

TRADE SECRET

Study Title

H-24678: Subchronic Toxicity
90-Day Oral Gavage Study in Rats

Volume 1 of 4

Laboratory Project ID: DuPont-6554

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3100 (1998)

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STUDY COMPLETED ON: April 22, 2002

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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WORK REQUEST NUMBER: [REDACTED]

SERVICE CODE NUMBER: [REDACTED]

CLINICAL PATHOLOGY
STUDY NUMBER: [REDACTED]

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards except for the item documented below. None of the items listed impact the validity of the study.

Test substance characterization and stability analyses were performed at Regional Analytical Services (RAS), Deepwater, NJ. None of the aforementioned analyses were performed under Good Laboratory Practice Standards; however, the analyses were conducted in compliance with ISO9002 regulations. All of the analyses are considered valid and sufficient for the purposes of this study.

Applicant / Sponsor: E.I. du Pont de Nemours and Company
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QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

24678; 24894

Dates of Inspections:

Protocol: April 11, 2002

Conduct: May 25, 2001; June 22,25, 2001; August 6, 13, 14, 2001

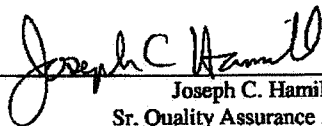
Records, Reports: January 11,14-18,21,22-25,28-31, 2002; February 1,2,4,11-15,
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Dates Findings Reported to:

Study Director: August 24, 2001; January 21,29, 2001; February 4,15, 2002;
April 1, 2002

Management: August 24, 2001; January 21,29, 2002; February 4,20, 2002;
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CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

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STUDY INFORMATION

Substance Tested:

[REDACTED]

Synonyms/Codes:

[REDACTED]

- H-24678

Haskell Number: 24678

Composition:

[REDACTED]

Known Impurities:

[REDACTED]

Physical Characteristics:

[REDACTED]

STUDY INFORMATION (CONTINUED)

9th Collective Nomenclature: 2-Propanol

Synonyms/Codes:

- Isopropanol
- Isopropyl alcohol
- IPA
- H-24894

Haskell Number: 24894

CAS Registry Number: 76-63-0

Composition: Isopropyl alcohol

Purity: 99.98%

Known Impurities: Not supplied by the sponsor

Physical Characteristics: Clear, colorless liquid

Sponsor: E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Initiated/Completed: 11-May-2001 / (see report cover page)

In-Life Initiated/Completed: 14-May-2001 / 13-Nov-2001

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SUMMARY

Four groups of young adult male and female Crl:CD[®](SDS)BR rats were administered H-24678 by gavage at dosages of 0, 10, 60, or 300 mg/kg/day. An additional control group of male and female rats was administered 60 mg/kg/day isopropanol. Selected animals from each group were designated for subchronic toxicity, recovery, and/or biochemical evaluations.

Body weights, food consumption, and clinical signs were evaluated weekly. Clinical pathology endpoints were evaluated during the dosing period on weeks 7 and 13 and then after one and three months recovery. Neurobehavioral assessments were performed prior to dosing and during week 12 of the dosing period. After 10 days of dosing, five animals/sex/dose were sacrificed and evaluated for biochemical endpoints. After 90 days of dosing, ten rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. One month after the 90-day dosing period, 10 animals/sex in the control and high-dose group were examined for recovery from effects. An additional five animals/sex/dose were evaluated for recovery three months following the end of the dosing period.

No compound-related mortality occurred in the study. No adverse clinical signs of toxicity or changes in neurobehavior parameters were observed in male or female rats in any dose group. Statistically significant lower body weight gain, food consumption, and food efficiency were observed in male rats administered 300 mg/kg/day when compared to controls. There were no adverse effects on these parameters at any dose level in female rats after 90 days of dosing and no adverse effects in males and females dosed with 300 mg/kg/day by the end of the one month recovery period.

During the 90-day exposure period, hepatic β -oxidation activity was statistically higher (50-100%) in male and female rats administered 60 and 300 mg/kg/day H-24678 compared to controls. The rate of hepatic peroxisome proliferation remained elevated in male and female rats throughout the recovery period. Due to the small magnitude of change in hepatic β -oxidation activity, these effects were not considered toxicologically adverse.

Test substance-related minimal to mild decreases in red cell mass parameters (red cell count, hemoglobin, and hematocrit) were observed in male rats administered 60 or 300 mg/kg/day during the dosing period. Due to the magnitude of the change in male rats dosed with 300 mg/kg/day, these decreases were considered toxicologically adverse. These changes persisted into the one and three month recovery periods, but showed evidence of partial recovery. Test substance-related and toxicologically adverse elevated liver enzymes (aspartate aminotransferase, alanine aminotransferase, and sorbitol dehydrogenase) were observed in male rats of all dose levels and female rats dosed with 300 mg/kg/day during the 90-day exposure period. After three months of recovery, increased enzyme activities were still evident in males of all dose groups and were more severe in male rats previously dosed with 300 mg/kg/day. After three months of recovery, enzyme activities for female rats previously dosed with H-24678 were similar to control group values.

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Elevated liver weights and hepatocellular hypertrophy were observed in male rats administered 60 and 300 mg/kg/day after the 90-day exposure period. Increased liver weights were also observed in female rats administered 300 mg/kg/day. Increased kidney weights and renal tubular hypertrophy were observed in male rats administered 60 and 300 mg/kg/day after the 90-day exposure period. Elevated kidney weights were also observed in female rats administered 300 mg/kg/day. These changes were considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse. After three months of recovery, liver and kidney weights and microscopic observations were similar to controls in both male and female rats.

Test substance-related thyroid hypertrophy was observed in male and female rats administered 300 mg/kg/day and in male rats administered 60 mg/kg/day. Increased colloid alterations were also observed in male rats administered 300 mg/kg/day. Thyroid hypertrophy in male and female rats was considered test substance-related and potentially adverse. After three months of recovery, thyroid hypertrophy was reversible in male and female rats. Increases in colloid alterations were not considered toxicologically significant.

Minimal focal hepatocellular necrosis was observed in male rats administered 10 and 60 mg/kg/day after 90 days of exposure and in male rats given 60 mg/kg/day after three months recovery. Focal hepatocellular necrosis was not observed in male rats administered 300 mg/kg/day after the 90-day exposure period. Minimal to moderate focal hepatocellular necrosis was observed in male rats administered 300 mg/kg/day after three months recovery. Focal hepatocellular necrosis observed in male rats of all dose levels was considered test-substance-related and toxicologically adverse.

Target organs identified as having adverse effects in this 90-day subchronic toxicity study included liver, thyroid, and red blood cells. Based on the hepatocellular necrosis observed after the 90-day exposure period and/or after one and three months of recovery in male rats of all dose levels, a no-observed-effect level (NOEL)^a cannot be determined for male rats. A NOEL for female rats was 60 mg/kg/day, based on elevated liver enzymes and thyroid gland hypertrophy observed in female rats administered 300 mg/kg/day.

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^a The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency (1985) and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union (1994).

INTRODUCTION

The test substance, H-24678, is a [REDACTED]

[REDACTED] The dose levels for this study were selected based on toxicity observed in a range-finding study in which male rats were dosed by oral gavage with 10, 100, 1000, or 3000 mg/kg/day for 45 days.

Male rats exposed to 3000 mg/kg/day in the range-finding study exhibited statistically significant lower body weights (16% lower than controls) and reduced body weight gain (36% lower than controls) after 4 weeks of dosing. Due to this excessive loss in body weight gain the high dose was lowered to 2000 mg/kg/day for the remaining two weeks of study. Reductions in body weight gain (15% – 20% lower than controls) were also observed in rats exposed to 100 and 1000 mg/kg/day after 45 days of treatment. No treatment-related effects on body weight were observed in the low dose group of 10 mg/kg/day. No compound-related clinical signs of toxicity were observed in any group.

Compared to control rats, absolute and relative liver organ weights were significantly higher (40%-45%) in rats administered 1000 and 3000/2000 mg/kg/day H-24678. No compound-related effects on organ weight were observed in rats administered 10 or 100 mg/kg/day.

Therefore, 300 mg/kg/day was selected as the high-dose level for this 90-day study. This dose was expected to produce toxicity without excessive mortality. The low dose of 10 mg/kg/day was expected to be the no-observed-adverse-effect level, while the 60 mg/kg/day dose was expected to induce minimal or no toxicity.

The test substance, H-24678, is [REDACTED] isopropyl alcohol. Therefore, a concurrent control group of 10 male and 10 female rats was dosed with isopropyl alcohol in deionized water, at a dose equivalent to that received by the high-dose animals. This control group provided important information regarding the contribution of isopropanol in the overall toxicity of H-24678.

OBJECTIVE

The objective of this study was to evaluate the potential subchronic toxicity of H-24678 when administered by gavage to male and female rats. A recovery group was also included to investigate the reversibility of any observed toxicological effects. The oral route of administration was selected because it is a potential route of exposure.

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MATERIALS AND METHODS

A. Test Guidelines

The subchronic toxicity study design complies with the United States Environmental Protection Agency (EPA), Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Health Effects Test Guidelines, OPPTS 870.3100 90-Day Oral Toxicity in Rodents (AUG-1998).

B. Test Substance

The test substance, H-24678, was supplied by the sponsor as an [REDACTED] with known composition. The test substance is a suspension [REDACTED] in isopropanol and water. The stability analysis of the test substance before and during the study was conducted at DuPont Regional Analytical Services (RAS). A reserve sample of the test substance was collected and retained by Haskell Laboratory. The isopropyl alcohol (isopropanol) was supplied by ExxonMobil Chemical and assigned Haskell Number 24894.

C. Test Species

On April 26, 2001, 129 male and 127 female CrI:CD[®](SD)IGS BR rats, with an assigned birth date of March 25, 2001 were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study.

The rat was selected because it is the species recommended in the subchronic toxicity guidelines. The CrI:CD[®](SD)IGS BR strain was chosen because extensive background information is available from the literature, the supplier, and previous studies at Haskell Laboratory. This species/strain is considered suitable relative to longevity, hardiness, and low incidence of spontaneous diseases.

D. Animal Husbandry

1. Housing

All rats were housed one per cage, sexes separate, in stainless steel, wire-mesh cages suspended above cage boards. Cage racks were relocated within the animal room each week and cages were repositioned on the racks every 2 weeks. Animal rooms were maintained on a 12-hour light/dark cycle (fluorescent light) and at a temperature of $22 \pm 3^{\circ}\text{C}$ and a relative humidity of $50\% \pm 20\%$. Occasional excursions outside the acceptable ranges were minor and did not affect the study.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet[®] 5002 *ad libitum*.

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3. Identification

Prior to assignment to groups, each rat was temporarily identified by either the presence or absence of a colored tail mark and cage identification. Subsequently, an individual identification number was tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat.

4. Health Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

E. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 7 days of the 17-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury, weighed 3 times, and examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day -11 by the laboratory animal veterinarian designee.

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F. Study Design

Group		Dosage	Test Substance
Male	Female		
I	II	0 mg/kg/day	Vehicle control
III	IV	60 mg/kg/day	Isopropanol control [REDACTED] w/w active ingredient [REDACTED]
V	VI	10 mg/kg/day	H-24678 [REDACTED] w/w active ingredient)
VII	VIII	60 mg/kg/day	H-24678 [REDACTED] w/w active ingredient)
IX	X	300 mg/kg/day	H-24678 [REDACTED] w/w active ingredient)

Each group of study animals, except the isopropanol groups, consisted of the following subgroups: The first 10 rats in each group were designated for the evaluation of subchronic toxicity and are referred to in this report as the 90-day exposure animals. The next 5 rats in each group were initially designated as a subset for blood sampling and potential analysis of fluorine. However, to assess three-month recovery from test substance-related effects, these rats were also evaluated for biochemical, clinical, and anatomic pathology endpoints; these rats are reported as the three-month recovery animals. The next 10 rats in the control and high-dose groups were designated for recovery evaluations and are reported as the one-month recovery animals. The last 5 rats in each group were designated for evaluation of hepatic biochemical analysis following a 10-day exposure.

In the isopropanol groups, the first 10 rats in each group were included in the 90-day exposure subgroup and the last 5 rats were included in the hepatic biochemical analysis subgroup.

Male and female rats designated for the 90-day exposure evaluation were dosed through test days 91 (male) and 92 (female), and necropsied on test days 92 and 93, respectively. Male and female rats designated for the one- and three-month recovery evaluations were dosed for 91 days and necropsied 32 and 94 days postdosing, respectively.

Neurobehavioral evaluations were conducted on male and female animals designated for the 90-day exposure evaluation (predose and week 13) and on control and high-dose animals designated for the one-month recovery (predose, week 13). Clinical pathology evaluations were conducted on animals designated for the 90-day exposure evaluation on weeks 6 and 14 and on animals designated for the one-month and three-month recovery evaluations immediately prior to necropsy. Biochemical evaluations were conducted on selected animals designated for the 90-day exposure evaluation, the one-month and three-month recovery evaluations, and the 10-day exposure evaluation.

G. Assignment to Groups and Study Start

1. Rats Designated for the 90-Day Exposure, One-Month Recovery, and Three-Month Recovery Evaluations

Rats were selected for study use on the basis of adequate body weight gain, freedom from any ophthalmological abnormalities or clinical signs of disease or injury, and a body weight within $\pm 20\%$ of the mean within a sex. The selected rats were distributed by computerized, stratified randomization so that there were no statistically significant differences among group body weight means within a sex.

Oral administration of H-24678 began on test day 0, when the rats were approximately 50 days of age. Prior to the start of test substance administration, 5 male rats and 3 female rats with out-of-range body weights, clinical signs, or neurobehavioral findings during pretest were replaced. Replacement rats were selected on the basis of freedom from any clinical signs of disease or injury and a body weight $\pm 20\%$ of the mean within a sex.

2. Rats Designated for 10-Day Biochemical Analysis

Oral administration of H-24678 to male and female rats designated for the 10-day biochemical analysis began on test days 0 and 1, respectively. In-life data (body weight, food consumption, clinical observations) were collected from these animals and are in study records. However, these data are not included in this report.

H. Dose Solution Preparation

H-24678 and isopropanol were dissolved in deionized water. Dosing solutions of the test substance were prepared every day for the first week of study and then twice a week thereafter. Dosing solutions were stored refrigerated in closed glass containers to minimize evaporation of the isopropanol.

I. Test Substance Administration

Animals designated for the 90-day dosing period were dosed through test day 91 (males) or 92 (females). Animals designated for the one- and three-month recovery evaluations were dosed through test day 90. Animals designated for the 10-day biochemical evaluation were dosed through test day 10.

The test substance was administered daily to the study animals by oral gavage to achieve dosage levels of 10, 60, or 300 mg/kg body weight/day, based on the most recently recorded body weight. Deionized water was administered to control groups I and II and isopropanol (dissolved in deionized water) was administered to groups III and IV. Dose volumes for all groups were 7.5 mL/kg.

J. Test Substance Sampling

Samples containing H-24678 at the concentrations of 0, 1.33, 8.0 and 40.0 mg/mL and isopropyl alcohol control at the concentration of 8.0 mg/mL were collected on test day 1 for uniformity/concentration verification and 5-hour room temperature stability.

Samples from the same preparation were collected after being stored refrigerated for 7 days to determine if the test substance could be mixed twice a week with refrigerated storage. They were analyzed for 7-day refrigerated stability and for 7-day refrigerated followed by 5-hour room temperature stability.

Samples at the same concentrations were collected on test day 42 and test day 91 for concentration verification analysis.

All dosing solution samples were collected on the same day the solutions were prepared or as indicated by the stability analysis for the study.

K. Analytical Methods

1. Dosing Solution Treatment

Prior to analysis on the GC, the dosing samples were diluted with HPLC grade water to an expected concentration of 2.4 mg/mL isopropyl alcohol.

Prior to analysis on the LC/MS, each dosing sample was diluted with HPLC grade water and an equivalent amount of diluted isopropyl positive control to an expected concentration of 0.156, 0.160 or 0.168 mg/mL H-24678.

Samples submitted for analysis were analyzed the day the solutions were received or refrigerated until analyzed by the testing group.

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2. Chromatographic Conditions

G C Method

Instrument:	Hewlett-Packard Model 6890 GC
Column:	Restex RTX-5, 30 m x 0.25 mm ID, 0.25 μ m film thickness
Injector:	Split, 250°C
Detector:	FID; 250°C
Carrier Gas:	Helium (2.8 mL/min)
Split vent:	58.3 mL/min
Injection Volume:	1 microliter
Oven Program:	Gradient
Initial Temperature:	40°C
Initial Time	0.50 min.
Level 1 Rate:	5°C/min.
Level 1 Temperature:	60°C
Level 2 Rate:	25°C/min.
Level 2 Temperature:	300°C
Final Time	1.00 min.
Run Time:	15.10 minutes

LC/MS Method

HPLC Instrument:	Hewlett-Packard Model 1100 HPLC
MS Instrument	Micromass Quattro LC MS with "Z-spray" electrospray

LC parameters:

Column:	Zorbax @ SB-C8, 2.1mm x 15mm
Mobile Phase (Time Table):	
0.00 minutes:	50% methanol/50% 10 mM Ammonium Acetate-Triethylamine
10.00 minutes:	100% methanol/0% 10 mM Ammonium Acetate-Triethylamine
16.01 minutes:	50% methanol/50% 10 mM Ammonium Acetate-Triethylamine
Run Time:	23.0 minutes
Flow Rate:	0.20 mL/min.
Injection Volume:	20 microliter
Oven Temperature:	30°C

MS parameters:

Ionization mode:	Electrospray (ESI), negative ions
Capillary voltage:	3.0 kV
Cone Voltage:	20 V
Source Temperature:	120°
Desolvation Temperature:	300°
Scan function:	SIR: 443, 543, and 643 m/z 485, 585, and 685 m/z

time: 0-16 minutes **Company Sanitized. Does not contain TSCA CBI**

3. Calibration and Quantitation

A stock solution of the isopropyl alcohol (IPA) test material (a separate sample of H-24894, used as analytical reference) was made in HPLC grade water. Appropriate aliquots of the stock were diluted with the HPLC grade water. These solutions were used to make calibration standards that bracketed the target concentration of the diluted dosing samples. Peak areas from GC analysis of these standards were used to construct a calibration curve by least square regression (see Appendix A, Figure 1a for a representative calibration curve). Measured concentrations for dosing solutions were determined by applying the peak areas from replicate injections of the samples to the calibration curve.

A stock solution of the H-24678 test material (a separate sample of H-24678, used as analytical reference) was made in HPLC grade water. Appropriate aliquots of the stock were diluted with a solution of the initial diluted IPA positive control sample so that an amount of the IPA similar to the dosing samples would be maintained in each diluted standard. These solutions were used as calibration standards that bracketed the target concentration of the diluted dosing samples. Mass to charge ratio (m/z) from LC/MS analysis using negative ion electrospray ionization and selective ion monitoring of these standards over the mass range of 443 to 685 were used to construct calibration curves by the appropriate regression (see Appendix A, Figure 1b – 1g for representative calibration curves). Measured concentrations for dosing solutions were determined by applying the peak area or height from replicate injections of the samples to each calibration curve. The mean result from the concentrations at all selected m/z ($n = 6$) is reported as the concentration for the sample.

Test substance uniformity in the vehicle was evaluated by calculating the coefficient of variation ($C.V. = \text{standard deviation}/\text{mean} \times 100$) of the measured concentrations in duplicate samples for each dosing level. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution. The mean result of the duplicate samples for each dosing level was used to determine the concentration of the test substance for the respective dosing levels.

Stability was evaluated by using the mean result of the duplicate samples from the concentration verification as the baseline for comparing the corresponding stability results.

L. Body Weights

All rats were weighed once per week during the 90-day exposure phase of the study. In addition, the rats designated for neurobehavioral evaluations, undergoing functional observational battery and motor activity assessments, were weighed on the days of those observations.

M. Food Consumption and Food Efficiency

The amount of food consumed by each rat over each weighing interval was determined throughout the study. Each feeder was weighed at the beginning and end of the interval and the final weight of the feeder and the amount of spillage from the feeder during the interval was

subtracted from the initial feeder weight. From these measurements, mean daily food consumption over the interval was determined. From the food consumption and body weight data, the mean daily food efficiency was calculated.

Mean daily food consumption was determined for all animals designated for subchronic toxicity evaluations during the 90-day exposure period. Food consumption was also determined for animals designated for one- and three-month recovery evaluations through test day 119, but was not determined for animals designated for the three-month recovery evaluations after test day 119. Food consumption for the three-month recovery animals was inadvertently not collected on test day 84 prior to placement of rats in metabolism racks.

N. Detailed Clinical Observations and Mortality

During the test period, cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats were conducted at least twice daily. Moribund rats were sacrificed. At every weighing, each rat was individually handled and examined for abnormal behavior and appearance. Detailed clinical observations in a standardized arena were also evaluated on rats designated for the 90-day exposure and one-month recovery periods. The detailed clinical observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or unusual behavior.

