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Dr. John D. Walker  
Executive Secretary  
TSCA Interagency Testing Committee  
TS-792  
401 M Street, SW  
Washington, DC 20460

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Dear Dr. Walker: *John*

The Chemical Manufacturers Association makes public all final reports developed from research projects that it administers. The following report, recently completed, is enclosed:

**"Isopropanol Vapor Inhalation Oncogenicity Study in Fischer 344 Rats"**

This report does not include confidential information.

If you have any questions, please call Ms. Cecilia W. Spearing of my staff at 202/387-1305.

Sincerely,

Langley A. Spurlock, Ph.D., CAE  
Vice President, CHEMSTAR



Enclosures

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### STUDY TITLE

Isopropanol Vapor Inhalation Oncogenicity Study in Fischer 344 Rats

### TEST SUBSTANCE

Isopropyl Alcohol

### DATA REQUIREMENT

Isopropanol Final Test Rule, Section 4 of the Toxic Substances Control Act (TSCA), 40 CFR Part 795 and 799

### AUTHORS

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### STUDY COMPLETION DATE

June 2, 1994

### PERFORMING LABORATORY

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### LABORATORY PROJECT ID

91NG133

### SPONSOR

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Isopropanol Vapor Inhalation Oncogenicity Study in F-344 Rats

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The portions of this study conducted by BRRC meet the requirements of Toxic Substances Control Act (TSCA), 40 CFR Part 792.

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## Isopropanol Vapor Inhalation Oncogenicity Study in Fischer 344 Rats

SUMMARY

Four groups of animals, each consisting of 75 Fischer 344 rats/sex, were exposed to isopropanol vapor (CAS No. 67-63-0) at target concentrations of 0 (filtered air control), 500, 2500, or 5000 ppm. Animals were exposed for 6 hours/day, 5 consecutive days/week, for at least 104 weeks. Ten rats/sex/group were assigned to an interim sacrifice group and were sacrificed during Week 73. Monitors for toxic effects included clinical observations, body and organ weights, ophthalmology examinations, hematologic evaluations, urinalysis and urine chemistry evaluations, necropsy observations, and microscopic evaluations.

Mean ( $\pm$  SD) isopropanol analytical concentrations of 504 ( $\pm$  14), 2509 ( $\pm$  58), and 5037 ( $\pm$  15) ppm were measured. The mortality rates for male rats (including those sacrificed moribund but excluding interim sacrifice) from the 0, 500, 2500, and 5000 ppm groups were 82, 83, 91, and 100%, respectively. The last male rat from the 5000 ppm group died during Week 100. The corresponding values for female rats were 54, 48, 55, and 59%, respectively. The only difference ( $p < 0.01$ ) in mean survival time was noted for the 5000 ppm group of male rats.

Clinical signs for some male and female rats were observed during exposures to 5000 ppm and included hypoactivity, lack of a startle reflex, and narcosis. Hypoactivity and lack of a startle reflex were also noted for some male and female rats during exposure to 2500 ppm. Clinical signs noted during nonexposure periods for male rats from the 5000 ppm group included emaciation, dehydration, and urine stains; clinical signs observed during nonexposure periods for female rats included swollen pericocular tissue (5000 ppm group only) and urine stains (2500 and 5000 ppm groups). Decreased body weight and/or body weight gain were noted for male and female rats from the 5000 ppm group at the end of the first and second weeks of exposure. Following this timepoint, increased body weight and body weight gain were noted. For male rats from the 2500 and 5000 ppm groups, increased body weight and body weight gain were observed throughout the duration of the study. For female rats, concentration-related increases in body weight and body weight gain were observed throughout most of the study, although the increases observed for the 500 ppm group were slight and probably not biologically significant.

No exposure-related changes in hematologic parameters were observed for male or female rats from any isopropanol exposure group at any time period. At Weeks 57 and 58, urinalysis and urine chemistry for male and female rats from the 5000 ppm group revealed a decrease in osmolality and an increase in total protein (males only) and total volume. Similarly, for male and female rats from the 5000 ppm group, a decrease in osmolality as well as increases in total protein, total glucose (females only), and/or total volume were noted at Week 74 and at Week 108 (only female rats from the 5000 ppm group were surviving at this timepoint). Similar changes were observed for male rats from the 2500 ppm group at Week 74 and Week 104.

Absolute and/or relative (as a percentage of body and brain weight) liver and kidney weight were increased for male rats from the 5000 ppm group at the interim sacrifice and for male rats from the 2500 ppm group at the terminal sacrifice. Relative liver weight (as a percentage of brain weight) was also increased for male rats from the 2500 ppm group at the interim sacrifice. For female rats from the 5000 ppm group at Week 109, an increase in absolute and relative (as a percentage of body and brain weight) liver and kidney weight was noted. Other organ weight changes included a concentration-related increase in testes weight (absolute and relative as a percentage of body and brain weight) observed for male rats at the interim sacrifice

timepoint. An increase in absolute and relative (as a percentage of body and brain weight) lung weight was noted for female rats from the 5000 ppm group at Study Week 73, but not at Study Week 109.

At the interim sacrifice (Week 73), the only gross lesion noted was an exposure-related increase in granular kidneys for male rats from the 2500 and 5000 ppm groups. At the terminal sacrifice at Week 105, an increase in granular kidneys was observed again for male rats from the 2500 ppm group. For male rats which died or were sacrificed due to morbidity, an increased incidence of thickened stomachs, granular kidneys, and color change of the kidney was noted at necropsy for animals from the 2500 and 5000 ppm groups. No exposure-related gross lesions were observed for female rats from any of the isopropanol exposure groups at the interim or the terminal sacrifice. For female rats which died or were sacrificed due to morbidity, an increased incidence of thickened stomachs for animals from the 5000 ppm group and granular kidneys was noted for animals from the 2500 and 5000 ppm groups.

Microscopic evaluation revealed that the kidney was a target for nonneoplastic effects in rats exposed repeatedly to isopropanol vapor. Increased frequencies of a number of microscopic lesions were observed in the kidneys of male rats from the 2500 and 5000 ppm groups which died or were sacrificed moribund during the study and included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. In addition, an increase in the severity of many of these lesions was observed for male and female rats from the 2500 and 5000 ppm groups. An increased severity of glomerulosclerosis was observed for female rats from the 5000 ppm group at the terminal sacrifice (Week 109). An increase in the frequency of mineralization in a number of organs was also noted for male and female rats from the 2500 and 5000 ppm groups; this lesion was believed to be secondary to the renal lesions. Increased frequencies of other lesions which were believed to be a result of the renal lesions or increased soft tissue mineralization included cellular hyperplasia of the parathyroid glands (females only), myocardial degeneration/fibrosis, glandular ectasia within the gastric mucosa (females only), and fibrous osteodystrophy in male and female rats from the 5000 ppm group which died or were sacrificed due to morbidity.

Other nonneoplastic lesions which were observed with increased frequencies for male rats from the 5000 ppm group which died or were sacrificed due to morbidity included basophilic cell foci within the liver, splenic hemosiderosis, rhinitis and squamous metaplasia of the respiratory epithelium within the nasal cavity, and iridocyclitis. Other nonneoplastic lesions observed with increased frequencies for female rats from the 5000 ppm group which died or were sacrificed due to morbidity included atrial thrombosis, splenic hemosiderosis, ocular keratitis, rhinitis, dacryoscleritis (inflammation of the nasolacrimal duct), and squamous metaplasia of the respiratory epithelium within the nasal cavity.

The only neoplastic lesion observed during the study was interstitial cell adenomas of the testis. An increased frequency of testicular seminiferous tubule atrophy and interstitial cell adenomas of the testis was observed for male rats from the 5000 ppm group at the interim sacrifice. A concentration-related increase in interstitial cell adenomas of the testis was also noted for male rats which were found dead or sacrificed moribund during the study. For male rats found dead or sacrificed moribund, the frequencies of interstitial cell adenomas of the testis were 57.7, 72.2, 84.7, and 93.8% for the 0, 500, 2500, and 5000 ppm groups, respectively. The frequencies of this lesion for all male rats examined were 64.9, 77.3, 86.7, and 94.7% for the 0, 500, 2500, and 5000 ppm groups, respectively. A decrease in pituitary adenomas and granular lymphocyte leukemia was observed for male rats from the 5000 ppm group which died or were sacrificed due to morbidity:

however, this was believed to be a result of their early mortality. There were no increased frequencies of neoplastic lesions for female rats. However, an exposure-related decrease in the frequency of large granular lymphocyte leukemia was observed for isopropanol exposed female rats.

The main cause of death for male rats from the 5000 ppm group was chronic renal disease and was also considered to account for much of the mortality observed for the 2500 ppm group. The main cause of death for the male control rats was large granular lymphocyte leukemia. For female rats from the 5000 ppm group which died or were sacrificed due to morbidity, the main cause of death was chronic renal disease. The main cause of death for the female control rats was large granular lymphocyte leukemia.

In conclusion, exposure of rats to isopropanol vapor for 24 months produced clinical signs of toxicity (hypoactivity, lack of a startle reflex, or narcosis) during the exposures at 2500 and 5000 ppm as well as increases in body weight and body weight gain. Urine chemistry changes indicative of kidney damage were noted for male rats from the 2500 and 5000 ppm groups and female rats from the 5000 ppm group. A number of nonneoplastic lesions were observed, with the most significant lesions being observed in the kidney. The only neoplastic lesion observed for male rats was an increase in interstitial cell adenomas of the testis which was considered to represent marked hyperplasia and was not believed to represent autonomous growth. In addition, the increased incidences of testicular tumors in the isopropanol groups appear to be reflective of the lower incidence in the control group. No increased frequencies of neoplastic lesions were noted for female rats from any isopropanol exposure group. Thus, the no-observed-effect level (NOEL) for toxic effects was 500 ppm for both male and female rats. The NOEL for oncogenicity effects for both male and female rats was determined to be greater than 5000 ppm.

OBJECTIVE

The objective of this study was to obtain chronic inhalation toxicity data in order to assess the potential of isopropanol to produce nonneoplastic and neoplastic lesions in rats.

BACKGROUND INFORMATION

Two previous inhalation studies were conducted with isopropanol in F-344 rats at Bushy Run Research Center. In the 9-day inhalation study (BRRC Report 53-514), animals were exposed to isopropanol at target concentrations of 0 (control), 1000, 5000, 10,000, and 15,000 ppm for 6 hours/day, for 9 days over an 11-day period. Mean isopropanol analytical concentrations of 995, 5070, 9826, and 14,357 ppm were measured. All rats from the 15,000 ppm group died following the first exposure. Mortality for the 10,000 ppm group was 0 and 40% for male and female rats, respectively. No mortality occurred in the 1000 or 5000 ppm groups. Clinical signs observed during exposures at 10,000 ppm and the 1 exposure at 15,000 ppm included hypoactivity followed by narcosis. Clinical signs of prostration, narcosis, ocular irritation, and slow respiration were observed in rats from the 10,000 and 15,000 ppm groups following exposure. Other clinical signs noted during nonexposure periods for animals from the 10,000 ppm group were paresis, ataxia, emaciation, dehydration, and urogenital wetness. The narcosis and prostration observed following exposures at 10,000 ppm during the first week were absent by the second week of exposures. Differences from control animals observed in the functional observational battery included piloerection and mild to severe gait abnormality (duck-walk) for males in the 10,000 ppm group, a mild duck-walk for the 3 surviving females in the 10,000 ppm group, and a concentration-related increase in body temperature for males and females in the 1000, 5000, and 10,000 ppm groups. Surviving animals in the 10,000 ppm group had body weight losses at most timepoints during both weeks of the study. Decreases in body weight or body weight gain noted in the 5000 ppm group during the first week of the study were not present during the second week of the study. Increases in body weight gain were noted in males from the 1000 ppm group. Food and water consumption changes corresponded to the changes in body weight or body weight gain. There were no gross lesions observed to be exposure related in animals surviving until the end of the study. Concentration-related increases in liver weight were observed for both male and female rats. Males in the 5000 ppm group also showed an increase in kidney and lung weights (absolute and/or relative). Histologic examination of the kidneys and livers revealed hyaline droplet formation in the kidneys and cytoplasmic vacuolization in the livers of male rats.

