776	(E)	(E)	P=0.899
COCHRAN-ARMITAGE					P=0.756			
FISHER EXACT						P=1.000	P=1.000	P=0.882

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
All Organs Hemangiosarcoma								
OVERALL (A)	0/64 (0%)	2/66 (3%)	0/69 (0%)	4/67 (6%)	0/66 (0%)	0/67 (0%)	2/59 (3%)	0/61 (0%)
ADJUSTED (B)	0.0%	6.7%	0.0%	12.6%	0.0%	0.0%	5.0%	0.0%
FINAL (D)	0/23 (0%)	2/30 (7%)	0/26 (0%)	2/26 (8%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	726 (T)	---	561	---	---	619	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.034 *	P=0.298	(E)	P=0.082	P=0.698	(E)	P=0.244	(E)
INCIDENTAL TUMOR	P=0.025 *	P=0.298	(E)	P=0.047 *	P=0.582	(E)	P=0.186	(E)
LOGISTIC REGRESSION	P=0.034 *	P=0.298	(E)	P=0.072	P=0.685	(E)	P=0.225	(E)
COCHRAN-ARMITAGE	P=0.036 *				P=0.683			
FISHER EXACT		P=0.256	(E)	P=0.065		(E)	P=0.221	(E)
All Organs Histiocytic Sarcoma								
TUMOR RATES								
OVERALL (A)	3/64 (5%)	1/66 (2%)	0/69 (0%)	1/67 (1%)	2/66 (3%)	4/67 (6%)	2/59 (3%)	1/61 (2%)
ADJUSTED (B)	12.0%	2.6%	0.0%	3.3%	5.5%	8.9%	5.2%	2.8%
FINAL (D)	2/23 (9%)	0/30 (0%)	0/26 (0%)	0/26 (0%)	1/33 (3%)	2/38 (5%)	0/34 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	668	611	---	684	655	542	685	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.908	P=0.961	P=0.993	P=0.948	P=0.889	P=0.406	P=0.707	P=0.890
INCIDENTAL TUMOR	P=0.905	P=0.936	P=0.995	P=0.963	P=0.880	P=0.378	P=0.761	P=0.871
LOGISTIC REGRESSION	P=0.911	P=0.950	P=0.994	P=0.947	P=0.875	P=0.384	P=0.692	P=0.881
COCHRAN-ARMITAGE	P=0.908				P=0.869			
FISHER EXACT		P=0.944	P=1.000	P=0.946		P=0.347	P=0.647	P=0.863

TABLE S1a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
All Organs Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed								
TUMOR RATES								
OVERALL (A)	0/64 (0%)	2/66 (3%)	2/69 (3%)	1/67 (1%)	11/66 (11%)	6/67 (9%)	5/59 (8%)	5/61 (8%)
ADJUSTED (B)	0.0%	6.7%	4.8%	3.8%	26.8%	12.6%	11.8%	12.5%
FINAL (D)	0/23 (0%)	2/30 (7%)	0/26 (0%)	1/26 (4%)	6/33 (18%)	1/38 (3%)	1/34 (3%)	3/36 (8%)
FIRST INCIDENCE (DAYS)	---	726 (T)	443	726 (T)	463	573	546	611
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.574	P=0.298	P=0.281	P=0.524	P=0.929	P=0.965	P=0.967	P=0.972
INCIDENTAL TUMOR	P=0.632	P=0.298	P=0.298	P=0.524	P=0.855	P=0.971	P=0.949	P=0.934
LOGISTIC REGRESSION	P=0.576	P=0.298	P=0.256	P=0.524	P=0.819	P=0.959	P=0.961	P=0.965
COCHRAN-ARMITAGE	P=0.574				P=0.912			
FISHER EXACT		P=0.256	P=0.267	P=0.511		P=0.945	P=0.951	P=0.958

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

(A) NUMBER OF TUMOR-BEARING ANIMALS / NUMBER OFANIMALS EXAMINED AT SITE.
(B) KAPLAN-MEIER ESTIMATED LIFETIME TUMOR INCIDENCE AFTER ADJUSTMENT FOR INTERCURRENT MORTALITY.
(D) OBSERVED INCIDENCE AT FINAL NECROPSY.
(E) STATISTICAL EVALUATION NOT COMPUTED SINCE FULL GROUPS WERE NOT EXAMINED OR DATA DO NOT MEET CRITERIA FOR STATISTICAL TEST.
(F) BENEATH THE CONTROL INCIDENCE ARE THE P-VALUES ASSOCIATED WITH THE TREND TEST. BENEATH THE DOSED GROUP INCIDENCE ARE THE P-VALUES CORRESPONDING TO PAIRWISE COMPARISONS BETWEEN THE CONTROLS AND THAT DOSED GROUP. THE LIFE TABLE ANALYSIS REGARDS TUMORS IN ANIMALS DYING PRIOR TO FINAL NECROPSY AS BEING (DIRECTLY OR INDIRECTLY) THE CAUSE OF DEATH. THE INCIDENTAL TUMOR TEST REGARDS THESE LESIONS AS NON-FATAL. LOGISTIC REGRESSION IS AN ALTERNATIVE METHOD FOR ANALYZING THE INCIDENCE OF NON-FATAL TUMORS.THE COCHRAN-ARMITAGE AND FISHER'S EXACT TESTS COMPARE DIRECTLY THE OVERALLINCIDENCE RATES. FOR ALL TESTS, A NEGATIVE TREND IS INDICATED BY "N".
(G) DATA NOT PRESENTED DUE TO
1) ORGAN OR LESION NOT SEX APPROPRIATE
2) FEWER THAN TWO FINDINGS FOR ALL GROUPS
3) INTERPATHOLOGIST VARIATION
(I) INTERIM NECROPSY
(T) FINAL NECROPSY

* TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.05).
** TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.01).

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Abdominal Tissue								
Fat Necrosis								
LESION RATES								
OVERALL (A)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/1 (0%)	1/2 (50%)	0/0 (0%)	2/4 (50%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%
FINAL (D)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0	1/1 (100%)	0/0	2/2 (100%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Adrenal								
Accessory Adrenal Tissue								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	2/58 (3%)	0/61 (0%)	0/8 (0%)	0/3 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.6%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	450	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.248	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.198	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.245	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.257		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Adrenal Amyloidosis								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	0/58 (0%)	4/61 (7%)	0/8 (0%)	0/3 (0%)	1/58 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	11.1%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	3/32 (9%)	0/3 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	553	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.971
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.961
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.966
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.967
Adrenal Angiectasis								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	0/58 (0%)	0/61 (0%)	0/8 (0%)	0/3 (0%)	3/58 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.5%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	295
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.110
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.137
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.091
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.113

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Congestion								
LESION RATES								
OVERALL (A)	1/56 (2%)	0/7 (0%)	0/4 (0%)	0/58 (0%)	1/61 (2%)	1/8 (13%)	0/3 (0%)	2/58 (3%)
ADJUSTED (B)	1.5%	0.0%	0.0%	0.0%	1.9%	2.6%	0.0%	4.6%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	45	---	---	---	553	726	---	468
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.483
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.367
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.476
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.481
Adrenal Cortex, Hyperplasia								
LESION RATES								
OVERALL (A)	1/56 (2%)	0/7 (0%)	1/4 (25%)	2/58 (3%)	1/61 (2%)	0/8 (0%)	0/3 (0%)	2/58 (3%)
ADJUSTED (B)	4.2%	0.0%	100.0%	7.7%	3.1%	0.0%	0.0%	5.1%
FINAL (D)	0/23 (0%)	0/4 (0%)	1/1 (100%)	2/26 (8%)	1/32 (3%)	0/3 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	719	---	726 (T)	726 (T)	732 (T)	---	---	684
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.538	(E)	(E)	(E)	P=0.542
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.528	(E)	(E)	(E)	P=0.474
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.526	(E)	(E)	(E)	P=0.510
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.513		(E)	(E)	P=0.481

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Cortex, Hypertrophy								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	2/58 (3%)	2/61 (3%)	0/8 (0%)	0/3 (0%)	1/58 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	7.7%	6.3%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	2/26 (8%)	2/32 (6%)	0/3 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	P=0.899
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	P=0.899
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	P=0.899
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.257		(E)	(E)	P=0.869
Adrenal Cortex, Vacuolization								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	0/58 (0%)	2/61 (3%)	0/8 (0%)	0/3 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	6.3%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	2/32 (6%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Extramedullary Hematopoiesis								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/7 (0%)	0/4 (0%)	0/58 (0%)	2/61 (3%)	0/8 (0%)	0/3 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	4.9%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	632	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000
Adrenal Medulla, Hyperplasia								
LESION RATES								
OVERALL (A)	0/56 (0%)	3/7 (43%)	0/4 (0%)	0/58 (0%)	0/61 (0%)	0/8 (0%)	0/3 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	51.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	2/4 (50%)	0/1 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	564	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Pigmentation								
LESION RATES								
OVERALL (A)	1/56 (2%)	0/7 (0%)	0/4 (0%)	8/58 (14%)	2/61 (3%)	0/8 (0%)	0/3 (0%)	1/58 (2%)
ADJUSTED (B)	2.9%	0.0%	0.0%	23.9%	4.9%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/4 (0%)	0/1 (0%)	5/26 (19%)	1/32 (3%)	0/3 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	604	---	---	375	511	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.030 *	(E)	(E)	(E)	P=0.882
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.030 *	(E)	(E)	(E)	P=0.904
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.021 *	(E)	(E)	(E)	P=0.873
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.018 *		(E)	(E)	P=0.869
Adrenal Subcapsular Cell Hyperplasia								
LESION RATES								
OVERALL (A)	30/56 (54%)	5/7 (71%)	0/4 (0%)	42/58 (72%)	59/61 (97%)	7/8 (88%)	2/3 (67%)	54/58 (93%)
ADJUSTED (B)	87.0%	76.3%	0.0%	97.3%	100.0%	70.1%	100.0%	98.1%
FINAL (D)	19/23 (83%)	3/4 (75%)	0/1 (0%)	25/26 (96%)	32/32 (100%)	2/3 (67%)	1/1 (100%)	35/36 (97%)
FIRST INCIDENCE (DAYS)	108	564	---	243	127	608	664	76
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.102	(E)	(E)	(E)	P=0.913
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.057	(E)	(E)	(E)	P=0.941
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.020 *	(E)	(E)	(E)	P=0.950
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.029 *		(E)	(E)	P=0.908

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone Marrow Granulomatous Inflammation								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/0 (0%)	0/0 (0%)	2/65 (3%)	0/63 (0%)	0/0 (0%)	0/0 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	7.7%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	2/26 (8%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.265	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.260		(E)	(E)	(E)
Bone Marrow Hemosiderosis								
LESION RATES								
OVERALL (A)	30/62 (48%)	0/0 (0%)	0/0 (0%)	42/65 (65%)	50/63 (79%)	0/0 (0%)	0/0 (0%)	48/59 (81%)
ADJUSTED (B)	68.6%	0.0%	0.0%	81.0%	100.0%	0.0%	0.0%	90.3%
FINAL (D)	10/23 (43%)	0/0	0/0	17/26 (65%)	33/33 (100%)	0/0	0/0	31/36 (86%)
FIRST INCIDENCE (DAYS)	293	---	---	100	375	---	---	96
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.164	(E)	(E)	(E)	P=0.810
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.089	(E)	(E)	(E)	P=0.715
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.089	(E)	(E)	(E)	P=0.715
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.048 *		(E)	(E)	P=0.481

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone, Femur								
Myelofibrosis								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/0 (0%)	0/0 (0%)	0/63 (0%)	9/63 (14%)	0/0 (0%)	0/0 (0%)	7/59 (12%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	22.1%	0.0%	0.0%	17.7%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	5/33 (15%)	0/0	0/0	5/36 (14%)
FIRST INCIDENCE (DAYS)	---	---	---	---	26	---	---	418
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.815
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.796
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.796
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.746
Bone, Sternum								
Myelofibrosis								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/0 (0%)	0/0 (0%)	0/65 (0%)	28/61 (46%)	0/0 (0%)	0/0 (0%)	20/59 (34%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	70.9%	0.0%	0.0%	52.3%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	22/33 (67%)	0/0	0/0	18/36 (50%)
FIRST INCIDENCE (DAYS)	---	---	---	---	375	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.984
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.966
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.966
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.937

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone, Sternum								
Periostitis								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/0 (0%)	0/0 (0%)	0/65 (0%)	0/61 (0%)	0/0 (0%)	0/0 (0%)	2/59 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	4.8%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.252
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.115
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.115
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.240
Brain								
Brain Stem, Demyelination								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/6 (0%)	0/7 (0%)	2/65 (3%)	0/61 (0%)	0/0 (0%)	0/2 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	3.7%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	373	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.263	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.370	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.244	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.264		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Brain Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	1/6 (17%)	0/7 (0%)	1/65 (2%)	2/61 (3%)	0/0 (0%)	0/2 (0%)	6/56 (11%)
ADJUSTED (B)	0.0%	0.0%	0.0%	2.4%	4.2%	0.0%	0.0%	15.1%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	3/36 (8%)
FIRST INCIDENCE (DAYS)	---	342	---	523	495	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.495	(E)	(E)	(E)	P=0.158
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.615	(E)	(E)	(E)	P=0.072
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.512	(E)	(E)	(E)	P=0.072
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.516		(E)	(E)	P=0.110
Brain Thalamus, Mineralization								
LESION RATES								
OVERALL (A)	26/61 (43%)	0/6 (0%)	0/7 (0%)	26/65 (40%)	32/61 (52%)	0/0 (0%)	1/2 (50%)	17/56 (30%)
ADJUSTED (B)	71.8%	0.0%	0.0%	73.0%	70.1%	0.0%	0.0%	42.2%
FINAL (D)	14/23 (61%)	0/0	0/0	17/26 (65%)	20/33 (61%)	0/0	0/0	13/36 (36%)
FIRST INCIDENCE (DAYS)	360	---	---	445	298	---	685	638
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.749	(E)	(E)	(E)	P=0.999
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.782	(E)	(E)	(E)	P=0.997
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.758	(E)	(E)	(E)	P=0.997
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.684		(E)	(E)	P=0.996

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Epididymis								
Granulomatous Inflammation								
LESION RATES					(G)			
OVERALL (A)	2/60 (3%)	0/0 (0%)	0/0 (0%)	1/63 (2%)				
ADJUSTED (B)	6.1%	0.0%	0.0%	2.9%				
FINAL (D)	1/23 (4%)	0/0	0/0	0/26 (0%)				
FIRST INCIDENCE (DAYS)	234	---	---	647				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.894				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.882				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.882				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.887				
Epididymis								
Hypospermia								
LESION RATES					(G)			
OVERALL (A)	1/60 (2%)	0/0 (0%)	0/0 (0%)	2/63 (3%)				
ADJUSTED (B)	4.3%	0.0%	0.0%	6.5%				
FINAL (D)	1/23 (4%)	0/0	0/0	0/26 (0%)				
FIRST INCIDENCE (DAYS)	726 (T)	---	---	672				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.542				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.598				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.598				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.518				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Eye								
Cornea, Inflammation								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/0 (0%)	0/0 (0%)	0/64 (0%)	0/59 (0%)	2/5 (40%)	0/2 (0%)	1/58 (2%)
ADJUSTED (B)	4.0%	0.0%	0.0%	0.0%	0.0%	50.0%	0.0%	2.9%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	2/4 (50%)	0/2 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	714	---	---	---	---	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.512
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.512
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.512
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.496
Eye								
Cornea, Mineralization								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/0 (0%)	0/0 (0%)	3/64 (5%)	0/59 (0%)	0/5 (0%)	0/2 (0%)	3/58 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	9.9%	0.0%	0.0%	0.0%	7.5%
FINAL (D)	0/23 (0%)	0/0	0/0	2/26 (8%)	0/33 (0%)	0/4 (0%)	0/2 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	523	---	---	---	447
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.136	(E)	(E)	(E)	P=0.125
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.169	(E)	(E)	(E)	P=0.145
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.169	(E)	(E)	(E)	P=0.118
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.128		(E)	(E)	P=0.119

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Eye Cornea, Pigmentation								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/0 (0%)	0/0 (0%)	0/64 (0%)	2/59 (3%)	0/5 (0%)	0/2 (0%)	0/58 (0%)
ADJUSTED (B)	4.0%	0.0%	0.0%	0.0%	4.8%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	0/4 (0%)	0/2 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	714	---	---	---	543	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=1.000
Eye Inflammation								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/0 (0%)	0/0 (0%)	2/64 (3%)	2/59 (3%)	0/5 (0%)	0/2 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	6.0%	3.6%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	0/33 (0%)	0/4 (0%)	0/2 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	647	495	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.269	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.316	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.316	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.256		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Harderian Gland Degeneration, Cystic								
LESION RATES								
OVERALL (A)	2/62 (3%)	0/3 (0%)	0/1 (0%)	1/63 (2%)	0/60 (0%)	0/5 (0%)	0/3 (0%)	1/57 (2%)
ADJUSTED (B)	8.7%	0.0%	0.0%	3.8%	0.0%	0.0%	0.0%	2.9%
FINAL (D)	2/23 (9%)	0/2 (0%)	0/1 (0%)	1/26 (4%)	0/33 (0%)	0/4 (0%)	0/3 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	726 (T)	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.512
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.512
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.512
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.881		(E)	(E)	P=0.487
Harderian Gland Hyperplasia								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/3 (0%)	0/1 (0%)	0/63 (0%)	0/60 (0%)	0/5 (0%)	0/3 (0%)	4/57 (7%)
ADJUSTED (B)	4.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.9%
FINAL (D)	1/23 (4%)	0/2 (0%)	0/1 (0%)	0/26 (0%)	0/33 (0%)	0/4 (0%)	0/3 (0%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	---	---	---	---	697
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.073
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.065
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.066
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.053

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Harderian Gland Inflammation								
LESION RATES								
OVERALL (A)	0/62 (0%)	1/3 (33%)	0/1 (0%)	3/63 (5%)	1/60 (2%)	0/5 (0%)	0/3 (0%)	0/57 (0%)
ADJUSTED (B)	0.0%	50.0%	0.0%	9.3%	3.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	1/2 (50%)	0/1 (0%)	1/26 (4%)	1/33 (3%)	0/4 (0%)	0/3 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	726 (T)	---	646	732 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.151	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.172	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.132	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.125		(E)	(E)	(E)
Harderian Gland Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	2/62 (3%)	0/3 (0%)	0/1 (0%)	3/63 (5%)	4/60 (7%)	0/5 (0%)	0/3 (0%)	4/57 (7%)
ADJUSTED (B)	8.7%	0.0%	0.0%	11.5%	10.6%	0.0%	0.0%	9.5%
FINAL (D)	2/23 (9%)	0/2 (0%)	0/1 (0%)	3/26 (12%)	3/33 (9%)	0/4 (0%)	0/3 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	726 (T)	353	---	---	161
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.557	(E)	(E)	(E)	P=0.660
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.557	(E)	(E)	(E)	P=0.652
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.557	(E)	(E)	(E)	P=0.612
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.508		(E)	(E)	P=0.612

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Heart								
Cardiomyopathy, Chronic								
LESION RATES								
OVERALL (A)	5/62 (8%)	0/3 (0%)	0/3 (0%)	2/65 (3%)	5/62 (8%)	0/0 (0%)	0/0 (0%)	4/59 (7%)
ADJUSTED (B)	12.7%	0.0%	0.0%	7.7%	11.7%	0.0%	0.0%	8.9%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	2/26 (8%)	2/33 (6%)	0/0	0/0	1/36 (3%)
FIRST INCIDENCE (DAYS)	373	---	---	728 (T)	495	---	---	468
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.950	(E)	(E)	(E)	P=0.737
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.911	(E)	(E)	(E)	P=0.766
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.950	(E)	(E)	(E)	P=0.766
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.950		(E)	(E)	P=0.729
Heart								
Degeneration								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/3 (0%)	0/3 (0%)	0/65 (0%)	0/62 (0%)	0/0 (0%)	0/0 (0%)	4/59 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.5%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	3/36 (8%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	684
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.078
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.063
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.063
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.054

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Heart Mineralization								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/3 (0%)	0/3 (0%)	0/65 (0%)	3/62 (5%)	0/0 (0%)	0/0 (0%)	1/59 (2%)
ADJUSTED (B)	2.0%	0.0%	0.0%	0.0%	8.1%	0.0%	0.0%	1.8%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	0/26 (0%)	2/33 (6%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	373	---	---	---	570	---	---	412
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.939
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.923
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.923
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.934
Heart Myocarditis, Acute								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/3 (0%)	0/3 (0%)	2/65 (3%)	1/62 (2%)	0/0 (0%)	0/0 (0%)	2/59 (3%)
ADJUSTED (B)	1.9%	0.0%	0.0%	6.0%	2.8%	0.0%	0.0%	4.8%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	304	---	---	523	715	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.521	(E)	(E)	(E)	P=0.519
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.568	(E)	(E)	(E)	P=0.323
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.514	(E)	(E)	(E)	P=0.323
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.518		(E)	(E)	P=0.481

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Heart								
Thrombosis								
LESION RATES								
OVERALL (A)	4/62 (6%)	3/3 (100%)	2/3 (67%)	4/65 (6%)	4/62 (6%)	0/0 (0%)	0/0 (0%)	2/59 (3%)
ADJUSTED (B)	11.4%	100.0%	0.0%	12.1%	10.4%	0.0%	0.0%	5.3%
FINAL (D)	0/23 (0%)	1/1 (100%)	0/0	0/26 (0%)	0/33 (0%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	304	451	599	646	653	---	---	718
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.699	(E)	(E)	(E)	P=0.908
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.615	(E)	(E)	(E)	P=0.870
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.679	(E)	(E)	(E)	P=0.870
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.667		(E)	(E)	P=0.885
Intestine-Small, Jejunum								
Lymphoid Hyperplasia								
LESION RATES								
OVERALL (A)	0/56 (0%)	0/2 (0%)	0/4 (0%)	0/60 (0%)	0/58 (0%)	0/0 (0%)	0/0 (0%)	2/57 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/0	0/25 (0%)	0/33 (0%)	0/0	0/0	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.243

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Kidney Amyloidosis								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/26 (0%)	0/22 (0%)	0/65 (0%)	0/63 (0%)	0/8 (0%)	0/4 (0%)	2/59 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/11 (0%)	0/7 (0%)	0/26 (0%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.232
Kidney Cyst								
LESION RATES								
OVERALL (A)	3/62 (5%)	1/26 (4%)	5/22 (23%)	5/65 (8%)	0/63 (0%)	0/8 (0%)	0/4 (0%)	1/59 (2%)
ADJUSTED (B)	9.5%	9.1%	45.7%	18.5%	0.0%	0.0%	0.0%	2.8%
FINAL (D)	1/23 (4%)	1/11 (9%)	3/7 (43%)	4/26 (15%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	452	726 (T)	523	706	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.411	(E)	(E)	(E)	P=0.517
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.491	(E)	(E)	(E)	P=0.517
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.398	(E)	(E)	(E)	P=0.517
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.386		(E)	(E)	P=0.484

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney Embolism, Septic								
LESION RATES								
OVERALL (A)	0/62 (0%)	2/26 (8%)	0/22 (0%)	0/65 (0%)	2/63 (3%)	0/8 (0%)	0/4 (0%)	3/59 (5%)
ADJUSTED (B)	0.0%	10.8%	0.0%	0.0%	5.6%	0.0%	0.0%	7.4%
FINAL (D)	0/23 (0%)	1/11 (9%)	0/7 (0%)	0/26 (0%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	342	---	---	715	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.532
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.300
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.492
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.469
Kidney Hydronephrosis								
LESION RATES								
OVERALL (A)	1/62 (2%)	3/26 (12%)	4/22 (18%)	2/65 (3%)	1/63 (2%)	0/8 (0%)	0/4 (0%)	0/59 (0%)
ADJUSTED (B)	2.8%	20.0%	32.8%	6.5%	3.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	2/11 (18%)	2/7 (29%)	1/26 (4%)	1/33 (3%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	591	500	534	646	732 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.541	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.437	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.526	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.518		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney Infarct								
LESION RATES								
OVERALL (A)	2/62 (3%)	1/26 (4%)	0/22 (0%)	1/65 (2%)	0/63 (0%)	0/8 (0%)	0/4 (0%)	1/59 (2%)
ADJUSTED (B)	8.2%	2.0%	0.0%	3.8%	0.0%	0.0%	0.0%	2.6%
FINAL (D)	1/23 (4%)	0/11 (0%)	0/7 (0%)	1/26 (4%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	714	388	---	726 (T)	---	---	---	718
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.894	(E)	(E)	(E)	P=0.522
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.911	(E)	(E)	(E)	P=0.443
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.896	(E)	(E)	(E)	P=0.506
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.887		(E)	(E)	P=0.484
Kidney Inflammation, Suppurative								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/26 (0%)	0/22 (0%)	2/65 (3%)	1/63 (2%)	1/8 (13%)	0/4 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.8%	1.9%	2.6%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/11 (0%)	0/7 (0%)	0/26 (0%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	523	543	726	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.240	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.370	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.248	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.260		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	4/62 (6%)	1/26 (4%)	0/22 (0%)	3/65 (5%)	7/63 (11%)	3/8 (38%)	0/4 (0%)	11/59 (19%)
ADJUSTED (B)	15.8%	9.1%	0.0%	10.0%	21.2%	6.6%	0.0%	30.6%
FINAL (D)	3/23 (13%)	1/11 (9%)	0/7 (0%)	1/26 (4%)	7/33 (21%)	0/1 (0%)	0/1 (0%)	11/36 (31%)
FIRST INCIDENCE (DAYS)	637	726 (T)	---	646	732 (T)	614	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.828	(E)	(E)	(E)	P=0.273
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.798	(E)	(E)	(E)	P=0.273
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.816	(E)	(E)	(E)	P=0.273
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.799		(E)	(E)	P=0.180
Kidney Medulla, Tubule, Protein Casts								
LESION RATES								
OVERALL (A)	1/62 (2%)	1/26 (4%)	0/22 (0%)	3/65 (5%)	4/63 (6%)	0/8 (0%)	0/4 (0%)	3/59 (5%)
ADJUSTED (B)	4.3%	3.1%	0.0%	10.0%	9.8%	0.0%	0.0%	8.3%
FINAL (D)	1/23 (4%)	0/11 (0%)	0/7 (0%)	1/26 (4%)	2/33 (6%)	0/1 (0%)	0/1 (0%)	3/36 (8%)
FIRST INCIDENCE (DAYS)	726 (T)	689	---	672	495	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.352	(E)	(E)	(E)	P=0.796
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.393	(E)	(E)	(E)	P=0.771
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.332	(E)	(E)	(E)	P=0.770
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.328		(E)	(E)	P=0.752

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Microcalculi								
LESION RATES								
OVERALL (A)	7/62 (11%)	3/26 (12%)	2/22 (9%)	11/65 (17%)	4/63 (6%)	0/8 (0%)	1/4 (25%)	1/59 (2%)
ADJUSTED (B)	23.0%	27.3%	16.8%	37.9%	9.7%	0.0%	2.8%	1.8%
FINAL (D)	3/23 (13%)	3/11 (27%)	1/7 (14%)	9/26 (35%)	2/33 (6%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	527	726 (T)	681	517	375	---	715	412
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.301	(E)	(E)	(E)	P=0.966
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.329	(E)	(E)	(E)	P=0.965
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.269	(E)	(E)	(E)	P=0.958
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.257		(E)	(E)	P=0.966
Kidney								
Osseous Metaplasia								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/26 (0%)	0/22 (0%)	1/65 (2%)	3/63 (5%)	1/8 (13%)	0/4 (0%)	2/59 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	3.1%	9.1%	2.5%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/11 (0%)	0/7 (0%)	0/26 (0%)	3/33 (9%)	0/1 (0%)	0/1 (0%)	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	663	732 (T)	715	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.527	(E)	(E)	(E)	P=0.847
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.571	(E)	(E)	(E)	P=0.847
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.515	(E)	(E)	(E)	P=0.847
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.512		(E)	(E)	P=0.797

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Pyelonephritis								
LESION RATES								
OVERALL (A)	2/62 (3%)	5/26 (19%)	1/22 (5%)	2/65 (3%)	1/63 (2%)	1/8 (13%)	0/4 (0%)	2/59 (3%)
ADJUSTED (B)	4.8%	17.6%	2.9%	6.0%	2.3%	2.0%	0.0%	4.4%
FINAL (D)	0/23 (0%)	1/11 (9%)	0/7 (0%)	1/26 (4%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	526	388	681	517	591	615	---	516
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.702	(E)	(E)	(E)	P=0.490
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.725	(E)	(E)	(E)	P=0.307
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.715	(E)	(E)	(E)	P=0.469
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.708		(E)	(E)	P=0.475
Kidney								
Tubule, Casts, Pigmented								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/26 (0%)	0/22 (0%)	0/65 (0%)	2/63 (3%)	0/8 (0%)	0/4 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	4.3%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/11 (0%)	0/7 (0%)	0/26 (0%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	397	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Tubule, Hyperplasia								
LESION RATES								
OVERALL (A)	2/62 (3%)	0/26 (0%)	1/22 (5%)	2/65 (3%)	0/63 (0%)	0/8 (0%)	0/4 (0%)	1/59 (2%)
ADJUSTED (B)	8.7%	0.0%	3.7%	7.7%	0.0%	0.0%	0.0%	2.8%
FINAL (D)	2/23 (9%)	0/11 (0%)	0/7 (0%)	2/26 (8%)	0/33 (0%)	0/1 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	---	723	726 (T)	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.740	(E)	(E)	(E)	P=0.517
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.740	(E)	(E)	(E)	P=0.517
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.740	(E)	(E)	(E)	P=0.517
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.708		(E)	(E)	P=0.484
Larynx								
Inflammation, Chronic								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/0 (0%)	0/0 (0%)	2/63 (3%)	1/56 (2%)	0/0 (0%)	0/0 (0%)	1/56 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	7.1%	3.3%	0.0%	0.0%	2.9%
FINAL (D)	0/23 (0%)	0/0	0/0	1/25 (4%)	1/30 (3%)	0/0	0/0	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	672	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.264	(E)	(E)	(E)	P=0.795
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.305	(E)	(E)	(E)	P=0.795
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.305	(E)	(E)	(E)	P=0.795
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.260		(E)	(E)	P=0.752

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver Basophilic Focus								
LESION RATES								
OVERALL (A)	1/62 (2%)	3/28 (11%)	1/34 (3%)	2/64 (3%)	0/62 (0%)	0/33 (0%)	2/26 (8%)	0/59 (0%)
ADJUSTED (B)	4.3%	21.4%	6.7%	5.7%	0.0%	0.0%	10.2%	0.0%
FINAL (D)	1/23 (4%)	3/14 (21%)	1/15 (7%)	1/26 (4%)	0/33 (0%)	0/17 (0%)	1/12 (8%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	726 (T)	444	---	---	571	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.540	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.587	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.520	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.512		(E)	(E)	(E)
Liver Infarction								
LESION RATES								
OVERALL (A)	0/62 (0%)	0/28 (0%)	1/34 (3%)	0/64 (0%)	2/62 (3%)	0/33 (0%)	0/26 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	6.7%	0.0%	4.8%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/14 (0%)	1/15 (7%)	0/26 (0%)	1/33 (3%)	0/17 (0%)	0/12 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	---	495	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.982
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.988
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.982
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver Inflammation								
LESION RATES								
OVERALL (A)	4/62 (6%)	1/28 (4%)	2/34 (6%)	2/64 (3%)	10/62 (16%)	5/33 (15%)	5/26 (19%)	14/59 (24%)
ADJUSTED (B)	13.7%	7.1%	8.6%	5.9%	28.0%	21.0%	34.9%	36.8%
FINAL (D)	1/23 (4%)	1/14 (7%)	1/15 (7%)	1/26 (4%)	8/33 (24%)	3/17 (18%)	4/12 (33%)	12/36 (33%)
FIRST INCIDENCE (DAYS)	588	726 (T)	449	451	632	514	673	718
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.909	(E)	(E)	(E)	P=0.321
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.868	(E)	(E)	(E)	P=0.237
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.909	(E)	(E)	(E)	P=0.285
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.903		(E)	(E)	P=0.206
Liver Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/28 (0%)	0/34 (0%)	3/64 (5%)	15/62 (24%)	1/33 (3%)	3/26 (12%)	16/59 (27%)
ADJUSTED (B)	3.8%	0.0%	0.0%	11.5%	41.6%	5.9%	25.0%	43.2%
FINAL (D)	0/23 (0%)	0/14 (0%)	0/15 (0%)	3/26 (12%)	13/33 (39%)	1/17 (6%)	3/12 (25%)	15/36 (42%)
FIRST INCIDENCE (DAYS)	705	---	---	726 (T)	375	732 (T)	732 (T)	708
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.342	(E)	(E)	(E)	P=0.602
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.372	(E)	(E)	(E)	P=0.567
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.333	(E)	(E)	(E)	P=0.519
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.322		(E)	(E)	P=0.436

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Necrosis, Hepatocellular								
LESION RATES								
OVERALL (A)	7/62 (11%)	2/28 (7%)	1/34 (3%)	11/64 (17%)	3/62 (5%)	0/33 (0%)	2/26 (8%)	1/59 (2%)
ADJUSTED (B)	23.6%	3.4%	6.7%	21.6%	7.9%	0.0%	4.8%	2.7%
FINAL (D)	4/23 (17%)	0/14 (0%)	1/15 (7%)	2/26 (8%)	2/33 (6%)	0/17 (0%)	0/12 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	46	19	726 (T)	38	556	---	608	724
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.313	(E)	(E)	(E)	P=0.939
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.321	(E)	(E)	(E)	P=0.901
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.230	(E)	(E)	(E)	P=0.935
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.245		(E)	(E)	P=0.934
Lung								
Adenomatous Hyperplasia								
LESION RATES								
OVERALL (A)	2/61 (3%)	2/25 (8%)	0/30 (0%)	0/65 (0%)	1/62 (2%)	0/28 (0%)	1/11 (9%)	2/59 (3%)
ADJUSTED (B)	8.3%	25.0%	0.0%	0.0%	2.6%	0.0%	2.2%	5.6%
FINAL (D)	1/23 (4%)	2/8 (25%)	0/5 (0%)	0/26 (0%)	0/33 (0%)	0/11 (0%)	0/1 (0%)	2/36 (6%)
FIRST INCIDENCE (DAYS)	719	726 (T)	---	---	675	---	664	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.532
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.487
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.506
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.481

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lung Alveolar Histiocytosis								
LESION RATES								
OVERALL (A)	4/61 (7%)	1/25 (4%)	2/30 (7%)	3/65 (5%)	4/62 (6%)	1/28 (4%)	0/11 (0%)	3/59 (5%)
ADJUSTED (B)	14.2%	12.5%	5.1%	9.3%	11.0%	9.1%	0.0%	7.7%
FINAL (D)	2/23 (9%)	1/8 (13%)	0/5 (0%)	1/26 (4%)	2/33 (6%)	1/11 (9%)	0/1 (0%)	2/36 (6%)
FIRST INCIDENCE (DAYS)	475	726 (T)	599	561	675	732 (T)	---	611
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.811	(E)	(E)	(E)	P=0.806
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.837	(E)	(E)	(E)	P=0.714
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.820	(E)	(E)	(E)	P=0.784
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.806		(E)	(E)	P=0.759
Lung Congestion								
LESION RATES								
OVERALL (A)	8/61 (13%)	7/25 (28%)	13/30 (43%)	8/65 (12%)	2/62 (3%)	10/28 (36%)	4/11 (36%)	13/59 (22%)
ADJUSTED (B)	18.1%	13.7%	25.3%	20.3%	4.3%	22.9%	8.4%	22.9%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/5 (0%)	1/26 (4%)	0/33 (0%)	1/11 (9%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	46	19	18	40	495	24	352	96
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.645	(E)	(E)	(E)	P=0.004 **
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.578	(E)	(E)	(E)	P<0.001 **
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.644	(E)	(E)	(E)	P<0.001 **
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.657		(E)	(E)	P=0.002 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung								
Hemorrhage								
LESION RATES								
OVERALL (A)	0/61 (0%)	3/25 (12%)	2/30 (7%)	2/65 (3%)	4/62 (6%)	0/28 (0%)	0/11 (0%)	1/59 (2%)
ADJUSTED (B)	0.0%	4.7%	4.6%	5.5%	7.8%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/5 (0%)	1/26 (4%)	0/33 (0%)	0/11 (0%)	0/1 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	---	39	241	373	298	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.270	(E)	(E)	(E)	P=0.961
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.317	(E)	(E)	(E)	P=0.968
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.253	(E)	(E)	(E)	P=0.960
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.264		(E)	(E)	P=0.967
Lung								
Inflammation, Chronic								
LESION RATES								
OVERALL (A)	3/61 (5%)	0/25 (0%)	0/30 (0%)	4/65 (6%)	3/62 (5%)	0/28 (0%)	0/11 (0%)	0/59 (0%)
ADJUSTED (B)	10.3%	0.0%	0.0%	11.2%	6.6%	0.0%	0.0%	0.0%
FINAL (D)	2/23 (9%)	0/8 (0%)	0/5 (0%)	2/26 (8%)	0/33 (0%)	0/11 (0%)	0/1 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	234	---	---	40	298	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.543	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.530	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.533	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.536		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lung								
Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	2/61 (3%)	0/25 (0%)	0/30 (0%)	1/65 (2%)	10/62 (16%)	2/28 (7%)	0/11 (0%)	7/59 (12%)
ADJUSTED (B)	4.0%	0.0%	0.0%	3.8%	29.1%	18.2%	0.0%	19.4%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/5 (0%)	1/26 (4%)	9/33 (27%)	2/11 (18%)	0/1 (0%)	7/36 (19%)
FIRST INCIDENCE (DAYS)	234	---	---	726 (T)	671	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.887	(E)	(E)	(E)	P=0.902
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.900	(E)	(E)	(E)	P=0.893
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.887	(E)	(E)	(E)	P=0.894
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.889		(E)	(E)	P=0.825
Lymph Node, Iliac								
Hyperplasia								
LESION RATES								
OVERALL (A)	0/0 (0%)	0/1 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)	2/2 (100%)	0/0 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	100.0%	0.0%
FINAL (D)	0/0	0/1 (0%)	0/0	0/0	0/0	1/1 (100%)	1/1 (100%)	0/0
FIRST INCIDENCE (DAYS)	---	---	---	---	---	732 (T)	708	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Lumbar Hyperplasia								
LESION RATES								
OVERALL (A)	2/2 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/1 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
FIRST INCIDENCE (DAYS)	553	500	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Lymph Node, Mandibular Congestion								
LESION RATES								
OVERALL (A)	0/52 (0%)	0/3 (0%)	0/1 (0%)	1/52 (2%)	1/56 (2%)	4/18 (22%)	3/7 (43%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	3.1%	2.7%	28.7%	51.1%	5.4%
FINAL (D)	0/23 (0%)	0/2 (0%)	0/1 (0%)	0/24 (0%)	0/32 (0%)	3/11 (27%)	2/4 (50%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	663	711	608	664	718
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.527	(E)	(E)	(E)	P=0.526
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.567	(E)	(E)	(E)	P=0.474
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.505	(E)	(E)	(E)	P=0.521
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.500		(E)	(E)	P=0.500

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Mandibular Hemosiderosis								
LESION RATES								
OVERALL (A)	0/52 (0%)	0/3 (0%)	0/1 (0%)	2/52 (4%)	0/56 (0%)	0/18 (0%)	0/7 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	6.0%	0.0%	0.0%	0.0%	5.5%
FINAL (D)	0/23 (0%)	0/2 (0%)	0/1 (0%)	1/24 (4%)	0/32 (0%)	0/11 (0%)	0/4 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	444	---	---	---	724
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.256	(E)	(E)	(E)	P=0.262
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.289	(E)	(E)	(E)	P=0.232
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.239	(E)	(E)	(E)	P=0.256
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.248		(E)	(E)	P=0.248
Lymph Node, Mandibular Hyperplasia								
LESION RATES								
OVERALL (A)	2/52 (4%)	3/3 (100%)	0/1 (0%)	8/52 (15%)	9/56 (16%)	9/18 (50%)	1/7 (14%)	13/56 (23%)
ADJUSTED (B)	6.0%	100.0%	0.0%	22.1%	20.9%	65.3%	25.0%	33.2%
FINAL (D)	1/23 (4%)	2/2 (100%)	0/1 (0%)	3/24 (13%)	3/32 (9%)	7/11 (64%)	1/4 (25%)	10/35 (29%)
FIRST INCIDENCE (DAYS)	146	74	---	346	353	653	732 (T)	96
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.066	(E)	(E)	(E)	P=0.299
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.068	(E)	(E)	(E)	P=0.211
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.047 *	(E)	(E)	(E)	P=0.239
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.046 *		(E)	(E)	P=0.238

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Mesenteric Angiectasis								
LESION RATES								
OVERALL (A)	11/45 (24%)	11/18 (61%)	9/18 (50%)	16/43 (37%)	5/55 (9%)	7/22 (32%)	4/11 (36%)	10/50 (20%)
ADJUSTED (B)	36.5%	62.7%	48.3%	45.9%	15.2%	40.2%	66.7%	29.4%
FINAL (D)	5/23 (22%)	7/12 (58%)	4/10 (40%)	8/25 (32%)	5/33 (15%)	4/11 (36%)	4/6 (67%)	10/34 (29%)
FIRST INCIDENCE (DAYS)	554	564	599	444	732 (T)	542	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.268	(E)	(E)	(E)	P=0.136
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.263	(E)	(E)	(E)	P=0.136
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.220	(E)	(E)	(E)	P=0.136
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.143		(E)	(E)	P=0.094
Lymph Node, Mesenteric Atrophy								
LESION RATES								
OVERALL (A)	1/45 (2%)	0/18 (0%)	0/18 (0%)	0/43 (0%)	2/55 (4%)	0/22 (0%)	0/11 (0%)	0/50 (0%)
ADJUSTED (B)	2.4%	0.0%	0.0%	0.0%	3.4%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/12 (0%)	0/10 (0%)	0/25 (0%)	0/33 (0%)	0/11 (0%)	0/6 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	527	---	---	---	177	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Mesenteric Congestion								
LESION RATES								
OVERALL (A)	2/45 (4%)	4/18 (22%)	2/18 (11%)	7/43 (16%)	0/55 (0%)	2/22 (9%)	2/11 (18%)	0/50 (0%)
ADJUSTED (B)	8.7%	33.3%	20.0%	21.7%	0.0%	18.2%	18.8%	0.0%
FINAL (D)	2/23 (9%)	4/12 (33%)	2/10 (20%)	3/25 (12%)	0/33 (0%)	2/11 (18%)	1/6 (17%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	726 (T)	523	---	732 (T)	708	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.110	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.128	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.094	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.068		(E)	(E)	(E)
Lymph Node, Mesenteric Hyperplasia								
LESION RATES								
OVERALL (A)	3/45 (7%)	1/18 (6%)	2/18 (11%)	3/43 (7%)	3/55 (5%)	7/22 (32%)	2/11 (18%)	6/50 (12%)
ADJUSTED (B)	10.3%	2.7%	13.0%	8.8%	8.8%	40.5%	18.7%	17.6%
FINAL (D)	2/23 (9%)	0/12 (0%)	1/10 (10%)	1/25 (4%)	2/33 (6%)	4/11 (36%)	1/6 (17%)	6/34 (18%)
FIRST INCIDENCE (DAYS)	146	650	712	447	722	615	684	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.699	(E)	(E)	(E)	P=0.260
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.638	(E)	(E)	(E)	P=0.255
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.595	(E)	(E)	(E)	P=0.265
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.640		(E)	(E)	P=0.199

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, NOS **Hyperplasia**								
LESION RATES								
OVERALL (A)	0/1 (0%)	2/3 (67%)	0/1 (0%)	0/2 (0%)	1/4 (25%)	1/5 (20%)	1/1 (100%)	6/8 (75%)
ADJUSTED (B)	0.0%	100.0%	0.0%	0.0%	25.0%	0.0%	0.0%	72.1%
FINAL (D)	0/1 (0%)	1/1 (100%)	0/0	0/1 (0%)	1/4 (25%)	0/0	0/0	5/7 (71%)
FIRST INCIDENCE (DAYS)	---	388	---	---	732 (T)	660	708	697
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Nose 1 **Luminal Exudate**								
LESION RATES								
OVERALL (A)	0/58 (0%)	3/65 (5%)	4/68 (6%)	0/55 (0%)	1/60 (2%)	1/65 (2%)	0/58 (0%)	1/57 (2%)
ADJUSTED (B)	0.0%	6.7%	12.3%	0.0%	3.2%	1.9%	0.0%	2.6%
FINAL (D)	0/21 (0%)	0/30 (0%)	2/26 (8%)	0/22 (0%)	1/31 (3%)	0/38 (0%)	0/34 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	264	537	---	732 (T)	608	---	718
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.831	P=0.137	P=0.094	(E)	P=0.686	P=0.804	(E)	P=0.785
INCIDENTAL TUMOR	P=0.860	P=0.123	P=0.104	(E)	P=0.587	P=0.806	(E)	P=0.743
LOGISTIC REGRESSION	P=0.818	P=0.143	P=0.091	(E)	P=0.666	P=0.793	(E)	P=0.781
COCHRAN-ARMITAGE	P=0.816				P=0.664			
FISHER EXACT		P=0.144	P=0.081	(E)		P=0.772	P=1.000	P=0.739

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Squamous Epithelium, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/58 (0%)	6/65 (9%)	8/68 (12%)	9/55 (16%)	1/60 (2%)	11/65 (17%)	5/58 (9%)	15/57 (26%)
ADJUSTED (B)	0.0%	18.7%	26.0%	32.5%	2.6%	25.3%	12.4%	41.4%
FINAL (D)	0/21 (0%)	5/30 (17%)	6/26 (23%)	6/22 (27%)	0/31 (0%)	8/38 (21%)	2/34 (6%)	14/35 (40%)
FIRST INCIDENCE (DAYS)	---	597	422	447	671	544	619	638
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.007 **	P=0.042 *	P=0.010 *	P=0.003 **	P=0.002 **	P=0.009 **	P=0.133	P<0.001 **
INCIDENTAL TUMOR	P=0.009 **	P=0.031 *	P=0.010 **	P=0.005 **	P<0.001 **	P=0.008 **	P=0.107	P<0.001 **
LOGISTIC REGRESSION	P=0.005 **	P=0.030 *	P=0.010 *	P=0.002 **	P<0.001 **	P=0.007 **	P=0.109	P<0.001 **
COCHRAN-ARMITAGE	P=0.006 **				P<0.001 **			
FISHER EXACT		P=0.019 *	P=0.006 **	P=0.001 **		P=0.003 **	P=0.096	P<0.001 **
Nose 1 Squamous Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	16/58 (28%)	51/65 (78%)	57/68 (84%)	43/55 (78%)	30/60 (50%)	57/65 (88%)	53/58 (91%)	46/57 (81%)
ADJUSTED (B)	53.9%	96.0%	93.2%	97.3%	72.1%	98.2%	96.2%	91.7%
FINAL (D)	9/21 (43%)	28/30 (93%)	22/26 (85%)	21/22 (95%)	20/31 (65%)	37/38 (97%)	32/34 (94%)	31/35 (89%)
FIRST INCIDENCE (DAYS)	107	39	19	6	26	103	25	78
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.008 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.175	P=0.002 **	P=0.002 **	P=0.025 *
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.008 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.005 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P=0.008 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Squamous Epithelium, Microabscess								
LESION RATES								
OVERALL (A)	6/58 (10%)	22/65 (34%)	15/68 (22%)	15/55 (27%)	9/60 (15%)	20/65 (31%)	16/58 (28%)	15/57 (26%)
ADJUSTED (B)	21.6%	63.9%	43.5%	54.1%	25.8%	46.6%	43.2%	42.9%
FINAL (D)	3/21 (14%)	18/30 (60%)	8/26 (31%)	11/22 (50%)	7/31 (23%)	16/38 (42%)	14/34 (41%)	15/35 (43%)
FIRST INCIDENCE (DAYS)	452	39	537	346	26	514	25	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.189	P=0.007 **	P=0.079	P=0.036 *	P=0.396	P=0.056	P=0.121	P=0.187
INCIDENTAL TUMOR	P=0.148	P=0.003 **	P=0.056	P=0.028 *	P=0.377	P=0.040 *	P=0.111	P=0.171
LOGISTIC REGRESSION	P=0.156	P=0.002 **	P=0.072	P=0.019 *	P=0.324	P=0.042 *	P=0.105	P=0.125
COCHRAN-ARMITAGE	P=0.163				P=0.256			
FISHER EXACT		P=0.002 **	P=0.063	P=0.019 *		P=0.030 *	P=0.074	P=0.099
Nose 2 Luminal Exudate								
LESION RATES								
OVERALL (A)	4/60 (7%)	7/62 (11%)	8/65 (12%)	5/62 (8%)	12/60 (20%)	18/62 (29%)	9/54 (17%)	5/57 (9%)
ADJUSTED (B)	13.3%	20.5%	22.0%	14.5%	33.5%	44.7%	25.9%	11.5%
FINAL (D)	2/23 (9%)	5/28 (18%)	3/25 (12%)	1/25 (4%)	10/32 (31%)	14/35 (40%)	7/31 (23%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	380	17	59	373	177	514	445	412
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.599	P=0.360	P=0.253	P=0.566	P=0.996	P=0.219	P=0.818	P=0.985
INCIDENTAL TUMOR	P=0.615	P=0.300	P=0.186	P=0.637	P=0.996	P=0.179	P=0.794	P=0.980
LOGISTIC REGRESSION	P=0.611	P=0.287	P=0.230	P=0.545	P=0.994	P=0.237	P=0.782	P=0.978
COCHRAN-ARMITAGE	P=0.594				P=0.993			
FISHER EXACT		P=0.284	P=0.223	P=0.521		P=0.172	P=0.757	P=0.978

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Luminal Hemorrhage								
LESION RATES								
OVERALL (A)	0/60 (0%)	1/62 (2%)	1/65 (2%)	2/62 (3%)	1/60 (2%)	2/62 (3%)	0/54 (0%)	1/57 (2%)
ADJUSTED (B)	0.0%	3.6%	2.5%	7.1%	2.0%	4.7%	0.0%	2.9%
FINAL (D)	0/23 (0%)	1/28 (4%)	0/25 (0%)	0/25 (0%)	0/32 (0%)	1/35 (3%)	0/31 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	726 (T)	599	704	558	608	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.178	P=0.539	P=0.532	P=0.256	P=0.757	P=0.549	(E)	P=0.759
INCIDENTAL TUMOR	P=0.173	P=0.539	P=0.305	P=0.353	P=0.654	P=0.563	(E)	P=0.670
LOGISTIC REGRESSION	P=0.185	P=0.539	P=0.520	P=0.256	P=0.747	P=0.506	(E)	P=0.753
COCHRAN-ARMITAGE	P=0.179				P=0.747			
FISHER EXACT		P=0.508	P=0.520	P=0.256		P=0.512	P=1.000	P=0.739
Nose 2 Nasolacrimal Duct, Luminal Exudate								
LESION RATES								
OVERALL (A)	0/60 (0%)	2/62 (3%)	0/65 (0%)	1/62 (2%)	2/60 (3%)	1/62 (2%)	2/54 (4%)	2/57 (4%)
ADJUSTED (B)	0.0%	5.9%	0.0%	2.0%	4.3%	2.9%	3.7%	4.6%
FINAL (D)	0/23 (0%)	1/28 (4%)	0/25 (0%)	0/25 (0%)	0/32 (0%)	1/35 (3%)	0/31 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	597	---	445	298	732 (T)	269	412
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.600	P=0.280	(E)	P=0.517	P=0.516	P=0.888	P=0.687	P=0.695
INCIDENTAL TUMOR	P=0.576	P=0.184	(E)	P=0.615	P=0.490	P=0.844	P=0.660	P=0.682
LOGISTIC REGRESSION	P=0.603	P=0.254	(E)	P=0.495	P=0.511	P=0.870	P=0.655	P=0.668
COCHRAN-ARMITAGE	P=0.597				P=0.500			
FISHER EXACT		P=0.256	(E)	P=0.508		P=0.884	P=0.650	P=0.671

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Ciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/60 (0%)	3/62 (5%)	15/65 (23%)	12/62 (19%)	12/60 (20%)	9/62 (15%)	7/54 (13%)	21/57 (37%)
ADJUSTED (B)	0.0%	8.1%	38.4%	29.3%	31.6%	21.2%	17.5%	48.2%
FINAL (D)	0/23 (0%)	1/28 (4%)	5/25 (20%)	4/25 (16%)	8/32 (25%)	5/35 (14%)	3/31 (10%)	14/35 (40%)
FIRST INCIDENCE (DAYS)	---	403	241	100	495	599	352	161
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.154	P<0.001 **	P=0.001 **	P=0.011 *	P=0.885	P=0.925	P=0.083
INCIDENTAL TUMOR	P=0.002 **	P=0.145	P<0.001 **	P=0.001 **	P=0.003 **	P=0.899	P=0.892	P=0.048 *
LOGISTIC REGRESSION	P<0.001 **	P=0.129	P<0.001 **	P<0.001 **	P=0.004 **	P=0.896	P=0.909	P=0.038 *
COCHRAN-ARMITAGE	P<0.001 **				P=0.004 **			
FISHER EXACT		P=0.128	P<0.001 **	P<0.001 **		P=0.851	P=0.897	P=0.034 *
Nose 2 Respiratory Epithelium, Ciliated, Inflammation								
LESION RATES								
OVERALL (A)	0/60 (0%)	1/62 (2%)	0/65 (0%)	0/62 (0%)	5/60 (8%)	6/62 (10%)	0/54 (0%)	1/57 (2%)
ADJUSTED (B)	0.0%	3.6%	0.0%	0.0%	13.4%	16.4%	0.0%	2.3%
FINAL (D)	0/23 (0%)	1/28 (4%)	0/25 (0%)	0/25 (0%)	2/32 (6%)	5/35 (14%)	0/31 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	726 (T)	---	---	632	710	---	611
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.921	P=0.539	(E)	(E)	P=0.991	P=0.563	(E)	P=0.983
INCIDENTAL TUMOR	P=0.921	P=0.539	(E)	(E)	P=0.986	P=0.600	(E)	P=0.961
LOGISTIC REGRESSION	P=0.921	P=0.539	(E)	(E)	P=0.990	P=0.584	(E)	P=0.983
COCHRAN-ARMITAGE	P=0.922				P=0.988			
FISHER EXACT		P=0.508	(E)	(E)		P=0.523	P=1.000	P=0.984

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/62 (0%)	0/65 (0%)	0/62 (0%)	2/60 (3%)	0/62 (0%)	0/54 (0%)	1/57 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	6.3%	0.0%	0.0%	2.9%
FINAL (D)	0/23 (0%)	0/28 (0%)	0/25 (0%)	0/25 (0%)	2/32 (6%)	0/35 (0%)	0/31 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.773	(E)	(E)	P=0.895
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.773	(E)	(E)	P=0.895
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.773	(E)	(E)	P=0.895
COCHRAN-ARMITAGE	(E)				P=0.750			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=0.868
Nose 2 Respiratory Epithelium, Ciliated, Transitional Metaplasia								
LESION RATES								
OVERALL (A)	0/60 (0%)	3/62 (5%)	12/65 (18%)	15/62 (24%)	2/60 (3%)	3/62 (5%)	2/54 (4%)	8/57 (14%)
ADJUSTED (B)	0.0%	10.7%	30.1%	47.8%	5.7%	8.0%	4.6%	20.8%
FINAL (D)	0/23 (0%)	3/28 (11%)	3/25 (12%)	10/25 (40%)	1/32 (3%)	2/35 (6%)	0/31 (0%)	6/35 (17%)
FIRST INCIDENCE (DAYS)	---	726 (T)	241	447	711	710	619	440
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.156	P=0.001 **	P<0.001 **	P=0.018 *	P=0.540	P=0.708	P=0.064
INCIDENTAL TUMOR	P<0.001 **	P=0.156	P=0.001 **	P<0.001 **	P=0.009 **	P=0.570	P=0.680	P=0.057
LOGISTIC REGRESSION	P<0.001 **	P=0.156	P<0.001 **	P<0.001 **	P=0.011 *	P=0.549	P=0.672	P=0.048 *
COCHRAN-ARMITAGE	P<0.001 **				P=0.011 *			
FISHER EXACT		P=0.128	P<0.001 **	P<0.001 **		P=0.516	P=0.650	P=0.039 *