O. Ophthalmological Evaluations

Two ophthalmological examinations were conducted by a veterinary ophthalmologist. Both eyes were examined by focal illumination and indirect ophthalmoscopy. The examinations were conducted under subdued lighting after mydriasis had been produced with a 1% tropicamide solution.

On test day -17, the initial examination was performed on all rats received for the study, prior to selection and grouping. On test day 81, all surviving rats designated for the 90-day exposure and one-month recovery were examined again.

P. Neurotoxicity Evaluations

1. Sensory Function Evaluation

Prior to test substance administration and during week 13 of test substance administration, assessments of responses to approach/touch, sharp auditory stimulus, and tail pinch were made while the animal was in a standard arena. These assessments were conducted on the 10 animals per group designated for recovery from the control and high-dose groups, and on the 10 animals per group designated for subchronic toxicity for the isopropanol, low-dose, and mid-dose groups.

Fore- and hindlimb grip strength were measured by a strain gauge device (Chatillon® Digital Force gauge). Pupillary constriction was measured immediately prior to removing the rats from

the motor activity chambers (Section 2. Below) because the darkened room in which the apparatus was located facilitated observing the response. The presence or absence of pupillary constriction was assessed after a beam of light was directed into each eye. For all these assessments, the experimenter was unaware of the group designation of the animal.

2. Motor Activity

Following the evaluation of grip strength and sensory function, assessment of motor activity (MA) was conducted. Rats were individually tested in 1 of 30 nominally identical, automated activity monitors (Coulbourn® Infrared Motor Activity System). Group and gender were counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enables measurement of 2 dependent variables: duration of movement and number of movements. A continuous movement was counted as 1 movement regardless of duration. Each test session was 60 minutes in duration, and the results were expressed for the total session as well as for 6 successive 10-minute blocks.

Presence of defecation and urination on the cageboards below the motor activity monitor were also recorded following each motor activity session.

3. Test Facility Positive Control Data

Data on the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are described in four separate reports.^(1,2,3,4) These positive control studies are the basis of training certification for the individuals making judgments in the neurobehavioral and neuropathology tests. The data also document that the equipment and procedures are capable of detecting effects that may be seen in neurotoxicity studies of this type.

Q. Clinical Pathology

Samples for clinical pathology evaluations were collected from the first 10 male and 10 female rats per group in all groups on test days 38 and 92 (males), or 39 and 93 (females). After one month of recovery, samples for clinical pathology evaluations (excluding coagulation) were also collected from 10 recovery rats per group (control and 300 mg/kg/day only) on test day 122. Additionally, after 3 months of recovery, samples for clinical pathology evaluations (excluding coagulation and plasma fluoride), and including selected urinalysis tests) were collected from 4 (groups II and VIII) or 5 (all other groups) satellite recovery rats on test day 183.

The rats were fasted overnight (approximately 16 hours). During this interval, urine was collected from each rat into vials containing EDTA (except for test days 38/39). Blood samples for hematology and serum clinical chemistry measurements were collected from the orbital sinus of each fasted rat while the rat was under light carbon dioxide anesthesia. Blood samples for coagulation (end of dosing only) and plasma fluoride were collected from the abdominal vena cava while the rat was under carbon dioxide anesthesia, immediately prior to sacrifice. All blood samples were examined visually and observations recorded.

1. Hematology/Coagulation

Complete blood counts (including reticulocytes) were determined on a Bayer® Advia 120 hematology analyzer and determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all rats were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Coagulation times were determined on a BCS Behring Coagulation Analyzer. New methylene blue-stained blood smears were prepared from each rat undergoing hematology evaluation but were not needed for evaluation.

The following hematology and coagulation parameters were determined:

Red blood cell count (RBC)	Red cell distribution width (RDW)
Hemoglobin (HGB)	Absolute reticulocyte count (ARET)
Hematocrit (HCT)	Platelet count (PLT)
Mean corpuscular volume (MCV)	White blood cell count (WBC)
Mean corpuscular hemoglobin (MCH)	Differential leukocyte count
Mean corpuscular hemoglobin concentration (MCHC)	Microscopic blood smear examination

Prothrombin time (PT)

Activated partial thromboplastin time (APTT)

2. Clinical Chemistry

All clinical chemistry parameters were measured in serum, with the exception of fluoride, which was measured in EDTA plasma. Clinical chemistry parameters were measured or calculated on a Roche Diagnostics (BMC)/Hitachi® 917 clinical chemistry analyzer. Plasma fluoride concentration was determined using a phi/12pH meter with a fluoride-selective electrode.

The following clinical chemistry parameters were determined:

Aspartate aminotransferase (AST)	Total protein (TP)
Alanine aminotransferase (ALT)	Albumin (ALB)
Sorbitol dehydrogenase (SDH)	Globulin (GLOB)
Alkaline phosphatase (ALKP)	Calcium (CALC)
Total bilirubin (BILI)	Inorganic phosphorus (IPHS)
Urea nitrogen (BUN)	Sodium (NA)
Creatinine (CREA)	Potassium (K)
Cholesterol (CHOL)	Chloride (CL)
Triglyceride (TRIG)	Plasma fluoride (PFLU)
Glucose (GLUC)	

3. Urinalysis

The following urinalysis parameters were determined:

Appearance (quality, clarity, and color)	Bilirubin (UBIL)
Volume (VOL)	Blood (BLD)
Osmolality (UOSM)	Urobilinogen (URO)
Specific gravity (SG)	Urine fluoride (UFLU)
pH	Protein (UMTP)
Glucose (UGLU)	Microscopic urine examination
Ketones (KET)	

Urine volume and appearance were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek[®] Atlas[™] Automated Urine Chemistry analyzer. Urine protein was measured on a Roche Diagnostics (BMC)/Hitachi[®] 717 clinical chemistry analyzer. Urine osmolality was determined using an Advanced Osmometer 3900. Urine fluorides were determined by multiplication of measured urine volume by urine fluoride concentration (measured using a phi/12pH meter with a fluoride selective electrode). Sediments from all urine specimens were evaluated microscopically.

R. Collection of Blood, Urine, Feces, and Tissue (Three-Month Recovery)

On test day -4 (pre-bleed) and test days 0, 3, 9, 21, 35, 56, 77, and 88, blood (approximately 0.5 - 1 mL) was collected from the orbital sinus of designated animals (5 rats/sex/dose) while the rat was under light carbon dioxide anesthesia for possible analysis of total fluorine. On test day 35 blood was not collected from two animals in group V because they were misdosed with isopropanol dose solution. On the day of blood collection (except test day -4), blood was collected from the animals 2 hours ($\pm$ 30 minutes) after dosing. The blood was collected in plastic tubes containing EDTA while on ice. The blood was then separated into plasma and RBCs by centrifugation and stored frozen. For each bleeding, blood was collected at approximately the same time of day. During the last week of the 90-day exposure period, urine and feces were collected daily at 24-hour intervals from each animal. The animals were placed in metabolism cages for collection of feces and urine. The exact time period of collection of urine and feces was documented along with the total volume of urine obtained. Urine and feces were stored frozen.

Blood was also collected for possible analysis at 3, 7, 12, 19, 26, 37, 51, 72, and 93 days postdosing for both male and female animals of each dose group and stored frozen. Animals were sacrificed at the end of the three-month recovery period. The testes, liver, kidney and fat samples were collected and frozen for possible analysis of total fluorine.

The collected blood, urine, feces, and tissues may be evaluated in the future for total fluorine. Resulting data will be reported separately.

S. Biochemical Measurements

Following 10 days or 91 and 92 days for males and females, respectively, of compound administration, or after a one-month or three-month recovery period, 4 or 5 rats from each group designated for biochemical evaluation were weighed and then euthanized by CO₂ anesthesia and exsanguination. At each time point, the livers were removed, weighed, and then a portion was homogenized (1 gram tissue/4 mL buffer) in homogenization buffer (50 mM Tris-HCl, 50 mM Trizma-base, 0.25 M sucrose, and 5.4 mM EDTA, pH 7.4). Hepatic peroxisomes were prepared using differential centrifugation. The resulting peroxisomal pellets were resuspended in the homogenization buffer, aliquoted, and stored between -65° and -85°C until analyzed for peroxisomal β -oxidation activity. The peroxisomal suspensions were diluted to a protein concentration of approximately 0.25 or 0.5 mg/mL. Peroxisomal β -oxidation activity was determined using [14C]palmitoyl CoA as the substrate.⁽⁵⁾ The protein content of the peroxisomes was determined before and after analysis by the Biorad method.⁽⁶⁾ Final rate calculations were made using the post-assay protein concentrations.

T. Anatomic Pathology

After approximately 90 days (test days 92 and 93 for males and females, respectively), groups of 10 male and 10 female rats from the 0, 10, 60, and 300 mg/kg/day H-24678 groups (and the 60 mg/kg/day isopropanol group) were sacrificed and necropsied. Additional groups of 10 male and 10 female rats from 0 and 300 mg/kg/day groups were sacrificed and necropsied approximately 1 month after the last exposure (test day 122). In addition, groups of 5 male and 4 or 5 female rats from all groups (except the isopropanol group), designated for analysis of blood for parent compound and metabolites were sacrificed and necropsied approximately 3 months after the last exposure (test day 183). In the discussion of pathology findings, groups sacrificed after approximately 90 days of exposure are referred to as exposure groups, and groups sacrificed on test days 122 and 183 are referred to as one-month and three-month recovery groups, respectively.

Rats were euthanatized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all male and female rats. The following tissues were collected from exposure and one-month recovery group rats sacrificed by design, or rats that were found dead, sacrificed *in extremis*, or accidentally killed.

<u>Digestive System</u>	<u>Cardiovascular System</u>	<u>Musculoskeletal System</u>
liver	heart	skeletal muscle
esophagus	aorta	femur/knee joint
stomach		sternum
duodenum	<u>Hematopoietic System</u>	
jejunum	spleen	<u>Reproductive System</u>
ileum	thymus	<u>Male</u>
cecum	mandibular lymph node	testes
colon	mesenteric lymph node	epididymides
rectum	bone marrow ^a	prostate
salivary glands		seminal vesicles
pancreas	<u>Endocrine System</u>	<u>Female</u>
	pituitary gland	ovaries
<u>Urinary System</u>	thyroid gland	uterus
kidneys	parathyroid glands	mammary gland
urinary bladder	adrenal glands	
	<u>Nervous System</u>	<u>Miscellaneous</u>
<u>Respiratory System</u>	brain (including cerebrum,	skin
lungs	cerebellum, medulla/pons)	eyes (including optic
trachea	spinal cord (3 levels: cervical,	nerve)
nose	mid-thoracic, lumbar)	gross observations
larynx	sciatic nerve	
pharynx		

a Bone marrow was collected with the femur and sternum.

Liver, kidneys, testes, thyroid gland, and fat were collected from three-month recovery group rats sacrificed by design. Small portions of liver and kidneys and the entire thyroid gland were fixed in 10% neutral buffered formalin. The remaining fresh liver and kidney tissue, testes, and fat (approximately 1 gram) were frozen.

The following tissues were weighed from rats sacrificed by design in all 90-day exposure groups and one-month recovery groups: liver, kidneys, adrenal glands, brain, spleen, thymus, heart, ovaries, uterus, epididymides, and testes. Organ weight/final body weight and organ weight/brain weight ratios were calculated. Liver, kidneys, thyroid gland, and testes (males) from rats sacrificed by design after 3 months recovery were weighed and organ weight/final body weight ratios were calculated. Organ weight/brain weight ratios were not determined for three-month sacrifice rats.

Gross lesions which were diagnosed at necropsy and for which microscopic examination was not appropriate (e.g., fluid accumulation, ruffled fur, missing anatomic parts) were generally not collected. Gross lesions for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

Testes, epididymides, and eyes were fixed in Bouin's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, cut at a nominal thickness of 5 micrometers, stained with hematoxylin and eosin (H&E), and examined microscopically.

All collected tissues from the control and 300 mg/kg/day exposure group rats, and all found dead, sacrificed *in extremis*, or accidentally killed rats were processed and received a full histopathological examination. Liver (males only), kidneys (males only), and thyroid gland were processed to slides and microscopically examined from the 60 mg/kg/day isopropanol treated group. Liver, kidneys (males only), and thyroid gland were processed to slides from 10 and 60 mg/kg/day exposure group rats and from all one-month recovery rats. Liver and kidneys from males and thyroid gland from males and females were microscopically examined from 10 and 60 mg/kg/day exposure rats and from one-month recovery rats in descending order of dose until a no effect level was reached. Liver, kidneys, and thyroid gland from males and females from all groups sacrificed after the three-month recovery period were processed to slides. Liver (males only) and thyroid gland were microscopically examined from three-month recovery rats in descending order of dose until a no effect level was reached. The key to Appendix G describes the lesion grading system used in this study.

U. Statistical Analyses

Except for Bartlett's test ($p < 0.005$), significance was judged at $p < 0.05$. Separate analyses were performed on the data for each gender.

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Organ Weight Biochemical Measurements	Test for lack of trend ⁽⁹⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾	Preliminary tests for pairwise comparison
	OR ^a		
	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Motor Activity ^c	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	Repeated measures analysis of variance ⁽¹⁶⁾ followed by contrasts ⁽¹⁷⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾
Grip Strength	Bartlett's test ⁽¹⁸⁾ for homogeneity of variances	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Clinical Pathology ^d	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Survival Incidence of Clinical Observations Incidence of Ophthalmology Observations Incidence of FOB Descriptive Parameters	None	Cochran-Armitage test for trend ^{(14)e}	
Incidence of Microscopic Lesions	None	None	

- Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.
- If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used.
- Test day and block (10-minute EPOCH) was used as repeated-measure factors.
- When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1 , 0.05 was used for any calculations performed with that bilirubin data.
- If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁹⁾ with a Bonferroni correction was used.

RECORDS AND SAMPLE STORAGE

Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

A sample of the test substance was collected for archive purposes and retained at Haskell Laboratory. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware. Clinical pathology slides and raw data will be retained at Haskell Laboratory, Newark, Delaware. Test Substance characterization data will be stored at Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey. Characterization data used to support test substance stability will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

RESULTS AND DISCUSSION

ANALYTICAL EVALUATIONS

A. Chromatography

Isopropyl alcohol (H-24894) eluted from the GC column as a resolved peak with retention time of approximately 1.0 minute. Representative GC chromatograms are shown in Appendix A, Figures 2(a - c).

H-24678 eluted from the HPLC column as resolved peaks over mass to charge (m/z) range of approximately 443 to 685. For the purpose of quantitation, the m/z of 443, 543, 643 for the "mono" substituted components [REDACTED] and 485, 585, 685 for the "mixed bis" substituted components [REDACTED] were determined to be representative of the H-24678 in the dosing matrix. Representative LC/MS chromatograms are shown in Appendix A, Figures 2(d - f). Test substance was not detected in the 0 mg/mL control.

B. Uniformity of Mixing, Concentration Verification and Stability Samples

Analytical results from dosing solutions prepared test day 1 and analyzed for uniformity/concentration verification and stability are shown in Appendix A, Table I and Summary Table 1.

The following table summarizes the results for uniformity/concentration verification and stability analyses for the H-24678 sample preparation on test day 1 along with the refrigerated stability needed to change mixing to twice a week.

Preparation Day	Nominal ^a mg/mL	Measured ^b mg/mL	Average % Nominal	CV %	Stability ^c % Nominal	Stability ^{b,d} % Nominal	Stability ^e % Nominal
Test Day 1	1.33	1.51, 1.48	112.8	1	106.0	112.0	119.5
	8.00	7.32, 7.99	95.8	6	97.5	108.9	107.9
	40.0	40.4, 36.8	96.5	6	95.5	112.0	108.5

a Dosing solution concentration mg H-24678/mL based on 7.5 mL dose volume. H-24678 is [REDACTED]

b Duplicate samples analyzed.

c Stability samples held for 5 hours at room temperature. % Nominal based on measured.

d Stability samples held for 7 days refrigerated and sampled. Average % Nominal based on measured. Solutions not administered to the animals.

e Stability samples held for 7 days refrigerated followed by 5 hours at room temperature. % Nominal based on measured. Solutions not administered to the animals.

The results for H-24678 samples prepared on test day 1, show that the test substance was adequately mixed (CV's less than 10), at the targeted levels (target = $\pm 12.8\%$ of nominal) and stable in the vehicle when held 5 hours at room temperature. Samples from the same preparation collected after 7 days refrigeration and analyzed for refrigerated stability followed by 5 hours room temperature indicated that the test substance was stable for the required storage time in the

and resulted in a mixing time interval of twice a week. Test substance was not detected in the 0 mg/mL sample.

The following table summarizes the results for uniformity/concentration verification and stability analyses for the test day 1 of the isopropyl alcohol positive control and the 40 mg/mL dosing sample along with the refrigerated stability information needed to change the mixing to twice a week.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %	Stability ^b % Nominal	Stability ^{a, c} % Nominal	Stability ^d % Nominal
Test Day 1	8.00/IPA	8.71, 8.68	108.8	0	108.3	110.0	113.0
	40.0 ^e	7.80, 7.97	98.6	2	100.4	99.9	97.9

a Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.

b Stability samples held for 5 hours at room temperature. % Nominal based on measured.

c Stability samples held for 7 days refrigerated and sampled. Average % Nominal based on measured. Solutions not administered to the animals.

d Stability samples held for 7 days refrigerated followed by 5 hours at room temperature. % Nominal based on measured. Solutions not administered to the animals.

e 40 mg/mL H-24678 sample was analyzed to show that it contained 20% or 8 mg/mL of isopropyl alcohol.

The results for positive control sample and the 40 mg/mL dosing sample prepared on test day 1, show that the isopropyl alcohol was adequately mixed (CV's less than 10), at the targeted levels (target = $\pm 8.8\%$ of nominal) and stable in the vehicle when held 5 hours at room temperature. Samples from the same preparation collected after 7 days refrigeration and analyzed for refrigerated stability followed by 5 hours at room temperature indicated that the isopropyl alcohol was stable for the required storage time in the study to change the mixing time interval to twice a week.

C. Concentration Verification Samples During the Study

Analytical results from dosing solutions prepared test day 42 and test day 91 and analyzed for concentration verification are shown in Appendix A, Table II and Summary Table 1.

The following table summarizes the results for concentration verification analyses for the test days 42 and 91 of the H-24678 sample preparation.

Preparation Day	Nominal ^a mg/mL	Measured ^b mg/mL	Average % Nominal	CV %
Test Day 42	1.33	1.22, 1.20	91.0	2
	8.00	7.56, 7.62	94.9	1
	40.0	41.6, 36.3	97.5	10
Test Day 91	1.33	1.39, 1.33	102.3	3
	8.00	8.49, 7.96	102.9	5
	40.0	37.9, 38.3	95.3	1

a Dosing solution concentration mg H-24678/mL based on 7.5 mL dose volume. H-24678 is [REDACTED]

b Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.

The results for samples prepared on test day 42 and 91 indicate that the test substance was adequately mixed ($CV \geq 10$) and at the targeted levels (target = $\pm 9.0\%$ of nominal) for all H-24678 samples. Test substance was not detected in the 0 mg/mL sample.

The following table summarizes the results for concentration verification analyses for the test days 42 and 91 of the isopropyl alcohol sample preparation.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test Day 42	8.00/IPA	9.20, 9.02	113.9	1
	40.0 ^b	7.59, 7.41	93.8	2
Test Day 91	8.00/IPA	9.31, 9.64	118.5	2
	40.0	7.27, 7.35	91.4	1

a Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.

b 40 mg/mL H-24678 sample was analyzed to show that it contained 20% or 8 mg/mL of isopropyl alcohol.

The results for the isopropanol control sample and the 40 mg/mL dosing solution prepared on test day 42 and 91 indicate that the isopropyl alcohol was adequately mixed (CV less than 10) and at the targeted levels ($\pm 18.5\%$ of nominal) for these samples.

D. Analytical Conclusions

Results from the analysis of the test substance dosing solutions during the study indicate that the test substance was mixed properly, at the targeted levels and stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples.

Results from the analysis of the isopropyl alcohol in the 40 mg/mL samples and the isopropyl alcohol control samples during the study indicate that the isopropyl alcohol was mixed properly, at the targeted levels and stable under the conditions of the study.

IN-LIFE TOXICOLOGY

A. Dosage Data (Tables 2-3, Appendix B)

The amount of test substance and isopropanol (IPA) administered to each animal was calculated using individual body weights and the design dosage (0, 10, 60, and 300 mg H-24678/kg/day or 60 mg IPA/kg/day). The test substance, H-24678, is [REDACTED] isopropanol, used as an additional control in this study, was administered at the same dosage (60 mg IPA/kg/day) as that received in the high dose group (300 mg H-24678/kg/day).

Animals were dosed with the test substance and IPA diluted to varying concentrations in water. The test substance concentrations in water were 0, 1.33, 8, and 40 mg/mL for the 0, 10, 60, and 300 mg/kg/day dosage groups, respectively. The IPA concentration in water was 8 mg/mL. Tables 2 and 3 depict the average amount of diluted test substance and IPA administered to each group during the 90-day exposure period.