In the subchronic inhalation study (BRRC Report 53-589), F-344 rats were exposed to isopropanol at target concentrations of 0 (control), 100, 500, 1500, or 5000 ppm for 6 hours/day, 5 days/week, for at least 13 weeks. Mean isopropanol analytical concentrations of 100, 506, 1508, and 5008 ppm were measured. No exposure-related mortalities occurred during the study. Clinical signs observed in some of the rats during exposures at 1500 and 5000 ppm included ataxia, narcosis, lack of a startle reflex (5000 ppm group only), and hypoactivity. The clinical signs noted during exposures were either seldom observed or completely absent following exposures. Clinical signs that were observed following exposures in the 5000 ppm group included swollen periocular tissue (females only), perinasal encrustation (males only), ataxia (1 male), and paresis (1 female). Perinasal encrustation (males only) was also observed in animals in the 500 and 1500 ppm groups. Neurobehavioral evaluations indicated no changes in the functional observational battery. Increased motor activity for females in the 5000 ppm group was noted at Weeks 9 and 13. Decreases in absolute body weight and body weight gain were observed in animals from the 5000 ppm group at the end of the first week of exposure. Absolute body weight

and body weight gain were also slightly decreased in the 1500 ppm group of females. The decreases in body weight and body weight gain observed during the first week of exposure were, however, transient. Increased body weight and/or body weight gain were observed in males and females from the 1500 and 5000 ppm groups during the remaining weeks of the study. Increases in food and water consumption generally corresponded to changes in body weight and body weight gain. At Study Week 6, decreases in total erythrocytes, hemoglobin, hematocrit, and platelet counts were observed in both sexes from the 5000 ppm group. In addition, increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were observed in males from the 5000 ppm group. Increased MCV and/or MCH were also noted in both sexes from the 5000 ppm group at Study Week 14. These changes indicated that a slight anemia was present at Study Week 6 but not Study Week 14. Platelet counts were increased for the males in the 1500 and 5000 ppm groups at Study Week 14. There were no exposure-related changes in serum chemistry parameters for males or females. The only organ weight effect noted was an increased relative liver weight in both sexes from the 5000 ppm group. Histologic examination revealed hyaline droplets within the kidneys of all males including controls. However, the size and frequency of the hyaline droplets were increased for the exposure groups, albeit not in a concentration-related manner. Neuropathologic examination revealed no exposure-related lesions in the central or peripheral nervous system of exposed rats.

#### TARGET CONCENTRATION SELECTION

Target isopropanol concentrations of 0 (control), 500, 1500 or 5000 ppm were selected by the Sponsor based on the results from the previous inhalation studies conducted in F-344 rats.

#### MATERIALS AND METHODS

This study was conducted in accordance with the New and Revised Health Effects Test Guidelines, Toxic Substances Control Act (TSCA), 40 CFR Part 798.3300, and the Isopropanol Final Test Rule, Section 4 of the Toxic Substances Control Act (TSCA), 40 CFR Part 795 and 799. The protocol and any protocol amendments (BRRC Project No. 90-81-69004) detailing the design and conduct of this study are included in Appendix 12. Protocol deviations are included in Appendix 12.

#### Test Substance

Twenty-three 55-gallon drums of isopropanol were received from Union Carbide Corporation (UCC; Texas City, TX). The drums of test substance were shipped to Nitro, WV, where they were stored. Drums were then shipped periodically (typically 2 at a time) to BRRC as the test substance was needed. The assigned BRRC Sample Numbers and the dates that the drums were received at BRRC are presented in Appendix 1. The drums were stored at BRRC in an outdoor chemical storage area. When needed, a 55-gallon drum of isopropanol was moved to and stored in Room 112. Samples of the test substance were then dispensed into fireproof containers or a glass bottle and stored in Room 139. The test substance was a colorless liquid with a characteristic odor. Compositional analyses were performed before, during, and after the study by the GLP Analytical Skill Center at the UCC South Charleston, WV, Technical Center and the report is included as Attachment 2 to Appendix 1. A 2-year stability study was also conducted on isopropanol by the GLP Analytical Skill Center at the UCC South Charleston, WV, Technical Center and the report is included as Attachment 1 of Appendix 1 of this report. The purity of the test substance was determined to be 99.9%; the test substance remained stable during the exposure regimen. The method of synthesis of the test substance was documented by the Sponsor. Pertinent chemical and physical properties of isopropanol are included in Appendix 1.

### Animals and Husbandry

Three-hundred and fifty-two male and 354 female Fischer 344 rats arrived on January 28, 1991, from Harlan Sprague Dawley Inc. (Indianapolis, IN). They were designated by the supplier to be approximately 28-30 days old (the birth dates were recorded as December 31, 1990 to January 2, 1991). The females were nulliparous and nonpregnant.

Animals were housed in Room 166 from arrival until termination of the study except during exposures. Within 2 days of receipt, the animals were examined by a clinical veterinarian, and representative animals were subjected to a pretest health screen including full necropsy, histologic examination of selected tissues, including respiratory tract, serum viral antibody analyses performed at Charles River Laboratories (Wilmington, MA), and examinations for fecal parasites. Based on the results of these data, the clinical veterinarian indicated that these animals were in good health and suitable for use.

All animals were assigned unique numbers and identified by cage tags. Animals considered available for the study were also identified by a tail tattooing procedure.

The animals were housed 2/cage for approximately 15 days in stainless steel, wire mesh cages (15 x 22 x 18 cm). The purpose of housing animals in pairs was to help acclimate the animals to their new surroundings. DACB® (Deotized Animal Cage Board; Shepherd Specialty Papers, Inc.) was placed under each cage and changed at least 3 times each week. Cages were changed and sanitized at least once every 2 weeks. The racks were rotated once every 2 weeks in order to better ensure equivalent environmental conditions for all animals. Cages were rotated once every 4 weeks according to a predetermined schedule. An automatic timer was set to provide fluorescent lighting for a 12-hour photoperiod (approximately 0500 to 1700 hours for the light phase). Temperature and relative humidity were recorded in the animal housing room (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 64-79°F; relative humidity was routinely maintained at 40-70%. Any exceptions to these specified ranges were noted in the raw data.

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) was available ad libitum except during exposures and was delivered by an automatic watering system with demand control valves mounted on each rack. Water analyses were provided by the supplier, Balliburton NUS Environmental Laboratories, Materials Engineering & Testing Company, and Lancaster Laboratories, Inc. at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Pelleted, certified AGWAY® FROLAB® Animal Diet Rat 3000 (Agway Inc.) was available ad libitum except during exposures. Analyses for chemical composition and possible contaminants of each feed lot were performed by Agway Inc., and the results were included in the raw data. The maximum levels of known contaminants in the feed were below standards which could interfere with the study results.

### Animal Acclimation

The acclimation period was approximately 3 weeks. During this period, the animals were weighed at least 3 times at scheduled intervals. Detailed clinical observations were conducted in conjunction with body weight measurements. Cage-side animal observations and mortality checks were conducted once daily (morning). The animals were examined just prior to the end of the acclimation period by a clinical veterinarian. Animals considered unacceptable for the study, based on the clinical

Signs, body weights, or body weight gains, were rejected. The fate of rejected animals and the reasons for rejection were presented in the raw data.

#### Study Organization

Following the second pretest body weight, the animals were assigned to 3 exposure groups and a control group using a stratified randomization procedure based on body weight. At the time of group assignment, only animals with body weight within  $\pm 20\%$  of the population mean for each sex were included. The body weight range on the day of first exposure was 121.2 to 131.9 g for males and 93.6 to 124.3 g for females. The following table summarizes the organization of the study.

	Core Group <sup>a</sup>	Interim Sacrifice Group <sup>b</sup>	Target Concentration (ppm)
Control	65	10	0
Low	65	10	500
Intermediate	65	10	2500
High	65	10	5000

<sup>a</sup>Number of animals/sex

The exposures began on February 18, 1991 (Study Day 1). Animals were exposed for 6 hours/day for 5 consecutive days/week for at least 104 weeks. Animals were not exposed during designated BRRRC holidays. The 6-hour exposure period was defined as the time when the generation system was turned on and subsequently turned off. All control animals were exposed to filtered air only using the same exposure regimen. Ten animals/sex/group assigned to the interim sacrifice group were sacrificed on July 7, 1992 (males), or July 8, 1992 (females) after at least 72 weeks of exposure. The final sacrifice dates were February 16, 1993 (males, Study Week 105), and March 15-17, 1993 (females, Study Week 109).

#### Administration of Test Substance

##### *Inhalation Chamber Description and Operation*

The inhalation chambers (Wahmann Manufacturing Company, Timonium, MD) used for this study were located in Room 139. The chambers, constructed from stainless steel with glass windows for animal observation, were rectangular (207 x 98 x 213 cm) in shape. The volume of each chamber was approximately 4320 liters, and the airflow was set at approximately 1000 l/min (14 air changes/hr) for approximately the first month of the study. The chamber airflow rate was lowered to 900 l/min (12.5 air changes/hr) for all of the chambers (including the control chamber) during the second month of the study in an effort to keep chamber temperature within the range of 22 to 4°C. A Dwyer Magnehelic<sup>®</sup> pressure gauge (Dwyer Instruments, Inc., Michigan City, IN) was used to monitor chamber airflow. The theoretically-derived time ( $t_{99}$ ) required for the chambers to reach 99% of the target concentration was calculated to be 20-22 min.

##### *Vapor Generation*

Liquid isopropanol was metered from a container by a piston pump (G-6 FMI pump with a 3/8" piston for the 500 ppm exposure chamber, G-20 FMI pump with a 3/8" piston for

the 2500 ppm exposure chamber, and a G-50 FMI pump with a 3/8" piston for the 5000 ppm exposure chamber; Fluid Metering, Inc., Oyster Bay, NY) into a heated glass evaporator similar in design to that described by Snellings and Dodd (1990). Two or 3 evaporators were connected together in series in order to generate the 2500 and 5000 ppm target concentrations in an effort to increase the surface area for evaporation of the test substance and reduce the amount of heat needed to produce the vapor. In addition, to further increase the evaporative surface area, marbles were added to one of the heated glass evaporators used to generate the 5000 ppm concentration. The temperature of the evaporators was maintained at the lowest level sufficient to vaporize the test substance. Evaporator temperatures were measured during preliminary level setting and at approximately 1-month intervals during the study. Evaporator temperatures were determined without the test substance using a thermocouple attached to a digital recorder (Type K thermocouple with a Model 400A Doric Trendicator; Doric Scientific Division, San Diego, CA). During the study, the temperature probe was always positioned on the glass evaporator at the first spiral from the top. The oxygen content of the exposure chambers was also measured during preliminary level setting and 4 times during the study using an MSA® Oxygen Indicator Model 245R (Mine Safety Appliance Company, Pittsburgh, PA). A TSI Aerodynamic Particle Sizer (TSI Incorporated, St. Paul, MN) was used to check for the possibility of an aerosol in the 0 ppm and 5000 ppm chambers during preliminary level setting and 5 times during the study.