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Nonciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	1/60 (2%)	4/62 (6%)	26/65 (40%)	39/62 (63%)	8/60 (13%)	35/62 (56%)	48/54 (89%)	43/57 (75%)
ADJUSTED (B)	2.2%	8.5%	67.5%	78.9%	20.8%	78.4%	100.0%	89.3%
FINAL (D)	0/23 (0%)	0/28 (0%)	14/25 (56%)	16/25 (64%)	4/32 (13%)	26/35 (74%)	31/31 (100%)	30/35 (86%)
FIRST INCIDENCE (DAYS)	452	80	83	100	570	486	55	76
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.207	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P=0.198	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.189	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.193	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **
Nose 2 Respiratory Epithelium, Nonciliated, Inflammation								
LESION RATES								
OVERALL (A)	1/60 (2%)	1/62 (2%)	3/65 (5%)	1/62 (2%)	5/60 (8%)	5/62 (8%)	8/54 (15%)	15/57 (26%)
ADJUSTED (B)	3.6%	3.6%	10.6%	4.0%	14.3%	13.5%	23.1%	37.6%
FINAL (D)	0/23 (0%)	1/28 (4%)	2/25 (8%)	1/25 (4%)	3/32 (9%)	4/35 (11%)	6/31 (19%)	11/35 (31%)
FIRST INCIDENCE (DAYS)	668	726 (T)	673	726 (T)	711	674	605	423
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.624	P=0.805	P=0.372	P=0.780	P=0.003 **	P=0.684	P=0.274	P=0.023 *
INCIDENTAL TUMOR	P=0.676	P=0.798	P=0.448	P=0.823	P=0.001 **	P=0.714	P=0.266	P=0.012 *
LOGISTIC REGRESSION	P=0.637	P=0.787	P=0.361	P=0.783	P=0.001 **	P=0.700	P=0.262	P=0.013 *
COCHRAN-ARMITAGE	P=0.629				P=0.001 **			
FISHER EXACT		P=0.760	P=0.340	P=0.760		P=0.649	P=0.214	P=0.009 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Nonciliated, Squamous Metaplasia								
LESION RATES								
OVERALL (A)	12/60 (20%)	10/62 (16%)	22/65 (34%)	14/62 (23%)	0/60 (0%)	4/62 (6%)	1/54 (2%)	24/57 (42%)
ADJUSTED (B)	38.8%	27.8%	47.1%	38.4%	0.0%	10.7%	2.2%	50.9%
FINAL (D)	7/23 (30%)	6/28 (21%)	7/25 (28%)	7/25 (28%)	0/32 (0%)	3/35 (9%)	0/31 (0%)	14/35 (40%)
FIRST INCIDENCE (DAYS)	45	101	19	6	---	674	664	76
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.314	P=0.857	P=0.085	P=0.491	P<0.001 **	P=0.078	P=0.529	P<0.001 **
INCIDENTAL TUMOR	P=0.330	P=0.833	P=0.060	P=0.492	P<0.001 **	P=0.082	P=0.550	P<0.001 **
LOGISTIC REGRESSION	P=0.303	P=0.794	P=0.060	P=0.466	P<0.001 **	P=0.078	P=0.483	P<0.001 **
COCHRAN-ARMITAGE	P=0.304				P<0.001 **			
FISHER EXACT		P=0.785	P=0.062	P=0.450		P=0.064	P=0.474	P<0.001 **
Nose 2 Respiratory Epithelium, Nonciliated, Submucosal Mucous Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	1/60 (2%)	0/62 (0%)	1/65 (2%)	0/62 (0%)	2/60 (3%)	0/62 (0%)	0/54 (0%)	2/57 (4%)
ADJUSTED (B)	2.1%	0.0%	1.9%	0.0%	6.3%	0.0%	0.0%	5.7%
FINAL (D)	0/23 (0%)	0/28 (0%)	0/25 (0%)	0/25 (0%)	2/32 (6%)	0/35 (0%)	0/31 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	380	---	325	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.907	(E)	P=0.777	(E)	P=0.445	(E)	(E)	P=0.727
INCIDENTAL TUMOR	P=0.910	(E)	P=0.779	(E)	P=0.445	(E)	(E)	P=0.727
LOGISTIC REGRESSION	P=0.896	(E)	P=0.773	(E)	P=0.445	(E)	(E)	P=0.727
COCHRAN-ARMITAGE	P=0.902				P=0.405			
FISHER EXACT		P=1.000	P=0.772	P=1.000		P=1.000	P=1.000	P=0.671

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Nonciliated, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	1/60 (2%)	0/62 (0%)	0/65 (0%)	0/62 (0%)	2/60 (3%)	1/62 (2%)	0/54 (0%)	6/57 (11%)
ADJUSTED (B)	3.2%	0.0%	0.0%	0.0%	6.3%	2.4%	0.0%	14.6%
FINAL (D)	0/23 (0%)	0/28 (0%)	0/25 (0%)	0/25 (0%)	2/32 (6%)	0/35 (0%)	0/31 (0%)	4/35 (11%)
FIRST INCIDENCE (DAYS)	637	---	---	---	732 (T)	710	---	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.969	(E)	(E)	(E)	P=0.020 *	P=0.893	(E)	P=0.157
INCIDENTAL TUMOR	P=0.945	(E)	(E)	(E)	P=0.024 *	P=0.901	(E)	P=0.170
LOGISTIC REGRESSION	P=0.968	(E)	(E)	(E)	P=0.014 *	P=0.898	(E)	P=0.124
COCHRAN-ARMITAGE	P=0.967				P=0.014 *			
FISHER EXACT		P=1.000	P=1.000	P=1.000		P=0.884	P=1.000	P=0.120
Nose 2 Respiratory Epithelium, Nonciliated, Submucosal Mucous Glands, Inflammation								
LESION RATES								
OVERALL (A)	1/60 (2%)	1/62 (2%)	0/65 (0%)	0/62 (0%)	0/60 (0%)	1/62 (2%)	0/54 (0%)	3/57 (5%)
ADJUSTED (B)	4.3%	3.1%	0.0%	0.0%	0.0%	2.4%	0.0%	7.4%
FINAL (D)	1/23 (4%)	0/28 (0%)	0/25 (0%)	0/25 (0%)	0/32 (0%)	0/35 (0%)	0/31 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	726 (T)	689	---	---	---	710	---	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.959	P=0.800	(E)	(E)	P=0.044 *	P=0.520	(E)	P=0.131
INCIDENTAL TUMOR	P=0.969	P=0.798	(E)	(E)	P=0.047 *	P=0.550	(E)	P=0.142
LOGISTIC REGRESSION	P=0.962	P=0.791	(E)	(E)	P=0.037 *	P=0.525	(E)	P=0.112
COCHRAN-ARMITAGE	P=0.959				P=0.038 *			
FISHER EXACT		P=0.760	P=1.000	P=1.000		P=0.508	(E)	P=0.112

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Respiratory Epithelium, Nonciliated, Transitional Metaplasia								
LESION RATES								
OVERALL (A)	10/60 (17%)	27/62 (44%)	31/65 (48%)	38/62 (61%)	5/60 (8%)	29/62 (47%)	47/54 (87%)	22/57 (39%)
ADJUSTED (B)	31.2%	63.0%	73.0%	78.3%	13.8%	58.3%	100.0%	54.1%
FINAL (D)	5/23 (22%)	14/28 (50%)	15/25 (60%)	16/25 (64%)	3/32 (9%)	16/35 (46%)	31/31 (100%)	17/35 (49%)
FIRST INCIDENCE (DAYS)	46	39	59	6	591	486	25	418
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.008 **	P<0.001 **	P<0.001 **	P=0.073	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P=0.002 **	P<0.001 **	P<0.001 **	P=0.018 *	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.001 **	P<0.001 **	P<0.001 **	P=0.018 *	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P=0.018 *			
FISHER EXACT		P=0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **
Nose 2 Septum, Amyloid-like Substance								
LESION RATES								
OVERALL (A)	4/60 (7%)	17/62 (27%)	11/65 (17%)	5/62 (8%)	4/60 (7%)	9/62 (15%)	3/54 (6%)	1/57 (2%)
ADJUSTED (B)	8.7%	34.6%	26.9%	10.7%	10.7%	21.3%	8.8%	2.9%
FINAL (D)	0/23 (0%)	5/28 (18%)	2/25 (8%)	0/25 (0%)	3/32 (9%)	6/35 (17%)	2/31 (6%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	360	19	205	380	127	489	685	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.897	P=0.007 **	P=0.095	P=0.580	P=0.985	P=0.162	P=0.776	P=0.971
INCIDENTAL TUMOR	P=0.950	P=0.002 **	P=0.105	P=0.675	P=0.985	P=0.111	P=0.786	P=0.969
LOGISTIC REGRESSION	P=0.920	P<0.001 **	P=0.053	P=0.657	P=0.981	P=0.131	P=0.740	P=0.961
COCHRAN-ARMITAGE	P=0.901				P=0.981			
FISHER EXACT		P=0.002 **	P=0.067	P=0.521		P=0.133	P=0.735	P=0.967

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 2 Teeth, Dysplasia								
LESION RATES								
OVERALL (A)	3/60 (5%)	14/62 (23%)	5/65 (8%)	5/62 (8%)	2/60 (3%)	6/62 (10%)	6/54 (11%)	3/57 (5%)
ADJUSTED (B)	13.0%	42.4%	18.0%	20.0%	6.3%	15.9%	16.9%	7.8%
FINAL (D)	3/23 (13%)	10/28 (36%)	4/25 (16%)	5/25 (20%)	2/32 (6%)	5/35 (14%)	4/31 (13%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	590	553	726 (T)	732 (T)	608	571	708
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.818	P=0.012 *	P=0.401	P=0.399	P=0.667	P=0.170	P=0.135	P=0.539
INCIDENTAL TUMOR	P=0.784	P=0.006 **	P=0.329	P=0.399	P=0.577	P=0.171	P=0.112	P=0.496
LOGISTIC REGRESSION	P=0.840	P=0.006 **	P=0.447	P=0.399	P=0.632	P=0.175	P=0.123	P=0.526
COCHRAN-ARMITAGE	P=0.818				P=0.604			
FISHER EXACT		P=0.005 **	P=0.404	P=0.377		P=0.147	P=0.104	P=0.476
Nose 3 Luminal Exudate								
LESION RATES								
OVERALL (A)	1/60 (2%)	3/66 (5%)	5/67 (7%)	4/62 (6%)	3/63 (5%)	4/65 (6%)	7/58 (12%)	11/56 (20%)
ADJUSTED (B)	1.8%	8.3%	15.9%	13.3%	7.8%	10.5%	19.4%	27.2%
FINAL (D)	0/22 (0%)	2/30 (7%)	2/26 (8%)	2/25 (8%)	2/33 (6%)	4/38 (11%)	6/34 (18%)	7/34 (21%)
FIRST INCIDENCE (DAYS)	146	264	537	517	511	732 (T)	608	295
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.209	P=0.367	P=0.144	P=0.210	P=0.006 **	P=0.574	P=0.171	P=0.027 *
INCIDENTAL TUMOR	P=0.242	P=0.375	P=0.174	P=0.221	P=0.005 **	P=0.554	P=0.122	P=0.021 *
LOGISTIC REGRESSION	P=0.205	P=0.339	P=0.136	P=0.193	P=0.003 **	P=0.577	P=0.156	P=0.014 *
COCHRAN-ARMITAGE	P=0.198				P=0.003 **			
FISHER EXACT		P=0.346	P=0.131	P=0.193		P=0.518	P=0.130	P=0.012 *

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Luminal Hemorrhage								
LESION RATES								
OVERALL (A)	1/60 (2%)	2/66 (3%)	1/67 (1%)	1/62 (2%)	1/63 (2%)	1/65 (2%)	1/58 (2%)	1/56 (2%)
ADJUSTED (B)	3.7%	3.8%	3.2%	3.6%	2.0%	2.6%	2.3%	1.8%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	1/38 (3%)	0/34 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	703	39	707	704	558	732 (T)	673	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.736	P=0.532	P=0.801	P=0.772	P=0.641	P=0.790	P=0.774	P=0.745
INCIDENTAL TUMOR	P=0.721	P=0.454	P=0.875	P=0.822	P=0.578	P=0.799	P=0.715	P=0.676
LOGISTIC REGRESSION	P=0.739	P=0.533	P=0.807	P=0.780	P=0.617	P=0.774	P=0.742	P=0.722
COCHRAN-ARMITAGE	P=0.738				P=0.617			
FISHER EXACT		P=0.536	P=0.779	P=0.760		P=0.760	P=0.731	P=0.722
Nose 3 Nasolacrimal Duct, Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	1/67 (1%)	2/62 (3%)	1/63 (2%)	2/65 (3%)	0/58 (0%)	1/56 (2%)
ADJUSTED (B)	0.0%	0.0%	2.0%	6.0%	3.0%	4.7%	0.0%	2.3%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	1/38 (3%)	0/34 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	---	443	646	732 (T)	646	---	638
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.087	(E)	P=0.513	P=0.272	P=0.759	P=0.548	(E)	P=0.769
INCIDENTAL TUMOR	P=0.125	(E)	P=0.500	P=0.290	P=0.690	P=0.546	(E)	P=0.662
LOGISTIC REGRESSION	P=0.076	(E)	P=0.519	P=0.253	P=0.737	P=0.551	(E)	P=0.746
COCHRAN-ARMITAGE	P=0.074				P=0.733			
FISHER EXACT		(E)	P=0.528	P=0.256		P=0.512	P=1.000	P=0.722

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 3 Nasolacrimal Duct, Luminal Exudate								
LESION RATES								
OVERALL (A)	0/60 (0%)	1/66 (2%)	1/67 (1%)	2/62 (3%)	3/63 (5%)	1/65 (2%)	2/58 (3%)	0/56 (0%)
ADJUSTED (B)	0.0%	2.9%	2.0%	5.9%	7.4%	2.6%	4.6%	0.0%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	1/38 (3%)	1/34 (3%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	675	443	523	511	732 (T)	269	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.183	P=0.552	P=0.513	P=0.245	P=0.962	P=0.949	P=0.809	(E)
INCIDENTAL TUMOR	P=0.290	P=0.500	P=0.500	P=0.333	P=0.963	P=0.942	P=0.791	(E)
LOGISTIC REGRESSION	P=0.175	P=0.530	P=0.519	P=0.251	P=0.958	P=0.949	P=0.786	(E)
COCHRAN-ARMITAGE	P=0.172				P=0.958			
FISHER EXACT		P=0.524	P=0.528	P=0.256		P=0.944	P=0.791	P=1.000
Nose 3 Olfactory Epithelium, Atrophy								
LESION RATES								
OVERALL (A)	8/60 (13%)	8/66 (12%)	19/67 (28%)	26/62 (42%)	2/63 (3%)	13/65 (20%)	12/58 (21%)	22/56 (39%)
ADJUSTED (B)	25.1%	19.1%	53.5%	61.1%	3.4%	29.6%	31.9%	56.9%
FINAL (D)	3/22 (14%)	3/30 (10%)	12/26 (46%)	11/25 (44%)	0/33 (0%)	9/38 (24%)	9/34 (26%)	18/34 (53%)
FIRST INCIDENCE (DAYS)	373	39	83	100	298	544	671	423
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.735	P=0.042 *	P=0.003 **	P<0.001 **	P=0.008 **	P=0.007 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P=0.611	P=0.024 *	P<0.001 **	P<0.001 **	P=0.004 **	P=0.006 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.687	P=0.035 *	P<0.001 **	P<0.001 **	P=0.004 **	P=0.004 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.682	P=0.031 *	P<0.001 **		P=0.003 **	P=0.003 **	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Olfactory Epithelium, Bowman's Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	1/67 (1%)	1/62 (2%)	1/63 (2%)	0/65 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	3.8%	2.0%	3.0%	0.0%	0.0%	5.9%
FINAL (D)	0/22 (0%)	0/30 (0%)	1/26 (4%)	0/25 (0%)	1/33 (3%)	0/38 (0%)	0/34 (0%)	2/34 (6%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	445	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.282	(E)	P=0.533	P=0.517	P=0.201	(E)	(E)	P=0.510
INCIDENTAL TUMOR	P=0.346	(E)	P=0.533	P=0.615	P=0.201	(E)	(E)	P=0.510
LOGISTIC REGRESSION	P=0.274	(E)	P=0.533	P=0.500	P=0.201	(E)	(E)	P=0.511
COCHRAN-ARMITAGE	P=0.271				P=0.180			
FISHER EXACT		(E)	P=0.528	P=0.508		P=1.000	P=1.000	P=0.456
Nose 3 Olfactory Epithelium, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	2/60 (3%)	7/66 (11%)	18/67 (27%)	22/62 (35%)	17/63 (27%)	24/65 (37%)	42/58 (72%)	18/56 (32%)
ADJUSTED (B)	6.6%	22.2%	48.4%	50.6%	44.2%	48.4%	87.1%	41.2%
FINAL (D)	1/22 (5%)	6/30 (20%)	9/26 (35%)	8/25 (32%)	13/33 (39%)	14/38 (37%)	28/34 (82%)	11/34 (32%)
FIRST INCIDENCE (DAYS)	452	650	144	100	495	489	166	76
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.160	P<0.001 **	P<0.001 **	P=0.566	P=0.282	P<0.001 **	P=0.509
INCIDENTAL TUMOR	P<0.001 **	P=0.151	P<0.001 **	P<0.001 **	P=0.356	P=0.240	P<0.001 **	P=0.373
LOGISTIC REGRESSION	P<0.001 **	P=0.123	P<0.001 **	P<0.001 **	P=0.370	P=0.247	P<0.001 **	P=0.359
COCHRAN-ARMITAGE	P<0.001 **				P=0.371			
FISHER EXACT		P=0.107	P<0.001 **	P<0.001 **		P=0.155	P<0.001 **	P=0.339

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 3 Olfactory Epithelium, Inflammation								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	3/67 (4%)	0/62 (0%)	0/63 (0%)	0/65 (0%)	1/58 (2%)	5/56 (9%)
ADJUSTED (B)	0.0%	0.0%	10.3%	0.0%	0.0%	0.0%	1.9%	13.2%
FINAL (D)	0/22 (0%)	0/30 (0%)	2/26 (8%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	4/34 (12%)
FIRST INCIDENCE (DAYS)	---	---	673	---	---	---	445	161
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.665	(E)	P=0.161	(E)	P=0.001 **	(E)	P=0.489	P=0.035 *
INCIDENTAL TUMOR	P=0.684	(E)	P=0.177	(E)	P=0.002 **	(E)	P=0.388	P=0.030 *
LOGISTIC REGRESSION	P=0.665	(E)	P=0.158	(E)	P<0.001 **	(E)	P=0.464	P=0.024 *
COCHRAN-ARMITAGE	P=0.662				P<0.001 **			
FISHER EXACT		(E)	P=0.144	(E)		(E)	P=0.479	P=0.021 *
Nose 3 Respiratory Epithelium, Ciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/60 (0%)	6/66 (9%)	37/67 (55%)	50/62 (81%)	27/63 (43%)	24/65 (37%)	47/58 (81%)	42/56 (75%)
ADJUSTED (B)	0.0%	17.2%	89.6%	97.9%	66.4%	45.8%	91.9%	83.3%
FINAL (D)	0/22 (0%)	3/30 (10%)	22/26 (85%)	24/25 (96%)	20/33 (61%)	12/38 (32%)	30/34 (88%)	26/34 (76%)
FIRST INCIDENCE (DAYS)	---	629	83	40	463	486	55	76
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.040 *	P<0.001 **	P<0.001 **	P=0.001 **	P=0.894	P=0.002 **	P=0.014 *
INCIDENTAL TUMOR	P<0.001 **	P=0.022 *	P<0.001 **	P<0.001 **	P<0.001 **	P=0.892	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.027 *	P<0.001 **	P<0.001 **	P<0.001 **	P=0.898	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.018 *	P<0.001 **	P<0.001 **		P=0.807	P<0.001 **	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Respiratory Epithelium, Ciliated, Inflammation								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	0/67 (0%)	0/62 (0%)	2/63 (3%)	0/65 (0%)	1/58 (2%)	3/56 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	5.7%	0.0%	2.6%	8.0%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	0/38 (0%)	0/34 (0%)	2/34 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	711	---	711	611
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.198	(E)	P=0.882	P=0.513
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.122	(E)	P=0.907	P=0.399
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.169	(E)	P=0.886	P=0.476
COCHRAN-ARMITAGE	(E)				P=0.165			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=0.862	P=0.444
Nose 3 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	1/60 (2%)	2/66 (3%)	3/67 (4%)	0/62 (0%)	7/63 (11%)	0/65 (0%)	2/58 (3%)	3/56 (5%)
ADJUSTED (B)	4.5%	6.2%	8.4%	0.0%	21.2%	0.0%	4.3%	8.2%
FINAL (D)	1/22 (5%)	1/30 (3%)	1/26 (4%)	0/25 (0%)	7/33 (21%)	0/38 (0%)	0/34 (0%)	2/34 (6%)
FIRST INCIDENCE (DAYS)	726 (T)	685	325	---	732 (T)	---	445	697
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.894	P=0.598	P=0.364	(E)	P=0.814	(E)	P=0.983	P=0.958
INCIDENTAL TUMOR	P=0.900	P=0.572	P=0.399	(E)	P=0.806	(E)	P=0.981	P=0.953
LOGISTIC REGRESSION	P=0.896	P=0.573	P=0.355	(E)	P=0.783	(E)	P=0.981	P=0.957
COCHRAN-ARMITAGE	P=0.891				P=0.773			
FISHER EXACT		P=0.536	P=0.352	P=1.000		P=1.000	P=0.978	P=0.930

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/60 (0%)	1/66 (2%)	3/67 (4%)	0/62 (0%)	2/63 (3%)	4/65 (6%)	19/58 (33%)	11/56 (20%)
ADJUSTED (B)	0.0%	3.3%	8.4%	0.0%	5.8%	8.9%	46.3%	29.8%
FINAL (D)	0/22 (0%)	1/30 (3%)	1/26 (4%)	0/25 (0%)	1/33 (3%)	2/38 (5%)	13/34 (38%)	9/34 (26%)
FIRST INCIDENCE (DAYS)	---	726 (T)	443	---	717	510	166	570
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.758	P=0.562	P=0.151	(E)	P=0.009 **	P=0.402	P<0.001 **	P=0.011 *
INCIDENTAL TUMOR	P=0.798	P=0.562	P=0.167	(E)	P=0.003 **	P=0.378	P<0.001 **	P=0.004 **
LOGISTIC REGRESSION	P=0.755	P=0.562	P=0.145	(E)	P=0.003 **	P=0.389	P<0.001 **	P=0.007 **
COCHRAN-ARMITAGE	P=0.749				P=0.003 **			
FISHER EXACT		P=0.524	P=0.144	(E)		P=0.355	P<0.001 **	P=0.004 **
Nose 3 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Inflammation								
LESION RATES								
OVERALL (A)	1/60 (2%)	1/66 (2%)	0/67 (0%)	0/62 (0%)	3/63 (5%)	2/65 (3%)	3/58 (5%)	2/56 (4%)
ADJUSTED (B)	4.5%	3.3%	0.0%	0.0%	7.0%	4.4%	7.6%	5.2%
FINAL (D)	1/22 (5%)	1/30 (3%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	1/38 (3%)	2/34 (6%)	1/34 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	---	---	463	599	445	638
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.961	P=0.828	(E)	(E)	P=0.697	P=0.858	P=0.661	P=0.816
INCIDENTAL TUMOR	P=0.961	P=0.828	(E)	(E)	P=0.605	P=0.851	P=0.528	P=0.714
LOGISTIC REGRESSION	P=0.961	P=0.828	(E)	(E)	P=0.662	P=0.827	P=0.622	P=0.786
COCHRAN-ARMITAGE	P=0.959				P=0.662			
FISHER EXACT		P=0.775	P=1.000	P=1.000		P=0.827	P=0.620	P=0.779

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Respiratory Epithelium, Ciliated, Transitional Metaplasia								
LESION RATES								
OVERALL (A)	1/60 (2%)	3/66 (5%)	13/67 (19%)	30/62 (48%)	1/63 (2%)	1/65 (2%)	4/58 (7%)	11/56 (20%)
ADJUSTED (B)	4.5%	7.6%	34.3%	76.7%	2.7%	2.6%	9.8%	29.8%
FINAL (D)	1/22 (5%)	1/30 (3%)	6/26 (23%)	17/25 (68%)	0/33 (0%)	1/38 (3%)	2/34 (6%)	9/34 (26%)
FIRST INCIDENCE (DAYS)	726 (T)	264	73	346	711	732 (T)	546	516
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.384	P=0.003 **	P<0.001 **	P<0.001 **	P=0.784	P=0.197	P=0.004 **
INCIDENTAL TUMOR	P<0.001 **	P=0.326	P=0.003 **	P<0.001 **	P<0.001 **	P=0.788	P=0.177	P=0.003 **
LOGISTIC REGRESSION	P<0.001 **	P=0.344	P=0.002 **	P<0.001 **	P<0.001 **	P=0.794	P=0.169	P=0.002 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.346	P=0.001 **	P<0.001 **		P=0.760	P=0.158	P=0.001 **
Nose 3 Respiratory Epithelium, Nonciliated, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	0/67 (0%)	0/62 (0%)	2/63 (3%)	0/65 (0%)	0/58 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	6.1%	0.0%	0.0%	0.0%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	2/33 (6%)	0/38 (0%)	0/34 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.978	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.978	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.978	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				P=0.976			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Respiratory Epithelium, Nonciliated, Inflammation								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	0/67 (0%)	0/62 (0%)	1/63 (2%)	0/65 (0%)	0/58 (0%)	8/56 (14%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%	20.9%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	0/38 (0%)	0/34 (0%)	5/34 (15%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	611
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P<0.001 **	(E)	(E)	P=0.024 *
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P<0.001 **	(E)	(E)	P=0.010 **
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P<0.001 **	(E)	(E)	P=0.015 *
COCHRAN-ARMITAGE	(E)				P<0.001 **			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=0.010 *
Nose 3 Respiratory Epithelium, Nonciliated, Squamous Metaplasia								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	1/67 (1%)	0/62 (0%)	0/63 (0%)	0/65 (0%)	0/58 (0%)	3/56 (5%)
ADJUSTED (B)	0.0%	0.0%	3.4%	0.0%	0.0%	0.0%	0.0%	8.3%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	2/34 (6%)
FIRST INCIDENCE (DAYS)	---	---	719	---	---	---	---	708
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.783	(E)	P=0.538	(E)	P=0.009 **	(E)	(E)	P=0.130
INCIDENTAL TUMOR	P=0.812	(E)	P=0.607	(E)	P=0.006 **	(E)	(E)	P=0.109
LOGISTIC REGRESSION	P=0.785	(E)	P=0.545	(E)	P=0.008 **	(E)	(E)	P=0.119
COCHRAN-ARMITAGE	P=0.781				P=0.007 **			
FISHER EXACT		(E)	P=0.528	(E)		(E)	(E)	P=0.101

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Respiratory Epithelium, Nonciliated, Submucosal Mucous Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	0/67 (0%)	0/62 (0%)	4/63 (6%)	0/65 (0%)	0/58 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	10.9%	0.0%	0.0%	0.0%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	3/33 (9%)	0/38 (0%)	0/34 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	556	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.993	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.991	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.992	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				P=0.992			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=1.000
Nose 3 Respiratory Epithelium, Nonciliated, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/66 (0%)	0/67 (0%)	0/62 (0%)	0/63 (0%)	0/65 (0%)	0/58 (0%)	3/56 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.8%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	3/34 (9%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.009 **	(E)	(E)	P=0.126
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.009 **	(E)	(E)	P=0.126
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.009 **	(E)	(E)	P=0.124
COCHRAN-ARMITAGE	(E)				P=0.007 **			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.101

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Septum, Amyloid-like Substance								
LESION RATES								
OVERALL (A)	57/60 (95%)	66/66 (100%)	66/67 (99%)	60/62 (97%)	52/63 (83%)	61/65 (94%)	55/58 (95%)	39/56 (70%)
ADJUSTED (B)	98.2%	100.0%	98.5%	98.2%	87.7%	95.3%	100.0%	76.8%
FINAL (D)	21/22 (95%)	30/30 (100%)	25/26 (96%)	24/25 (96%)	26/33 (79%)	35/38 (92%)	34/34 (100%)	23/34 (68%)
FIRST INCIDENCE (DAYS)	45	17	18	6	127	103	25	76
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.608	P=0.620	P=0.484	P=0.653	P=0.990	P=0.473	P=0.462	P=0.972
INCIDENTAL TUMOR	P=0.665	P=0.096	P=0.254	P=0.505	P=0.997	P=0.075	P=0.024 *	P=0.951
LOGISTIC REGRESSION	P=0.662	P=0.100	P=0.272	P=0.502	P=0.999	P=0.046 *	P=0.038 *	P=0.970
COCHRAN-ARMITAGE	P=0.655				P=0.999			
FISHER EXACT		P=0.105	P=0.269	P=0.484		P=0.042 *	P=0.032 *	P=0.970
Nose 3 Teeth, Dysplasia								
LESION RATES								
OVERALL (A)	6/60 (10%)	10/66 (15%)	16/67 (24%)	12/62 (19%)	6/63 (10%)	8/65 (12%)	7/58 (12%)	3/56 (5%)
ADJUSTED (B)	24.8%	29.7%	45.6%	42.3%	17.2%	18.6%	17.0%	8.4%
FINAL (D)	5/22 (23%)	7/30 (23%)	9/26 (35%)	10/25 (40%)	5/33 (15%)	5/38 (13%)	4/34 (12%)	2/34 (6%)
FIRST INCIDENCE (DAYS)	588	653	514	373	653	608	166	718
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.128	P=0.417	P=0.046 *	P=0.140	P=0.920	P=0.500	P=0.531	P=0.925
INCIDENTAL TUMOR	P=0.122	P=0.349	P=0.018 *	P=0.137	P=0.872	P=0.505	P=0.494	P=0.909
LOGISTIC REGRESSION	P=0.125	P=0.339	P=0.040 *	P=0.123	P=0.893	P=0.505	P=0.466	P=0.918
COCHRAN-ARMITAGE	P=0.129				P=0.887			
FISHER EXACT		P=0.276	P=0.032 *	P=0.114		P=0.413	P=0.436	P=0.887

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 3 Teeth, Inflammation								
LESION RATES								
OVERALL (A)	0/60 (0%)	2/66 (3%)	0/67 (0%)	0/62 (0%)	0/63 (0%)	1/65 (2%)	0/58 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	4.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.0%
FINAL (D)	0/22 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	1/38 (3%)	0/34 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	264	---	---	---	732 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.924	P=0.244	(E)	(E)	P=0.919	P=0.528	(E)	(E)
INCIDENTAL TUMOR	P=0.933	P=0.247	(E)	(E)	P=0.919	P=0.528	(E)	(E)
LOGISTIC REGRESSION	P=0.923	P=0.260	(E)	(E)	P=0.919	P=0.528	(E)	(E)
COCHRAN-ARMITAGE	P=0.925				P=0.914			
FISHER EXACT		P=0.272	(E)	(E)		P=0.508	(E)	(E)
Nose 4 Congestion								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	2/63 (3%)	0/65 (0%)	0/58 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	4.6%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	553	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.977	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.974	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.976	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				P=0.976			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Luminal Exudate								
LESION RATES								
OVERALL (A)	1/61 (2%)	1/66 (2%)	2/68 (3%)	0/63 (0%)	1/63 (2%)	3/65 (5%)	7/58 (12%)	10/56 (18%)
ADJUSTED (B)	2.1%	3.3%	5.4%	0.0%	1.8%	7.9%	18.6%	26.0%
FINAL (D)	0/23 (0%)	1/30 (3%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	3/38 (8%)	5/34 (15%)	8/35 (23%)
FIRST INCIDENCE (DAYS)	380	726 (T)	537	---	511	732 (T)	546	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.889	P=0.800	P=0.544	(E)	P=0.002 **	P=0.354	P=0.037 *	P=0.007 **
INCIDENTAL TUMOR	P=0.929	P=0.789	P=0.587	(E)	P=0.002 **	P=0.330	P=0.024 *	P=0.007 **
LOGISTIC REGRESSION	P=0.889	P=0.780	P=0.538	(E)	P<0.001 **	P=0.342	P=0.029 *	P=0.004 **
COCHRAN-ARMITAGE	P=0.888				P<0.001 **			
FISHER EXACT		P=0.771	P=0.541	P=1.000		P=0.321	P=0.023 *	P=0.002 **
Nose 4 Luminal Hemorrhage								
LESION RATES								
OVERALL (A)	2/61 (3%)	4/66 (6%)	2/68 (3%)	3/63 (5%)	0/63 (0%)	2/65 (3%)	1/58 (2%)	1/56 (2%)
ADJUSTED (B)	7.9%	9.6%	4.5%	10.0%	0.0%	4.2%	1.8%	2.9%
FINAL (D)	1/23 (4%)	1/30 (3%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	1/38 (3%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	703	39	442	663	---	486	394	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.561	P=0.412	P=0.738	P=0.536	P=0.554	P=0.270	P=0.490	P=0.512
INCIDENTAL TUMOR	P=0.636	P=0.385	P=0.703	P=0.643	P=0.603	P=0.238	P=0.388	P=0.512
LOGISTIC REGRESSION	P=0.557	P=0.375	P=0.739	P=0.710	P=0.526	P=0.227	P=0.460	P=0.512
COCHRAN-ARMITAGE	P=0.551				P=0.533			
FISHER EXACT		P=0.378	P=0.730	P=0.515		P=0.256	P=0.479	P=0.471

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Nasolacrimal Duct, Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	2/63 (3%)	1/63 (2%)	3/65 (5%)	0/58 (0%)	4/56 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	6.8%	3.0%	7.9%	0.0%	11.4%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	1/25 (4%)	1/33 (3%)	3/38 (8%)	0/34 (0%)	4/35 (11%)
FIRST INCIDENCE (DAYS)	---	---	---	647	732 (T)	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.041 *	(E)	(E)	P=0.263	P=0.156	P=0.356	(E)	P=0.196
INCIDENTAL TUMOR	P=0.049 *	(E)	(E)	P=0.289	P=0.156	P=0.356	(E)	P=0.196
LOGISTIC REGRESSION	P=0.040 *	(E)	(E)	P=0.251	P=0.156	P=0.356	(E)	P=0.196
COCHRAN-ARMITAGE	P=0.041 *				P=0.121			
FISHER EXACT		(E)	(E)	P=0.256		P=0.321	P=1.000	P=0.148
Nose 4 Nasolacrimal Duct, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	1/63 (2%)	0/65 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	1.9%	0.0%	0.0%	5.7%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	543	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.194	(E)	(E)	P=0.495
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.232	(E)	(E)	P=0.529
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.182	(E)	(E)	P=0.473
COCHRAN-ARMITAGE	(E)				P=0.180			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=0.456

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Nasolacrimal Duct, Luminal Exudate								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	2/63 (3%)	1/65 (2%)	1/58 (2%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	5.7%	2.6%	1.7%	0.0%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	1/38 (3%)	0/34 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	715	732 (T)	269	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.956	P=0.899	P=0.873	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.952	P=0.900	P=0.882	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.949	P=0.903	P=0.858	(E)
COCHRAN-ARMITAGE	(E)				P=0.950			
FISHER EXACT		(E)	(E)	(E)		P=0.884	P=0.862	P=1.000
Nose 4 Olfactory Epithelium, Atrophy								
LESION RATES								
OVERALL (A)	0/61 (0%)	3/66 (5%)	11/68 (16%)	28/63 (44%)	3/63 (5%)	9/65 (14%)	14/58 (24%)	19/56 (34%)
ADJUSTED (B)	0.0%	7.7%	33.5%	64.2%	6.3%	22.5%	38.7%	43.0%
FINAL (D)	0/23 (0%)	1/30 (3%)	7/26 (27%)	12/25 (48%)	1/33 (3%)	7/38 (18%)	12/34 (35%)	12/35 (34%)
FIRST INCIDENCE (DAYS)	---	342	449	243	298	710	708	161
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.155	P=0.002 **	P<0.001 **	P<0.001 **	P=0.102	P=0.005 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P=0.114	P=0.002 **	P<0.001 **	P<0.001 **	P=0.065	P=0.004 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.136	P=0.002 **	P<0.001 **	P<0.001 **	P=0.089	P=0.004 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.137	P<0.001 **	P<0.001 **		P=0.071	P=0.002 **	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 4 Olfactory Epithelium, Bowman's Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	0/61 (0%)	1/66 (2%)	2/68 (3%)	3/63 (5%)	0/63 (0%)	5/65 (8%)	9/58 (16%)	3/56 (5%)
ADJUSTED (B)	0.0%	3.3%	7.7%	10.7%	0.0%	12.7%	25.5%	8.6%
FINAL (D)	0/23 (0%)	1/30 (3%)	2/26 (8%)	2/25 (8%)	0/33 (0%)	4/38 (11%)	8/34 (24%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	---	726 (T)	726 (T)	647	---	710	708	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.069	P=0.553	P=0.265	P=0.140	P=0.378	P=0.047 *	P=0.003 **	P=0.131
INCIDENTAL TUMOR	P=0.076	P=0.553	P=0.265	P=0.154	P=0.355	P=0.048 *	P=0.003 **	P=0.131
LOGISTIC REGRESSION	P=0.067	P=0.553	P=0.265	P=0.130	P=0.372	P=0.045 *	P=0.003 **	P=0.131
COCHRAN-ARMITAGE	P=0.073				P=0.294			
FISHER EXACT		P=0.520	P=0.276	P=0.128		P=0.031 *	P<0.001 **	P=0.101
Nose 4 Olfactory Epithelium, Bowman's Glands, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	1/63 (2%)	0/65 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%	5.7%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	0/38 (0%)	0/34 (0%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.208	(E)	(E)	P=0.521
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.208	(E)	(E)	P=0.521
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.208	(E)	(E)	P=0.521
COCHRAN-ARMITAGE	(E)				P=0.180			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=0.456

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Olfactory Epithelium, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	1/61 (2%)	1/66 (2%)	9/68 (13%)	31/63 (49%)	10/63 (16%)	9/65 (14%)	29/58 (50%)	43/56 (77%)
ADJUSTED (B)	2.6%	2.7%	29.9%	74.4%	29.2%	19.1%	61.7%	85.6%
FINAL (D)	0/23 (0%)	0/30 (0%)	6/26 (23%)	16/25 (64%)	9/33 (27%)	4/38 (11%)	17/34 (50%)	28/35 (80%)
FIRST INCIDENCE (DAYS)	553	650	443	100	711	510	55	412
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.793	P=0.018 *	P<0.001 **	P<0.001 **	P=0.788	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P=0.709	P=0.017 *	P<0.001 **	P<0.001 **	P=0.776	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.781	P=0.018 *	P<0.001 **	P<0.001 **	P=0.799	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.771	P=0.013 *	P<0.001 **		P=0.716	P<0.001 **	P<0.001 **
Nose 4 Respiratory Epithelium, Ciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	2/61 (3%)	4/66 (6%)	15/68 (22%)	34/63 (54%)	18/63 (29%)	6/65 (9%)	20/58 (34%)	35/56 (63%)
ADJUSTED (B)	5.0%	12.4%	40.1%	74.9%	47.3%	13.5%	44.1%	80.9%
FINAL (D)	0/23 (0%)	3/30 (10%)	7/26 (27%)	15/25 (60%)	14/33 (42%)	4/38 (11%)	11/34 (32%)	27/35 (77%)
FIRST INCIDENCE (DAYS)	452	650	83	346	269	510	55	412
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.429	P=0.003 **	P<0.001 **	P<0.001 **	P=1.000	P=0.466	P=0.003 **
INCIDENTAL TUMOR	P<0.001 **	P=0.364	P<0.001 **	P<0.001 **	P<0.001 **	P=0.999	P=0.359	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P=0.386	P=0.002 **	P<0.001 **	P<0.001 **	P=1.000	P=0.342	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P=0.378	P=0.001 **	P<0.001 **		P=0.999	P=0.307	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 4 Respiratory Epithelium, Ciliated, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	1/63 (2%)	0/65 (0%)	1/58 (2%)	5/56 (9%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	1.8%	0.0%	2.9%	12.3%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	1/34 (3%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	---	---	---	---	511	---	732 (T)	447
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.007 **	(E)	P=0.755	P=0.107
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.007 **	(E)	P=0.704	P=0.085
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.005 **	(E)	P=0.743	P=0.079
COCHRAN-ARMITAGE	(E)				P=0.005 **			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=0.731	P=0.079
Nose 4 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	2/61 (3%)	0/66 (0%)	1/68 (1%)	0/63 (0%)	5/63 (8%)	3/65 (5%)	0/58 (0%)	4/56 (7%)
ADJUSTED (B)	4.5%	0.0%	1.9%	0.0%	13.5%	7.9%	0.0%	11.4%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	4/33 (12%)	3/38 (8%)	0/34 (0%)	4/35 (11%)
FIRST INCIDENCE (DAYS)	452	---	328	---	298	732 (T)	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.950	(E)	P=0.882	(E)	P=0.651	P=0.901	(E)	P=0.779
INCIDENTAL TUMOR	P=0.965	(E)	P=0.900	(E)	P=0.645	P=0.866	(E)	P=0.755
LOGISTIC REGRESSION	P=0.951	(E)	P=0.896	(E)	P=0.601	P=0.896	(E)	P=0.727
COCHRAN-ARMITAGE	P=0.952				P=0.583			
FISHER EXACT		P=1.000	P=0.897	P=1.000		P=0.873	P=1.000	P=0.692

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	1/61 (2%)	2/66 (3%)	5/68 (7%)	4/63 (6%)	2/63 (3%)	4/65 (6%)	9/58 (16%)	26/56 (46%)
ADJUSTED (B)	2.9%	6.7%	12.6%	12.7%	5.7%	8.9%	21.8%	60.8%
FINAL (D)	0/23 (0%)	2/30 (7%)	0/26 (0%)	2/25 (8%)	1/33 (3%)	2/38 (5%)	5/34 (15%)	19/35 (54%)
FIRST INCIDENCE (DAYS)	598	726 (T)	83	542	711	510	166	412
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.157	P=0.577	P=0.144	P=0.213	P<0.001 **	P=0.399	P=0.038 *	P<0.001 **
INCIDENTAL TUMOR	P=0.186	P=0.508	P=0.148	P=0.187	P<0.001 **	P=0.378	P=0.029 *	P<0.001 **
LOGISTIC REGRESSION	P=0.152	P=0.545	P=0.131	P=0.199	P<0.001 **	P=0.388	P=0.023 *	P<0.001 **
COCHRAN-ARMITAGE	P=0.146				P<0.001 **			
FISHER EXACT		P=0.530	P=0.131	P=0.193		P=0.355	P=0.019 *	P<0.001 **
Nose 4 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Inflammation								
LESION RATES								
OVERALL (A)	1/61 (2%)	1/66 (2%)	1/68 (1%)	2/63 (3%)	6/63 (10%)	3/65 (5%)	3/58 (5%)	11/56 (20%)
ADJUSTED (B)	2.4%	3.3%	3.8%	5.1%	16.4%	6.4%	8.0%	30.3%
FINAL (D)	0/23 (0%)	1/30 (3%)	1/26 (4%)	0/25 (0%)	5/33 (15%)	1/38 (3%)	2/34 (6%)	10/35 (29%)
FIRST INCIDENCE (DAYS)	527	726 (T)	726 (T)	542	177	514	671	692
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.357	P=0.792	P=0.779	P=0.521	P=0.024 *	P=0.940	P=0.925	P=0.170
INCIDENTAL TUMOR	P=0.468	P=0.789	P=0.785	P=0.672	P=0.019 *	P=0.910	P=0.924	P=0.142
LOGISTIC REGRESSION	P=0.362	P=0.783	P=0.790	P=0.515	P=0.013 *	P=0.926	P=0.906	P=0.123
COCHRAN-ARMITAGE	P=0.356				P=0.012 *			
FISHER EXACT		P=0.771	P=0.778	P=0.512		P=0.925	P=0.897	P=0.095

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 4 Respiratory Epithelium, Ciliated, Transitional Metaplasia								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	1/68 (1%)	3/63 (5%)	0/63 (0%)	0/65 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	3.8%	8.9%	0.0%	0.0%	0.0%	5.2%
FINAL (D)	0/23 (0%)	0/30 (0%)	1/26 (4%)	1/25 (4%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	542	---	---	---	692
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.020 *	(E)	P=0.524	P=0.142	P=0.045 *	(E)	(E)	P=0.258
INCIDENTAL TUMOR	P=0.034 *	(E)	P=0.524	P=0.188	P=0.030 *	(E)	(E)	P=0.214
LOGISTIC REGRESSION	P=0.020 *	(E)	P=0.524	P=0.132	P=0.036 *	(E)	(E)	P=0.234
COCHRAN-ARMITAGE	P=0.019 *				P=0.034 *			
FISHER EXACT		(E)	P=0.527	P=0.128		(E)	(E)	P=0.219
Nose 4 Respiratory Epithelium, Nonciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	1/68 (1%)	0/63 (0%)	0/63 (0%)	0/65 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	3.8%	0.0%	0.0%	0.0%	0.0%	4.6%
FINAL (D)	0/23 (0%)	0/30 (0%)	1/26 (4%)	0/25 (0%)	0/33 (0%)	0/38 (0%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	---	---	---	---	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.779	(E)	P=0.524	(E)	P=0.041 *	(E)	(E)	P=0.242
INCIDENTAL TUMOR	P=0.779	(E)	P=0.524	(E)	P=0.057	(E)	(E)	P=0.261
LOGISTIC REGRESSION	P=0.779	(E)	P=0.524	(E)	P=0.033 *	(E)	(E)	P=0.200
COCHRAN-ARMITAGE	P=0.781				P=0.034 *			
FISHER EXACT		(E)	P=0.527	(E)		(E)	(E)	P=0.219

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Respiratory Epithelium, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/68 (0%)	0/63 (0%)	2/63 (3%)	0/65 (0%)	0/58 (0%)	1/56 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	5.3%	0.0%	0.0%	2.9%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/26 (0%)	0/25 (0%)	1/33 (3%)	0/38 (0%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	632	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.764	(E)	(E)	P=0.885
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.704	(E)	(E)	P=0.833
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.748	(E)	(E)	P=0.873
COCHRAN-ARMITAGE	(E)				P=0.739			
FISHER EXACT		(E)	(E)	(E)		P=1.000	P=1.000	P=0.855
Nose 4 Septum, Amyloid-like Substance								
LESION RATES								
OVERALL (A)	55/61 (90%)	58/66 (88%)	61/68 (90%)	55/63 (87%)	51/63 (81%)	46/65 (71%)	41/58 (71%)	40/56 (71%)
ADJUSTED (B)	94.6%	94.9%	95.2%	96.2%	89.2%	77.6%	81.0%	82.9%
FINAL (D)	20/23 (87%)	27/30 (90%)	23/26 (88%)	23/25 (92%)	27/33 (82%)	25/38 (66%)	25/34 (74%)	27/35 (77%)
FIRST INCIDENCE (DAYS)	45	17	19	6	127	103	55	418
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.616	P=0.795	P=0.558	P=0.730	P=0.925	P=0.946	P=0.954	P=0.972
INCIDENTAL TUMOR	P=0.811	P=0.716	P=0.679	P=0.891	P=0.805	P=0.961	P=0.947	P=0.940
LOGISTIC REGRESSION	P=0.737	P=0.756	P=0.652	P=0.809	P=0.845	P=0.964	P=0.946	P=0.960
COCHRAN-ARMITAGE	P=0.710				P=0.830			
FISHER EXACT		P=0.755	P=0.646	P=0.784		P=0.940	P=0.938	P=0.925

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 4 Teeth, Dysplasia								
LESION RATES								
OVERALL (A)	5/61 (8%)	14/66 (21%)	5/68 (7%)	13/63 (21%)	7/63 (11%)	6/65 (9%)	2/58 (3%)	3/56 (5%)
ADJUSTED (B)	19.6%	40.3%	17.7%	37.0%	17.8%	12.7%	4.4%	8.6%
FINAL (D)	4/23 (17%)	10/30 (33%)	4/26 (15%)	6/25 (24%)	4/33 (12%)	2/38 (5%)	1/34 (3%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	588	590	673	445	553	542	166	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.111	P=0.072	P=0.714	P=0.057	P=0.943	P=0.797	P=0.982	P=0.954
INCIDENTAL TUMOR	P=0.097	P=0.036 *	P=0.686	P=0.037 *	P=0.900	P=0.803	P=0.971	P=0.920
LOGISTIC REGRESSION	P=0.117	P=0.041 *	P=0.738	P=0.047 *	P=0.927	P=0.774	P=0.975	P=0.944
COCHRAN-ARMITAGE	P=0.119				P=0.926			
FISHER EXACT		P=0.034 *	P=0.695	P=0.042 *		P=0.740	P=0.978	P=0.930
Nose 5 Luminal Exudate								
LESION RATES								
OVERALL (A)	0/61 (0%)	4/66 (6%)	2/64 (3%)	7/60 (12%)	2/62 (3%)	3/63 (5%)	7/58 (12%)	22/56 (39%)
ADJUSTED (B)	0.0%	9.0%	4.4%	29.2%	4.9%	7.8%	18.3%	52.1%
FINAL (D)	0/23 (0%)	1/30 (3%)	0/24 (0%)	7/24 (29%)	1/32 (3%)	2/36 (6%)	5/34 (15%)	16/35 (46%)
FIRST INCIDENCE (DAYS)	---	39	501	726 (T)	511	674	571	295
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.009 **	P=0.084	P=0.258	P=0.009 **	P<0.001 **	P=0.552	P=0.101	P<0.001 **
INCIDENTAL TUMOR	P=0.010 **	P=0.078	P=0.257	P=0.009 **	P<0.001 **	P=0.529	P=0.068	P<0.001 **
LOGISTIC REGRESSION	P=0.008 **	P=0.074	P=0.248	P=0.009 **	P<0.001 **	P=0.541	P=0.080	P<0.001 **
COCHRAN-ARMITAGE	P=0.008 **				P<0.001 **			
FISHER EXACT		P=0.070	P=0.260	P=0.006 **		P=0.508	P=0.067	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Luminal Hemorrhage								
LESION RATES								
OVERALL (A)	3/61 (5%)	6/66 (9%)	4/64 (6%)	4/60 (7%)	2/62 (3%)	5/63 (8%)	4/58 (7%)	1/56 (2%)
ADJUSTED (B)	9.6%	14.6%	10.7%	9.7%	5.1%	12.0%	11.8%	1.5%
FINAL (D)	1/23 (4%)	2/30 (7%)	1/24 (4%)	0/24 (0%)	1/32 (3%)	3/36 (8%)	4/34 (12%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	293	39	325	40	558	486	732 (T)	76
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.604	P=0.332	P=0.549	P=0.542	P=0.890	P=0.272	P=0.361	P=0.872
INCIDENTAL TUMOR	P=0.608	P=0.273	P=0.593	P=0.534	P=0.872	P=0.261	P=0.308	P=0.788
LOGISTIC REGRESSION	P=0.565	P=0.285	P=0.528	P=0.485	P=0.863	P=0.248	P=0.349	P=0.830
COCHRAN-ARMITAGE	P=0.567				P=0.863			
FISHER EXACT		P=0.287	P=0.527	P=0.491		P=0.226	P=0.308	P=0.858
Nose 5 Nasolacrimal Duct, Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	1/60 (2%)	0/62 (0%)	3/63 (5%)	2/58 (3%)	4/56 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.2%	0.0%	7.4%	5.6%	11.4%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	1/24 (4%)	0/32 (0%)	2/36 (6%)	1/34 (3%)	4/35 (11%)
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)	---	611	715	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.195	(E)	(E)	P=0.508	P=0.101	P=0.148	P=0.246	P=0.074
INCIDENTAL TUMOR	P=0.195	(E)	(E)	P=0.508	P=0.069	P=0.151	P=0.271	P=0.074
LOGISTIC REGRESSION	P=0.195	(E)	(E)	P=0.508	P=0.084	P=0.141	P=0.252	P=0.074
COCHRAN-ARMITAGE	P=0.198				P=0.071			
FISHER EXACT		(E)	(E)	P=0.496		P=0.125	P=0.232	P=0.048 *

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Olfactory Epithelium, Atrophy								
LESION RATES								
OVERALL (A)	1/61 (2%)	3/66 (5%)	9/64 (14%)	6/60 (10%)	0/62 (0%)	7/63 (11%)	13/58 (22%)	25/56 (45%)
ADJUSTED (B)	3.0%	8.8%	27.9%	22.4%	0.0%	17.5%	33.2%	55.2%
FINAL (D)	0/23 (0%)	1/30 (3%)	5/24 (21%)	5/24 (21%)	0/32 (0%)	5/36 (14%)	10/34 (29%)	16/35 (46%)
FIRST INCIDENCE (DAYS)	608	629	439	447	---	542	394	295
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.064	P=0.382	P=0.016 *	P=0.068	P<0.001 **	P=0.016 *	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P=0.072	P=0.245	P=0.011 *	P=0.051	P<0.001 **	P=0.013 *	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P=0.057	P=0.346	P=0.013 *	P=0.060	P<0.001 **	P=0.015 *	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P=0.055				P<0.001 **			
FISHER EXACT		P=0.340	P=0.010 *	P=0.054		P=0.007 **	P<0.001 **	P<0.001 **
Nose 5 Olfactory Epithelium, Bowman's Glands, Degeneration, Cystic								
LESION RATES								
OVERALL (A)	0/61 (0%)	1/66 (2%)	5/64 (8%)	4/60 (7%)	0/62 (0%)	2/63 (3%)	4/58 (7%)	22/56 (39%)
ADJUSTED (B)	0.0%	3.1%	16.9%	16.7%	0.0%	4.4%	11.8%	52.6%
FINAL (D)	0/23 (0%)	0/30 (0%)	3/24 (13%)	4/24 (17%)	0/32 (0%)	1/36 (3%)	4/34 (12%)	16/35 (46%)
FIRST INCIDENCE (DAYS)	---	689	439	726 (T)	---	542	732 (T)	423
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.040 *	P=0.534	P=0.043 *	P=0.066	P<0.001 **	P=0.265	P=0.070	P<0.001 **
INCIDENTAL TUMOR	P=0.054	P=0.500	P=0.048 *	P=0.066	P<0.001 **	P=0.235	P=0.070	P<0.001 **
LOGISTIC REGRESSION	P=0.038 *	P=0.527	P=0.040 *	P=0.066	P<0.001 **	P=0.238	P=0.070	P<0.001 **
COCHRAN-ARMITAGE	P=0.040 *				P<0.001 **			
FISHER EXACT		P=0.520	P=0.033 *	P=0.057		P=0.252	P=0.052	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Olfactory Epithelium, Bowman's Glands, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	1/60 (2%)	1/62 (2%)	0/63 (0%)	0/58 (0%)	4/56 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.2%	3.1%	0.0%	0.0%	11.4%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	1/24 (4%)	1/32 (3%)	0/36 (0%)	0/34 (0%)	4/35 (11%)
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.195	(E)	(E)	P=0.508	P=0.020 *	(E)	(E)	P=0.206
INCIDENTAL TUMOR	P=0.195	(E)	(E)	P=0.508	P=0.020 *	(E)	(E)	P=0.206
LOGISTIC REGRESSION	P=0.195	(E)	(E)	P=0.508	P=0.020 *	(E)	(E)	P=0.206
COCHRAN-ARMITAGE	P=0.198				P=0.014 *			
FISHER EXACT		(E)	(E)	P=0.496		P=1.000	P=1.000	P=0.152
Nose 5 Olfactory Epithelium, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	2/64 (3%)	5/60 (8%)	0/62 (0%)	1/63 (2%)	3/58 (5%)	19/56 (34%)
ADJUSTED (B)	0.0%	0.0%	6.1%	12.0%	0.0%	2.0%	8.2%	45.4%
FINAL (D)	0/23 (0%)	0/30 (0%)	1/24 (4%)	1/24 (4%)	0/32 (0%)	0/36 (0%)	1/34 (3%)	13/35 (37%)
FIRST INCIDENCE (DAYS)	---	---	443	375	---	614	712	412
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.003 **	(E)	P=0.251	P=0.046 *	P<0.001 **	P=0.530	P=0.129	P<0.001 **
INCIDENTAL TUMOR	P=0.005 **	(E)	P=0.256	P=0.039 *	P<0.001 **	P=0.545	P=0.151	P<0.001 **
LOGISTIC REGRESSION	P=0.002 **	(E)	P=0.250	P=0.032 *	P<0.001 **	P=0.494	P=0.131	P<0.001 **
COCHRAN-ARMITAGE	P=0.002 **				P<0.001 **			
FISHER EXACT		(E)	P=0.260	P=0.027 *		P=0.504	P=0.110	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Olfactory Epithelium, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	0/60 (0%)	0/62 (0%)	0/63 (0%)	0/58 (0%)	3/56 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.6%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	0/24 (0%)	0/32 (0%)	0/36 (0%)	0/34 (0%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.010 *	(E)	(E)	P=0.137
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.010 *	(E)	(E)	P=0.137
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.010 *	(E)	(E)	P=0.137
COCHRAN-ARMITAGE	(E)				P=0.007 **			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.104
Nose 5 Respiratory Epithelium, Ciliated, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	2/64 (3%)	3/60 (5%)	4/62 (6%)	1/63 (2%)	1/58 (2%)	9/56 (16%)
ADJUSTED (B)	0.0%	0.0%	8.3%	10.2%	12.5%	2.0%	2.7%	24.9%
FINAL (D)	0/23 (0%)	0/30 (0%)	2/24 (8%)	2/24 (8%)	4/32 (13%)	0/36 (0%)	0/34 (0%)	8/35 (23%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	445	732 (T)	614	712	724
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.028 *	(E)	P=0.247	P=0.132	P=0.010 **	P=0.975	P=0.970	P=0.152
INCIDENTAL TUMOR	P=0.036 *	(E)	P=0.247	P=0.158	P=0.005 **	P=0.976	P=0.973	P=0.138
LOGISTIC REGRESSION	P=0.028 *	(E)	P=0.247	P=0.122	P=0.007 **	P=0.977	P=0.973	P=0.144
COCHRAN-ARMITAGE	P=0.028 *				P=0.005 **			
FISHER EXACT		(E)	P=0.260	P=0.119		P=0.972	P=0.966	P=0.085