On test day 35, seven male rats in Group V (5 designated for 90-day exposure period, 2 designated for three-month recovery) were dosed with IPA (60 mg/kg/day) instead of the test substance (10 mg/kg/day). On test day 87, one male rat in Group VII (60 mg/kg/day) inadvertently received 5 ml instead of the desired 3.8 mL of test substance. These errors in dosing did not affect the validity of the study.

B. Mean Body Weights and Body Weight Gains (Tables 4-7, Figures 1-2, Appendix C)

Mean body weight in male rats administered 300 mg/kg/day H-24678 was statistically lower than control rats beginning on test day 42 and throughout the remainder of the 90-day exposure period. Mean body weight gain in this dose group was also lower than controls during the majority of the exposure period. At the end of the 90-day exposure period, mean body weights were approximately 6% lower in male rats given 300 mg/kg/day compared to control rats. The overall weight gain in male rats administered 300 mg/kg/day was approximately 11% lower than controls. This reduction in body weight gain was considered test substance-related and toxicologically adverse due to parallel reductions in food efficiency (See Section C).

After a one-month recovery period, mean body weights of male rats that received 300 mg/kg/day H-24678 were similar to male control rats. Mean body weight gain in the male 300 mg/kg/day dose group was statistically higher (↑67%) than in the male control group after recovery, indicating that the test substance-related adverse effects on body weight were reversible.

There were no adverse, test substance-related effects on body weight or body weight gain in female rats.

C. Food Consumption and Food Efficiency
(Tables 8-11, Appendix D)

Mean daily food consumption in male rats administered 300 mg/kg/day H-24678 was statistically lower than control rats beginning on test day 42 and through most of the remainder of the 90-day exposure period. Mean daily food efficiency in this dose group was also lower than controls during the majority of the exposure period. At the end of the 90-day exposure period, food consumption was approximately 6% lower in male rats given 300 mg/kg/day than in control rats. The overall food efficiency in this dose group was 8% lower than controls. This reduction in food efficiency was considered test substance-related and toxicologically adverse.

During the one-month recovery period, food consumption in male rats given 300 mg/kg/day H-24678 was similar to that observed in control rats. Food efficiency was statistically higher after one and three weeks of recovery and for the overall recovery period ($\uparrow$ 64%). Therefore, the test substance-related effects on food consumption and food efficiency were reversible.

There were no adverse, test substance-related effects on food consumption or food efficiency in female rats.

D. Clinical Observations and Mortality
(Tables 12-17, Appendix E-F)

There were no adverse test substance-related clinical or ophthalmological signs of toxicity in male or female rats. A statistically significant increase in the number of animals with hair loss in male rats administered 60 and 300 mg/kg/day H-24678 compared to controls (5/10 vs 0/10) was observed. This observation was considered a spurious finding since a similar number of female control animals demonstrated hair loss (5/10).

A higher incidence in hyperactivity and/or hyperreactivity was observed in male and female rats administered 300 mg/kg/day H-24678 compared to controls. This activity was not considered test-substance related due to the hyperactivity and/or hyperreactivity also observed in control animals (water and isopropanol) and the lack of test substance-related motor activity findings in the neurobehavioral assessment.

No test substance-related effects on survival were observed in male or female rats. During the 90-day exposure period, one male Group I rat was accidentally killed and one male Group IX rat was found dead due to misdosing. One Group II female rat was accidentally killed at the end of the one-month recovery period during orbital sinus blood collection. One Group X female rat was found dead on test day 5 with cause of death undetermined. One Group VI female rat was sacrificed *in extremis* due to a mammary tumor during the three-month recovery period.

E. In-Life Toxicology Conclusions

Based on the decrements in body weight gain and food efficiency in males dosed with 300 mg/kg/day H-24678 for 90-days, the NOEL for in-life parameters for male rats is 60 mg/kg/day. The NOEL for female rats is 300 mg/kg/day since no adverse in-life effects were observed in female rats during the 90-day dosing period.

NEUROBEHAVIORAL TOXICOLOGY

A. Sensory Function Evaluations

1. Forelimb Grip Strength (Table 18-19, Figures 3-4, Appendix G)

There were no test substance-related effects or statistically significant differences on forelimb grip strength in males or females administered any dosage of H-24678 or isopropanol.

2. Hindlimb Grip Strength (Table 18-19, Figures 5-6, Appendix G)

There were no test substance-related effects or statistically significant differences in hindlimb grip strength for either males or females administered any dosage of H-24678 or isopropanol.

3. Sensory Function Observation (Table 20-21, Appendix H)

There were no test substance-related changes or statistically significant differences in neurobehavioral parameters in males or females administered any dosage of H-24678 or isopropanol.

B. Motor Activity (Tables 22-25, Figures 7-10, Appendices I-J)

There were no test substance-related or statistically significant differences on duration of movement or number of movements for males or females for any dosage of H-24678 or isopropanol.

C. Neurobehavioral Toxicity Conclusions

Under the conditions of the study, the no-observed-effect level (NOEL) for neurobehavioral parameters was 300 mg/kg/day of H-24678 in males and females, the highest concentration tested.

CLINICAL PATHOLOGY

Rats dosed with isopropanol had no significant changes in hematology, coagulation, clinical chemistry, or urinalysis parameters, compared to controls. All references in this report refer only to rats dosed with H-24678, except where indicated otherwise.

A. Hematology/Coagulation (Tables 26-29, Appendix K)

Males dosed with 60 or 300 mg/kg/day had minimal to mild dose-related decreases in some or all parameters indicating red cell mass (hemoglobin, hematocrit, and/or red cell count) (Clinical Pathology Text Table). The red cell mass decrements occurred without associated clinical or anatomic evidence of accelerated red cell production during the study. These changes persisted into the recovery period (variable statistical significance), but showed evidence of partial recovery after one and three months of recovery. In addition, during recovery, there was a minimal (not statistically significant) tendency towards increased reticulocytes in males previously dosed with 60 or 300 mg/kg/day.

Clinical Pathology Text Table: Changes in red cell mass parameters for male rats*

		Group V	Group VII	Group IX
Parameter	Day/Dose	10 mg/kg/day	60 mg/kg/day	300 mg/kg/day
RBC	Test Day 38	101%	99%	96%
	Test Day 92	99%	97%	94%
	Test Day 122R	ND	ND	90%
	Test Day 183R	97%	94%	97%
HGB	Test Day 38	99%	97%	93%
	Test Day 92	95%	95%	91%
	Test Day 122R	ND	ND	94%
	Test Day 183R	97%	94%	92%
HCT	Test Day 38	100%	98%	94%
	Test Day 92	96%	95%	91%
	Test Day 122R	ND	ND	93%
	Test Day 183R	98%	94%	93%

R: recovery time point.

ND: not done

*Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

The red cell mass changes in male rats dosed with 300 mg/kg/day were considered adverse due to the magnitude of the change during dosing and the persistence of the change into recovery.

All other statistically significant changes in hematology or coagulation parameters were considered unrelated to treatment and/or non-adverse (not toxicologically significant). These changes are detailed below.

- In the 300 mg/kg/day males, minimal changes in MCV (decreased at test day 92, increased at test day 122) and MCH (increased at test day 122, decreased at test day 183) were of uncertain relationship to treatment. These parameters changed without relationship to other red cell parameters. At test day 92, MCV in rats dosed with 300 mg/kg/day was similar to that of isopropyl alcohol rats. Therefore, these changes were minimal and had no relationship to other changes in red cell parameters, and thus were considered non-adverse.
- Neutrophils were transiently and minimally increased in females dosed with 300 mg/kg/day at test day 39. This change is possibly related to treatment; however, a change of this magnitude is not expected to have adverse effects.

The following statistically significant changes in hematology or coagulation parameters were considered to be unrelated to treatment because they did not occur in a dose-related manner, or occurred only after one or three months of recovery:

- Minimally decreased basophils in males dosed with 60 mg/kg/day at test day 92.
- Minimally decreased hemoglobin and hematocrit in females previously dosed with 10 mg/kg/day after 3 months of recovery.
- Increased lymphocytes and eosinophils (test day 122) in females dosed with 300 mg/kg/day.

B. Clinical Chemistry (Tables 30-31, Appendix K)

Liver Tests

Males dosed with 10, 60, or 300 mg/kg/day had mild to markedly increased activities of AST and ALT during dosing. Some rats also had less prominent increased SDH activities as well. Changes in activities of these three enzymes were of similar magnitude at both the 38- and 92-day time points during dosing, but became more severe during three months of recovery in rats previously dosed with 60 or 300 mg/kg/day. In addition, after three months of recovery, one of five males previously dosed with 10 mg/kg/day also had increased AST, ALT, and SDH activities. Increased serum activities of AST, ALT, and SDH indicate hepatocellular injury. In all groups of males dosed with test compound, serum enzyme changes that occurred during dosing and persisted into recovery were considered adverse.

Some females dosed with 300 mg/kg/day had increased AST and ALT activities during the dosing period (not statistically significant). After one month of recovery, one of ten females previously dosed with 300 mg/kg/day still had increased AST and ALT, along with increased SDH; this change was of uncertain relationship to treatment. After three months of recovery, females previously dosed with test compound had transaminase activities that were similar to

control values. In females dosed with 300 mg/kg/day, serum enzyme changes that occurred during dosing were considered adverse.

All other statistically significant changes in clinical chemistry parameters were considered unrelated to treatment and/or non-adverse (not toxicologically significant). These changes are detailed below.

- Males dosed with 60 or 300 mg/kg/day had mildly increased ALKP activities during dosing. The mild changes in ALKP were not present after one or three months of recovery in rats previously dosed with test substance. Increased ALKP is generally caused by enzyme induction, either by increased biliary pressure (cholestasis) or by direct action of a xenobiotic compound. The cause of ALKP activity increase in these rats is not known. However, mildly increased ALKP activity is not, by itself, associated with adverse effects.
- Bilirubin was minimally decreased in females dosed with 60 or 300 mg/kg/day during dosing. After one and three months of recovery, females previously dosed with test compound had bilirubin concentrations that were similar to control values. This change was considered to be non-adverse because mildly decreased bilirubin has no known toxicologic significance.
- Urea nitrogen was decreased in females dosed with 60 mg/kg/day (test day 93), and increased in females previously dosed with 300 mg/kg/day after one month, but not three months, of recovery. These changes were considered unrelated to treatment because there was generally a lack of dose response and no consistency in the change during the course of the study.
- Creatinine was minimally decreased (no dose relationship) during dosing in all groups of males, and in females dosed with 300 mg/kg/day. Creatinine was also decreased after one month but not three months of recovery in males dosed with 300 mg/kg/day. The decreases in creatinine may be related to treatment, but were not considered adverse because minimally decreased creatinine has no known toxicologic significance.
- Males dosed with 10, 60, or 300 mg/kg/day had minimally decreased protein during dosing. The decreased protein was due primarily to decreased globulin; globulin was minimally decreased in rats dosed with 60 or 300 mg/kg/day. After one month of recovery, protein, along with globulin, was still decreased in males previously dosed with 300 mg/kg/day. After three months of recovery, both total protein and globulins were similar to control values in rats previously dosed with 10, 60, or 300 mg/kg/day.
- After one month of recovery, females previously dosed with 300 mg/kg/day had minimally decreased total protein, due to decreased globulin. The decreased total protein was considered possibly related to treatment, due to the similarity of the effect with that in males. However, because the changes in proteins were mild and not expected to have adverse effects, this change was considered non-adverse.
- Cholesterol was minimally decreased in males dosed with 60 or 300 mg/kg/day at test day 92. The change resolved by one month of recovery (measured for 300 mg/kg/day only). This change was considered related to treatment, but non-adverse, because this magnitude of the

effect was not expected to have adverse effects. Cholesterol was also transiently and minimally decreased in females dosed with 10 mg/kg/day at test day 39; this change was considered to be unrelated to treatment due to the lack of dose-response relationship.

- Triglycerides were minimally decreased in females dosed with 300 mg/kg/day. This change was considered unrelated to treatment because the effect was due to increased triglycerides in some control females rather than a true decrease in treated females. Additionally, this change occurred only after one month of recovery, and is therefore unlikely to be related to dosing.
- Glucose was minimally increased in males dosed with 300 mg/kg/day at test day 92, and in females dosed with 60 mg/kg/day at test day 183. Although the change at test day 92 may have been related to dosing, increased glucose of this magnitude was not expected to have adverse effects.
- Calcium was variably and minimally decreased in males dosed with 10, 60, or 300 mg/kg/day at test days 38 and 92; there was no dose-relationship at 300 mg/kg/day. Calcium exists in serum in two forms, either bound to albumin or unbound ("ionized" calcium). Ionized calcium is the physiologically active form, and is tightly regulated. Decreases in albumin are necessarily associated with physiologically appropriate decreased bound calcium, with resultant decreased total calcium. However, ionized calcium is unaffected. Therefore, due to the lack of dose-response and the correlation with albumin changes, this change was considered non-adverse.
- Calcium was minimally decreased in females previously dosed with 300 mg/kg/day after one month of recovery. The mean calcium concentration was within the range of means for other groups on this study. In addition, albumin was minimally decreased at this time point as well (not statistically significant); minimally decreased albumin could have contributed to the change in calcium. However, the change in calcium was very small, and the change only occurred after one month of recovery. Therefore, this change was considered unrelated to treatment.

The following statistically significant changes in chemistry parameters were considered to be unrelated to treatment because there was no dose-relationship or they occurred only during recovery.

- Albumin was minimally decreased in males dosed with 10 or 60 mg/kg/day at test day 92. At test day 183, albumin was decreased only in rats dosed with 60 mg/kg/day. Due to the lack of a dose response, this change was not considered to be treatment-related.
- Cholesterol was minimally increased in males previously dosed with 10 mg/kg/day after 3 months of recovery. This was considered unrelated to treatment because of the lack of dose-response relationship, and because the change only occurred after three months of recovery.
- Sodium was transiently increased in males dosed with 10 mg/kg/day at test day 38. This was considered unrelated to treatment because of the lack of dose-response relationship.

- Chloride was increased in males dosed with 60 or 300 mg/kg/day at test day 92; however, there was no dose relationship to the response. This change was considered unrelated to treatment because of the lack of relationship to dose.

C. Urinalysis
(Tables 32-33, Appendix K)

Urine pH was minimally decreased in male rats previously dosed with 300 mg/kg/day at day 122. Urine protein (UMTP) was mildly decreased in female rats previously dosed with 300 mg/kg/day at day 122. These two statistically significant changes were considered to be unrelated to treatment because they occurred only during recovery.

D. Plasma and urine fluoride
(Tables 30-33, Appendix K)

Plasma fluoride was minimally increased only in males dosed with 300 mg/kg/day at test day 92. After one month of recovery, plasma fluoride was similar to control values. Plasma fluoride in females was not affected by dosing.

There was a dose-dependent increase in urine fluoride. Urine fluoride was increased in males dosed with 10, 60, or 300 mg/kg/day at test day 92, and in males dosed with 300 mg/kg/day after one month of recovery. After three months of recovery, urine fluoride was minimally increased in males previously dosed with 60 or 300 mg/kg/day; the relationship of this change to dosing is equivocal, because the values overlapped with historical results.

Urine fluoride was increased in females dosed with 60 or 300 mg/kg/day at test day 93. For rats dosed with 10 mg/kg/day, the number of samples available for analysis was too few to make a conclusion. After one month of recovery, urine fluoride was still minimally above controls in females previously dosed with 300 mg/kg/day. The relationship of this change to dosing is equivocal, because the values overlapped with historical results. After three months of recovery, urine fluoride was similar to control amounts in females previously dosed with test substance.

The presence of increased plasma and/or urine fluoride indicates exposure to a fluoride-containing compound, but was not considered adverse.

E. Clinical Pathology Conclusions

Under the conditions of this study and for the parameters measured, the no adverse effect level for males was not determined due to increased serum activities for AST, ALT, and SDH during the dosing and/or recovery periods in all dose groups. In addition, at the end of dosing, males dosed with 300 mg/kg/day had decreases in parameters indicating red cell mass (hemoglobin, hematocrit, and red cell counts). The no adverse effect level for female rats was 60 mg/kg/day, based on the presence of increased serum activities for AST and ALT in some rats dosed with 300 mg/kg/day during the dosing period. There were no adverse findings for coagulation or urinalysis parameters for either sex.

BIOCHEMICAL MEASUREMENTS

F. Biochemical Measurements (Table 34-35, Appendix L)

The rate of hepatic β -oxidation, a measure of peroxisome proliferation, was determined in male and female rats after 10 days or 91 days (males) or 92 days (females) of test substance administration or following a one-month or three-month recovery period.

There were no statistically significant differences in the rate of hepatic β -oxidation between the untreated control and the isopropanol control group after 10 days or 91 days (males) or 92 days (females) of test substance administration. As a result, all statistical analyses for male rats were compared to the untreated control group. At the 10-day time point in male rats, the rate of hepatic β -oxidation was increased in rats dosed with 300 mg/kg/day H-24678 (181% of untreated control), although the increase was not statistically significant. At the 90-day time point, the rate of hepatic β -oxidation was increased in a dose-dependant manner and was statistically significantly increased in rats dosed with 60 and 300 mg/kg/day H-24678 (144% and 206% of untreated controls, respectively). At the one-month recovery time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 300 mg/kg/day H-24678 (167% of untreated control). At the three-month recovery time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 300 mg/kg/day H-24678 (153% of untreated control). At the 90-day and one-month recovery time points, the increases in hepatic β -oxidation activity were accompanied by slight increases in relative liver weights.

In female rats, there was a statistically significant difference between the untreated control group and the isopropanol control group at the 10-day time point (isopropanol control was 67% of the untreated control). This finding was considered spurious since it was not replicated at the 90-day time point in female rats or at either time point in male rats. In addition, no other parameters of the study showed statistically significant differences between the two control groups. As a result, all statistical analyses for female rats were compared to the untreated control group. At the 10-day time point in female rats, the rate of hepatic β -oxidation was increased in a dose-dependant manner and was statistically significantly increased in rats dosed with 60 and 300 mg/kg/day H-24678 (129% and 154% of untreated control, respectively). At the 90-day time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 300 mg/kg/day H-24678 (130% of untreated control). At the one-month recovery time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 300 mg/kg/day H-24678 (122% of untreated control). At the three-month recovery time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 60 and 300 mg/kg/day H-24678 (130% and 133% of untreated control, respectively). At the 90-day time point, the increases in hepatic β -oxidation activity were accompanied by slight increases in relative liver weights.

In-life data (body weight, nutritional and clinical observations parameters) and liver weights collected for the rats evaluated for 10-day biochemical evaluations are not included in this report but are in study records.

G. Biochemical Measurements Conclusions

Under the conditions of this study, H-24678 was a mild inducer of hepatic peroxisomal β -oxidation in male and female rats. At dosages of 60 mg/kg/day and greater, changes in the rate of hepatic peroxisome proliferation were considered to be biologically significant but not toxicologically adverse effects. The rate of hepatic peroxisome proliferation remained elevated in male and female rats dosed with 60 mg/kg/day (females only) or 300 mg/kg/day H-24678 throughout the recovery period. Due to the small magnitude of test substance-related changes in hepatic biochemical measurements, the no-observed-effect level (NOEL) was the highest dose tested (300 mg/kg/day) for both male and female rats.

ANATOMICAL PATHOLOGY

A. Mortality (Appendix N)

There were no compound-related deaths. Two control rats (male animal no. 648294 and female animal no. 648439) were accidentally killed. One female rat dosed with 10 mg/kg/day in the three-month recovery group (animal no. 648352) was sacrificed *in extremis* due to a mammary tumor. One male rat dosed with 300 mg/kg/day in the one-month recovery group (animal no. 648231) was found dead with foreign material in its nose and lungs which is consistent with a misdose into the lungs. A cause of death was not determined for a 300 mg/kg/day female one-month recovery rat (animal no. 648375) that was found dead on test day 5.

B. Organ Weight Data (Tables 36-37, Appendix M)

Compound-related and/or statistically significant increases, compared to controls, in liver weight parameters were present in 300 mg/kg/day males and females and 60 mg/kg/day males (liver weight relative to body weight) sacrificed at the end of the exposure period. At the 300 mg/kg/day dose level, liver weight parameters remained increased above controls in the one-month recovery group males, although the magnitude of this effect was decreased relative to that observed at the end of the exposure period. No statistically significant liver weight effects were present in one-month recovery group females or in three-month recovery groups previously dosed with 300, 60, or 10 mg/kg/day (there were no intermediate dose groups at the one-month recovery timeline). In 60 and 300 mg/kg/day exposure group male rats and 300 mg/kg/day one-month recovery male rats increased liver weights correlated with microscopic hepatocellular hypertrophy (see discussion under Microscopic Findings).

Compound-related and/or statistically significant increases, compared to controls, in one or more kidney weight parameters occurred in male and female rats dosed with 300 mg/kg/day and in male rats given 60 mg/kg/day and sacrificed at the end of the exposure period. Some kidney weight parameters remained increased in males in the 300 mg/kg/day one-month recovery group. However, there were no statistically significant kidney weight changes in female one-month recovery rats at 300 mg/kg/day or in any dosed group following a 3 month recovery. In male rats, increased kidney weight correlated with microscopic tubular hypertrophy in the 300 mg/kg/day group sacrificed at the end of the exposure period (see discussion under Microscopic Findings). There were no microscopic correlates to kidney weight changes in females.