#### *Chamber Atmosphere Measurements*

Each exposure chamber atmosphere was analyzed for isopropanol approximately twice each hour during each 6-hour exposure period by flame ionization gas chromatography. The nominal concentration was calculated by dividing the total amount of isopropanol delivered to the chambers by the total airflow rate.

The distribution of isopropanol vapor within each of the 3 exposure chambers was examined. Each chamber was tested once prior to the initiation of the study and once during the sixth, twelfth, eighteenth, and twenty-fourth months of the exposure regimen. A description and the results of the chamber distributions are included in Appendix 1.

Chamber temperature and relative humidity were recorded using a Fisherbrand® dial-type thermometer (Fisher Scientific, Pittsburgh, PA) and an Airguide humidity indicator (Airguide Instrument Co., Chicago, IL). Temperature and relative humidity measurements were recorded approximately 2 times/hour during each 6-hour exposure.

#### Observations and Measurements

##### *In-life Evaluations*

All animals were individually observed for signs of toxic effects except during the exposures. During the exposures, observations were recorded on a group basis. These observations noted during exposures are hand recorded and located with the raw data. Preceding and following each exposure, observations were recorded for animals exhibiting overt clinical signs. On nonexposure days, the animals were observed twice a day for overt clinical signs and mortality. At the time of body weight collection, detailed observations were performed on all animals. These examinations included, but were not necessarily limited to, an external physical examination, gentle palpation of internal organs, and an assessment for abnormal behavior or clinical signs.

Individual body weights were measured weekly for the first 14 weeks and every other week thereafter. On the weeks that body weights were not measured, detailed observations were performed.

Prior to the first exposure, the eyes of all rats were examined by a Veterinary Ophthalmologist using indirect ophthalmoscopy and slit lamp biomicroscopy following dilation of eyes with MYDRIACYL® 1% Ophthalmic Solution. During Study Week 71, 80, 104 (males), and 107 (females), the eyes of all rats were again examined by a Veterinary Ophthalmologist using the same methodology. Details of the ophthalmology examination procedures are included in Appendix 4.

#### *Clinical Pathology Evaluations*

Blood smears were obtained for all surviving core animals at approximately 13 months (Study Week 58 for males and Study Week 59 for females), 19 months (Study Week 82 for males and Study Week 83 for females), and 25 months (Study Week 105 for males and Study Week 109 for females). Differential leukocyte counts were evaluated for all surviving core animals from the control and high concentration groups at these timepoints. Hematology measurements were also made for all surviving core rats at the terminal sacrifice. Blood was obtained using a retroorbital bleeding procedure. Prior to the bleeding procedure, the animals were slightly anesthetized with methoxyflurane. Animals were not fasted prior to the bleeding procedures.

The following were measured or calculated:

#### Hematology

hematocrit	total leukocyte count
hemoglobin	differential leukocyte count
erythrocyte count	platelet count
mean corpuscular volume (MCV)	
mean corpuscular hemoglobin (MCH)	
mean corpuscular hemoglobin concentration (MCHC)	

Samples for urinalysis and urine chemistry were collected from 10 animals/sex/group at Study Week 57. Animals were given access to food and water during these collection periods. The following were measured:

protein  
glucose  
renal epithelial cells  
volume

Samples were also collected from another group of 10 animals/sex/group at Study Week 58 for osmolality determinations. Animals at this timepoint were given access to food but not water during the collection period.

Samples were also collected at Study Weeks 74 (males and females), 104 (males), and 108 (females). Animals were given access to food and water during these collection periods. The following parameters were measured:

protein  
glucose  
volume  
osmolality

Details of the clinical pathology procedures are included in Appendix 3.

#### Anatomic Pathology Evaluations

At sacrifice, nonfasted animals were anesthetized by methoxyflurane and killed by severing the brachial vessels to permit exsanguination. On the day of sacrifice, body weight was obtained to allow expression of relative organ weights. A complete necropsy was performed on all animals. The liver, kidneys, brain, heart, lungs, testes (male), and spleen were weighed for all sacrificed animals. The following tissues were collected and retained in 10% neutral buffered formalin:

gross lesions	testes	rectum
brain	epididymis	urinary bladder
cerebral cortex	prostate	lymph nodes
cerebellar cortex	seminal vesicles	mesenteric
medulla/pons	ovaries	submandibular
pituitary	uterus	sciatic nerve
thyroid/parathyroid	corpus and cervix	spinal cord
thymic region	vagina	sternum (including marrow)
trachea	mammary gland (females)	femur (including articular surface)
lungs	skin	thigh musculature
heart	esophagus	eyes
salivary gland	stomach	aorta
liver (3 lobes)	duodenum	nasal cavity (4 sections)
spleen	jejunum	pharynx
kidneys	ileum	larynx
adrenals	cecum	
pancreas	colon	

Tails were saved for identification purposes.

Microscopic examinations were performed on the tissues listed above for all animals from the control and high concentration groups (interim and core groups). The kidneys and tissues with gross lesions were examined from all animals in the low and intermediate concentration groups. Lesions were graded, when possible, into 5 categories (minimal, mild, moderate, marked and severe). Causes of death were assigned, whenever possible, to the rats in the control and high concentration groups. (This could not be done for the rats in the low and intermediate concentration groups, because only a limited tissue sample was examined microscopically for these animals.) If the cause of death could not be determined from the microscopic examination, it was recorded as "undetermined." For most of the rats, only one cause of death was assigned. For a small number of rats in which two debilitating processes were present concurrently, neither one of which was considered to have been of sufficient severity to singularly produce death, both processes were recorded as the cause of death. When tissues specified for evaluation were missing upon microscopic examination, a recut or examination of the residual wet tissues was usually performed, except in some cases in which the tissues were markedly autolyzed or when, for a variety of reasons, recovery of the missing tissue was considered unlikely. Recuts were not performed for missing parathyroid glands unless these glands were grossly lesioned.

Details of the anatomic pathology procedures are included in Appendix 2. Also included in Appendix 2 are the reports of two independent consulting pathologists who were requested to submit their viewpoints about the biologic significance of one of the microscopic findings observed in this study. These reports are included as Attachment 1 of Appendix 2.

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### Data Analyses

The data for quantitative, continuous variables were intercompared for the 3 exposure groups and the control group by use of Levene's test for equality of variances, analysis of variance (ANOVA), and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated similar variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons.

Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U-test. Mortality data were analyzed by life-table analysis. Incidence and mean time to first palpable mass were analyzed by life-table analyses. Incidence data were compared using Fisher's Exact Test. For all statistical tests (except for the tumor analyses), the probability value of  $< 0.05$  (two-tailed) was used as the critical level of significance. The probability value of  $< 0.05$  (one-tailed) was used as the critical level of significance for the tumor analyses.

Various models of calculators, computers, and computer programs may have been used to analyze data for this study. Since various models round or truncate numbers differently, values in some tables may differ slightly from those in other tables or from independently calculated data. The integrity of the study and interpretation of the data were unaffected by these differences.

### RETENTION OF RECORDS

All raw data, documentation, the protocol and any amendments, specimens, and a copy of the final report generated as a result of this study will be retained in the BRRC Archives for at least 10 years. A reserve sample of test substance from each container used during the study will also be stored in the BRRC Archives.

### RESULTS AND DISCUSSION

All references of differences in group mean values in the following text refer to comparisons of statistically significant differences between the exposure group and the control group, unless otherwise noted. Repeated reference to the control group and the statistical significance will not be made in order to simplify the text.

#### Chamber Atmosphere

Detailed results and discussion of the chamber atmosphere measurements are included in Appendix 1.

The target concentrations were 0 (control), 500, 2500, and 5000 ppm of isopropanol vapor. Control animals were exposed to filtered air only. The following table presents the mean analytical concentrations ( $\pm$  SD), the mean nominal concentrations ( $\pm$  SD), and the mean of the analytical-to-nominal concentration ratios. No daily mean concentration of isopropanol vapor above the estimated minimum detection limit was measured in the control chamber.

Target Concentration (ppm)	Analytical Concentration (ppm)	Nominal Concentration (ppm)	Analytical-to-Nominal Concentration Ratio
500	504 ± 14	493 ± 13.8	1.02
2500	2509 ± 58	2522 ± 52.6	1.00
5000	5037 ± 115	5012 ± 108.1	1.01

The means ( $\pm$  SD) of the daily mean chamber temperature values were 24.1 ( $\pm$  1.13), 23.8 ( $\pm$  1.16), 24.3 ( $\pm$  1.10), and 23.9 ( $\pm$  1.24) °C for the 0, 500, 2500, and 5000 ppm exposure chambers, respectively. The means of the daily mean chamber relative humidity values were 48.5 ( $\pm$  3.24), 50.1 ( $\pm$  3.14), 48.2 ( $\pm$  2.94), and 51.9 ( $\pm$  2.80) percent for the 0, 500, 2500, and 5000 ppm exposure chambers, respectively. The heated evaporator temperatures ranged from 18-77°C; the large range in evaporator temperatures was a result of the large range in exposure concentrations. Proper vapor distribution within the exposure chambers was demonstrated repeatedly throughout the study; coefficient of variation values of less than 3% were found for each one of the chamber distribution evaluations. Plots of number and mass concentration of particles indicated no differences between the 5000 ppm and 0 ppm exposure atmospheres indicating that an aerosol of isopropanol was not present in the 5000 ppm chamber. The oxygen content within the exposure chambers was 20.8% throughout the study.

#### Clinical Observations, Mortality, and Palpable Masses

Summaries of mortality and palpable masses are presented in Table 1. Summaries of the clinical observations are presented in Tables 2 and 3. Individual animal clinical observation data are included in Appendix 6. Individual animal fate data are included in Appendix 5. Individual palpable mass data are included in Appendix 7.

The mortality rates for male rats (including those sacrificed moribund but excluding interim sacrifice) in the 0, 500, 2500, and 5000 ppm groups were 82, 83, 91, and 100%, respectively. The last male rat from the 5000 ppm group died during Week 100. The corresponding values for female rats were 54, 48, 55, and 69%, respectively. The only difference ( $p < 0.01$ ) in mean survival time was noted for the 5000 ppm group of male rats. No differences in mean survival time were noted for male rats from the 500 or 2500 ppm groups or for any isopropanol exposure group of female rats.

Clinical signs noted in some male and female rats during exposures to 5000 ppm included hypoactivity, lack of a startle reflex, and narcosis. Hypoactivity and lack of a startle reflex were also noted for some male and female rats during exposure to 2500 ppm. No clinical signs were noted for male or female rats during exposures to 500 ppm.

Clinical signs noted during nonexposure periods included emaciation and dehydration for male rats from the 5000 ppm group. These signs are believed to be related to the increased mortality observed for this group of animals and the debilitated condition of these animals prior to their death. In addition, there were slightly greater numbers of rats from the 5000 ppm group which were noted to have urine stains (males and females) and swollen periocular tissue (females only). Urine

stains were also observed in more female rats of the 2500 ppm group as compared with the control group. There were no clinical signs noted during nonexposure periods that were believed to be exposure related for male rats from the 2500 ppm group or male and female rats from the 500 ppm group. Increased frequencies of other clinical signs in isopropanol exposed rats were not believed to be related to exposures due to the lack of a concentration-response relationship and the frequency of the observed sign in control animals.

There were no exposure-related effects on the incidence of palpable masses for male or female rats. A decrease in the time to development of palpable masses was noted for male rats from the 2500 ppm group; however, this was not believed to be exposure related due to the small number of animals with masses, the lack of histopathologic evidence of increased incidences of tumors which were palpable, and the lack of a concentration-response relationship. There were no exposure-related effects on the time to development of palpable masses for female rats.

#### Body Weights

Summaries of absolute body weight and body weight gain are presented in Tables 4 to 7. Graphs of body weight (grams) versus time (weeks) are presented in Figures 1 and 2. Individual animal body weight data are included in Appendix 8.