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Eosinophilic Globules								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	0/60 (0%)	0/62 (0%)	0/63 (0%)	0/58 (0%)	4/56 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.2%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	0/24 (0%)	0/32 (0%)	0/36 (0%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	684
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.003 **	(E)	(E)	P=0.082
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P<0.001 **	(E)	(E)	P=0.035 *
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.002 **	(E)	(E)	P=0.064
COCHRAN-ARMITAGE	(E)				P=0.001 **			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.048 *
Nose 5 Respiratory Epithelium, Ciliated, Submucosal Mucous Glands, Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	0/60 (0%)	0/62 (0%)	0/63 (0%)	0/58 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.2%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	0/24 (0%)	0/32 (0%)	0/36 (0%)	0/34 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	684
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.047 *	(E)	(E)	P=0.264
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.031 *	(E)	(E)	P=0.217
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.038 *	(E)	(E)	P=0.237
COCHRAN-ARMITAGE	(E)				P=0.035 *			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.223

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Septum, Amyloid-like Substance								
LESION RATES								
OVERALL (A)	1/61 (2%)	2/66 (3%)	5/64 (8%)	2/60 (3%)	2/62 (3%)	0/63 (0%)	0/58 (0%)	1/56 (2%)
ADJUSTED (B)	2.0%	6.7%	13.6%	6.0%	3.8%	0.0%	0.0%	2.7%
FINAL (D)	0/23 (0%)	2/30 (7%)	2/24 (8%)	1/24 (4%)	0/32 (0%)	0/36 (0%)	0/34 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	360	726 (T)	328	443	543	---	---	724
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.471	P=0.564	P=0.122	P=0.536	P=0.745	(E)	(E)	P=0.866
INCIDENTAL TUMOR	P=0.488	P=0.569	P=0.123	P=0.513	P=0.695	(E)	(E)	P=0.811
LOGISTIC REGRESSION	P=0.439	P=0.531	P=0.115	P=0.491	P=0.740	(E)	(E)	P=0.858
COCHRAN-ARMITAGE	P=0.435				P=0.743			
FISHER EXACT		P=0.530	P=0.115	P=0.494		P=1.000	P=1.000	P=0.858
Nose 5 Teeth, Dysplasia								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/66 (0%)	0/64 (0%)	0/60 (0%)	0/62 (0%)	4/63 (6%)	0/58 (0%)	0/56 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	8.6%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/30 (0%)	0/24 (0%)	0/24 (0%)	0/32 (0%)	2/36 (6%)	0/34 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	103	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.947	P=0.081	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.928	P=0.041 *	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.936	P=0.039 *	(E)	(E)
COCHRAN-ARMITAGE	(E)				P=0.940			
FISHER EXACT		(E)	(E)	(E)		P=0.061	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose, 1 and 2 Cage Contaminant Associated Lesion								
LESION RATES								
OVERALL (A)	18/58 (31%)	52/64 (81%)	51/59 (86%)	37/57 (65%)	30/58 (52%)	39/59 (66%)	32/48 (67%)	38/50 (76%)
ADJUSTED (B)	59.7%	98.0%	95.6%	89.0%	80.5%	86.0%	90.5%	92.3%
FINAL (D)	11/22 (50%)	28/29 (97%)	19/21 (90%)	20/24 (83%)	24/31 (77%)	28/34 (82%)	24/27 (89%)	30/33 (91%)
FIRST INCIDENCE (DAYS)	373	39	59	195	543	514	25	76
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.162	P<0.001 **	P<0.001 **	P=0.004 **	P=0.192	P=0.203	P=0.197	P=0.132
INCIDENTAL TUMOR	P=0.045 *	P<0.001 **	P<0.001 **	P<0.001 **	P=0.023 *	P=0.186	P=0.087	P=0.024 *
LOGISTIC REGRESSION	P=0.025 *	P<0.001 **	P<0.001 **	P<0.001 **	P=0.020 *	P=0.219	P=0.106	P=0.019 *
COCHRAN-ARMITAGE	P=0.031 *				P=0.013 *			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.082	P=0.087	P=0.008 **
Nose, 1 and 2 Septal Fenestration								
LESION RATES								
OVERALL (A)	0/58 (0%)	17/64 (27%)	24/59 (41%)	15/57 (26%)	3/58 (5%)	3/59 (5%)	12/48 (25%)	18/50 (36%)
ADJUSTED (B)	0.0%	48.6%	72.2%	46.4%	9.7%	8.8%	39.7%	43.0%
FINAL (D)	0/22 (0%)	12/29 (41%)	13/21 (62%)	9/24 (38%)	3/31 (10%)	3/34 (9%)	10/27 (37%)	11/33 (33%)
FIRST INCIDENCE (DAYS)	---	264	325	195	732 (T)	732 (T)	445	423
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.018 *	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.707	P=0.006 **	P<0.001 **
INCIDENTAL TUMOR	P=0.007 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.707	P=0.004 **	P<0.001 **
LOGISTIC REGRESSION	P=0.008 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.707	P=0.005 **	P<0.001 **
COCHRAN-ARMITAGE	P=0.011 *				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.669	P=0.004 **	P<0.001 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Ovary Abscess(es)								
LESION RATES	(G)							
OVERALL (A)					2/52 (4%)	7/64 (11%)	6/55 (11%)	22/47 (47%)
ADJUSTED (B)					5.7%	17.4%	16.4%	58.5%
FINAL (D)					0/31 (0%)	5/35 (14%)	4/32 (13%)	17/32 (53%)
FIRST INCIDENCE (DAYS)					675	489	608	516
STATISTICAL TESTS (F)								
LIFE TABLE					P<0.001 **	P=0.128	P=0.165	P<0.001 **
INCIDENTAL TUMOR					P<0.001 **	P=0.161	P=0.202	P<0.001 **
LOGISTIC REGRESSION					P<0.001 **	P=0.145	P=0.162	P<0.001 **
COCHRAN-ARMITAGE					P<0.001 **			
FISHER EXACT						P=0.142	P=0.154	P<0.001 **
Ovary Cyst(s)								
LESION RATES	(G)							
OVERALL (A)					12/52 (23%)	14/64 (22%)	7/55 (13%)	7/47 (15%)
ADJUSTED (B)					32.0%	32.5%	20.5%	20.7%
FINAL (D)					8/31 (26%)	8/35 (23%)	6/32 (19%)	6/32 (19%)
FIRST INCIDENCE (DAYS)					375	510	571	692
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.957	P=0.580	P=0.944	P=0.944
INCIDENTAL TUMOR					P=0.933	P=0.660	P=0.917	P=0.933
LOGISTIC REGRESSION					P=0.927	P=0.658	P=0.954	P=0.914
COCHRAN-ARMITAGE					P=0.912			
FISHER EXACT						P=0.648	P=0.951	P=0.902

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Oviduct Dilatation								
LESION RATES	(G)							
OVERALL (A)					7/53 (13%)	0/51 (0%)	1/46 (2%)	2/38 (5%)
ADJUSTED (B)					20.9%	0.0%	3.6%	8.3%
FINAL (D)					5/30 (17%)	0/29 (0%)	1/28 (4%)	2/24 (8%)
FIRST INCIDENCE (DAYS)					560	---	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.914	(E)	P=0.994	P=0.968
INCIDENTAL TUMOR					P=0.895	(E)	P=0.993	P=0.956
LOGISTIC REGRESSION					P=0.905	(E)	P=0.995	P=0.964
COCHRAN-ARMITAGE					P=0.885			
FISHER EXACT						P=1.000	P=0.995	P=0.951
Oviduct Inflammation, Suppurative								
LESION RATES	(G)							
OVERALL (A)					0/53 (0%)	1/51 (2%)	0/46 (0%)	5/38 (13%)
ADJUSTED (B)					0.0%	3.4%	0.0%	16.8%
FINAL (D)					0/30 (0%)	1/29 (3%)	0/28 (0%)	3/24 (13%)
FIRST INCIDENCE (DAYS)					---	732 (T)	---	638
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.002 **	P=0.493	(E)	P=0.028 *
INCIDENTAL TUMOR					P<0.001 **	P=0.493	(E)	P=0.014 *
LOGISTIC REGRESSION					P<0.001 **	P=0.493	(E)	P=0.017 *
COCHRAN-ARMITAGE					P<0.001 **			
FISHER EXACT						P=0.490	(E)	P=0.011 *

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pancreas								
Acinar Cell Hyperplasia								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/2 (0%)	0/3 (0%)	0/62 (0%)	0/59 (0%)	0/3 (0%)	0/8 (0%)	2/58 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/2 (0%)	0/26 (0%)	0/33 (0%)	0/3 (0%)	0/6 (0%)	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.258
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.244
Pancreas								
Atrophy, Acinar								
LESION RATES								
OVERALL (A)	1/55 (2%)	0/2 (0%)	0/3 (0%)	1/62 (2%)	1/59 (2%)	1/3 (33%)	4/8 (50%)	0/58 (0%)
ADJUSTED (B)	1.6%	0.0%	0.0%	1.8%	2.9%	33.3%	66.7%	0.0%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/2 (0%)	0/26 (0%)	0/33 (0%)	1/3 (33%)	4/6 (67%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	46	---	---	375	722	732 (T)	732 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.777	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.820	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.852	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.781		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pancreas Cyst(s)								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/2 (0%)	0/3 (0%)	0/62 (0%)	0/59 (0%)	1/3 (33%)	4/8 (50%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	33.3%	66.7%	0.0%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/2 (0%)	0/26 (0%)	0/33 (0%)	1/3 (33%)	4/6 (67%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	732 (T)	732 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Pancreas Inflammation, Chronic								
LESION RATES								
OVERALL (A)	1/55 (2%)	0/2 (0%)	1/3 (33%)	1/62 (2%)	2/59 (3%)	0/3 (0%)	0/8 (0%)	2/58 (3%)
ADJUSTED (B)	1.8%	0.0%	50.0%	3.8%	3.9%	0.0%	0.0%	5.1%
FINAL (D)	0/23 (0%)	0/1 (0%)	1/2 (50%)	1/26 (4%)	0/33 (0%)	0/3 (0%)	0/6 (0%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	234	---	726 (T)	726 (T)	543	---	---	692
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.781	(E)	(E)	(E)	P=0.687
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.786	(E)	(E)	(E)	P=0.661
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.798	(E)	(E)	(E)	P=0.688
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.781		(E)	(E)	P=0.684

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pancreas Islet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	3/55 (5%)	1/2 (50%)	0/3 (0%)	6/62 (10%)	3/59 (5%)	0/3 (0%)	1/8 (13%)	1/58 (2%)
ADJUSTED (B)	9.5%	100.0%	0.0%	18.0%	8.2%	0.0%	16.7%	2.8%
FINAL (D)	1/23 (4%)	1/1 (100%)	0/2 (0%)	4/26 (15%)	2/33 (6%)	0/3 (0%)	1/6 (17%)	1/36 (3%)
FIRST INCIDENCE (DAYS)	304	726 (T)	---	6	591	---	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.305	(E)	(E)	(E)	P=0.943
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.319	(E)	(E)	(E)	P=0.918
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.309	(E)	(E)	(E)	P=0.940
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.309		(E)	(E)	P=0.939
Pancreas Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/2 (0%)	0/3 (0%)	0/62 (0%)	4/59 (7%)	0/3 (0%)	0/8 (0%)	7/58 (12%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	12.1%	0.0%	0.0%	19.4%
FINAL (D)	0/23 (0%)	0/1 (0%)	0/2 (0%)	0/26 (0%)	4/33 (12%)	0/3 (0%)	0/6 (0%)	7/36 (19%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.309
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.309
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.309
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.254

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Parathyroid Cyst								
LESION RATES								
OVERALL (A)	3/49 (6%)	0/0 (0%)	0/0 (0%)	0/52 (0%)	0/54 (0%)	0/0 (0%)	0/0 (0%)	4/51 (8%)
ADJUSTED (B)	12.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	11.5%
FINAL (D)	2/20 (10%)	0/0	0/0	0/22 (0%)	0/31 (0%)	0/0	0/0	3/33 (9%)
FIRST INCIDENCE (DAYS)	626	---	---	---	---	---	---	724
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.075
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.057
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.057
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.052
Penis Inflammation								
LESION RATES					(G)			
OVERALL (A)	0/0 (0%)	2/4 (50%)	2/3 (67%)	0/0 (0%)				
ADJUSTED (B)	0.0%	51.1%	51.5%	0.0%				
FINAL (D)	0/0	1/2 (50%)	1/2 (50%)	0/0				
FIRST INCIDENCE (DAYS)	---	500	681	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pituitary Pars Anterior, Cyst(s)								
LESION RATES								
OVERALL (A)	2/46 (4%)	0/0 (0%)	0/2 (0%)	0/40 (0%)	0/42 (0%)	0/10 (0%)	0/1 (0%)	0/31 (0%)
ADJUSTED (B)	9.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	2/21 (10%)	0/0	0/0	0/18 (0%)	0/25 (0%)	0/8 (0%)	0/0	0/27 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	(E)
Pituitary Pars Anterior, Hyperplasia								
LESION RATES								
OVERALL (A)	1/46 (2%)	0/0 (0%)	0/2 (0%)	0/40 (0%)	3/42 (7%)	1/10 (10%)	0/1 (0%)	6/31 (19%)
ADJUSTED (B)	4.8%	0.0%	0.0%	0.0%	9.4%	12.5%	0.0%	20.3%
FINAL (D)	1/21 (5%)	0/0	0/0	0/18 (0%)	2/25 (8%)	1/8 (13%)	0/0	5/27 (19%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	---	177	732 (T)	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.268
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.091
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.077
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.114

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Prepuce Congestion								
LESION RATES					(G)			
OVERALL (A)	0/12 (0%)	0/7 (0%)	0/8 (0%)	2/5 (40%)				
ADJUSTED (B)	0.0%	0.0%	0.0%	5.5%				
FINAL (D)	0/7 (0%)	0/3 (0%)	0/3 (0%)	0/1 (0%)				
FIRST INCIDENCE (DAYS)	---	---	---	517				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Prepuce Inflammation								
LESION RATES					(G)			
OVERALL (A)	11/12 (92%)	7/7 (100%)	8/8 (100%)	2/5 (40%)				
ADJUSTED (B)	100.0%	100.0%	100.0%	100.0%				
FINAL (D)	7/7 (100%)	3/3 (100%)	3/3 (100%)	1/1 (100%)				
FIRST INCIDENCE (DAYS)	653	500	653	375				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Preputial Gland Abscess								
LESION RATES					(G)			
OVERALL (A)	2/4 (50%)	0/7 (0%)	3/5 (60%)	2/7 (29%)				
ADJUSTED (B)	100.0%	0.0%	67.9%	50.0%				
FINAL (D)	1/1 (100%)	0/3 (0%)	2/3 (67%)	2/4 (50%)				
FIRST INCIDENCE (DAYS)	608	---	723	726 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Preputial Gland Cystic Degeneration								
LESION RATES					(G)			
OVERALL (A)	1/4 (25%)	5/7 (71%)	2/5 (40%)	4/7 (57%)				
ADJUSTED (B)	4.2%	100.0%	35.1%	30.3%				
FINAL (D)	0/1 (0%)	3/3 (100%)	1/3 (33%)	1/4 (25%)				
FIRST INCIDENCE (DAYS)	719	388	653	375				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Preputial Gland Inflammation								
LESION RATES					(G)			
OVERALL (A)	0/4 (0%)	2/7 (29%)	0/5 (0%)	0/7 (0%)				
ADJUSTED (B)	0.0%	35.4%	0.0%	0.0%				
FINAL (D)	0/1 (0%)	1/3 (33%)	0/3 (0%)	0/4 (0%)				
FIRST INCIDENCE (DAYS)	---	688	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Prostate Inflammation, Suppurative								
LESION RATES					(G)			
OVERALL (A)	7/61 (11%)	0/0 (0%)	2/2 (100%)	1/64 (2%)				
ADJUSTED (B)	19.5%	0.0%	0.0%	3.7%				
FINAL (D)	1/23 (4%)	0/0	0/0	0/26 (0%)				
FIRST INCIDENCE (DAYS)	234	---	523	706				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.995				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.991				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.991				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.997				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Salivary Gland Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	9/60 (15%)	0/2 (0%)	0/3 (0%)	15/64 (23%)	25/58 (43%)	0/1 (0%)	0/0 (0%)	22/58 (38%)
ADJUSTED (B)	34.4%	0.0%	0.0%	50.1%	59.8%	0.0%	0.0%	54.6%
FINAL (D)	7/23 (30%)	0/0	0/0	12/26 (46%)	17/33 (52%)	0/0	0/0	18/36 (50%)
FIRST INCIDENCE (DAYS)	373	---	---	451	495	---	---	447
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.189	(E)	(E)	(E)	P=0.846
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.197	(E)	(E)	(E)	P=0.799
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.171	(E)	(E)	(E)	P=0.799
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.168		(E)	(E)	P=0.775
Sciatic Nerve Inflammation								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/0 (0%)	0/0 (0%)	0/64 (0%)	5/59 (8%)	0/0 (0%)	0/0 (0%)	1/59 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	15.2%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/0	0/0	0/25 (0%)	5/33 (15%)	0/0	0/0	1/36 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.987
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.987
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.987
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.986

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Skeletal Muscle								
Lymphocytic Infiltration								
LESION RATES								
OVERALL (A)	0/61 (0%)	0/0 (0%)	0/0 (0%)	0/65 (0%)	1/62 (2%)	0/1 (0%)	0/0 (0%)	2/59 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	1/33 (3%)	0/0	0/0	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.481
Skin								
Inflammation								
LESION RATES								
OVERALL (A)	2/62 (3%)	1/10 (01%)	1/15 (7%)	1/64 (2%)	0/63 (0%)	1/47 (2%)	0/23 (0%)	0/59 (0%)
ADJUSTED (B)	8.7%	11.1%	14.3%	4.0%	0.0%	2.5%	0.0%	0.0%
FINAL (D)	2/23 (9%)	1/9 (11%)	1/7 (14%)	1/25 (4%)	0/35 (0%)	0/32 (0%)	0/21 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	726 (T)	726 (T)	---	715	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.895	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.895	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.895	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.884		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spinal Cord Inflammation, Chronic								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/0 (0%)	0/0 (0%)	0/65 (0%)	3/63 (5%)	0/0 (0%)	0/0 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	8.1%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	2/33 (6%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	563	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000
Spinal Cord Mineralization								
LESION RATES								
OVERALL (A)	0/60 (0%)	0/0 (0%)	0/0 (0%)	0/65 (0%)	2/63 (3%)	0/0 (0%)	0/0 (0%)	0/59 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	5.1%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	1/33 (3%)	0/0	0/0	0/36 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	563	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen Atrophy								
LESION RATES								
OVERALL (A)	7/58 (12%)	2/11 (18%)	4/19 (21%)	9/59 (15%)	3/61 (5%)	0/31 (0%)	0/15 (0%)	3/59 (5%)
ADJUSTED (B)	13.2%	4.5%	6.7%	15.3%	5.1%	0.0%	0.0%	5.1%
FINAL (D)	0/23 (0%)	0/3 (0%)	0/4 (0%)	0/26 (0%)	0/33 (0%)	0/15 (0%)	0/7 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	45	101	73	6	177	---	---	240
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.428	(E)	(E)	(E)	P=0.626
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.362	(E)	(E)	(E)	P=0.619
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.293	(E)	(E)	(E)	P=0.729
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.409		(E)	(E)	P=0.644
Spleen Congestion								
LESION RATES								
OVERALL (A)	1/58 (2%)	0/11 (0%)	1/19 (5%)	1/59 (2%)	1/61 (2%)	5/31 (16%)	1/15 (7%)	3/59 (5%)
ADJUSTED (B)	4.2%	0.0%	2.5%	2.8%	2.8%	28.1%	14.3%	7.0%
FINAL (D)	0/23 (0%)	0/3 (0%)	0/4 (0%)	0/26 (0%)	0/33 (0%)	4/15 (27%)	1/7 (14%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	719	---	599	646	715	608	732 (T)	468
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.789	(E)	(E)	(E)	P=0.322
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.842	(E)	(E)	(E)	P=0.254
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.776	(E)	(E)	(E)	P=0.295
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.756		(E)	(E)	P=0.297

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen Extramedullary Hematopoiesis								
LESION RATES								
OVERALL (A)	11/58 (19%)	3/11 (27%)	11/19 (58%)	9/59 (15%)	12/61 (20%)	21/31 (68%)	6/15 (40%)	25/59 (42%)
ADJUSTED (B)	34.5%	36.4%	80.0%	27.2%	26.5%	83.5%	46.8%	56.0%
FINAL (D)	5/23 (22%)	1/3 (33%)	3/4 (75%)	3/26 (12%)	3/33 (9%)	12/15 (80%)	3/7 (43%)	17/36 (47%)
FIRST INCIDENCE (DAYS)	146	388	422	451	397	542	664	418
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.823	(E)	(E)	(E)	P=0.024 *
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.870	(E)	(E)	(E)	P=0.005 **
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.801	(E)	(E)	(E)	P=0.006 **
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.782		(E)	(E)	P=0.006 **
Spleen Hemosiderosis								
LESION RATES								
OVERALL (A)	16/58 (28%)	1/11 (9%)	1/19 (5%)	18/59 (31%)	39/61 (64%)	10/31 (32%)	2/15 (13%)	45/59 (76%)
ADJUSTED (B)	39.9%	1.4%	2.0%	45.8%	83.9%	60.9%	28.6%	89.7%
FINAL (D)	4/23 (17%)	0/3 (0%)	0/4 (0%)	7/26 (27%)	26/33 (79%)	9/15 (60%)	2/7 (29%)	31/36 (86%)
FIRST INCIDENCE (DAYS)	108	19	442	381	177	669	732 (T)	240
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.545	(E)	(E)	(E)	P=0.311
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.456	(E)	(E)	(E)	P=0.193
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.452	(E)	(E)	(E)	P=0.097
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.443		(E)	(E)	P=0.101

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen Lymphoid Hyperplasia								
LESION RATES								
OVERALL (A)	1/58 (2%)	1/11 (9%)	1/19 (5%)	2/59 (3%)	5/61 (8%)	2/31 (6%)	3/15 (20%)	24/59 (41%)
ADJUSTED (B)	4.3%	33.3%	25.0%	7.7%	15.2%	13.3%	42.9%	62.8%
FINAL (D)	1/23 (4%)	1/3 (33%)	1/4 (25%)	2/26 (8%)	5/33 (15%)	2/15 (13%)	3/7 (43%)	22/36 (61%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	726 (T)	726 (T)	732 (T)	732 (T)	732 (T)	471
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.543	(E)	(E)	(E)	P<0.001 **
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.543	(E)	(E)	(E)	P<0.001 **
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.543	(E)	(E)	(E)	P<0.001 **
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.506		(E)	(E)	P<0.001 **
Spleen Lymphoid Necrosis								
LESION RATES								
OVERALL (A)	2/58 (3%)	0/11 (0%)	0/19 (0%)	1/59 (2%)	0/61 (0%)	0/31 (0%)	0/15 (0%)	0/59 (0%)
ADJUSTED (B)	6.7%	0.0%	0.0%	2.4%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/3 (0%)	0/4 (0%)	0/26 (0%)	0/33 (0%)	0/15 (0%)	0/7 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	591	---	---	523	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.880	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.866	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.884	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.881		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen								
Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	1/58 (2%)	2/11 (18%)	0/19 (0%)	0/59 (0%)	3/61 (5%)	0/31 (0%)	0/15 (0%)	1/59 (2%)
ADJUSTED (B)	1.9%	3.3%	0.0%	0.0%	8.0%	0.0%	0.0%	2.2%
FINAL (D)	0/23 (0%)	0/3 (0%)	0/4 (0%)	0/26 (0%)	0/33 (0%)	0/15 (0%)	0/7 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)	304	19	---	---	653	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.939
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.879
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.934
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.936
Stomach								
Forestomach, Cystic Hyperplasia								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/12 (0%)	0/13 (0%)	0/64 (0%)	3/60 (5%)	0/34 (0%)	0/16 (0%)	3/58 (5%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	9.1%	0.0%	0.0%	8.6%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/3 (0%)	0/26 (0%)	3/33 (9%)	0/30 (0%)	0/14 (0%)	3/35 (9%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.691
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.691
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.691
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.644

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach Glandular Adenomatous Cystic Hyperplasia								
LESION RATES								
OVERALL (A)	1/55 (2%)	1/12 (8%)	0/13 (0%)	3/64 (5%)	2/60 (3%)	0/34 (0%)	0/16 (0%)	0/58 (0%)
ADJUSTED (B)	4.3%	12.5%	0.0%	11.5%	5.9%	0.0%	0.0%	0.0%
FINAL (D)	1/23 (4%)	1/8 (13%)	0/3 (0%)	3/26 (12%)	1/33 (3%)	0/30 (0%)	0/14 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	726 (T)	726 (T)	---	726 (T)	722	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.348	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.348	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.348	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.369		(E)	(E)	P=1.000
Stomach Glandular Mucosa, Cystic Degeneration								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/12 (0%)	0/13 (0%)	3/64 (5%)	0/60 (0%)	0/34 (0%)	0/16 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	10.8%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/3 (0%)	2/26 (8%)	0/33 (0%)	0/30 (0%)	0/14 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	684	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.144	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.169	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.138	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.152		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach								
Glandular Mucosa, Erosion								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/12 (0%)	2/13 (15%)	2/64 (3%)	0/60 (0%)	0/34 (0%)	2/16 (13%)	1/58 (2%)
ADJUSTED (B)	0.0%	0.0%	4.2%	3.3%	0.0%	0.0%	4.2%	2.4%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/3 (0%)	0/26 (0%)	0/33 (0%)	0/30 (0%)	0/14 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	20	195	---	---	571	684
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.259	(E)	(E)	(E)	P=0.525
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.257	(E)	(E)	(E)	P=0.469
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.335	(E)	(E)	(E)	P=0.496
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.287		(E)	(E)	P=0.492
Stomach								
Hemorrhage								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/12 (0%)	0/13 (0%)	3/64 (5%)	0/60 (0%)	0/34 (0%)	0/16 (0%)	0/58 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	5.9%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	0/8 (0%)	0/3 (0%)	0/26 (0%)	0/33 (0%)	0/30 (0%)	0/14 (0%)	0/35 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	373	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.138	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.218	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.160	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.152		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach Inflammation								
LESION RATES								
OVERALL (A)	7/55 (13%)	3/12 (25%)	0/13 (0%)	1/64 (2%)	6/60 (10%)	20/34 (59%)	9/16 (56%)	6/58 (10%)
ADJUSTED (B)	24.5%	37.5%	0.0%	3.8%	18.2%	61.9%	64.3%	17.1%
FINAL (D)	4/23 (17%)	3/8 (38%)	0/3 (0%)	1/26 (4%)	6/33 (18%)	18/30 (60%)	9/14 (64%)	6/35 (17%)
FIRST INCIDENCE (DAYS)	380	726 (T)	---	726 (T)	732 (T)	701	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.997	(E)	(E)	(E)	P=0.665
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.997	(E)	(E)	(E)	P=0.665
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.997	(E)	(E)	(E)	P=0.665
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.998		(E)	(E)	P=0.595
Stomach Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	0/55 (0%)	0/12 (0%)	1/13 (8%)	0/64 (0%)	3/60 (5%)	0/34 (0%)	0/16 (0%)	1/58 (2%)
ADJUSTED (B)	0.0%	0.0%	33.3%	0.0%	8.0%	0.0%	0.0%	2.9%
FINAL (D)	0/23 (0%)	0/8 (0%)	1/3 (33%)	0/26 (0%)	2/33 (6%)	0/30 (0%)	0/14 (0%)	1/35 (3%)
FIRST INCIDENCE (DAYS)	---	---	726 (T)	---	560	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.938
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.914
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.935
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.936

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach Squamous Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	10/55 (18%)	7/12 (58%)	3/13 (23%)	10/64 (16%)	11/60 (18%)	32/34 (94%)	14/16 (88%)	17/58 (29%)
ADJUSTED (B)	31.7%	75.7%	100.0%	21.1%	33.3%	100.0%	100.0%	45.3%
FINAL (D)	5/23 (22%)	6/8 (75%)	3/3 (100%)	1/26 (4%)	11/33 (33%)	30/30 (100%)	14/14 (100%)	15/35 (43%)
FIRST INCIDENCE (DAYS)	380	685	726 (T)	6	732 (T)	669	732 (T)	295
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.663	(E)	(E)	(E)	P=0.163
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.778	(E)	(E)	(E)	P=0.157
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.740	(E)	(E)	(E)	P=0.147
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.732		(E)	(E)	P=0.118
Stomach Ulceration								
LESION RATES								
OVERALL (A)	2/55 (4%)	1/12 (8%)	0/13 (0%)	0/64 (0%)	6/60 (10%)	14/34 (41%)	5/16 (31%)	2/58 (3%)
ADJUSTED (B)	4.8%	12.5%	0.0%	0.0%	18.2%	46.7%	35.7%	5.7%
FINAL (D)	0/23 (0%)	1/8 (13%)	0/3 (0%)	0/26 (0%)	6/33 (18%)	14/30 (47%)	5/14 (36%)	2/35 (6%)
FIRST INCIDENCE (DAYS)	380	726 (T)	---	---	732 (T)	732 (T)	732 (T)	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.975
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.975
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.975
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.966

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Testis								
Interstitial Cell Hyperplasia								
LESION RATES					(G)			
OVERALL (A)	0/61 (0%)	0/0 (0%)	0/1 (0%)	3/63 (5%)				
ADJUSTED (B)	0.0%	0.0%	0.0%	11.5%				
FINAL (D)	0/23 (0%)	0/0	0/0	3/26 (12%)				
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.142				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.142				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.142				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.128				
Testis								
Seminiferous Tubule, Degeneration								
LESION RATES					(G)			
OVERALL (A)	1/61 (2%)	0/0 (0%)	0/1 (0%)	5/63 (8%)				
ADJUSTED (B)	4.3%	0.0%	0.0%	13.4%				
FINAL (D)	1/23 (4%)	0/0	0/0	0/26 (0%)				
FIRST INCIDENCE (DAYS)	726 (T)	---	---	447				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.131				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.204				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.204				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.111				

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thymus Atrophy								
LESION RATES								
OVERALL (A)	17/45 (38%)	0/1 (0%)	0/1 (0%)	23/44 (52%)	9/49 (18%)	0/5 (0%)	0/3 (0%)	5/47 (11%)
ADJUSTED (B)	36.7%	0.0%	0.0%	55.2%	17.7%	0.0%	0.0%	10.9%
FINAL (D)	2/21 (10%)	0/0	0/0	9/23 (39%)	1/28 (4%)	0/4 (0%)	0/2 (0%)	0/31 (0%)
FIRST INCIDENCE (DAYS)	45	---	---	6	298	---	---	447
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.279	(E)	(E)	(E)	P=0.897
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.081	(E)	(E)	(E)	P=0.910
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.084	(E)	(E)	(E)	P=0.865
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.123		(E)	(E)	P=0.914
Thymus Hyperplasia								
LESION RATES								
OVERALL (A)	0/45 (0%)	0/1 (0%)	0/1 (0%)	0/44 (0%)	1/49 (2%)	2/5 (40%)	1/3 (33%)	0/47 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	2.0%	50.0%	50.0%	0.0%
FINAL (D)	0/21 (0%)	0/0	0/0	0/23 (0%)	0/28 (0%)	2/4 (50%)	1/2 (50%)	0/31 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	558	732 (T)	732 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thyroid Follicular Cell Hyperplasia								
LESION RATES								
OVERALL (A)	19/59 (32%)	0/0 (0%)	0/0 (0%)	28/63 (44%)	20/61 (33%)	0/0 (0%)	0/0 (0%)	25/56 (45%)
ADJUSTED (B)	69.8%	0.0%	0.0%	87.3%	54.9%	0.0%	0.0%	63.9%
FINAL (D)	15/23 (65%)	0/0	0/0	22/26 (85%)	17/33 (52%)	0/0	0/0	22/36 (61%)
FIRST INCIDENCE (DAYS)	608	---	---	604	560	---	---	570
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.114	(E)	(E)	(E)	P=0.326
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.050	(E)	(E)	(E)	P=0.186
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.050	(E)	(E)	(E)	P=0.186
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.115		(E)	(E)	P=0.130
Thyroid Follicular Cyst								
LESION RATES								
OVERALL (A)	0/59 (0%)	0/0 (0%)	0/0 (0%)	1/63 (2%)	4/61 (7%)	0/0 (0%)	0/0 (0%)	1/56 (2%)
ADJUSTED (B)	0.0%	0.0%	0.0%	3.8%	12.1%	0.0%	0.0%	2.8%
FINAL (D)	0/23 (0%)	0/0	0/0	1/26 (4%)	4/33 (12%)	0/0	0/0	1/36 (3%)
FIRST INCIDENCE (DAYS)	---	---	---	726 (T)	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	P=0.974
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	P=0.974
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	P=0.974
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.518		(E)	(E)	P=0.964

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thyroid Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	2/59 (3%)	0/0 (0%)	0/0 (0%)	1/63 (2%)	3/61 (5%)	0/0 (0%)	0/0 (0%)	2/56 (4%)
ADJUSTED (B)	8.7%	0.0%	0.0%	3.8%	8.2%	0.0%	0.0%	5.0%
FINAL (D)	2/23 (9%)	0/0	0/0	1/26 (4%)	2/33 (6%)	0/0	0/0	1/36 (3%)
FIRST INCIDENCE (DAYS)	726 (T)	---	---	726 (T)	591	---	---	611
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.833
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.721
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.902	(E)	(E)	(E)	P=0.721
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.890		(E)	(E)	P=0.790
Thyroid Parafollicular Cell Hyperplasia								
LESION RATES								
OVERALL (A)	0/59 (0%)	0/0 (0%)	0/0 (0%)	0/63 (0%)	1/61 (2%)	0/0 (0%)	0/0 (0%)	2/56 (4%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%	5.6%
FINAL (D)	0/23 (0%)	0/0	0/0	0/26 (0%)	1/33 (3%)	0/0	0/0	2/36 (6%)
FIRST INCIDENCE (DAYS)	---	---	---	---	732 (T)	---	---	732 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.530
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.468

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Urinary Bladder Epithelium, Hyperplasia								
LESION RATES								
OVERALL (A)	0/61 (0%)	1/22 (5%)	1/23 (4%)	2/63 (3%)	0/57 (0%)	0/3 (0%)	0/5 (0%)	0/55 (0%)
ADJUSTED (B)	0.0%	7.7%	2.2%	3.8%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	0/23 (0%)	1/13 (8%)	0/11 (0%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/4 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	---	726 (T)	523	373	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.261	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.354	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.229	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.256		(E)	(E)	(E)
Urinary Bladder Inflammation								
LESION RATES								
OVERALL (A)	2/61 (3%)	5/22 (23%)	5/23 (22%)	0/63 (0%)	0/57 (0%)	0/3 (0%)	0/5 (0%)	0/55 (0%)
ADJUSTED (B)	7.4%	21.3%	18.9%	0.0%	0.0%	0.0%	0.0%	0.0%
FINAL (D)	1/23 (4%)	2/13 (15%)	1/11 (9%)	0/26 (0%)	0/32 (0%)	0/3 (0%)	0/4 (0%)	0/34 (0%)
FIRST INCIDENCE (DAYS)	637	388	653	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	(E)

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Urinary Bladder								
Lymphoid Infiltration								
LESION RATES								
OVERALL (A)	1/61 (2%)	1/22 (5%)	0/23 (0%)	1/63 (2%)	18/57 (32%)	0/3 (0%)	0/5 (0%)	11/55 (20%)
ADJUSTED (B)	4.3%	3.2%	0.0%	3.2%	50.6%	0.0%	0.0%	29.9%
FINAL (D)	1/23 (4%)	0/13 (0%)	0/11 (0%)	0/26 (0%)	15/32 (47%)	0/3 (0%)	0/4 (0%)	9/34 (26%)
FIRST INCIDENCE (DAYS)	726 (T)	694	---	672	570	---	---	471
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.788	(E)	(E)	(E)	P=0.973
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.811	(E)	(E)	(E)	P=0.962
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.782	(E)	(E)	(E)	P=0.969
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.760		(E)	(E)	P=0.947
Uterus								
Endometrium, Cystic Hyperplasia								
LESION RATES	(G)							
OVERALL (A)					46/56 (82%)	50/66 (76%)	42/56 (75%)	48/57 (84%)
ADJUSTED (B)					93.7%	94.2%	93.1%	97.9%
FINAL (D)					29/32 (91%)	34/37 (92%)	30/33 (91%)	35/36 (97%)
FIRST INCIDENCE (DAYS)					127	486	248	161
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.645	P=0.781	P=0.870	P=0.735
INCIDENTAL TUMOR					P=0.393	P=0.899	P=0.853	P=0.559
LOGISTIC REGRESSION					P=0.302	P=0.922	P=0.902	P=0.545
COCHRAN-ARMITAGE					P=0.290			
FISHER EXACT						P=0.860	P=0.875	P=0.483

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Uterus								
Endometrium, Stromal Polyp								
LESION RATES	(G)							
OVERALL (A)					3/56 (5%)	1/66 (2%)	0/56 (0%)	0/57 (0%)
ADJUSTED (B)					8.9%	2.7%	0.0%	0.0%
FINAL (D)					2/32 (6%)	1/37 (3%)	0/33 (0%)	0/36 (0%)
FIRST INCIDENCE (DAYS)					675	732 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.989	P=0.952	(E)	(E)
INCIDENTAL TUMOR					P=0.989	P=0.959	(E)	(E)
LOGISTIC REGRESSION					P=0.989	P=0.959	(E)	(E)
COCHRAN-ARMITAGE					P=0.988			
FISHER EXACT						P=0.958	P=1.000	P=1.000
Uterus								
Inflammation, Suppurative								
LESION RATES	(G)							
OVERALL (A)					12/56 (21%)	11/66 (17%)	10/56 (18%)	25/57 (44%)
ADJUSTED (B)					29.9%	28.5%	25.5%	59.3%
FINAL (D)					6/32 (19%)	10/37 (27%)	6/33 (18%)	19/36 (53%)
FIRST INCIDENCE (DAYS)					463	615	608	570
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.002 **	P=0.809	P=0.791	P=0.029 *
INCIDENTAL TUMOR					P<0.001 **	P=0.829	P=0.742	P=0.007 **
LOGISTIC REGRESSION					P<0.001 **	P=0.842	P=0.783	P=0.011 *
COCHRAN-ARMITAGE					P<0.001 **			
FISHER EXACT						P=0.817	P=0.762	P=0.009 **

TABLE S1b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN MICE(B6C3F1) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Uterus								
Vaginitis								
LESION RATES	(G)							
OVERALL (A)					11/56 (20%)	11/66 (17%)	5/56 (9%)	12/57 (21%)
ADJUSTED (B)					31.1%	28.6%	15.2%	31.0%
FINAL (D)					9/32 (28%)	10/37 (27%)	5/33 (15%)	10/36 (28%)
FIRST INCIDENCE (DAYS)					353	653	732 (T)	516
STATISTICAL TESTS (F)								
LIFE TABLE					P=0.511	P=0.741	P=0.977	P=0.614
INCIDENTAL TUMOR					P=0.486	P=0.740	P=0.973	P=0.571
LOGISTIC REGRESSION					P=0.444	P=0.783	P=0.978	P=0.561
COCHRAN-ARMITAGE					P=0.402			
FISHER EXACT						P=0.747	P=0.972	P=0.519

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

(A) NUMBER OF TUMOR-BEARING ANIMALS / NUMBER OFANIMALS EXAMINED AT SITE.
(B) KAPLAN-MEIER ESTIMATED LIFETIME TUMOR INCIDENCE AFTER ADJUSTMENT FOR INTERCURRENT MORTALITY.
(C) OBSERVED INCIDENCE AT INTERIM NECROPSY.
(D) OBSERVED INCIDENCE AT FINAL NECROPSY.
(E) STATISTICAL EVALUATION NOT COMPUTED SINCE FULL GROUPS WERE NOT EXAMINED OR DATA DO NOT MEET CRITERIA FOR STATISTICAL TEST.
(F) BENEATH THE CONTROL INCIDENCE ARE THE P-VALUES ASSOCIATED WITH THE TREND TEST. BENEATH THE DOSED GROUP INCIDENCE ARE THE P-VALUES CORRESPONDING TO PAIRWISE COMPARISONS BETWEEN THE CONTROLS AND THAT DOSED GROUP. THE LIFE TABLE ANALYSIS REGARDS TUMORS IN ANIMALS DYING PRIOR TO FINAL NECROPSY AS BEING (DIRECTLY OR INDIRECTLY) THE CAUSE OF DEATH. THE INCIDENTAL TUMOR TEST REGARDS THESE LESIONS AS NON-FATAL. LOGISTIC REGRESSION IS AN ALTERNATIVE METHOD FOR ANALYZING THE INCIDENCE OF NON-FATAL TUMORS.THE COCHRAN-ARMITAGE AND FISHER'S EXACT TESTS COMPARE DIRECTLY THE OVERALLINCIDENCE RATES. FOR ALL TESTS, A NEGATIVE TREND IS INDICATED BY "N".
(G) DATA NOT PRESENTED DUE TO
1) ORGAN OR LESION NOT SEX APPROPRIATE
2) FEWER THAN TWO FINDINGS FOR ALL GROUPS
3) INTERPATHOLOGIST VARIATION
(I) INTERIM NECROPSY
(T) FINAL NECROPSY

* TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.05).
** TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.01).

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal								
Pheochromocytoma								
TUMOR RATES								
OVERALL (A)	6/67 (9%)	5/9 (56%)	7/9 (78%)	10/66 (15%)	2/68 (3%)	0/6 (0%)	1/7 (14%)	1/70 (1%)
ADJUSTED (B)	13.9%	71.4%	86.0%	20.7%	4.0%	0.0%	33.3%	2.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	1/10 (10%)	0/9 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	5/42 (12%)	5/7 (71%)	6/7 (86%)	9/46 (20%)	2/50 (4%)	0/2 (0%)	1/3 (33%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	718	725 (T)	636	368 (I)	739 (T)	---	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.266	(E)	(E)	(E)	P=0.871
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.223	(E)	(E)	(E)	P=0.871
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.206	(E)	(E)	(E)	P=0.871
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.203		(E)	(E)	P=0.883
Brain								
Astrocytoma								
TUMOR RATES								
OVERALL (A)	2/68 (3%)	0/1 (0%)	1/3 (33%)	0/68 (0%)	(G)			
ADJUSTED (B)	3.7%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/0	1/1 (100%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Ear Canal								
Zymbal's Gland Carcinoma, Unilateral								
TUMOR RATES								
OVERALL (A)	2/67 (3%)	0/1 (0%)	1/1 (100%)	0/67 (0%)	1/69 (1%)	1/1 (100%)	0/0 (0%)	1/68 (1%)
ADJUSTED (B)	4.5%	0.0%	0.0%	0.0%	2.0%	100.0%	0.0%	1.8%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	1/42 (2%)	0/0	0/0	0/46 (0%)	1/50 (2%)	1/1 (100%)	0/0	0/48 (0%)
FIRST INCIDENCE (DAYS)	713	---	718	---	739 (T)	739 (T)	---	615
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.756
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.756
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.756
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.748
Epididymis								
Mesothelioma								
TUMOR RATES								
OVERALL (A)	5/68 (7%)	2/3 (67%)	3/4 (75%)	1/67 (1%)	(G)			
ADJUSTED (B)	9.5%	50.9%	100.0%	2.2%				
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/0	0/0	0/10 (0%)				
FINAL (D)	2/43 (5%)	1/2 (50%)	2/2 (100%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	368 (I)	642	661	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.982				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.986				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.981				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.985				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Intestine-Small, Ileum								
Leiomyoma, Leiomyosarcoma								
TUMOR RATES								
OVERALL (A)	0/68 (0%)	0/1 (0%)	1/3 (33%)	0/67 (0%)	2/69 (3%)	0/0 (0%)	0/0 (0%)	0/70 (0%)
ADJUSTED (B)	0.0%	0.0%	100.0%	0.0%	4.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/43 (0%)	0/1 (0%)	1/1 (100%)	0/46 (0%)	2/50 (4%)	0/0	0/0	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	725 (T)	---	739 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=1.000
Liver								
Hepatocellular Adenoma								
TUMOR RATES								
OVERALL (A)	4/68 (6%)	3/25 (12%)	2/13 (15%)	4/68 (6%)	2/69 (3%)	5/27 (19%)	7/32 (22%)	6/70 (9%)
ADJUSTED (B)	9.3%	16.7%	40.0%	8.7%	4.0%	22.7%	30.4%	12.5%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	4/43 (9%)	3/18 (17%)	2/5 (40%)	4/46 (9%)	2/50 (4%)	5/22 (23%)	7/23 (30%)	6/48 (13%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	725 (T)	725 (T)	739 (T)	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.680	(E)	(E)	(E)	P=0.123
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.680	(E)	(E)	(E)	P=0.123
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.680	(E)	(E)	(E)	P=0.123
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.641		(E)	(E)	P=0.142

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung Alveolar/Bronchiolar Adenoma								
TUMOR RATES								
OVERALL (A)	2/68 (3%)	1/14 (7%)	0/13 (0%)	0/68 (0%)	0/69 (0%)	1/20 (5%)	1/11 (9%)	2/70 (3%)
ADJUSTED (B)	3.7%	20.0%	0.0%	0.0%	0.0%	6.7%	33.3%	4.2%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/2 (0%)	0/3 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	1/43 (2%)	1/5 (20%)	0/0	0/46 (0%)	0/50 (0%)	1/15 (7%)	1/3 (33%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	---	---	---	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.230
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.230
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.230
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.252
Lung Alveolar/Bronchiolar Carcinoma								
TUMOR RATES								
OVERALL (A)	3/68 (4%)	0/14 (0%)	0/13 (0%)	1/68 (1%)	0/69 (0%)	0/20 (0%)	0/11 (0%)	0/70 (0%)
ADJUSTED (B)	6.4%	0.0%	0.0%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	2/43 (5%)	0/5 (0%)	0/0	1/46 (2%)	0/50 (0%)	0/15 (0%)	0/3 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	601	---	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.941	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.946	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.937	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.940		(E)	(E)	(E)

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma								
TUMOR RATES								
OVERALL (A)	5/68 (7%)	1/14 (7%)	0/13 (0%)	1/68 (1%)	0/69 (0%)	1/20 (5%)	1/11 (9%)	2/70 (3%)
ADJUSTED (B)	10.0%	20.0%	0.0%	2.2%	0.0%	6.7%	33.3%	4.2%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/2 (0%)	0/3 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	3/43 (7%)	1/5 (20%)	0/0	1/46 (2%)	0/50 (0%)	1/15 (7%)	1/3 (33%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	---	725 (T)	---	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.983	(E)	(E)	(E)	P=0.230
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.984	(E)	(E)	(E)	P=0.230
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.982	(E)	(E)	(E)	P=0.230
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.986		(E)	(E)	P=0.252
Lymph Node, Mesenteric Mesothelioma								
TUMOR RATES								
OVERALL (A)	2/66 (3%)	0/4 (0%)	0/4 (0%)	0/68 (0%)	(G)			
ADJUSTED (B)	3.6%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/41 (0%)	0/2 (0%)	0/1 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	580	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Mammary Gland Adenocarcinoma, Adenoma, Fibroadenoma								
TUMOR RATES								
OVERALL (A)	0/69 (0%)	0/70 (0%)	0/70 (0%)	0/69 (0%)	11/69 (16%)	7/69 (10%)	4/69 (6%)	6/70 (9%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	21.0%	13.4%	7.5%	12.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	9/50 (18%)	5/49 (10%)	1/48 (2%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	---	---	---	---	656	537	625	678
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.887	P=0.885	P=0.980	P=0.926
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.916	P=0.893	P=0.990	P=0.934
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.902	P=0.898	P=0.993	P=0.936
COCHRAN-ARMITAGE	(E)				P=0.910			
FISHER EXACT		(E)	(E)	(E)		P=0.897	P=0.987	P=0.944
Mammary Gland Fibroadenoma								
TUMOR RATES								
OVERALL (A)	0/69 (0%)	0/70 (0%)	0/70 (0%)	0/69 (0%)	11/69 (16%)	7/69 (10%)	3/69 (4%)	5/70 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	21.0%	13.4%	5.6%	10.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	9/50 (18%)	5/49 (10%)	1/48 (2%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	---	---	---	---	656	537	625	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.946	P=0.885	P=0.992	P=0.962
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.959	P=0.893	P=0.996	P=0.964
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.953	P=0.898	P=0.994	P=0.966
COCHRAN-ARMITAGE	(E)				P=0.957			
FISHER EXACT		(E)	(E)	(E)		P=0.897	P=0.996	P=0.972

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Ovary Cystadenocarcinoma, Unilateral								
TUMOR RATES	(G)							
OVERALL (A)					0/69 (0%)	2/28 (7%)	0/17 (0%)	0/70 (0%)
ADJUSTED (B)					0.0%	8.7%	0.0%	0.0%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/4 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)					0/50 (0%)	2/23 (9%)	0/11 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)					---	739 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	(E)
Pancreas Carcinoma, Islet Cells								
TUMOR RATES								
OVERALL (A)	2/67 (3%)	0/4 (0%)	0/3 (0%)	0/67 (0%)	(G)			
ADJUSTED (B)	4.2%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/3 (0%)	0/1 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	621	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Peritoneum								
Mesothelioma								
TUMOR RATES								
OVERALL (A)	1/1 (100%)	0/0 (0%)	2/3 (67%)	0/0 (0%)	(G)			
ADJUSTED (B)	0.0%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	0/0	0/0	1/1 (100%)	0/0				
FIRST INCIDENCE (DAYS)	601	---	661	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Pituitary								
Adenoma, Pars Distalis								
TUMOR RATES								
OVERALL (A)	12/65 (18%)	18/24 (75%)	10/14 (71%)	17/67 (25%)	20/69 (29%)	20/35 (57%)	14/30 (47%)	22/67 (33%)
ADJUSTED (B)	25.0%	75.6%	73.8%	34.4%	38.2%	62.8%	50.6%	44.8%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/1 (0%)	1/1 (100%)	0/10 (0%)	0/10 (0%)	0/1 (0%)	0/3 (0%)	0/10 (0%)
FINAL (D)	8/42 (19%)	14/19 (74%)	8/11 (73%)	14/46 (30%)	18/50 (36%)	17/28 (61%)	11/23 (48%)	21/48 (44%)
FIRST INCIDENCE (DAYS)	368 (I)	634	368 (I)	549	465	537	495	662
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.272	(E)	(E)	(E)	P=0.358
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.212	(E)	(E)	(E)	P=0.364
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.230	(E)	(E)	(E)	P=0.355
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.227		(E)	(E)	P=0.382

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Pituitary Carcinoma, Pars Distalis								
TUMOR RATES								
OVERALL (A)	1/65 (2%)	0/24 (0%)	0/14 (0%)	0/67 (0%)	0/69 (0%)	1/35 (3%)	0/30 (0%)	3/67 (4%)
ADJUSTED (B)	2.4%	0.0%	0.0%	0.0%	0.0%	1.9%	0.0%	6.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/1 (0%)	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/1 (0%)	0/3 (0%)	0/10 (0%)
FINAL (D)	1/42 (2%)	0/19 (0%)	0/11 (0%)	0/46 (0%)	0/50 (0%)	0/28 (0%)	0/23 (0%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	---	---	698	---	671
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.115
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.119
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.114
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.117
Preputial Gland Carcinoma								
TUMOR RATES								
OVERALL (A)	2/2 (100%)	3/4 (75%)	1/1 (100%)	1/3 (33%)	(G)			
ADJUSTED (B)	100.0%	67.3%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	2/2 (100%)	2/3 (67%)	0/0	0/0				
FIRST INCIDENCE (DAYS)	725 (T)	670	634	636				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Prostate Mesothelioma								
TUMOR RATES								
OVERALL (A)	2/66 (3%)	0/0 (0%)	0/0 (0%)	0/64 (0%)	(G)			
ADJUSTED (B)	3.6%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/0	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	580	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				
Skin Fibroma, Fibrosarcoma, Keratoacanthanoma								
TUMOR RATES								
OVERALL (A)	2/69 (3%)	3/70 (4%)	2/70 (3%)	2/69 (3%)	1/69 (1%)	2/69 (3%)	2/69 (3%)	0/70 (0%)
ADJUSTED (B)	4.7%	6.0%	4.5%	4.3%	2.0%	3.8%	3.9%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	2/43 (5%)	2/48 (4%)	1/43 (2%)	2/46 (4%)	1/50 (2%)	1/49 (2%)	1/48 (2%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	681	717	725 (T)	739 (T)	636	661	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.688	P=0.542	P=0.695	P=0.718	P=0.904	P=0.493	P=0.488	(E)
INCIDENTAL TUMOR	P=0.660	P=0.498	P=0.668	P=0.718	P=0.919	P=0.573	P=0.512	(E)
LOGISTIC REGRESSION	P=0.682	P=0.513	P=0.683	P=0.718	P=0.910	P=0.500	P=0.498	(E)
COCHRAN-ARMITAGE	P=0.682				P=0.912			
FISHER EXACT		P=0.507	P=0.696	P=0.690		P=0.500	P=0.500	P=1.000

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Skin/Mass Keratoacanthoma								
TUMOR RATES								
OVERALL (A)	2/69 (3%)	2/70 (3%)	1/70 (1%)	1/69 (1%)	0/69 (0%)	0/69 (0%)	0/69 (0%)	0/70 (0%)
ADJUSTED (B)	4.7%	4.2%	2.2%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	2/43 (5%)	2/48 (4%)	0/43 (0%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	717	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.846	P=0.733	P=0.878	P=0.890	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.833	P=0.733	P=0.860	P=0.890	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.842	P=0.733	P=0.873	P=0.890	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.841				(E)			
FISHER EXACT		P=0.696	P=0.880	P=0.878		(E)	(E)	(E)
Skin/Mass Squamous Cell Papilloma								
TUMOR RATES								
OVERALL (A)	1/69 (1%)	1/70 (1%)	2/70 (3%)	1/69 (1%)	0/69 (0%)	0/69 (0%)	0/69 (0%)	0/70 (0%)
ADJUSTED (B)	2.3%	2.1%	4.7%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	1/48 (2%)	2/43 (5%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	725 (T)	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.643	P=0.785	P=0.500	P=0.776	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.643	P=0.785	P=0.500	P=0.776	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.643	P=0.785	P=0.500	P=0.776	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.633				(E)			
FISHER EXACT		P=0.755	P=0.505	P=0.752		(E)	(E)	(E)