Compound-related and/or statistically significant increases, compared to controls, in one or more thyroid gland weight parameters occurred in female rats dosed with 300 mg/kg/day and sacrificed at the end of the exposure period and at the one-month and three-month recovery periods. However, there were no statistically significant thyroid gland weight changes in male rats sacrificed at any time period. In female rats, increased thyroid gland weight correlated with

follicular hypertrophy in the 300 mg/kg/day group that was sacrificed at the end of the exposure period (see discussion under Microscopic Findings).

There were no other compound-related organ weight effects. All other statistically significant organ weight changes in exposure and recovery groups were either secondary to changes in body weight, did not exhibit a dose related response, did not have compound-related microscopic findings, and/or the degree of weight change was biologically inconsequential. The following is a list of statistically significant organ weights that were considered not compound-related and not biologically meaningful:

- Adrenal gland - decreased absolute and relative to brain weights in male 60 and 300 mg/kg/day exposure groups.
- Adrenal gland - decreased relative to brain weight in male 60 mg/kg/day isopropanol exposure group.
- Heart - increased relative to body weight in male 60 and 300 mg/kg/day exposure groups.
- Heart - increased absolute weight in male 60 mg/kg/day isopropanol exposure group.
- Testes - increased absolute weight in male 60 and 300 mg/kg/day exposure groups and increased relative to body weight in male 300 mg/kg/day exposure group.
- Brain - increased relative to body weight in male 300 mg/kg/day exposure group.
- Testes - increased relative to body weight in male 300 mg/kg/day one-month recovery group.
- Epididymides - decreased absolute weight in male 300 mg/kg/day one-month recovery group.
- Thymus - increased relative to body weight in male 300 mg/kg/day one-month recovery group.
- Brain - increased absolute weight in female 300 mg/kg/day exposure group.

C. Gross Observations
(Tables 38-39, Appendix N)

Gross observations noted were sporadic across groups and were not compound-related.

D. Microscopic Findings
(Tables 40-45, Appendix N)

Compound-related microscopic findings were present in liver, kidneys, and thyroid gland from male rats and thyroid gland from female rats.

Anatomical Pathology Text Table:
Incidences and Average Lesion Grades of Compound-Related Microscopic Findings
In Male and Female Rats

Dose: mg/kg/day	60 Isopropanol	0 Control	10	60	300
<u>Males: 90-Day Exposure Group</u>					
Liver:					
Hypertrophy, hepatocyte, centrilobular	0/10 ^a (0.0) ^b	0/10 (0.0)	0/10 (0.0)	1/10 (0.1)	10/11 (1.9)
Necrosis, focal	0/10 (0.0)	0/10 (0.0)	4/10 (0.4)	3/10 (0.3)	0/11 (0.0)
Kidneys:					
Hypertrophy, tubular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	11/11 (1.0)
Thyroid gland:					
Hypertrophy, follicular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	2/10 (0.2)	7/11 (0.7)
Alteration, colloid	8/10 (1.2)	5/10 (0.9)	8/10 (0.8)	4/10 (0.4)	10/11 (2.4)
<u>Males: One-Month Recovery</u>					
Liver:					
Hypertrophy, hepatocyte, centrilobular	NA	0/10 (0.0)	NA	NA	6/9 (0.7)
Necrosis, focal	NA	0/10 (0.0)	NA	NA	1/9 (0.1)
Thyroid gland:					
Hypertrophy, follicular	NA	0/10 (0.0)	NA	NA	6/9 (0.7)
Alteration, colloid	NA	5/10 (0.8)	NA	NA	9/9 (2.7)
<u>Males: Three-Month Recovery</u>					
Liver:					
Necrosis, focal	NA	0/5 (0.0)	0/5 (0.0)	1/5 (0.2)	3/5 (0.8)
Thyroid gland:					
Alteration, colloid	NA	5/5 (1.2)	5/5 (1.0)	5/5 (1.2)	5/5 (2.0)

**Anatomical Pathology Text Table (Continued):
Incidences and Average Lesion Grades of Compound-Related Microscopic Findings
In Male and Female Rats**

Dose: mg/kg/day	60	0 Control	10	60	300
	Isopropanol				

Females: 90-Day Exposure Group

Thyroid gland:

Hypertrophy, follicular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	1/11 (0.1)
Alteration, colloid	2/10 (0.2)	5/10 (0.5)	3/10 (0.3)	4/10 (0.4)	3/11 (0.3)

Females: One-Month Recovery

Thyroid gland:

Alteration, colloid	NA	2/10 (0.2)	NA	NA	9/9 (1.1)
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Females: Three-Month Recovery

Thyroid gland:

Alteration, colloid	NA	5/5 (1.0)	5/5 (1.2)	4/5 (1.2)	4/5 (1.0)
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a. Numerator indicates incidence of rats with microscopic lesion. Denominator indicates number of rats in group.

b. Number in parentheses indicates group average severity of lesion.

NA Tissue not available since no animals were dosed at these levels.

Focal hepatocellular necrosis accompanied by a minimal inflammatory response was present in 10 and 60 mg/kg/day male exposure groups, in 300 mg/kg/day one-month recovery males, and in 60 and 300 mg/kg/day three-month recovery males. In addition, liver enzymes were increased in all test compound dosed male groups at all time points (see Clinical Pathology results). There was correlation (not 100%) between rats with liver necrosis and elevated liver enzymes. Focal liver necrosis was considered to be a compound-related adverse finding in 10, 60, and 300 mg/kg/day male rats.

Hypertrophy of centrilobular hepatocytes was present in 60 and 300 mg/kg/day males sacrificed at the end of the exposure period. In male rats previously dosed with 300 mg/kg/day, hepatocellular hypertrophy was present, but showed partial reversibility, after a one-month recovery period and was not present after a three-month recovery period. Taken together, these findings suggest that microscopic hepatocellular hypertrophy was reversible in males following a three-month recovery. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within hepatocytes. Hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related physiologic response to metabolism of a xenobiotic and not toxicologically adverse. ^(23,24,25)

Renal tubular hypertrophy was present in 300 mg/kg/day male rats sacrificed at the end of the exposure period. This change was not observed in rats sacrificed at the one-month recovery

period. Thus, kidney tubular hypertrophy appeared to be reversible during the one-month recovery period. Microscopically, tubular hypertrophy was characterized by increased eosinophilic staining of cortical tubule epithelium and a slight increase in cell height. Cortical tubule epithelial cells appeared to contain more granular cytoplasmic material than cortical tubules of control rats. There was no histomorphologic evidence of renal damage, and no changes indicative of adverse effects were present in renal clinical pathology parameters (see clinical pathology section). Thus, the renal tubular hypertrophy (and the associated increase in kidney weights) was considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse.⁽²⁶⁾

Thyroid follicular hypertrophy was present in males administered 60 and 300 mg/kg/day and females administered 300 mg/kg/day. Follicular hypertrophy was characterized by short columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Hypertrophy was reversible in both male and female rats, as this change was not present in dosed male rats following the three-month recovery period or in female rats following the 1- month and three-month recovery periods. Thyroid hypertrophy was minimal and unassociated with proliferative thyroid lesions. However, this hypertrophy indicates possible disruption of thyroid homeostasis and thus was considered potentially adverse.

In the thyroid gland, the relative degree of altered colloid was increased in the 300 mg/kg/day males at the end of the exposure and at the 1- and three-month recovery periods. Incidence of altered colloid was also increased in 300 mg/kg/day males at the end of exposure and at one-month recovery. In 300 mg/kg/day females the relative degree of altered colloid and incidence was increased only at the one-month recovery period. The diagnosis of "alteration, colloid" was used for colloid changes characterized by stippled, granular, clumped, and/or diffusely basophilic colloid. A 4-level grading scheme was applied based on an estimate of the percentage of follicles that contained altered colloid. A grade of 1 was applied when 1 follicle to about 25% of the follicles were involved, with grades 2, 3, and 4 applied for each 25% increase in follicular involvement. The size, density, or staining intensity of stipples, granules, clumps, or diffuse basophilia within individual follicles did not impact the grading. There was no consistent association between the presence or absence of altered colloid and the presence of hypertrophy of thyroid follicular cells.

Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence correlating to increasing age.⁽²⁷⁾ Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and since increases in its grading score did not consistently correlate with other morphologic alterations in the thyroid gland, altered colloid was interpreted as not biologically meaningful and not adverse.

All other microscopic observations noted are known to occur spontaneously in rats of this strain and age and were not present in a dose response fashion in either incidence or severity.

E. Anatomical Pathology Conclusions

Exposure of the test compound for approximately 90 days produced focal hepatocellular necrosis in male rats at 10, 60, and 300 mg/kg/day dose groups and was considered to be toxicologically adverse.

Increased liver weights were present in males at 60 and 300 mg/kg/day and in females at 300 mg/kg/day groups. The increased liver weights correlated with microscopic centrilobular hepatocellular hypertrophy in males at 60 and 300 mg/kg/day groups. Hepatocellular hypertrophy was reversible in males following a three-month recovery. Increased kidney weights were present in 60 and 300 mg/kg/day males and 300 mg/kg/day female groups. In males, these kidney weight changes correlated with microscopic renal tubular hypertrophy. The increased kidney weights and male renal tubular hypertrophy appeared to be reversible by the three-month recovery period. These liver and kidney changes were considered to represent a physiologic response to metabolism of a xenobiotic and thus were not considered to be toxicologically significant.

Thyroid gland hypertrophy in 60 and 300 mg/kg/day males and in 300 mg/kg/day females, was reversible at three-months recovery in males and at one-month recovery in females, and was considered to be potentially adverse. The severity of altered colloid in thyroid glands increased beyond control level at the male 300 mg/kg/day dose level, however, it was not consistently associated with any other morphologic alteration and was not considered biologically adverse.

Under the conditions of this study, there was no NOEL for pathology for male rats based on liver necrosis at all dose levels. The NOEL for female rats was 60 mg/kg/day based on thyroid gland hypertrophy at 300 mg/kg/day.

CONCLUSIONS

No test substance-related mortality or clinical signs of toxicity were observed in male or female rats. Statistically significant and toxicologically adverse lower body weights, weight gain, and food efficiency were observed in male rats administered 300 mg/kg/day compared to controls. Food consumption was also significantly lower in male rats administered 300 mg/kg/day. After a one-month recovery period these parameters were similar to controls. No effects on body weight, weight gain, food consumption, or food efficiency were observed in female rats at any dose level.

Test substance-related and toxicologically adverse decreases in red cell mass parameters (red cell count, hemoglobin, and hematocrit) were observed in male rats administered 300 mg/kg/day during the dosing period and after one and three months of recovery. Adverse findings of elevated liver enzymes (AST, ALT and SDH) were observed in male rats of all dose levels and female rats dosed with 300 mg/kg/day after the 90-day exposure period. The enzyme changes in males were still present after three months of recovery and were more severe in high-dose males, while female rats recovered.

Increased liver and kidney weights were observed in male rats administered 60 and 300 mg/kg/day and in female rats administered 300 mg/kg/day after the 90-day exposure period. In male rats these organ weight changes correlated with microscopic observations of hepatocellular hypertrophy and renal tubular hypertrophy, respectively. These changes were considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse. After three months of recovery, liver and kidney weights and microscopic observations were similar to controls in both male and female rats.

Thyroid hypertrophy was observed in male rats administered 60 and 300 mg/kg/day and in female rats administered 300 mg/kg/day after the 90-day exposure period. These changes were considered test substance-related and toxicologically adverse. After three months of recovery, thyroid hypertrophy was not observed in male or female rats of any dose group.

Test substance-related and toxicologically adverse focal hepatocellular necrosis was observed in male rats of all dose groups after the 90-day exposure and/or one and three month recovery periods. Focal liver necrosis was considered to be a test substance-related adverse finding.

Based on focal liver necrosis observed in male rats of all dose groups, a no-observed-effect-level (NOEL)^a cannot be determined for male rats. A NOEL of 60 mg/kg/day was determined for female rats based on elevated liver enzymes and thyroid hypertrophy observed in females administered 300 mg/kg/day.

a The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency ⁽²⁸⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union ⁽²⁹⁾.

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TABLES

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EXPLANATORY NOTES

Study Design

<u>Group</u>		<u>Dosage</u>	<u>Test Substance</u>
<u>Male</u>	<u>Female</u>		
I	II	0 mg/kg/day	Vehicle control
III	IV	60 mg/kg/day	Isopropanol control
V	VI	10 mg/kg/day	H-24678
VII	VIII	60 mg/kg/day	H-24678
IX	X	300 mg/kg/day	H-24678

Critical Dates

- Day 90 ➤ Last day of test substance administration for male and female rats designated for the one-month and 3-month recovery periods.
- Day 91 ➤ Last day of test substance administration for male rats designated for the 90-day exposure period.
- Recovery period begins for rats designated for the one-month and 3-month recovery periods.
- Day 92 ➤ Last day of test substance administration for female rats designated for the 90-day exposure period.
- Male rats designated for the 90-day exposure period were sacrificed.
- Day 93 ➤ Female rats designated for the 90-day exposure period were sacrificed.
- Day 122 ➤ Male and female rats designated for the one-month recovery period were sacrificed.

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular volume
MCH	-	mean corpuscular hemoglobin
MCHC	-	mean corpuscular hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ANPR	-	absolute neutrophil precursor
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
ABLT	-	absolute blast leukocyte
AMSC	-	absolute miscellaneous leukocyte
AHSN	-	absolute hypersegmented neutrophil
ABAN	-	absolute neutrophil band
AMET	-	absolute neutrophil metamyelocyte
AMYE	-	absolute neutrophil myelocyte
APRO	-	absolute neutrophil promyelocyte
AMYB	-	absolute neutrophil myeloblast
ARL	-	absolute reactive lymphocyte
AAL	-	absolute atypical lymphocyte
AIL	-	absolute immature lymphocyte
ACL	-	absolute clefted lymphocyte
ABLB	-	absolute lymphoblast
AIE	-	absolute immature eosinophil
AIM	-	absolute immature monocyte
APLA	-	absolute plasma cell count
NC	-	not calculated or not calculable

Summary of Coagulation Values

PT	-	prothrombin time
APTT	-	activated partial thromboplastin time

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Serum and Plasma Chemistry Values

AST	-	aspartate aminotransferase
ALT	-	alanine aminotransferase
SDH	-	sorbitol dehydrogenase
ALKP	-	alkaline phosphatase
BILI	-	total bilirubin
BUN	-	urea nitrogen
CREA	-	creatinine
CHOL	-	cholesterol
TRIG	-	triglycerides
GLUC	-	glucose
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
CALC	-	calcium
IPHS	-	inorganic phosphorous
NA	-	sodium
K	-	potassium
CL	-	chloride
PFLU	-	plasma fluoride

Summary of Urinalysis Values

VOL	-	volume
UOSM	-	urine osmolality
SG	-	specific gravity
pH	-	the logarithm of the reciprocal of the hydrogen ion concentration
URO	-	urobilinogen
UFLU	-	urine fluoride
UMTP	-	urine protein

Notes for Clinical Pathology data:

When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083, 1.083 was used for any calculations performed with that specific gravity data.

TABLE 1
SUMMARY OF DOSING SOLUTION ANALYSES

Sample Type	Dosing Concentrations and Stability of H-24678 (mg/mL) ^a			
Test Day 1	Nominal:	1.33	8.00	40.0
<u>Concentration Verification</u>		1.51	7.32	40.4
		(113.5) ^b	(91.5)	(101.0)
		1.48	7.99	36.8
		(111.3)	(99.9)	(92.0)
Average Measured Conc.^c		1.50	7.66	38.6
Average Percent Nominal^c		(112.8)	(95.8)	(96.5)
Standard Deviation^c		± 0.02	± 0.47	± 2.5
Coefficient of Variation^c		1%	6%	6%
<u>Stability</u>				
0-Day Room Temperature ^d		1.50	7.66	38.6
		(112.8)	(95.8)	(96.5)
5-hour Room Temperature ^e		1.41	7.80	38.2
		(106.0)	(97.5)	(95.5)
7-Day Refrigerated		1.49	8.71	44.8
		(112.0)	(108.9)	(112.0)
7-Day Refrigerated/5 hr.		1.59	8.63	43.4
		(119.5)	(107.9)	(108.5)
<u>Concentration Verification^f</u>				
Test Day 42		1.21	7.59	39.0
		(91.0)	(94.9)	(97.5)
Test Day 91		1.36	8.23	38.1
		(102.3)	(102.9)	(95.3)

^a Dosing solution concentration mg H-24678/mL based on 7.5 mL dose volume. H-24678 is [REDACTED]

^b Numbers in parentheses are the respective percent of nominal values.

^c Mean, S.D., and C.V. for duplicate samples calculated to verify uniformity of mixture.

^d Mean result for Test Day 1 concentration verification samples used for baseline for stability samples.

^e Samples (Test Day 1) held at room temperature for 5 hours.

^f Duplicate samples submitted. Mean result reported.

Table 1 (continued)
Summary of Dosing Solution Analyses

Sample Type	Dosing Concentrations and Stability of Isopropyl Alcohol (mg/mL)		
Test Day 1	Nominal:	8.00	40.0 ^a
<u>Concentration Verification</u>		8.71 (108.9) ^b	7.80 (97.5)
		8.68 (108.5)	7.97 (99.6)
Average Measured Conc.^c		8.70	7.89
Average Percent Nominal^c		(108.8)	(98.6)
Standard Deviation^c		± 0.02	± 0.12
Coefficient of Variation^c		0%	2%
<u>Stability</u>			
0-Day Room Temperature ^d		8.70 (108.8)	7.89 (98.6)
5-hour Room Temperature ^e		8.66 (108.3)	8.03 (100.4)
7-Day Refrigerated		8.80 (110.0)	7.99 (99.9)
7-Day Refrigerated/5 hr.		9.04 (113.0)	7.83 (97.9)
<u>Concentration Verification^f</u>			
Test Day 42		9.11 (113.9)	7.50 (93.8)
Test Day 91		9.48 (118.5)	7.31 (91.4)

a 40 mg/mL H-24678 sample was analyzed to show that it contained 20% or 8 mg/mL of isopropyl alcohol.

b Numbers in parentheses are the respective percent of nominal values.

c Mean, S.D. and C.V. for duplicate samples calculated to verify uniformity of mixture.

d Mean result for Test Day 1 concentration verification samples used for baseline for stability samples.

e Samples (Test Day 1) held at room temperature for 5 hours.

f Duplicate samples submitted. Mean result reported.