Decreased body weight gain was observed for male rats from the 5000 ppm group at the end of the first and second weeks of exposure. Following this timepoint, the body weight of these rats increased, and, by the end of Week 6, increased body weight and body weight gain were noted. Increased body weight and body weight gain were also observed for male rats from the 2500 ppm group. These increases were typically observed throughout the remainder of the study, although statistical significance was rarely achieved following Week 72. At the end of Week 72 (at roughly the time of the 16-month interim sacrifice), mean body weight was increased approximately 3 and 4% for male rats from the 2500 and 5000 ppm groups, respectively.

For female rats from the 5000 ppm group, decreased body weight and body weight gain were noted at the end of the first and second weeks of exposure. Similar to the male rats from the 5000 ppm group, the body weight for female rats from the 5000 ppm group increased, and, by the end of Week 5, increased body weight and body weight gain were noted. From this timepoint on, concentration-related increases in body weight and body weight gain were typically observed for female rats; however, the increases in body weight and body weight gain observed for the 500 ppm group were slight, and statistical significance was rarely achieved for this group. At the end of Week 72 (at roughly the time of the 16-month interim sacrifice), mean body weight was increased approximately 1, 5, and 5% for female rats from the 500, 2500 and 5000 ppm groups, respectively.

#### Ophthalmology Examinations

Individual animal ophthalmic observations are included in Appendix 11. Detailed results and discussion of the ophthalmology examinations are included in Appendix 4.

No exposure-related ophthalmic lesions were noted for male or female rats prior to the study termination.

#### Clinical Pathology Evaluations

Summaries of the hematology measurements are presented in Tables 8 to 13. Summaries of urinalysis measurements are presented in Tables 16 and 17. Summaries of urine chemistry measurements are presented in Tables 14 and 15 and 18 to 21. Detailed

results and discussion of the clinical pathology measurements are included in Appendix 3. Individual clinical pathology data are included in Appendix 10.

No exposure-related changes in hematologic parameters were observed for male or female rats from any of the isopropanol exposed groups examined at Weeks 58-59, Weeks 82-83, or at the terminal sacrifice.

At Weeks 57 and/or 58, urinalysis and urine chemistry revealed a decrease in osmolality and an increase in total protein and total volume for male rats from the 5000 ppm group. Similarly, at Week 74, a decrease in osmolality as well as increases in total protein and total volume were noted for male rats from the 5000 ppm group. Similar changes were observed for male rats from the 2500 ppm group at Week 74; however, none of the changes were statistically significant. At Week 104, a decrease in osmolality and increases in total protein and total volume were noted again for male animals from the highest exposure group with surviving animals (2500 ppm group), although none of the changes was statistically significant.

For female rats from the 5000 ppm group, urinalysis and urine chemistry at Week 57 and/or 58 revealed a decrease in osmolality and an increase in total volume, although statistical significance was not achieved for the former parameter. At Week 74, decreases in osmolality and increases in total protein and total volume were noted for females from the 5000 ppm group. The total glucose (glucose x volume) excreted in the urine was also increased for females from the 5000 ppm group at Week 74. A decrease in osmolality as well as an increase in urine total volume and total glucose (glucose x volume) were noted again for female rats from the 5000 ppm group at Week 108.

#### Organ Weights, Necropsy Observations, and Microscopic Diagnoses

Summary results of organ weights, organ weights relative to final body weight, and organ weights relative to brain weight are presented in Tables 22 to 33. Summary results of necropsy observations are presented in Tables 34 to 39. Summary results of microscopic diagnoses are presented in Tables 40 to 53 (results of neoplastic microscopic diagnoses are presented in Tables 46 and 53). Detailed results and discussion of the anatomic pathology results are included in Appendix 2. Individual anatomic pathology data are included in Appendix 9.

Some statistically significant changes in absolute or relative organ weight were believed to be a result of a change in the final body weight and were not believed to be exposure related. Some other changes in organ weights were also not believed to be exposure related due to the lack of a concentration-response relationship. Only the organ weight changes that are considered to be exposure related will be discussed.

At the interim sacrifice, absolute and relative (as a percentage of body and brain weight) liver and kidney weights were increased for male rats from the 5000 ppm group; however, statistical significance was not achieved for relative kidney weight (as a percentage of body weight). Relative liver weight (as a percentage of brain weight) was also increased for male rats from the 2500 ppm group at the interim sacrifice. Concentration-related increases in absolute and relative testes weight (as a percentage of body and brain weight) were also observed for male rats at the interim sacrifice timepoint; however, statistical significance was not achieved for the 500 ppm group. The only organ weight change noted for female rats at Study Week 73 was an increase in absolute and relative (as a percentage of body and brain weight) lung weight for animals from the 5000 ppm group, although statistical significance was not achieved for relative lung weight as a percentage of body

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weight. There were no other changes in organ weights at Week 73 which were believed to be exposure related for male or female rats.

At the terminal sacrifice, an increased relative liver weight (as a percentage of body and brain weight) was noted for male rats from the highest surviving concentration group (2500 ppm). Slight increases in absolute and relative kidney weight (as a percentage of body and brain weight), although not statistically significant, were also noted for male rats from the 2500 ppm group at Week 105. For female rats at Week 109, an increase in absolute and relative liver weight (as a percentage of body and brain weight) was noted for the 5000 ppm group. The only other change in organ weight noted for female rats at Week 109 was an increased absolute and relative (as a percentage of body and brain weight) kidney weight for animals from the 5000 ppm group; however, statistical significance was not achieved for relative kidney weight (as a percentage of body weight).

At the interim sacrifice (Week 73), the only gross lesion noted was an exposure-related increase in granular kidneys for male rats from the 2500 and 5000 ppm groups. At the terminal sacrifice at Week 105, an increase in granular kidneys was observed again for male rats from the 2500 ppm group (there were no surviving male rats from the 5000 ppm group at Week 105). Increased frequencies of gross lesions noted for male rats which died or were sacrificed due to morbidity, included an increased incidence of thickened stomachs, granular kidneys, and color change of the kidney for animals from the 2500 and 5000 ppm groups.

No exposure-related gross lesions were observed for female rats from the 500, 2500 or 5000 ppm groups at the interim or the terminal sacrifice. For female rats which died or were sacrificed due to morbidity, an increased incidence of thickened stomachs was noted for animals from the 5000 ppm group and granular kidneys was noted for animals from the 2500 and 5000 ppm groups.

Upon microscopic evaluation, male rats from the 5000 ppm group at the interim sacrifice (Week 73) had an increased frequency of testicular seminiferous tubule atrophy. The grades for some of the lesions associated with chronic renal disease were increased (although frequencies were not increased) at the interim sacrifice for male rats from the 2500 and 5000 ppm groups.

At Week 105, no exposure-related differences in frequencies of lesions were observed for male rats which were sacrificed. Increased frequencies of a number of microscopic lesions were observed in the kidneys of male rats from the 2500 and 5000 ppm groups which died or were sacrificed moribund during the study. These renal lesions included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. In addition, an increase in the severity of these lesions was observed for male rats from the 2500 and 5000 ppm groups.

An increase in the frequency of mineralization in a number of organs was noted for male rats from the 2500 and 5000 ppm groups which were found dead or sacrificed moribund; this lesion was believed to be secondary to the renal lesions. Increases in the frequency of mineralization were noted in the heart (5000 ppm only), aorta, vasculature (5000 ppm only), stomach, larynx (5000 ppm only), trachea (5000 ppm only), lungs, kidney, cornea (5000 ppm only), and testes (5000 ppm only). Other lesions which were noted in male rats from the 5000 ppm group which died or were sacrificed due to morbidity and were believed to be a result of the renal lesions or increased soft tissue mineralization, included an increased frequency of myocardial degeneration/fibrosis and fibrous osteodystrophy.

Other nonneoplastic lesions which were observed with increased frequencies for male rats from the 5000 ppm group which died or were sacrificed due to morbidity included basophilic cell foci within the liver, splenic hemosiderosis, rhinitis and squamous metaplasia of the respiratory epithelium within the nasal cavity, and iridocyclitis.

The only neoplastic lesion observed for male rats was a concentration-related increase in interstitial cell adenomas of the testis. At the interim sacrifice, an increase in testicular interstitial cell adenomas was observed for male rats from the 5000 ppm group. Concentration-related increases in interstitial cell adenomas of the testes were observed for male rats found dead or sacrificed moribund during the study as well as for all animals on the study. For male rats found dead or sacrificed moribund, the frequencies of interstitial cell adenomas of the testis were 57.7, 72.2, 84.7, and 93.8% for the 0, 500, 2500, and 5000 ppm groups, respectively. The frequencies of this lesion for all male rats examined were 64.9, 77.3, 86.7, and 94.7% for the 0, 500, 2500, and 5000 ppm groups, respectively. Both of the independent consulting pathologists indicated that the frequency of testicular interstitial cell tumors in the control group was unusually low, causing the frequencies observed for the exposed groups to appear to be significant. One of the pathologists indicated that a possible mechanism for the increased development of these tumors is a perturbation of hormonal levels, especially pituitary hormones such as leutinizing hormone.

A decrease in pituitary adenomas and mononuclear leukemia was observed for male rats from the 5000 ppm group which died or were sacrificed due to morbidity; however, this was believed to be a result of their early mortality.

The main cause of death for male rats from the 5000 ppm group was chronic renal disease which was considered to account for much of the mortality observed for the 2500 ppm group. The main cause of death for the male control rats was large granular lymphocyte leukemia.

No increased frequencies of nonneoplastic lesions were observed for female rats at the interim sacrifice at Week 73. In addition, at the terminal sacrifice at Week 109, there were no increased frequencies of nonneoplastic lesions for female rats, although an increased severity of glomerulosclerosis was observed for female rats from the 5000 ppm group. The severity of some of the key components for chronic renal disease (e.g. tubular proteinosis, glomerulosclerosis, interstitial nephritis, and interstitial fibrosis) were increased for all female rats on the study from the 2500 and 5000 ppm groups.

For female rats from the 5000 ppm group which died or were sacrificed due to morbidity, increased frequencies of mineralization were evident in the heart, aorta, vasculature, stomach, larynx, trachea, lungs, and kidney. An associated (to the mineralization within the heart) increase in myocardial degeneration/fibrosis as well as an increased frequency of glandular ectasia within the gastric mucosa was also evident for female rats from the 5000 ppm group which died or were sacrificed in moribund condition. Increased frequencies of mineralization were also observed in the lungs and kidneys of female rats from the 2500 ppm group which died or were sacrificed due to morbidity. An increased incidence of fibrous osteodystrophy and cellular hyperplasia of the parathyroid glands was also noted for female rats from the 5000 ppm group which died or were sacrificed due to morbidity.

Other lesions observed with increased incidences for female rats from the 5000 ppm group which died or were sacrificed due to morbidity included atrial thrombosis, splenic hemosiderosis, and ocular keratitis. In addition, inflammatory and metaplastic changes within the nasal cavity such as rhinitis, dacryosolenitis (inflammation of the nasolacrimal duct), and squamous metaplasia of the respiratory

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epithelium were noted for female rats from the 5000 ppm group which died or were sacrificed due to morbidity.

There were no increased frequencies of neoplastic lesions for female rats. An exposure-related decrease in the frequency of large granular lymphocyte leukemia was observed, however, for isopropanol exposed female rats; this decreased frequency was not a result of decreased survival since no differences in mean survival time were observed between control and isopropanol exposed female rats.

The main cause of death was chronic renal disease for female rats from the 5000 ppm group which died or were sacrificed due to morbidity. The main cause of death for the female control rats was large granular lymphocyte leukemia.