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Subcutaneous Tissue Fibroma								
TUMOR RATES								
OVERALL (A)	2/7 (29%)	0/2 (0%)	2/4 (50%)	0/0 (0%)	(G)			
ADJUSTED (B)	26.3%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/1 (0%)	0/0				
FINAL (D)	1/4 (25%)	0/2 (0%)	2/2 (100%)	0/0				
FIRST INCIDENCE (DAYS)	558	---	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Testis Interstitial Cell Tumor								
TUMOR RATES								
OVERALL (A)	55/68 (81%)	54/59 (92%)	45/47 (96%)	50/67 (75%)	(G)			
ADJUSTED (B)	96.5%	100.0%	95.7%	96.1%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/1 (0%)	0/0	0/10 (0%)				
FINAL (D)	41/43 (95%)	47/47 (100%)	37/39 (95%)	44/46 (96%)				
FIRST INCIDENCE (DAYS)	520	579	534	597				
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.952	P=0.902	P=0.912	P=0.967				
INCIDENTAL TUMOR	P=0.988	P=0.645	P=0.596	P=0.964				
LOGISTIC REGRESSION	P=0.987	P=0.659	P=0.547	P=0.977				
COCHRAN-ARMITAGE	P=0.972							
FISHER EXACT		P=0.071	P=0.017 *	P=0.860				

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Testis								
Mesothelioma, Tunica Albuginea								
TUMOR RATES								
OVERALL (A)	4/68 (6%)	1/59 (2%)	2/47 (4%)	1/67 (1%)	(G)			
ADJUSTED (B)	7.2%	2.1%	4.6%	2.2%				
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/1 (0%)	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	1/47 (2%)	1/39 (3%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	661	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.919	P=0.943	P=0.796	P=0.966				
INCIDENTAL TUMOR	P=0.921	P=0.907	P=0.666	P=0.973				
LOGISTIC REGRESSION	P=0.915	P=0.929	P=0.701	P=0.965				
COCHRAN-ARMITAGE	P=0.912							
FISHER EXACT		P=0.959	P=0.787	P=0.970				
Thyroid								
C-Cell Adenoma, Unilateral								
TUMOR RATES								
OVERALL (A)	1/67 (1%)	0/2 (0%)	0/1 (0%)	1/66 (2%)	6/69 (9%)	0/2 (0%)	0/7 (0%)	6/69 (9%)
ADJUSTED (B)	1.8%	0.0%	0.0%	2.2%	12.0%	0.0%	0.0%	12.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/42 (0%)	0/2 (0%)	0/1 (0%)	1/46 (2%)	6/50 (12%)	0/2 (0%)	0/5 (0%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	580	---	---	725 (T)	739 (T)	---	---	704
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.772	(E)	(E)	(E)	P=0.587
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.770	(E)	(E)	(E)	P=0.593
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.758	(E)	(E)	(E)	P=0.587
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.748		(E)	(E)	P=0.618

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thyroid C-Cell Carcinoma, Unilateral								
TUMOR RATES								
OVERALL (A)	3/67 (4%)	1/2 (50%)	0/1 (0%)	2/66 (3%)	4/69 (6%)	1/2 (50%)	4/7 (57%)	2/69 (3%)
ADJUSTED (B)	6.7%	50.0%	0.0%	4.3%	8.0%	50.0%	60.8%	4.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	2/42 (5%)	1/2 (50%)	0/1 (0%)	2/46 (4%)	4/50 (8%)	1/2 (50%)	3/5 (60%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	702	725 (T)	---	725 (T)	739 (T)	739 (T)	730	698
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.837	(E)	(E)	(E)	P=0.883
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.802	(E)	(E)	(E)	P=0.886
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.827	(E)	(E)	(E)	P=0.887
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.813		(E)	(E)	P=0.896
Thyroid Follicular Cell Adenoma, Unilateral								
TUMOR RATES								
OVERALL (A)	1/67 (1%)	1/2 (50%)	0/1 (0%)	1/66 (2%)	2/69 (3%)	1/2 (50%)	1/7 (14%)	2/69 (3%)
ADJUSTED (B)	2.2%	50.0%	0.0%	2.2%	4.0%	50.0%	1.9%	4.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/42 (0%)	1/2 (50%)	0/1 (0%)	1/46 (2%)	2/50 (4%)	1/2 (50%)	0/5 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	713	725 (T)	---	725 (T)	739 (T)	739 (T)	661	704
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.773	(E)	(E)	(E)	P=0.673
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.698	(E)	(E)	(E)	P=0.682
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.766	(E)	(E)	(E)	P=0.682
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.748		(E)	(E)	P=0.690

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Urinary Bladder Mesothelioma								
TUMOR RATES								
OVERALL (A)	2/66 (3%)	0/3 (0%)	1/4 (25%)	0/65 (0%)	0/66 (0%)	0/20 (0%)	0/13 (0%)	0/67 (0%)
ADJUSTED (B)	3.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/1 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/2 (0%)	0/0	0/46 (0%)	0/47 (0%)	0/18 (0%)	0/8 (0%)	0/47 (0%)
FIRST INCIDENCE (DAYS)	580	---	661	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	(E)
Uterus Endometrial Stromal Polyp								
TUMOR RATES	(G)							
OVERALL (A)					8/69 (12%)	12/29 (41%)	4/19 (21%)	12/70 (17%)
ADJUSTED (B)					15.2%	48.6%	30.8%	23.5%
INTERIM NECROPSY 1 (C)					0/10 (0%)	1/4 (25%)	0/2 (0%)	1/10 (10%)
FINAL (D)					6/50 (12%)	11/23 (48%)	4/13 (31%)	10/48 (21%)
FIRST INCIDENCE (DAYS)					697	367 (I)	739 (T)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.204
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.209
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.223
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.245

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Uterus Endometrial Stromal Sarcoma								
TUMOR RATES	(G)							
OVERALL (A)					1/69 (1%)	2/29 (7%)	0/19 (0%)	2/70 (3%)
ADJUSTED (B)					1.7%	8.7%	0.0%	3.8%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/4 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)					0/50 (0%)	2/23 (9%)	0/13 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)					465	739 (T)	---	501
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.493
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.681
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.652
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.505
Uterus Leiomyoma, Leiomyosarcoma								
TUMOR RATES	(G)							
OVERALL (A)					1/69 (1%)	2/29 (7%)	0/19 (0%)	0/70 (0%)
ADJUSTED (B)					1.7%	3.6%	0.0%	0.0%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/4 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)					0/50 (0%)	0/23 (0%)	0/13 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)					590	599	---	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=1.000

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Uterus								
Leiomyosarcoma								
TUMOR RATES	(G)							
OVERALL (A)					0/69 (0%)	2/29 (7%)	0/19 (0%)	0/70 (0%)
ADJUSTED (B)					0.0%	3.6%	0.0%	0.0%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/4 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)					0/50 (0%)	0/23 (0%)	0/13 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)					---	599	---	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	(E)
All Organs								
Histiocytic Sarcoma								
TUMOR RATES								
OVERALL (A)	2/69 (3%)	0/70 (0%)	0/70 (0%)	1/69 (1%)	0/69 (0%)	0/69 (0%)	0/69 (0%)	0/70 (0%)
ADJUSTED (B)	3.7%	0.0%	0.0%	1.8%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	520	---	---	597	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.760	(E)	(E)	P=0.875	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.748	(E)	(E)	P=0.816	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.764	(E)	(E)	P=0.873	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.763				(E)			
FISHER EXACT		P=1.000	P=1.000	P=0.878		(E)	(E)	(E)

TABLE S2a

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
All Organs: Malignant Lymphoma								
TUMOR RATES								
OVERALL (A)	0/69 (0%)	2/70 (3%)	0/70 (0%)	0/69 (0%)	0/69 (0%)	0/69 (0%)	0/69 (0%)	0/70 (0%)
ADJUSTED (B)	0.0%	4.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	2/48 (4%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	725 (T)	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.923	P=0.263	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.923	P=0.263	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.923	P=0.263	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.922				(E)			
FISHER EXACT		P=0.252	(E)	(E)		(E)	(E)	(E)
All Organs: Mononuclear Cell Leukemia								
TUMOR RATES								
OVERALL (A)	9/69 (13%)	9/70 (13%)	9/70 (13%)	10/69 (14%)	27/69 (39%)	12/69 (17%)	13/69 (19%)	32/70 (46%)
ADJUSTED (B)	18.6%	16.3%	17.7%	18.9%	47.2%	22.9%	23.6%	56.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	5/43 (12%)	3/48 (6%)	3/43 (7%)	5/46 (11%)	20/50 (40%)	9/49 (18%)	7/48 (15%)	23/48 (48%)
FIRST INCIDENCE (DAYS)	551	461	534	549	465	599	529	443
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.458	P=0.653	P=0.582	P=0.540	P=0.018 *	P=0.998	P=0.994	P=0.209
INCIDENTAL TUMOR	P=0.417	P=0.389	P=0.522	P=0.479	P=0.022 *	P=0.999	P=1.000	P=0.339
LOGISTIC REGRESSION	P=0.489	P=0.485	P=0.593	P=0.504	P=0.023 *	P=1.000	P=1.000	P=0.354
COCHRAN-ARMITAGE	P=0.437				P=0.022 *			
FISHER EXACT		P=0.612	P=0.612	P=0.500		P=0.999	P=0.998	P=0.270

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

(A) NUMBER OF TUMOR-BEARING ANIMALS / NUMBER OFANIMALS EXAMINED AT SITE.
(B) KAPLAN-MEIER ESTIMATED LIFETIME TUMOR INCIDENCE AFTER ADJUSTMENT FOR INTERCURRENT MORTALITY.
(C) OBSERVED INCIDENCE AT INTERIM NECROPSY.
(D) OBSERVED INCIDENCE AT FINAL NECROPSY.
(E) STATISTICAL EVALUATION NOT COMPUTED SINCE FULL GROUPS WERE NOT EXAMINED OR DATA DO NOT MEET CRITERIA FOR STATISTICAL TEST.
(F) BENEATH THE CONTROL INCIDENCE ARE THE P-VALUES ASSOCIATED WITH THE TREND TEST. BENEATH THE DOSED GROUP INCIDENCE ARE THE P-VALUES CORRESPONDING TO PAIRWISE COMPARISONS BETWEEN THE CONTROLS AND THAT DOSED GROUP. THE LIFE TABLE ANALYSIS REGARDS TUMORS IN ANIMALS DYING PRIOR TO FINAL NECROPSY AS BEING (DIRECTLY OR INDIRECTLY) THE CAUSE OF DEATH. THE INCIDENTAL TUMOR TEST REGARDS THESE LESIONS AS NON-FATAL. LOGISTIC REGRESSION IS AN ALTERNATIVE METHOD FOR ANALYZING THE INCIDENCE OF NON-FATAL TUMORS.THE COCHRAN-ARMITAGE AND FISHER'S EXACT TESTS COMPARE DIRECTLY THE OVERALLINCIDENCE RATES. FOR ALL TESTS, A NEGATIVE TREND IS INDICATED BY "N".
(G) DATA NOT PRESENTED DUE TO
1) ORGAN OR LESION NOT SEX APPROPRIATE
2) FEWER THAN TWO FINDINGS FOR ALL GROUPS
3) INTERPATHOLOGIST VARIATION
(I) INTERIM NECROPSY
(T) FINAL NECROPSY
LESION RATES BASED ON NUMBER OF ANIMALS NECROPSIED.

* TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.05).
** TO THE RIGHT OF ANY STATISTICAL RESULT, INDICATES SIGNIFICANCE AT (P<=0.01).

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Cytoplasmic Vacuolation, Adrenal Cortex								
LESION RATES								
OVERALL (A)	25/67 (37%)	2/9 (22%)	2/9 (22%)	27/66 (41%)	(G)			
ADJUSTED (B)	45.5%	15.9%	3.9%	52.7%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	13/42 (31%)	1/7 (14%)	0/7 (0%)	22/46 (48%)				
FIRST INCIDENCE (DAYS)	520	642	634	629				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.544				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.253				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.413				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.402				
Adrenal Hyperplasia, Adrenal Cortex								
LESION RATES								
OVERALL (A)	19/67 (28%)	2/9 (22%)	1/9 (11%)	25/66 (38%)	19/68 (28%)	0/6 (0%)	0/7 (0%)	13/70 (19%)
ADJUSTED (B)	40.7%	28.6%	14.3%	50.9%	37.1%	0.0%	0.0%	25.8%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/9 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	15/42 (36%)	2/7 (29%)	1/7 (14%)	22/46 (48%)	18/50 (36%)	0/2 (0%)	0/3 (0%)	11/48 (23%)
FIRST INCIDENCE (DAYS)	611	725 (T)	725 (T)	636	636	---	---	615
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.270	(E)	(E)	(E)	P=0.904
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.170	(E)	(E)	(E)	P=0.930
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.162	(E)	(E)	(E)	P=0.915
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.163		(E)	(E)	P=0.934

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Adrenal Hyperplasia, Adrenal Medulla								
LESION RATES								
OVERALL (A)	25/67 (37%)	4/9 (44%)	2/9 (22%)	16/66 (24%)	2/68 (3%)	1/6 (17%)	0/7 (0%)	2/70 (3%)
ADJUSTED (B)	50.5%	43.9%	16.0%	33.1%	3.9%	1.7%	0.0%	4.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/9 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	18/42 (43%)	3/7 (43%)	1/7 (14%)	14/46 (30%)	1/50 (2%)	0/2 (0%)	0/3 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	551	579	636	629	713	599	---	698
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.983	(E)	(E)	(E)	P=0.671
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.969	(E)	(E)	(E)	P=0.690
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.974	(E)	(E)	(E)	P=0.689
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.966		(E)	(E)	P=0.701
Adrenal Pigmentation, Adrenal Medulla								
LESION RATES								
OVERALL (A)	5/67 (7%)	0/9 (0%)	0/9 (0%)	5/66 (8%)	(G)			
ADJUSTED (B)	11.9%	0.0%	0.0%	10.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	5/42 (12%)	0/7 (0%)	0/7 (0%)	5/46 (11%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.687				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.687				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.687				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.618				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone Marrow, Femur Hypercellularity								
LESION RATES								
OVERALL (A)	11/67 (16%)	0/0 (0%)	1/1 (100%)	4/67 (6%)	1/69 (1%)	1/1 (100%)	0/1 (0%)	1/67 (1%)
ADJUSTED (B)	20.3%	0.0%	0.0%	8.3%	2.0%	0.0%	0.0%	1.7%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	2/42 (5%)	0/0	0/0	3/46 (7%)	1/50 (2%)	0/0	0/1 (0%)	0/47 (0%)
FIRST INCIDENCE (DAYS)	520	---	634	636	739 (T)	599	---	501
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.984	(E)	(E)	(E)	P=0.753
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.973	(E)	(E)	(E)	P=0.828
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.973	(E)	(E)	(E)	P=0.761
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.987		(E)	(E)	P=0.744
Bone Marrow, Femur Hypocellularity								
LESION RATES								
OVERALL (A)	3/67 (4%)	0/0 (0%)	0/1 (0%)	6/67 (9%)	(G)			
ADJUSTED (B)	6.7%	0.0%	0.0%	11.1%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	2/42 (5%)	0/0	0/0	2/46 (4%)				
FIRST INCIDENCE (DAYS)	691	---	---	549				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.277				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.254				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.254				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.246				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone Marrow, Femur Myelofibrosis								
LESION RATES								
OVERALL (A)	1/67 (1%)	0/0 (0%)	0/1 (0%)	0/67 (0%)	1/69 (1%)	0/1 (0%)	0/1 (0%)	2/67 (3%)
ADJUSTED (B)	2.3%	0.0%	0.0%	0.0%	2.0%	0.0%	0.0%	4.3%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/42 (0%)	0/0	0/0	0/46 (0%)	1/50 (2%)	0/0	0/1 (0%)	2/47 (4%)
FIRST INCIDENCE (DAYS)	718	---	---	---	739 (T)	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.478
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.478
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.478
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.489
Bone Marrow, Femur Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	6/67 (9%)	0/0 (0%)	0/1 (0%)	6/67 (9%)	11/69 (16%)	0/1 (0%)	1/1 (100%)	15/67 (22%)
ADJUSTED (B)	13.2%	0.0%	0.0%	12.2%	21.2%	0.0%	100.0%	31.9%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/0	0/0	1/10 (10%)	1/10 (10%)	0/0	0/0	0/10 (0%)
FINAL (D)	5/42 (12%)	0/0	0/0	5/46 (11%)	10/50 (20%)	0/0	1/1 (100%)	15/47 (32%)
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)	367 (I)	---	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.671	(E)	(E)	(E)	P=0.198
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.671	(E)	(E)	(E)	P=0.198
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.671	(E)	(E)	(E)	P=0.202
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.618		(E)	(E)	P=0.231

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone Marrow, Sternum Hypercellularity								
LESION RATES								
OVERALL (A)	10/66 (15%)	0/0 (0%)	0/0 (0%)	5/68 (7%)	1/69 (1%)	1/1 (100%)	0/0 (0%)	0/70 (0%)
ADJUSTED (B)	18.6%	0.0%	0.0%	10.2%	2.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	2/42 (5%)	0/0	0/0	3/46 (7%)	1/60 (2%)	0/0	0/0	0/48 (0%)
FIRST INCIDENCE (DAYS)	520	---	---	636	739 (T)	599	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.949	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.933	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.933	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.957		(E)	(E)	P=1.000
Bone Marrow, Sternum Hypocellularity								
LESION RATES								
OVERALL (A)	1/66 (2%)	0/0 (0%)	0/0 (0%)	4/68 (6%)	(G)			
ADJUSTED (B)	2.0%	0.0%	0.0%	7.4%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/42 (0%)	0/0	0/0	1/46 (2%)				
FIRST INCIDENCE (DAYS)	691	---	---	549				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.196				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.185				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.185				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.192				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Bone Marrow, Sternum								
Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	0/66 (0%)	0/0 (0%)	0/0 (0%)	1/68 (1%)	5/69 (7%)	0/1 (0%)	0/0 (0%)	9/70 (13%)
ADJUSTED (B)	0.0%	0.0%	0.0%	2.2%	10.0%	0.0%	0.0%	18.3%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/42 (0%)	0/0	0/0	1/46 (2%)	5/50 (10%)	0/0	0/0	8/48 (17%)
FIRST INCIDENCE (DAYS)	---	---	---	725 (T)	739 (T)	---	---	678
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.518	(E)	(E)	(E)	P=0.174
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.518	(E)	(E)	(E)	P=0.177
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.518	(E)	(E)	(E)	P=0.177
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.507		(E)	(E)	P=0.207
Brain								
Hemorrhage								
LESION RATES								
OVERALL (A)	1/68 (1%)	1/1 (100%)	1/3 (33%)	2/68 (3%)	(G)			
ADJUSTED (B)	2.1%	0.0%	2.1%	3.8%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/0	0/1 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	703	657	661	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.502				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.408				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.500				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Brain								
Ventral Compression								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/1 (0%)	0/3 (0%)	2/68 (3%)	(G)			
ADJUSTED (B)	0.0%	0.0%	0.0%	4.1%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/0	0/1 (0%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	---	---	---	676				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.247				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.195				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.240				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.248				
Ear Canal								
Cystic Duct, Auditory Sebaceous Gland								
LESION RATES								
OVERALL (A)	4/67 (6%)	0/1 (0%)	0/1 (0%)	0/67 (0%)	(G)			
ADJUSTED (B)	9.5%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	4/42 (10%)	0/0	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Ear Canal Inflammation, Subacute								
LESION RATES								
OVERALL (A)	2/67 (3%)	0/1 (0%)	0/1 (0%)	1/67 (1%)	1/69 (1%)	0/1 (0%)	0/0 (0%)	0/68 (0%)
ADJUSTED (B)	4.8%	0.0%	0.0%	1.8%	1.4%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	2/42 (5%)	0/0	0/0	0/46 (0%)	0/50 (0%)	0/1 (0%)	0/0	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	573	262	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.889	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.896	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.879	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.878		(E)	(E)	P=1.000
Ear Canal Inflammation, Subacute, Auditory Sebaceous Gland								
LESION RATES								
OVERALL (A)	3/67 (4%)	0/1 (0%)	0/1 (0%)	0/67 (0%)	(G)			
ADJUSTED (B)	7.1%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	3/42 (7%)	0/0	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Ear Canal								
Mineralization, Blood Vessels								
LESION RATES								
OVERALL (A)	2/67 (3%)	0/1 (0%)	0/1 (0%)	6/67 (9%)	(G)			
ADJUSTED (B)	4.8%	0.0%	0.0%	13.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	2/42 (5%)	0/0	0/0	6/46 (13%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.165				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.165				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.165				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.137				
Epididymis								
Hypospermia, Bilateral								
LESION RATES								
OVERALL (A)	54/68 (79%)	0/3 (0%)	0/4 (0%)	52/67 (78%)	(G)			
ADJUSTED (B)	96.4%	0.0%	0.0%	96.3%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	41/43 (95%)	0/2 (0%)	0/2 (0%)	44/46 (96%)				
FIRST INCIDENCE (DAYS)	520	---	---	573				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.886				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.710				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.848				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.679				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Epididymis								
Hypospermia, Unilateral								
LESION RATES								
OVERALL (A)	6/68 (9%)	0/3 (0%)	0/4 (0%)	3/67 (4%)	(G)			
ADJUSTED (B)	10.0%	0.0%	0.0%	6.1%				
INTERIM NECROPSY 1 (C)	3/10 (30%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/2 (0%)	0/2 (0%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	629				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.921				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.936				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.915				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.914				
Eye								
Cataractous Change, Lens, Unilateral, or Bilateral								
LESION RATES								
OVERALL (A)	32/68 (47%)	6/10 (60%)	4/5 (80%)	38/68 (56%)	1/69 (1%)	1/3 (33%)	2/5 (40%)	2/69 (3%)
ADJUSTED (B)	65.3%	100.0%	100.0%	77.5%	2.0%	50.0%	100.0%	4.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	1/1 (100%)	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	26/43 (60%)	5/5 (100%)	2/2 (100%)	35/46 (76%)	1/50 (2%)	1/2 (50%)	2/2 (100%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	691	681	368 (I)	584	739 (T)	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.292	(E)	(E)	(E)	P=0.486
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.166	(E)	(E)	(E)	P=0.486
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.168	(E)	(E)	(E)	P=0.486
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.196		(E)	(E)	P=0.500

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Eye Degeneration, Retina, Unilateral or Bilateral								
LESION RATES								
OVERALL (A)	49/68 (72%)	8/10 (80%)	4/5 (80%)	47/68 (69%)	10/69 (14%)	1/3 (33%)	2/5 (40%)	16/69 (23%)
ADJUSTED (B)	96.1%	100.0%	100.0%	94.0%	20.0%	50.0%	100.0%	31.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	2/10 (20%)
FINAL (D)	41/43 (95%)	5/5 (100%)	2/2 (100%)	43/46 (93%)	10/50 (20%)	1/2 (50%)	2/2 (100%)	14/48 (29%)
FIRST INCIDENCE (DAYS)	691	681	368 (I)	675	739 (T)	739 (T)	739 (T)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.925	(E)	(E)	(E)	P=0.111
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.914	(E)	(E)	(E)	P=0.111
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.866	(E)	(E)	(E)	P=0.123
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.714		(E)	(E)	P=0.138
Eye Inspissated Secretion, Lacrimal Duct								
LESION RATES								
OVERALL (A)	1/68 (1%)	1/10 (10%)	0/5 (0%)	2/68 (3%)	(G)			
ADJUSTED (B)	2.3%	2.0%	0.0%	4.3%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/5 (0%)	0/2 (0%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	725 (T)	681	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.524				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.524				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.524				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Eye								
Keratitis, Suppurative								
LESION RATES								
OVERALL (A)	3/68 (4%)	0/10 (0%)	0/5 (0%)	0/68 (0%)	(G)			
ADJUSTED (B)	6.1%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/5 (0%)	0/2 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	660	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				
Eye								
Mineralization, Blood Vessels								
LESION RATES								
OVERALL (A)	0/68 (0%)	2/10 (20%)	0/5 (0%)	4/68 (6%)	(G)			
ADJUSTED (B)	0.0%	21.6%	0.0%	8.7%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	1/5 (20%)	0/2 (0%)	4/46 (9%)				
FIRST INCIDENCE (DAYS)	---	681	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.072				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.072				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.072				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.060				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Eye								
Mineralization, Cornea								
LESION RATES								
OVERALL (A)	1/68 (1%)	1/10 (10%)	0/5 (0%)	5/68 (7%)	1/69 (1%)	0/3 (0%)	0/5 (0%)	2/69 (3%)
ADJUSTED (B)	2.3%	2.0%	0.0%	10.5%	2.0%	0.0%	0.0%	3.5%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	1/10 (10%)
FINAL (D)	1/43 (2%)	0/5 (0%)	0/2 (0%)	4/46 (9%)	1/50 (2%)	0/2 (0%)	0/2 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	725 (T)	681	---	636	739 (T)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.120	(E)	(E)	(E)	P=0.491
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.126	(E)	(E)	(E)	P=0.491
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.107	(E)	(E)	(E)	P=0.509
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.104		(E)	(E)	P=0.500
Eye								
Mineralization, Lens								
LESION RATES								
OVERALL (A)	(G)				0/69 (0%)	0/3 (0%)	0/5 (0%)	4/69 (6%)
ADJUSTED (B)					0.0%	0.0%	0.0%	8.3%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)					0/50 (0%)	0/2 (0%)	0/2 (0%)	4/48 (8%)
FIRST INCIDENCE (DAYS)					---	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.059
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.059
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.059
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.060

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Eye Mineralization, Sclera								
LESION RATES								
OVERALL (A)	43/68 (63%)	4/10 (40%)	3/5 (60%)	35/68 (51%)	2/69 (3%)	0/3 (0%)	0/5 (0%)	0/69 (0%)
ADJUSTED (B)	80.8%	42.2%	100.0%	69.8%	4.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/0	0/1 (0%)	1/10 (10%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	33/43 (77%)	2/5 (40%)	2/2 (100%)	31/46 (67%)	2/50 (4%)	0/2 (0%)	0/2 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	507	649	368 (I)	739 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.976	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.958	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.964	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.941		(E)	(E)	P=1.000
Eye Vascularization, Cornea								
LESION RATES								
OVERALL (A)	2/68 (3%)	1/10 (10%)	1/5 (20%)	0/68 (0%)	(G)			
ADJUSTED (B)	4.4%	2.0%	50.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/5 (0%)	1/2 (50%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	713	681	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Fat, Mesentery Necrosis								
LESION RATES								
OVERALL (A)	(G)				5/5 (100%)	13/13 (100%)	4/4 (100%)	5/5 (100%)
ADJUSTED (B)					100.0%	100.0%	100.0%	100.0%
INTERIM NECROPSY 1 (C)					0/0	0/0	0/0	0/0
FINAL (D)					5/5 (100%)	11/11 (100%)	4/4 (100%)	5/5 (100%)
FIRST INCIDENCE (DAYS)					739 (T)	643	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	(E)
Harderian Gland Inflammation, Chronic								
LESION RATES								
OVERALL (A)	6/68 (9%)	0/0 (0%)	0/0 (0%)	2/68 (3%)	0/69 (0%)	0/3 (0%)	0/5 (0%)	0/69 (0%)
ADJUSTED (B)	8.7%	0.0%	0.0%	2.9%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	6/10 (60%)	0/0	0/0	2/10 (20%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/43 (0%)	0/0	0/0	0/46 (0%)	0/50 (0%)	0/2 (0%)	0/2 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.987	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.987	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.987	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.969		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Harderian Gland Inflammation, Subacute								
LESION RATES								
OVERALL (A)	8/68 (12%)	0/0 (0%)	0/0 (0%)	5/68 (7%)	9/69 (13%)	0/3 (0%)	1/5 (20%)	11/69 (16%)
ADJUSTED (B)	17.7%	0.0%	0.0%	10.9%	17.2%	0.0%	50.0%	20.7%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	1/10 (10%)	0/0	0/0	2/10 (20%)
FINAL (D)	7/43 (16%)	0/0	0/0	5/46 (11%)	8/50 (16%)	0/2 (0%)	1/2 (50%)	8/48 (17%)
FIRST INCIDENCE (DAYS)	520	---	---	725 (T)	367 (I)	---	739 (T)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.903	(E)	(E)	(E)	P=0.370
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.853	(E)	(E)	(E)	P=0.375
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.853	(E)	(E)	(E)	P=0.397
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.879		(E)	(E)	P=0.405
Harderian Gland Mononuclear Cells								
LESION RATES								
OVERALL (A)	8/68 (12%)	0/0 (0%)	0/0 (0%)	9/68 (13%)	(G)			
ADJUSTED (B)	18.6%	0.0%	0.0%	18.4%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	8/43 (19%)	0/0	0/0	7/46 (15%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	629				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.557				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.569				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.569				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Heart								
Cardiomyopathy								
LESION RATES								
OVERALL (A)	56/68 (82%)	0/0 (0%)	0/1 (0%)	55/68 (81%)	17/69 (25%)	0/1 (0%)	0/1 (0%)	23/70 (33%)
ADJUSTED (B)	100.0%	0.0%	0.0%	100.0%	34.0%	0.0%	0.0%	45.6%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	1/10 (10%)
FINAL (D)	43/43 (100%)	0/0	0/0	46/46 (100%)	17/50 (34%)	0/0	0/0	21/48 (44%)
FIRST INCIDENCE (DAYS)	520	---	---	549	739 (T)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.864	(E)	(E)	(E)	P=0.125
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.834	(E)	(E)	(E)	P=0.126
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.834	(E)	(E)	(E)	P=0.142
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.671		(E)	(E)	P=0.189
Heart								
Mineralization, Blood Vessels								
LESION RATES								
OVERALL (A)	3/68 (4%)	0/0 (0%)	0/1 (0%)	2/68 (3%)	0/69 (0%)	0/1 (0%)	0/1 (0%)	2/70 (3%)
ADJUSTED (B)	7.0%	0.0%	0.0%	4.3%	0.0%	0.0%	0.0%	3.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	3/43 (7%)	0/0	0/0	2/46 (4%)	0/50 (0%)	0/0	0/0	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)	---	---	---	443
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.840	(E)	(E)	(E)	P=0.240
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.840	(E)	(E)	(E)	P=0.401
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.840	(E)	(E)	(E)	P=0.260
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.817		(E)	(E)	P=0.252

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Heart								
Myocarditis, Subchronic								
LESION RATES								
OVERALL (A)	9/68 (13%)	0/0 (0%)	0/1 (0%)	9/68 (13%)	(G)			
ADJUSTED (B)	13.0%	0.0%	0.0%	13.0%				
INTERIM NECROPSY 1 (C)	9/10 (90%)	0/0	0/0	9/10 (90%)				
FINAL (D)	0/43 (0%)	0/0	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.766				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.766				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.766				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.600				
Intestine-Large, Cecum								
Inflammation, Subacute								
LESION RATES								
OVERALL (A)	(G)				2/69 (3%)	0/2 (0%)	0/1 (0%)	1/70 (1%)
ADJUSTED (B)					3.7%	0.0%	0.0%	2.1%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)					1/50 (2%)	0/1 (0%)	0/1 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)					636	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.867
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.912
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.878
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.880

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Intestine-Large, Cecum Suppurative Typhlitis								
LESION RATES								
OVERALL (A)	0/68 (0%)	2/4 (50%)	0/2 (0%)	0/66 (0%)	(G)			
ADJUSTED (B)	0.0%	66.7%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	2/3 (67%)	0/1 (0%)	0/45 (0%)				
FIRST INCIDENCE (DAYS)	---	725 (T)	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Kidney Abscess(es)								
LESION RATES								
OVERALL (A)	0/68 (0%)	1/32 (3%)	0/26 (0%)	2/68 (3%)	(G)			
ADJUSTED (B)	0.0%	1.9%	0.0%	3.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/24 (0%)	0/17 (0%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	---	670	---	573				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.251				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.264				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.238				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.248				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney Mononuclear Cells								
LESION RATES								
OVERALL (A)	8/68 (12%)	0/32 (0%)	0/26 (0%)	8/68 (12%)	(G)			
ADJUSTED (B)	11.6%	0.0%	0.0%	11.6%				
INTERIM NECROPSY 1 (C)	8/10 (80%)	0/0	0/1 (0%)	8/10 (80%)				
FINAL (D)	0/43 (0%)	0/24 (0%)	0/17 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.707				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.707				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.707				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.605				
Kidney Nephropathy, Chronic								
LESION RATES								
OVERALL (A)	57/68 (84%)	31/32 (97%)	23/26 (88%)	56/68 (82%)	57/69 (83%)	12/14 (86%)	11/14 (79%)	49/70 (70%)
ADJUSTED (B)	100.0%	100.0%	100.0%	100.0%	98.3%	100.0%	88.4%	90.6%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	2/10 (20%)	0/0	0/0	2/10 (20%)
FINAL (D)	43/43 (100%)	24/24 (100%)	17/17 (100%)	46/46 (100%)	49/50 (98%)	7/7 (100%)	7/8 (88%)	43/48 (90%)
FIRST INCIDENCE (DAYS)	520	461	534	549	367 (I)	599	495	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.856	(E)	(E)	(E)	P=0.940
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.926	(E)	(E)	(E)	P=0.986
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.912	(E)	(E)	(E)	P=0.992
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.676		(E)	(E)	P=0.975

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney Pelvic Microcalculi								
LESION RATES								
OVERALL (A)	4/68 (6%)	2/32 (6%)	1/26 (4%)	1/68 (1%)	(G)			
ADJUSTED (B)	7.4%	8.3%	2.2%	2.2%				
INTERIM NECROPSY 1 (C)	2/10 (20%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	2/43 (5%)	2/24 (8%)	0/17 (0%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	711	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.969				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.969				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.966				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.971				
Kidney Pigmentation, Tubular Epithelium								
LESION RATES								
OVERALL (A)	64/68 (94%)	30/32 (94%)	24/26 (92%)	63/68 (93%)	55/69 (80%)	7/14 (50%)	6/14 (43%)	48/70 (69%)
ADJUSTED (B)	100.0%	100.0%	100.0%	100.0%	93.1%	47.0%	63.2%	82.3%
INTERIM NECROPSY 1 (C)	9/10 (90%)	0/0	1/1 (100%)	10/10 (100%)	6/10 (60%)	0/0	0/0	7/10 (70%)
FINAL (D)	43/43 (100%)	24/24 (100%)	17/17 (100%)	46/46 (100%)	46/50 (92%)	3/7 (43%)	5/8 (63%)	38/48 (79%)
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	368 (I)	367 (I)	599	599	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.875	(E)	(E)	(E)	P=0.898
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.814	(E)	(E)	(E)	P=0.935
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.831	(E)	(E)	(E)	P=0.952
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.754		(E)	(E)	P=0.955

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Postmortem Congestion								
LESION RATES								
OVERALL (A)	0/68 (0%)	1/32 (3%)	2/26 (8%)	1/68 (1%)	(G)			
ADJUSTED (B)	0.0%	2.0%	3.9%	1.8%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/24 (0%)	0/17 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	---	681	524	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.507				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.531				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.498				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				
Kidney								
Proteinaceous Casts								
LESION RATES								
OVERALL (A)	9/68 (13%)	1/32 (3%)	1/26 (4%)	10/68 (15%)	(G)			
ADJUSTED (B)	13.0%	1.4%	1.7%	14.5%				
INTERIM NECROPSY 1 (C)	9/10 (90%)	0/0	1/1 (100%)	10/10 (100%)				
FINAL (D)	0/43 (0%)	0/24 (0%)	0/17 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.500				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.500				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.500				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Tubular Hyaline Droplets								
LESION RATES								
OVERALL (A)	2/68 (3%)	8/32 (25%)	5/26 (19%)	2/68 (3%)	1/69 (1%)	0/14 (0%)	1/14 (7%)	3/70 (4%)
ADJUSTED (B)	4.1%	33.3%	29.4%	4.3%	2.0%	0.0%	12.5%	6.3%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	1/43 (2%)	8/24 (33%)	5/17 (29%)	2/46 (4%)	1/50 (2%)	0/7 (0%)	1/8 (13%)	3/48 (6%)
FIRST INCIDENCE (DAYS)	580	725 (T)	725 (T)	725 (T)	739 (T)	---	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.712	(E)	(E)	(E)	P=0.291
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.724	(E)	(E)	(E)	P=0.291
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.696	(E)	(E)	(E)	P=0.291
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.690		(E)	(E)	P=0.315
Kidney								
Tubular Mineralization								
LESION RATES								
OVERALL (A)	28/68 (41%)	12/32 (38%)	11/26 (42%)	23/68 (34%)	(G)			
ADJUSTED (B)	51.0%	43.8%	45.5%	40.4%				
INTERIM NECROPSY 1 (C)	6/10 (60%)	0/0	1/1 (100%)	5/10 (50%)				
FINAL (D)	18/43 (42%)	10/24 (42%)	7/17 (41%)	14/46 (30%)				
FIRST INCIDENCE (DAYS)	368 (I)	461	368 (I)	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.891				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.874				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.855				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.856				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Kidney								
Tubular Regeneration								
LESION RATES								
OVERALL (A)	8/68 (12%)	1/32 (3%)	1/26 (4%)	9/68 (13%)	(G)			
ADJUSTED (B)	11.6%	1.4%	1.7%	13.0%				
INTERIM NECROPSY 1 (C)	8/10 (80%)	0/0	1/1 (100%)	9/10 (90%)				
FINAL (D)	0/43 (0%)	0/24 (0%)	0/17 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.500				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.500				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.500				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				
Larynx								
Foreign Body								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/0 (0%)	0/0 (0%)	3/67 (4%)	(G)			
ADJUSTED (B)	0.0%	0.0%	0.0%	6.5%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/0	0/0	3/46 (7%)				
FIRST INCIDENCE (DAYS)	---	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.134				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.134				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.134				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.119				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Larynx Inflammation, Subacute								
LESION RATES								
OVERALL (A)	47/68 (69%)	0/0 (0%)	0/0 (0%)	46/67 (69%)	7/68 (10%)	0/0 (0%)	0/0 (0%)	1/69 (1%)
ADJUSTED (B)	86.8%	0.0%	0.0%	88.3%	14.3%	0.0%	0.0%	2.1%
INTERIM NECROPSY 1 (C)	2/10 (20%)	0/0	0/0	2/10 (20%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	36/43 (84%)	0/0	0/0	40/46 (87%)	7/49 (14%)	0/0	0/0	1/48 (2%)
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)	739 (T)	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.809	(E)	(E)	(E)	P=0.994
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.606	(E)	(E)	(E)	P=0.994
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.606	(E)	(E)	(E)	P=0.994
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.596		(E)	(E)	P=0.997
Larynx Mineralization								
LESION RATES								
OVERALL (A)	17/68 (25%)	0/0 (0%)	0/0 (0%)	9/67 (13%)	(G)			
ADJUSTED (B)	34.4%	0.0%	0.0%	18.3%				
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/0	0/0	0/10 (0%)				
FINAL (D)	12/43 (28%)	0/0	0/0	7/46 (15%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.980				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.974				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.974				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.973				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Basophilic Focus (Foci)								
LESION RATES								
OVERALL (A)	38/68 (56%)	12/25 (48%)	5/13 (38%)	40/68 (59%)	38/69 (55%)	15/27 (56%)	16/32 (50%)	35/70 (50%)
ADJUSTED (B)	78.8%	66.7%	80.4%	83.3%	74.4%	64.3%	69.6%	65.9%
INTERIM NECROPSY 1 (C)	2/10 (20%)	0/0	0/1 (0%)	0/10 (0%)	1/10 (10%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	33/43 (77%)	12/18 (67%)	4/5 (80%)	38/46 (83%)	37/50 (74%)	14/22 (64%)	16/23 (70%)	30/48 (63%)
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	711	676	367 (I)	643	739 (T)	501
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.621	(E)	(E)	(E)	P=0.685
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.548	(E)	(E)	(E)	P=0.760
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.441	(E)	(E)	(E)	P=0.742
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.431		(E)	(E)	P=0.779
Liver								
Bile Duct Hyperplasia								
LESION RATES								
OVERALL (A)	66/68 (97%)	25/25 (100%)	13/13 (100%)	67/68 (99%)	19/69 (28%)	10/27 (37%)	11/32 (34%)	23/70 (33%)
ADJUSTED (B)	100.0%	100.0%	100.0%	100.0%	36.9%	42.0%	44.5%	45.5%
INTERIM NECROPSY 1 (C)	10/10 (100%)	0/0	1/1 (100%)	10/10 (100%)	1/10 (10%)	0/0	0/2 (0%)	1/10 (10%)
FINAL (D)	43/43 (100%)	18/18 (100%)	5/5 (100%)	46/46 (100%)	18/50 (36%)	9/22 (41%)	10/23 (43%)	21/48 (44%)
FIRST INCIDENCE (DAYS)	368 (I)	345	368 (I)	368 (I)	367 (I)	643	599	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.745	(E)	(E)	(E)	P=0.231
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.592	(E)	(E)	(E)	P=0.251
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.499	(E)	(E)	(E)	P=0.265
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.500		(E)	(E)	P=0.309

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Clear Cell Focus (Foci)								
LESION RATES								
OVERALL (A)	0/68 (0%)	7/25 (28%)	0/13 (0%)	1/68 (1%)	1/69 (1%)	0/27 (0%)	0/32 (0%)	0/70 (0%)
ADJUSTED (B)	0.0%	38.9%	0.0%	2.2%	2.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	7/18 (39%)	0/5 (0%)	1/46 (2%)	1/50 (2%)	0/22 (0%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	725 (T)	---	725 (T)	739 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.513	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.513	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.513	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.500		(E)	(E)	P=1.000
Liver								
Cystic Degeneration								
LESION RATES								
OVERALL (A)	5/68 (7%)	3/25 (12%)	1/13 (8%)	2/68 (3%)	(G)			
ADJUSTED (B)	11.6%	16.7%	2.0%	4.3%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	5/43 (12%)	3/18 (17%)	0/5 (0%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	649	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.951				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.951				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.951				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.942				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Eosinophilic Focus (Foci)								
LESION RATES								
OVERALL (A)	10/68 (15%)	0/25 (0%)	1/13 (8%)	12/68 (18%)	4/69 (6%)	2/27 (7%)	1/32 (3%)	1/70 (1%)
ADJUSTED (B)	22.6%	0.0%	20.0%	26.1%	8.0%	9.1%	1.7%	2.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	9/43 (21%)	0/18 (0%)	1/5 (20%)	12/46 (26%)	4/50 (8%)	2/22 (9%)	0/23 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	713	---	725 (T)	725 (T)	739 (T)	739 (T)	495	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.473	(E)	(E)	(E)	P=0.963
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.450	(E)	(E)	(E)	P=0.963
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.441	(E)	(E)	(E)	P=0.963
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.408		(E)	(E)	P=0.972
Liver								
Hepatitis, Chronic								
LESION RATES								
OVERALL (A)	1/68 (1%)	0/25 (0%)	0/13 (0%)	0/68 (0%)	28/69 (41%)	4/27 (15%)	15/32 (47%)	31/70 (44%)
ADJUSTED (B)	2.3%	0.0%	0.0%	0.0%	51.3%	18.2%	54.7%	56.5%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	2/10 (20%)	0/0	1/2 (50%)	4/10 (40%)
FINAL (D)	1/43 (2%)	0/18 (0%)	0/5 (0%)	0/46 (0%)	24/50 (48%)	4/22 (18%)	12/23 (52%)	25/48 (52%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	---	367 (I)	739 (T)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.294
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.320
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.364
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	P=0.394

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Hepatitis, Subacute								
LESION RATES								
OVERALL (A)	3/68 (4%)	0/25 (0%)	0/13 (0%)	0/68 (0%)	(G)			
ADJUSTED (B)	4.3%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	3/10 (30%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/18 (0%)	0/5 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				
Liver								
Hepatocellular Vacuolation								
LESION RATES								
OVERALL (A)	2/68 (3%)	4/25 (16%)	1/13 (8%)	2/68 (3%)	4/69 (6%)	0/27 (0%)	0/32 (0%)	0/70 (0%)
ADJUSTED (B)	4.3%	14.3%	1.7%	4.2%	8.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	1/1 (100%)	0/10 (0%)	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	2/18 (11%)	0/5 (0%)	1/46 (2%)	4/50 (8%)	0/22 (0%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	691	461	368 (I)	679	739 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.699	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.623	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.698	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.690		(E)	(E)	P=1.000

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Herniated Lobe								
LESION RATES								
OVERALL (A)	4/68 (6%)	3/25 (12%)	1/13 (8%)	1/68 (1%)	3/69 (4%)	4/27 (15%)	5/32 (16%)	2/70 (3%)
ADJUSTED (B)	9.3%	16.7%	20.0%	2.2%	5.4%	18.2%	21.7%	4.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	1/10 (10%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	4/43 (9%)	3/18 (17%)	1/5 (20%)	1/46 (2%)	2/50 (4%)	4/22 (18%)	5/23 (22%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	725 (T)	725 (T)	367 (I)	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.972	(E)	(E)	(E)	P=0.808
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.972	(E)	(E)	(E)	P=0.808
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.972	(E)	(E)	(E)	P=0.823
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.971		(E)	(E)	P=0.822
Liver								
Microgranulomas								
LESION RATES								
OVERALL (A)	51/68 (75%)	11/25 (44%)	3/13 (23%)	53/68 (78%)	(G)			
ADJUSTED (B)	92.3%	61.1%	60.0%	92.8%				
INTERIM NECROPSY 1 (C)	10/10 (100%)	0/0	0/1 (0%)	8/10 (80%)				
FINAL (D)	39/43 (91%)	11/18 (61%)	3/5 (60%)	42/46 (91%)				
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	725 (T)	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.680				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.659				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.425				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.420				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Mononuclear Cells								
LESION RATES								
OVERALL (A)	11/68 (16%)	2/25 (8%)	1/13 (8%)	2/68 (3%)	2/69 (3%)	0/27 (0%)	0/32 (0%)	0/70 (0%)
ADJUSTED (B)	19.3%	11.1%	20.0%	2.9%	2.9%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	5/10 (50%)	0/0	0/1 (0%)	2/10 (20%)	2/10 (20%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	4/43 (9%)	2/18 (11%)	1/5 (20%)	0/46 (0%)	0/50 (0%)	0/22 (0%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	725 (T)	368 (I)	367 (I)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.999	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.999	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.999	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.999		(E)	(E)	P=1.000
Liver								
Necrosis, Acute								
LESION RATES								
OVERALL (A)	9/68 (13%)	9/25 (36%)	5/13 (38%)	8/68 (12%)	(G)			
ADJUSTED (B)	17.4%	29.2%	26.0%	13.4%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	2/10 (20%)				
FINAL (D)	3/43 (7%)	4/18 (22%)	1/5 (20%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	551	461	418	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.709				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.729				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.686				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.697				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Periportal Fibrosis								
LESION RATES								
OVERALL (A)	64/68 (94%)	24/25 (96%)	8/13 (62%)	66/68 (97%)	(G)			
ADJUSTED (B)	100.0%	100.0%	100.0%	98.5%				
INTERIM NECROPSY 1 (C)	8/10 (80%)	0/0	0/1 (0%)	10/10 (100%)				
FINAL (D)	43/43 (100%)	18/18 (100%)	5/5 (100%)	45/46 (98%)				
FIRST INCIDENCE (DAYS)	368 (I)	461	649	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.664				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.392				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.342				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.340				
Liver								
Postmortem Congestion								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/25 (0%)	2/13 (15%)	0/68 (0%)	(G)			
ADJUSTED (B)	0.0%	0.0%	3.9%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/18 (0%)	0/5 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	---	---	418	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Liver								
Telangiectasis, Focal								
LESION RATES								
OVERALL (A)	5/68 (7%)	3/25 (12%)	0/13 (0%)	0/68 (0%)	0/69 (0%)	1/27 (4%)	0/32 (0%)	0/70 (0%)
ADJUSTED (B)	11.6%	16.7%	0.0%	0.0%	0.0%	4.5%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
FINAL (D)	5/43 (12%)	3/18 (17%)	0/5 (0%)	0/46 (0%)	0/50 (0%)	1/22 (5%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	---	---	---	739 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	(E)
Liver								
Vacuolar Degeneration, Hepatocytes								
LESION RATES								
OVERALL (A)	5/68 (7%)	4/25 (16%)	0/13 (0%)	7/68 (10%)	(G)			
ADJUSTED (B)	11.6%	22.2%	0.0%	14.7%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/1 (0%)	0/10 (0%)				
FINAL (D)	5/43 (12%)	4/18 (22%)	0/5 (0%)	6/46 (13%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	---	629				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.427				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.433				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.388				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.382				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung								
Alveolar Hemorrhage								
LESION RATES								
OVERALL (A)	5/68 (7%)	5/14 (36%)	3/13 (23%)	3/68 (4%)	(G)			
ADJUSTED (B)	11.2%	43.1%	0.0%	6.5%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/2 (50%)	2/3 (67%)	0/10 (0%)				
FINAL (D)	4/43 (9%)	2/5 (40%)	0/0	3/46 (7%)				
FIRST INCIDENCE (DAYS)	703	368 (I)	368 (I)	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.881				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.864				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.870				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.863				
Lung								
Alveolar Macrophage Accumulation								
LESION RATES								
OVERALL (A)	14/68 (21%)	2/14 (14%)	5/13 (38%)	17/68 (25%)	18/69 (26%)	2/20 (10%)	2/11 (18%)	13/70 (19%)
ADJUSTED (B)	30.6%	21.5%	0.0%	34.6%	33.3%	13.3%	3.7%	23.6%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)	2/10 (20%)	0/0	0/0	2/10 (20%)
FINAL (D)	12/43 (28%)	1/5 (20%)	0/0	14/46 (30%)	15/50 (30%)	2/15 (13%)	0/3 (0%)	9/48 (19%)
FIRST INCIDENCE (DAYS)	558	634	151	676	367 (I)	739 (T)	656	25
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.409	(E)	(E)	(E)	P=0.864
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.364	(E)	(E)	(E)	P=0.881
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.350	(E)	(E)	(E)	P=0.898
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.342		(E)	(E)	P=0.898

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung								
Alveolar/Bronchiolar Hyperplasia								
LESION RATES								
OVERALL (A)	5/68 (7%)	0/14 (0%)	2/13 (15%)	3/68 (4%)	(G)			
ADJUSTED (B)	11.6%	0.0%	0.0%	6.5%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	1/3 (33%)	0/10 (0%)				
FINAL (D)	5/43 (12%)	0/5 (0%)	0/0	3/46 (7%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	368 (I)	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.886				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.886				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.886				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.863				
Lung								
Congestion								
LESION RATES								
OVERALL (A)	(G)				0/69 (0%)	3/20 (15%)	4/11 (36%)	0/70 (0%)
ADJUSTED (B)					0.0%	5.3%	6.8%	0.0%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)					0/50 (0%)	0/15 (0%)	0/3 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)					---	537	495	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung Granuloma(s)								
LESION RATES								
OVERALL (A)	(G)				1/69 (1%)	0/20 (0%)	0/11 (0%)	2/70 (3%)
ADJUSTED (B)					1.4%	0.0%	0.0%	2.9%
INTERIM NECROPSY 1 (C)					1/10 (10%)	0/0	0/0	2/10 (20%)
FINAL (D)					0/50 (0%)	0/15 (0%)	0/3 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)					367 (I)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.500
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.500
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.614
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.505
Lung Interstitial Fibrosis								
LESION RATES								
OVERALL (A)	1/68 (1%)	0/14 (0%)	2/13 (15%)	0/68 (0%)	(G)			
ADJUSTED (B)	2.3%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/5 (0%)	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	718	---	534	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung Mineralization, Blood Vessels								
LESION RATES								
OVERALL (A)	57/68 (84%)	14/14 (100%)	13/13 (100%)	61/68 (90%)	2/69 (3%)	0/20 (0%)	0/11 (0%)	2/70 (3%)
ADJUSTED (B)	90.3%	100.0%	0.0%	92.3%	2.9%	0.0%	0.0%	3.8%
INTERIM NECROPSY 1 (C)	8/10 (80%)	2/2 (100%)	3/3 (100%)	10/10 (100%)	2/10 (20%)	0/0	0/0	0/10 (0%)
FINAL (D)	37/43 (86%)	5/5 (100%)	0/0	41/46 (89%)	0/50 (0%)	0/15 (0%)	0/3 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	368 (I)	345	151	368 (I)	367 (I)	---	---	615
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.485	(E)	(E)	(E)	P=0.690
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.215	(E)	(E)	(E)	P=0.750
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.223	(E)	(E)	(E)	P=0.736
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.224		(E)	(E)	P=0.696
Lung Peribronchial/Peribronchiolar Mononuclear Cells								
LESION RATES								
OVERALL (A)	67/68 (99%)	13/14 (93%)	9/13 (69%)	67/68 (99%)	55/69 (80%)	16/20 (80%)	3/11 (27%)	54/70 (77%)
ADJUSTED (B)	100.0%	100.0%	0.0%	100.0%	93.1%	93.6%	67.2%	89.7%
INTERIM NECROPSY 1 (C)	10/10 (100%)	2/2 (100%)	3/3 (100%)	10/10 (100%)	6/10 (60%)	0/0	0/0	8/10 (80%)
FINAL (D)	43/43 (100%)	5/5 (100%)	0/0	46/46 (100%)	46/50 (92%)	14/15 (93%)	2/3 (67%)	42/48 (88%)
FIRST INCIDENCE (DAYS)	368 (I)	345	151	368 (I)	367 (I)	537	495	25
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.798	(E)	(E)	(E)	P=0.507
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.735	(E)	(E)	(E)	P=0.608
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.764	(E)	(E)	(E)	P=0.600
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.752		(E)	(E)	P=0.717

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lung Perivascular Mononuclear Cells								
LESION RATES								
OVERALL (A)	9/68 (13%)	0/14 (0%)	0/13 (0%)	8/68 (12%)	(G)			
ADJUSTED (B)	13.7%	0.0%	0.0%	13.6%				
INTERIM NECROPSY 1 (C)	8/10 (80%)	0/2 (0%)	0/3 (0%)	4/10 (40%)				
FINAL (D)	1/43 (2%)	0/5 (0%)	0/0	3/46 (7%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.754				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.759				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.716				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.697				
Lung Pneumonitis, Focal								
LESION RATES								
OVERALL (A)	4/68 (6%)	2/14 (14%)	1/13 (8%)	7/68 (10%)	(G)			
ADJUSTED (B)	9.3%	40.0%	0.0%	15.2%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	4/43 (9%)	2/5 (40%)	0/0	7/46 (15%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	711	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.301				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.301				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.301				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.266				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lung								
Postmortem Congestion								
LESION RATES								
OVERALL (A)	1/68 (1%)	3/14 (21%)	3/13 (23%)	2/68 (3%)	(G)			
ADJUSTED (B)	2.2%	5.2%	0.0%	3.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/5 (0%)	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	713	345	151	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.517				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.408				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.501				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.500				
Lymph Node, Mandibular								
Hemorrhage								
LESION RATES								
OVERALL (A)	9/62 (15%)	12/16 (75%)	9/13 (69%)	8/66 (12%)	7/69 (10%)	6/13 (46%)	4/15 (27%)	6/68 (9%)
ADJUSTED (B)	22.2%	79.7%	86.4%	14.0%	14.0%	46.5%	44.4%	12.2%
INTERIM NECROPSY 1 (C)	1/9 (11%)	2/2 (100%)	3/3 (100%)	4/10 (40%)	0/10 (0%)	0/0	0/1 (0%)	0/9 (0%)
FINAL (D)	8/38 (21%)	7/9 (78%)	6/7 (86%)	3/44 (7%)	7/50 (14%)	5/11 (45%)	4/9 (44%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	739 (T)	681	739 (T)	678
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.789	(E)	(E)	(E)	P=0.693
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.773	(E)	(E)	(E)	P=0.697
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.745	(E)	(E)	(E)	P=0.695
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.745		(E)	(E)	P=0.710