TABLE 2

MEAN DAILY DOSE VOLUMES (mL) FOR MALE RATS

	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY0-DAY6	1.9 0.1(25)	2.0 0.1(10)	1.9 0.2(15)	1.9 0.2(15)	1.9 0.1(25)
DAY7-DAY14	2.3 0.2(25)	2.4 0.1(10)	2.3 0.2(15)	2.3 0.2(15)	2.3 0.2(25)
DAY15-DAY20	2.7 0.2(25)	2.8 0.1(10)	2.7 0.2(15)	2.7 0.2(15)	2.6 0.2(25)
DAY21-DAY27	2.9 0.2(25)	3.1 0.2(10)	3.0 0.3(15)	2.9 0.3(15)	2.9 0.2(25)
DAY28-DAY34	3.2 0.2(25)	3.3 0.2(10)	3.3 0.3(15)	3.2 0.3(15)	3.1 0.3(25)
DAY35-DAY41	3.4 0.3(25)	3.6 0.3(10)	3.5 0.3(15)	3.4 0.4(15)	3.3 0.3(25)
DAY42-DAY48	3.5 0.3(24)	3.6 0.2(10)	3.6 0.3(15)	3.5 0.4(15)	3.4 0.3(25)
DAY49-DAY55	3.7 0.3(24)	3.8 0.3(10)	3.7 0.3(15)	3.6 0.4(15)	3.5 0.3(25)
DAY56-DAY62	3.8 0.3(24)	4.0 0.3(10)	3.9 0.3(15)	3.8 0.4(15)	3.6 0.3(25)
DAY63-DAY69	3.9 0.4(24)	4.1 0.3(10)	4.0 0.4(15)	3.9 0.5(15)	3.7 0.3(24)
DAY70-DAY76	4.0 0.4(24)	4.2 0.3(10)	4.1 0.4(15)	4.0 0.5(15)	3.9 0.4(24)
DAY77-DAY83	4.1 0.4(24)	4.3 0.3(10)	4.2 0.4(15)	4.1 0.5(15)	3.9 0.4(24)
DAY84-DAY90	4.2 0.4(24)	4.4 0.3(10)	4.3 0.4(15)	4.1 0.5(15)	4.0 0.4(24)
DAY91	4.4 0.2(9)	4.4 0.3(10)	4.5 0.4(10)	4.4 0.5(10)	4.2 0.5(10)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

TABLE 3

MEAN DAILY DOSE VOLUMES (mL) FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY0-DAY6	1.4 0.1(25)	1.5 0.2(10)	1.4 0.1(15)	1.5 0.1(15)	1.5 0.1(25)
DAY7-DAY14	1.6 0.2(25)	1.6 0.1(10)	1.6 0.1(15)	1.6 0.1(15)	1.6 0.1(24)
DAY15-DAY20	1.8 0.2(25)	1.8 0.1(10)	1.7 0.1(15)	1.8 0.1(15)	1.8 0.1(24)
DAY21-DAY27	1.9 0.2(25)	1.9 0.2(10)	1.8 0.1(15)	1.9 0.1(15)	1.9 0.1(24)
DAY28-DAY34	2.0 0.2(25)	2.0 0.1(10)	1.9 0.1(15)	2.0 0.2(15)	2.0 0.1(24)
DAY35-DAY41	2.1 0.2(25)	2.1 0.1(10)	2.0 0.1(15)	2.1 0.2(15)	2.1 0.1(24)
DAY42-DAY48	2.2 0.2(25)	2.1 0.1(10)	2.1 0.2(15)	2.2 0.2(15)	2.1 0.2(24)
DAY49-DAY55	2.2 0.2(25)	2.2 0.1(10)	2.1 0.2(15)	2.2 0.2(15)	2.2 0.2(24)
DAY56-DAY62	2.3 0.3(25)	2.2 0.1(10)	2.2 0.2(15)	2.3 0.2(15)	2.3 0.2(24)
DAY63-DAY69	2.3 0.3(25)	2.2 0.1(10)	2.2 0.2(15)	2.3 0.2(15)	2.3 0.2(24)
DAY70-DAY76	2.4 0.3(25)	2.3 0.1(10)	2.2 0.2(15)	2.3 0.2(15)	2.4 0.2(24)
DAY77-DAY83	2.4 0.3(25)	2.4 0.1(10)	2.3 0.2(15)	2.4 0.2(15)	2.4 0.2(24)
DAY84-DAY90	2.5 0.3(25)	2.4 0.1(10)	2.3 0.2(15)	2.4 0.2(15)	2.4 0.2(24)
DAY91-DAY92	2.5 0.2(10)	2.4 0.1(10)	2.3 0.2(10)	2.5 0.4(10)	2.6 0.2(10)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is

TABLE 4
MEAN BODY WEIGHTS (g) OF MALE RATS

Dosing Period

	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY0	254.7 18.4(25)	262.9 13.9(10)	256.1 19.7(15)	257.1 20.0(15)	255.0 17.4(25)
DAY7	308.5 23.2(25)	322.6 16.8(10)	311.5 24.9(15)	308.5 26.5(15)	305.8 22.5(25)
DAY15	359.3 26.6(25)	377.7 20.2(10)	363.3 28.5(15)	360.4 31.7(15)	351.9 25.8(25)
DAY21	393.5 29.2(25)	413.6 22.9(10)	402.0 33.7(15)	393.7 35.2(15)	383.3 31.5(25)
DAY28	424.8 31.6(25)	444.0 27.4(10)	434.2 37.6(15)	424.5 44.1(15)	415.1 35.8(25)
DAY35	450.9 35.0(25)	473.2 33.2(10)	464.5 41.2(15)	453.7 49.3(15)	441.1 38.4(25)
DAY42	468.4 38.0(24)	481.8 33.5(10)	480.0 37.3(15)	462.6 48.3(15)	449.5# 38.4(25)
DAY49	490.8 39.7(24)	507.0 34.3(10)	497.6 38.0(15)	483.0 50.9(15)	467.0# 38.6(25)
DAY56	511.1 42.6(24)	528.5 36.0(10)	520.2 41.3(15)	503.7 52.7(15)	486.2# 42.2(25)
DAY63	519.9 58.8(24)	544.7 38.2(10)	536.8 44.9(15)	520.3 60.1(15)	497.0# 45.2(24)
DAY70	537.3 54.7(24)	563.6 38.9(10)	548.1 45.2(15)	531.7 62.8(15)	512.5# 47.9(24)
DAY77	550.4 50.9(24)	570.8 41.3(10)	562.1 48.0(15)	543.2 64.8(15)	522.5# 48.2(24)
DAY84	557.7 55.3(24)	581.0 43.0(10)	567.2 58.9(15)	547.4 70.7(15)	529.7# 51.3(24)
DAY91	567.7 54.4(24)	589.2 44.0(10)	574.6 57.0(15)	552.5 68.9(15)	535.9# 52.3(24)

TABLE 4 (CONTINUED)

MEAN BODY WEIGHTS (g) OF MALE RATS

One-Month Recovery Period

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY98	562.0 69.2 (15)	531.1 40.5 (5)	505.8 53.7 (5)	535.9 45.0 (14)
DAY105	575.2 67.4 (15)	544.1 37.4 (5)	517.2 54.9 (5)	553.2 48.3 (14)
DAY113	581.5 79.9 (15)	558.9 35.0 (5)	523.5 63.8 (5)	572.0 46.9 (14)
DAY119	590.9 74.9 (15)	565.5 37.6 (5)	529.7 65.0 (5)	579.5 48.4 (14)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group III (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups I and III at $p < 0.05$ by pairwise comparisons.

TABLE 5
MEAN BODY WEIGHTS (g) OF FEMALE RATS

Dosing Period

	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY0	193.5 14.9(25)	193.9 17.2(11)	193.0 10.5(15)	195.5 12.0(15)	197.3 13.4(25)
DAY7	216.2 19.9(25)	211.7 16.2(10)	210.9 10.4(15)	216.1 13.3(15)	215.6 14.5(24)
DAY15	239.6 23.6(25)	236.3 17.9(10)	230.1 16.3(15)	237.9 18.2(15)	237.9 17.4(24)
DAY21	254.1 25.1(25)	249.9 19.5(10)	243.7 16.8(15)	251.2 16.0(15)	249.0 19.7(24)
DAY28	267.4 29.6(25)	265.7 16.4(10)	255.1 16.7(15)	267.5 20.3(15)	264.5 18.0(24)
DAY35	279.1 30.6(25)	273.6 17.6(10)	269.2 16.3(15)	280.2 24.4(15)	277.5 20.2(24)
DAY42	287.1 31.9(25)	280.0 14.0(10)	273.3 19.4(15)	287.1 27.4(15)	284.9 19.7(24)
DAY49	297.1 33.0(25)	289.0 15.8(10)	279.5 21.0(15)	295.3 25.6(15)	291.8 20.6(24)
DAY56	306.3 35.4(25)	297.8 15.7(10)	288.2 22.2(15)	306.8 26.7(15)	307.1 26.3(24)
DAY63	308.8 39.0(25)	297.2 14.1(10)	291.0 20.0(15)	310.9 32.6(15)	307.9 23.1(24)
DAY70	316.8 38.2(25)	308.7 11.9(10)	296.7 23.2(15)	313.8 30.3(15)	317.1 26.3(24)
DAY77	321.3 38.8(25)	313.0 10.9(10)	300.4 22.3(15)	319.1 34.3(15)	317.9 26.3(24)
DAY84	326.9 40.6(25)	319.9 15.7(10)	306.8 23.1(15)	326.4 34.7(15)	322.2 27.0(24)
DAY91	326.1 41.0(25)	318.8 13.8(10)	310.3 22.1(15)	328.6 38.9(15)	325.6 30.0(24)

TABLE 5 (CONTINUED)
MEAN BODY WEIGHTS (g) OF FEMALE RATS

One-Month Recovery Period

	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY98	337.5 56.4(15)	314.3 30.6(5)	322.5 17.6(5)	321.3 27.9(14)
DAY105	344.8 59.6(15)	332.4 26.9(5)	334.8 20.9(5)	327.2 27.9(14)
DAY113	349.0 59.3(15)	339.3 29.7(5)	341.1 22.8(5)	334.4 30.4(14)
DAY119	353.2 61.8(15)	339.7 30.8(5)	340.8 24.0(5)	340.0 32.6(14)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test. Group IV (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups II and IV at $p < 0.05$ by pairwise comparisons.

TABLE 6
MEAN BODY WEIGHT GAINS (G) OF MALE RATS

Dosing Period

	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY0-DAY7	53.8 8.3(25)	59.7 6.6(10)	55.4 8.5(15)	51.4 8.7(15)	50.8 9.1(25)
DAY7-DAY15	50.9 8.4(25)	55.1 9.0(10)	51.8 7.3(15)	51.9 8.3(15)	46.1# 9.8(25)
DAY15-DAY21	34.1 7.1(25)	36.0 4.2(10)	38.7 9.2(15)	33.3 7.4(15)	31.3# 10.0(25)
DAY21-DAY28	31.3 5.6(25)	30.4 6.8(10)	32.2 7.4(15)	30.8 10.8(15)	31.8 8.3(25)
DAY28-DAY35	26.1 8.6(25)	29.1 8.0(10)	30.3 6.5(15)	29.2 6.5(15)	26.0 8.1(25)
DAY35-DAY42	18.1 6.3(24)	8.6 * 6.9(10)	15.5 9.5(15)	8.9# 6.4(15)	8.4# 8.9(25)
DAY42-DAY49	22.4 6.5(24)	25.2 5.6(10)	17.6 5.8(15)	20.4 9.9(15)	17.5# 7.0(25)
DAY49-DAY56	20.3 6.3(24)	21.5 3.8(10)	22.5 6.4(15)	20.6 6.2(15)	19.3 6.6(25)
DAY56-DAY63	8.7 24.4(24)	16.2 5.4(10)	16.6 10.2(15)	16.6 8.8(15)	9.8 11.3(24)
DAY63-DAY70	17.5 12.6(24)	18.9 3.4(10)	11.3 2.7(15)	11.4 7.5(15)	15.5 6.8(24)
DAY70-DAY77	13.0 8.1(24)	7.3 @ 4.4(10)	14.0 5.2(15)	11.5 5.6(15)	10.0 5.8(24)
DAY77-DAY84	7.4 9.4(24)	10.2 5.9(10)	5.1 18.9(15)	4.2 8.9(15)	7.2 7.9(24)
DAY84-DAY91	10.0 7.3(24)	8.1 12.6(10)	7.5 5.4(15)	5.1# 7.9(15)	6.2# 8.0(24)
DAY0-DAY91	314.2 46.9(24)	326.2 41.8(10)	318.5 47.0(15)	295.5 55.6(15)	281.2# 39.8(24)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

One-Month Recovery Period

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY91-DAY98	4.6 11.6(15)	1.3 8.1(5)	5.0 7.8(5)	12.1# 11.4(14)
DAY98-DAY105	13.1 3.8(15)	13.0 7.2(5)	11.4 4.1(5)	17.3 7.5(14)
DAY105-DAY113	6.4 19.4(15)	14.8 3.4(5)	6.4 11.2(5)	18.8# 7.2(14)
DAY113-DAY119	9.4 11.3(15)	6.6 8.1(5)	6.2 6.1(5)	7.5 4.3(14)
DAY91-DAY119	33.4 19.5(15)	35.7 22.9(5)	28.9 22.3(5)	55.8# 17.0(14)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group III (isopropanol control) was excluded from trend comparisons.

* Statistically significant difference from control (Group I) at $p < 0.05$ by Dunnett's test.

@ Statistically significant difference from control (Group I) at $p < 0.05$ by Dunn's test.

TABLE 7

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

Dosing Period

	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY0-DAY7	22.6 8.8(25)	18.2 11.8(10)	18.0 5.7(15)	20.6 6.5(15)	18.3 7.1(24)
DAY7-DAY15	23.4 7.2(25)	24.5 5.8(10)	19.2 8.7(15)	21.7 9.3(15)	22.3 6.0(24)
DAY15-DAY21	14.5 8.0(25)	13.6 9.2(10)	13.6 7.4(15)	13.3 9.2(15)	11.1 7.5(24)
DAY21-DAY28	13.3 7.5(25)	15.9 4.6(10)	11.4 6.9(15)	16.3 8.4(15)	15.5 8.9(24)
DAY28-DAY35	11.7 8.4(25)	7.8 7.4(10)	14.0 5.4(15)	12.7 6.2(15)	13.0 7.0(24)
DAY35-DAY42	8.1 7.4(25)	6.4 7.8(10)	4.1 7.7(15)	6.9 8.1(15)	7.4 6.1(24)
DAY42-DAY49	9.9 6.0(25)	9.0 6.7(10)	6.2 6.8(15)	8.1 7.9(15)	7.0 5.7(24)
DAY49-DAY56	9.2 6.7(25)	8.8 3.0(10)	8.7 5.7(15)	11.5 9.2(15)	15.2 20.7(24)
DAY56-DAY63	2.5 8.2(25)	-0.6 9.1(10)	2.7 7.6(15)	4.2 9.4(15)	0.8 22.0(24)
DAY63-DAY70	7.9 6.5(25)	11.5 5.0(10)	5.7 5.7(15)	2.9 9.7(15)	9.3 6.3(24)
DAY70-DAY77	4.5 5.9(25)	4.3 5.3(10)	3.8 6.9(15)	5.2 6.9(15)	0.8# 4.6(24)
DAY77-DAY84	5.6 7.3(25)	6.9 5.7(10)	6.4 6.3(15)	7.3 7.3(15)	4.3 6.7(24)
DAY84-DAY91	-0.9 7.6(25)	-1.1 5.4(10)	3.5 7.3(15)	2.2 7.2(15)	3.4# 8.4(24)
DAY0-DAY91	132.5 29.9(25)	125.3 17.0(10)	117.3 16.3(15)	133.1 31.6(15)	128.3 21.7(24)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

One-Month Recovery Period

	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY91-DAY98	11.0 9.3(15)	2.7 11.9(5)	0.8 12.0(5)	6.5 7.7(14)
DAY98-DAY105	7.4 6.3(15)	18.1 11.4(5)	12.3 7.2(5)	5.9 7.4(14)
DAY105-DAY113	4.1 4.4(15)	6.9 5.7(5)	6.3 10.6(5)	7.2 6.9(14)
DAY113-DAY119	4.2 8.9(15)	0.4 3.9(5)	-0.3 9.4(5)	5.6 9.3(14)
DAY91-DAY119	26.7 16.0(15)	28.1 10.9(5)	19.0 20.3(5)	25.2 15.9(14)

Data summarized as: Mean
 Standard Deviation (n)

a. H-24678 is [REDACTED]

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group IV (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups II and IV at $p < 0.05$ by pairwise comparisons.

TABLE 8
MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

Dosing Period

	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY7	26.6 2.4(25)	28.5 * 1.6(10)	27.4 2.6(15)	27.6 2.5(15)	26.9 2.6(25)
DAY15	27.7 2.1(25)	28.9 1.8(10)	28.1 2.3(15)	28.3 2.8(15)	27.3 2.7(25)
DAY21	28.7 2.5(25)	30.0 2.5(10)	30.2 2.9(15)	29.1 3.0(15)	28.2 3.1(25)
DAY28	29.6 2.5(25)	29.7 2.0(10)	30.0 3.0(14)	28.9 3.1(15)	28.2 3.0(25)
DAY35	29.0 2.9(25)	29.3 2.8(10)	30.0 2.6(15)	28.8 3.2(15)	27.4 3.2(25)
DAY42	27.5 2.6(24)	25.6 2.2(10)	27.2 1.7(15)	25.9 2.6(15)	25.2# 2.4(25)
DAY49	30.2 2.8(24)	30.3 2.3(10)	29.8 2.7(15)	28.9 3.2(15)	27.2# 2.7(25)
DAY56	29.7 2.9(24)	30.5 2.6(10)	30.1 2.5(15)	29.5 3.6(15)	28.2# 2.7(25)
DAY63	28.3 4.7(24)	29.4 2.8(10)	28.3 2.8(15)	27.8 3.7(15)	27.2 3.1(24)
DAY70	28.7 3.7(24)	30.4 2.5(10)	28.9 2.1(15)	28.2 3.7(15)	27.1# 2.9(24)
DAY77	29.0 2.9(24)	29.8 3.0(10)	29.9 2.2(15)	28.8 3.1(15)	28.0 3.0(24)
DAY84 ^b	30.1 3.1(19)	29.9 2.6(10)	30.0 2.1(10)	28.7 2.9(10)	28.0# 2.9(19)
DAY91	28.0 3.6(24)	28.2 2.3(10)	26.4 3.3(15)	25.3 2.8(15)	26.8 3.5(24)
DAY0-DAY91 ^b	29.5 1.8(19)	29.3 2.0(10)	29.9 1.4(9)	29.2 2.3(10)	27.7# 2.2(19)

TABLE 8 (CONTINUED)

MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

One-Month Recovery Period

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY98	25.7 4.6(15)	23.8 0.7(5)	24.3 3.4(5)	27.3 3.3(14)
DAY105	27.6 3.0(15)	25.6 2.1(5)	24.9 2.7(5)	28.6 3.1(14)
DAY113	28.1 4.1(15)	27.2 2.1(5)	25.4 4.6(5)	29.1 2.6(14)
DAY119	28.0 3.2(15)	26.6 3.0(5)	24.7 4.3(5)	28.5 2.4(14)
DAY91-DAY119	27.4 3.5(15)	25.8 1.8(5)	24.9 3.6(5)	28.4 2.7(14)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is

b. On test day 84, food consumption data were inadvertently not collected for 5 rats/group designated for 3-month recovery.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group III (isopropanol control) was excluded from trend comparisons.

* Statistically significant difference from control (Group I) at $p < 0.05$ by Dunnett's test.

TABLE 9
MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

Dosing Period	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY7	20.0 2.3(25)	20.2 0.9(10)	19.6 1.7(15)	19.4 1.5(15)	19.4 1.6(24)
DAY15	20.8 2.6(25)	20.6 1.2(10)	19.9 2.1(15)	20.6 1.8(15)	20.1 2.2(24)
DAY21	21.5 2.7(25)	21.6 1.3(10)	21.0 2.3(15)	20.8 2.3(15)	20.6 2.2(24)
DAY28	22.1 3.3(25)	21.0 0.9(10)	20.9 1.6(15)	21.1 2.2(15)	21.2 1.8(24)
DAY35	21.3 2.9(25)	20.8 0.8(10)	20.9 1.5(15)	20.7 2.1(15)	21.2 1.9(24)
DAY42	19.9 2.8(25)	19.2 1.2(10)	18.9 1.8(15)	20.2 2.4(15)	19.5 2.0(24)
DAY49	21.6 2.4(25)	21.5 1.2(10)	20.8 2.2(15)	21.9 2.0(15)	21.7 1.7(24)
DAY56	21.5 2.8(25)	21.3 1.1(10)	21.1 2.0(15)	22.0 2.4(15)	21.5 1.9(24)
DAY63	20.3 2.5(25)	19.8 2.3(10)	19.6 1.6(15)	20.9 2.2(15)	20.4 2.0(24)
DAY70	21.1 2.9(25)	21.4 1.4(10)	20.3 2.1(15)	21.0 2.3(15)	21.2 1.9(24)
DAY77	20.7 2.6(25)	20.9 1.7(10)	20.6 2.1(15)	21.0 2.5(15)	20.6 1.9(24)
DAY84 ^b	21.7 3.5(20)	21.1 2.1(10)	21.0 2.1(10)	21.9 3.1(10)	20.5 1.8(19)
DAY91	19.3 2.6(25)	20.1 1.3(10)	20.0 2.2(15)	20.5 2.8(15)	19.8 2.2(24)
DAY0-DAY91 ^b	21.4 2.4(20)	20.7 0.5(10)	20.4 1.7(10)	21.2 2.3(10)	20.8 1.5(19)

TABLE 9 (CONTINUED)
MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

One-Month Recovery Period

	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY98	20.2 3.3(15)	20.3 4.5(5)	19.9 2.7(5)	19.9 2.2(14)
DAY105	20.7 3.8(15)	21.8 2.3(5)	21.2 3.0(5)	21.0 2.0(14)
DAY113	21.0 2.9(15)	23.2 2.2(5)	22.8 3.6(5)	21.5 2.0(14)
DAY119	20.5 2.9(15)	21.4 1.7(5)	21.1 2.0(5)	21.2 2.3(14)
DAY91-DAY119	20.6 2.9(15)	21.7 2.4(5)	21.3 2.5(5)	20.9 1.9(14)

Data summarized as: Mean
Standard Deviation (n)

- a. H-24678 is [REDACTED]
- b. On test day 84, food consumption data were inadvertently not collected for 5 rats/group designated for 3-month recovery.

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test. Group IV (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups II and IV at $p < 0.05$ by pairwise comparisons.