#### CONCLUSIONS

The potential for isopropanol vapor exposure to produce oncogenicity effects in rats was investigated in this study. Other evaluations and measurements (clinical observations, body and organ weights, ophthalmic examinations, hematology, urinalysis and urine chemistry, necropsy observations, and histopathology) were also performed during the 24-month study. The narcotic effects of isopropanol were noted during exposures to 2500 and 5000 ppm and included signs of hypoactivity, lack of a startle reflex, and narcosis (5000 ppm group only).

Increased body weight and/or body weight gain were observed for male rats from the 2500 and 5000 ppm exposure groups throughout most of the study duration. A concentration-related increase in body weight and body weight gain was also observed for female rats; however, the increase observed for the 500 ppm group was very slight and may not be biologically significant. This increased body weight effect has been noted in previously performed inhalation studies on isopropanol vapor (BRRC Reports 53-514, 53-589, and 91N0132; Burleigh-Flayer *et al.*, 1992; Burleigh-Flayer *et al.*, 1994).

Increased liver weight was noted for male rats from the 2500 and 5000 ppm groups at the interim sacrifice and for male rats from the 2500 ppm group as well as for female rats from the 5000 ppm group at the end of 24 months. This finding has been previously noted for mice exposed to similar exposure concentrations for 12 and 18 months (BRRC Report 91N0132). The increased liver weight was most likely a result of microsomal enzyme induction, representing a metabolic response of the liver to isopropanol.

Another organ weight effect noted in the study was an increase in lung weight for female animals from the 5000 ppm group at the interim sacrifice. This increased lung weight was not considered to be biologically significant due to the lack of any exposure-related microscopic lesions in the lung and the lack of effect at the terminal sacrifice.

The kidney appeared to be a target for nonneoplastic effects in rats exposed repeatedly to isopropanol vapor. An exacerbation of chronic renal disease was observed in isopropanol exposed rats. Endpoints which characterize this disease state and were observed for isopropanol exposed male rats from the 2500 and 5000 ppm groups and female rats from the 5000 ppm group included changes in kidney weight, an increased incidence of gross lesions in the kidney noted at necropsy, and increased frequencies of renal microscopic changes as well as urinalysis and urine chemistry changes. Increases in kidney weight were noted for male rats from the 5000 ppm group at the interim sacrifice and for male rats from the 2500 ppm group and female rats from the 5000 ppm group at the terminal sacrifice. In addition, changes in urinalysis and urine chemistry indicative of renal damage and loss of concentrating

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ability of the kidney (e.g., decreases in osmolality as well as increases in total protein, total volume, and total glucose) were observed for male rats from the 2500 and 5000 ppm groups and female rats from the 5000 ppm group. An increased incidence of granular kidneys was noted for male rats from the 2500 and 5000 ppm groups at Week 73, for male rats from the 2500 ppm group at Week 104, and for rats (male and female) from the 2500 and 5000 ppm groups which were found dead or sacrificed moribund during the study. Granular kidneys are the result of chronic renal disease.

For male rats from the 2500 and 5000 ppm groups which were found dead or sacrificed due to morbidity during the study, increased frequencies of a number of kidney lesions associated with chronic renal disease were observed microscopically and included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. In addition, the severity of some of the lesions associated with chronic renal disease was increased at the interim and terminal sacrifice timepoints for male rats from the 2500 and 5000 ppm groups (as well as for all male rats on the study) and for all female rats on the study from the 2500 and 5000 ppm groups. An increase in the severity of glomerulosclerosis was also noted at the terminal sacrifice for female rats from the 5000 ppm group. Increased frequencies of a number of other lesions (e.g. mineralization, cellular hyperplasia of the parathyroid glands, and fibrous osteodystrophy) believed to be secondary to the chronic renal disease were also observed for male and female rats from the 2500 and 5000 ppm groups which died or were sacrificed in moribund condition. Associated with the increased soft tissue mineralization were increases in myocardial degeneration/fibrosis and/or glandular ectasia within the gastric mucosa for these rats from the 5000 ppm group. The main cause of death and the resultant early mortality for male rats from the 5000 ppm group as well as female rats from the 5000 ppm groups was determined to be chronic renal disease. In addition, chronic renal disease was believed to account for much of the mortality of male rats from the 2500 ppm group.

Other nonneoplastic lesions which were observed upon histopathologic evaluation with increased frequencies for male rats from the 5000 ppm group which died or were sacrificed due to morbidity included basophilic cell foci within the liver, splenic hemosiderosis, rhinitis and squamous metaplasia of the respiratory epithelium within the nasal cavity, and iridocyclitis. Other lesions observed with increased frequencies for female rats from the 5000 ppm group which died or were sacrificed due to morbidity included atrial thrombosis, myocardial degeneration, splenic hemosiderosis, and ocular keratitis. In addition, inflammatory and metaplastic changes within the nasal cavity such as rhinitis, dacryosolenitis (inflammation of the nasolacrimal duct), and squamous metaplasia of the respiratory epithelium were noted for female rats from the 5000 ppm group which died or were sacrificed due to morbidity.

The only neoplastic lesion found to be increased in frequency in isopropanol exposed animals was observed in the testis of male rats. A concentration-related increase in testes weight was observed for male rats at the interim sacrifice timepoint. Upon microscopic evaluation, an increased frequency of testicular seminiferous tubule atrophy and interstitial cell adenomas was noted for male rats from the 5000 ppm group at this interim timepoint. The frequency of interstitial (Leydig) cell tumors of the testis was also increased in a concentration-related fashion for all male rats on the study. However, the interstitial cell tumor of the testis is typically the most frequently observed spontaneous tumor in aged male Fischer 344 rats (Takaki *et al.*, 1989; Haseman *et al.*, 1990). Nearly all male Fischer rats will develop these proliferative tumors if they are allowed to complete their lifespan (Boorman *et al.*, 1990). The frequencies of this tumor in male rats from the low (77.3%), intermediate (86.7%), and high (94.7%) concentration groups in this study

were similar to the mean incidence of 88% reported by Haseman *et al.* (1990) for control male Fischer 344 rats from numerous 2-year NTP carcinogenic studies. In addition, the incidences observed for the isopropanol exposure groups were similar to frequencies noted during previously conducted studies at BRC for male control Fischer 344 rats (86 and 91%; BRC Historical Control Data). Contrary to these data, the incidence observed for the control group (64.9%) was well below these values for control male Fischer 344 rats. Both of the independent consultant pathologists who were requested to express their opinions about the biological significance of interstitial cell tumors of the testes in the Fischer 344 rat noted that the incidence of this tumor for the control group in this study was unusually low. Thus, the increased incidences of testicular tumors in the isopropanol exposure groups may be spurious and reflective of the lower incidence in the control group.

If the increase in testicular interstitial cell tumors is not a result of the lower incidence of this tumor in the control group, a possible mechanism may be that these tumors developed as a result of hormonal imbalances produced as a result of exposure to isopropanol. Exposure to some drugs and chemicals has been shown to produce testicular adenomas in the male rat through imbalances in circulating hormones such as leutinizing hormone (Cook *et al.*, 1992; Cook *et al.*, 1993; Prentice *et al.* 1992). Increased circulating levels of leutinizing hormone may occur as a result of decreased testosterone synthesis or inhibition of the action of testosterone as a result of exposure to these chemicals. This increased level of leutinizing hormone results in the stimulation of the sensitive interstitial (Leydig) cell population in the testes of rats which produces proliferative changes including hyperplasia and adenomas (Chatani *et al.*, 1990).

Interstitial cell adenomas of the testes are believed to represent severe hyperplasia rather than autonomous growth (Boorman *et al.*, 1990). It is often difficult to differentiate between focal hyperplasia and adenomas in the testes of Fischer 344 male rats because these interstitial adenomas originate as focal hyperplasia and the transformation from hyperplasia to adenoma represents a continuous spectrum of morphologic change occurring within the testes of these aged male rats. Furthermore, there was no evidence from this study to indicate the development of carcinomas of the testes in the male rat nor has isopropanol been found to be genotoxic in a variety of assays (Kapp *et al.*, 1993).

In conclusion, exposure of rats to isopropanol vapor for 24 months produced clinical signs of toxicity (hypoactivity, lack of a startle reflex, or narcosis) during the exposures at 2500 and 5000 ppm as well as increases in body weight and body weight gain. Urinalysis and urine chemistry changes indicative of kidney damage were noted for male rats from the 2500 and 5000 ppm groups and female rats from the 5000 ppm group. A number of nonneoplastic lesions were observed, with the most significant lesions being observed in the kidney. The only neoplastic lesion observed for male rats was an increase in interstitial cell adenomas of the testis which was considered to represent marked hyperplasia and was not believed to represent autonomous growth. In addition, the increased incidences of testicular tumors in the isopropanol groups appear to be reflective of the lower incidence in the control group. No increased frequencies of neoplastic lesions were noted for female rats from any isopropanol exposure group. Thus, the no-observed-effect level (NOEL) for toxic effects was 500 ppm for both male and female rats. The NOEL for oncogenicity effects for both male and female rats was determined to be greater than 5000 ppm.

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REVIEW AND APPROVAL

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 Heather D. Burleigh-Flayer, Ph.D. Date

Associate Director: James D. Sun 6-2-94  
 James D. Sun, Ph.D. Date

Director: John P. Van Miller 6-2-94  
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Additional personnel are listed in the raw data.

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TABLE 1  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF MORTALITY

	<u>MALES</u>			
	<u>CONCENTRATION</u>			
	<u>0 ppm</u>	<u>500 ppm</u>	<u>2500 ppm</u>	<u>5000 ppm</u>
Total Number of Animals	75	75	75	75
Interim Sacrifice Group	10	10	10	10
Core Group	65	65	65	65
Number Sacrificed	12	11	6	0
Number Found Dead	36	37	40	45
Number Sacrificed Moribund	17	17	19	20
Mean Survival Time (Days) <sup>a</sup>	631	634	612	577 <sup>**</sup>
Mortality Rate (%) <sup>b</sup>	82	83	91	100

	<u>FEMALES</u>			
	<u>CONCENTRATION</u>			
	<u>0 ppm</u>	<u>500 ppm</u>	<u>2500 ppm</u>	<u>5000 ppm</u>
Total Number of Animals	75	75	75	75
Interim Sacrifice Group	10	10	10	10
Core Group	65	65	65	65
Number Sacrificed	30	34	29	20
Number Found Dead	27	23	24	28
Number Sacrificed Moribund	8	8	12	17
Mean Survival Time (Days) <sup>a</sup>	699	714	692	698
Mortality Rate (%) <sup>b</sup>	54	48	55	69

<sup>a</sup>Statistics were performed for mean survival time only. A statistical difference of  $p < 0.01$  (\*\*) was observed for the male 5000 ppm group. No other statistical difference was observed for either sex.

<sup>b</sup>Mortality rates include animals that were sacrificed moribund but not interim sacrifice animals.

TABLE 1 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF PALPABLE MASSES

<u>MALES</u>				
	<u>0 ppm</u>	<u>500 ppm</u>	<u>2500 ppm</u>	<u>5000 ppm</u>
Total Number of Animals	75	75	75	75
Total Number Animals with Masses <sup>a</sup>	12	11	9	9
Total Number Animals with Persistent Masses (at least one persistent)	11	11	9	7
Total Number Animals with Multiple Persistent Masses <sup>c</sup>	1	1	2	2
Mean Number Days to First Persistent Mass <sup>b</sup>	576	584	466	584

<u>FEMALES</u>				
	<u>0 ppm</u>	<u>500 ppm</u>	<u>2500 ppm</u>	<u>5000 ppm</u>
Total Number of Animals	75	75	75	75
Total Number Animals with Masses <sup>a</sup>	13	10	19	13
Total Number Animals with Persistent Masses (at least one persistent)	12	10	19	10
Total Number Animals with Multiple Persistent Masses <sup>c</sup>	2	1	2	1
Mean Number Days to First Persistent Mass <sup>b</sup>	643	639	572	677

- <sup>a</sup> Includes persistent masses (masses present at death or sacrifice) as well as masses that disappeared.
- <sup>b</sup> Statistical analysis was performed on the mean number of days to first persistent mass for all groups combined, then individually. The 2500 ppm group of males was significantly different from the control  $p < 0.01$ .
- <sup>c</sup> Includes animals with two or more masses, one of which was persistent.