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Mandibular Increased Plasma Cells								
LESION RATES								
OVERALL (A)	44/62 (71%)	11/16 (69%)	10/13 (77%)	43/66 (65%)	49/69 (71%)	11/13 (85%)	7/15 (47%)	32/68 (47%)
ADJUSTED (B)	89.2%	79.3%	86.7%	74.5%	81.4%	91.1%	57.2%	56.9%
INTERIM NECROPSY 1 (C)	6/9 (67%)	1/2 (50%)	2/3 (67%)	8/10 (80%)	4/10 (40%)	0/0	0/1 (0%)	1/9 (11%)
FINAL (D)	33/38 (87%)	7/9 (78%)	6/7 (86%)	30/44 (68%)	39/50 (78%)	10/11 (91%)	5/9 (56%)	24/48 (50%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	367 (I)	636	656	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.920	(E)	(E)	(E)	P=0.995
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.896	(E)	(E)	(E)	P=0.999
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.856	(E)	(E)	(E)	P=0.999
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.814		(E)	(E)	P=0.999
Lymph Node, Mandibular Lymphangiectasis								
LESION RATES								
OVERALL (A)	7/62 (11%)	2/16 (13%)	5/13 (38%)	6/66 (9%)	(G)			
ADJUSTED (B)	18.4%	22.2%	71.4%	13.6%				
INTERIM NECROPSY 1 (C)	0/9 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	7/38 (18%)	2/9 (22%)	5/7 (71%)	6/44 (14%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	725 (T)	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.813				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.813				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.813				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.759				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lymph Node, Mandibular Lymphoid Hyperplasia								
LESION RATES								
OVERALL (A)	1/62 (2%)	0/16 (0%)	1/13 (8%)	2/66 (3%)	(G)			
ADJUSTED (B)	2.0%	0.0%	1.4%	4.5%				
INTERIM NECROPSY 1 (C)	0/9 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	0/38 (0%)	0/9 (0%)	0/7 (0%)	2/44 (5%)				
FIRST INCIDENCE (DAYS)	702	---	23	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.529				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.480				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.527				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.524				
Lymph Node, Mandibular Pigmentation								
LESION RATES								
OVERALL (A)	(G)				2/69 (3%)	0/13 (0%)	0/15 (0%)	2/68 (3%)
ADJUSTED (B)					3.4%	0.0%	0.0%	3.5%
INTERIM NECROPSY 1 (C)					1/10 (10%)	0/0	0/1 (0%)	1/9 (11%)
FINAL (D)					1/50 (2%)	0/11 (0%)	0/9 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)					367 (I)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.668
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.668
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.710
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.685

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lymph Node, Mandibular Postmortem Congestion								
LESION RATES								
OVERALL (A)	2/62 (3%)	0/16 (0%)	3/13 (23%)	1/66 (2%)	(G)			
ADJUSTED (B)	4.1%	0.0%	5.3%	1.8%				
INTERIM NECROPSY 1 (C)	0/9 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)				
FINAL (D)	0/38 (0%)	0/9 (0%)	0/7 (0%)	0/44 (0%)				
FIRST INCIDENCE (DAYS)	621	---	23	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.881				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.876				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.889				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.889				
Lymph Node, Mandibular Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	(G)				0/69 (0%)	0/13 (0%)	3/15 (20%)	3/68 (4%)
ADJUSTED (B)					0.0%	0.0%	23.6%	5.5%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/1 (0%)	1/9 (11%)
FINAL (D)					0/50 (0%)	0/11 (0%)	2/9 (22%)	1/48 (2%)
FIRST INCIDENCE (DAYS)					---	---	625	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.110
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.116
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.122
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.120

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lymph Node, Mesenteric Increased Plasma Cells								
LESION RATES								
OVERALL (A)	0/66 (0%)	1/4 (25%)	0/4 (0%)	0/68 (0%)	0/67 (0%)	3/7 (43%)	0/5 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	1.9%	0.0%	0.0%	0.0%	41.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/9 (0%)
FINAL (D)	0/41 (0%)	0/2 (0%)	0/1 (0%)	0/46 (0%)	0/48 (0%)	2/5 (40%)	0/3 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	642	---	---	---	599	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Lymph Node, Mesenteric Pigmentation								
LESION RATES								
OVERALL (A)	0/66 (0%)	0/4 (0%)	0/4 (0%)	0/68 (0%)	1/67 (1%)	0/7 (0%)	0/5 (0%)	2/68 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%	2.9%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	2/9 (22%)
FINAL (D)	0/41 (0%)	0/2 (0%)	0/1 (0%)	0/46 (0%)	1/48 (2%)	0/5 (0%)	0/3 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	739 (T)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.475
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.475
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.539
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.506

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Mesenteric Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	4/66 (6%)	0/4 (0%)	0/4 (0%)	1/68 (1%)	27/67 (40%)	2/7 (29%)	2/5 (40%)	30/68 (44%)
ADJUSTED (B)	8.7%	0.0%	0.0%	2.2%	52.7%	40.0%	66.7%	55.8%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	3/9 (33%)
FINAL (D)	2/41 (5%)	0/2 (0%)	0/1 (0%)	1/46 (2%)	24/48 (50%)	2/5 (40%)	2/3 (67%)	25/48 (52%)
FIRST INCIDENCE (DAYS)	601	---	---	725 (T)	465	739 (T)	739 (T)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.970	(E)	(E)	(E)	P=0.343
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.966	(E)	(E)	(E)	P=0.360
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.970	(E)	(E)	(E)	P=0.380
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.973		(E)	(E)	P=0.392
Lymph Node, Other Congestion								
LESION RATES								
OVERALL (A)	(G)				2/8 (25%)	0/8 (0%)	0/3 (0%)	0/2 (0%)
ADJUSTED (B)					28.6%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)					0/0	0/0	0/0	0/0
FINAL (D)					2/7 (29%)	0/7 (0%)	0/2 (0%)	0/0
FIRST INCIDENCE (DAYS)					739 (T)	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Other Hemorrhage								
LESION RATES								
OVERALL (A)	0/1 (0%)	1/3 (33%)	1/3 (33%)	0/0 (0%)	1/8 (13%)	7/8 (88%)	2/3 (67%)	0/2 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	14.3%	86.0%	51.0%	0.0%
INTERIM NECROPSY 1 (C)	0/0	0/0	1/1 (100%)	0/0	0/0	0/0	0/0	0/0
FINAL (D)	0/0	0/0	0/0	0/0	1/7 (14%)	6/7 (86%)	1/2 (50%)	0/0
FIRST INCIDENCE (DAYS)	---	461	368 (I)	---	739 (T)	726	703	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)
Lymph Node, Other Increased Plasma Cells								
LESION RATES								
OVERALL (A)	1/1 (100%)	0/3 (0%)	1/3 (33%)	0/0 (0%)	0/8 (0%)	2/8 (25%)	0/3 (0%)	0/2 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	28.6%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/0	0/0	0/1 (0%)	0/0	0/0	0/0	0/0	0/0
FINAL (D)	0/0	0/0	0/0	0/0	0/7 (0%)	2/7 (29%)	0/2 (0%)	0/0
FIRST INCIDENCE (DAYS)	713	---	711	---	---	739 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Lymph Node, Other Reticuloendothelial Hyperplasia								
LESION RATES								
OVERALL (A)	(G)				1/8 (13%)	0/8 (0%)	3/3 (100%)	0/2 (0%)
ADJUSTED (B)					14.3%	0.0%	100.0%	0.0%
INTERIM NECROPSY 1 (C)					0/0	0/0	0/0	0/0
FINAL (D)					1/7 (14%)	0/7 (0%)	2/2 (100%)	0/0
FIRST INCIDENCE (DAYS)					739 (T)	---	703	---
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	(E)
INCIDENTAL TUMOR					(E)	(E)	(E)	(E)
LOGISTIC REGRESSION					(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=1.000
Lymph Node, Thymic Hemorrhage								
LESION RATES								
OVERALL (A)	3/10 (30%)	2/2 (100%)	1/4 (25%)	0/2 (0%)	(G)			
ADJUSTED (B)	41.2%	100.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	2/5 (40%)	1/1 (100%)	1/1 (100%)	0/2 (0%)				
FIRST INCIDENCE (DAYS)	621	642	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Lymph Node, Thymic Increased Plasma Cells								
LESION RATES								
OVERALL (A)	2/10 (20%)	0/2 (0%)	0/4 (0%)	0/2 (0%)	(G)			
ADJUSTED (B)	21.7%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	1/5 (20%)	0/1 (0%)	0/1 (0%)	0/2 (0%)				
FIRST INCIDENCE (DAYS)	703	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Lymph Node, Thymic Pigment-Laden Macrophages								
LESION RATES								
OVERALL (A)	5/10 (50%)	0/2 (0%)	1/4 (25%)	0/2 (0%)	(G)			
ADJUSTED (B)	80.4%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	4/5 (80%)	0/1 (0%)	1/1 (100%)	0/2 (0%)				
FIRST INCIDENCE (DAYS)	703	---	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Mammary Gland Galactocele								
LESION RATES								
OVERALL (A)	7/54 (13%)	1/2 (50%)	1/1 (100%)	4/56 (7%)	4/68 (6%)	2/16 (13%)	3/13 (23%)	5/67 (7%)
ADJUSTED (B)	17.2%	2.0%	100.0%	9.2%	8.2%	10.0%	26.5%	10.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/7 (0%)	0/10 (0%)	0/0	0/0	0/8 (0%)
FINAL (D)	4/34 (12%)	0/1 (0%)	1/1 (100%)	3/41 (7%)	4/49 (8%)	1/12 (8%)	2/8 (25%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	611	681	725 (T)	676	739 (T)	643	697	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.927	(E)	(E)	(E)	P=0.487
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.900	(E)	(E)	(E)	P=0.487
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.927	(E)	(E)	(E)	P=0.487
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.910		(E)	(E)	P=0.491
Mammary Gland Inflammation, Subacute								
LESION RATES								
OVERALL (A)	(G)				1/68 (1%)	3/16 (19%)	1/13 (8%)	1/67 (1%)
ADJUSTED (B)					2.0%	25.0%	12.5%	2.1%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/8 (0%)
FINAL (D)					1/49 (2%)	3/12 (25%)	1/8 (13%)	1/48 (2%)
FIRST INCIDENCE (DAYS)					739 (T)	739 (T)	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.757
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.757
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.757
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.748

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Mammary Gland								
Lactation								
LESION RATES								
OVERALL (A)	(G)				35/68 (51%)	12/16 (75%)	7/13 (54%)	35/67 (52%)
ADJUSTED (B)					68.5%	76.3%	64.0%	65.9%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/8 (0%)
FINAL (D)					33/49 (67%)	9/12 (75%)	5/8 (63%)	30/48 (63%)
FIRST INCIDENCE (DAYS)					465	537	697	615
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.516
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.496
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.543
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.533
Mesentery								
Inflammation, Subacute								
LESION RATES								
OVERALL (A)	2/3 (67%)	0/0 (0%)	0/2 (0%)	0/0 (0%)	(G)			
ADJUSTED (B)	100.0%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	1/1 (100%)	0/0	0/1 (0%)	0/0				
FIRST INCIDENCE (DAYS)	713	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Epithelial Microabscess(es)								
LESION RATES								
OVERALL (A)	2/68 (3%)	5/69 (7%)	1/70 (1%)	11/65 (17%)	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	4.1%	10.0%	2.1%	23.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	4/48 (8%)	0/43 (0%)	9/44 (20%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	580	642	661	584	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.002 **	P=0.257	P=0.871	P=0.012 *	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.003 **	P=0.171	P=0.847	P=0.012 *	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.002 **	P=0.225	P=0.882	P=0.007 **	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.002 **				(E)			
FISHER EXACT		P=0.226	P=0.883	P=0.007 **		(E)	(E)	(E)
Nose 1 Fibrin Thrombi								
LESION RATES								
OVERALL (A)	2/68 (3%)	0/69 (0%)	0/70 (0%)	0/65 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	4.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	0/48 (0%)	0/43 (0%)	0/44 (0%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	520	---	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.978	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.992	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.979	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.978				(E)			
FISHER EXACT		P=1.000	P=1.000	P=1.000		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 1 Goblet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	3/68 (4%)	2/69 (3%)	0/70 (0%)	0/65 (0%)	2/68 (3%)	4/68 (6%)	7/68 (10%)	1/68 (1%)
ADJUSTED (B)	6.0%	3.5%	0.0%	0.0%	4.1%	6.8%	11.0%	1.4%
INTERIM NECROPSY 1 (C)	1/10 (10%)	1/9 (11%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)	5/10 (50%)	1/10 (10%)
FINAL (D)	2/43 (5%)	1/48 (2%)	0/43 (0%)	0/44 (0%)	2/49 (4%)	2/49 (4%)	2/48 (4%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	---	---	739 (T)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.989	P=0.826	(E)	(E)	P=0.835	P=0.339	P=0.074	P=0.874
INCIDENTAL TUMOR	P=0.989	P=0.826	(E)	(E)	P=0.835	P=0.339	P=0.074	P=0.874
LOGISTIC REGRESSION	P=0.990	P=0.829	(E)	(E)	P=0.875	P=0.330	P=0.066	P=0.883
COCHRAN-ARMITAGE	P=0.989				P=0.830			
FISHER EXACT		P=0.822	P=1.000	P=1.000		P=0.340	P=0.082	P=0.878
Nose 1 Hyperplasia, Squamous Epithelium								
LESION RATES								
OVERALL (A)	0/68 (0%)	7/69 (10%)	1/70 (1%)	0/65 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	13.4%	2.3%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/9 (11%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	5/48 (10%)	1/43 (2%)	0/44 (0%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	368 (I)	725 (T)	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.962	P=0.014 *	P=0.500	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.965	P=0.009 **	P=0.500	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.961	P=0.010 *	P=0.500	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.961				(E)			
FISHER EXACT		P=0.007 **	P=0.507	(E)		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Inflammation, Acute, Nasolacrimal Duct								
LESION RATES								
OVERALL (A)	1/68 (1%)	4/69 (6%)	1/70 (1%)	1/65 (2%)	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	2.0%	7.6%	2.3%	2.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	1/48 (2%)	1/43 (2%)	1/44 (2%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	691	842	725 (T)	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.834	P=0.203	P=0.751	P=0.758	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.800	P=0.075	P=0.729	P=0.689	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.830	P=0.185	P=0.756	P=0.753	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.831				(E)			
FISHER EXACT		P=0.187	P=0.759	P=0.740		(E)	(E)	(E)
Nose 1 Inflammation, Subacute								
LESION RATES								
OVERALL (A)	45/68 (66%)	58/69 (84%)	57/70 (81%)	50/65 (77%)	2/68 (3%)	6/68 (9%)	11/68 (16%)	13/68 (19%)
ADJUSTED (B)	86.0%	90.5%	90.2%	92.4%	4.1%	9.6%	17.0%	20.8%
INTERIM NECROPSY 1 (C)	6/10 (60%)	7/9 (78%)	10/10 (100%)	3/10 (30%)	0/10 (0%)	4/10 (40%)	8/10 (80%)	8/10 (80%)
FINAL (D)	36/43 (84%)	42/48 (88%)	37/43 (86%)	40/44 (91%)	2/49 (4%)	2/49 (4%)	3/48 (6%)	5/48 (10%)
FIRST INCIDENCE (DAYS)	368 (I)	345	151	368 (I)	739 (T)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.475	P=0.060	P=0.017 *	P=0.274	P<0.001 **	P=0.133	P=0.005 **	P=0.002 **
INCIDENTAL TUMOR	P=0.246	P=0.016 *	P=0.028 *	P=0.145	P<0.001 **	P=0.133	P=0.005 **	P=0.002 **
LOGISTIC REGRESSION	P=0.283	P=0.017 *	P=0.026 *	P=0.101	P=0.002 **	P=0.118	P=0.004 **	P=0.003 **
COCHRAN-ARMITAGE	P=0.287				P=0.003 **			
FISHER EXACT		P=0.013 *	P=0.032 *	P=0.119		P=0.137	P=0.008 **	P=0.002 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Mucopurulent Exudate								
LESION RATES								
OVERALL (A)	1/68 (1%)	5/69 (7%)	2/70 (3%)	3/65 (5%)	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	1.9%	9.2%	4.0%	5.9%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	1/48 (2%)	0/43 (0%)	1/44 (2%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	621	461	534	573	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.494	P=0.121	P=0.496	P=0.319	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.381	P=0.038 *	P=0.590	P=0.272	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.506	P=0.037 *	P=0.519	P=0.290	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.470				(E)			
FISHER EXACT		P=0.108	P=0.511	P=0.293		(E)	(E)	(E)
Nose 1 Ulcers								
LESION RATES								
OVERALL (A)	2/68 (3%)	2/69 (3%)	4/70 (6%)	1/65 (2%)	0/68 (0%)	1/68 (1%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	4.2%	3.7%	7.6%	1.8%	0.0%	2.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	0/48 (0%)	0/43 (0%)	0/44 (0%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	621	642	534	573	---	704	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.782	P=0.714	P=0.329	P=0.882	P=0.914	P=0.489	(E)	(E)
INCIDENTAL TUMOR	P=0.780	P=0.534	P=0.352	P=0.901	P=0.925	P=0.455	(E)	(E)
LOGISTIC REGRESSION	P=0.858	P=0.810	P=0.314	P=0.871	P=0.919	P=0.501	(E)	(E)
COCHRAN-ARMITAGE	P=0.772				P=0.919			
FISHER EXACT		P=0.696	P=0.354	P=0.869		P=0.500	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 1 Vascular Thrombi								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/69 (0%)	0/70 (0%)	0/65 (0%)	3/68 (4%)	1/68 (1%)	1/68 (1%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	5.2%	2.0%	1.7%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	0/43 (0%)	0/44 (0%)	0/49 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	465	704	529	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.975	P=0.929	P=0.930	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.988	P=0.960	P=0.987	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.989	P=0.979	P=0.993	(E)
COCHRAN-ARMITAGE	(E)				P=0.978			
FISHER EXACT		(E)	(E)	(E)		P=0.940	P=0.940	P=1.000
Nose 2 Eosinophilic Globules, Glandular Epithelium								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/69 (0%)	0/70 (0%)	0/67 (0%)	0/69 (0%)	3/68 (4%)	1/67 (1%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	5.7%	2.1%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	2/49 (4%)	1/47 (2%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	537	739 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.898	P=0.122	P=0.488	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.912	P=0.160	P=0.488	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.900	P=0.119	P=0.488	(E)
COCHRAN-ARMITAGE	(E)				P=0.901			
FISHER EXACT		(E)	(E)	(E)		P=0.120	P=0.493	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Eosinophilic Globules, Respiratory Epithelium								
LESION RATES								
OVERALL (A)	1/67 (1%)	1/69 (1%)	0/70 (0%)	0/67 (0%)	9/69 (13%)	11/68 (16%)	13/67 (19%)	6/68 (9%)
ADJUSTED (B)	2.0%	2.1%	0.0%	0.0%	17.5%	21.2%	27.0%	12.5%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	1/48 (2%)	0/43 (0%)	0/46 (0%)	8/50 (16%)	9/49 (18%)	12/47 (26%)	6/48 (13%)
FIRST INCIDENCE (DAYS)	691	725 (T)	---	---	697	537	683	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.956	P=0.773	(E)	(E)	P=0.858	P=0.385	P=0.193	P=0.844
INCIDENTAL TUMOR	P=0.949	P=0.726	(E)	(E)	P=0.868	P=0.428	P=0.208	P=0.847
LOGISTIC REGRESSION	P=0.957	P=0.771	(E)	(E)	P=0.861	P=0.391	P=0.197	P=0.844
COCHRAN-ARMITAGE	P=0.958				P=0.871			
FISHER EXACT		P=0.759	P=1.000	P=1.000		P=0.391	P=0.220	P=0.856
Nose 2 Epithelial Microabscess(es)								
LESION RATES								
OVERALL (A)	6/67 (9%)	11/69 (16%)	16/70 (23%)	29/67 (43%)	1/69 (1%)	4/68 (6%)	3/67 (4%)	1/68 (1%)
ADJUSTED (B)	12.0%	21.4%	30.9%	58.9%	2.0%	7.9%	6.4%	2.1%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	3/42 (7%)	9/48 (19%)	9/43 (21%)	26/46 (57%)	1/50 (2%)	3/49 (6%)	3/47 (6%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	573	739 (T)	681	739 (T)	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.207	P=0.023 *	P<0.001 **	P=0.793	P=0.176	P=0.284	P=0.752
INCIDENTAL TUMOR	P<0.001 **	P=0.228	P=0.024 *	P<0.001 **	P=0.799	P=0.165	P=0.284	P=0.752
LOGISTIC REGRESSION	P<0.001 **	P=0.165	P=0.019 *	P<0.001 **	P=0.795	P=0.176	P=0.284	P=0.752
COCHRAN-ARMITAGE	P<0.001 **				P=0.803			
FISHER EXACT		P=0.166	P=0.023 *	P<0.001 **		P=0.178	P=0.299	P=0.748

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Fibrin Thrombi								
LESION RATES								
OVERALL (A)	2/67 (3%)	0/69 (0%)	0/70 (0%)	0/67 (0%)	2/69 (3%)	2/68 (3%)	1/67 (1%)	0/68 (0%)
ADJUSTED (B)	4.1%	0.0%	0.0%	0.0%	3.4%	3.9%	1.8%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/42 (2%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	520	---	---	---	465	704	599	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.978	(E)	(E)	(E)	P=0.962	P=0.685	P=0.874	(E)
INCIDENTAL TUMOR	P=0.992	(E)	(E)	(E)	P=0.974	P=0.756	P=0.941	(E)
LOGISTIC REGRESSION	P=0.979	(E)	(E)	(E)	P=0.979	P=0.796	P=0.984	(E)
COCHRAN-ARMITAGE	P=0.979				P=0.965			
FISHER EXACT		P=1.000	P=1.000	P=1.000		P=0.685	P=0.872	P=1.000
Nose 2 Goblet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	24/67 (36%)	51/69 (74%)	23/70 (33%)	12/67 (18%)	10/69 (14%)	55/68 (81%)	62/67 (93%)	60/68 (88%)
ADJUSTED (B)	41.8%	83.2%	37.9%	21.4%	18.2%	88.4%	96.8%	96.7%
INTERIM NECROPSY 1 (C)	8/10 (80%)	6/9 (67%)	6/10 (60%)	5/10 (50%)	1/10 (10%)	10/10 (100%)	10/10 (100%)	7/10 (70%)
FINAL (D)	12/42 (29%)	38/48 (79%)	9/43 (21%)	7/46 (15%)	7/50 (14%)	42/49 (86%)	45/47 (96%)	46/48 (96%)
FIRST INCIDENCE (DAYS)	368 (I)	345	23	368 (I)	367 (I)	367 (I)	367 (I)	25
STATISTICAL TESTS (F)								
LIFE TABLE	P=1.000	P<0.001 **	P=0.646	P=0.998	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P=1.000	P<0.001 **	P=0.804	P=0.997	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P=1.000	P<0.001 **	P=0.817	P=0.997	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P=1.000				P<0.001 **			
FISHER EXACT		P<0.001 **	P=0.707	P=0.995		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 **Hemorrhage**								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/69 (0%)	2/70 (3%)	0/67 (0%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	4.7%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	2/43 (5%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	725 (T)	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.706	(E)	P=0.244	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.706	(E)	P=0.244	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.706	(E)	P=0.244	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.699				(E)			
FISHER EXACT		(E)	P=0.259	(E)		(E)	(E)	(E)
Nose 2 **Hyperplasia, Squamous Epithelium**								
LESION RATES								
OVERALL (A)	5/67 (7%)	17/69 (25%)	19/70 (27%)	18/67 (27%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	11.9%	33.8%	39.7%	35.6%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	5/42 (12%)	15/48 (31%)	15/43 (35%)	14/46 (30%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	642	368 (I)	584	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.034 *	P=0.011 *	P=0.002 **	P=0.006 **	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.032 *	P=0.007 **	P=0.001 **	P=0.004 **	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.023 *	P=0.006 **	P=0.001 **	P=0.003 **	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.023 *				(E)			
FISHER EXACT		P=0.006 **	P=0.002 **	P=0.003 **		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Inflammation, Acute, Nasolacrimal Duct								
LESION RATES								
OVERALL (A)	3/67 (4%)	2/69 (3%)	1/70 (1%)	0/67 (0%)	3/69 (4%)	3/68 (4%)	1/67 (1%)	0/68 (0%)
ADJUSTED (B)	5.6%	3.9%	2.3%	0.0%	5.7%	6.1%	2.1%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	1/43 (2%)	0/46 (0%)	1/50 (2%)	3/49 (6%)	1/47 (2%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	551	657	725 (T)	---	708	739 (T)	739 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.980	P=0.822	P=0.927	(E)	P=0.982	P=0.645	P=0.924	(E)
INCIDENTAL TUMOR	P=0.974	P=0.650	P=0.912	(E)	P=0.985	P=0.622	P=0.946	(E)
LOGISTIC REGRESSION	P=0.982	P=0.828	P=0.940	(E)	P=0.984	P=0.655	P=0.931	(E)
COCHRAN-ARMITAGE	P=0.982				P=0.984			
FISHER EXACT		P=0.826	P=0.945	P=1.000		P=0.653	P=0.937	P=1.000
Nose 2 Inflammation, Subacute								
LESION RATES								
OVERALL (A)	60/67 (90%)	67/69 (97%)	65/70 (93%)	63/67 (94%)	3/69 (4%)	8/68 (12%)	7/67 (10%)	17/68 (25%)
ADJUSTED (B)	100.0%	100.0%	98.5%	100.0%	6.0%	12.8%	10.5%	28.9%
INTERIM NECROPSY 1 (C)	9/10 (90%)	9/9 (100%)	10/10 (100%)	8/10 (80%)	0/10 (0%)	5/10 (50%)	6/10 (60%)	7/10 (70%)
FINAL (D)	42/42 (100%)	48/48 (100%)	42/43 (98%)	46/46 (100%)	3/50 (6%)	3/49 (6%)	1/47 (2%)	10/48 (21%)
FIRST INCIDENCE (DAYS)	368 (I)	345	151	368 (I)	739 (T)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.697	P=0.439	P=0.248	P=0.681	P<0.001 **	P=0.095	P=0.139	P<0.001 **
INCIDENTAL TUMOR	P=0.509	P=0.098	P=0.282	P=0.397	P<0.001 **	P=0.095	P=0.139	P<0.001 **
LOGISTIC REGRESSION	P=0.411	P=0.125	P=0.290	P=0.304	P<0.001 **	P=0.086	P=0.124	P<0.001 **
COCHRAN-ARMITAGE	P=0.405				P<0.001 **			
FISHER EXACT		P=0.076	P=0.352	P=0.266		P=0.099	P=0.151	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 2 Inspissated Mucus								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/69 (0%)	2/70 (3%)	0/67 (0%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	368 (I)	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.702	(E)	P=0.238	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.676	(E)	P=0.377	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.714	(E)	P=0.333	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.699				(E)			
FISHER EXACT		(E)	P=0.259	(E)		(E)	(E)	(E)
Nose 2 Mineralization								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/69 (0%)	0/70 (0%)	2/67 (3%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	0/43 (0%)	2/46 (4%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.046 *	(E)	(E)	P=0.259	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.046 *	(E)	(E)	P=0.259	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.046 *	(E)	(E)	P=0.259	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.041 *				(E)			
FISHER EXACT		(E)	(E)	P=0.248		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 **Mucopurulent Exudate**								
LESION RATES								
OVERALL (A)	1/67 (1%)	5/69 (7%)	4/70 (6%)	7/67 (10%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	3/68 (4%)
ADJUSTED (B)	2.2%	9.2%	7.5%	13.2%	0.0%	0.0%	0.0%	6.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	1/48 (2%)	0/43 (0%)	2/46 (4%)	0/50 (0%)	0/49 (0%)	0/47 (0%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	713	579	534	573	---	---	---	662
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.060	P=0.123	P=0.180	P=0.044 *	P=0.009 **	(E)	(E)	P=0.116
INCIDENTAL TUMOR	P=0.023 *	P=0.026 *	P=0.182	P=0.008 **	P=0.010 **	(E)	(E)	P=0.119
LOGISTIC REGRESSION	P=0.055	P=0.078	P=0.167	P=0.035 *	P=0.009 **	(E)	(E)	P=0.115
COCHRAN-ARMITAGE	P=0.049 *				P=0.010 **			
FISHER EXACT		P=0.111	P=0.197	P=0.031 *		(E)	(E)	P=0.120
Nose 2 **Serous Exudate**								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/69 (0%)	0/70 (0%)	2/67 (3%)	2/69 (3%)	2/68 (3%)	1/67 (1%)	5/68 (7%)
ADJUSTED (B)	0.0%	0.0%	0.0%	4.3%	3.6%	4.0%	2.1%	9.9%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/48 (0%)	0/43 (0%)	2/46 (4%)	0/50 (0%)	1/49 (2%)	1/47 (2%)	4/48 (8%)
FIRST INCIDENCE (DAYS)	---	---	---	725 (T)	636	704	739 (T)	815
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.046 *	(E)	(E)	P=0.259	P=0.092	P=0.675	P=0.863	P=0.203
INCIDENTAL TUMOR	P=0.046 *	(E)	(E)	P=0.259	P=0.087	P=0.693	P=0.883	P=0.202
LOGISTIC REGRESSION	P=0.046 *	(E)	(E)	P=0.259	P=0.092	P=0.690	P=0.873	P=0.207
COCHRAN-ARMITAGE	P=0.041 *				P=0.097			
FISHER EXACT		(E)	(E)	P=0.248		P=0.685	P=0.872	P=0.214

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 2 Ulcers								
LESION RATES								
OVERALL (A)	2/67 (3%)	1/69 (1%)	4/70 (6%)	2/67 (3%)	1/69 (1%)	1/68 (1%)	0/67 (0%)	1/68 (1%)
ADJUSTED (B)	4.6%	1.9%	7.9%	3.7%	2.0%	2.0%	0.0%	1.9%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/42 (2%)	0/48 (0%)	1/43 (2%)	0/46 (0%)	1/50 (2%)	0/49 (0%)	0/47 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	718	642	550	573	739 (T)	726	---	662
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.523	P=0.892	P=0.338	P=0.710	P=0.673	P=0.758	(E)	P=0.752
INCIDENTAL TUMOR	P=0.528	P=0.814	P=0.270	P=0.595	P=0.696	P=0.733	(E)	P=0.756
LOGISTIC REGRESSION	P=0.578	P=0.885	P=0.347	P=0.696	P=0.675	P=0.758	(E)	P=0.756
COCHRAN-ARMITAGE	P=0.513				P=0.679			
FISHER EXACT		P=0.883	P=0.361	P=0.690		P=0.748	P=1.000	P=0.748
Nose 3 Cystic Glands								
LESION RATES								
OVERALL (A)	0/68 (0%)	3/69 (4%)	0/70 (0%)	1/67 (1%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	6.0%	0.0%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	2/48 (4%)	0/43 (0%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	681	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.693	P=0.138	(E)	P=0.513	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.663	P=0.107	(E)	P=0.513	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.689	P=0.125	(E)	P=0.513	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.689				(E)			
FISHER EXACT		P=0.125	(E)	P=0.496		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Degeneration, Olfactory Epithelium								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/69 (0%)	0/70 (0%)	2/67 (3%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	3.9%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	0/43 (0%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	573	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.046 *	(E)	(E)	P=0.251	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.064	(E)	(E)	P=0.264	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.041 *	(E)	(E)	P=0.235	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.041 *				(E)			
FISHER EXACT		(E)	(E)	P=0.244		(E)	(E)	(E)
Nose 3 Eosinophilic Globules, Glandular Epithelium								
LESION RATES								
OVERALL (A)	1/68 (1%)	29/69 (42%)	34/70 (49%)	47/67 (70%)	16/69 (23%)	27/68 (40%)	51/68 (75%)	52/68 (76%)
ADJUSTED (B)	2.3%	59.0%	67.2%	82.0%	29.4%	54.0%	90.9%	85.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/9 (11%)	4/10 (40%)	7/10 (70%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	7/10 (70%)
FINAL (D)	1/43 (2%)	28/48 (58%)	27/43 (63%)	36/46 (78%)	12/50 (24%)	26/49 (53%)	43/48 (90%)	39/48 (81%)
FIRST INCIDENCE (DAYS)	725 (T)	368 (I)	368 (I)	368 (I)	465	726	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.025 *	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.022 *	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.023 *	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.028 *	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Eosinophilic Globules, Olfactory Epithelium								
LESION RATES								
OVERALL (A)	8/68 (12%)	57/69 (83%)	56/70 (80%)	55/67 (82%)	36/69 (52%)	62/68 (91%)	67/68 (99%)	67/68 (99%)
ADJUSTED (B)	15.9%	93.3%	91.6%	91.4%	67.6%	98.4%	100.0%	100.0%
INTERIM NECROPSY 1 (C)	2/10 (20%)	6/9 (67%)	10/10 (100%)	9/10 (90%)	2/10 (20%)	8/10 (80%)	10/10 (100%)	10/10 (100%)
FINAL (D)	5/43 (12%)	44/48 (92%)	38/43 (88%)	41/46 (89%)	33/50 (66%)	48/49 (98%)	48/48 (100%)	48/48 (100%)
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **
Nose 3 Eosinophilic Globules, Respiratory Epithelium								
LESION RATES								
OVERALL (A)	2/68 (3%)	23/69 (33%)	36/70 (51%)	49/67 (73%)	48/69 (70%)	58/68 (85%)	57/68 (84%)	63/68 (93%)
ADJUSTED (B)	4.7%	44.6%	66.9%	82.5%	82.6%	98.3%	100.0%	98.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/9 (11%)	5/10 (50%)	10/10 (100%)	2/10 (20%)	4/10 (40%)	2/10 (20%)	9/10 (90%)
FINAL (D)	2/43 (5%)	20/48 (42%)	26/43 (60%)	36/46 (78%)	40/50 (80%)	48/49 (98%)	48/48 (100%)	47/48 (98%)
FIRST INCIDENCE (DAYS)	725 (T)	368 (I)	368 (I)	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.001 **	P=0.025 *	P=0.023 *	P=0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.014 *	P=0.015 *	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.013 *	P=0.014 *	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P=0.002 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.022 *	P=0.038 *	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Epithelial Microabscess(es)								
LESION RATES								
OVERALL (A)	1/68 (1%)	2/69 (3%)	1/70 (1%)	0/67 (0%)	6/69 (9%)	0/68 (0%)	1/68 (1%)	0/68 (0%)
ADJUSTED (B)	1.8%	4.2%	2.3%	0.0%	12.0%	0.0%	1.4%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	0/10 (0%)
FINAL (D)	0/43 (0%)	2/48 (4%)	1/43 (2%)	0/46 (0%)	6/50 (12%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	551	725 (T)	725 (T)	---	739 (T)	---	367 (I)	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.935	P=0.523	P=0.752	(E)	P=0.996	(E)	P=0.988	(E)
INCIDENTAL TUMOR	P=0.941	P=0.447	P=0.740	(E)	P=0.996	(E)	P=0.988	(E)
LOGISTIC REGRESSION	P=0.934	P=0.505	P=0.770	(E)	P=0.996	(E)	P=0.990	(E)
COCHRAN-ARMITAGE	P=0.934				P=0.996			
FISHER EXACT		P=0.506	P=0.759	P=1.000		P=1.000	P=0.993	P=1.000
Nose 3 Fibrin Thrombi								
LESION RATES								
OVERALL (A)	2/68 (3%)	0/69 (0%)	0/70 (0%)	0/67 (0%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	4.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	520	---	---	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.978	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.992	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.979	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.978				(E)			
FISHER EXACT		P=1.000	P=1.000	P=1.000		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Foreign Body								
LESION RATES								
OVERALL (A)	0/68 (0%)	1/69 (1%)	0/70 (0%)	2/67 (3%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	2.1%	0.0%	4.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	1/48 (2%)	0/43 (0%)	2/46 (4%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	725 (T)	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.151	P=0.522	(E)	P=0.253	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.151	P=0.522	(E)	P=0.253	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.151	P=0.522	(E)	P=0.253	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.141				(E)			
FISHER EXACT		P=0.504	(E)	P=0.244		(E)	(E)	(E)
Nose 3 Goblet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	8/68 (12%)	56/69 (81%)	61/70 (87%)	62/67 (93%)	3/69 (4%)	48/68 (71%)	61/68 (90%)	62/68 (91%)
ADJUSTED (B)	17.5%	96.5%	100.0%	100.0%	6.0%	90.5%	100.0%	98.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	3/9 (33%)	7/10 (70%)	10/10 (100%)	0/10 (0%)	2/10 (20%)	10/10 (100%)	10/10 (100%)
FINAL (D)	6/43 (14%)	46/48 (96%)	43/43 (100%)	46/46 (100%)	3/50 (6%)	44/49 (90%)	48/48 (100%)	47/48 (98%)
FIRST INCIDENCE (DAYS)	660	359	368 (I)	368 (I)	739 (T)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Hemorrhage								
LESION RATES								
OVERALL (A)	0/68 (0%)	1/69 (1%)	2/70 (3%)	1/67 (1%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	2.1%	3.7%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	1/48 (2%)	1/43 (2%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	725 (T)	151	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.454	P=0.522	P=0.238	P=0.513	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.383	P=0.522	P=0.500	P=0.513	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.437	P=0.522	P=0.322	P=0.513	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.441				(E)			
FISHER EXACT		P=0.504	P=0.255	P=0.496		(E)	(E)	(E)
Nose 3 Inflammation, Acute, Nasolacrimal Duct								
LESION RATES								
OVERALL (A)	4/68 (6%)	3/69 (4%)	0/70 (0%)	0/67 (0%)	5/69 (7%)	0/68 (0%)	1/68 (1%)	0/68 (0%)
ADJUSTED (B)	7.8%	5.7%	0.0%	0.0%	9.2%	0.0%	2.1%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	0/48 (0%)	0/43 (0%)	0/46 (0%)	2/50 (4%)	0/49 (0%)	1/48 (2%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	551	642	---	---	636	---	739 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.994	P=0.792	(E)	(E)	P=0.991	(E)	P=0.976	(E)
INCIDENTAL TUMOR	P=0.994	P=0.579	(E)	(E)	P=0.993	(E)	P=0.984	(E)
LOGISTIC REGRESSION	P=0.997	P=0.768	(E)	(E)	P=0.992	(E)	P=0.981	(E)
COCHRAN-ARMITAGE	P=0.995				P=0.992			
FISHER EXACT		P=0.786	P=1.000	P=1.000		P=1.000	P=0.985	P=1.000

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Nose 3 Inflammation, Subacute								
LESION RATES								
OVERALL (A)	32/68 (47%)	52/69 (75%)	60/70 (86%)	57/67 (85%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	64.5%	88.0%	98.3%	90.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	2/10 (20%)	5/9 (56%)	5/10 (50%)	10/10 (100%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	26/43 (60%)	41/48 (85%)	42/43 (98%)	40/46 (87%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	151	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P=0.003 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P<0.001 **				(E)			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		(E)	(E)	(E)
Nose 3 Inspissated Mucus								
LESION RATES								
OVERALL (A)	1/68 (1%)	2/69 (3%)	3/70 (4%)	1/67 (1%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	2.3%	4.2%	6.1%	2.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	2/48 (4%)	2/43 (5%)	1/46 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	368 (I)	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.705	P=0.538	P=0.307	P=0.776	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.705	P=0.538	P=0.307	P=0.776	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.691	P=0.538	P=0.318	P=0.776	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.690				(E)			
FISHER EXACT		P=0.506	P=0.321	P=0.748		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Mineralized Concretion(s)								
LESION RATES								
OVERALL (A)	2/68 (3%)	4/69 (6%)	1/70 (1%)	8/67 (12%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	4.7%	7.6%	2.3%	15.6%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/9 (11%)	0/10 (0%)	2/10 (20%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	2/43 (5%)	3/48 (6%)	1/43 (2%)	6/46 (13%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	368 (I)	725 (T)	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.024 *	P=0.373	P=0.879	P=0.060	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.024 *	P=0.373	P=0.879	P=0.060	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.019 *	P=0.344	P=0.879	P=0.048 *	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.019 *				(E)			
FISHER EXACT		P=0.347	P=0.883	P=0.046 *		(E)	(E)	(E)
Nose 3 Mucopurulent Exudate								
LESION RATES								
OVERALL (A)	3/68 (4%)	5/69 (7%)	5/70 (7%)	7/67 (10%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	2/68 (3%)
ADJUSTED (B)	6.3%	9.4%	9.9%	13.7%	0.0%	0.0%	0.0%	3.7%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	2/48 (4%)	1/43 (2%)	4/46 (9%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	660	579	550	573	---	---	---	615
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.164	P=0.397	P=0.351	P=0.188	P=0.042 *	(E)	(E)	P=0.231
INCIDENTAL TUMOR	P=0.131	P=0.201	P=0.250	P=0.107	P=0.038 *	(E)	(E)	P=0.240
LOGISTIC REGRESSION	P=0.168	P=0.365	P=0.357	P=0.158	P=0.043 *	(E)	(E)	P=0.235
COCHRAN-ARMITAGE	P=0.139				P=0.042 *			
FISHER EXACT		P=0.367	P=0.375	P=0.156		(E)	(E)	P=0.245

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 3 Subepithelial Mineralization								
LESION RATES								
OVERALL (A)	5/68 (7%)	6/69 (9%)	1/70 (1%)	6/67 (9%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	10.2%	11.1%	2.3%	11.8%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	1/10 (10%)	2/9 (22%)	0/10 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	3/43 (7%)	4/48 (8%)	1/43 (2%)	4/46 (9%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	725 (T)	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.506	P=0.527	P=0.980	P=0.528	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.468	P=0.499	P=0.978	P=0.446	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.475	P=0.513	P=0.982	P=0.489	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.476				(E)			
FISHER EXACT		P=0.510	P=0.987	P=0.490		(E)	(E)	(E)
Nose 4 Eosinophilic Globules, Glandular Epithelium								
LESION RATES								
OVERALL (A)	6/68 (9%)	54/69 (78%)	53/70 (76%)	54/67 (81%)	2/69 (3%)	21/68 (31%)	42/68 (62%)	40/68 (59%)
ADJUSTED (B)	14.0%	91.4%	92.8%	94.6%	4.0%	41.0%	83.9%	72.5%
INTERIM NECROPSY 1 (C)	0/10 (0%)	3/9 (33%)	4/10 (40%)	5/10 (50%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	1/10 (10%)
FINAL (D)	6/43 (14%)	43/48 (90%)	39/43 (91%)	43/46 (93%)	2/50 (4%)	19/49 (39%)	40/48 (83%)	33/48 (69%)
FIRST INCIDENCE (DAYS)	725 (T)	359	368 (I)	368 (I)	739 (T)	643	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Eosinophilic Globules, Olfactory Epithelium								
LESION RATES								
OVERALL (A)	7/68 (10%)	50/69 (72%)	58/70 (83%)	60/67 (90%)	41/69 (59%)	59/68 (87%)	59/68 (87%)	61/68 (90%)
ADJUSTED (B)	16.3%	87.5%	98.3%	96.7%	77.3%	100.0%	100.0%	98.4%
INTERIM NECROPSY 1 (C)	0/10 (0%)	3/9 (33%)	6/10 (60%)	9/10 (90%)	0/10 (0%)	2/10 (20%)	3/10 (30%)	7/10 (70%)
FINAL (D)	7/43 (16%)	41/48 (85%)	42/43 (98%)	44/46 (96%)	38/50 (76%)	49/49 (100%)	48/48 (100%)	47/48 (98%)
FIRST INCIDENCE (DAYS)	725 (T)	359	368 (I)	368 (I)	656	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **
Nose 4 Eosinophilic Globules, Respiratory Epithelium								
LESION RATES								
OVERALL (A)	14/68 (21%)	55/69 (80%)	56/70 (80%)	62/67 (93%)	48/69 (70%)	61/68 (90%)	60/68 (88%)	64/68 (94%)
ADJUSTED (B)	26.5%	90.1%	93.2%	100.0%	85.6%	100.0%	100.0%	100.0%
INTERIM NECROPSY 1 (C)	4/10 (40%)	4/9 (44%)	9/10 (90%)	9/10 (90%)	2/10 (20%)	5/10 (50%)	3/10 (30%)	9/10 (90%)
FINAL (D)	8/43 (19%)	42/48 (88%)	39/43 (91%)	46/46 (100%)	42/50 (84%)	49/49 (100%)	48/48 (100%)	48/48 (100%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.001 **	P=0.003 **	P=0.004 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.003 **	P=0.006 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Epithelial Microabscess(es)								
LESION RATES								
OVERALL (A)	0/68 (0%)	5/69 (7%)	0/70 (0%)	1/67 (1%)	3/69 (4%)	1/68 (1%)	2/68 (3%)	1/68 (1%)
ADJUSTED (B)	0.0%	10.0%	0.0%	2.2%	6.0%	2.0%	3.5%	1.8%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	0/10 (0%)
FINAL (D)	0/43 (0%)	4/48 (8%)	0/43 (0%)	1/46 (2%)	3/50 (6%)	1/49 (2%)	1/48 (2%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	634	---	725 (T)	739 (T)	739 (T)	367 (I)	615
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.823	P=0.045 *	(E)	P=0.513	P=0.853	P=0.934	P=0.808	P=0.931
INCIDENTAL TUMOR	P=0.836	P=0.029 *	(E)	P=0.513	P=0.848	P=0.934	P=0.808	P=0.931
LOGISTIC REGRESSION	P=0.816	P=0.036 *	(E)	P=0.513	P=0.857	P=0.934	P=0.814	P=0.932
COCHRAN-ARMITAGE	P=0.816				P=0.857			
FISHER EXACT		P=0.030 *	(E)	P=0.496		P=0.938	P=0.813	P=0.938
Nose 4 Goblet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	8/68 (12%)	61/69 (88%)	61/70 (87%)	59/67 (88%)	10/69 (14%)	36/68 (53%)	57/68 (84%)	59/68 (87%)
ADJUSTED (B)	17.0%	100.0%	100.0%	96.6%	18.7%	67.4%	100.0%	96.6%
INTERIM NECROPSY 1 (C)	1/10 (10%)	6/9 (67%)	9/10 (90%)	9/10 (90%)	1/10 (10%)	3/10 (30%)	5/10 (50%)	9/10 (90%)
FINAL (D)	6/43 (14%)	48/48 (100%)	43/43 (100%)	44/46 (96%)	8/50 (16%)	32/49 (65%)	48/48 (100%)	46/48 (96%)
FIRST INCIDENCE (DAYS)	368 (I)	359	151	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 **Hemorrhage**								
LESION RATES								
OVERALL (A)	0/68 (0%)	1/69 (1%)	3/70 (4%)	0/67 (0%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	2.0%	5.4%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	0/48 (0%)	1/43 (2%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	681	151	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.743	P=0.504	P=0.122	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.654	P=0.406	P=0.377	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.750	P=0.503	P=0.181	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.743				(E)			
FISHER EXACT		P=0.504	P=0.128	(E)		(E)	(E)	(E)
Nose 4 **Inflammation, Acute, Nasolacrimal Duct**								
LESION RATES								
OVERALL (A)	3/68 (4%)	2/69 (3%)	1/70 (1%)	0/67 (0%)	1/69 (1%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	5.9%	3.7%	2.3%	0.0%	1.9%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	0/48 (0%)	1/43 (2%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	551	642	725 (T)	---	708	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.980	P=0.827	P=0.929	(E)	P=0.963	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.980	P=0.673	P=0.918	(E)	P=0.969	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.981	P=0.779	P=0.937	(E)	P=0.965	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.981				P=0.965			
FISHER EXACT		P=0.822	P=0.944	P=1.000		P=1.000	P=1.000	P=1.000

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Inflammation, Subacute								
LESION RATES								
OVERALL (A)	39/68 (57%)	58/69 (84%)	54/70 (77%)	60/67 (90%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	71.3%	95.0%	100.0%	96.7%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	4/10 (40%)	7/9 (78%)	1/10 (10%)	9/10 (90%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	28/43 (65%)	45/48 (94%)	43/43 (100%)	44/46 (96%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.005 **	P=0.006 **	P=0.007 **	P=0.001 **	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P=0.002 **	P<0.001 **	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P=0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P<0.001 **				(E)			
FISHER EXACT		P<0.001 **	P=0.011 *	P<0.001 **		(E)	(E)	(E)
Nose 4 Inspissated Mucus								
LESION RATES								
OVERALL (A)	0/68 (0%)	7/69 (10%)	6/70 (9%)	1/67 (1%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	13.6%	12.6%	1.9%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	0/43 (0%)	5/48 (10%)	4/43 (9%)	0/46 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	461	368 (I)	629	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.820	P=0.014 *	P=0.020 *	P=0.511	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.816	P=0.009 **	P=0.017 *	P=0.531	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.809	P=0.010 *	P=0.019 *	P=0.496	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.808				(E)			
FISHER EXACT		P=0.007 **	P=0.015 *	P=0.496		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Mineralized Concretion(s)								
LESION RATES								
OVERALL (A)	3/68 (4%)	0/69 (0%)	1/70 (1%)	6/67 (9%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	7.0%	0.0%	2.3%	13.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	3/43 (7%)	0/48 (0%)	1/43 (2%)	6/46 (13%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	725 (T)	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.033 *	(E)	P=0.937	P=0.276	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.033 *	(E)	P=0.937	P=0.276	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.033 *	(E)	P=0.937	P=0.276	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.028 *				(E)			
FISHER EXACT		P=1.000	P=0.944	P=0.239		(E)	(E)	(E)
Nose 4 Mucopurulent Exudate								
LESION RATES								
OVERALL (A)	1/68 (1%)	3/69 (4%)	1/70 (1%)	3/67 (4%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	2.3%	5.9%	2.2%	6.1%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	1/43 (2%)	2/48 (4%)	0/43 (0%)	2/46 (4%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	642	711	629	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.340	P=0.342	P=0.760	P=0.330	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.357	P=0.275	P=0.729	P=0.339	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.326	P=0.312	P=0.755	P=0.303	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.323				(E)			
FISHER EXACT		P=0.315	P=0.759	P=0.304		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 4 Subepithelial Mineralization								
LESION RATES								
OVERALL (A)	16/68 (24%)	13/69 (19%)	5/70 (7%)	6/67 (9%)	0/69 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
ADJUSTED (B)	32.1%	24.7%	9.3%	12.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	2/10 (20%)	2/9 (22%)	2/10 (20%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
FINAL (D)	11/43 (26%)	10/48 (21%)	2/43 (5%)	5/46 (11%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.996	P=0.847	P=0.997	P=0.996	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.995	P=0.802	P=0.997	P=0.993	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.995	P=0.811	P=0.998	P=0.994	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.995				(E)			
FISHER EXACT		P=0.811	P=0.999	P=0.995		(E)	(E)	(E)
Nose 5 Eosinophilic Globules, Glandular Epithelium								
LESION RATES								
OVERALL (A)	0/65 (0%)	10/69 (14%)	4/69 (6%)	12/64 (19%)	0/69 (0%)	6/68 (9%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	20.8%	9.5%	27.9%	0.0%	12.2%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	0/40 (0%)	10/48 (21%)	4/42 (10%)	12/43 (28%)	0/50 (0%)	6/49 (12%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	725 (T)	725 (T)	725 (T)	---	739 (T)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.004 **	P=0.003 **	P=0.070	P<0.001 **	P=0.964	P=0.017 *	(E)	(E)
INCIDENTAL TUMOR	P=0.004 **	P=0.003 **	P=0.070	P<0.001 **	P=0.964	P=0.017 *	(E)	(E)
LOGISTIC REGRESSION	P=0.004 **	P=0.003 **	P=0.070	P<0.001 **	P=0.964	P=0.017 *	(E)	(E)
COCHRAN-ARMITAGE	P=0.003 **				P=0.965			
FISHER EXACT		P<0.001 **	P=0.067	P<0.001 **		P=0.013 *	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Eosinophilic Globules, Olfactory Epithelium								
LESION RATES								
OVERALL (A)	47/65 (72%)	62/69 (90%)	62/69 (90%)	57/64 (89%)	36/69 (52%)	49/68 (72%)	58/67 (87%)	64/68 (94%)
ADJUSTED (B)	81.7%	98.4%	100.0%	98.2%	63.0%	77.3%	93.4%	98.4%
INTERIM NECROPSY 1 (C)	6/10 (60%)	7/9 (78%)	9/10 (90%)	8/10 (80%)	1/10 (10%)	9/10 (90%)	8/9 (89%)	9/10 (90%)
FINAL (D)	30/40 (75%)	47/48 (98%)	42/42 (100%)	42/43 (98%)	29/50 (58%)	35/49 (71%)	44/48 (92%)	47/48 (98%)
FIRST INCIDENCE (DAYS)	368 (I)	368 (I)	368 (I)	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.209	P=0.097	P=0.016 *	P=0.135	P<0.001 **	P=0.020 *	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P=0.041 *	P=0.001 **	P=0.001 **	P=0.013 *	P<0.001 **	P=0.014 *	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P=0.034 *	P=0.007 **	P=0.003 **	P=0.014 *	P<0.001 **	P=0.013 *	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P=0.040 *				P<0.001 **			
FISHER EXACT		P=0.008 **	P=0.008 **	P=0.014 *		P=0.013 *	P<0.001 **	P<0.001 **
Nose 5 Eosinophilic Globules, Respiratory Epithelium								
LESION RATES								
OVERALL (A)	5/65 (8%)	49/69 (71%)	50/69 (72%)	46/64 (72%)	6/69 (9%)	18/68 (26%)	35/67 (52%)	38/68 (56%)
ADJUSTED (B)	12.5%	85.7%	98.1%	88.1%	12.0%	35.1%	62.1%	68.8%
INTERIM NECROPSY 1 (C)	0/10 (0%)	3/9 (33%)	3/10 (30%)	5/10 (50%)	0/10 (0%)	0/10 (0%)	2/9 (22%)	2/10 (20%)
FINAL (D)	5/40 (13%)	40/48 (83%)	40/42 (95%)	37/43 (86%)	6/50 (12%)	16/49 (33%)	27/48 (56%)	31/48 (65%)
FIRST INCIDENCE (DAYS)	725 (T)	359	368 (I)	368 (I)	739 (T)	537	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.005 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.006 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.005 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P<0.001 **			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P=0.005 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Foreign Body (Hair Shaft)								
LESION RATES								
OVERALL (A)	1/65 (2%)	0/69 (0%)	0/69 (0%)	2/64 (3%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	2.5%	0.0%	0.0%	3.7%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	1/40 (3%)	0/48 (0%)	0/42 (0%)	1/43 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.212	(E)	(E)	P=0.517	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.212	(E)	(E)	P=0.517	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.196	(E)	(E)	P=0.493	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.198				(E)			
FISHER EXACT		P=1.000	P=1.000	P=0.494		(E)	(E)	(E)
Nose 5 Goblet Cell Hyperplasia								
LESION RATES								
OVERALL (A)	5/65 (8%)	45/69 (65%)	38/69 (55%)	39/64 (61%)	1/69 (1%)	13/68 (19%)	19/67 (28%)	14/68 (21%)
ADJUSTED (B)	11.3%	81.7%	76.7%	84.6%	2.0%	25.3%	37.8%	26.4%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/9 (0%)	4/10 (40%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	1/10 (10%)
FINAL (D)	4/40 (10%)	38/48 (79%)	31/42 (74%)	36/43 (84%)	1/50 (2%)	11/49 (22%)	17/48 (35%)	10/48 (21%)
FIRST INCIDENCE (DAYS)	368 (I)	359	368 (I)	368 (I)	739 (T)	537	599	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.013 *	P<0.001 **	P<0.001 **	P<0.001 **
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.014 *	P=0.001 **	P<0.001 **	P<0.001 **
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	P=0.012 *	P<0.001 **	P<0.001 **	P<0.001 **
COCHRAN-ARMITAGE	P<0.001 **				P=0.015 *			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		P<0.001 **	P<0.001 **	P<0.001 **