TABLE 10

MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

Dosing Period

	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY0-DAY7	0.288 0.031(25)	0.299 0.025(10)	0.288 0.029(15)	0.265# 0.031(15)	0.269# 0.037(25)
DAY7-DAY15	0.229 0.029(25)	0.237 0.031(10)	0.232 0.035(15)	0.229 0.029(15)	0.212 0.040(25)
DAY15-DAY21	0.197 0.029(25)	0.200 0.018(10)	0.212 0.037(15)	0.190 0.035(15)	0.183# 0.041(25)
DAY21-DAY28	0.151 0.021(25)	0.145 0.029(10)	0.152 0.028(14)	0.149 0.041(15)	0.159 0.032(25)
DAY28-DAY35	0.127 0.036(25)	0.141 0.029(10)	0.144 0.027(15)	0.144 0.023(15)	0.136 0.037(25)
DAY35-DAY42	0.093 0.029(24)	0.048 * 0.037(10)	0.081 0.049(15)	0.049# 0.035(15)	0.046# 0.049(25)
DAY42-DAY49	0.105 0.027(24)	0.118 0.023(10)	0.085 0.028(15)	0.099 0.042(15)	0.091 0.035(25)
DAY49-DAY56	0.097 0.025(24)	0.101 0.016(10)	0.107 0.028(15)	0.100 0.029(15)	0.097 0.029(25)
DAY56-DAY63	0.004 0.294(24)	0.079 0.025(10)	0.081 0.043(15)	0.082 0.040(15)	0.048 0.066(24)
DAY63-DAY70	0.093 0.098(24)	0.089 0.017(10)	0.056 0.013(15)	0.056 0.040(15)	0.081 0.035(24)
DAY70-DAY77	0.064 0.040(24)	0.034 @ 0.019(10)	0.066 0.022(15)	0.057 0.026(15)	0.050 0.026(24)
DAY77-DAY84 ^b	0.043 0.032(19)	0.049 0.029(10)	0.048 0.033(10)	0.042 0.029(10)	0.047 0.029(19)
DAY84-DAY91	0.051 0.042(24)	0.039 0.061(10)	0.042 0.031(15)	0.029 0.044(15)	0.031# 0.041(24)
DAY0-DAY91 ^b	0.123 0.008(19)	0.122 0.011(10)	0.124 0.011(9)	0.118 0.011(10)	0.113# 0.010(19)

TABLE 10 (CONTINUED)

MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

One-Month Recovery Period

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
DAY91-DAY98	0.018 0.074(15)	0.008 0.049(5)	0.027 0.049(5)	0.057# 0.070(14)
DAY98-DAY105	0.069 0.024(15)	0.072 0.038(5)	0.065 0.021(5)	0.085 0.032(14)
DAY105-DAY113	0.016 0.123(15)	0.068 0.016(5)	0.024 0.054(5)	0.081# 0.032(14)
DAY113-DAY119	0.058 0.076(15)	0.038 0.049(5)	0.040 0.046(5)	0.043 0.023(14)
DAY91-DAY119	0.042 0.026(15)	0.048 0.030(5)	0.039 0.030(5)	0.069# 0.018(14)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

b. On test day 84, food consumption data were inadvertently not collected for 5 rats/group designated for 3-month recovery.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group III (isopropanol control) was excluded from trend comparisons.

* Statistically significant difference from control (Group I) at $p < 0.05$ by Dunnett's test.

@ Statistically significant difference from control (Group I) at $p < 0.05$ by Dunn's test.

TABLE 11

MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS
(g body weight gain/g food consumed)

Dosing Period

	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY0-DAY7	0.159 0.049 (25)	0.129 0.083 (10)	0.131 0.040 (15)	0.149 0.040 (15)	0.135 0.049 (24)
DAY7-DAY15	0.139 0.033 (25)	0.149 0.035 (10)	0.118 0.043 (15)	0.129 0.045 (15)	0.138 0.034 (24)
DAY15-DAY21	0.110 0.054 (25)	0.104 0.070 (10)	0.109 0.059 (15)	0.109 0.079 (15)	0.090 0.060 (24)
DAY21-DAY28	0.083 0.039 (25)	0.108 0.034 (10)	0.078 0.046 (15)	0.107 0.048 (15)	0.104 0.058 (24)
DAY28-DAY35	0.077 0.053 (25)	0.054 0.052 (10)	0.097 0.038 (15)	0.086 0.038 (15)	0.086 0.046 (24)
DAY35-DAY42	0.057 0.053 (25)	0.045 0.058 (10)	0.029 0.056 (15)	0.046 0.056 (15)	0.053 0.045 (24)
DAY42-DAY49	0.065 0.038 (25)	0.060 0.044 (10)	0.041 0.045 (15)	0.053 0.051 (15)	0.045 0.037 (24)
DAY49-DAY56	0.060 0.041 (25)	0.059 0.021 (10)	0.058 0.036 (15)	0.072 0.054 (15)	0.103 0.156 (24)
DAY56-DAY63	0.015 0.056 (25)	-0.011 0.075 (10)	0.020 0.055 (15)	0.024 0.061 (15)	0.001 0.178 (24)
DAY63-DAY70	0.054 0.043 (25)	0.077 0.033 (10)	0.038 0.038 (15)	0.018 0.076 (15)	0.061 0.038 (24)
DAY70-DAY77	0.030 0.038 (25)	0.028 0.034 (10)	0.025 0.045 (15)	0.033 0.044 (15)	0.005# 0.032 (24)
DAY77-DAY84 ^b	0.038 0.052 (20)	0.047 0.040 (10)	0.036 0.033 (10)	0.054 0.048 (10)	0.033 0.043 (19)
DAY84-DAY91	-0.010 0.053 (25)	-0.007 0.039 (10)	0.022 0.051 (15)	0.012 0.047 (15)	0.020# 0.065 (24)
DAY0-DAY91 ^b	0.070 0.009 (20)	0.066 0.009 (10)	0.063 0.006 (10)	0.069 0.012 (10)	0.069 0.008 (19)

TABLE 11 (CONTINUED)

MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS
(g body weight gain/g food consumed)

One-Month Recovery Period

	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
DAY91-DAY98	0.070 0.066(15)	0.004 0.084(5)	-0.003 0.096(5)	0.046 0.052(14)
DAY98-DAY105	0.048 0.039(15)	0.119 0.075(5)	0.079 0.040(5)	0.039 0.048(14)
DAY105-DAY113	0.023 0.024(15)	0.036 0.030(5)	0.029 0.058(5)	0.041 0.037(14)
DAY113-DAY119	0.030 0.069(15)	0.002 0.030(5)	-0.005 0.076(5)	0.040 0.078(14)
DAY91-DAY119	0.044 0.023(15)	0.045 0.013(5)	0.029 0.032(5)	0.043 0.027(14)

Data summarized as: Mean
Standard Deviation (n)

- a. H-24678 is [REDACTED]
- b. On test day 84, food consumption data were inadvertently not collected for 5 rats/group designated for 3-month recovery.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group IV (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups II and IV at $p < 0.05$ by pairwise comparisons.

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS OF MALE RATS

Treatment Group	I	III	V	VII	IX
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Mass Inguen Left					
Mass #1					
Not Ulcerated					
Incidence	0	1	0	0	0
Mean onset (Days)	-	88	-	-	-
Eye Observations					
Corneal Opacity					
Incidence	0	0	0	2	1
Mean onset (Days)	-	-	-	105	105
Exophthalmus					
Incidence	0	0	0	1	1
Mean onset (Days)	-	-	-	81	98
Enophthalmus/Partially Closed					
Incidence	0	0	0	1	1
Mean onset (Days)	-	-	-	74	98
Scab					
Head					
Incidence	0	0	1	0	0
Mean onset (Days)	-	-	84	-	-

TABLE 12 (CONTINUED)
SUMMARY OF CLINICAL OBSERVATIONS OF MALE RATS

Treatment Group	I 0 mg/kg/day	III 60 mg/kg/day Isopropanol	V 10 mg/kg/day	VII 60 mg/kg/day ^a	IX 300 mg/kg/day ^a
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
General Teeth Observations					
Broken					
Incidence	0	0	0	0	1
Mean onset (Days)	-	-	-	-	63
Discharge					
Eye					
Black					
Incidence	0	0	1	2	1
Mean onset (Days)	-	-	147	58	98
Nose					
Incidence	1	0	0	1	0
Mean onset (Days)	49	-	-	98	-
Mouth					
Incidence	0	0	0	0	1
Mean onset (Days)	-	-	-	-	84
Penis					
Red					
Incidence	1	0	0	0	0
Mean onset (Days)	98	-	-	-	-

TABLE 12 (CONTINUED)
SUMMARY OF CLINICAL OBSERVATIONS OF MALE RATS

Treatment Group	I 0 mg/kg/day	III 60 mg/kg/day Isopropanol	V 10 mg/kg/day	VII 60 mg/kg/day ^a	IX 300 mg/kg/day ^a
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Hair Loss					
Incidence	0	2	2	5 #	5 #
Mean onset (Days)	-	58	70	41	71
Wound					
Superficial					
Incidence	0	0	2	2	2
Mean onset (Days)	-	-	72	67	84
Hyperreactive					
Incidence	3	2	2	0	7
Mean onset (Days)	38	56	53	-	54
Aggressive Behavior					
Incidence	1	0	0	0	0
Mean onset (Days)	56	-	-	-	-
Misshapen Observations					
Ear					
Left					
Incidence	0	0	0	1	0
Mean onset (Days)	-	-	-	56	-

TABLE 12 (CONTINUED)
SUMMARY OF CLINICAL OBSERVATIONS OF MALE RATS

Treatment Group	I	III	V	VII	IX
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Protrusion Umbilical Hernia					
Incidence	1	0	0	0	0
Mean onset (Days)	49	-	-	-	-
Stain Fur/Skin					
Incidence	0	1	1	1	0
Mean onset (Days)	-	84	175	35	-
Swollen Observations Nose					
Incidence	0	0	0	1	0
Mean onset (Days)	-	-	-	66	-

Incidence - The number of animals for which an observation was recorded.

Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

a. H-24678 is [REDACTED]

Statistically significant difference at $p < 0.05$ by Cochran-Armitage trend test. Group III (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups I and III at $p < 0.05$ by Fisher's Exact test.

TABLE 13
SUMMARY OF CLINICAL OBSERVATIONS OF FEMALE RATS

Treatment Group	II 0 mg/kg/day	IV 60 mg/kg/day Isopropanol	VI 10 mg/kg/day	VIII 60 mg/kg/day ^a	X 300 mg/kg/day ^a
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Mass Perineum					
Mass #1					
Not Ulcerated					
Incidence	0	0	1	0	0
Mean onset (Days)	-	-	154	-	-
Eye Observations					
Dark					
Right					
Incidence	3	0	1	0	2
Mean onset (Days)	98	-	98	-	123
Pale					
Right					
Incidence	1	0	0	0	0
Mean onset (Days)	63	-	-	-	-
Corneal Opacity					
Incidence	5	0	1	3	0
Mean onset (Days)	81	-	126	98	-

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS OF FEMALE RATS

Treatment Group	II 0 mg/kg/day	IV 60 mg/kg/day Isopropanol	VI 10 mg/kg/day	VIII 60 mg/kg/day ^a	X 300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Exophthalmus					
Incidence	3	0	1	3	1
Mean onset (Days)	93	-	98	100	63
Enophthalmus/Partially Closed					
Incidence	2	0	1	2	1
Mean onset (Days)	140	-	113	97	126
Closed					
Incidence	0	0	1	1	1
Mean onset (Days)	-	-	147	35	70
Scab Head					
Incidence	0	0	0	0	1
Mean onset (Days)	-	-	-	-	84
General Teeth Observations					
Clipped					
Incidence	1	0	0	0	0
Mean onset (Days)	84	-	-	-	-

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS OF FEMALE RATS

Treatment Group		II	IV	VI	VIII	X
Dose		0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day ^a	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count		25	10	15	15	25
Discharge Eye	Incidence	2	1	1	3	0
	Mean onset (Days)	119	49	98	86	-
Nose Black	Incidence	0	0	0	0	1
	Mean onset (Days)	-	-	-	-	70
Hair Loss	Incidence	5	2	3	1	6
	Mean onset (Days)	73	46	58	60	58
Wound Superficial	Incidence	1	0	0	1	2
	Mean onset (Days)	70	-	-	62	82
Hyperreactive	Incidence	0	1	0	0	1
	Mean onset (Days)	-	84	-	-	21

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS OF FEMALE RATS

Treatment Group	II 0 mg/kg/day	IV 60 mg/kg/day Isopropanol	VI 10 mg/kg/day	VIII 60 mg/kg/day ^a	X 300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Hyperactive					
Incidence	1	3	0	1	4
Mean onset (Days)	56	63	-	77	61
Misshapen Observations					
Ear					
Right					
Incidence	0	0	1	0	0
Mean onset (Days)	-	-	28	-	-
Stain Fur/Skin					
Head					
Brown					
Incidence	1	0	0	0	0
Mean onset (Days)	182	-	-	-	-

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS OF FEMALE RATS

Treatment Group	II	IV	VI	VIII	X
Dose	0 mg/kg/day	60 mg/kg/day Isopropanol	10 mg/kg/day	60 mg/kg/day ^a	300 mg/kg/day ^a
Animal Count	25	10	15	15	25
Swollen Observations Face					
Incidence	2	0	1	0	0
Mean onset (Days)	106	-	105	-	-

Incidence - The number of animals for which an observation was recorded.

Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

a. H-24678 is

[REDACTED]

There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test. Group III (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences from control (Group II) at $p < 0.05$ by Fisher's exact test.

TABLE 14
SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII	IX
Dose	0 mg/kg/day	60 mg/kg/day	10 mg/kg/day ^a	60 mg/kg/day ^a	300 mg/kg/day ^a
Number of Rats Examined	19	10	10	10	19
Examination Day : Test Day 81					
Retina					
Retinal Degeneration Focal					
Left					
Incidence	1 (5%)	0	1 (10%)	0 (0%)	0 (0%)

Incidence - The number of animals (percent of animals examined) for which an observation was recorded.

a. H-24678 is [REDACTED]

There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test. Group III (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups I and III at $p < 0.05$ by Fisher's Exact test.

TABLE 15
SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	III	VI	VIII	X
Dose	0 mg/kg/day	60 mg/kg/day	10 mg/kg/day ^a	60 mg/kg/day ^a	300 mg/kg/day ^a
Number of Rats Examined	20	10	10	10	19
Examination Day : Test Day 81					
Retina					
Retinal Degeneration Focal					
Right					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

Incidence - The number of animals (percent of animals examined) for which an observation was recorded.

a. H-24678 is [REDACTED]
There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test. Group IV (isopropanol control) was excluded from trend comparisons.
There were no statistically significant differences between Groups II and IV at $p < 0.05$ by Fisher's Exact test.

TABLE 16

PERCENT SURVIVAL OF MALE RATS

Days on Test	Group I 0 mg/kg/day	Group III 60 mg/kg/day 10 Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
0	100	100	100	100	100
7	100	100	100	100	100
15	100	100	100	100	100
21	100	100	100	100	100
28	100	100	100	100	100
35	100	100	100	100	100
42	100	100	100	100	100
49	100	100	100	100	100
56	100	100	100	100	100
63	100	100	100	100	96
70	100	100	100	100	96
77	100	100	100	100	96
84	100	100	100	100	96
91 ^b	100	100	100	100	96
98 ^c	100	- ^c	100	100	93
105	100		100	100	93
113	100		100	100	93
119	100		100	100	93
Number at study start	25	10	15	15	25
Accidentally Killed	1	0	0	0	0
Found Dead	0	0	0	0	1
Sacrificed by design	9	10	10	10	10
Alive on test day 119	15	0	5	5	14

Percent Survival = (AE/Number of rats at risk)*100

Number of rats at risk = Number at study start - number of rats
accidentally killed - number sacrificed by design.

- a. H-24678 is [REDACTED]
b. Recovery period began on test day 91.
c. Rats designated for the 90-day exposure period were sacrificed on
test days 92. There were no rats designated for recovery in Group III.

There were no statistically significant decreases in survival at $p < 0.05$ by Cochran-Armitage trend test. Group III (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups I and III at $p < 0.05$ by Fisher's Exact test.

TABLE 17

PERCENT SURVIVAL OF FEMALE RATS

Days on Test	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
0	100	100	100	100	100
7	100	100	100	100	96
15	100	100	100	100	96
21	100	100	100	100	96
28	100	100	100	100	96
35	100	100	100	100	96
42	100	100	100	100	96
49	100	100	100	100	96
56	100	100	100	100	96
63	100	100	100	100	96
70	100	100	100	100	96
77	100	100	100	100	96
84	100	100	100	100	96
91 ^b	100	100	100	100	96
98 ^c	100	- ^c	100	100	93
105	100		100	100	93
113	100		100	100	93
119	100		100	100	93
Number at study start	25	10	15	15	25
Found Dead	0	0	0	0	1
Sacrificed by design	10	10	10	10	10
Alive on test day 119	15	0	5	5	14

Percent Survival = (AE/Number of rats at risk)*100

Number of rats at risk = Number at study start - number sacrificed by design.

- a. H-24678 is [REDACTED]
b. Recovery period began on test day 91.
c. Rats designated for the 90-day exposure period were sacrificed on test days 93.

There were no statistically significant decreases in survival at $p < 0.05$ by Cochran-Armitage trend test. Group IV (isopropanol control) was excluded from trend comparisons.

There were no statistically significant differences between Groups II and IV at $p < 0.05$ by Fisher's Exact test.

TABLE 18
MEAN FORELIMB AND HINDLIMB GRIP STRENGTH FOR MALE RATS
(MEAN OF THREE TRIALS)

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	I	0 (control)	0.64 (0.09)	0.28 (0.05)
	III	60 (Isopropanol)	0.62 (0.11)	0.31 (0.06)
	V	10 ^a	0.65 (0.13)	0.28 (0.09)
	VII	60 ^a	0.65 (0.13)	0.29 (0.09)
	IX	300 ^a	0.66 (0.07)	0.31 (0.08)
<u>Week 13</u>				
	I	0 (control)	1.31 (0.36)	0.43 (0.08)
	III	60 (Isopropanol)	1.43 (0.38)	0.50 (0.15)
	V	10 ^a	1.47 (0.17)	0.48 (0.09)
	VII	60 ^a	1.18 (0.18)	0.46 (0.10)
	IX	300 ^a	1.31 (0.33)	0.38 (0.09)

Data arranged as: Mean (Standard Deviation)

a. H-24678 is [REDACTED]

There were no statistically significant differences from control by one-way analysis of variance followed by Dunnett's test; $p < 0.05$.

TABLE 19

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH FOR FEMALE RATS
(MEAN OF THREE TRIALS)

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	II	0 (control)	0.59 (0.16)	0.29 (0.08)
	IV	60 (Isopropanol)	0.50 (0.15)	0.26 (0.08)
	VI	10 ^a	0.49 (0.11)	0.30 (0.06)
	VIII	60 ^a	0.64 (0.15)	0.28 (0.07)
	X	300 ^a	0.60 (0.11)	0.29 (0.08)
<u>Week 13</u>				
	II	0 (control)	1.15 (0.42)	0.46 (0.14)
	IV	60 (Isopropanol)	1.06 (0.21)	0.39 (0.06)
	VI	10 ^a	1.07 (0.22)	0.43 (0.04)
	VIII	60 ^a	1.10 (0.27)	0.47 (0.13)
	X	300 ^a	1.01 (0.29)	0.35 (0.06)

Data arranged as: Mean (Standard Deviation)

a. H-24678 is

There were no statistically significant differences from control by one-way analysis of variance followed by Dunnett's test; $p < 0.05$.

TABLE 20
SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS
FOR MALE RATS

Group:	Baseline					Week 13				
	I	III	V	VII	IX	I	III	V	VII	X
Dosage (mg/kg/day):	0	60	10 ^a	60 ^a	300 ^a	0	60	10 ^a	60 ^a	300 ^a
Number Examined:	10	10	10	10	10	10	10	10	10	9 ^b
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	9
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:										
no reaction	0	0	0	0	1	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	9	10	10	10	10	9
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
TAIL PINCH:										
no response	0	0	0	0	0	0	1	1	0	0
normal (turns toward site)	10	10	10	10	10	10	9	9	10	9
exaggerated response	0	0	0	0	0	0	0	0	0	0
IN MOTOR ACTIVITY MONITOR:										
DEFECATION:										
present	8	8	7	8	8	3	2	6	8	6
absent	2	2	3	2	2	7	8	4	2	3
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	9	9	8	8	10	9	10	10	10	8
absent	1	1	2	2	0	1	0	0	0	1
PUPILLARY RESPONSE:										
present	10	10	10	10	10	10	10	10	10	9
absent	0	0	0	0	0	0	0	0	0	0

- a. H-24678 is [REDACTED]
b. One rat died prior to the week 13 evaluation.

There were no statistically significant differences by Cochran-Armitage test for trend; $p < 0.05$.