0 0 3 2

TABLE 2  
ISOPROP. NOL VIUFOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
BEHAVIOR/CBS HYPOACTIVE		P	2 (657)	1 (657)	2 (587-706)	3 (423-657)
	PARESIS (LEG-HIND-BOTH)	P	0	2 (625-629)	1 (628)	1 (562)
	PARALYSIS (LEG-HIND-BOTH)	P	1 (538-540)	0	0	0
	TREMOR	P	0	1 (636)	0	2 (260-349)
	PROSTRATION	P	11 (449-720)	12 (464-687)	13 (499-715)	11 (281-652)
HEAD TILT	P	3 (550-713)	1 (636)	5 (559-713)	0	
BODY	EMACIATED	P	46 (333-730)	45 (419-730)	55 (389-730)	59 (274-694)
	DEHYDRATED	P	48 (104-730)	46 (402-730)	55 (340-730)	59 (212-694)
	SWELLING (ABDOMEN)	10	6	6	8	9
		P	3 (461-601)	0	0	3 (482-622)
	(FACE)	P	1 (335-342)	0	0	0
	(GENITAL)	P	7 (83-524)	2 (209-506)	4 (209-506)	3 (209-608)
	(MOUTH)	P	0	1 (604)	0	1 (552-566)
	(PAW-HIND-RIGHT)	P	0	1 (706)	1 (706)	0
	(PENIS)	P	1 (587)	2 (636-678)	3 (559-730)	1 (587)
	(SCROTUM)	P	0	0	0	1 (461-510)
(SIDE-RIGHT)	P	0	0	0	1 (370)	
(TAIL)	P	0	0	0	1 (349-356)	

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 1500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
<b>BODY</b>						
ABDOMINAL DISTENSION	P	0	4(587-712)	0	1 (472)	
URINEPT	P	3(545-664)	8(513-706)	5(467-706)	7(440-636)	
URINE STAINS	P	19(125-669)	22( 62-730)	22( 97-715)	25(118-652)	
COLD EXTREMITIES (LEGS-ALL)	P	0	6	10	6	
(PANS-ALL)	P	0	0	1 (517)	0	
(PAM-FORE-BOTH)	P	5(587-719)	6(587-685)	9(587-730)	4(474-642)	
(PAM-HIND-BOTH)	P	0	0	1(629-636)	0	
PALLOR (ENTIRE BODY)	P	0	0	0	2(281-629)	
(MULTIPLE AREAS-MOS)	P	5	3	3	3	
HUNCHED POSTURE	P	1 (551)	0	1 (587)	2(419-587)	
UROGENITAL (EYES, RED)	P	4(586-669)	3(439-687)	2(573-608)	1 (541)	
TRAUMATIZED (ABDOMEN)	P	6(551-692)	13(439-692)	14(587-730)	3(541-587)	
(EYE-LEFT)	P	0	1 (342)	1 (706)	0	
(EYE-RIGHT)	P	12	15	14	15	
(GENITAL)	P	1 (586)	0	1 (612)	1(510-517)	
	P	0	0	0	1(573-580)	
	P	0	1 (513)	0	0	
	P	0	0	0	1 (508)	

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
<b>BODY</b>						
TRAUMATIZED (CONTINUED)						
(HEAD)	P	1 (333)	0	0	0	0
(MOUTH)	P	0	1(475-496)	0	0	0
(NECK)	P	0	0	0	0	1 (614)
(PAW-FORE-LEFT)	P	0	1 (433)	0	0	1( 20- 27)
(PAW-FORE-RIGHT)	P	1(234-237)	2(104-237)	1(104-111)	0	0
(PAW-HIND-BOTH)	P	0	2(265-335)	0	0	0
(PAW-HIND-LEFT)	P	0	4(265-524)	2(183-339)	1(265-272)	0
(PAW-HIND-RIGHT)	P	1 (149)	0	3( 93-447)	3( 24-316)	0
(SIDE-RIGHT)	P	1(475-496)	0	0	0	0
(TAIL)	P	8( 4-669)	5( 6-712)	9( 6-695)	8( 3-634)	0
UROGENITAL AREA WETNESS	P	11(160-720)	13(118-730)	18(104-713)	11( 90-652)	0
<b>CARDIO-PULMONARY</b>						
LABORED RESPIRATION	P	2(551-664)	3(650-687)	2(587-715)	4(550-652)	0
AUDIBLE RESPIRATION	P	0	2 (629)	0	1 (281)	0
RAPID RESPIRATION	P	0	3(636-678)	0	7(281-657)	0
SLOW RESPIRATION	P	1 (703)	0	1 (645)	0	0
<b>EYES/NOSE/MOUSE</b>						
REDDENED EYES		2	1	2	2	2

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
EYES/NASES/NOSES REDDENED EYES (CONTINUED) (EYE-LEFT)	P	2	2(719-730)	1(706)	0	1(591)
			0	0	2(440-715)	2(573-587)
CORNEAL ULCERATION (EYE-BOTH)	P	1	1(719)	0	2	1
			0	0	1(713-715)	0
EXOPHTHALMIA (EYE-RIGHT)	P	1	0	0	1(685)	1(587-594)
			1(587-636)	0	0	0
OPACITY (EYE-BOTH)	P	3	4	4	7	7
			1(706-719)	1(678)	1(678)	1(601)
OPACITY (CONTINUED) (EYE-LEFT)	P	1	1(503)	2(587-720)	2(573-594)	4(552-636)
			1(132-153)	1(230-237)	4(342-706)	2(230-587)
PALE EYES (EYE-BOTH)	P	20	22	17	15	15
			19(333-730)	20(216-713)	16(467-695)	14(419-657)
SHRUNKEN EYES (EYE-RIGHT)	P	1	1(657)	3(513-678)	1(559)	0
			1(125)	0	0	1(657)
LACRIMATION (EYE-BOTH)	P	2	1(510)	0	0	0
			1(517)	0	0	1(279)
OCULAR DISCHARGE (EYE-BOTH)	P	1	1(538)	0	0	0
			7	15	7	3
	P	2	2(468-642)	7(478-699)	2(622-713)	1(634)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
EYES/NOSE OCULAR DISCHARGE (CONTINUED) (EYE-LEFT)	P		4(342-685)	6(475-720)	3(475-587)	2(454-587)
	P		3(132-594)	4(559-727)	3(475-692)	0
(EYE-RIGHT)	P		0	0	1(715)	1(591)
NASAL DISCHARGE						
SWOLLEN PERIOCULAR TISSUE (EYE-BOTH)	P		16	19	24	17
	P		7(167-650)	7( 62-727)	9( 48-713)	6( 20-615)
(EYE-LEFT)	P		6( 76-685)	10( 62-720)	14( 6-712)	9( 6-645)
(EYE-RIGHT)	P		9( 34-678)	6( 62-636)	8( 34-699)	5( 6-251)
PERIOCULAR ENCRUSTATION (EYE-BOTH)	P		20	25	17	15
(EYE-LEFT)	P		7(342-643)	9(405-706)	3(552-713)	2(279-615)
(EYE-RIGHT)	P		11( 90-692)	13(104-730)	10(160-712)	11( 69-636)
PERINASAL ENCRUSTATION	P		10( 69-678)	7(174-730)	10( 34-699)	3( 55-652)
MICROPTALMIA (EYE-RIGHT)	P		5( 6-720)	5(559-720)	5(573-730)	8(251-652)
BLEPHAROSPASM (EYE-BOTH)	P		0	0	0	1(573-580)
(EYE-LEFT)	P		5	4	4	0
(EYE-RIGHT)	P		1( 587)	4(587-657)	1( 645)	0
LINEAR OPACITY (EYE-LEFT)	P		2(587-636)	1(629-636)	2(587-678)	0
(EYE-RIGHT)	P		2(601-678)	0	1( 706)	0
LINEAR OPACITY (EYE-LEFT)	P		0	0	1	3
(EYE-RIGHT)	P		0	0	1( 657)	0
	P		0	0	0	3(636-657)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "-" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 2 (Continued)  
 ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
EYES/NOSE/ROSE IRREGULAR OPACITY (EYE-LEFT)	P		1 (41-76)	1 (580)	2 (475-503)	0
	P		0	0	1 (657)	0
	P		0	2 (83-223)	0	1
	P		0	1 (83-223)	0	0
PUNCTATE OPACITY (EYE-BOTH)	P		0	2 (41-237)	0	1 (41-370)
	P		0	1 (41-76)	0	0
MISSING EYE (EYE-LEFT)	P		1	0	0	1 (601)
	P		0	0	0	1 (601)
	P		1 (706)	0	0	0
EXCRETA LOOSE FECES	P		0	0	0	1 (645)
	P		0	0	1 (587)	0
BLACK ("TARRY") FECES	P		0	0	0	0
	P		0	0	1 (587)	0
ORAL/TEMPAL OVERGROWN INCISORS	P		1 (475-580)	1 (513)	1 (587)	1 (552-573)
	P		1 (650-656)	0	1 (587)	1 (552-566)
ORAL LESION	P		U	0	1 (587)	1 (622)
MALOCCLUSION	P		0	0	0	2 (505-636)
PERIORAL ENCRUSTATION	P		0	0	0	0
SALIVATION	P		1 (656)	0	0	0

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROFANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
SKIN ALOPECIA (ABDOMEN) (BACK) (EYE-LEFT) (EYE-RIGHT) (FACE) (GENITAL) (LEG-FRONT-BOTH) (LEG-FORE-LEFT) (LEG-FORE-RIGHT) (MULTIPLE AREAS-NOS) (PAW-FORE-BOTH) (PAW-FORE-LEFT) (PAW-FORE-RIGHT) EXFOLIATIVE (TAIL) EXCORIATED (TAIL) CRUST (ABDOMEN) (BACK)	P	12	21	15	18	
	0	0	0	1(650-657)	2(594-685)	
	P	0	0	0	1(596)	
	P	1(419)	0	0	0	
	P	1(419-447)	0	0	0	
	P	3(559-657)	7(559-720)	3(559-657)	5(281-594)	
	P	1(587)	1(608-622)	1(678-730)	2(433-596)	
	P	4(104-730)	2(62-167)	1(216-286)	2(132-293)	
	P	0	5(6-657)	1(160-216)	2(132-167)	
	P	4(6-692)	2(307-678)	0	2(104-286)	
	P	0	0	1(636)	0	
	P	4(20-321)	6(55-300)	8(6-286)	4(6-114)	
	P	1(48-76)	6(6-681)	2(83-230)	3(132-272)	
	P	4(6-692)	0	2(167-230)	6(62-321)	
	P	3	0	1(90-139)	0	
P	0	0	0	1(258-307)		
P	20	18	13	9		
P	4(391-517)	4(440-629)	0	0		
P	1(552)	0	1(657-678)	1(587-594)		

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 1500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS

SUMMARY OF CLINICAL OBSERVATIONS

MALES

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)	
SKIN	CRUST (CONTINUED)						
	(HEAD)	P	0	1(580-594)	0	0	
	(MOUTH)	P	1(664)	0	1(447)	0	
	(PAW-FORB-RIGHT)	P	0	0	1(62-69)	0	
	(PAW-HIND-BOTH)	P	0	1(643)	1(706)	0	
	(PAW-HIND-RIGHT)	P	1(643-664)	0	1(643-699)	0	
	(SCROTUM)	P	0	1(475-496)	1(531-566)	0	
	(SIDE-RIGHT)	P	2(304-517)	0	0	0	
	(TAIL)	P	14(244-730)	13(251-730)	9(251-730)	8(223-657)	
	ULCER	(ABDOMEN)	P	12	11	8	2
		(BACK)	P	2(468-580)	2(503-594)	2(475-566)	1(503-594)
		(GENITAL)	P	0	0	0	1(524-538)
		(LUNG-HIND-RIGHT)	P	1(377)	0	0	0
(PAMB-ALL)		P	0	0	1(608)	0	
(PAMB-HIND-BOTH)		P	0	0	1(713-715)	0	
(PAMB-HIND-LEFT)	P	5(342-720)	1(650-657)	1(391-412)	0		
(PAMB-HIND-RIGHT)	P	2(356-506)	1(615-622)	0	0		
(SCROTUM)	P	3(342-384)	4(391-713)	3(342-426)	0		
	P	0	0	1(433-475)	0		

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROPIANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
SKIN						
ULCER (CONTINUED) (TAIL)	P	0	3(258-506)	0	0	0
SCAR (ABDOMEN)	P	0	2 1(559-587)	1	1	1
(BACK)	P	1(559-601)	0	0	0	0
(TAIL)	P	5( 20-342)	1(594-636)	1( 20- 34)	1( 20- 34)	1( 20- 34)
COLOR CHANGE (TAIL)	P	0	1(622-625)	0	0	2(590-657)
BLUE CUTIS (ABDOMEN)	P	1 1(552-580)	3 1( 629)	0	0	2 2(503-587)
(SCROTUM)	P	0	2(503-678)	0	0	1(468-510)
YELLOW CUTIS (ENTIRE BODY)	P	3 1( 573)	12 1( 514)	5 1(524-540)	4 0	0
(EAR-BOTH)	P	1( 551)	6(461-636)	5(454-692)	2(587-634)	0
(EAR-LEFT)	P	0	1( 503)	0	0	0
(EAR-RIGHT)	P	0	1( 503)	0	0	0
(EYE-BOTH)	P	0	1( 692)	0	0	0
(LEG-HIND-BOTH)	P	0	1( 461)	1( 461)	0	0
(MULTIPLE AREAS-NOS)	P	1(608-622)	6(439-681)	2(467-643)	2(573-594)	0
(NOSE)	P	0	0	1( 461)	0	0
(PAWS-ALL)	P	0	4(503-692)	4(510-692)	1( 629)	0

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 2 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
MALES						
SKIN						
YELLOW CUTIS (CONTINUED)						
(PAW-FORE-BOTH)	P	0	1 (461)	1 (461)	0	0
(SCROTUM)	P	0	0	0	1 (461)	1 (461)
(TAIL)	P	0	0	1 (461)	0	0
PAPULE (ABDOMEN)	P	13	12	8	7	7
(ANUS)	P	3(342-552)	2(531-678)	1(643-730)	0	0
	P	0	0	0	1(608-622)	0
PAPULE (EAR-LEFT)	P	0	2(356-615)	0	0	0
(EAR-RIGHT)	P	2(468-730)	2(461-730)	0	0	0
(GENITAL)	P	1(342-370)	1(615-622)	1(356-370)	0	0
(HEAD)	P	1(454-461)	1(566-560)	0	0	0
(MOUTH)	P	2(475-566)	0	0	0	0
(NOSE)	P	0	2(531-730)	1(342-552)	1(559-685)	0
(PENIS)	P	1 (601)	0	0	0	0
(SCROTUM)	P	0	0	1(503-524)	0	0
(SIDE-LEFT)	P	0	0	1(650-657)	0	0
(SIDE-RIGHT)	P	1(461-468)	0	0	1 (657)	0
(TAIL)	P	4(440-594)	4(552-730)	4(440-730)	4(349-650)	0
PUSTULE (ABDOMEN)	P	2	4	1	1	1
	P	0	2(559-643)	1 (636)	0	0

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 2 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	MALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
SKIN						
	FUSTULE (CONTINUED) (GENITAL)	P	2(251-395)	1(608-629)	0	1(559-566)
	(HEAD)	P	0	1(587-594)	0	0
	(SHOULDER-LEFT)	P	0	1(643)	0	0
	(SHOULDER-RIGHT)	P	0	1(643)	0	0
	ABSCESS (ABDOMEN)	P	0	0	2	1
	(MOUTH)	P	0	0	0	1(671-685)
	(PAN-HIND-RIGHT)	P	0	0	1(496-506)	0
	NECROSIS (TAIL)	P	3(678-730)	4(125-730)	3(695-730)	2(559-657)
MASSSES						
	MASS(ES) PRESENT	P	12(309-730)	11(386-730)	9(307-650)	9(433-664)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 3  
ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

FEMALES

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
NEBULATION/CM						
HYPRACTIVE	P	P	1 (657)	2(657-706)	1 (515)	1 (657)
ATAZIA	P	P	0	0	1 (733)	0
TREMOR	P	P	0	2 (670)	0	0
PROSTRATION	P	P	6(433-757)	5(416-737)	8(515-745)	13(506-754)
HEAD TILT	P	P	3(433-757)	7(601-757)	3(670-758)	0
BOOY						
EMACIATED	P	P	34(417-759)	25(304-757)	30(372-758)	42(302-758)
DEHYDRATED	P	P	34(417-759)	25(160-757)	30(372-758)	42(302-758)
SWELLING (ABDOMEN)						
	P	P	1 (510-517)	2 (636)	6 (3475-601)	7 (3500-671)
(AXILLA-LEFT)	P	P	0	1(101-100)	0	0
(GENITAL)	P	P	0	0	2(335-419)	1 (510)
(LEG-FORR-RIGHT)	P	P	0	0	0	1 (733)
SWELLING (CONFURED) (LEG-HIND-LEFT)						
	P	P	0	0	0	1 (733)
(TAIL)	P	P	0	0	2( 62-328)	2(670-758)
(VAGINA)	P	P	0	0	1(524-545)	1(531-545)
ABDOMINAL DISTENSION	P	P	0	2(629-699)	2(405-594)	2(601-685)
URINE/PT	P	P	6(475-741)	5(531-741)	2(685-744)	4(608-741)
URINE STAINS	P	P	43(132-759)	34( 27-759)	52( 20-758)	53( 20-757)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 3 (Continued)  
ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	FEMALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
<b>BODY</b>						
COLD EXTREMITIES (LEGS-ALL)	P	P	5 (1 (433))	8 (0)	9 (0)	7 (0)
(PAWs-ALL)	P	P	4 (664-751)	7 (552-737)	6 (608-744)	7 (685-754)
(PAW-HIND-BOTH)	P	P	1 (1 (17))	1 (629)	3 (706-745)	0
PALLOR (MULTIPLE AREAS-NOS)	P	P	2 (696-734)	3 (650-734)	3 (608-718)	0
HUNCHED POSTURE	P	P	11 (559-759)	9 (573-734)	9 (636-713)	12 (395-758)
UROGENITAL DISCHARGE, RED	P	P	2 (293-580)	0	1 (447)	2 (482-755)
UROGENITAL DISCHARGE, OTHER	P	P	0	0	0	1 (636)
VAGINAL PROLAPSE	P	P	0	0	1 (524-757)	0
RECTAL PROLAPSE	P	P	0	0	0	1 (573-757)
TRAUMATIZED (CHEST)	P	P	12 (0)	17 (0)	15 (1 (486))	19 (0)
(EYE-LEFT)	P	P	1 (580-594)	4 (580-594)	2 (580-594)	2 (580-594)
(FACE)	P	P	0	0	0	1 (461-468)
(HEAD)	P	P	0	0	1 (370)	0
(LEG-FORE-LEFT)	P	P	0	0	0	1 (706-720)
(LEG-FORE-RIGHT)	P	P	0	0	0	1 (733)
(MOUTH)	P	P	0	1 (755-757)	0	0
(NOSE)	P	P	0	0	1 (394-398)	0

GROUP LEGS: D: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 3 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

FEMALES

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
BODY TRAUMATISED (CONTINUED) (PAW-FORE-LEFT) (PAW-FORE-RIGHT) (PAW-HIND-BOTH) (PAW-HIND-LEFT) (PAW-HIND-RIGHT) (TAIL) (VAGINA)	P	0	0	0	1 (130)	1 (741-746)
	P	0	1 (265-300)	0	0	0
	P	0	1 (678)	0	0	0
	P	1 (265-272)	0	1 (248)	0	0
	P	1 (142-146)	2 (397-671)	1 (215-216)	1 (734-741)	
	P	4 (16-745)	6 (382-720)	3 (9-671)	7 (15-674)	
	P	5 (370-552)	3 (289-433)	6 (369-524)	5 (265-377)	
UROGENITAL AREA WETNESS	P	30 (104-759)	26 (20-741)	30 (20-757)	26 (34-756)	
CARDIO-PULMONARY LABORED RESPIRATION	P	2 (433-757)	2 (559-653)	0	4 (573-754)	
	P	0	0	1 (657)	1 (720-758)	
	P	1 (751)	1 (601)	0	0	
	P	4 (607-734)	2 (678-720)	6 (636-706)	3 (635-731)	
	P	0	0	1 (643)	0	
SLOW RESPIRATION	P	1 (678)	1 (678)	1 (678-685)	1 (663)	
	P	2 (601-664)	0	2 (580-671)	0	
YES/NOSES REDDENED EYES (EYE-LEFT)	P	2 (601-664)	0	2 (580-671)	0	

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "-" represent earliest to latest day a finding of the specified grade was observed.

TABLE 3 (Continued)  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	FEMALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
ETES/EARS/NOSE						
REDDENED EYES (CONTINUED) (EYE-RIGHT)	P	0	0	1 (671)	2 (503-594)	
CORNEAL ULCERATION (EYE-BOTH)	P	5	3 (759)	1 (745)	1	0
(EYE-LEFT)	P	4 (587-759)	3 (587-720)	0	1 (587-636)	
EXOPHTHALMIA (EYE-LEFT)	P	1 (587-759)	2 (587-741)	0	1	0
EXOPHTHALMIA (CONTINUED) (EYE-RIGHT)	P	0	1 (758)	0	1 (475-503)	
OPACITY (EYE-BOTH)	P	9	13 (755)	10 (601-759)	8 (636-755)	
(EYE-LEFT)	P	4 (335-758)	7 (335-757)	3 (636-759)	3 (223-777)	
(EYE-RIGHT)	P	5 (342-759)	4 (76-758)	5 (657-757)	4 (216-748)	
PALE EYES (EYE-BOTH)	P	15	19 (545-758)	21 (414-757)	19 (524-758)	
(EYE-LEFT)	P	0	1 (748-755)	3 (657-718)	2 (730-754)	
(EYE-RIGHT)	P	2 (559-748)	4 (601-657)	1 (601-608)	0	
SHRUNKEN EYES (EYE-LEFT)	P	0	2 (706-720)	1 (757)	1 (757)	
(EYE-RIGHT)	P	0	1 (590)	1 (503)	0	
LACRIMATION (EYE-BOTH)	P	5	4 (433)	1 (733)	2	0
		2			0	

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 3 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