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 **Hemorrhage**								
LESION RATES								
OVERALL (A)	0/65 (0%)	0/69 (0%)	3/69 (4%)	0/64 (0%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	5.5%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	0/40 (0%)	0/48 (0%)	1/42 (2%)	0/43 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	368 (I)	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.663	(E)	P=0.126	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.626	(E)	P=0.199	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.657	(E)	P=0.159	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.653				(E)			
FISHER EXACT		(E)	P=0.134	(E)		(E)	(E)	(E)
Nose 5 **Inflammation, Subacute**								
LESION RATES								
OVERALL (A)	8/65 (12%)	28/69 (41%)	27/69 (39%)	36/64 (56%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	18.0%	57.1%	59.7%	69.7%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/9 (0%)	0/10 (0%)	3/10 (30%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	6/40 (15%)	27/48 (56%)	24/42 (57%)	28/43 (65%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	681	474	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P<0.001 **	P<0.001 **	P<0.001 **	P<0.001 **	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P<0.001 **				(E)			
FISHER EXACT		P<0.001 **	P<0.001 **	P<0.001 **		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Inflammation, Tooth								
LESION RATES								
OVERALL (A)	0/65 (0%)	0/69 (0%)	0/69 (0%)	0/64 (0%)	0/69 (0%)	1/68 (1%)	2/67 (3%)	0/68 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%	4.2%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	0/40 (0%)	0/48 (0%)	0/42 (0%)	0/43 (0%)	0/50 (0%)	1/49 (2%)	2/48 (4%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	739 (T)	739 (T)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	P=0.775	P=0.496	P=0.230	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	P=0.775	P=0.496	P=0.230	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	P=0.775	P=0.496	P=0.230	(E)
COCHRAN-ARMITAGE	(E)				P=0.780			
FISHER EXACT		(E)	(E)	(E)		P=0.496	P=0.241	(E)
Nose 5 Mucopurulent Exudate								
LESION RATES								
OVERALL (A)	3/65 (5%)	1/69 (1%)	2/69 (3%)	0/64 (0%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	6.6%	2.1%	4.5%	0.0%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	1/40 (3%)	1/48 (2%)	1/42 (2%)	0/43 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	703	725 (T)	711	---	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.965	P=0.948	P=0.818	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.952	P=0.921	P=0.778	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.965	P=0.948	P=0.822	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.965				(E)			
FISHER EXACT		P=0.947	P=0.835	P=1.000		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose 5 Periodontitis								
LESION RATES								
OVERALL (A)	1/65 (2%)	0/69 (0%)	0/69 (0%)	2/64 (3%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	2.5%	0.0%	0.0%	4.7%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	1/40 (3%)	0/48 (0%)	0/42 (0%)	2/43 (5%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.207	(E)	(E)	P=0.525	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=0.207	(E)	(E)	P=0.525	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=0.207	(E)	(E)	P=0.525	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=0.198				(E)			
FISHER EXACT		P=1.000	P=1.000	P=0.494		(E)	(E)	(E)
Nose 5 Subepithelial Mineralization								
LESION RATES								
OVERALL (A)	55/65 (85%)	59/69 (86%)	51/69 (74%)	38/64 (59%)	0/69 (0%)	0/68 (0%)	0/67 (0%)	0/68 (0%)
ADJUSTED (B)	94.6%	89.3%	84.6%	72.2%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	8/10 (80%)	8/9 (89%)	6/10 (60%)	3/10 (30%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/10 (0%)
FINAL (D)	37/40 (93%)	41/48 (85%)	33/42 (79%)	29/43 (67%)	0/50 (0%)	0/49 (0%)	0/48 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	345	368 (I)	368 (I)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	P=1.000	P=0.738	P=0.857	P=1.000	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	P=1.000	P=0.470	P=0.914	P=1.000	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	P=1.000	P=0.541	P=0.941	P=1.000	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	P=1.000				(E)			
FISHER EXACT		P=0.538	P=0.959	P=1.000		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Nose, 1 and 2 Cage Contaminant Associated Lesion								
LESION RATES								
OVERALL (A)	56/66 (85%)	64/69 (93%)	64/67 (96%)	56/66 (85%)	49/68 (72%)	56/68 (82%)	52/67 (78%)	58/68 (85%)
ADJUSTED (B)	94.7%	98.4%	96.9%	93.1%	82.6%	87.3%	83.5%	90.5%
INTERIM NECROPSY 1 (C)	9/10 (90%)	8/9 (89%)	9/10 (90%)	8/10 (80%)	8/10 (80%)	9/10 (90%)	9/9 (100%)	10/10 (100%)
FINAL (D)	39/42 (93%)	47/48 (98%)	41/43 (95%)	41/45 (91%)	39/49 (80%)	41/49 (84%)	37/47 (79%)	42/48 (88%)
FIRST INCIDENCE (DAYS)	368 (I)	345	151	368 (I)	367 (I)	367 (I)	367 (I)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.838	P=0.346	P=0.121	P=0.786	P=0.057	P=0.115	P=0.182	P=0.031 *
INCIDENTAL TUMOR	P=0.765	P=0.070	P=0.049 *	P=0.606	P=0.056	P=0.112	P=0.226	P=0.030 *
LOGISTIC REGRESSION	P=0.790	P=0.175	P=0.042 *	P=0.651	P=0.076	P=0.111	P=0.292	P=0.044 *
COCHRAN-ARMITAGE	P=0.778				P=0.077			
FISHER EXACT		P=0.117	P=0.036 *	P=0.596		P=0.110	P=0.293	P=0.046 *
Optic Nerve Gliosis								
LESION RATES								
OVERALL (A)	(G)				0/66 (0%)	0/3 (0%)	0/5 (0%)	2/66 (3%)
ADJUSTED (B)					0.0%	0.0%	0.0%	4.3%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)					0/47 (0%)	0/2 (0%)	0/2 (0%)	2/46 (4%)
FIRST INCIDENCE (DAYS)					---	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.234
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.234
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.234
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.248

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Ovary								
Cyst(s)								
LESION RATES								
OVERALL (A)	(G)				15/69 (22%)	8/28 (29%)	10/17 (59%)	13/70 (19%)
ADJUSTED (B)					28.4%	25.4%	73.8%	24.9%
INTERIM NECROPSY 1 (C)					1/10 (10%)	3/4 (75%)	0/2 (0%)	1/10 (10%)
FINAL (D)					13/50 (26%)	5/23 (22%)	8/11 (73%)	10/48 (21%)
FIRST INCIDENCE (DAYS)					367 (I)	367 (I)	661	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.694
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.728
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.734
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.751
Pancreas								
Atrophy, Acinar Cells								
LESION RATES								
OVERALL (A)	27/67 (40%)	2/4 (50%)	0/3 (0%)	19/67 (28%)	8/69 (12%)	0/1 (0%)	0/1 (0%)	9/70 (13%)
ADJUSTED (B)	52.8%	34.7%	0.0%	38.3%	15.2%	0.0%	0.0%	17.9%
INTERIM NECROPSY 1 (C)	3/10 (30%)	0/0	0/0	1/10 (10%)	1/10 (10%)	0/0	0/0	1/10 (10%)
FINAL (D)	20/43 (47%)	1/3 (33%)	0/1 (0%)	16/46 (35%)	7/50 (14%)	0/0	0/1 (0%)	8/48 (17%)
FIRST INCIDENCE (DAYS)	368 (I)	681	---	368 (I)	367 (I)	---	---	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.968	(E)	(E)	(E)	P=0.468
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.941	(E)	(E)	(E)	P=0.468
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.953	(E)	(E)	(E)	P=0.499
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.949		(E)	(E)	P=0.513

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pancreas Cellular Change, Acinar Cells								
LESION RATES								
OVERALL (A)	1/67 (1%)	0/4 (0%)	0/3 (0%)	2/67 (3%)	0/69 (0%)	0/1 (0%)	0/1 (0%)	0/70 (0%)
ADJUSTED (B)	2.3%	0.0%	0.0%	4.3%	0.0%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	1/43 (2%)	0/3 (0%)	0/1 (0%)	2/46 (4%)	0/50 (0%)	0/0	0/1 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)	---	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.524	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.500		(E)	(E)	(E)
Pancreas Inflammation, Subacute								
LESION RATES								
OVERALL (A)	6/67 (9%)	1/4 (25%)	0/3 (0%)	8/67 (12%)	1/69 (1%)	0/1 (0%)	0/1 (0%)	1/70 (1%)
ADJUSTED (B)	13.2%	2.0%	0.0%	16.7%	2.0%	0.0%	0.0%	2.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	5/43 (12%)	0/3 (0%)	0/1 (0%)	7/46 (15%)	1/50 (2%)	0/0	0/1 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	551	681	---	573	739 (T)	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.435	(E)	(E)	(E)	P=0.752
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.453	(E)	(E)	(E)	P=0.752
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.394	(E)	(E)	(E)	P=0.752
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.389		(E)	(E)	P=0.755

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pancreas Mononuclear Cells								
LESION RATES								
OVERALL (A)	7/67 (10%)	0/4 (0%)	0/3 (0%)	2/67 (3%)	(G)			
ADJUSTED (B)	12.4%	0.0%	0.0%	4.3%				
INTERIM NECROPSY 1 (C)	4/10 (40%)	0/0	0/0	0/10 (0%)				
FINAL (D)	3/43 (7%)	0/3 (0%)	0/1 (0%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.985				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.985				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.982				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.984				
Pancreas Polyarteritis								
LESION RATES								
OVERALL (A)	1/67 (1%)	3/4 (75%)	0/3 (0%)	0/67 (0%)	(G)			
ADJUSTED (B)	2.3%	100.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	3/3 (100%)	0/1 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.979				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.979				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.979				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Parathyroid Hyperplasia								
LESION RATES								
OVERALL (A)	2/63 (3%)	1/1 (100%)	0/0 (0%)	4/64 (6%)	(G)			
ADJUSTED (B)	4.7%	100.0%	0.0%	8.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/39 (3%)	1/1 (100%)	0/0	4/45 (9%)				
FIRST INCIDENCE (DAYS)	713	725 (T)	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.396				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.340				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.340				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.347				
Pituitary Angiectasis								
LESION RATES								
OVERALL (A)	1/65 (2%)	6/24 (25%)	1/14 (7%)	2/67 (3%)	4/69 (6%)	10/35 (29%)	6/30 (20%)	4/67 (6%)
ADJUSTED (B)	2.0%	23.8%	9.1%	4.3%	8.0%	31.1%	26.1%	8.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	1/1 (100%)	0/1 (0%)	0/10 (0%)	0/10 (0%)	1/1 (100%)	0/3 (0%)	0/10 (0%)
FINAL (D)	0/42 (0%)	4/19 (21%)	1/11 (9%)	2/46 (4%)	4/50 (8%)	8/28 (29%)	6/23 (26%)	3/48 (6%)
FIRST INCIDENCE (DAYS)	702	368 (I)	725 (T)	725 (T)	739 (T)	367 (I)	739 (T)	678
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.516	(E)	(E)	(E)	P=0.617
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.457	(E)	(E)	(E)	P=0.622
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.514	(E)	(E)	(E)	P=0.618
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.511		(E)	(E)	P=0.624

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Pituitary Cyst(s)								
LESION RATES								
OVERALL (A)	8/65 (12%)	0/24 (0%)	1/14 (7%)	3/67 (4%)	8/69 (12%)	6/35 (17%)	6/30 (20%)	12/67 (18%)
ADJUSTED (B)	15.9%	0.0%	2.2%	6.1%	14.1%	19.3%	23.2%	22.1%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/1 (0%)	0/1 (0%)	0/10 (0%)	2/10 (20%)	0/1 (0%)	0/3 (0%)	2/10 (20%)
FINAL (D)	4/42 (10%)	0/19 (0%)	0/11 (0%)	2/46 (4%)	5/50 (10%)	5/28 (18%)	5/23 (22%)	8/48 (17%)
FIRST INCIDENCE (DAYS)	368 (I)	---	711	629	367 (I)	599	683	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.973	(E)	(E)	(E)	P=0.214
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.972	(E)	(E)	(E)	P=0.215
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.974	(E)	(E)	(E)	P=0.215
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.976		(E)	(E)	P=0.213
Pituitary Hemorrhage								
LESION RATES								
OVERALL (A)	2/65 (3%)	0/24 (0%)	0/14 (0%)	0/67 (0%)	0/69 (0%)	0/35 (0%)	1/30 (3%)	0/67 (0%)
ADJUSTED (B)	3.9%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/1 (0%)	0/1 (0%)	0/10 (0%)	0/10 (0%)	0/1 (0%)	1/3 (33%)	0/10 (0%)
FINAL (D)	0/42 (0%)	0/19 (0%)	0/11 (0%)	0/46 (0%)	0/50 (0%)	0/28 (0%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	611	---	---	---	---	---	367 (I)	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=1.000		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

DOSE	MALES 0.0 PPM	MALES 0.4 PPM	MALES 1.0 PPM	MALES 2.5 PPM	FEMALES 0.0 PPM	FEMALES 0.4 PPM	FEMALES 1.0 PPM	FEMALES 2.5 PPM
Pituitary Hyperplasia, Pars Distalis								
LESION RATES								
OVERALL (A)	21/65 (32%)	4/24 (17%)	5/14 (36%)	16/67 (24%)	9/69 (13%)	5/35 (14%)	1/30 (3%)	1/67 (1%)
ADJUSTED (B)	44.8%	21.1%	37.7%	32.0%	16.3%	16.0%	1.6%	2.0%
INTERIM NECROPSY 1 (C)	1/10 (10%)	0/1 (0%)	0/1 (0%)	0/10 (0%)	1/10 (10%)	0/1 (0%)	1/3 (33%)	0/10 (0%)
FINAL (D)	17/42 (40%)	4/19 (21%)	4/11 (36%)	13/46 (28%)	6/50 (12%)	4/28 (14%)	0/23 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	368 (I)	725 (T)	661	573	367 (I)	704	367 (I)	678
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.923	(E)	(E)	(E)	P=0.998
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.931	(E)	(E)	(E)	P=0.998
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.908	(E)	(E)	(E)	P=0.999
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.898		(E)	(E)	P=0.999
Pituitary Pigmentation								
LESION RATES								
OVERALL (A)	1/65 (2%)	0/24 (0%)	0/14 (0%)	3/67 (4%)	(G)			
ADJUSTED (B)	2.4%	0.0%	0.0%	5.6%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/1 (0%)	0/1 (0%)	0/10 (0%)				
FINAL (D)	1/42 (2%)	0/19 (0%)	0/11 (0%)	1/46 (2%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	573				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.329				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.383				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.317				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.321				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Prostate Acinar Cell Hyperplasia								
LESION RATES								
OVERALL (A)	9/66 (14%)	0/0 (0%)	0/0 (0%)	7/64 (11%)	(G)			
ADJUSTED (B)	20.5%	0.0%	0.0%	15.2%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	8/43 (19%)	0/0	0/0	7/46 (15%)				
FIRST INCIDENCE (DAYS)	718	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.831				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.806				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.806				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.768				
Prostate Inflammation, Subacute								
LESION RATES								
OVERALL (A)	33/66 (50%)	0/0 (0%)	0/0 (0%)	28/64 (44%)	(G)			
ADJUSTED (B)	60.2%	0.0%	0.0%	51.8%				
INTERIM NECROPSY 1 (C)	3/10 (30%)	0/0	0/0	3/10 (30%)				
FINAL (D)	22/43 (51%)	0/0	0/0	21/46 (46%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.886				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.808				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.808				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.813				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Prostate Mononuclear Cells								
LESION RATES								
OVERALL (A)	2/66 (3%)	0/0 (0%)	0/0 (0%)	0/64 (0%)	(G)			
ADJUSTED (B)	2.9%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	2/10 (20%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/0	0/0	0/46 (0%)				
FIRST INCIDENCE (DAYS)	368 (I)	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				
Salivary Gland Atrophy								
LESION RATES								
OVERALL (A)	2/68 (3%)	3/5 (60%)	1/1 (100%)	0/68 (0%)	(G)			
ADJUSTED (B)	4.1%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/0	1/1 (100%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	580	461	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Seminal Vesicle Decreased Secretion								
LESION RATES								
OVERALL (A)	41/66 (62%)	34/37 (92%)	20/23 (87%)	24/63 (38%)	(G)			
ADJUSTED (B)	78.7%	94.0%	90.1%	49.7%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	32/43 (74%)	28/30 (93%)	17/19 (89%)	21/45 (47%)				
FIRST INCIDENCE (DAYS)	520	461	636	573				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=1.000				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.999				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=1.000				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.998				
Seminal Vesicle Rupture (Iatrogenic)								
LESION RATES								
OVERALL (A)	0/66 (0%)	0/37 (0%)	0/23 (0%)	2/63 (3%)	(G)			
ADJUSTED (B)	0.0%	0.0%	0.0%	2.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	2/10 (20%)				
FINAL (D)	0/43 (0%)	0/30 (0%)	0/19 (0%)	0/45 (0%)				
FIRST INCIDENCE (DAYS)	---	---	---	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.234				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.234				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.234				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.237				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Skin/Lesion								
Abscess(es)								
LESION RATES								
OVERALL (A)	2/2 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	(G)			
ADJUSTED (B)	100.0%	0.0%	100.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0 (0%)	0/0	0/0	0/0				
FINAL (D)	1/1 (100%)	0/0	1/1 (100%)	0/0				
FIRST INCIDENCE (DAYS)	703	---	725 (T)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Spleen								
Accessory Spleen								
LESION RATES								
OVERALL (A)	0/67 (0%)	0/17 (0%)	0/19 (0%)	0/68 (0%)	0/69 (0%)	3/11 (27%)	0/13 (0%)	0/70 (0%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	0.0%	34.4%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	1/1 (100%)	0/0	0/10 (0%)
FINAL (D)	0/43 (0%)	0/10 (0%)	0/11 (0%)	0/46 (0%)	0/50 (0%)	2/6 (33%)	0/6 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	---	---	---	---	---	367 (I)	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	(E)

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen Congestion								
LESION RATES								
OVERALL (A)	0/67 (0%)	2/17 (12%)	7/19 (37%)	0/68 (0%)	(G)			
ADJUSTED (B)	0.0%	20.0%	55.6%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	2/10 (20%)	6/11 (55%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	---	725 (T)	718	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Spleen Fibrosis								
LESION RATES								
OVERALL (A)	2/67 (3%)	3/17 (18%)	0/19 (0%)	4/68 (6%)	(G)			
ADJUSTED (B)	4.7%	30.0%	0.0%	7.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	2/43 (5%)	3/10 (30%)	0/11 (0%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	725 (T)	725 (T)	---	584				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.365				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.350				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.346				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.347				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Spleen Leukemoid Reaction								
LESION RATES								
OVERALL (A)	2/67 (3%)	0/17 (0%)	0/19 (0%)	0/68 (0%)	(G)			
ADJUSTED (B)	4.0%	0.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/43 (0%)	0/10 (0%)	0/11 (0%)	0/46 (0%)				
FIRST INCIDENCE (DAYS)	660	---	---	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=1.000				
Spleen Pigmentation								
LESION RATES								
OVERALL (A)	56/67 (84%)	12/17 (71%)	16/19 (84%)	59/68 (87%)	58/69 (84%)	3/11 (27%)	6/13 (46%)	55/70 (79%)
ADJUSTED (B)	96.4%	100.0%	92.0%	96.6%	93.4%	34.4%	83.6%	89.9%
INTERIM NECROPSY 1 (C)	10/10 (100%)	0/0	0/0	10/10 (100%)	10/10 (100%)	1/1 (100%)	0/0	10/10 (100%)
FINAL (D)	41/43 (95%)	10/10 (100%)	10/11 (91%)	44/46 (96%)	46/50 (92%)	2/6 (33%)	5/6 (83%)	42/48 (88%)
FIRST INCIDENCE (DAYS)	368 (I)	657	534	368 (I)	262	367 (I)	599	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.603	(E)	(E)	(E)	P=0.713
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.519	(E)	(E)	(E)	P=0.785
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.277	(E)	(E)	(E)	P=0.848
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.391		(E)	(E)	P=0.852

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Stomach								
Inflammation, Chronic								
LESION RATES								
OVERALL (A)	0/68 (0%)	0/5 (0%)	0/3 (0%)	0/68 (0%)	1/69 (1%)	0/1 (0%)	0/1 (0%)	2/70 (3%)
ADJUSTED (B)	0.0%	0.0%	0.0%	0.0%	1.9%	0.0%	0.0%	4.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	0/43 (0%)	0/1 (0%)	0/2 (0%)	0/46 (0%)	0/50 (0%)	0/1 (0%)	0/1 (0%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	---	---	---	---	708	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.477
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.491
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)	(E)	(E)	(E)	P=0.491
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	(E)		(E)	(E)	P=0.505
Stomach								
Ulcer(s), Forestomach								
LESION RATES								
OVERALL (A)	3/68 (4%)	1/5 (20%)	0/3 (0%)	1/68 (1%)	2/69 (3%)	0/1 (0%)	0/1 (0%)	0/70 (0%)
ADJUSTED (B)	6.6%	2.0%	0.0%	1.9%	3.9%	0.0%	0.0%	0.0%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	1/43 (2%)	0/1 (0%)	0/2 (0%)	0/46 (0%)	1/50 (2%)	0/1 (0%)	0/1 (0%)	0/48 (0%)
FIRST INCIDENCE (DAYS)	713	716	---	629	713	---	---	---
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.939	(E)	(E)	(E)	(E)
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.915	(E)	(E)	(E)	(E)
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.937	(E)	(E)	(E)	(E)
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.940		(E)	(E)	P=1.000

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Subcutaneous Tissue								
Granulomatous Fat Necrosis								
LESION RATES								
OVERALL (A)	2/7 (29%)	0/2 (0%)	2/4 (50%)	0/0 (0%)	(G)			
ADJUSTED (B)	26.7%	0.0%	3.7%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	1/1 (100%)	0/0				
FINAL (D)	1/4 (25%)	0/2 (0%)	0/2 (0%)	0/0				
FIRST INCIDENCE (DAYS)	713	---	368 (I)	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				
Testis								
Interstitial Cell Hyperplasia								
LESION RATES					(G)			
OVERALL (A)	11/68 (16%)	5/59 (8%)	6/47 (13%)	15/67 (22%)				
ADJUSTED (B)	17.2%	9.1%	13.8%	25.9%				
INTERIM NECROPSY 1 (C)	5/10 (50%)	1/1 (100%)	0/0	5/10 (50%)				
FINAL (D)	1/43 (2%)	2/47 (4%)	4/39 (10%)	7/46 (15%)				
FIRST INCIDENCE (DAYS)	368 (I)	359	534	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.148	P=0.753	P=0.574	P=0.280				
INCIDENTAL TUMOR	P=0.077	P=0.760	P=0.373	P=0.169				
LOGISTIC REGRESSION	P=0.107	P=0.705	P=0.267	P=0.192				
COCHRAN-ARMITAGE	P=0.071							
FISHER EXACT		P=0.944	P=0.779	P=0.243				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Testis								
Tubular Atrophy/Degeneration								
LESION RATES								
OVERALL (A)	12/68 (18%)	14/59 (24%)	10/47 (21%)	11/67 (16%)	(G)			
ADJUSTED (B)	22.1%	25.5%	23.7%	20.3%				
INTERIM NECROPSY 1 (C)	3/10 (30%)	1/1 (100%)	0/0	2/10 (20%)				
FINAL (D)	6/43 (14%)	8/47 (17%)	8/39 (21%)	6/46 (13%)				
FIRST INCIDENCE (DAYS)	368 (I)	359	534	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.796	P=0.217	P=0.429	P=0.709				
INCIDENTAL TUMOR	P=0.694	P=0.205	P=0.327	P=0.626				
LOGISTIC REGRESSION	P=0.780	P=0.120	P=0.235	P=0.659				
COCHRAN-ARMITAGE	P=0.747							
FISHER EXACT		P=0.265	P=0.400	P=0.662				
Testis								
Tubular Mineralization								
LESION RATES								
OVERALL (A)	26/68 (38%)	24/59 (41%)	17/47 (36%)	24/67 (36%)	(G)			
ADJUSTED (B)	50.9%	46.5%	39.8%	44.2%				
INTERIM NECROPSY 1 (C)	3/10 (30%)	0/1 (0%)	0/0	3/10 (30%)				
FINAL (D)	19/43 (44%)	20/47 (43%)	14/39 (36%)	17/46 (37%)				
FIRST INCIDENCE (DAYS)	368 (I)	359	634	368 (I)				
STATISTICAL TESTS (F)								
LIFE TABLE	P=0.747	P=0.668	P=0.848	P=0.768				
INCIDENTAL TUMOR	P=0.715	P=0.601	P=0.732	P=0.690				
LOGISTIC REGRESSION	P=0.687	P=0.553	P=0.769	P=0.685				
COCHRAN-ARMITAGE	P=0.705							
FISHER EXACT		P=0.460	P=0.662	P=0.680				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thymus								
Involution								
LESION RATES								
OVERALL (A)	55/58 (95%)	1/1 (100%)	0/3 (0%)	60/61 (98%)	54/67 (81%)	5/6 (83%)	4/6 (67%)	54/64 (84%)
ADJUSTED (B)	100.0%	0.0%	0.0%	98.3%	94.7%	100.0%	100.0%	100.0%
INTERIM NECROPSY 1 (C)	10/10 (100%)	0/0	0/0	10/10 (100%)	1/10 (10%)	0/0	0/0	2/10 (20%)
FINAL (D)	37/37 (100%)	0/0	0/1 (0%)	43/44 (98%)	47/50 (94%)	4/4 (100%)	4/4 (100%)	46/46 (100%)
FIRST INCIDENCE (DAYS)	368 (I)	642	---	368 (I)	367 (I)	726	739 (T)	367 (I)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.777	(E)	(E)	(E)	P=0.225
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.310	(E)	(E)	(E)	P=0.216
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.288	(E)	(E)	(E)	P=0.219
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.290		(E)	(E)	P=0.368
Thyroid								
C-Cell Hyperplasia								
LESION RATES								
OVERALL (A)	14/67 (21%)	1/2 (50%)	0/1 (0%)	5/66 (8%)	5/69 (7%)	0/2 (0%)	0/7 (0%)	2/69 (3%)
ADJUSTED (B)	31.2%	50.0%	0.0%	10.6%	9.3%	0.0%	0.0%	4.2%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	12/42 (29%)	1/2 (50%)	0/1 (0%)	4/46 (9%)	3/50 (6%)	0/2 (0%)	0/5 (0%)	2/48 (4%)
FIRST INCIDENCE (DAYS)	520	725 (T)	---	696	636	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.996	(E)	(E)	(E)	P=0.929
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.991	(E)	(E)	(E)	P=0.943
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.994	(E)	(E)	(E)	P=0.937
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.994		(E)	(E)	P=0.942

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Thyroid Cystic Follicle(s)								
LESION RATES								
OVERALL (A)	1/67 (1%)	0/2 (0%)	1/1 (100%)	2/66 (3%)	(G)			
ADJUSTED (B)	2.4%	0.0%	100.0%	4.3%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/42 (2%)	0/2 (0%)	1/1 (100%)	2/46 (4%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	725 (T)	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.532				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.532				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.532				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.494				
Tongue Inflammation, Subacute								
LESION RATES								
OVERALL (A)	1/68 (1%)	0/1 (0%)	0/0 (0%)	5/68 (7%)	(G)			
ADJUSTED (B)	2.3%	0.0%	0.0%	10.9%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/0	0/0	5/46 (11%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.120				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.120				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.120				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.104				

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Tongue								
Mineralization, Blood Vessels								
LESION RATES								
OVERALL (A)	1/68 (1%)	0/1 (0%)	0/0 (0%)	3/68 (4%)	(G)			
ADJUSTED (B)	2.3%	0.0%	0.0%	6.5%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	1/43 (2%)	0/0	0/0	3/46 (7%)				
FIRST INCIDENCE (DAYS)	725 (T)	---	---	725 (T)				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.330				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.330				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.330				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.310				
Trachea								
Inflammation, Subacute								
LESION RATES								
OVERALL (A)	9/68 (13%)	0/1 (0%)	0/0 (0%)	13/68 (19%)	0/69 (0%)	0/2 (0%)	0/7 (0%)	1/69 (1%)
ADJUSTED (B)	20.3%	0.0%	0.0%	27.4%	0.0%	0.0%	0.0%	2.1%
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)	0/10 (0%)	0/0	0/0	0/10 (0%)
FINAL (D)	8/43 (19%)	0/0	0/0	12/46 (26%)	0/50 (0%)	0/2 (0%)	0/5 (0%)	1/48 (2%)
FIRST INCIDENCE (DAYS)	703	---	---	584	---	---	---	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.291	(E)	(E)	(E)	P=0.492
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.277	(E)	(E)	(E)	P=0.492
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.277	(E)	(E)	(E)	P=0.492
COCHRAN-ARMITAGE	(E)				(E)			
FISHER EXACT		(E)	(E)	P=0.243		(E)	(E)	P=0.500

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Urinary Bladder								
Seminal Coagulum								
LESION RATES								
OVERALL (A)	0/66 (0%)	0/3 (0%)	0/4 (0%)	3/65 (5%)	(G)			
ADJUSTED (B)	0.0%	0.0%	0.0%	6.0%				
INTERIM NECROPSY 1 (C)	0/10 (0%)	0/0	0/0	0/10 (0%)				
FINAL (D)	0/42 (0%)	0/2 (0%)	0/0	2/46 (4%)				
FIRST INCIDENCE (DAYS)	---	---	---	549				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	P=0.135				
INCIDENTAL TUMOR	(E)	(E)	(E)	P=0.134				
LOGISTIC REGRESSION	(E)	(E)	(E)	P=0.119				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	P=0.119				
Uterus								
Dilatation								
LESION RATES								
OVERALL (A)	(G)				7/69 (10%)	1/29 (3%)	3/19 (16%)	2/70 (3%)
ADJUSTED (B)					13.5%	1.6%	17.0%	4.2%
INTERIM NECROPSY 1 (C)					0/10 (0%)	1/4 (25%)	0/2 (0%)	0/10 (0%)
FINAL (D)					6/50 (12%)	0/23 (0%)	2/13 (15%)	2/48 (4%)
FIRST INCIDENCE (DAYS)					590	367 (I)	683	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.978
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.984
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.980
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.984

TABLE S2b

STATISTICAL ANALYSIS OF NON-NEOPLASTIC LESIONS IN RATS(FISCHER344) -- CHLORINE

	MALES				FEMALES			
DOSE	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM	0.0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
Uterus								
Endometrial Hyperplasia/Cyst(s)								
LESION RATES								
OVERALL (A)	(G)				4/69 (6%)	5/29 (17%)	6/19 (32%)	4/70 (6%)
ADJUSTED (B)					8.0%	21.7%	33.3%	8.3%
INTERIM NECROPSY 1 (C)					0/10 (0%)	0/4 (0%)	0/2 (0%)	0/10 (0%)
FINAL (D)					4/60 (8%)	5/23 (22%)	4/13 (31%)	4/48 (8%)
FIRST INCIDENCE (DAYS)					739 (T)	739 (T)	625	739 (T)
STATISTICAL TESTS (F)								
LIFE TABLE					(E)	(E)	(E)	P=0.621
INCIDENTAL TUMOR					(E)	(E)	(E)	P=0.621
LOGISTIC REGRESSION					(E)	(E)	(E)	P=0.621
COCHRAN-ARMITAGE					(E)			
FISHER EXACT						(E)	(E)	P=0.649
Vas Deferens								
Mineralization								
LESION RATES								
OVERALL (A)	0/0 (0%)	2/2 (100%)	1/1 (100%)	0/1 (0%)	(G)			
ADJUSTED (B)	0.0%	100.0%	0.0%	0.0%				
INTERIM NECROPSY 1 (C)	0/0	0/0	0/0	0/0				
FINAL (D)	0/0	1/1 (100%)	0/0	0/0				
FIRST INCIDENCE (DAYS)	---	681	634	---				
STATISTICAL TESTS (F)								
LIFE TABLE	(E)	(E)	(E)	(E)				
INCIDENTAL TUMOR	(E)	(E)	(E)	(E)				
LOGISTIC REGRESSION	(E)	(E)	(E)	(E)				
COCHRAN-ARMITAGE	(E)							
FISHER EXACT		(E)	(E)	(E)				

APPENDIX T

HEMATOLOGY DETERMINATION METHODOLOGY

TEST NAME	SUPPLIER	REFERENCE
White Blood Cell Count	Coulter	Bessman, J.D. and Johnson, R.K.: Erythrocytes volume distribution in normal and abnormal subjects. Blood 46, 369-379 (1975).
Red Blood	Coulter	Britten, G.M., Brecher, G. and Cell CountJohnson, C.A.: Evaluation of the Coulter Counter Model S. Am. J. Clin. Path. 52, 679-689 (1969).
Hemoglobin	Coulter	Schulz, J. and Thom, R.: Electrical sizing and counting of platelets in whole blood. Medical and Biological Engineering 11, 447-455 (1973).
Hematocrit	Coulter	
Mean Corpuscular Volume	Coulter	
Mean Corpuscular Hemoglobin	Coulter	
Red Cell Distribution Width	Coulter	
Platelets, Thrombocytes	Coulter	
Platelets, Hematocrit	Coulter	
Mean Platelet Volume	Coulter	
Platelet Distribution Width	Coulter	
Lymphocyte Percent	Coulter	
Lymphocyte Absolute	Coulter	

APPENDIX U

CLINICAL CHEMISTRY DETERMINATION METHODOLOGY

TEST NAME	SUPPLIER	REFERENCE
Serum Glucose	Abbott	Richterich, R. and Dauwalder, H.: Determination of Blood Glucose Concentration by the Hexokinase/Glucose-6-Phosphate Method. Schweizerische Medizinische Wochenschrift, 101, 615-618 (1971).
Blood Urea Nitrogen	Abbott	Talke, H. and Schubert, G.E.: Enzymatische Harnstoffbestimmung in Blut und Serum in Optischen Test nuch Warburg. Klinische Wochenschrift, 43, 174-175 (1965).
GGT	Fischer	Szasz, G.: A Kinetic Photometric Method of Serum y-Glutamyl Transpeptidase. Clinical Chemistry, 15, 124-136 (1969).
ALT	Abbott	Bergmeyer, H.U., Scheibe, P. and Wahlefeld, A.W.: Optimization of Methods for Aspartate Aminotransferase and Alanine Aminotransferase. Clinical Chemistry, 24, 58-73 (1978).
AST	Abbott	Bergmeyer, H.U., Scheibe, P. and Wahlefeld, A.W.: Optimization of Methods for Aspartate Aminotransferase and Alanine Aminotransferase. Clinical Chemistry, 24, 58-73 (1978).
Alkaline Phosphatase	Abbott	Bowers, G.N., Jr. and McComb, R.B.: A Continuous Spectrophotometric Method for Measuring the Activity of Serum Alkaline Phosphatase. Clinical Chemistry, 12, 70-89 (1966).
Phosphatase		
Phosphorus	Abbott	Amador, E. and Urban, J.: Simplified Serum Phosphorus Analysis by Continuous-Flow Ultraviolet Spectrophotometry. Clinical Chemistry, 187, 601 (19720.
Total Protein	Abbott	Gornall, R.J., Bardawill, C.J. and David, M.M.: Determination of Serum Proteins by Means of the Biuret Reaction. Journal of Biological Chemistry, 177, 751-766 (1949).

Albumin	Abbott	Doumas, B.T., Watson, W.A. and Bigg, H.G.: Albumin Standards and the Measurement of Serum Albumin with Bromocresol Green. Clinica Chemica Acta, 31, 87-96 (1971).
Bilirubin	Abbott	Malloy, H.T. and Evelyn, K.A.: The Determination of Bilirubin with the Photoelectric Colorimeter. Journal of Biological Chemistry, 119, 481-490 (1937).
Calcium	Abbott	Connerty, H.V. and Briggs, A.R.: Determination of Serum Calcium by Means of Orthocresolphthalein Complexone. American Journal of Clinical Pathology, 45, 290-296 (1966).
Chloride	Manual	Corning 920--Direct Reading Digital Chloride Meter Instrument Manual. Tietz, Fundamentals of Clinical Chemistry.

APPENDIX V

SUMMARY OF RETROSPECTIVE AUDIT/QUALITY ASSURANCE REVIEWS ON STUDIES, 8437, 8436 AND 8321

SUMMARY OF
RETROSPECTIVE AUDIT/QUALITY ASSURANCE REVIEWS
ON STUDIES 8437, 8436 and 8321

Study Title: A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats

Protocol Numbers: 8437, 8436 and 8321

I. Research Triangle Institute (RTI)

An independent retrospective audit of the raw data, study records, and final report was conducted by a contract laboratory, Research Triangle Institute (RTI), Research Triangle Park, NC, for CIIT. RTI's Retrospective Audit Statement is included in Appendix W. Their conclusion was that (1) the above mentioned study was not conducted in compliance with US EPAs TSCA Good Laboratory Practice regulations; (2) the results and methods presented in the final report are consistent with the study records and raw data, and (3) the study records allow reconstruction of the conduct of the study.

II. Experimental Pathology Laboratories (EPL)

Tissues from this study were submitted to a contract laboratory, Experimental Pathology Laboratories, Inc. (EPL), Research Triangle Park, NC, for histopathological evalution for CIIT. Various phases of their histopathology work were inspected by EPLs Quality Assurance Unit. The dates of EPLs inspections and the dates that findings were reported to the EPL Study Director and Management are listed on the EPL Quality Assurance Final Certification sheets, a copy of which is included in Appendix W.

III. Pathology Associates, Inc.

Pathology Associates, Inc., Fredrick, MD, a contract laboratory, conducted an independent quality assurance pathology review for CIIT. The quality assurance pathology review (Appendix X) consisted of 1) a complete review of all slides from a 20% of the animals in the high dose and control groups, 2) Validation of compound-related lesions from selected target organs of all animals, 3) correlation of gross/microscopic diagnosis, 4) conduct a peer review, with resolution of any discrepancies that impacted on the interpretation of the study.

SUMMARY OF
RETROSPECTIVE AUDIT/QUALITY ASSURANCE REVIEWS
ON STUDIES 8437, 8436 and 8321

IV. Chemical Industry Institute of Toxicology (CIIT)

The CIIT Report Quality Assurance Coordinator activities, from December, 1990, involved providing archival storage and retrieval of raw data and specimens and managing the performance of the RTI retrospective quality assurance audit of the raw data, study records and final report. The CIIT Quality Assurance Coordinator also acted as a coordinator between RTI personnel and CIIT study personnel during the preparation of the final report.

Although this study was not conducted in compliance with US EPAs TSCA Good Laboratory Practice regulations, the conduct of the study was subjected to periodic Quality Assurance (QA) inspections during 1983-1986 by former CIIT QA Specialist, Garris D. Parker, Jr. The dates of CIITs QA inspections and the dates that findings were reported to CIITs Study Director and Managment are listed in Appendix Y.

V. CIITs Study Director's Statement

To the best of my knowledge, I agree with the above referenced retrospective audit and Quality Assurance Statements, inculding RTIs assessment that the results and methods presented in the final report are consistent with the raw data, and that the study records allow reconstruction of the conduct of the study.

Study Director: James A. Popp — Dec 31, 1993

James A. Popp, D.V.M., Ph.D
Study Director - CIIT

Date

APPENDIX W

RESEARCH TRIANGLE INSTITUTE

RETROSPECTIVE AUDIT STATEMENT

AND

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION SHEETS

ON STUDIES 8437, 8436 and 8321

RTI Retrospective Audit Statement

Title:	A CHRONIC INHALATION TOXICITY STUDY OF CHLORINE IN FEMALE AND MALE B6C3F1 MICE AND FISCHER 344 RATS
SPONSOR:	Chemical Industry Institue of Toxicology P.O. Box 12137 Research Triangle Park, North Carolina 27709
Study Code No.:	CIIT Protocol Numbers: #8321 (Male Rats), 8436 (Female Rats) and 8437 (Male and Female Mice)
Study Director:	James A. Popp, D.V.M., Ph.D.
Audit Performed by:	Research Triangle Institute P.O. Box 12194 Research Triangle Park, North Carolina 27709

Research Triangle Institute (RTI) was contracted by CIIT to perform an independent retrospective audit of the raw data, study records, manuscript, and final report from the chlorine chronic inhalation toxicity study. An audit team of eight quality assurance specialists and scientists performed this audit from October, 1992 through December, 1993. The draft pathology review report was submitted on December 7, 1992 and will be included in the final audit report. The initial raw data findings were submitted with the initial manuscript audit report on February 15, 1993. CIIT responded to the audit findings and a follow-up audit was conducted by RTI. The final report audit was initiated in June 1993. Throughout the audit period, RTI worked closely with CIIT staff to resolve findings and clarify issues. Final report and data audit findings were submitted to CIIT in November, 1993.

RTI concluded that the chlorine chronic inhalation study was not conducted in compliance with the Environmental Protection Agency TSCA GLPs, primarily in the areas of the GLP requirements for recordkeeping,

error corrections, data completeness, and the role of the QAU. As part of the audit findings, RTI made recommendations that would improve the audit trail and the ability to reconstruct the study events from the study records. Final CIIT responses to the report and data audit findings were received by RTI on December 13, 1993. Throughout the audit, CIIT responded with considerable additional documentation and clarification of the study records, and extensive clarification in the final report, including a section on problems encountered in the study and a discussion of the impact on the quality and integrity of the results. In a final follow-up audit, RTI verified the remedial actions.

The RTI audit team concludes that the results and methods presented in the final report are consistent with the study records and raw data, and that the study records allow reconstruction of the conduct of the study.

Stephanie M. Taulbee 12/28/93

Stephanie M. Taulbee, B.S.
Task Leader
Research Triangle Institute

Karen Gold 12/28/93

Karen Gold, Ph.D.
Contract Manager
Research Triangle Institute

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Risk Assessment Study of Chlorine in Rats

Client Study: Study Number 8436 EPL Project Coordinator: Dr. Hardisty

EPL Project Number: 304-337 EPL Pathologist: Dr. Proctor

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	December 31, 1987; March 28, 1988; April 5, 1988	December 31, 1987; March 28, 1988; April 5, 1988
Project Setup	January 8, 1988	January 8, 1988
Histology Setup	January 8, 1988	January 8, 1988
Histology Complete	January 13, 1988	January 13, 1988
Rough Draft Report	July 12, 1988	July 12, 1988
Final Report	June 10, 1992	June 10, 1992
Other		

Date of last quarterly facility inspection April, 1992

This study is certified to have been performed in compliance with the appropriate Good Laboratory Practice regulations.

Jane Hanson
EPL Quality Assurance Unit

June 10, 1992
Date

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Risk Assessment Study of Chlorine in Mice

Client Study: Study Number 8437 EPL Project Coordinator: Dr. Hardisty

EPL Project Number: 304-338 EPL Pathologist: Dr. Riley

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Study Director and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	March 28, 1988; July 15, 1988; August 9, 1988; January 4, 1989; March 30, 1989; May 18, 1989	March 28, 1988; July 15, 1988; August 9, 1988; January 4, 1989; March 30, 1989; May 18, 1989
Project Setup	March 9, 1989	March 9, 1989
Histology Setup	August 30, 1988; March 1, 1989	August 30, 1988; March 1, 1989
Histology Complete	August 9, 1988; September 9, 1988; November 21, 1988; December 6, 1988; January 3, 1989	August 9, 1988; September 9, 1988; November 21, 1988; December 6, 1988; January 3, 1989
Rough Draft Report	May 10,12,19,25, 1989	May 10,12,19,25, 1989
Final Report	April 28, 1992	April 28, 1992
Other		

Date of last quarterly facility inspection April, 1992

This study is certified to have been performed in compliance with the appropriate Good Laboratory Practice regulations.

Jane Hansen
EPL Quality Assurance Unit

April 28, 1992
Date

Form No. 28 (Revised 2/91)

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Risk Assessment Study of Chlorine in Rats

Client Study: 8321

EPL Project Coordinator: Dr. Jerry Hardisty

EPL Project Number: 304-332

EPL Pathologist: Dr. Marilyn Wolfe

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	9/18/87; 10/20/87; 11/2/87	9/18/87; 10/20/87; 11/2/87
Project Setup	10/14, 22/87; 12/29/87	10/14, 22/87; 12/29/87
Histology Setup	10/22/87	10/22/87
Histology Complete	12/10/87	12/10/87
Rough Draft Report	12/28, 29/87; 5/3-6, 9/88; 6/8, 9, 14, 15, 17, 27/88	12/28, 29/87; 5/3-6, 9/88; 6/8, 9, 14, 15, 17, 27/88
Final Report	6/12/92	6/12/92
Other	N/A	N/A

Date of last quarterly facility inspection 4/92

This study is certified to have been performed in compliance with the appropriate Good Laboratory Practice regulations.

Patricia L. Runge
EPL Quality Assurance Unit

6/12/92
Date

Form No. 45 (Revised 5/92)

APPENDIX X

SUMMARY REPORTS: PATHOLOGY QUALITY ASSESSMENTS

PATHOLOGY ASSOCIATES, INC.

ON STUDIES 8437, 8436 and 8321

PAI

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RISK ASSESSMENT STUDY OF CHLORINE IN MICE STUDY NUMBER 8437

QUALITY ASSESSMENT REPORT

VOLUME I OF IV

Prepared by:

Pathology Associates, Inc.
4915-D Prospectus Drive
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Submitted to:

CIIT
6 Davis Drive
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Research Triangle Drive, NC

May 28, 1992

RISK ASSESSMENT STUDY OF CHLORINE IN MICE

STUDY NUMBER 8437

QUALITY ASSESSMENT NARRATIVE

Introduction

The pathology narrative, histopathology incidence tables, and hematoxylin and eosin stained microscopic slides used in the risk assessment study of chlorine in mice were received by Pathology Associates, Inc (PAI). The tissues had previously been examined and the data reported by a pathologist for Experimental Pathology Laboratories, Inc. (EPL). The data and slides were reviewed by Dr. Thomas M. Monticello of Pathology Associates, Inc., the quality assurance pathologist (QAP). The results are summarized in this report. The following tasks were completed during the review:

Task I: Complete review (CR) of all slides for 20% of the animals in the high dose and control groups. The selection of animals for this task was performed by CIIT staff.

Task II: Validation of compound-related lesions in selected target organs of all study animals. Designated target organs included 5 sections of nasal cavity for both sexes and the ovaries and uterus for female mice.

Task III: Correlation of gross and microscopic diagnosis.

Task IV. Conduction of a Peer Review. Substantive discrepancies, if any, that impacted on the interpretation of the study, were addressed and resolved.

Slide Review Work Sheets

The Slide Review Work Sheets are presented in Volumes II- IV. Slide Review Work Sheets for Task I (CR) animals list all tissues evaluated by the Study Pathologist (SP). For Task II, the Slide Review Work Sheets list diagnoses for all target organs. All tissues listed in the Slide Review Work Sheets were reviewed by the QAP. Entries under Reviewing Pathologist's Comments indicate either an agreement (concur) by the QAP with the SP or a disagreement with the SP's diagnosis. In each instance, space was provided to record remarks made during the Slide Review.

Correlation of Gross and Microscopic Diagnosis

The QAP reviewed the SP's gross to microscopic correlation tables for discrepancies which were recorded on photocopies of the tables. The tables are presented in Appendix 1 of this volume.

Pathology Group Peer Review (PGPR)

Following completion of the QA review, the QAP met with CIIT pathologists (Dr. K. Morgan and Dr. D. Wolf) and a pathologist from EPL (Dr. J. Hardisty) on April 29, 1992, to review selected slides from the study. The set of slides selected for review included representative examples of differences of opinion involving nasal lesion diagnoses. In addition, slides from ovaries, uterus and extra-nasal incidental neoplastic diagnoses were reviewed. The pathology group peer review consensus was recorded on Pathology Group Peer Review Worksheets which are presented in Appendix 2 of this volume.

Results

Nasal Cavity

The SP used the diagnosis "transitional metaplasia" to indicate "mild or early epithelial metaplasia which had not progressed to the extent of forming demonstrable squamous cells". The pathology group peer review (PGPR) determined this diagnosis was not the most appropriate term in describing the nasal lesion. The lesion in question was characterized by respiratory epithelial hyperplasia and hypertrophy usually confined to the walls of the anterior lateral meatus which is normally lined by cuboidal-transitional epithelium. Associated with the hyperplasia was a marked increase in the formation of intracytoplasmic eosinophilic inclusions which was associated with the cellular hypertrophy. Occasionally there was focal or multifocal squamous metaplasia associated with the epithelial hyperplasia; however, this was not the predominant feature of the lesion. It was the consensus of the QA and PGPR that the lesion termed "transitional metaplasia" be interpreted as "epithelial hyperplasia". The SP's term of "transitional metaplasia" was used consistently across all groups, including controls. It was concluded that the use of this diagnosis would not change the interpretation of the study results, and that "transitional metaplasia" (a.k.a. epithelial hyperplasia) was a treatment-induced lesion. The presence of "transitional metaplasia" in the lowest concentration group (0.4 ppm), indicates that a no observable effect dose (concentration) level (NOEL) did not exist for this lesion.

The SP diagnosed eosinophilic globules present in the squamous epithelium of the nasal vestibule, usually in association with squamous hyperplasia. The QAP and PGPR agreed with the diagnoses. It was concluded that eosinophilic globules in squamous epithelium were a treatment-induced lesion and present in a concentration-related manner, including the lowest concentration studied, 0.4 ppm. A NOEL did not exist for this lesion.

An additional nasal lesion was diagnosed by both the QAP and PGPR following the review of the nasal slides from this study. The lesion, diagnosed as septal perforation, was characterized by a focal, full thickness defect in the anterior nasal septum (usually the nares or vestibule). The borders of the perforated septum were either ulcerated, covered by a fibrinocellular cap, or covered by stratified squamous epithelium. The lesion, present in both males and females, was treatment related and concentration-dependent (Table 1).

Table 1. Incidence of Nasal Septal Perforation in Mice*

Treatment Group	Conc. (ppm)	Males Incidence (%)	Females Incidence (%)
1	0	0/58 (0)	0/60 (0)
2	0.4	16/65 (25)	3/66 (5)
3	1.0	21/68 (31)	10/58 (17)
4	2.5	15/55 (27)	13/57 (23)

* Unaudited Data

The diagnostic term "olfactory epithelium, atrophy" was used by the SP. The QAP agreed with the SP in some examples of olfactory atrophy which was characterized by a reduction and/or loss of sensory cells. In many cases, however, the QAP noted that the lesion was not present in the section(s) examined. The PGPR examined representative examples in which there was a discrepancy between the QAP and SP regarding the diagnosis of "olfactory atrophy". The lesion in question, which was most often localized to the walls of the anterior dorsal medial meatus, was characterized by a replacement of the olfactory epithelium with a respiratory or respiratory-like epithelium. The interpretation of this lesion by the PGPR was that either respiratory epithelium was normally present in this location since the level was anterior to the site where olfactory epithelium of the dorsal medial

meatus begins, or, that there was a replacement of olfactory epithelium by a respiratory-like epithelium (termed "respiratory-like metaplasia"). This latter lesion was difficult to confirm in every case due to variation in section level. The use of the diagnosis "olfactory atrophy" by the SP encompassed the following diagnoses: olfactory atrophy, respiratory-like metaplasia, and/or normal respiratory epithelium. The diagnosis of olfactory atrophy was made consistently across groups. It was concluded that even though "olfactory atrophy" was not the most appropriate diagnosis to use, and was used to describe both olfactory atrophy and respiratory-like metaplasia, it would have no substantive bearing on the overall interpretation of the study.

Ovary

Discrepancies between the SP and QAP regarding ovarian neoplasms were evaluated by the PGPR. In a control animal (289) a granulosa cell tumor diagnosed by the SP was downgraded to a cyst adenoma. A tubular adenoma diagnosed by the SP in control animal 307 was determined to be a nonneoplastic lesion consisting of a pyogranuloma. Another tubular adenoma, diagnosed in control animal 341 by the SP, was diagnosed by the QAP and PGPR as tubular hyperplasia. A tubulostromal adenoma was diagnosed by the QAP and PGPR in a Group 2 female (413). The QAP and PGPR agreed with the SP's conclusions regarding the types and incidence of ovarian tumors in the study in that these were incidental findings commonly seen in B6C3F1 mice, that occurred for the most part, at comparable incidences in control and treated groups.

Uterus

An additional diagnosis of endometrial stromal polyp was made by the QAP and PGPR for both animal 299 (Group 1) and animal 378 (Group 2). The SP's original diagnosis in control animal 307 of 'invasion, tubular adenoma" was changed to endometrial stromal

polyp by the QAP and PGPR. A granular cell tumor of the cervix was diagnosed in animal 359 (Group 2) and animal 520 (Group 4) by the QAP, both of which were confirmed by the PGPR.

A high incidence of ovarian abscesses and suppurative inflammation of the uterus was present in this study. The QAP and PGPR agreed with the SP's overall interpretation of the reproductive tract inflammatory lesions. These lesions were attributed to an infectious condition frequently associated with Klebsiella sp. (Rao. et al., 1987).

Miscellaneous Lesions

A follicular cell carcinoma in animal 256 (Group 4) was determined to be a C-cell tumor based on the QAP and PGPR. The terminology of a pituitary tumor in a control female (286) was changed from "pars anterior, adenoma" to the correct diagnosis of "pars distalis, adenoma". These minor discrepancies did not affect the interpretation of the study.

Summary and Conclusions

The interpretation of the pathology results from this study are in agreement with the SP. Inhalation of chlorine at concentrations of either 0.4, 1.0 or 2.5 ppm in B6C3F1 mice for two years resulted in nonneoplastic lesions confined to the nasal passages. Treatment-induced lesions were observed in all treatment groups, including the lowest concentration studied, 0.4 ppm. Significant treatment-induced nasal lesions were: 1) presence of eosinophilic intracytoplasmic inclusions in the squamous, respiratory and olfactory epithelium; 2) hyperplasia of the squamous epithelium (nasal vestibule); 3) septal perforation; and, 4) hyperplasia of the cuboidal-transitional epithelium in the anterior lateral meatus (termed "transitional metaplasia" by the SP). The lesion of olfactory atrophy was confirmed in some cases, however, many of the lesions diagnosed as olfactory atrophy by the SP consisted of either normal respiratory epithelium or respiratory-like metaplasia. This latter lesion was difficult to confirm due to variation in section level. It was the consensus of the QAP and PGPR that chlorine-induced lesions exhibited an anterio-posterior distribution and severity gradient, in contrast to the SP statement that the lesions were most severe at nasal levels 3 and 4.

Thomas M. Monticello, DVM, PhD
Diplomate, ACVP

5/28/92
Date

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RISK ASSESSMENT STUDY OF CHLORINE IN RATS STUDY NUMBER 8436

QUALITY ASSESSMENT REPORT

VOLUME I OF III

Prepared by:

Pathology Associates, Inc.
4915-D Prospectus Drive
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Submitted to:

CIIT
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Research Triangle Drive, NC

June 17, 1992

RISK ASSESSMENT STUDY OF CHLORINE IN RATS

STUDY NUMBER 8436

QUALITY ASSESSMENT NARRATIVE

Introduction

The pathology narrative, histopathology incidence tables, and hematoxylin and eosin stained microscopic slides used in the risk assessment study of chlorine in female F344 rats were received by Pathology Associates, Inc (PAI). The tissues had previously been examined and the data reported by a pathologist for Experimental Pathology Laboratories, Inc. (EPL). The data and slides were reviewed by Dr. Thomas M. Monticello of Pathology Associates, Inc., the quality assurance pathologist (QAP). The results are summarized in this report. The following tasks were completed during the review:

Task I: Complete review (CR) of all slides for 20% of the animals in the high dose and control groups. The selection of animals for this task was performed by CIIT staff.

Task II: Validation of compound-related lesions in the selected target organ, nasal cavity, of all study animals.

Task III: Correlation of gross and microscopic diagnosis.

Task IV. Conduction of a Peer Review. Substantive discrepancies, if any, that impacted on the interpretation of the study, were addressed and resolved.

Slide Review Work Sheets

The Slide Review Work Sheets are presented in Volumes II and III. Slide Review Work Sheets for Task I (CR) animals list all tissues evaluated by the Study Pathologist (SP). For Task II, the Slide Review Work Sheets list diagnoses for the target organ. All tissues listed in the Slide Review Work Sheets were reviewed by the QAP. Entries under Reviewing Pathologist's Comments indicate either an agreement (concur) by the QAP with the SP or a disagreement with the SP's diagnosis. In each instance, space was provided to record remarks made during the Slide Review.

Correlation of Gross and Microscopic Diagnosis

The QAP reviewed the SP's gross to microscopic correlation tables for discrepancies which were recorded on photocopies of the tables. The tables are presented in Appendix 1 of this volume.

Pathology Group Peer Review (PGPR)

Following completion of the QA review, the QAP met with CIIT pathologists (Dr. K. Morgan and Dr. D. Wolf) and a pathologist from EPL (Dr. J. Hardisty) on June 9, 1992, to review selected slides from the study. The set of slides selected for review included representative examples of chlorine-induced nasal lesions, and differences of opinion involving nasal lesion diagnoses. In addition, differences of opinion involving incidental neoplastic diagnoses were reviewed. The pathology group peer review consensus was recorded on Pathology Group Peer Review Worksheets which are presented in Appendix 2 of this volume.

Results

Nasal Cavity

The SP used the diagnosis "goblet cell hyperplasia" to indicate an increase in the number of goblet cells present in the nasal epithelium. Goblet cell hyperplasia was a treatment-induced lesion and was present primarily, but not confined to; the cuboidal-transitional epithelium lining the walls of the anterior lateral meatus and the medial aspect of the maxilloturbinate. Goblet cell hyperplasia was confirmed by the PGPR across all concentration groups, including the lowest concentration studied, 0.4 ppm, indicating that a no observable effect level concentration (NOEL) did not exist for this lesion. The QAP and PGPR discussed the use of the diagnosis "goblet cell hyperplasia", since this diagnosis infers that goblet cells are a normal cell type in the epithelium, and increased in number. Goblet cells are normally absent, or present in very low numbers, however, in nasal epithelium of the vestibule, lateral meatus, and medial aspect of the maxilloturbinate. Therefore, a more appropriate diagnosis would be "goblet cell metaplasia and/or hyperplasia". It was decided by the PGPR that the diagnosis of goblet cell hyperplasia would be interpreted as an increase in number of goblet cells and a transition from a squamous or cuboidal cell to a goblet cell (i.e. goblet cell metaplasia).