TABLE 21
SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS
FOR FEMALE RATS

	Baseline					Week 13				
	II	IV	VI	VIII	X	II	IV	VI	VIII	X
Group:										
Dosage (mg/kg/day):	0	60	10 ^a	60 ^a	300 ^a	0	60	10 ^a	60 ^a	300 ^a
Number Examined:	10	10	10	10	10	10	10	10	10	9 ^b
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	9
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:										
no reaction	0	0	0	1	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	9	10	10	10	10	10	9
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
TAIL PINCH:										
no response	0	0	0	0	0	0	0	0	1	0
normal (turns toward site)	10	10	10	10	10	10	10	10	9	9
exaggerated response	0	0	0	0	0	0	0	0	0	0
IN MOTOR ACTIVITY MONITOR:										
DEFECATION:										
present	4	8	7	6	6	3	2	7	4	5
absent	6	2	3	4	4	7	8	3	6	4
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	8	9	7	8	8	9	10	10	10	9
absent	2	1	3	2	2	1	0	0	0	0
PUPILLARY RESPONSE:										
present	10	10	10	10	10	10	10	10	10	9
absent	0	0	0	0	0	0	0	0	0	0

a. H-24678 is [REDACTED]

b. One rat died prior to the week 13 evaluation.

There were no statistically significant differences by Cochran-Armitage test for trend; $p < 0.05$.

TABLE 22
MOTOR ACTIVITY ASSESSMENT:
MEAN DURATION OF MOVEMENTS (sec) FOR MALE RATS

ASSESSMENT PERIOD	GROUP	N	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
				1	2	3	4	5	6	TOTAL
<u>BASELINE</u>	I	10	0 (control)	399(61)	347(50)	262(69)	152(117)	124(134)	27(47)	1311(337)
	III	10	60 (Isopropanol)	407(43)	326(49)	258(86)	135(133)	51(85)	28(60)	1204(328)
	V	10	10 ^a	397(78)	294(82)	210(110)	124(106)	91(104)	42(68)	1158(305)
	VII	10	60 ^a	408(62)	353(53)	255(89)	130(145)	102(93)	32(50)	1280(356)
	IX	10	300 ^a	395(28)	306(53)	268(109)	135(121)	55(63)	31(55)	1191(313)
<u>WEEK 13</u>	I	10	0 (control)	419(55)	323(111)	322(80)	271(97)	190(116)	158(127)	1683(528)
	III	10	60 (Isopropanol)	408(36)	334(55)	295(52)	259(61)	215(92)	177(104)	1688(292)
	V	10	10 ^a	385(36)	304(40)	261(104)	200(69)	207(74)	175(105)	1532(223)
	VII	10	60 ^a	415(36)	337(37)	314(50)	251(112)	217(113)	149(98)	1682(350)
	IX	9 ^b	300 ^a	395(44)	331(49)	318(53)	239(91)	192(120)	129(110)	1605(361)

Data arranged as: Mean (Standard Deviation).

- a. H-24678 is [REDACTED]
b. One rat died prior to the week 13 evaluation.

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control; $p < 0.05$.

TABLE 23
MOTOR ACTIVITY ASSESSMENT:
MEAN DURATION OF MOVEMENTS (sec) FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	N	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
				1	2	3	4	5	6	TOTAL
BASELINE										
II	10	10	0 (control)	386(34)	262(68)	232(76)	197(59)	153(97)	142(121)	1372(240)
IV	10	10	60 (Isopropanol)	363(64)	291(92)	270(100)	229(112)	228(119)	216(123)	1597(539)
VI	10	10	10 ^a	384(42)	293(71)	249(81)	233(85)	184(82)	150(109)	1493(282)
VIII	10	10	60 ^a	377(69)	280(111)	257(141)	239(84)	180(94)	131(103)	1463(445)
X	10	10	300 ^a	376(73)	307(77)	229(93)	242(91)	177(80)	131(90)	1462(393)
WEEK 13										
II	10	10	0 (control)	402(38)	307(61)	244(55)	226(31)	210(97)	157(62)	1545(214)
IV	10	10	60 (Isopropanol)	431(74)	356(113)	273(148)	239(140)	245(163)	219(99)	1763(646)
VI	10	10	10 ^a	411(43)	338(54)	271(62)	220(98)	164(101)	139(132)	1542(388)
VIII	10	10	60 ^a	394(64)	320(93)	279(103)	262(129)	218(127)	170(115)	1642(530)
X	9 ^b	9 ^b	300 ^a	389(75)	302(109)	250(126)	190(128)	165(151)	124(155)	1419(681)

Data arranged as: Mean (Standard Deviation).

a. H-24678 is

b. One rat died prior to the week 13 evaluation.

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control; $p < 0.05$.

TABLE 24
MOTOR ACTIVITY ASSESSMENT:
MEAN NUMBER OF MOVEMENTS FOR MALE RATS

ASSESSMENT PERIOD	GROUP	N	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
				1	2	3	4	5	6
BASELINE									
I	10	0 (control)	128(18)	136(10)	134(30)	91(53)	74(55)	21(25)	TOTAL 583(119)
III	10	60 (Isopropanol)	135(12)	141(16)	133(32)	79(66)	38(51)	20(40)	546(169)
V	10	10 ^a	118(31)	120(28)	100(49)	76(61)	49(50)	31(44)	493(204)
VII	10	60 ^a	127(20)	139(12)	130(18)	67(68)	65(54)	23(24)	551(140)
IX	10	300 ^a	138(13)	138(20)	127(26)	84(63)	44(49)	26(40)	559(151)
WEEK 13									
I	10	0 (control)	133(25)	130(22)	139(21)	126(17)	100(51)	80(54)	TOTAL 709(108)
III	10	60 (Isopropanol)	140(11)	137(17)	136(19)	127(28)	112(42)	105(46)	756(118)
V	10	10 ^a	132(6)	127(17)	120(43)	106(30)	110(33)	99(57)	695(117)
VII	10	60 ^a	131(16)	137(19)	139(18)	125(40)	115(52)	89(57)	735(150)
IX	9 ^b	300 ^a	134(16)	135(19)	136(20)	115(44)	88(56)	82(58)	690(125)

Data arranged as: Mean (Standard Deviation).

a. H-24678 is [REDACTED]

b. One rat died prior to the week 13 evaluation.

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control; $p < 0.05$.

TABLE 25
MOTOR ACTIVITY ASSESSMENT:
MEAN NUMBER OF MOVEMENTS FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	N	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
				1	2	3	4	5	6	TOTAL
BASELINE										
II	10	10	0 (control)	135(16)	132(20)	123(26)	125(37)	93(50)	82(52)	691(101)
IV	10	10	60 (Isopropanol)	128(16)	123(19)	125(33)	118(15)	111(39)	112(43)	715(72)
VI	10	10	10 ^a	135(18)	131(19)	122(26)	121(36)	111(34)	101(51)	721(114)
VIII	10	10	60 ^a	133(17)	131(32)	109(44)	135(19)	114(51)	84(49)	706(131)
X	10	10	300 ^a	119(21)	117(27)	105(27)	111(24)	103(30)	80(52)	636(132)
WEEK 13										
II	10	10	0 (control)	132(10)	133(15)	131(18)	133(14)	122(37)	99(26)	749(77)
IV	10	10	60 (Isopropanol)	127(23)	129(27)	122(38)	111(46)	114(50)	119(27)	723(109)
VI	10	10	10 ^a	132(9)	138(9)	136(21)	126(45)	100(41)	87(62)	718(129)
VIII	10	10	60 ^a	136(14)	123(17)	127(39)	113(41)	103(44)	108(42)	709(125)
X	9 ^b	9 ^b	300 ^a	130(32)	131(34)	127(30)	116(25)	101(50)	80(48)	686(138)

Data arranged as: Mean (Standard Deviation).

a. H-24678 is [REDACTED]

b. One rat died prior to the week 13 evaluation.

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test were used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control; $p < 0.05$.

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
RBC (x10 ⁶ /μL)					
DAY 38	8.07 0.46(7)	8.39 0.35(8)	8.14 0.37(10)	7.97 0.18(10)	7.75 0.47(9)
DAY 92	8.41 0.38(9)	8.51 0.70(10) _b	8.29 0.43(10) _b	8.18 0.34(10) _b	7.90 0.43(10)
DAY 122	8.94 0.31(10)				8.09* 0.46(8)
DAY 183	8.87 0.32(4)	_b	8.61 0.29(5)	8.34 0.49(5)	8.64 0.21(4)
HGB (g/dL)					
DAY 38	15.2 0.7(7)	15.3 0.4(8)	15.0 0.5(10)	14.8 0.4(10)	14.2* 0.6(9)
DAY 92	15.2 0.4(9)	15.0 1.1(10) _b	14.5 0.5(10) _b	14.4@ 0.4(10) _b	13.8@ 0.5(10)
DAY 122	15.5 0.6(10)				14.5* 0.7(8)
DAY 183	15.6 0.3(4)	_b	15.1 0.5(5)	14.7 0.7(5)	14.4* 0.7(4)
HCT (%)					
DAY 38	47.6 2.4(7)	48.5 2.1(8)	47.4 1.9(10)	46.6 0.9(10)	44.7* 1.8(9)
DAY 92	47.4 1.8(9)	47.1 2.9(10) _b	45.7 1.8(10) _b	45.0* 1.3(10) _b	43.0* 2.0(10)
DAY 122	47.6 1.6(10)				44.5* 1.9(8)
DAY 183	48.4 1.0(4)	_b	47.6 1.3(5)	45.5* 2.2(5)	45.1* 1.3(4)
MCV (fl)					
DAY 38	59.0 1.5(7)	57.8 0.7(8)	58.4 2.0(10)	58.4 0.8(10)	57.7 2.1(9)
DAY 92	56.4 1.1(9)	55.5 2.0(10) _b	55.2 1.6(10) _b	55.1 1.3(10) _b	54.4* 1.8(10)
DAY 122	53.2 0.7(10)				55.1* 1.7(8)
DAY 183	54.6 1.0(4)	_b	55.3 1.4(5)	54.6 0.9(5)	52.2 1.3(4)

TABLE 26 (Continued)
SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
MCH (pg)					
DAY 38	18.8 0.4(7)	18.2 0.3(8)	18.4 0.6(10)	18.5 0.4(10)	18.3 0.6(9)
DAY 92	18.1 0.5(9)	17.7 0.4(10) _b	17.6 0.7(10) _b	17.6 0.5(10) _b	17.4 0.7(10)
DAY 122	17.3 0.5(10)				17.9* 0.5(8)
DAY 183	17.6 0.5(4)	_b	17.6 0.4(5)	17.6 0.4(5)	16.7* 0.6(4)
MCHC (g/dL)					
DAY 38	31.8 0.5(7)	31.5 0.6(8)	31.6 0.6(10)	31.7 0.5(10)	31.8 0.4(9)
DAY 92	32.1 0.5(9)	31.9 0.6(10) _b	31.8 0.6(10) _b	32.0 0.4(10) _b	32.0 0.7(10)
DAY 122	32.5 0.7(10)				32.6 0.6(8)
DAY 183	32.3 0.6(4)	_b	31.8 0.6(5)	32.2 0.5(5)	32.0 0.5(4)
RDW (%)					
DAY 38	11.3 0.4(7)	11.4 0.8(8)	11.5 0.3(10)	11.5 0.6(10)	11.6 0.5(9)
DAY 92	13.0 0.8(9)	13.0 1.3(10) _b	12.9 0.5(10) _b	12.5 0.8(10) _b	13.5 0.8(10)
DAY 122	13.5 0.8(10)				13.4 0.4(8)
DAY 183	12.9 0.8(4)	_b	13.5 0.5(5)	13.8 1.0(5)	13.9 0.4(4)
ARET (x10 ³ /μL)					
DAY 38	186 13(7)	189 41(8)	198 37(10)	182 31(10)	196 27(9)
DAY 92	189 23(9)	194 44(10) _b	180 34(10) _b	169 14(10) _b	175 27(10)
DAY 122	183 28(10)				190 26(8)
DAY 183	156 52(4)	_b	186 14(5)	201 31(5)	193 38(4)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
PLT (x10 ³ /μL)					
DAY 38	1173 69(7)	1184 149(6)	1122 100(9)	1209 102(10)	1313 127(7)
DAY 92	1155 62(9)	1110 141(9) _b	1092 117(10) _b	1186 106(10) _b	1242 138(9)
DAY 122	1048 134(10)				1101 140(8)
DAY 183	1001 169(3)	_b	1085 219(5)	1011 126(4)	933 148(3)
WBC (x10 ³ /μL)					
DAY 38	15.86 3.41(7)	15.04 3.79(8)	16.37 2.84(10)	14.24 2.84(10)	16.98 1.39(9)
DAY 92	12.76 2.71(9)	13.11 3.54(10) _b	12.90 2.41(10) _b	12.23 2.69(10) _b	13.77 1.57(10)
DAY 122	10.75 2.73(10)				11.50 2.80(8)
DAY 183	11.63 3.15(4)	_b	11.36 2.29(5)	11.75 2.78(5)	11.25 2.65(4)
ANEU (x10 ³ /μL)					
DAY 38	1.42 0.27(7)	1.65 0.48(8)	1.81 0.70(10)	1.78 0.40(10)	1.97 0.45(9)
DAY 92	1.63 0.46(9)	2.18 1.42(10) _b	2.37 1.03(10) _b	2.23 0.82(10) _b	2.17 0.56(10)
DAY 122	2.08 0.43(10)				2.11 0.56(8)
DAY 183	1.63 0.45(4)	_b	1.79 1.16(5)	2.43 1.14(5)	2.23 1.08(4)
ALYM (x10 ³ /μL)					
DAY 38	13.60 3.35(7)	12.58 3.32(8)	13.61 2.33(10)	11.57 2.47(10)	13.96 1.66(9)
DAY 92	10.48 2.47(9)	10.11 2.43(10) _b	9.93 2.21(10) _b	9.36 2.10(10) _b	10.89 1.30(10)
DAY 122	8.05 2.36(10)				8.80 2.25(8)
DAY 183	9.42 2.83(4)	_b	9.04 1.63(5)	8.65 1.68(5)	8.42 3.03(4)

Company Sanitized. Does not contain TSCA CBI

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
AMON (x10 ³ /μL)					
DAY 38	0.47 0.11(7)	0.53 0.18(8)	0.54 0.13(10)	0.50 0.18(10)	0.63 0.21(9)
DAY 92	0.23 0.08(9)	0.37 0.20(10) ^b	0.26 0.11(10) ^b	0.29 0.10(10) ^b	0.33 0.08(10)
DAY 122	0.30 0.11(10)				0.28 0.08(8)
DAY 183	0.29 0.16(4)	^b	0.21 0.07(5)	0.31 0.13(5)	0.33 0.12(4)
AEOS (x10 ³ /μL)					
DAY 38	0.15 0.06(7)	0.13 0.08(8)	0.18 0.13(10)	0.19 0.08(10)	0.22 0.13(9)
DAY 92	0.14 0.07(9)	0.14 0.06(10) ^b	0.11 0.06(10) ^b	0.16 0.06(10) ^b	0.17 0.13(10)
DAY 122	0.13 0.04(10)				0.12 0.06(8)
DAY 183	0.13 0.06(4)	^b	0.16 0.07(5)	0.18 0.15(5)	0.10 0.01(4)
ABAS (x10 ³ /μL)					
DAY 38	0.12 0.03(7)	0.08 0.04(8)	0.13 0.05(10)	0.09 0.05(10)	0.11 0.05(9)
DAY 92	0.16 0.07(9)	0.16 0.08(10) ^b	0.10 0.06(10) ^b	0.08* 0.04(10) ^b	0.09 0.04(10)
DAY 122	0.11 0.07(10)				0.09 0.04(8)
DAY 183	0.09 0.04(4)	^b	0.07 0.03(5)	0.09 0.02(5)	0.07 0.04(4)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
ALUC (x10 ³ /μL)					
DAY 38	0.09 0.02(7)	0.08 0.05(8)	0.10 0.04(10)	0.12 0.11(10)	0.10 0.02(9)
DAY 92	0.13 0.06(9)	0.16 0.09(10) _b	0.12 0.06(10) _b	0.10 0.04(10) _b	0.12 0.05(10)
DAY 122	0.08 0.03(10)				0.09 0.03(8)
DAY 183	0.08 0.04(4)	_b	0.09 0.02(5)	0.08 0.02(5)	0.09 0.02(4)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 27

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
RBC (x10 ⁶ /μL)					
DAY 39	8.29 0.28(10)	8.23 0.29(10)	8.10 0.34(9)	7.95 0.31(10)	8.09 0.61(10)
DAY 93	8.24 0.45(10)	8.20 0.49(10) _b	8.14 0.36(10) _b	8.06 0.30(10) _b	7.84 0.52(10)
DAY 122	7.94 0.49(8)				8.01 0.29(9)
DAY 183	8.48 0.28(4)	_b	7.96 0.22(3)	8.11 0.36(4)	8.38 0.46(5)
HGB (g/dL)					
DAY 39	15.4 0.5(10)	15.3 0.4(10)	15.0 0.4(9)	15.0 0.6(10)	15.2 0.9(10)
DAY 93	15.4 0.8(10)	15.2 0.8(10) _b	15.1 0.5(10) _b	15.2 0.5(10) _b	14.8 0.7(10)
DAY 122	15.1 0.7(8)				15.2 0.5(9)
DAY 183	15.8 0.4(4)	_b	14.7* 0.6(3)	15.7 0.2(4)	15.4 0.6(5)
HCT (%)					
DAY 39	48.1 2.3(10)	47.3 1.5(10)	47.0 1.3(9)	46.5 2.0(10)	47.1 2.9(10)
DAY 93	46.9 2.5(10)	46.4 2.7(10) _b	46.3 1.9(10) _b	46.2 1.4(10) _b	45.0 2.6(10)
DAY 122	45.3 2.4(8)				45.7 1.7(9)
DAY 183	48.6 1.5(4)	_b	45.4* 1.4(3)	47.9 1.8(4)	47.3 1.4(5)
MCV (fl)					
DAY 39	58.0 1.4(10)	57.6 1.0(10)	58.0 1.1(9)	58.5 1.2(10)	58.2 1.3(10)
DAY 93	57.0 1.6(10)	56.6 0.9(10) _b	56.9 0.7(10) _b	57.4 1.5(10) _b	57.5 1.2(10)
DAY 122	57.1 1.5(8)				57.1 1.3(9)
DAY 183	57.3 1.5(4)	_b	57.0 0.2(3)	59.2 1.4(4)	56.5 1.8(5)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
MCH (pg)					
DAY 39	18.6 0.4(10)	18.6 0.4(10)	18.5 0.4(9)	18.8 0.5(10)	18.9 0.7(10)
DAY 93	18.7 0.5(10)	18.5 0.5(10) _b	18.6 0.4(10) _b	18.8 0.6(10) _b	18.9 0.5(10)
DAY 122	19.0 0.6(8)				18.9 0.5(9)
DAY 183	18.7 0.4(4)	_b	18.5 0.3(3)	19.4 0.7(4)	18.5 0.8(5)
MCHC (g/dL)					
DAY 39	32.1 0.5(10)	32.3 0.3(10)	31.9 0.4(9)	32.2 0.4(10)	32.4 0.5(10)
DAY 93	32.8 0.5(10)	32.7 0.5(10) _b	32.7 0.4(10) _b	32.8 0.5(10) _b	32.8 0.4(10)
DAY 122	33.2 0.8(8)				33.2 0.6(9)
DAY 183	32.6 0.7(4)	_b	32.5 0.4(3)	32.7 0.9(4)	32.6 0.6(5)
RDW (%)					
DAY 39	11.1 0.5(10)	10.9 0.3(10)	11.2 0.2(9)	11.2 0.3(10)	11.0 0.3(10)
DAY 93	11.4 0.6(10)	11.2 0.4(10) _b	11.3 0.4(10) _b	11.4 0.3(10) _b	11.2 0.3(10)
DAY 122	12.1 0.6(8)				11.9 0.6(9)
DAY 183	11.6 0.3(4)	_b	11.9 0.4(3)	11.9 1.0(4)	11.6 0.2(5)
ARET (x10 ³ /μL)					
DAY 39	192 36(10)	188 20(10)	183 21(9)	193 32(10)	198 27(10)
DAY 93	163 42(10)	138 17(10) _b	145 24(10) _b	160 40(10) _b	177 30(10)
DAY 122	151 22(8)				171 22(9)
DAY 183	144 23(4)	_b	154 30(3)	162 8(4)	150 22(5)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
PLT (x10 ³ /μL)					
DAY 39	1122 102(8)	1156 151(9)	1135 167(9)	1145 135(8)	1030 149(8)
DAY 93	1100 67(8)	1047 126(8) _b	1065 176(9) _b	1102 89(9) _b	960 105(8)
DAY 122	958 94(8)				1061 126(9)
DAY 183	815 160(4)	_b	879 281(3)	807 237(4)	984 119(4)
WBC (x10 ³ /μL)					
DAY 39	10.80 2.67(10)	11.84 2.60(10)	11.08 1.77(9)	12.66 4.24(10)	13.00 1.99(10)
DAY 93	8.90 1.50(10)	8.89 1.34(10) _b	9.32 2.20(10) _b	9.14 2.62(10) _b	9.64 1.98(10)
DAY 122	8.15 1.96(8)				9.83 1.52(9)
DAY 183	7.35 0.99(4)	_b	9.26 3.70(3)	7.17 2.35(4)	8.28 1.70(5)
ANEU (x10 ³ /μL)					
DAY 39	0.80 0.31(10)	1.41* 0.55(10)	1.21 0.51(9)	1.35 0.57(10)	1.52* 0.49(10)
DAY 93	1.22 0.49(10)	0.97 0.37(10) _b	1.04 0.43(10) _b	1.20 0.47(10) _b	1.53 0.64(10)
DAY 122	1.33 0.73(8)				1.47 0.34(9)
DAY 183	1.32 0.52(4)	_b	2.37 1.86(3)	1.41 0.83(4)	1.33 0.48(5)
ALYM (x10 ³ /μL)					
DAY 39	9.51 2.49(10)	9.81 2.08(10)	9.12 1.64(9)	10.64 3.78(10)	10.76 1.98(10)
DAY 93	7.16 1.09(10)	7.37 1.37(10) _b	7.65 2.05(10) _b	7.32 2.55(10) _b	7.64 1.38(10)
DAY 122	6.29 1.46(8)				7.77* 1.18(9)
DAY 183	5.55 0.69(4)	_b	5.88 1.25(3)	5.28 1.56(4)	6.44 1.24(5)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
AMON (x10 ³ /μL)					
DAY 39	0.22 0.09(10)	0.29 0.07(10)	0.39 0.34(9)	0.28 0.10(10)	0.30 0.07(10)
DAY 93	0.18 0.05(10)	0.19 0.04(10) b	0.23 0.07(10) b	0.18 0.05(10) b	0.18 0.10(10)
DAY 122	0.26 0.12(8)				0.28 0.06(9)
DAY 183	0.24 0.08(4)	b	0.66 0.60(3)	0.24 0.13(4)	0.25 0.10(5)
AEOS (x10 ³ /μL)					
DAY 39	0.12 0.10(10)	0.13 0.04(10)	0.12 0.05(9)	0.17 0.07(10)	0.18 0.13(10)
DAY 93	0.13 0.07(10)	0.13 0.03(10) b	0.15 0.08(10) b	0.15 0.04(10) b	0.12 0.06(10)
DAY 122	0.11 0.03(8)				0.16* 0.04(9)
DAY 183	0.13 0.03(4)	b	0.15 0.08(3)	0.14 0.08(4)	0.14 0.06(5)
ABAS (x10 ³ /μL)					
DAY 39	0.07 0.06(10)	0.09 0.05(10)	0.10 0.04(9)	0.10 0.04(10)	0.11 0.06(10)
DAY 93	0.11 0.05(10)	0.11 0.04(10) b	0.13 0.06(10) b	0.15 0.06(10) b	0.09 0.06(10)
DAY 122	0.09 0.07(8)				0.08 0.03(9)
DAY 183	0.07 0.03(4)	b	0.09 0.04(3)	0.05 0.01(4)	0.06 0.03(5)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
ALUC ($\times 10^3/\mu\text{L}$)					
DAY 39	0.09 0.06(10)	0.12 0.05(10)	0.13 0.06(9)	0.12 0.04(10)	0.13 0.06(10)
DAY 93	0.09 0.03(10)	0.12 0.09(10)	0.12 0.02(10)	0.14 0.08(10)	0.09 0.06(10)
DAY 122	0.07 0.02(8)	^b	^b	^b	0.07 0.03(9)
DAY 183	0.05 0.01(4)	^b	0.11 0.07(3)	0.06 0.02(4)	0.05 0.02(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).