CATS/DOGS FINDING (LOCATION)	GROUP:	GRADE	FEMALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
ETES/NASES/NOSES LACRIMATION (CONTINUED) (EYE-LEFT)	P	3	3(321-538)	0	0	1 (328)
(EYE-RIGHT)	P	0	3(321-433)	1 (328)	1 (433)	
OCULAR DISCHARGE (EYE-BOTH)	P	12	9(475-750)	7(510-757)	4(335-744)	8(496-752)
(EYE-LEFT)	P	12	10(48-759)	10(335-759)	9(265-699)	15(293-758)
(EYE-RIGHT)	P	7	7(265-757)	14( 48-759)	13( 76-759)	11(454-759)
NASAL DISCHARGE	P	0	0	0	0	1 (663)
SWOLLEN PERI OCULAR TISSUE (EYE-BOTH)	P	40	26( 90-758)	23( 6-757)	14( 97-759)	38( 20-757)
(EYE-LEFT)	P	20	20( 41-759)	17( 20-759)	17( 27-706)	26( 20-759)
(EYE-RIGHT)	P	18	18( 76-759)	23( 20-759)	21( 34-759)	24( 20-759)
PERI OCULAR ENCRUSTATION (EYE-BOTH)	P	41	16(433-758)	16( 97-757)	13(251-759)	12(496-757)
(EYE-LEFT)	P	24	24( 48-759)	14( 6-759)	9(342-758)	26(104-759)
(EYE-RIGHT)	P	15	15(132-759)	23( 20-759)	18(195-759)	15(433-759)
PERI NASAL ENCRUSTATION	P	12	12(433-755)	10(454-758)	10(335-757)	13(125-758)
MICROPTHALMIA (EYE-LEFT)	P	1	1	2	1	1
(EYE-RIGHT)	P	0	1(755-757)	1 (759)	1(391-433)	
(EYE-RIGHT)	P	1	1(758)	1(342-377)	0	0
BLEPHAROSPASM	P	8	5	1	1	7

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 3 (Continued)  
 ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 34 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

FEMALES

CATEGORY FINDING (LOCATION)	GROUP:	GRADE	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
YES/HAIR/MOSE						
BLEPHAROSPASM (CONTINUED)						
(EYE-BOTH)	P		6(629-755)	3(587-636)	0	5(601-727)
(EYE-LEFT)	P		2(657-706)	2(601-629)	0	2(657-741)
(EYE-RIGHT)	P		2(601-748)	2(601-678)	1(678-685)	1(629)
LINEAR OPACITY						
(EYE-BOTH)	P		0	1	1	4
(EYE-LEFT)	P		0	0	0	3(720-741)
(EYE-RIGHT)	P		0	0	1(657)	0
LINEAR OPACITY (CONTINUED)						
(EYE-RIGHT)	P		0	1(720)	0	1(741)
IRREGULAR OPACITY						
(EYE-LEFT)	P		2(475-503)	0	1(580)	1(601)
(EYE-RIGHT)	P		1(475-507)	1(454-468)	0	0
CLOUDY (EYE-LEFT)	P		1(69)	1(727-741)	0	0
MISSING EYE						
(EYE-LEFT)	P		3	3	3	3
(EYE-RIGHT)	P		2(601-759)	2(601-757)	1(601)	2(601-757)
SECRET						
LOOSE FECES	P		1(757)	1(601)	2(601-706)	1(601)
ORAL/DENTAL						
OVERGROWN INCISORS	P		0	0	1(685)	0
ORAL LESION	P		1(321-755)	1(643-678)	1(706)	2(643-692)
	P		1(629)	1(636-643)	1(706-718)	1(643)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 3 (Continued)  
ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE:	1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
ORAL/DENTAL MALOCCLUSION		P	1(699-758)	1(678-706)	1(734-741)	0
PERIORAL WETNESS		P	1(433)	0	0	0
PERIORAL ENCRUSTATION		P	0	0	1(745)	0
SKIN						
ALOPECIA (ABDOMEN)		P	31 5(550-734)	33 1(174)	30 1(636)	38 4(552-757)
(BACK)		P	1(706-713)	0	0	0
(EYE-BOTH)		P	0	0	0	1(160-167)
(FACE)		P	16(559-758)	19(440-759)	16(552-741)	21( 20-758)
(GENITAL)		P	3(335-678)	2(636-734)	2(384-759)	3(363-671)
(HEAD)		P	1(601)	0	0	1(587-594)
(INGUINAL-RIGHT)		P	1(657)	0	0	0
(LEG-FRONT-BOTH)		P	2( 27-759)	1(657-713)	3( 20-758)	1(209-314)
(LEG-FORE-LEFT)		P	3(559-685)	5( 48-758)	2(706-759)	7( 20-759)
(LEG-FORE-RIGHT)		P	3(552-748)	1(720)	5( 62-758)	4(552-757)
(MULTIPLE AREAS-NOS)		P	2(666-758)	4(727-759)	1(699-759)	3(674-730)
(PAW-FORE-BOTH)		P	4( 27-426)	4( 48-759)	3( 20-328)	8( 20-636)
(PAW-FORE-LEFT)		P	6( 20-594)	8( 20-636)	4( 48-531)	8( 20-759)
(PAW-FORE-RIGHT)		P	4( 20-314)	3( 48-643)	5( 90-741)	4( 20-636)

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

TABLE 3 (Continued)  
 ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
 SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP:	GRADE:	FEMALES			
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)
SKIN	ALOPECIA (CONTINUED) (PAW-HIND-RIGHT)	P	1(377-426)	0	0	0
	(SHOULDER-RIGHT)	P	0	1(664-671)	0	0
	EXCORIATED (TAIL)	P	0	0	0	1(727)
	CRUST (ABDOMEN)	P	7	12	7	10
		P	0	0	0	1(706-723)
	CRUST (CONTINUED) (TAIL)	P	7(48-758)	12(20-759)	7(20-758)	9(307-757)
	SCAR (HEAD)	P	3	2	1	2
		P	0	0	1(342-363)	0
	(TAIL)	P	3(20-34)	2(20-636)	0	2(20-34)
	COLOR CHANGE (TAIL)	P	1(758)	1(685-706)	1(612)	0
YELLOW CUTIS (ENTIRE BODY)	BLUE CUTIS (ABDOMEN)	P	0	2	1	2
		P	0	1(636)	0	2(629-643)
	(MULTIPLE AREAS-NOS)	P	0	0	1(414)	0
	(PAW-HIND-RIGHT)	P	0	1(540)	0	0
	YELLOW CUTIS (ENTIRE BODY)	P	8	8	4	1
		P	1(538-541)	0	0	1(531-538)
	(EAR-BOTH)	P	5(559-696)	5(540-653)	2(629-671)	0
	(MULTIPLE AREAS-NOS)	P	4(622-727)	4(622-706)	2(706-744)	1(541)
	(PAWS-ALL)	P	2(629-664)	2(636-653)	1(664-671)	0

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
 Numbers represent the number of animals exhibiting the finding at least once during the study.  
 Parenthetical numbers "()" represent earliest to latest day a finding of the specified grade was observed.

TABLE 3 (Continued)  
ISOPROPANOL VAPOR IRRADIATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF CLINICAL OBSERVATIONS

CATEGORY FINDING (LOCATION)	GROUP	GRADE	FEMALES						
			1 (DAYS)	2 (DAYS)	3 (DAYS)	4 (DAYS)	5 (DAYS)	6 (DAYS)	
SKIN PAPULE (ABDOMEN) (BACK) (EAR-RIGHT) (GENITAL) (NOSE) (TAIL) PUSTULE (ABDOMEN) (GENITAL) (MOUTH) ABSCESS (ABDOMEN) (GENITAL) (MOUTH) (VAGINA) NECROSIS (TAIL)	P	0	5	6	5	0	0	0	4(657-723)
	P	1(706-713)	0	0	0	0	0	0	0
	P	0	1(664-757)	0	0	0	0	0	0
	P	1(734)	0	0	0	0	0	1(719)	0
	P	2(594-759)	0	0	0	0	0	0	0
	P	1(643-759)	5(573-758)	5(384-759)	2(734-759)	0	0	0	0
	P	1(587-601)	1(678-692)	1(692)	4(622-757)	0	0	0	0
	P	1(706-741)	2(706-748)	0	2(626-650)	0	0	0	0
	P	0	0	0	0	0	0	2(643-699)	0
	P	1(748-757)	2(699-759)	0	2(671-727)	0	0	0	0
WAGONS MASS(ES) PRESENT	P	1(727)	1(727-734)	0	1(734-748)	0	0	0	0
	P	0	0	1(755-758)	3(755-758)	0	0	0	0
	P	0	0	1(510-517)	0	0	0	0	0
P	0	1(699-741)	1(741-757)	3(657-759)	0	0	0	0	
P	13(510-758)	10(195-759)	19(335-759)	13(552-759)	0	0	0	0	

GROUP LEGEND: 1 is 0 PPM, 2 is 500 PPM, 3 is 2500 PPM, 4 is 5000 PPM

Grades: P = present, 1 = mild, 2 = moderate, 3 = severe.  
Numbers represent the number of animals exhibiting the finding at least once during the study.  
Parenthetical numbers "( )" represent earliest to latest day a finding of the specified grade was observed.

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TABLE 4  
ISOPROPANOL VAPOR INHALATION ONCOGENICITY STUDY IN FISCHER 344 RATS  
SUMMARY OF BODY WEIGHT (GRAMS)

GROUP: FPN	MALES			
	0	500	2500	5000
WEEK 0				
MEAN	141.4	142.2	141.0	141.5
S.D.	9.10	7.75	8.91	8.99
N	75	75	75	75
WEEK 1				
MEAN	167.1	167.3	167.3	164.2
S.D.	11.10	8.75	11.21	9.92
N	75	75	75	75
WEEK 2				
MEAN	199.5	199.7	201.7	196.8
S.D.	11.74	10.33	12.45	10.08
N	75	75	75	75
WEEK 3				
MEAN	224.8	223.9	226.9	224.5
S.D.	12.37	11.39	13.45	10.59
N	75	75	75	75
WEEK 4				
MEAN	242.3	243.6	248.0**	246.3
S.D.	12.92	11.92	14.17	11.12
N	75	75	75	75
WEEK 5				
MEAN	262.2	262.5	267.1*	266.0
S.D.	12.69	12.17	14.79	11.12
N	75	75	75	75
WEEK 6				
MEAN	272.7	274.6	281.4**	282.1**
S.D.	14.28	12.94	15.68	12.23
N	75	75	75	75
WEEK 7				
MEAN	285.5	287.5	294.4**	296.4**
S.D.	15.66	14.11	16.06	12.62
N	75	75	75	75
WEEK 8				
MEAN	296.7	298.6	305.9**	309.0**
S.D.	15.11	14.40	16.70	13.83
N	75	75	75	75
WEEK 9				
MEAN	310.5	311.5	319.2**	322.6**
S.D.	16.04	15.26	16.82	14.68
N	75	75	75	75
WEEK 10				
MEAN	318.2	319.2	327.8**	331.2**
S.D.	15.96	15.21	17.74	15.31
N	75	75	75	75
WEEK 11				
MEAN	325.2	325.9	335.8**	339.9**
S.D.	15.81	16.22	17.60	16.17
N	75	75	75	75
WEEK 12				
MEAN	328.6	329.6	340.4**	344.7**
S.D.	16.01	15.68	17.99	16.74
N	75	75	75	75
WEEK 13				
MEAN	340.4	340.6	351.2**	354.8**
S.D.	16.23	17.34	18.30	17.13
N	75	75	75	75
WEEK 14				
MEAN	344.8	343.9	354.3**	358.4**
S.D.	17.67	17.49	18.79	17.53
N	75	75	75	75

\* Significantly different from control group ( $\bar{r} < .05$ )

\*\* Significantly different from control group ( $p < .01$ )

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