Based on the incidence table for goblet cell hyperplasia, there was a clear treatment-induced response, however, it was difficult to appreciate a clear concentration response. It was suggested by the PGPR to have the severity grades calculated and reported in order to determine if a concentration-response exists. The severity grades used by the SP were generally in agreement with the QAP, however, when severity grades differed, it was noted on the slide review worksheets.

An additional diagnosis was made by the QAP and confirmed by the PGPW. The lesion, respiratory epithelial hyperplasia, was characterized by an increase in number of the cuboidal-transitional cells lining the walls of the anterior lateral meatus and medial maxilloturbinate. This lesion was associated with goblet cell hyperplasia/metaplasia. It was decided that the addition of this diagnosis would not alter the interpretation of the study.

Other treatment-induced nasal lesions, confirmed by the PGPR, were eosinophilic globules present in the olfactory, respiratory, and glandular epithelium. A NOEL was not present for these lesions.

Miscellaneous Lesions

Mononuclear cell leukemia was diagnosed in the spleen and/or liver by the SP. It was determined by the QAP and PGPR that this lesion was not present (i.e. overdiagnosed) in three (3) control animals and six (6) Group 4 animals. An incidental kidney lesion in a Group 4 animal, originally diagnosed by the SP as a liposarcoma, was determined by the QAP and PGPW to be a nonneoplastic lesion diagnosed as marked, focal, tubular hyperplasia.

Summary and Conclusions

The interpretation of the pathology results from this study are in agreement with the SP. Inhalation of chlorine at concentrations of either 0.4, 1.0 or 2.5 ppm in female F344 rats for two years resulted in nonneoplastic lesions confined to the nasal passages. Chlorine-induced lesions were observed in all treatment groups, including the lowest concentration studied, 0.4 ppm. Significant treatment-induced nasal lesions were: 1) goblet cell hyperplasia/metaplasia; 2) respiratory epithelial hyperplasia; 3) presence of eosinophilic intracytoplasmic globules in the respiratory, glandular, and olfactory epithelium, and; 4) subacute inflammation in anterior sections.

Thomas M Monticello

Thomas M. Monticello, DVM, PhD

Diplomate, ACVP

6/17/92

Date

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RISK ASSESSMENT STUDY OF CHLORINE IN RATS STUDY NUMBER 8321

QUALITY ASSESSMENT REPORT

VOLUME I OF III

Prepared by:

Pathology Associates, Inc.
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Submitted to:

CIIT
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June 17, 1992

RISK ASSESSMENT STUDY OF CHLORINE IN RATS

STUDY NUMBER 8321

QUALITY ASSESSMENT NARRATIVE

Introduction

The pathology narrative, histopathology incidence tables, and hematoxylin and eosin stained microscopic slides used in the risk assessment study of chlorine in male F344 rats were received by Pathology Associates, Inc (PAI). The tissues had previously been examined and the data reported by a pathologist for Experimental Pathology Laboratories, Inc. (EPL). The data and slides were reviewed by Dr. Thomas M. Monticello of Pathology Associates, Inc., the quality assurance pathologist (QAP). The results are summarized in this report. The following tasks were completed during the review:

Task I: Complete review (CR) of all slides for 20% of the animals in the high dose and control groups. The selection of animals for this task was performed by CIIT staff.

Task II: Validation of compound-related lesions in the selected target organ, nasal cavity, of all study animals.

Task III: Correlation of gross and microscopic diagnosis.

Task IV. Conduction of a Peer Review. Substantive discrepancies, if any, that impacted on the interpretation of the study, were addressed and resolved.

Slide Review Work Sheets

The Slide Review Work Sheets are presented in Volumes II and III. Slide Review Work Sheets for Task I (CR) animals list all tissues evaluated by the Study Pathologist (SP). For Task II, the Slide Review Work Sheets list diagnoses for the target organ. All tissues listed in the Slide Review Work Sheets were reviewed by the QAP. Entries under Reviewing Pathologist's Comments indicate either an agreement (concur) by the QAP with the SP or a disagreement with the SP's diagnosis. In each instance, space was provided to record remarks made during the Slide Review.

Correlation of Gross and Microscopic Diagnosis

The QAP reviewed the SP's gross to microscopic correlation tables for discrepancies which were recorded on photocopies of the tables. The tables are presented in Appendix 1 of this volume.

Pathology Group Peer Review (PGPR)

Following completion of the QA review, the QAP met with CIIT pathologists (Dr. K. Morgan and Dr. D. Wolf) and a pathologist from EPL (Dr. J. Hardisty) on June 9, 1992, to review selected slides from the study. The set of slides selected for review included representative examples of chlorine-induced nasal lesions, and differences of opinion involving nasal lesion diagnoses. The pathology group peer review consensus was recorded on Pathology Group Peer Review Worksheets which are presented in Appendix 2 of this volume.

Results

Nasal Cavity

The SP used the diagnosis "goblet cell hyperplasia" to indicate an increase in the number of goblet cells present in the nasal epithelium. Goblet cell hyperplasia was a treatment-induced lesion and was present primarily, but not confined to, the cuboidal-transitional epithelium lining the walls of the anterior lateral meatus and the medial aspect of the maxilloturbinate. Goblet cell hyperplasia was confirmed by the PGPR across all concentration groups, including the lowest concentration studied, 0.4 ppm, indicating that a no observable effect level concentration (NOEL) did not exist for this lesion. The QAP and PGPR discussed the use of the diagnosis "goblet cell hyperplasia", since this diagnosis infers that goblet cells are a normal cell type in the epithelium, and increased in number. Goblet cells are normally absent, or present in very low numbers, however, in nasal epithelium of the vestibule, lateral meatus, and medial aspect of the maxilloturbinate. Therefore, a more appropriate diagnosis would be "goblet cell metaplasia and/or hyperplasia". It was decided by the PGPR that the diagnosis of goblet cell hyperplasia would be interpreted as an increase in number of goblet cells and a transition from a squamous or cuboidal cell to a goblet cell (i.e. goblet cell metaplasia).

Based on the incidence table for goblet cell hyperplasia, there was a clear treatment-induced response, however, it was difficult to appreciate a clear concentration response. It was suggested by the PGPR to have the severity grades calculated and reported in order to determine if a concentration-response exists. The severity grades used by the SP were generally in agreement with the QAP, however, when severity grades differed, it was noted on the slide review worksheets.

An additional diagnosis was made by the QAP and confirmed by the PGPR. The lesion, respiratory epithelial hyperplasia, was characterized by an increase in number of the cuboidal-transitional cells lining the walls of the lateral meatus and medial maxilloturbinate, and was associated with goblet cell hyperplasia/metaplasia. The lesion was present primarily in the anterior portion of the lateral meatus and was not seen consistently in every treated animal due to variation in sectioning levels of the anterior nose. It was determined that the addition of this diagnosis would have no major bearing on the interpretation of the the study. Other additional diagnoses made by the QAP and confirmed by the PGPR included atrioturbinate atrophy in a one Group 3 and Group 4 animal, and nasal septal perforation in a Group 4 animal.

The PGPR confirmed other treatment-induced nasal lesions that were diagnosed by the SP. These lesions consisted of eosinophilic globules present in the olfactory, respiratory, and glandular epithelium. A NOEL was not present for these lesions.

A nasal adenocarcinoma, present in a Group 3 animal, was diagnosed by the SP in the study. The tumor was confirmed by the QAP and PGPR. The PGPR noted that the tumor had characteristics suggestive of a low grade malignancy. The PGPR agreed with the SP in that the nasal tumor was an incidental finding.

Summary and Conclusions

The interpretation of the pathology results from this study are in agreement with the SP. Inhalation of chlorine at concentrations of either 0.4, 1.0 or 2.5 ppm in male F344 rats for two years resulted in nonneoplastic lesions confined to the nasal passages. Chlorine-induced lesions were observed in all treatment groups, including the lowest concentration studied, 0.4 ppm. Significant treatment-induced nasal lesions were: 1) goblet cell hyperplasia/metaplasia; 2) respiratory epithelial hyperplasia; 3) presence of eosinophilic intracytoplasmic globules in the respiratory, glandular, and olfactory epithelium, and; 4) subacute inflammation in anterior sections.

Thomas M. Monticello

Thomas M. Monticello, DVM, PhD

Diplomate, ACVP

6/17/92

Date

APPENDIX Y

CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY

QUALITY ASSURANCE LIST OF INSPECTION AND REPORTING DATES

ON STUDIES 8437, 8436 and 8321

Chemical Industry Institute of Toxicology

QUALITY ASSURANCE INSPECTION AND REPORTING DATES

Study Title: A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats

Protocol Numbers: 8437, 8436 and 8321

Dates of CIIT QA Inspections	Dates of Report to CIIT's Study Director/Management
02/14/83	02/15/83
04/08/83	04/15/83
04/11/83	04/15/83
04/20/83	05/13/83
04/21/83	05/13/83
05/11/83	05/13/83
08/03/83	08/17/83
09/14/83	09/16/83
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09/18/85	09/18/85
12/10/85	12/13/85
12/18-19/85	02/20/86
01/22/86	02/20/86
04/17/86	04/29/86
04/29/86	04/29/86

Signed: Garris D. Parker, Jr. 12/14/93

Garris D. Parker, Jr./Date
(Former QA Specialist, CIIT)

APPENDIX Z

CIIT

Justification for Selection of Exposure Concentrations
Intramural Chronic Studies

Chemical: Chlorine

Study Title: Risk Assessment study of Chlorine in Rats and Mice

Contractor:

Project Director: Dr. Craig Barrow

Exposure Concentration: High: 2.5 ppm
Mid: 1.0 ppm
Low: 0.4 ppm

Justification*: An earlier study of Cl_2 (Appendix A) in F-344 rats (exposures were 1, 3, or 9 ppm, 6 hr/day, 5 days/wk for 45 days) revealed unequivocal respiratory tract toxicity at 9 ppm with much less severe changes at 1 or 3 ppm. Additionally, a very recent unpublished 9 day probe study (2.5 ppm, 6 hrs/day, 5 days/week for 2 weeks) in F-344 rats and B6C3F1 mice demonstrated only minimal changes in the nasal cavity of exposed animals (Appendix B). Based on these studies a top concentration of 2.5 ppm has been chosen. A low concentration of 0.4 ppm has been selected to minimize interferences from chloramines. The mid-concentration of 1.0 ppm is equidistant log spacing between 0.4 and 2.5 ppm.

*Attach all documents to support justification. Label as: Exhibit A, B, C, etc.

APPROVALS:

Director of Research — Date 4/5/83

Project Director — Date 4/5/83

PRC 0003-B

Appendix A

TOXICOLOGY AND APPLIED PHARMACOLOGY 49, 77–88 (1979)

An Inhalation Toxicity Study of Chlorine in Fischer 344 Rats following 30 Days of Exposure[1]

CRAIG S. BARROW,[2] RICHARD J. KOCIBA,[3] LARRY W. RAMPY,[3] DAVID G. KEYES,[3] AND RALPH R. ALBEE[3]

Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina, 27709, and Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical, U.S.A., Midland, Michigan 48640

Received August 1, 1978; accepted December 4, 1978

An Inhalation Toxicity Study of Chlorine in Fischer 344 Rats following 30 Days of Exposure. BARROW, C. S., KOCIBA, R. J., RAMPY, L. W., KEYES, D. G., AND ALBEE, R. R. (1979). *Toxicol. Appl. Pharmacol.* 49, 77–88. A subacute study was completed in groups of 10 male and 10 female Fischer 344 rats exposed to air (controls), 1, 3, or 9 ppm chlorine for 6 hr/day, 5 days/week, for 6 weeks. Concentration related decreases in body weight gain were seen at all exposure concentrations in females and at 3 and 9 ppm in males. Additionally, three females at 9 ppm died before the end of Day 30 of exposure. Urinalysis, hematology, and clinical chemistry evaluations were completed on the surviving animals. The urine specific gravity was elevated at all exposure concentrations in the females and at 3 and 9 ppm in the males. The hematocrit and white blood cell count were increased in the females exposed to 9 ppm. Elevations in alkaline phosphatase activity, blood urea nitrogen, γ-glutamyl transpeptidase, and serum glutamic–pyruvic transaminase occurred at 9 ppm; alkaline phosphatase was elevated at 3 ppm in rats of both sexes. Widespread evidence of inflammation was seen throughout the respiratory tract with hyperplasia and hypertrophy of epithelial cells of the respiratory bronchioles, alveolar ducts, and alveoli of male and female rats exposed to 9 ppm. Changes in male rats at 3 or 1 ppm consisted of focal inflammation of the nasal turbinates and a slight to moderate inflammatory reaction around the respiratory bronchioles and alveolar ducts. Increased eosinophilic cytoplasmic homogeneity and decreased granularity of the epithelial cells of the proximal convoluted tubules were seen in the kidneys of male rats exposed to 9 ppm. The livers of rats of both sexes at 9 or 3 ppm had an increased hepatocellular cytoplasmic vacuolation. These data indicated that repeated exposure of Fischer 344 rats to chlorine resulted in pulmonary effects at all levels of chlorine used, and hepatic and renal effects at 9 and 3 ppm.

The acute toxicity of chlorine, a general respiratory tract irritant, has been studied in animals following single exposures to high concentrations. The median times to death (Lt50) of rats and mice exposed to 1000 ppm of chlorine were 28 and 53 min, respectively. The Lt50 at 250 ppm was approximately 7 hr in both species (Weedon *et al.*, 1940). The median lethal concentrations (LC50) of chlorine in three strains of mice, using 10-min exposures and 10-day observation periods, were 524, 596, and 676 ppm (Silver and McGrath, 1942; Silver *et al.*, 1942). A

[1] This work was presented in part at the 1978 meeting of the Society of Toxicology, San Francisco, Calif.

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30-min LC50 was 127 ppm in mice (National Research Council, 1976) and 655 to 872 ppm in dogs (Underhill, 1925). The pathological changes noted following acute exposure to chlorine include pulmonary edema and hemorrhage (Weedeon *et al.*, 1940; Silver *et al.*, 1942), emphysematous alveoli (Klotz, 1917; Winternitz, 1920), atelectasis, and severe upper respiratory tract injury (Winternitz, 1920). Liver and kidney congestion have also been reported (Weedon *et al.*, 1940).

Effects of low level, repeated chlorine exposure are not well described. Exposure of rabbits and guinea pigs to 1.7 ppm chlorine, 1 hr/day, for several days, caused a "decreased nutritional state," blood alterations and a decreased resistance to infection (Flury and Zernick, 1931), but no effects were demonstrated with 0.7 ppm chlorine under the same exposure conditions. Exposure of 30 female rats to the air in a Russian chlorine plant for 5 h/day for 4 months showed that, compared to a group of controls, the exposed animals had greater inflammation of the upper respiratory tract, lower body weights, leukocytosis, and longer estrous cycles (National Research Council, 1976). Guinea pigs exposed to 1.7 ppm of chlorine and tubercle bacilli for 5 hr/day for 47 days resulted in shortened survival times when compared to groups exposed to only chlorine or tubercle bacilli (Arloing *et al.*, 1940). Rabbits exposed to chlorine concentrations of 0.7 to 1.7 ppm for 5 hr/day, every other day, for up to 9 months showed weight loss, nasal discharge, metaplasia and hemorrhage of the bronchi, emphysema, atelectasis, and an increased incidence of respiratory tract infection (Sklyanskaya and Rappoport, 1935). In rats with spontaneous pulmonary disease, exposure to chlorine at approximately 16 ppm, 1 hr/day for 4 weeks or 40 ppm, 2 hr/day for 5 weeks produced inflammatory changes in the trachea and bronchi, bronchitis, and death (Elmes and Bell, 1963). In a later study, specific pathogen-free (SPF) rats and rats with spontaneous pulmonary disease (SPD) exposed to approximately 90 ppm, 3 hr/day for 20 days or 104 ppm, 3 hr/day for 6 days demonstrated that the SPD rats were more sensitive to chlorine inhalation than SPF rats based upon mortality (Bell and Elmes, 1965). Additionally, the lungs of SPD rats exhibited a more severe cellular response as indicated by increased numbers of goblet and polymorphonuclear cells and a higher incidence of emphysema and pneumonia.

These studies have not adequately described the pulmonary response of animals exposed repeatedly to low levels of chlorine, nor have they indicated whether organ systems other than the lung are affected. The purpose of the present investigation was to determine the toxic effects of chlorine in male and female rats exposed to various concentrations of chlorine for 6 hr/day, 5 days/week, for a total of 30 exposures.

METHODS

Animals, exposure concentrations, and generation and analysis of test atmospheres. Eighty 6- to 8-week-old Fischer 344 rats (10 males and 10 females/exposure group) were exposed to 0 (controls), 1, 3, or 9 ppm chlorine for 6 hr/day, 5 days/week for 6 weeks, resulting in a total of 30 exposures. Mixtures of chlorine and nitrogen were metered and mixed with charcoal-filtered air prior to being introduced into 3.7 m^3 exposure chambers. Total chamber airflow varied between 500 to 650 liters/min. The animal loading was approximately 0.12%. Chlorine concentrations were measured by a colorimetric method based upon the oxidation of a methyl orange solution by free chlorine at a pH of approximately 3.0 (Katz, 1977). Chemical analyses were conducted four times/day/chamber and a time-weighted average was calculated. Chamber temperature and humidity were recorded at each sampling time. Control rats were exposed to charcoal-filtered room air in an exposure chamber identical to that of the chlorine-treated animals. Food and water were withheld from the rats during the actual exposures, but were provided *ad libitum* at all other times. Following each exposure, all animals were removed from the exposure chambers and kept in a holding room.

Experimental evaluation of animals. Clinical signs of chlorine toxicity, particularly those which were indicative of respiratory tract irritation, were recorded daily. Body weights were recorded three times/week beginning 1 week prior to exposure and continuing

until the study was concluded. Blood, obtained from the tail vein and urine, obtained by compressing the bladder, were collected from all males prior to Day 29 of exposure and all females prior to Day 30 of exposure for hematology and urinalysis evaluation. The hematology parameters included hemoglobin concentration, hematocrit, erythrocyte count, and leukocyte count (total and differential). The parameters evaluated for urinalysis were appearance, occult blood, specific gravity, protein, pH, ketones, glucose, and bilirubin. Clinical chemistry determinations were obtained on blood taken at necropsy following decapitation. The parameters included blood urea nitrogen concentration, and serum activities of γ-glutamyl transpeptidase, alkaline phosphatase, glutamic pyruvic transaminase, and glutamic oxaloacetic transaminase.

All surviving rats were fasted overnight and killed 1 (males) or 2 (females) days after the last day of exposure for gross pathological examination. The weights of the following organs were recorded: brain, heart, kidneys, liver, lungs, spleen, thymus, testes or ovaries. Tissues for histopathological study were fixed in 10% buffered formalin except for the eyes which were fixed in Zenker's solution. Tissue sections were prepared and stained with hematoxylin and eosin for light microscopic examination.

Statistical evaluation. Body weights, hematology and clinical chemistry parameters, urine specific gravity and pH, organ weights, and organ weight to body weight ratios were analyzed by an analysis of variance. Dunnett's test was used to determine the statistical significance of group mean comparisons (Steel and Torrie, 1960). Comparisons were limited to within-sex analysis. Differences were judged to be statistically significant if comparisons yielded values for $p < 0.05$.

RESULTS

Exposure Chamber Data

The mean time-weighted averages over the 30-day exposure period for target concentrations of 1.00, 3,00, and 9.00 ppm were 1.00 (±0.04, 0.89–1.08; SD and range), 3.00 (±0.10, 2.74–3.23), and 8.99 (±0.45, 8.03–10.08). The ranges for temperature and relative humidity in all chambers were 21.7 to 24.6°C and 47.5 to 62.0%, respectively.

Daily Observations of Animals and Mortality

Clinical signs of ocular and upper respiratory tract irritation such as lacrimation, hyperemia of the conjunctiva, nasal discharge, and salivation were seen throughout the study in rats exposed to 9 or 3 ppm of chlorine. Rats exposed to 1 ppm of chlorine also occasionally showed slight indications of irritation. Respiratory difficulty (gasping, lung rales, mouth breathing) was also observed in rats exposed to 9 ppm. All groups of chlorine-exposed rats showed varying degrees of urinary staining and wetness of the fur surrounding the genitalia. The control rats appeared normal and healthy throughout the study and no responses such as those described for the chlorine-exposed rats were observed.

Based upon clinical signs and later histopathological findings, beginning with the last week of exposure, sialodacryoadenitis occurred in the control group and all exposure groups of treated rats.

During the course of the study, four rats died. One of these was a control male that died with lesions attributed to sialodacryoadenitis. The remaining three deaths were female rats from the highest exposure level (9 ppm). Each of these rats showed a spectrum of lesions considered to be related to the chlorine exposures. The lesions were similar to those observed in the rats of the high exposure group at the termination of the experiment.

Body Weights

There was a concentration-dependent reduction in body weight gain (Figs. 1 and 2) for the chlorine-treated animals. Reductions in body weight gain of male rats exposed to 3 or 9 ppm were statistically significant ($p < 0.05$) when compared to the control animals. Statistically significant decreases in body weight gain of female rats exposed to 3 or 9 ppm were present throughout the study. On experimental Days 16–26, 30–37, and 42 until necropsy, statistically significant decreases were also seen in the 1-ppm group. The decrease in body weight gain which occurred in all groups after Day 33 on experiment coincides with the onset of sialodacryoadenitis. Similarly, the abrupt decrease from

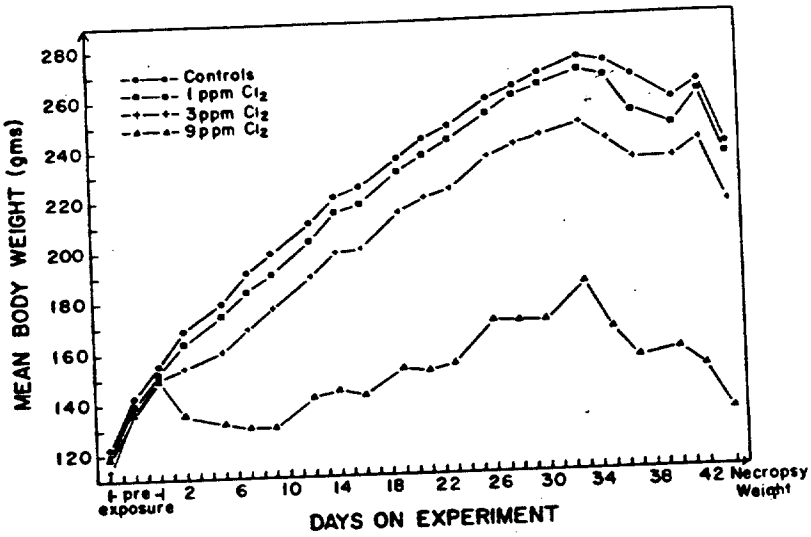

FIG. 1. Time-response curves for body weight gain of male Fischer 344 rats exposed to 0 (controls), 1, 3, or 9 ppm chlorine.

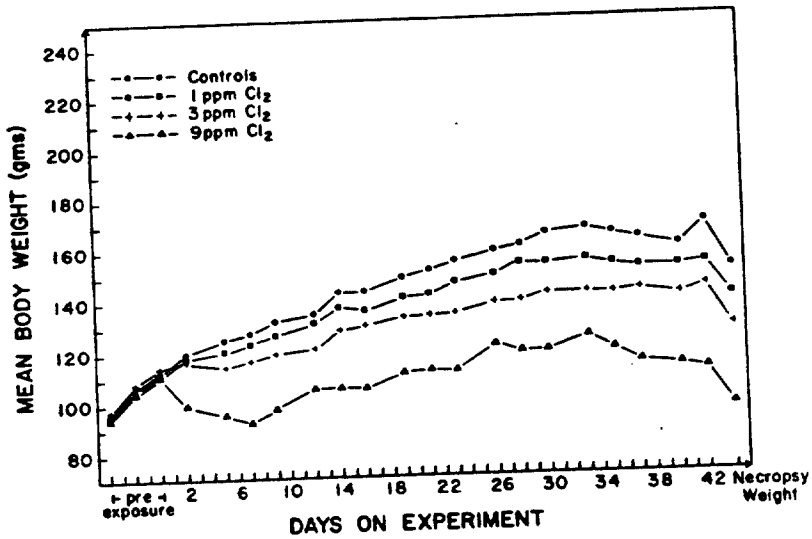

FIG. 2. Time-response curves for body weight gain of female Fischer 344 rats exposed to 0 (controls), 1, 3, or 9 ppm chlorine.

Day 42 until necropsy coincides with the fact that the animals were fasted prior to necropsy.

Hematology, Urinalysis, and Clinical Chemistry

Segmented neutrophils were elevated in both sexes exposed to 9 ppm (Tables 1 and 2) and hematocrit was elevated in females exposed to 9 ppm chlorine (Table 2). Elevations in urine specific gravity in females at all exposure concentrations and males at 3 and 9 ppm showed an exposure concentration response relationship (Table 2). Similarly, the increases in alkaline phosphatase activity in rats of both sexes exposed to 3 or 9 ppm showed an exposure-concentration related

TABLE 1

SUMMARY OF STATISTICALLY SIGNIFICANT HEMATOLOGICAL, CLINICAL CHEMISTRY, AND URINALYSIS PARAMETERS FROM MALE FISCHER 344 CONTROL AND CHLORINE-TREATED RATS[a]

Parameter examined	Control	Exposure group (ppm) 1	3	9
Segmented neutrophils ($\times 10^3/mm^3$)				
$\bar{x}$	2.4	NS[b]	NS	5.9
±SD	1.0			1.4
Blood urea nitrogen (mg/100 ml)				
$\bar{x}$	19.0	NS	NS	34.0
±SD	2.0			10.0
Serum alkaline phosphatase (mU/ml)				
$\bar{x}$	97.0	NS	124.0	138.0
±SD	10.0		19.0	19.0
Serum γ-glutamyl transpeptidase (mU/ml)				
$\bar{x}$	4.0	NS	NS	9.0
±SD	1.0			2.0
Urine specific gravity				
$\bar{x}$	1.031	NS	1.048	1.059
±SD	0.015		0.012	0.011

[a] $p < 0.05$.
[b] Not statistically significant ($p > 0.05$).

change (Tables 1 and 2). Serum glutamic pyruvic transaminase was elevated in females exposed to 9 ppm (Table 2). γ-Glutamyl transpeptidase and blood urea nitrogen were elevated in rats of both sexes exposed to 9 ppm (Tables 1 and 2).

Gross Pathological Changes

Evidence of general toxicity in rats of both sexes, as indicated by decreased size of the carcass, emaciation, and decreased adipose deposits, was seen following 30 exposures to 9 ppm chlorine. Females exposed to 3 ppm also showed evidence of general toxicity.

The upper and/or lower respiratory tract of rats exposed to 3 or 9 ppm had gross evidence of inflammatory reactions. This included hyperemia and accumulation of inflammatory material in the upper nasal passageways and pulmonary inflammatory reactions. The latter conditions caused some of the lungs of the rats from the 9-ppm group to deflate more slowly after removal, possibly indicating a decrease in lung compliance.

The gastric mucosa of rats exposed to 9 ppm chlorine was characterized by multiple ulcerations, erosions, edema, and subsequent hemorrhage into the lumen of the gut.

The kidneys of rats exposed to 9 ppm chlorine were slightly darkened in appearance. Matting of the perineal haircoat, possibly as a result of profuse urination, was seen in males and females exposed to 9 ppm chlorine and females exposed to 3 ppm chlorine.

Histopathological Changes

The upper and lower respiratory tracts of male and female rats exposed to 9 ppm of chlorine had multiple indications of inflammatory reaction. In the nasal turbinates, there

TABLE 2

SUMMARY OF STATISTICALLY SIGNIFICANT HEMATOLOGICAL, CLINICAL CHEMISTRY, AND URINALYSIS PARAMETERS FROM FEMALE FISCHER 344 CONTROL AND CHLORINE-TREATED RATS[a]

Parameter examined	Control	Exposure group (ppm)		
		1	3	9
Hematocrit (%)				
$\bar{x}$	47.3	NS[b]	NS	50.5
±SD	3.0			2.0
Segmented neutrophils ($\times 10^3/mm^3$)				
$\bar{x}$	4.4	NS	NS	7.1
±SD	1.3			2.5
Blood urea nitrogen (mg/100 ml)				
$\bar{x}$	21.0	NS	NS	44.0
±SD	2.0			7.0
Serum glutamic pyruvic transaminase (mU/ml)				
$\bar{x}$	21.0	NS	NS	28.0
±SD	5.0			6.0
Serum alkaline phosphatase (mU/ml)				
$\bar{x}$	100.0	NS	124.0	150.0
±SD	10.0		13.0	10.0
Serum γ-glutamyl transpeptidase (mU/ml)				
$\bar{x}$	3.0	NS	NS	8.0
±SD	2.0			1.0
Urine specific gravity				
$\bar{x}$	1.037	1.050	1.052	1.066
±SD	0.015	0.010	0.010	0.010

[a] $p < 0.05$.
[b] Not statistically significant ($p > 0.05$).

was focal to multifocal mucopurulent inflammation, with increased secretory material and necrotic erosions of the mucosal epithelium (Fig. 3). The tracheal–bronchiolar portion of the respiratory tract typically showed hyperplasia of the epithelial lining, with some inflammation, mucopurulent exudate, and increased secretory material (Fig. 4). There was also an increase in peribronchiolar lymphoid activity. The respiratory bronchioles and alveolar ducts showed hyperplasia and hypertrophy of the epithelial lining (males) and these changes were surrounded by an inflammatory reaction (Fig. 5). The alveolar sacs contained an increased number of alveolar macrophages and secretory material, and there were focal necrosis, hypertrophy and hyperplasia of alveolar epithelial cells adjacent to the alveolar ducts (Fig. 6). Areas of atelectasis were noted and there was a focal to multifocal interstitial inflammation within the lungs of the rats of this high exposure group.

The respiratory tract of rats exposed to 3 or 1 ppm chlorine had less extensive changes. Overall, the degree of pulmonary pathology appeared to be very similar at the 3- or 1-ppm exposure level. Changes in the upper

FIG. 3. Photomicrograph of nasal turbinates from rat exposed to 9 ppm of chlorine. Note mucopurulent type of inflammatory response, with accumulation of inflammatory material within nasal passageways. Hematoxylin and eosin stain. × 200.

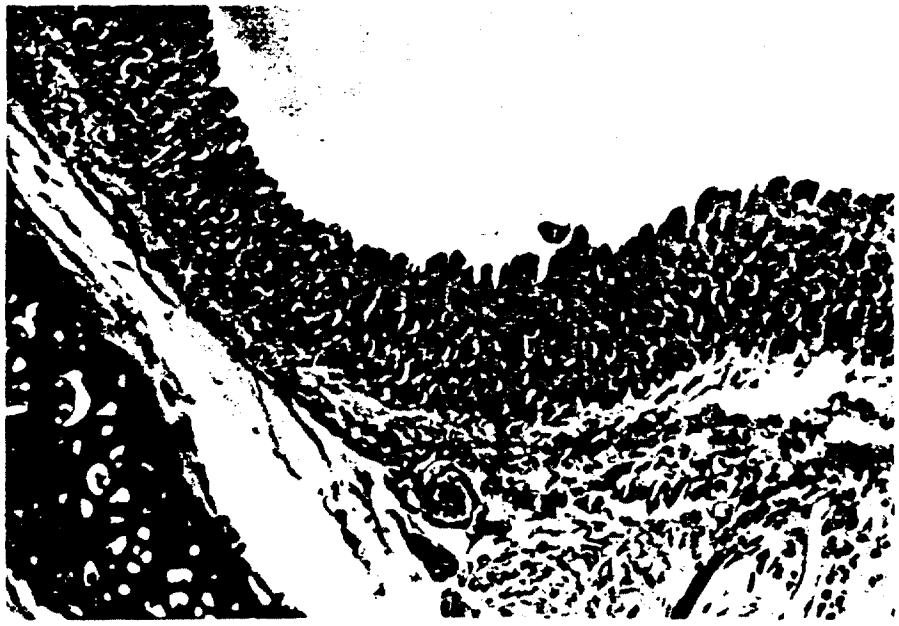

FIG. 4. Photomicrograph of terminal trachea from rat exposed to 9 ppm of chlorine. Note hyperplasia of epithelial lining. Hematoxylin and eosin stain. × 100.

FIG. 5. Photomicrograph of bronchiolar portion of respiratory tract from rat exposed to 9 ppm of chlorine. Note hyperplasia of epithelial lining and slight peribronchiolar inflammatory reaction Hematoxylin and eosin stain. ×200.

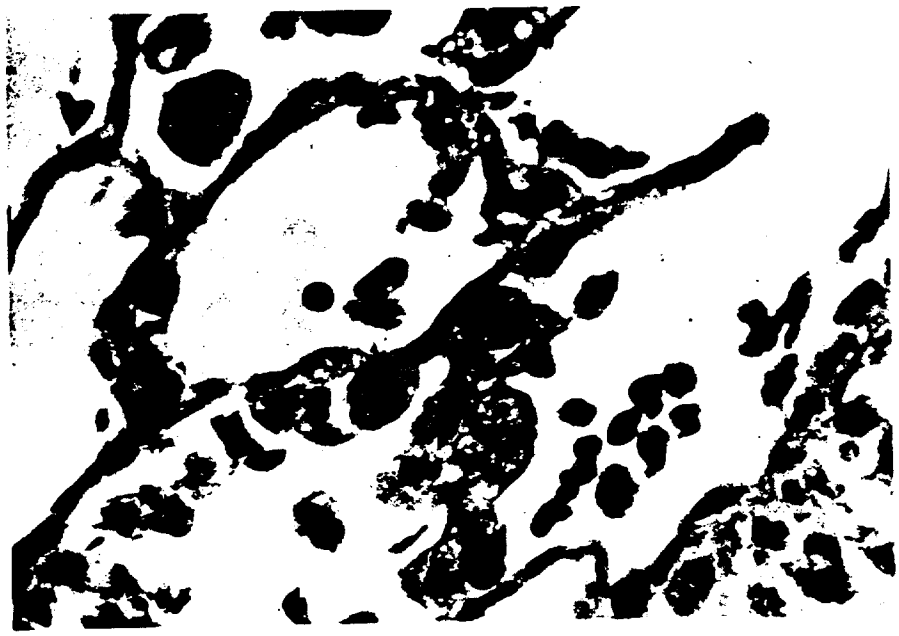

FIG. 6. Photomicrograph of alveolar portion of respiratory tract from rat exposed to 9 ppm of chlorine. Note hypertrophy and hyperplasia of alveolar epithelial cells, with alveoli containing increased numbers of alveolar macrophages and other inflammatory cells. Hematoxylin and eosin stain. ×400.

respiratory tract of rats from the two lower exposure levels were limited to a focal mucopurulent inflammation of the nasal turbinates (females). There were isolated instances of submucosal inflammation of the tracheal epithelium (males). Peribronchiolar lymphoid activity was slightly increased to the same degree in rats exposed to 3 or 1 ppm of chlorine. Deeper pulmonary changes noted in male rats exposed to 3 or 1 ppm of chlorine included a slight to moderate inflammatory reaction around the respiratory bronchioles and alveolar ducts, increased numbers of alveolar macrophages within alveoli, and isolated areas of atelectasis.

The spleen and thymus of rats exposed to 9 ppm of chlorine had a decreased content of lymphoid elements which was not noted in the rats exposed to 3 or 1 ppm of chlorine. Kidneys of the rats of both sexes exposed to 9 ppm of chlorine had a slight to moderate degree of congestion. The males at this high exposure level had renal tubular epithelial cells which showed increased eosinophilic cytoplasmic homogeneity and decreased granularity, with swelling in some cases. The livers of males and females exposed to 9 or 3 ppm of chlorine had an increase in the degree of hepatocellular cytoplasmic vacuolation. Increased hepatocellular cytoplasmic eosinophilic homogeneity was also seen in the livers of rats exposed to 9 ppm.

A majority of rats exposed to 9 ppm of chlorine had focal erosion of the gastric mucosa which was usually accompanied by focal inflammation of the adjacent submucosal areas. The salivary glands of females exposed to 9, 3, or 1 ppm of chlorine had an apparent decrease in the content of serous and/or mucinous secretory material within the acinar structures. However, there were variable degrees of inflammation in the salivary glands and ducts of rats from all control and exposure groups due to the occurrence of infectious sialodacryoadenitis during the latter stages of the study. These observations may have been associated with the concurrent infectious process, or may have been a secondary response to the general toxicity from chlorine exposure.

Organ Weights

Statistically significant ($p<0.05$) alterations in absolute organ weights and relative organ weights (in relation to body weights) comprised decreased spleen and thymus weights and increased weight of the lungs of rats of both sexes exposed to 9 ppm of chlorine.

DISCUSSION

The results of this study indicated that unequivocal upper and lower respiratory tract changes were produced in Fischer 344 rats exposed to 9 ppm of chlorine, 6 hr/day for a total of 30 exposures. This conclusion was supported by the clinical signs of generalized respiratory tract irritation, increased lung weights and lung to body weight ratios, and the histopathological changes which extended throughout the upper and lower respiratory tract of rats exposed to 9 ppm. The increases in the total number of segmented neutrophils at 9 ppm correlated very well with the inflammation and mucopurulent exudate of the upper and lower respiratory tract.

The wide spectrum of effects extending from the upper to the lower respiratory tract seen at 9 ppm would be expected from an irritant such as chlorine. For gaseous irritants in general, the locus of action within the respiratory tract is dependent not so much in the differences in their chemical properties, but rather their physical characteristics and, particularly, their water solubilities. The moist mucosa of the upper respiratory tract effectively absorbs irritants, such as hydrogen chloride, which have a high water solubility, but those irritants with low water solubility, such as phosgene, can readily reach the lower pulmonary structures. Chlorine, which has a water solubility between that of hydrogen chloride and phosgene, is capable of exerting its effects over the entire respiratory tract.

The respiratory tract effects found in animals exposed to 3 or 1 ppm chlorine were very similar and much less severe than those seen at 9 ppm. These results are difficult to interpret as they pertain to human exposures (current Threshold Limit Value = 1 ppm), largely because of differences between rats and humans regarding pulmonary anatomy, patterns of respiration, and amount of pulmonary ventilation.

Regarding pulmonary anatomy, humans are known to possess relatively long, well-defined respiratory bronchioles which terminate into distinct alveolar ducts. On the other hand, in the rat, the respiratory bronchioles are poorly defined. A question which remains unanswered regarding the toxicity of chlorine is whether repeated exposure of workers can result in an increased incidence of chronic obstructive pulmonary disease where the site of injury within the lungs is at the level of the respiratory bronchiole and alveolar ducts. The rat is probably not the most suitable species for evaluating chronic obstructive pulmonary disease at the level of the respiratory bronchiole and alveolar duct.

Patterns of respiration also differ significantly in the rat as compared to man. The rat is an obligatory nose breather with a greater surface area-to-volume ratio of the upper respiratory tract (Hatch and Gross, 1964). It may be anticipated that a greater severity of pathological change may result in the nasal area of the rat versus man when exposed to equal concentrations for equal amounts of time.

Compared to man, the rat has a pulmonary ventilation approximately eight times greater, expressed as liters of air per minute per kilogram. As a result, the rat can be expected to receive a higher net effective dose of chlorine for any given concentration and duration of exposure. However, there are some data available with other airborne chemical irritants that suggest that the differences between species regarding pulmonary ventilation may not be important in assessing the effects on the lung. A recent study has reported good agreement between the site and degree of damage in the lung betwee rats and Bonnet monkeys exposed to ozone at similar concentrations for 1 week (Castleman *et al.*, 1977). However, further da would be needed based upon longer exposu times before it could be concluded that the species sensitivity was similar. Earlier studi in guinea pigs (Alarie *et al.*, 1970) ar cynomolgus monkeys (Alarie *et al.*, 1972) exposed to similar exposure concentrations and similar durations of exposure to S(did not show any pulmonary effects measured by pulmonary functions tests and histopathological examination. Althou these observations suggest equal sensitiviti it cannot be concluded that this is so since neither species showed any functional morphological change. A later study (Ala *et al.*, 1973) demonstrated that cynomolgus monkeys had a greater pulmonary sensitivity as compared with guinea pigs when expos to sulfuric acid mist. However, sulfuric ac mist is an aerosol and different species exposed to the same concentration and parti size can show different sensitivities simply d to differences in the site of deposition of the particle within the lung (Hatch and Gro 1964). In summary, differences in pulmon ventilation may well be critical in the evaluation of the effects of airborne chemical irritants on the lung.

These considerations, taken in conjuncti with the fact that the existing chlorine lierature does not provide adequate co parisons of other species repeatedly expo to chlorine, make it difficult to conclude whether the effects reported in the lungs Fischer 344 rats at 3 or 1 ppm are sim to what would occur in a higher order mammal such as man. Future studies involving repeated exposure to chlorine other species would be necessary in order extrapolate the effects to humans.

Renal and hepatic effects have not b previously reported in animals repeate exposed to chlorine. Concentration-dependent elevations were seen in urine specifi

gravity at all exposure concentrations in females and 9 or 3 ppm in males. Blood urea nitrogen was raised in both sexes exposed to 9 ppm. The kidneys of both sexes exposed to 9 ppm were darkened in appearance and the histopathological examination of males exposed to 9 ppm showed swelling of the epithelial cells of the proximal convoluted tubules with increased eosinophilic cytoplasmic homogeneity and decreased granularity. The presence of renal effects was also supported by the clinical observation of urinary staining and matting of the fur around the genitalia in both sexes exposed to 9 or 3 ppm chlorine.

Evidence of hepatic effects were seen from elevations of the activity of several enzymes. A concentration related increase in alkaline phosphatase was seen in rats of both sexes exposed to 9 or 3 ppm. Additionally, γ-glutamyl transpeptidase was elevated in both sexes exposed to 9 ppm and serum glutamic pyruvic transaminase was elevated in females at 9 ppm. Animals exposed to 9 ppm showed an increased hepatocellular cytoplasmic eosinophilic homogeneity. Furthermore, an increase in the degree of hepatocellular cytoplasmic vacuolation was seen at 9 or 3 ppm.

Other effects resulting from repeated exposure to chlorine were seen in the spleen, thymus, and stomach. The spleen and thymus of rats exposed to 9 ppm showed a decreased content of lymphoid elements. This finding correlated with the statistically significant decreases in absolute and relative weights of these two organs at 9 ppm which may have been a function of the poor physical condition and decreased nutritional state of these rats. Ulceration and edema of the stomach wall was found in both sexes exposed to 9 ppm. A plausible explanation for this observation includes general stress or perhaps ingestion of hydrochloric and/or hypochlorous acids as a result of natural grooming or deposition in the oral cavity, either directly or via the mucus escalator.

Ammonia, evolved from animal urine and feces, has been shown to be present in inhalation chambers at levels ranging from approximately 0.2 to 2.4 ppm depending upon the variables of time, percentage animal loading, and chamber air flow (Barrow and Dodd, 1979). Furthermore, chloramines were formed in a dynamically operated exposure chamber containing chlorine and ammonia (ca. 1 ppm each). These data suggest that the concentrations of ammonia present in inhalation chambers are sufficient to react with low levels of chlorine, to form chloramines. The results of the current investigation as well as previous studies on the toxicity of chlorine, based upon repeated exposure, may have been affected by the presence of chloramines.

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Appendix B

Report on chlorine probe study (Path 83/1)

o Dr. Craig Barrow, with a copy to Dr. Tomm Hamm.

rom Kevin Morgan:

Date: 3.23.83

3 day exposure

n rats there was a SLIGHT increase in sub-pleural mononuclear cell (lymphocytes and macrophages) aggregates.

Chlorine exposure induced lesions in the nasal passages. These esions comprised localized areas of deciliation and non-keratinizing squamous metaplasia on the naso- and maxillo-urbinates, lateral wall and nasal septum. These lesions were onfined to the anterior sections of the nasal passages (1 and 2), and they were of MINIMAL severity. Inflammatory response was also inimal.

here were no chlorine induced lesions in the larynx, trachea and lungs.

There was no apparent difference between males and females, or rats nd mice.

9 day exposure

ontrols: as above and see note below.

Treated: There was minimal evidence of progression of the treatment induced lesions in the nose as follows:-

Mice - slightly more extensive, focal damage to the olfactory epithelium in the dorsal meatus.

Rats - prominent goblet cell hyperplasia in some animals, in section 2.

There was no apparent difference between males and females. There were no treatment related lesions in the larynx, trachea and lungs.

NOTE: The presence of lymphoid aggregates was associated with MINIMAL focal, alveolar wall thickening in one animal. This finding suggests that the animals may not be completely clean of pulmonary infection (probably viral). This may be a red-herring, but it warrants a check of the animal health records for rats from this supplier.

APPENDIX AA

CIIT PRELIMINARY STUDY OF CHLORINE TOXICITY IN FEMALE RATS

(STUDY 8321PRELIM)

CIIT PRELIMINARY STUDY OF CHLORINE TOXICITY IN FEMALE RATS

(STUDY 8321PRELIM)

Summary

The original study design for this bioassay included both male and female rats with an identical exposure regimen. During the early stage of this study considerable losses occurred in female rats, resulting in the necessity to abandon this component of the study, with groups of rats being used for a 12 month preliminary toxicology study. The slides for this work were processed and examined using identical procedures to those outlined in the main body of the report. Additional studies were carried out with these animals in order to ascertain the cause of death in females exposed to chlorine. We failed to determine why female rats were so sensitive to chlorine exposure. During the early phase of the study, in an effort to maintain the original study plan through reduction of intercurrent mortality, the study was continued with a modified chlorine exposure regimen as outlined below. The study was terminated at the 12 month timepoint with a necropsy of 10 animals per group. All animals remaining were donated to research projects or euthanized.

Materials and Methods

On March 16, 1983 three hundred and twenty female inbred Fischer 344 rats (CDF[F344]/CrlBR) (F-344) were received from Charles River Breeding Laboratories, Stoneridge Plant, Kingston, New York to be used on the chronic chlorine study (PATH/TOX #8321 referred to in this report as 8321 PRELIM). These rats, 36 days of age, were placed in

the CIIT animal facility quarantine room and moved to Rms 308, 309, 310 and 311 prior to the initiation of chlorine exposures on April 11, 1983.

Female rats in this study (8321PRELIM) were exposed 5 d/wk for the first 6 wks of the study, then, due to concerns for their health on May 19, 1983 the 1.0 and 2.5 ppm groups were converted to a 3 d/wk exposure schedule (Monday, Wednesday, Friday), and at 8 wks on June 6, 1983 the 0.4 ppm group of female rats were also transferred to this reduced exposure schedule. This reduced exposure schedule was continued for 12 months. On August 8, 1983, 5 control and 2.5 ppm chlorine exposed female rats were necropsied and liver and kidney samples collected for neutron activation analysis for metal toxicity from iron, zinc, cobalt, mercury, selenium, arsenic, antimony, chromium, and nickel. On April 12, 1984 10 animals per group were necropsied. Complete histopathology was carried out as described for rats in the body of this report, and slides were assessed by light microscopy by an EPL study pathologist. The remaining animals were removed from the study and donated to other research projects (AA1 and AA2).

Note: The female rat portion of the bioassay was repeated using the reduced exposure schedule as outlined in the body of the report (Study 8436). Because of the confusing nature of the exposures for animals in this portion of the study, no attempt will be made to present a detailed report. Only an outline of the relevant findings will be provided.

Results

Total animal accounting for study 8321 PRELIM is presented as AA1 and AA2. A body weight graph for the female rats in Study 8321 PRELIM is presented in AA3. The results of statistical analyses of maximum body weight are presented in AA4. There is evidence of reduced body weight in female rats at all levels of chlorine exposure.

The survival curve for female rats (8321 PRELIM) is depicted in AA5. Statistical analyses of survival data are presented in AA6. Survival analyses indicate significant chlorine exposure related a decrease in survival for female rats (trend test $p < 0.001$). Overall survival for female rats (Kaplan-Meier, 98.4%, 94.3%, 74.1% and 77.7% for 0, 0.4, 1.0, and 2.5 ppm chlorine exposure, respectively) was very low for 1.0 and 2.5 ppm chlorine exposed groups at the end of 1 year, resulting in termination of the study.

There were more early deaths among treated female rats (37) than among the control female rats (1), especially in 1.0 (18) and 2.5 (15) ppm exposed rats. In general, chlorine-exposed female rats that died early were described as dehydrated and/or emaciated with depletion of body fat. Necropsy terminal body and organ weight data for brain, kidney and liver (AA7 to AA10) indicated reduced terminal body weights in all exposed groups. Reduced liver weight was seen in the 1.0 and 2.5 ppm exposed female rats as well as reduced liver, kidney and brain weight ratios in some groups. Organ to body weight ratios were increased due to body weight depression seen in this study.

Metal analysis failed to reveal elevated levels of iron, zinc, cobalt, mercury, selenium, arsenic, antimony, chromium, or nickel in liver or kidney tissue from chlorine exposed female rats.

A number of neoplastic and non-neoplastic lesions were observed in treated and control female rats, as would be expected in animals of this age and sex. Neoplastic lesions of the reproductive tract occurred sporadically in treated groups, including a leiomyoma of the cervix and endometrial stromal polyps of the uterus. Treatment-related lesions were confined to the nasal passages of both male and female rats. These lesions were essentially identical to those reported in the main body of this document, and they will not be described further.

Conclusions

The cause of the high mortality of female rats in this study was not determined. The details of this study are relevant to the selection of a modified exposure protocol in female rats (Study 8436). No attempt will be made to compare the responses observed in animals in this study with the repetition of the 12 mo time point in study 8436, because the exposure regimens are not comparable.

Table AA1

Complete Animal Accounting 8321 PRELIM

F344 Rats

	Females			
Exposure Conc. (ppm)	0	0.4	1.0	2.5
Interim Necropsy I	5*	0	0	5*
Interim Necropsy II	10	10	10	10
Final Necropsy	0	0	0	0
Found Dead	1	4	17	14
Left Study as Missing	0	0	0	0
Accidental Trauma	0	0	0	0
Found Moribund	0	0	1	1
Removed for Research	54	56	42	40
Total	70	70	70	70

* Five animals from the control and high exposure concentration groups were removed for metal analysis.

Table AA2
CHLORINE STUDY
Unscheduled Deaths

STUDY # 8321 PRELIM
SPECIES F344 Rats
SEX Female

Exposure Conc. (ppm)	0	0.4	1.0	2.5
Found Dead	318	351,367,374, 394	424,432,433, 436,437,440, 444,453,454, 462,467,474, 476,483,484, 485,489	491,503,514, 515,527,528, 529,531,538, 545,546,548, 554,559
Total	1	4	17	14

Exposure Conc. (ppm)	0	0.4	1.0	2.5
Left Study as Missing	---	---	---	---
Total	0	0	0	0

Exposure Conc. (ppm)	0	0.4	1.0	2.5
Found Moribund, Necropsied	---	---	469	501
Total	0	0	1	1

Exposure Conc. (ppm)	0	0.4	1.0	2.5
Accidental Trauma, Necropsied	---	---	---	---
Total	0	0	0	0

(cont'd)

Table AA2
CHLORINE STUDY
in F344 Rats and B6C3F1 Mice
Animals Removed for Research

STUDY # 8321 PRELIM
SPECIES F344 Rats
SEX Female

(cont'd)

Exposure Conc. (ppm)	0	0.4	1.0	2.5
	291,292,293, 294,296,297, 298,299,300, 301,302,303, 304,305,306, 307,308,310, 311,312,313, 314,315,316, 317,319,320, 321,322,324, 325,326,328, 329,330,331, 332,333,334, 335,336,337, 338,339,340, 341,342,343, 344,345,346, 347,348,349	361,363,364, 365,366,368, 369,370,371, 372,373,375, 376,377,378, 379,380,381, 382,383,384, 385,386,387, 388,389,390, 391,392,393, 395,396,397, 398,399,400, 401,402,403, 404,405,406, 407,408,409, 410,411,412, 413,414,415, 416,417,418, 419,420	431,435,438, 439,441,442, 443,445,446, 447,448,449, 450,451,452, 455,456,457, 458,459,460 461,463,464, 465,466,468, 470,471,472, 473,475,477, 478,479,480, 481,482,486, 487,488,490	500,502,507, 508,509,510, 511,512,513, 516,517,518, 520,521,522, 523,524,525, 526,530,532, 534,535,536, 537,539,540, 541,542,543, 544,549,550, 551,552,553, 555,556,557, 558
Total	54	56	42	40

Total	55	60	60	55

Table AA3

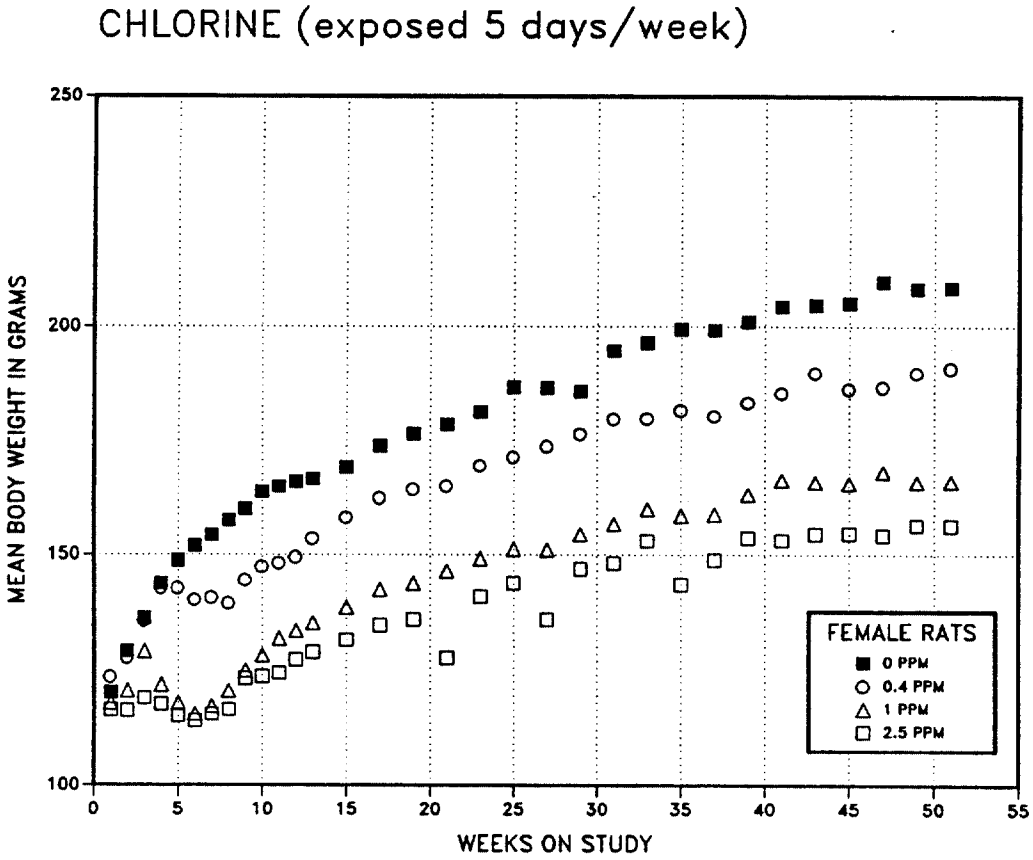
CHLORINE (exposed 5 days/week)
MEAN BODY WEIGHT IN GRAMS
250
200
150
100
0
5
10
15
20
25
30
35
40
45
50
55
WEEKS ON STUDY
FEMALE RATS
0 PPM
0.4 PPM
1 PPM
2.5 PPM

Table AA4

Dose	Female Rats, Exposed 5 days/week, Sacrificed Early Adjusted Mean	Unadjusted Mean	S.E.	N
0	209.7	212.6	2.6	70
0.4	186.7**	190.3**	2.0	70
1.0	166.6**	164.1**	2.3	70
2.5	155.0**	151.0**	2.2	70

* $p<0.05$
** $p<0.01$

Table AA5

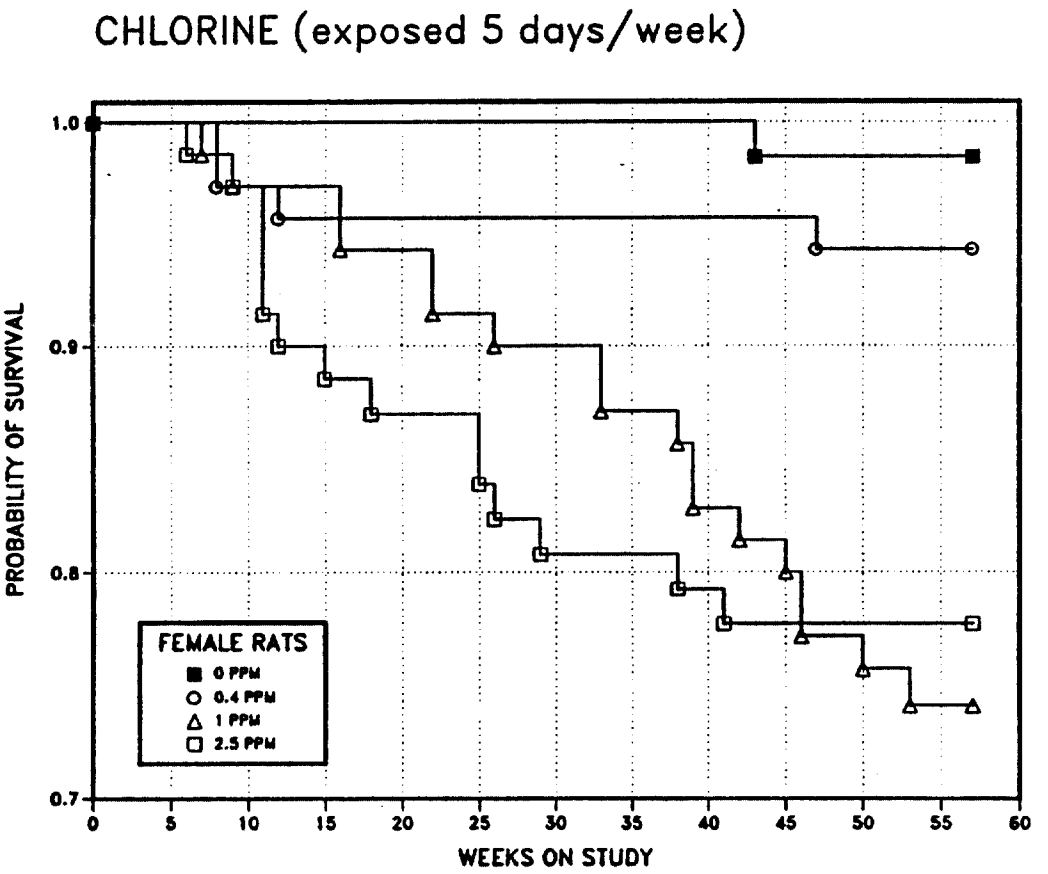
CHLORINE (exposed 5 days/week)
PROBABILITY OF SURVIVAL
1.0
0.9
0.8
0.7
0
5
10
15
20
25
30
35
40
45
50
55
60
WEEKS ON STUDY
FEMALE RATS
0 PPM
0.4 PPM
1 PPM
2.5 PPM

Table AA6

STATISTICAL ANALYSIS OF SURVIVAL DATA
FEMALE RATS
FIRST TERMINAL SACRIFICE AT 396 DAYS

KAPLAN-MEIER SURVIVAL PROBABILITY ESTIMATES (%)

DOSE	TIME (DAYS) 90	180	270	365	396 (A)
0 PPM	100.0	100.0	100.0	98.4	98.4
0.4 PPM	95.7	95.7	95.7	94.3	94.3
1.0 PPM	97.1	90.0	82.9	74.1	74.1
2.5 PPM	90.0	83.9	79.2	77.7	77.7

SURVIVAL SUMMARY STATISTICS

	DOSE 0 PPM	0.4 PPM	1.0 PPM	2.5 PPM
SURVIVAL AT END OF STUDY (KAPLAN-MEIER)	98.4%	94.3%	74.1%	77.7%
SIGNIFICANCE (B) (LIFE TABLE)	P<0.001	P=0.379	P<0.001	P<0.001
MEAN DAY OF NATURAL DEATHS (C) (STANDARD ERROR)	295.0 (.)	128.0 (66.9)	222.3 (23.6)	132.0 (19.6)
MEAN LIFE SPAN (D) (STANDARD ERROR)	355.0 (8.2)	363.0 (7.9)	334.6 (10.0)	302.4 (13.9)

(A) FIRST TERMINAL SACRIFICE
(B) THE FIRST ENTRY IS THE TREND TEST (TARONE, 1975) RESULT. SUBSEQUENT ENTRIES ARE THE RESULTS OF PAIRWISE TESTS (COX,1972). NEGATIVE TRENDS ARE INDICATED BY "N".
(C) MEAN OF ALL UNCENSORED DEATHS PRIOR TO TERMINAL SACRIFICE
(D) MEAN OF ALL DEATHS (UNCENSORED, CENSORED, TERMINAL SACRIFICE)

TABLE AA7 ANALYSIS OF INITIAL AND FINAL BODY WEIGHTS OF RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	INITIAL WT. (grams) MEAN	INITIAL WT. (grams) S.E.	FINAL WT. (grams) MEAN	FINAL WT. (grams) S.E.	RELATIVE TO CONTROLS (c)	WT. CHANGE (b) MEAN	WT. CHANGE (b) S.E.	RELATIVE TO CONTROLS (c)
0	10 (10)	111.6	2.6	201.8	3.0	-	90.17	3.30	-
0.4	12 (10)	**124.2	1.9	*192.5	3.0	-4.60	**70.42	2.91	-21.91
1	14 (10)	118.1	1.7	**156.4	4.0	-22.51	**43.71	3.64	-51.53
2.5	16 (10)	117.4	1.3	**150.8	2.2	-25.28	**34.44	1.89	-61.80
TREND(d)		+ (P=0.909)		- (P<0.001)			- (P<0.001)		
TEST USED(e)		Dunnett		Williams			Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals per dose group (Number surviving at final necropsy).
(b) Mean weight change of the animals in each dose group.
(c) [(Dosed group mean - Control group mean)/Control group mean] X 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE AA8 ANALYSIS OF BRAIN WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	BRAIN (grams) MEAN	BRAIN (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	1.806	0.018	201.8	3.0	8.96	0.10	-
0.4	10	1.803	0.023	*192.5	3.0	9.38	0.12	105
1	10	1.760	0.031	**156.4	4.0	**11.33	0.38	126
2.5	10	1.787	0.017	**150.8	2.2	**11.87	0.18	132
TREND(d)		- (P=0.272)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Brain and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE AA9 ANALYSIS OF KIDNEY WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	RIGHT KIDNEY (grams) MEAN	RIGHT KIDNEY (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	1.441	0.023	201.8	3.0	7.14	0.10	-
0.4	10	1.500	0.035	*192.5	3.0	*7.80	0.19	109
1	10	1.433	0.026	**156.4	4.0	**9.20	0.24	129
2.5	10	1.436	0.035	**150.8	2.2	**9.54	0.26	134
TREND(d)		- (P=0.638)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Dunnett		Williams		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Kidney and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

TABLE AA10 ANALYSIS OF LIVER WEIGHT RELATIVE TO BODY WEIGHT AT NECROPSY IN RATS AT FINAL NECROPSY IN THE TOXICITY TEST OF CHLORINE

5 DAY EXPOSURE

FEMALES

DOSE PPM	NUMBER (a)	LIVER (grams) MEAN	LIVER (grams) S.E.	BODY WEIGHT (grams) MEAN	BODY WEIGHT (grams) S.E.	RATIO (b) MEAN	RATIO (b) S.E.	PERCENT OF CONTROLS (c)
0	10	5.539	0.144	201.8	3.0	27.45	0.61	-
0.4	10	5.419	0.103	*192.5	3.0	28.18	0.55	103
1	10	**4.495	0.139	**156.4	4.0	28.73	0.39	105
2.5	10	**4.478	0.083	**150.8	2.2	**29.70	0.35	108
TREND(d)		- (P<0.001)		- (P<0.001)		+ (P<0.001)		
TEST USED(e)		Williams		Williams		Williams		

*=Significantly different from the control group (P=0.05)
**=Significantly different from the control group (P=0.01)

(a) Number of animals with both Liver and Body weight measured.
(b) Mean of the individual ratios of organ weight (mg) to body weight (grams).
(c) (Dosed group ratio / Control group ratio) x 100.
(d) Direction and significance of trend (Jonckheere's test).
(e) Multiple comparisons test comparing dose group to control group.

APPENDIX BB

REVIEW OF FEMALE REPRODUCTIVE TRACTS IN FEMALE B6C3F1 MICE

REVIEW OF FEMALE REPRODUCTIVE TRACTS IN FEMALE B6C3F1 MICE

After review of the original study pathologists summary incidence tables it was felt that there was an apparent treatment effect in the female mouse reproductive tract. All of the untrimmed female mouse reproductive tracts from the mid-concentration groups (2 and 3) were trimmed and then all female mouse reproductive tracts (groups 1, 2, 3, and 4) were read by a CIIT pathologist (Dr. D. Wolf). The results of that reading are included in this appendix (Table BB1, Finding Codes; BB2, Findings by Animal) and the statistical analysis are included in Table S1b. The interpretation of these results, conclusions and significance are present within the appropriate sections in the body of the report.

Chlorine codes

Organ (400)	Lesion	Code
Organ (400)		
Organ (400)	Abcess	231
Organ (400)	Cyst	238
Organ (400)	Cystadenoma	1238
Organ (400)	Granulosa Cell Tumor	697
Organ (400)	Hemorrhage	100
Organ (400)	Histiocytic sarcoma	171
Organ (400)	Malignant Lymphoma, lymphocytic	740
Organ (400)	Malignant Lymphoma, mixed	741
Organ (400)	Tubular Adenoma	1217
Oviduct (1510)	Dilatation	235
Oviduct (1510)	Inflammation, suppurative	1036
Oviduct (1510)	Malignant Lymphoma, lymphocytic	740
Uterus (710)	Endometrium, cystic hyperplasia	1197
Uterus (710)	Endometrium, stromal polyp	1226
Uterus (710)	Histiocytic Sarcoma	171
Uterus (710)	Inflammation, suppurative	1036
Uterus (710)	Invasion, tubular adenoma, ovary	1218
Uterus (710)	Leiomyoma	291
Uterus (710)	Malignant Lymphoma, lymphocytic	740
Uterus (710)	Malignant Lymphoma, mixed	741
Uterus (710)	Vaginitis	742
Uterus (710)	Inflammation	175
Uterus (710)	Vaginal Squamous Cell Carcinoma	743
General	Not examined, missing	10
General	No remarkable findings	20
General	Autolyzed	30

Animal #	Organ #	Finding #	Severity Code
278	400	238	3
278	1510	20	
278	710	1197	2
278	710	1036	1
278	710	742	2
279	400	20	
279	1510	20	
279	710	1197	3
279	710	1036	1
280	400	20	
280	1510	20	
280	710	1197	2
280	710	1036	1
282	400	20	
282	1510	20	
282	710	1036	1
283	400	238	2
283	1510	20	
283	710	1197	2
283	710	1036	2
284	400	20	
284	1510	10	
284	710	1197	1
284	710	175	3
286	400	20	
286	1510	20	
286	710	1197	2
287	400	238	1
287	1510	20	
287	710	1197	3
288	400	231	5
288	1510	10	
288	710	1197	3
288	710	1036	2
289	400	1298	
289	400	238	5
289	1510	20	
289	710	1197	3
291	400	740	
291	1510	740	
291	710	740	
298	400	20	
298	1510	20	
298	710	1197	1
299	400	10	
299	1510	20	
299	710	1197	2
299	710	1226	
301	1510	20	
301	710	1197	1

302	400	20	
302	1510	20	
302	710	1197	2
302	710	1036	1
303	400	740	
303	1510	740	
303	710	740	
304	400	20	
304	1510	20	
304	710	20	
305	400	10	
305	1510	20	
305	710	30	
306	400	238	3
306	1510	235	1
306	710	1197	3
307	400	231	4
307	1510	20	
307	710	1226	
308	400	20	
308	1510	20	
308	710	1036	4
308	710	742	3
309	400	20	
309	1510	20	
309	710	1197	2
309	710	742	1
309	710	1036	2
310	400	20	
310	1510	20	
310	710	1197	3
310	710	742	1
311	400	20	
311	1510	20	
311	710	1197	3
312	400	20	
312	1510	20	
312	710	20	
313	400	20	
313	1510	20	
313	710	1197	2
314	400	238	2
314	1510	20	
314	710	1197	2
315	400	20	
315	1510	20	
315	710	1197	2
316	400	20	
316	1510	20	
316	710	1197	1
317	400	20	

317	1510	235	2
317	710	1197	2
319	400	20	
319	1510	20	
319	710	1197	1
320	400	20	
320	1510	20	
320	710	20	
321	400	20	
321	1510	20	
321	710	1197	3
322	400	20	
322	1510	235	1
322	710	1197	3
323	400	20	
323	1510	235	1
323	710	1197	4
324	400	20	
324	1510	742	1
324	710	1197	3
324	710	325	1
325	400	20	
325	1510	20	
325	710	1197	2
326	400	238	2
326	1510	20	
326	710	1197	2
326	710	1036	2
328	400	740	
328	1510	20	
328	710	1197	3
328	710	1226	3
329	400	20	
329	1510	20	
329	710	1197	2
330	400	10	
330	1510	20	
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332	400	20	
332	1510	10	
332	710	1197	2
332	710	742	2
332	710	743	
333	400	20	
333	1510	20	
333	710	1197	1
333	710	742	1
334	400	20	

334	1510	235	1
334	710	1197	3
334	710	1036	1
335	400	20	
335	1510	20	
335	710	20	
336	400	238	1
336	1510	10	
336	710	1197	1
336	710	742	1
337	400	10	
337	1510	20	
337	710	1197	1
337	710	742	1
338	400	20	
338	1510	20	
338	710	1197	3
340	400	238	4
340	1510	20	
340	710	1197	2
340	710	742	1
341	400	20	
341	1510	20	
341	710	1197	3
341	710	742	1
341	710	743	1
342	400	20	
342	1510	235	1
342	710	1197	2
342	710	742	2
343	400	238	3
343	1510	235	1
343	710	1197	2
344	400	238	4
344	1510	20	
344	710	1197	2
345	400	238	3
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345	710	20	
346	400	20	
346	1510	20	
346	710	1197	1
347	400	20	
347	1510	20	
347	710	1197	1
347	710	1036	1
348	400	238	2
348	1510	20	
348	710	1197	1
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349	710	742	2
350	400	20	
350	1510	20	
350	710	1197	2
350	710	1036	2
350	710	742	1
351	400	20	
351	1510	20	
351	710	1197	2
351	710	1036	1
351	710	742	1
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352	1510	10	
352	710	1197	1
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359	710	1197	1
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360	710	20	
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361	710	1036	2
362	400	20	
362	1510	20	
362	710	1197	2
362	710	1036	2
362	710	742	2
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363	1510	10	
363	710	1197	3

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371	1510	10	
371	710	1197	1
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372	1510	20	
372	710	20	
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374	1510	20	
374	710	1197	2
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376	710	291	
377	400	238	4
377	1510	20	
377	710	20	
378	400	238	2
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378	710	1036	1
378	710	742	1
379	400	231	4

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394	710	1197	3
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395	1510	20	
395	710	20	
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397	710	20	
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399	1510	20	
399	710	1197	2
399	710	1036	2
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403	710	1197	2
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404	1510	20	
404	710	1197	1
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416	1510	20	
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431	710	20	
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432	710	1197	2
432	710	1036	1
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475	710	20	
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491	710	20	

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520	710	1036	1
520	710	742	1
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521	1510	235	1
521	710	1197	3
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522	710	1197	1

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524	1510	20	
524	710	1197	2
524	710	742	1
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525	1510	20	
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526	400	10	
526	1510	20	
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527	710	742	2
528	400	231	4
528	1510	20	
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531	710	1197	4
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537	710	1197	1

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539	1510	10	
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540	1510	20	
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541	1510	20	
541	710	1197	1
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542	710	1197	1
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544	1510	20	
544	710	1197	3
544	710	1036	2
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546	1510	20	
546	710	1197	2
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547	1510	1036	2
547	710	1197	3
547	710	1036	3
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554	1510	20	
554	710	20	
555	400	10	
555	1510	10	
555	710	1197	3
555	710	1036	2
555	710	742	1
557	400	697	
557	1510	10	
557	710	20	

APPENDIX CC

REVIEW OF NASAL VESTIBULAR PATHOLOGY FOR SEPTAL FENESTRATION AND 'CAGE CONTAMINANT' ASSOCIATED LESION

REVIEW OF NASAL VESTIBULAR PATHOLOGY FOR SEPTAL FENESTRATION AND 'CAGE CONTAMINANT' ASSOCIATED LESION

Prepared by: Kevin T. Morgan, April, 1993.

Introduction

During review of the pathology narratives generated by the original study pathologists (Appendix Q), and quality assurance pathologist (Appendix X), and individual slides during preparation of the manuscript associated with this work, two lesions were detected that were not considered adequately addressed in the original pathology narrative. These lesions were (a) perforation (fenestration) of the nasal septum, and (b) background lesions attributable to environmental contamination by ammonia or other gases, as described recently in rats by Bolon et al. (1991).

Materials and Methods

The first two sections of the nasal passages of all rats and mice in studies 8321, 8436 and 8437 were examined by light microscopy and scored subjectively for the two lesions referred to above.

(a) Septal fenestration was scored as present or absent. If there was necrosis of the septum but no evidence of a direct communication between the left and right nasal airways a

negative score was used. Positive scores were confined to animals with direct communication between the left and right nasal passages, in the anterior septum, in a region in which the two airways are distinctly separated (see Morgan et al., 1991). This lesion has been reported previously in rodents exposed to airborne gaseous irritants (Buckley et al., 1985). Care should be taken to avoid confusing this lesion with the septal window, a normal feature of the posterior region of the nose of rats and mice.

(b) Background lesions in the nasal vestibule that have been attributed to environmental exposure to cage contaminants, including ammonia (Bolon et al., 1991). Reference to the latter publication provides detailed information on this lesion in rats. However, this response has not been reported or studied (we believe) in mice. In mice, the lymphocytic infiltrate is less prominent, while epithelial hyperplasia, with considerable folding is a more salient feature. Whether these responses in rats and mice are equivalent etiologically remains to be determined. These lesions were scored subjectively, using a scale of 0 to 5, as follows: 0 = normal (apparently healthy); 1 = very slight response, of doubtful biological significance; 2 = slight but distinct lesion; 3 = moderately severe lesion; 4 = severe lesion; 5 = very severe lesion. The group mean of these scores was then determined and the result interpreted.

Results

Individual animal data is presented in Table CC1. The summary of results for septal fenestration is in Tables 5 and 6, and the mean scores for background vestibular pathology are presented in Tables S1b and S2b.

(a) **Septal fenestration.** In rats, septal fenestration was confined to one male (#8321-222), which was in the 2.5 ppm group, and no evidence of this lesion was detected in females. In mice, however, this lesion was much more frequent (Table S1b), being present with a frequency of over 40% in the group 3 males. In male mice the frequency of this lesion exhibited no evidence of a concentration-response relationship, being present in all treated groups and absent in controls. In female mice, there was a clear concentration-response relationship, with the 0.4 ppm group having a similar incidence (5%) to that observed in the controls (5.2%).

Chlorine exposure clearly contributed to the incidence of septal fenestration in the anterior nose of mice, and induced a very low incidence of the same lesion in male rats exposed to 2.5 ppm.

(b) **Background 'cage contaminant' associated lesions.** Mean scores for these responses in rats and mice demonstrated their presence in all groups, including controls. In rats this lesion was unaffected by treatment, while in mice the mean score for this response was significantly higher in the exposed groups compared to controls. The latter observation suggests that features of the background lesion may not be distinguishable from certain chlorine-induced responses in this site.

References

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Morgan, K.T., Kimbell, J.S., Monticello, T.M., Patra, A.L., and Fleishman, A. (1991). Studies of inspiratory airflow patterns in the nasal passages of the F344 rat and rhesus monkey using nasal molds: relevance to formaldehyde toxicity. Toxicol. Appl. Pharmacol., 110, 223-240.

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

K T Morgan 6/21/93

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	comments
1	0.0	M	n	1	
2	0.0	M	n	0	
3	0.0	M	n	0	
4	0.0	M	n	0	
5	0.0	M	n	0	
6	0.0	M	n	0	
7	0.0	M	n	0	
8	0.0	M	n	0	
9	0.0	M	n	2	
10	0.0	M	n	0	
11	0.0	M	no sample		
12	0.0	M	n	0	
13	0.0	M	n	0	
14	0.0	M	n	1	
15	0.0	M	n	0	
16	0.0	M	n	1	
17	0.0	M	no sample		
18	0.0	M	n	0	
19	0.0	M	n	0	
20	0.0	M	n	0	
21	0.0	M	n	0	
22	0.0	M	n	0	
23	0.0	M	n	0	
24	0.0	M	n	0	
25	0.0	M	n	1	
26	0.0	M	n	0	
27	0.0	M	0		
28	0.0	M	n	2	
29	0.0	M	0		
30	0.0	M	n	2	
31	0.0	M	n	0	
32	0.0	M	n	1	
33	0.0	M	n	1	
34	0.0	M	TM		
35	0.0	M	n	0	
36	0.0	M	n	0	
37	0.0	M	n	0	
38	0.0	M	0		
39	0.0	M	n	0	
40	0.0	M	n	0	
41	0.0	M	n	0	
42	0.0	M	n	0	
43	0.0	M	n	0	
44	0.0	M	n	0	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
45	0.0	M	n	1	
46	0.0	M	n	1	
47	0.0	M	n	1	
48	0.0	M	n	0	
49	0.0	M	n	2	
50	0.0	M	n	2	
51	0.0	M	n	2	
52	0.0	M	n	0	
53	0.0	M	n	0	
54	0.0	M	n	0	
55	0.0	M	n	0	
56	0.0	M	n	0	
57	0.0	M	n	0	
58	0.0	M	0		
59	0.0	M	tm		
60	0.0	M	n	1	
61	0.0	M	n	0	
62	0.0	M	n	2	
63	0.0	M	n	1	
64	0.0	M	n	0	
65	0.0	M	n	0	
66	0.0	M	n	0	
67	0.0	M	0		
68	0.4	M	n	1	
69	0.4	M	0		
70	0.4	M	y	3	
71	0.4	M	y	3	
72	0.4	M	y	2	
73	0.4	M	n	4	
74	0.4	M	y	4	
75	0.4	M	n	0	
76	0.4	M	n	0	
77	0.4	M	y	4	
78	0.4	M	n	4	
79	0.4	M	y	5	
80	0.4	M	0		
81	0.4	M	y	2	
82	0.4	M	n	2	
83	0.4	M	n	4	
84	0.4	M	n	2	
85	0.4	M	n	1	
86	0.4	M	n	3	
87	0.4	M	n	1	
88	0.4	M	0		

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
89	0.4	M	n	1	
90	0.4	M	y	3	
91	0.4	M	no sample		
92	0.4	M	n	1	
93	0.4	M	n	3	
94	0.4	M	0		
95	0.4	M	n	4	
96	0.4	M	y	3	
97	0.4	M	n	2	
98	0.4	M	y	3	
99	0.4	M	y	2	
100	0.4	M	n	0	
101	0.4	M	n	2	
102	0.4	M	y	1	
103	0.4	M	n	1	
104	0.4	M	n	1	
105	0.4	M	n	1	
106	0.4	M	n	2	
107	0.4	M	n	0	
108	0.4	M	n	1	
109	0.4	M	n	4	
110	0.4	M	n	1	
111	0.4	M	n	4	
112	0.4	M	y	4	
113	0.4	M	no sample		
114	0.4	M	y	1	
115	0.4	M	n	0	
116	0.4	M	n	2	
117	0.4	M	n	3	
118	0.4	M	y	3	
119	0.4	M	n	3	
120	0.4	M	n	1	
121	0.4	M	n	0	
122	0.4	M	n	1	
123	0.4	M	y	1	
124	0.4	M	y	4	
125	0.4	M	n	0	
126	0.4	M	n	2	
127	0.4	M	n	1	
128	0.4	M	n	1	
129	0.4	M	n	0	
130	0.4	M	n	2	
131	0.4	M	n	0	
132	0.4	M	n	0	
133	0.4	M	n	0	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
134	0.4	M	n	0	
135	0.4	M	n	3	
136	0.4	M	n	1	
137	0.4	M	n	2	
138	1.0	M	y	2	
139	1.0	M	y	2	
140	1.0	M	n	2	
141	1.0	M	n	0	
142	1.0	M	n	1	
143	1.0	M	y	3	
144	1.0	M	n	1	
145	1.0	M	n	1	
146	1.0	M	n	3	
147	1.0	M	y	3	
148	1.0	M	y	4	
149	1.0	M	y	3	
150	1.0	M	y	3	
151	1.0	M	y	2	
152	1.0	M	n	0	
153	1.0	M	n	2	
154	1.0	M	n	1	
155	1.0	M	y	3	
156	1.0	M	n	4	
157	1.0	M	n	1	
158	1.0	M	n	3	
159	1.0	M	n	1	
160	1.0	M	y	3	
161	1.0	M	n	1	
162	1.0	M	no sample		
163	1.0	M	no sample		
164	1.0	M	n	0	
165	1.0	M	no sample		
166	1.0	M	0		
167	1.0	M	n	1	
168	1.0	M	y	2	
169	1.0	M	no sample		
170	1.0	M	no sample		
171	1.0	M	n	3	
172	1.0	M	n	1	
173	1.0	M	y	4	
174	1.0	M	y	3	
175	1.0	M	y	3	
176	1.0	M	n	2	
177	1.0	M	no sample		

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
178	1.0	M	n	1	
179	1.0	M	n	1	
180	1.0	M	n	1	
181	1.0	M	y	2	
182	1.0	M	y	3	
183	1.0	M	y	3	
184	1.0	M	y	2	
185	1.0	M	no sample		
186	1.0	M	n	0	
187	1.0	M	n	2	
188	1.0	M	n	3	
189	1.0	M	no sample		
190	1.0	M	n	2	
191	1.0	M	y	3	
192	1.0	M	y	3	
193	1.0	M	n	1	
194	1.0	M	n	3	
195	1.0	M	y	3	
196	1.0	M	no sample		
197	1.0	M	n	1	
198	1.0	M	n	0	
199	1.0	M	y	4	
200	1.0	M	y	4	
201	1.0	M	n	1	
202	1.0	M	0		
203	1.0	M	n	1	
204	1.0	M	n	0	
205	1.0	M	y	4	
206	1.0	M	n	0	
207	1.0	M	n	0	
208	2.5	M	n	3	
209	2.5	M	n	0	
210	2.5	M	y	1	
211	2.5	M	n	0	
212	2.5	M	n	0	interesting nose
213	2.5	M	n	0	
214	2.5	M	y	1	
215	2.5	M	y	3	
216	2.5	M	n	1	
217	2.5	M	0		
218	2.5	M	n	1	
219	2.5	M	no sample		
220	2.5	M	no sample		
221	2.5	M	n	1	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
222	2.5	M	n	0	
223	2.5	M	n	0	
224	2.5	M	y	2	
225	2.5	M	y	2	
226	2.5	M	n	2	
227	2.5	M	y	2	
228	2.5	M	y	3	
229	2.5	M	n	1	
230	2.5	M	y	2	
231	2.5	M	n	1	
232	2.5	M	n	1	
233	2.5	M	n	0	
234	2.5	M	n	2	
235	2.5	M	no sample		
236	2.5	M	n	1	
237	2.5	M	n	2	
238	2.5	M	0		
239	2.5	M	0		
240	2.5	M	n	0	
241	2.5	M	n	0	
242	2.5	M	y	3	
243	2.5	M	n	0	
244	2.5	M	n	0	
245	2.5	M	n	1	
246	2.5	M	n	1	
247	2.5	M	n	0	
248	2.5	M	n	0	
249	2.5	M	no sample		
250	2.5	M	n	1	
251	2.5	M	y	3	
252	2.5	M	n	0	
253	2.5	M	n	2	
254	2.5	M	0		
255	2.5	M	n	0	
256	2.5	M	n	0	
257	2.5	M	n	1	
258	2.5	M	y	4	
259	2.5	M	n	1	
260	2.5	M	no sample		
261	2.5	M	y	2	
262	2.5	M	y	3	
263	2.5	M	n	2	
264	2.5	M	n	1	
265	2.5	M	y	2	
266	2.5	M	n	0	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
267	2.5	M	no sample		
268	2.5	M	n	0	
269	2.5	M	n	1	
270	2.5	M	no sample		
271	2.5	M	TM		
272	2.5	M	n	1	
273	2.5	M	y	4	
274	2.5	M	n	1	
275	2.5	M	n	0	
276	2.5	M	0		
277	2.5	M	n	0	
278	0.0	F	n	0	
279	0.0	F	n	2	
280	0.0	F	n	1	
281	0.0	F	0		
282	0.0	F	n	0	
283	0.0	F	n	0	
284	0.0	F	n	0	
285	0.0	F	0		
286	0.0	F	n	2	
287	0.0	F	y	2	
288	0.0	F	n	2	
289	0.0	F	n	3	
290	0.0	F	0		
291	0.0	F	n	0	
292	0.0	F	n	0	
293	0.0	F	0		
294	0.0	F	0		
295	0.0	F	n	0	
296	0.0	F	n	0	
297	0.0	F	n	0	
298	0.0	F	no sample		
299	0.0	F	n	0	
300	0.0	F	n	0	
301	0.0	F	n	1	
302	0.0	F	n	0	
303	0.0	F	n	2	
304	0.0	F	n	0	
305	0.0	F	n	0	
306	0.0	F	no sample		
307	0.0	F	n	0	
308	0.0	F	n	1	
309	0.0	F	n	3	
310	0.0	F	n	3	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
311	0.0	F	y	2	
312	0.0	F	n	0	
313	0.0	F	y	0	
314	0.0	F	n	0	
315	0.0	F	n	2	
316	0.0	F	n	1	
317	0.0	F	n	2	
318	0.0	F	0		
319	0.0	F	n	0	
320	0.0	F	n	0	
321	0.0	F	no sample		
322	0.0	F	n	2	
323	0.0	F	n	2	
324	0.0	F	n	2	
325	0.0	F	n	2	
326	0.0	F	n	0	
327	0.0	F	n	0	
328	0.0	F	n nearly fene.	3	
329	0.0	F	n	2	
330	0.0	F	n	1	
331	0.0	F	n	0	
332	0.0	F	n	0	
333	0.0	F	no sample		
334	0.0	F	n	1	
335	0.0	F	n	0	
336	0.0	F	n	2	
337	0.0	F	n	0	
338	0.0	F	n	3	
339	0.0	F	0		
340	0.0	F	n	1	
341	0.0	F	n	0	
342	0.0	F	n	2	
343	0.0	F	n	1	
344	0.0	F	n	3	
345	0.0	F	n	0	
346	0.0	F	n	2	
347	0.0	F	no sample		
348	0.4	F	n	1	
349	0.4	F	n	4	
350	0.4	F	n	3	
351	0.4	F	n	3	
352	0.4	F	n	4	
353	0.4	F	n	3	
354	0.4	F	n	0	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
355	0.4	F	no sample		
356	0.4	F	n	0	
357	0.4	F	n	1	
358	0.4	F	n	0	
359	0.4	F	y	2	
360	0.4	F	n	0	
361	0.4	F	n	2	
362	0.4	F	no sample		
363	0.4	F	n	3	
364	0.4	F	no sample		
365	0.4	F	n	3	
366	0.4	F	n	0	
367	0.4	F	n	0	
368	0.4	F	n	1	
369	0.4	F	n	0	
370	0.4	F	n	2	
371	0.4	F	n	3	
372	0.4	F	TM		
373	0.4	F	n	1	
374	0.4	F	n	3	
375	0.4	F	no sample		
376	0.4	F	no sample		
377	0.4	F	n	2	
378	0.4	F	n	3	
379	0.4	F	n	1	
380	0.4	F	n	1	
381	0.4	F	n	0	
382	0.4	F	n	0	
383	0.4	F	0		
384	0.4	F	n	0	
385	0.4	F	n	3	
386	0.4	F	n	4	
387	0.4	F	n	0	
388	0.4	F	n	0	
389	0.4	F	n	2	
390	0.4	F	n	3	
391	0.4	F	n	0	
392	0.4	F	n	0	
393	0.4	F	n	3	
394	0.4	F	n	1	
395	0.4	F	TM		
396	0.4	F	y	3	
397	0.4	F	n	0	
398	0.4	F	n	1	
399	0.4	F	n	2	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
400	0.4	F	n	0	
401	0.4	F	0		
402	0.4	F	n	0	
403	0.4	F	n	2	
404	0.4	F	no sample		
405	0.4	F	n	0	
406	0.4	F	n	2	
407	0.4	F	n	0	
408	0.4	F	n	2	
409	0.4	F	n	3	
410	0.4	F	n	3	
411	0.4	F	n	2	
412	0.4	F	y	3	
413	0.4	F	n	0	
414	0.4	F	n	2	
415	0.4	F	n	0	
416	0.4	F	n	3	
417	0.4	F	n	1	
418	1.0	F	0		
419	1.0	F	y	2	
420	1.0	F	0		
421	1.0	F	n	2	
422	1.0	F	n	1	
423	1.0	F	n	0	
424	1.0	F	n	2	
425	1.0	F	n	3	
426	1.0	F	y	3	
427	1.0	F	0		
428	1.0	F	no sample		
429	1.0	F	n	0	
430	1.0	F	n	0	
431	1.0	F	n	1	
432	1.0	F	n	3	
433	1.0	F	n	0	
434	1.0	F	n	3	
435	1.0	F	n	3	
436	1.0	F	no sample		
437	1.0	F	0		
438	1.0	F	n	0	
439	1.0	F	y	3	
440	1.0	F	n	3	
441	1.0	F	no sample		
442	1.0	F	0		
443	1.0	F	no sample		

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
444	1.0	F	n	3	
445	1.0	F	n	0	
446	1.0	F	0		
447	1.0	F	n	0	
448	1.0	F	n	0	
449	1.0	F	0		
450	1.0	F	no sample		
451	1.0	F	0		
452	1.0	F	no	0	
453	1.0	F	no sample		
454	1.0	F	n	0	
455	1.0	F	y	2	
456	1.0	F	n	1	
457	1.0	F	n	2	
458	1.0	F	n	0	
459	1.0	F	y	2	
460	1.0	F	no sample		
461	1.0	F	n	3	
462	1.0	F	n	0	
463	1.0	F	n	0	
464	1.0	F	no sample		
465	1.0	F	n	3	
466	1.0	F	y	1	
467	1.0	F	0		
468	1.0	F	n	1	
469	1.0	F	no sample		
470	1.0	F	n	0	
471	1.0	F	0		
472	1.0	F	y	3	
473	1.0	F	0		
474	1.0	F	n	3	
475	1.0	F	y	1	
476	1.0	F	y	3	
477	1.0	F	n	1	
478	1.0	F	y	3	
479	1.0	F	y	2	
480	1.0	F	no sample		
481	1.0	F	0		
482	1.0	F	n	0	
483	1.0	F	n	0	
484	1.0	F	y	1	
485	1.0	F	n	1	
486	1.0	F	n	1	
487	1.0	F	n	3	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Other	Comments
488	2.5	F	n	2	
489	2.5	F	n	2	
490	2.5	F	0		
491	2.5	F	n	0	
492	2.5	F	y	3	
493	2.5	F	n	2	
494	2.5	F	n	1	
495	2.5	F	n	0	
496	2.5	F	y	2	
497	2.5	F	0		
498	2.5	F	n	1	
499	2.5	F	n	3	
500	2.5	F	0		
501	2.5	F	n	1	
502	2.5	F	n	0	
503	2.5	F	n	1	
504	2.5	F	y	3	
505	2.5	F	n	3	
506	2.5	F	no sample		
507	2.5	F	n	0	
508	2.5	F	no sample		
509	2.5	F	n	1	
510	2.5	F	n	2	
511	2.5	F	n	1	
512	2.5	F	y	1	
513	2.5	F	0		
514	2.5	F	no sample		
515	2.5	F	n	3	
516	2.5	F	n	0	
517	2.5	F	n	2	
518	2.5	F	n	1	
519	2.5	F	n	1	
520	2.5	F	y	1	
521	2.5	F	y	1	
522	2.5	F	y	3	
523	2.5	F	0		
524	2.5	F	y	1	
525	2.5	F	y	2	
526	2.5	F	y	0	
527	2.5	F	n	3	
528	2.5	F	y	1	
529	2.5	F	y	3	
530	2.5	F	n	2	
531	2.5	F	n	1	
532	2.5	F	y	1	

8437 (Cl) male and female mice K. Morgan's reading 2/3-4/ 1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage contaminant Lesion	Comments
533	2.5	F	TM		
534	2.5	F	0		
535	2.5	F	no sample		
536	2.5	F	n	0	
537	2.5	F	n	2	
538	2.5	F	y	1	
539	2.5	F	y	0	
540	2.5	F	n	2	
541	2.5	F	n	1	
542	2.5	F	n	0	
543	2.5	F	0		
544	2.5	F	y	0	
545	2.5	F	no sample		
546	2.5	F	y	3	
547	2.5	F	n	1	
548	2.5	F	n	0	
549	2.5	F	0		
550	2.5	F	TM		
551	2.5	F	0		
552	2.5	F	n	0	
553	2.5	F	0		
554	2.5	F	no sample		
555	2.5	F	y	2	
556	2.5	F	0		
557	2.5	F	no sample		
PRESENT =y					
ABSENT= n					
Tissue missing /not taken at necropsy = TM					
No slides on animal = 0					
No sample (tissue not readable or tissue not present on slide)					

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

K Morgan 6/21/93

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	Comments
1	0.0	F	n	2	
2	0.0	F	n	2	
3	0.0	F	n	2	
4	0.0	F	n	1	
5	0.0	F	n	0	
6	0.0	F	n	0	
7	0.0	F	n	3	
8	0.0	F	n	2	
9	0.0	F	n	2	
10	0.0	F	n	2	
11	0.0	F	n	0	
12	0.0	F	n	1	
13	0.0	F	n	0	thrombosis
14	0.0	F	n	0	thrombosis
15	0.0	F	n	1	
16	0.0	F	n	3	
17	0.0	F	n	1	
18	0.0	F	n	2	
19	0.0	F	n	1	
20	0.0	F	n	1	
21	0.0	F	n	0	
22	0.0	F	n	1	
23	0.0	F	n	1	
24	0.0	F	n	2	
25	0.0	F	n	2	
26	0.0	F	n	0	
27	0.0	F	n	1	
28	0.0	F	n	2	
29	0.0	F	n	1	
30	0.0	F	n	0	
31	0.0	F	n	1	
32	0.0	F	no sample		
33	0.0	F	n	1	
34	0.0	F	n	1	
35	0.0	F	n	0	
36	0.0	F	n	1	
37	0.0	F	n	1	
38	0.0	F	n	2	
39	0.0	F	n	0	
40	0.0	F	n	1	nasal ld lesion
41	0.0	F	n	2	
42	0.0	F	n	3	
43	0.0	F	n	1	
44	0.0	F	n	0	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesior	Comments
45	0.0	F	n	0	
46	0.0	F	n	0	hyperostosis
47	0.0	F	n	1	
48	0.0	F	n	0	
49	0.0	F	n	1	
50	0.0	F	n	0	
51	0.0	F	n	1	
52	0.0	F	n	2	
53	0.0	F	n	0	
54	0.0	F	n	0	
55	0.0	F	n	1	
56	0.0	F	n	0	
57	0.0	F	n	1	
58	0.0	F	n	1	
59	0.0	F	n	1	
60	0.0	F	n	0	
61	0.0	F	n	1	
62	0.0	F	n	2	
63	0.0	F	n	1	
64	0.0	F	n	3	
65	0.0	F	n	3	
66	0.0	F	n	2	
67	0.0	F	n	1	
68	0.0	F	n	1	thrombosis
69	0.0	F	n	1	
70	0.0	F	0		
71	0.4	F	n	1	
72	0.4	F	n	1	
73	0.4	F	n	1	
74	0.4	F	n	1	
75	0.4	F	n	2	
76	0.4	F	n	1	
77	0.4	F	n	1	
78	0.4	F	n	0	
79	0.4	F	n	1	
80	0.4	F	n	1	
81	0.4	F	n	2	
82	0.4	F	n	0	
83	0.4	F	n	0	
84	0.4	F	n	3	thrombosis
85	0.4	F	n	3	
86	0.4	F	n	1	
87	0.4	F	TM		
88	0.4	F	n	2	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesior	Comments
89	0.4	F	n	0	
90	0.4	F	n	3	
91	0.4	F	n	1	
92	0.4	F	n	3	
93	0.4	F	n	1	
94	0.4	F	n	0	
95	0.4	F	n	1	
96	0.4	F	n	2	
97	0.4	F	n	0	
98	0.4	F	n	0	
99	0.4	F	n	2	
100	0.4	F	n	1	
101	0.4	F	n	0	
102	0.4	F	n	2	
103	0.4	F	n	1	
104	0.4	F	n	2	
105	0.4	F	n	1	
106	0.4	F	n	0	
107	0.4	F	n	2	
108	0.4	F	n	2	
109	0.4	F	n	0	
110	0.4	F	n	2	
111	0.4	F	n	2	
112	0.4	F	n	3	
113	0.4	F	n	1	
114	0.4	F	n	1	
115	0.4	F	n	1	
116	0.4	F	n	1	
117	0.4	F	n	0	
118	0.4	F	n	2	
119	0.4	F	n	1	
120	0.4	F	n	1	
121	0.4	F	n	1	
122	0.4	F	n	2	
123	0.4	F	n	3	
124	0.4	F	n	1	
125	0.4	F	n	2	
126	0.4	F	n	1	
127	0.4	F	0		
128	0.4	F	n	1	
129	0.4	F	n	1	
130	0.4	F	n	2	
131	0.4	F	n	1	
132	0.4	F	n	1	
133	0.4	F	n	1	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesion	Comments
134	0.4	F	n	0	
135	0.4	F	n	2	
136	0.4	F	n	1	
137	0.4	F	n	1	
138	0.4	F	n	1	
139	0.4	F	n	2	thrombosis
140	0.4	F	n	2	
141	1.0	F	n	1	
142	1.0	F	n	2	
143	1.0	F	n	2	
144	1.0	F	n	1	
145	1.0	F	n	1	
146	1.0	F	no sample		
147	1.0	F	n	2	
148	1.0	F	n	1	
149	1.0	F	n	1	
150	1.0	F	n	1	
151	1.0	F	n	0	
152	1.0	F	n	2	
153	1.0	F	n	0	
154	1.0	F	n	2	
155	1.0	F	n	0	
156	1.0	F	n	0	
157	1.0	F	n	0	
158	1.0	F	0		
159	1.0	F	n	1	hyperostosis
160	1.0	F	no sample		hyperostosis
161	1.0	F	n	0	
162	1.0	F	n	0	
163	1.0	F	n	2	
164	1.0	F	n	2	
165	1.0	F	n	2	
166	1.0	F	n	0	
167	1.0	F	n	1	
168	1.0	F	n	1	
169	1.0	F	n	1	
170	1.0	F	n	1	
171	1.0	F	n	2	
172	1.0	F	n	2	
173	1.0	F	n	0	
174	1.0	F	n	2	
175	1.0	F	n	0	
176	1.0	F	n	2	
177	1.0	F	n	2	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesior	Comments
178	1.0	F	n	0	
179	1.0	F	n	1	
180	1.0	F	n	1	
181	1.0	F	n	2	
182	1.0	F	n	3	
183	1.0	F	n	1	
184	1.0	F	n	1	
185	1.0	F	n	2	
186	1.0	F	n	1	nid lesion
187	1.0	F	n	2	
188	1.0	F	n	1	
189	1.0	F	n	0	
190	1.0	F	n	2	
191	1.0	F	n	2	
192	1.0	F	n	0	
193	1.0	F	n	2	
194	1.0	F	n	1	
195	1.0	F	n	0	
196	1.0	F	n	1	
197	1.0	F	n	1	
198	1.0	F	n	1	
199	1.0	F	n	2	
200	1.0	F	n	2	
201	1.0	F	n	1	
202	1.0	F	n	1	
203	1.0	F	n	1	
204	1.0	F	n	1	
205	1.0	F	n	0	
206	1.0	F	n	1	
207	1.0	F	n	1	
208	1.0	F	n	1	
209	1.0	F	n	3	
210	1.0	F	n	1	
211	2.5	F	n	1	
212	2.5	F	n	2	
213	2.5	F	n	2	
214	2.5	F	n	1	
215	2.5	F	n	1	
216	2.5	F	n	2	
217	2.5	F	n	1	
218	2.5	F	n	1	
219	2.5	F	n	2	
220	2.5	F	n	2	
221	2.5	F	n	0	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesior	Comments
222	2.5	F	n	1	
223	2.5	F	n	1	
224	2.5	F	n	1	
225	2.5	F	n	1	
226	2.5	F	n	1	
227	2.5	F	n	1	
228	2.5	F	n	0	
229	2.5	F	n	1	
230	2.5	F	n	0	
231	2.5	F	n	1	
232	2.5	F	n	0	
233	2.5	F	n	2	
234	2.5	F	n	0	
235	2.5	F	n	0	
236	2.5	F	n	1	
237	2.5	F	n	1	
238	2.5	F	n	1	
239	2.5	F	n	0	
240	2.5	F	n	1	
241	2.5	F	n	1	
242	2.5	F	n	2	
243	2.5	F	n	1	
244	2.5	F	n	1	
245	2.5	F	n	1	
246	2.5	F	n	3	
247	2.5	F	TM		
248	2.5	F	n	1	
249	2.5	F	n	1	
250	2.5	F	n	1	
251	2.5	F	n	0	
252	2.5	F	n	2	
253	2.5	F	n	1	
254	2.5	F	n	1	
255	2.5	F	n	3	
256	2.5	F	n	2	
257	2.5	F	n	1	
258	2.5	F	n	1	
259	2.5	F	n	1	
260	2.5	F	n	3	
261	2.5	F	n	1	
262	2.5	F	n	2	
263	2.5	F	n	1	
264	2.5	F	n	0	
265	2.5	F	n	1	
266	2.5	F	n	2	

8436 (Cl) F344 female rats - K. Morgan's slide reading 2/3-4/1993

Animal #	[Cl] ppm		Septal Fenestration	Cage Contaminant Lesior	Comments
267	2.5	F	n	1	
268	2.5	F	n	2	
269	2.5	F	n	1	
270	2.5	F	n	2	
271	2.5	F	n	0	
272	2.5	F	n	1	
273	2.5	F	n	2	
274	2.5	F	n	2	
275	2.5	F	n	1	
276	2.5	F	n	1	
277	2.5	F	n	1	
278	2.5	F	TM		
279	2.5	F	n	3	
280	2.5	F	n	2	
Present=y					
Absent=n					
Tissue missing (Nasal tissue not taken at necropsy) =TM					
0=no slides on animal					
no sample=(tissue is not readable or not present on slide)					

KGMorgan
6/21/93

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	comments
1	0.0	M	n	1	
2	0.0	M	0		
3	0.0	M	n	3	
4	0.0	M	n	2	
5	0.0	M	n	1	
6	0.0	M	n	1	
7	0.0	M	n	2	
8	0.0	M	n	1	
9	0.0	M	n	2	
10	0.0	M	n	1	
11	0.0	M	n	0	
12	0.0	M	n	2	tumor recut
13	0.0	M	n	1	
14	0.0	M	n	2	
15	0.0	M	n	1	
16	0.0	M	n	2	
17	0.0	M	n	1	
18	0.0	M	n	1	
19	0.0	M	n	1	
20	0.0	M	n	0	
21	0.0	M	n	2	
22	0.0	M	n	1	
23	0.0	M	n	1	
24	0.0	M	n	1	
25	0.0	M	n	2	interesting case
26	0.0	M	n	1	thrombosis recut
27	0.0	M	n	1	
28	0.0	M	n	2	
29	0.0	M	n	1	
30	0.0	M	n	1	
31	0.0	M	n	2	
32	0.0	M	n	0	
33	0.0	M	n	2	
34	0.0	M	n	0	
35	0.0	M	n	1	
36	0.0	M	n	3	
37	0.0	M	n	2	
38	0.0	M	n	2	
39	0.0	M	no sample		
40	0.0	M	n	2	
41	0.0	M	n	2	
42	0.0	M	n	1	
43	0.0	M	n	0	
44	0.0	M	n	2	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
45	0.0	M	n	2	
46	0.0	M	n	1	
47	0.0	M	n	1	
48	0.0	M	n	3	
49	0.0	M	0		
50	0.0	M	n	0	
51	0.0	M	n	2	
52	0.0	M	n	2	
53	0.0	M	n	3	
54	0.0	M	no sample		
55	0.0	M	n	0	
56	0.0	M	n	0	
57	0.0	M	n	1	
58	0.0	M	n	0	
59	0.0	M	n	1	
60	0.0	M	n	2	
61	0.0	M	n	1	
62	0.0	M	n	2	
63	0.0	M	n	2	
64	0.0	M	n	0	
65	0.0	M	n	1	
66	0.0	M	n	3	
67	0.0	M	n	2	
68	0.0	M	n	1	
69	0.0	M	n	1	
70	0.0	M	n	2	
71	0.4	M	n	1	
72	0.4	M	n	1	
73	0.4	M	n	1	
74	0.4	M	n	1	
75	0.4	M	n	0	
76	0.4	M	0		
77	0.4	M	n	1	
78	0.4	M	n	2	
79	0.4	M	n	1	
80	0.4	M	n	2	
81	0.4	M	n	2	
82	0.4	M	n	2	
83	0.4	M	n	1	
84	0.4	M	n	2	
85	0.4	M	n	1	
86	0.4	M	n	1	
87	0.4	M	n	2	
88	0.4	M	n	3	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
89	0.4	M	n	1	
90	0.4	M	n	2	
91	0.4	M	n	1	thrombosis
92	0.4	M	n	1	
93	0.4	M	n	2	
94	0.4	M	n	1	
95	0.4	M	n	0	
96	0.4	M	n	1	
97	0.4	M	n	2	
98	0.4	M	n	1	
99	0.4	M	n	1	
100	0.4	M	n	0	
101	0.4	M	n	1	
102	0.4	M	n	1	
103	0.4	M	n	1	
104	0.4	M	n	2	
105	0.4	M	n	1	
106	0.4	M	n	1	
107	0.4	M	n	2	
108	0.4	M	n	2	
109	0.4	M	n	3	
110	0.4	M	n	2	
111	0.4	M	n	0	
112	0.4	M	n	1	
113	0.4	M	n	1	
114	0.4	M	n	2	
115	0.4	M	n	3	
116	0.4	M	n	2	thrombosis
117	0.4	M	n	2	
118	0.4	M	n	2	
119	0.4	M	n	2	
120	0.4	M	n	2	
121	0.4	M	n	2	
122	0.4	M	n	3	
123	0.4	M	n	1	
124	0.4	M	n	2	
125	0.4	M	n	1	thrombosis
126	0.4	M	n	1	
127	0.4	M	n	1	
128	0.4	M	n	2	
129	0.4	M	n	2	
130	0.4	M	n	2	
131	0.4	M	n	1	
132	0.4	M	n	2	
133	0.4	M	n	2	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
134	0.4	M	n	2	
135	0.4	M	n	1	
136	0.4	M	n	0	thrombosis
137	0.4	M	n	2	
138	0.4	M	n	2	
139	0.4	M	n	1	
140	0.4	M	n	2	
141	1.0	M	n	3	
142	1.0	M	n	1	
143	1.0	M	n	1	
144	1.0	M	n	2	
145	1.0	M	n	2	
146	1.0	M	n	2	
147	1.0	M	n	1	
148	1.0	M	TM		
149	1.0	M	n	0	
150	1.0	M	n	1	
151	1.0	M	n	1	
152	1.0	M	n	1	
153	1.0	M	n	1	
154	1.0	M	n	2	
155	1.0	M	n	2	
156	1.0	M	n	1	
157	1.0	M	n	2	
158	1.0	M	n	2	
159	1.0	M	n	1	
160	1.0	M	n	1	
161	1.0	M	n	1	
162	1.0	M	n	1	thrombosis
163	1.0	M	n	2	
164	1.0	M	n	1	
165	1.0	M	n	2	
166	1.0	M	n	2	
167	1.0	M	n	1	
168	1.0	M	n	1	
169	1.0	M	n	2	
170	1.0	M	n	0	
171	1.0	M	n	1	
172	1.0	M	n	1	thrombosis
173	1.0	M	n	2	
174	1.0	M	n	2	thrombosis
175	1.0	M	n	1	
176	1.0	M	n	3	
177	1.0	M	n	1	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
178	1.0	M	n	1	
179	1.0	M	n	1	
180	1.0	M	n	1	
181	1.0	M	n	2	
182	1.0	M	n	2	
183	1.0	M	n	1	PA
184	1.0	M	n	2	
185	1.0	M	n	2	
186	1.0	M	n	2	
187	1.0	M	n	1	
188	1.0	M	n	2	
189	1.0	M	no sample		thrombosis
190	1.0	M	n	2	
191	1.0	M	n	2	
192	1.0	M	n	2	
193	1.0	M	n	1	
194	1.0	M	no sample		
195	1.0	M	n	1	
196	1.0	M	n	1	
197	1.0	M	n	1	
198	1.0	M	n	2	
199	1.0	M	n	1	
200	1.0	M	n	2	
201	1.0	M	n	0	
202	1.0	M	n	2	
203	1.0	M	n	2	
204	1.0	M	n	2	
205	1.0	M	n	1	
206	1.0	M	n	1	
207	1.0	M	n	1	
208	1.0	M	n	1	
209	1.0	M	n	1	
210	1.0	M	n	2	
211	2.5	M	0		
212	2.5	M	n	0	
213	2.5	M	n	2	
214	2.5	M	n	1	
215	2.5	M	n	0	
216	2.5	M	n	1	
217	2.5	M	n	1	
218	2.5	M	n	1	
219	2.5	M	n	1	
220	2.5	M	n	1	
221	2.5	M	n	2	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
222	2.5	M	yes	2	
223	2.5	M	n	0	thrombosis- a beauty
224	2.5	M	n	0	thrombosis
225	2.5	M	n	1	thrombosis
226	2.5	M	n	1	
227	2.5	M	n	2	
228	2.5	M	n	1	
229	2.5	M	n	0	
230	2.5	M	n	2	
231	2.5	M	n	1	
232	2.5	M	n	2	
233	2.5	M	n	3	
234	2.5	M	n	2	
235	2.5	M	n	1	
236	2.5	M	TM		
237	2.5	M	n	2	
238	2.5	M	n	2	
239	2.5	M	n	3	
240	2.5	M	n	2	
241	2.5	M	n	0	
242	2.5	M	n	1	
243	2.5	M	n	2	
244	2.5	M	n	2	
245	2.5	M	n	0	
246	2.5	M	n	1	
247	2.5	M	0		
248	2.5	M	n	2	
249	2.5	M	n	2	
250	2.5	M	n	2	
251	2.5	M	n	2	
252	2.5	M	n	2	
253	2.5	M	n	1	
254	2.5	M	no sample		
255	2.5	M	n	0	perfused!
256	2.5	M	n	1	perfused!
257	2.5	M	n	1	perfused!
258	2.5	M	n	1	
259	2.5	M	n	2	perfused!
260	2.5	M	n	2	
261	2.5	M	n	2	
262	2.5	M	n	2	
263	2.5	M	n	1	
264	2.5	M	n	1	
265	2.5	M	n	3	
266	2.5	M	n	1	

8321(Cl) Male Rats -K. Morgan 's reading 2/3-4/1993

Animal #	[Cl] ppm	Sex	Septal Fenestration	Cage Contaminant Lesion	
267	2.5	M	n	2	
268	2.5	M	n	2	
269	2.5	M	n	1	
270	2.5	M	n	0	
271	2.5	M	n	2	
272	2.5	M	n	3	
273	2.5	M	n	2	
274	2.5	M	n	1	
275	2.5	M	n	0	
276	2.5	M	n	2	
277	2.5	M	n	1	
278	2.5	M	n	1	
279	2.5	M	n	1	
280	2.5	M	n	2	
PRESENT = y					
ABSENT= n					
TISSUE MISSING = TM					
0= no slides taken from animal					
no sample (tissue not readable or not present on slide)					