TABLE 28

SUMMARY OF COAGULATION VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
PT (seconds) DAY 92	15.1 0.6(9)	15.0 0.8(10)	15.1 0.4(10)	14.9 0.5(10)	15.1 1.0(10)
APTT (seconds) DAY 92	19.0 1.2(9)	19.4 1.7(10)	19.0 2.1(10)	18.2 1.7(10)	17.6 2.7(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a. H-24678 is [REDACTED]

There were no statistically significant differences from control at $p < 0.05$ by parametric (Dunnett/Tamhane-Dunnett) and non-parametric (Dunn's) tests.

TABLE 29

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
PT (seconds) DAY 93	14.3 0.5(10)	14.0 0.5(10)	14.2 0.6(10)	14.6 0.7(10)	13.8 0.5(10)
APTT (seconds) DAY 93	16.8 1.6(10)	17.2 1.4(10)	17.3 1.6(10)	16.3 1.5(10)	16.3 2.1(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a. H-24678 is [REDACTED]

There were no statistically significant differences from control at $p < 0.05$ by parametric (Dunnett/Tamhane-Dunnett) and non-parametric (Dunn's) tests.

TABLE 30

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
AST (U/L)					
DAY 38	86 18(9)	90 21(10)	90 15(10)	138@ 50(10)	142@ 35(10)
DAY 92	74 9(9)	75 7(10) _b	128@ 82(10) _b	327@ 164(10) _b	148@ 50(10)
DAY 122	89 13(10)				178@ 142(9)
DAY 183	95 23(5)	_b	110 60(5)	137 12(5)	416 414(5)
ALT (U/L)					
DAY 38	31 5(9)	34 4(10)	34 8(10)	94@ 44(10)	109@ 34(10)
DAY 92	29 5(9)	31 6(10) _b	88@ 93(10) _b	291@ 166(10) _b	133@ 60(10)
DAY 122	37 9(10)				121@ 123(9)
DAY 183	38 6(5)	_b	57 38(5)	76 25(5)	312@ 371(5)
SDH (U/L)					
DAY 38	20.8 7.3(9)	19.2 5.3(10)	20.7 9.9(10)	26.4 6.9(10)	29.5 7.6(10)
DAY 92	21.8 5.5(9)	19.2 3.2(10) _b	32.1 30.4(10) _b	58.7 30.5(10) _b	34.3 13.6(10)
DAY 122	14.8 2.0(10)				20.1 12.9(9)
DAY 183	12.7 5.2(5)	_b	16.2 10.3(5)	17.8 4.8(5)	55.5 58.8(5)
ALKP (U/L)					
DAY 38	134 31(9)	144 31(10)	139 25(10)	174* 35(10)	222* 36(10)
DAY 92	85 19(9)	98 28(10) _b	100 22(10) _b	178* 48(10) _b	228* 44(10)
DAY 122	87 35(10)				105 27(9)
DAY 183	81 14(5)	_b	101 24(5)	99 15(5)	105 21(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
BILI (mg/dL)					
DAY 38	0.10 0.04(9)	0.09 0.03(10)	0.10 0.04(10)	0.09 0.04(10)	0.10 0.03(10)
DAY 92	0.11 0.04(9)	0.11 0.02(10) _b	0.12 0.03(10) _b	0.11 0.04(10) _b	0.11 0.04(10)
DAY 122	0.10 0.04(10)				0.08 0.04(9)
DAY 183	0.14 0.05(5)	_b	0.11 0.06(5)	0.11 0.04(5)	0.10 0.03(5)
BUN (mg/dL)					
DAY 38	15 1(9)	15 2(10)	14 2(10)	13 1(10)	16 3(10)
DAY 92	15 2(9)	16 2(10) _b	14 2(10) _b	15 2(10) _b	16 2(10)
DAY 122	16 2(10)				15 1(9)
DAY 183	15 1(5)	_b	15 0(5)	21 15(5)	15 3(5)
CREA (mg/dL)					
DAY 38	0.42 0.05(9)	0.41 0.05(10)	0.38 0.08(10)	0.37 0.04(10)	0.40 0.05(10)
DAY 92	0.42 0.05(9)	0.35* 0.05(10) _b	0.32* 0.05(10) _b	0.32* 0.04(10) _b	0.32* 0.06(10)
DAY 122	0.49 0.03(10)				0.43* 0.05(9)
DAY 183	0.44 0.06(5)	_b	0.43 0.03(5)	0.49 0.19(5)	0.38 0.05(5)
CHOL (mg/dL)					
DAY 38	70 10(9)	59 8(10)	65 11(10)	58 12(10)	61 14(10)
DAY 92	86 18(9)	71 12(10) _b	69 16(10) _b	60* 11(10) _b	59* 17(10)
DAY 122	76 16(10)				63 12(9)
DAY 183	67 14(5)	_b	95* 15(5)	117 51(5)	63 13(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
TRIG (mg/dL)					
DAY 38	66 24(9)	62 26(10)	76 41(10)	77 39(10)	58 29(10)
DAY 92	79 27(9)	73 27(10) _b	79 30(10) _b	68 30(10) _b	63 33(10)
DAY 122	82 36(10)				62 28(9)
DAY 183	60 14(5)	_b	86 32(5)	100 70(5)	69 30(5)
GLUC (mg/dL)					
DAY 38	104 18(9)	109 23(10)	100 19(10)	101 10(10)	107 10(10)
DAY 92	102 15(9)	99 6(10) _b	109 17(10) _b	102 7(10) _b	109@ 7(10)
DAY 122	101 4(10)				107 17(9)
DAY 183	105 12(5)	_b	109 11(5)	110 18(5)	110 13(5)
TP (g/dL)					
DAY 38	6.6 0.4(9)	6.7 0.4(10)	6.5 0.2(10)	6.2 0.3(10)	6.4 0.3(10)
DAY 92	7.1 0.3(9)	7.1 0.3(10) _b	6.6* 0.2(10) _b	6.6* 0.3(10) _b	6.7* 0.3(10)
DAY 122	7.3 0.2(10)				7.0* 0.2(9)
DAY 183	7.3 0.3(5)	_b	7.0 0.3(5)	6.9 0.4(5)	7.1 0.2(5)
ALB (g/dL)					
DAY 38	4.1 0.3(9)	4.3 0.2(10)	4.0 0.1(10)	3.9* 0.2(10)	4.1 0.2(10)
DAY 92	4.3 0.1(9)	4.3 0.2(10) _b	3.9* 0.2(10) _b	4.1* 0.2(10) _b	4.3 0.1(10)
DAY 122	4.3 0.1(10)				4.3 0.1(9)
DAY 183	4.4 0.2(5)	_b	4.3 0.3(5)	4.0* 0.3(5)	4.2 0.2(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
GLOB (g/dL)					
DAY 38	2.4 0.2(9)	2.5 0.3(10)	2.4 0.2(10)	2.3 0.2(10)	2.3 0.2(10)
DAY 92	2.8 0.3(9)	2.8 0.3(10) _b	2.7 0.1(10) _b	2.5* 0.2(10) _b	2.4* 0.2(10)
DAY 122	3.0 0.2(10)				2.7* 0.2(9)
DAY 183	2.9 0.2(5)	_b	2.7 0.2(5)	2.9 0.3(5)	2.9 0.3(5)
CALC (mg/dL)					
DAY 38	10.7 0.4(9)	10.8 0.3(10)	10.6 0.3(10)	10.3@ 0.3(10)	10.5 0.3(10)
DAY 92	10.8 0.2(9)	10.7 0.1(10) _b	10.4* 0.2(10) _b	10.3* 0.2(10) _b	10.5* 0.3(10)
DAY 122	10.5 0.3(10)				10.3 0.2(9)
DAY 183	11.1 0.4(5)	_b	11.0 0.2(5)	10.8 0.5(5)	10.9 0.4(5)
IPHS (mg/dL)					
DAY 38	9.3 1.1(9)	9.2 1.0(10)	8.6 1.1(10)	9.2 1.1(10)	10.0 1.0(10)
DAY 92	7.5 0.8(9)	7.2 0.3(10) _b	7.3 0.4(10) _b	7.7 0.5(10) _b	8.3 0.2(10)
DAY 122	7.9 0.8(10)				8.3 0.7(9)
DAY 183	7.1 1.1(5)	_b	6.8 0.5(5)	6.9 0.4(5)	7.8 1.2(5)
NA (mmol/L)					
DAY 38	144.7 1.7(9)	144.9 1.7(10)	146.4* 0.7(10)	144.9 1.5(10)	145.1 1.4(10)
DAY 92	148.7 1.5(9)	148.2 1.7(10) _b	147.8 1.2(10) _b	147.8 1.3(10) _b	147.4 0.7(10)
DAY 122	147.2 1.1(10)				147.3 1.3(9)
DAY 183	145.9 1.4(5)	_b	145.7 0.5(5)	146.0 0.8(5)	144.1 1.7(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
K (mmol/L)					
DAY 38	5.99 0.41(9)	5.97 0.50(10)	5.85 0.35(10)	6.05 0.43(10)	6.58 0.72(10)
DAY 92	6.25 0.47(9)	5.96 0.28(10) _b	5.86 0.34(10) _b	6.05 0.27(10) _b	6.07 0.43(10)
DAY 122	6.19 0.38(10)				6.14 0.33(9)
DAY 183	6.13 0.16(5)	_b	6.08 0.20(5)	5.86 0.31(5)	6.36 0.77(5)
CL (mmol/L)					
DAY 38	101.0 1.1(9)	100.5 2.0(10)	101.8 1.5(10)	102.0 1.1(10)	102.1 1.4(10)
DAY 92	100.7 1.5(9)	101.2 1.6(10) _b	102.6 1.3(10) _b	103.9@ 1.4(10) _b	102.9@ 1.3(10)
DAY 122	101.3 1.9(10)				102.8 1.4(9)
DAY 183	100.3 1.4(5)	_b	99.9 1.3(5)	100.3 2.2(5)	98.8 1.8(5)
PFLU (µg/mL)					
DAY 92	0.1 0.0(9)	0.1 0.0(10) _b	0.1 0.0(10) _b	0.1 0.0(10) _b	0.2@ 0.1(10)
DAY 122	0.1 0.0(10)				0.1 0.0(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 31

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
AST (U/L)					
DAY 39	89 13(10)	82 9(10)	95 41(10)	81 17(10)	123 132(10)
DAY 93	81 9(10)	81 12(10) _b	95 17(10) _b	78 8(10) _b	114 57(10)
DAY 122	80 29(9)				123 80(9)
DAY 183	215 166(4)	_b	315 343(4)	130 41(4)	92 19(5)
ALT (U/L)					
DAY 39	34 5(10)	29 3(10)	37 19(10)	30 5(10)	45 36(10)
DAY 93	33 5(10)	37 8(10) _b	42 18(10) _b	34 7(10) _b	55 32(10)
DAY 122	36 15(9)				68@ 58(9)
DAY 183	78 24(4)	_b	205 272(4)	70 28(4)	45 7(5)
SDH (U/L)					
DAY 39	19.1 3.6(10)	17.1 3.4(10)	19.3 8.1(10)	15.2@ 3.1(10)	26.8 35.0(10)
DAY 93	14.8 2.9(10)	15.5 3.9(10) _b	17.3 5.9(10) _b	13.9 2.8(10) _b	21.5 10.1(10)
DAY 122	14.1 3.9(9)				19.7 11.2(9)
DAY 183	28.4 11.0(4)	_b	65.6 84.3(4)	23.9 9.7(4)	13.8@ 2.6(5)
ALKP (U/L)					
DAY 39	92 23(10)	88 18(10)	83 15(10)	78 13(10)	72 22(10)
DAY 93	56 14(10)	47 13(10) _b	46 10(10) _b	43 7(10) _b	45 15(10)
DAY 122	33 4(9)				46 18(9)
DAY 183	58 16(4)	_b	35 19(4)	38 6(4)	34 13(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
BILI (mg/dL)					
DAY 39	0.16 0.03(10)	0.16 0.04(10)	0.14 0.03(10)	0.11@ 0.06(10)	0.10@ 0.05(10)
DAY 93	0.15 0.05(10)	0.15 0.04(10)	0.12 0.03(10)	0.13 0.03(10)	0.11@ 0.03(10)
DAY 122	0.12 0.03(9)	^b	^b	^b	0.10 0.04(9)
DAY 183	0.14 0.02(4)	^b	0.18 0.02(4)	0.12 0.07(4)	0.12 0.04(5)
BUN (mg/dL)					
DAY 39	18 2(10)	16 2(10)	17 3(10)	16 1(10)	16 3(10)
DAY 93	19 1(10)	17 2(10)	19 2(10)	16@ 2(10)	17 4(10)
DAY 122	16 3(9)	^b	^b	^b	19@ 4(9)
DAY 183	17 1(4)	^b	20 6(4)	15 3(4)	16 2(5)
CREA (mg/dL)					
DAY 39	0.49 0.04(10)	0.46 0.06(10)	0.45 0.04(10)	0.45 0.06(10)	0.43* 0.05(10)
DAY 93	0.51 0.04(10)	0.51 0.04(10)	0.50 0.05(10)	0.50 0.04(10)	0.50 0.05(10)
DAY 122	0.56 0.05(9)	^b	^b	^b	0.56 0.06(9)
DAY 183	0.49 0.06(4)	^b	0.59 0.06(4)	0.50 0.09(4)	0.53 0.08(5)
CHOL (mg/dL)					
DAY 39	87 26(10)	75 14(10)	65* 10(10)	72 11(10)	77 16(10)
DAY 93	95 29(10)	88 21(10)	73 15(10)	80 14(10)	86 21(10)
DAY 122	100 22(9)	^b	^b	^b	88 23(9)
DAY 183	109 24(4)	^b	127 19(4)	111 10(4)	106 27(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
TRIG (mg/dL)					
DAY 39	45 16(10)	38 9(10)	38 10(10)	42 13(10)	40 12(10)
DAY 93	72 57(10)	42 13(10) _b	39 11(10) _b	53 30(10) _b	55 28(10)
DAY 122	142 86(9)				65* 29(9)
DAY 183	59 15(4)	_b	93 38(4)	89 38(4)	122 92(5)
GLUC (mg/dL)					
DAY 39	98 8(10)	102 9(10)	105 12(10)	101 6(10)	102 12(10)
DAY 93	97 6(10)	102 5(10) _b	98 9(10) _b	98 9(10) _b	102 6(10)
DAY 122	109 10(9)				101 6(9)
DAY 183	101 7(4)	_b	107 8(4)	117* 3(4)	109 6(5)
TP (g/dL)					
DAY 39	7.4 0.5(10)	7.4 0.5(10)	7.2 0.3(10)	7.2 0.3(10)	7.2 0.3(10)
DAY 93	7.8 0.6(10)	7.9 0.4(10) _b	7.6 0.4(10) _b	7.8 0.5(10) _b	7.8 0.4(10)
DAY 122	8.6 0.5(9)				8.0* 0.5(9)
DAY 183	8.2 0.3(4)	_b	8.6 0.1(4)	8.5 0.5(4)	8.5 0.7(5)
ALB (g/dL)					
DAY 39	5.0 0.3(10)	5.1 0.4(10)	4.8 0.2(10)	4.9 0.3(10)	5.0 0.2(10)
DAY 93	5.3 0.4(10)	5.5 0.4(10) _b	5.1 0.3(10) _b	5.3 0.5(10) _b	5.5 0.3(10)
DAY 122	5.7 0.3(9)				5.4 0.4(9)
DAY 183	5.5 0.5(4)	_b	5.8 0.2(4)	5.4 0.7(4)	5.6 0.5(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
GLOB (g/dL)					
DAY 39	2.4 0.2(10)	2.3 0.3(10)	2.4 0.3(10)	2.4 0.2(10)	2.3 0.1(10)
DAY 93	2.5 0.3(10)	2.4 0.2(10) _b	2.5 0.2(10) _b	2.5 0.2(10) _b	2.4 0.2(10)
DAY 122	2.9 0.2(9)				2.6* 0.2(9)
DAY 183	2.8 0.3(4)	_b	2.8 0.3(4)	3.1 0.3(4)	2.9 0.3(5)
CALC (mg/dL)					
DAY 39	11.2 0.4(10)	11.1 0.4(10)	11.0 0.3(10)	11.0 0.3(10)	11.2 0.3(10)
DAY 93	11.0 0.4(10)	11.0 0.4(10) _b	10.8 0.4(10) _b	10.9 0.4(10) _b	11.0 0.3(10)
DAY 122	11.2 0.3(9)				10.8* 0.3(9)
DAY 183	11.6 0.4(4)	_b	11.7 0.3(4)	11.6 0.4(4)	11.6 0.4(5)
IPHS (mg/dL)					
DAY 39	8.0 0.7(10)	7.4 0.9(10)	7.5 1.1(10)	7.7 1.0(10)	7.7 0.8(10)
DAY 93	6.2 1.1(10)	6.1 1.0(10) _b	6.2 0.7(10) _b	5.8 0.3(10) _b	6.0 0.8(10)
DAY 122	6.2 0.7(9)				6.5 0.7(9)
DAY 183	4.8 0.5(4)	_b	5.1 1.5(4)	5.2 0.3(4)	4.9 0.6(5)
NA (mmol/L)					
DAY 39	142.9 1.7(10)	142.5 1.6(10)	143.6 1.0(10)	142.5 1.3(10)	142.7 1.2(10)
DAY 93	143.5 1.4(10)	143.4 1.1(10) _b	143.7 1.8(10) _b	143.8 1.1(10) _b	143.7 2.1(10)
DAY 122	144.8 1.4(9)				145.9 1.3(9)
DAY 183	144.2 1.5(4)	_b	143.7 1.0(4)	145.5 2.0(4)	144.3 0.9(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
K (mmol/L)					
DAY 39	5.81 0.55(10)	5.41 0.47(10)	5.52 0.35(10)	5.35 0.20(10)	5.56 0.43(10)
DAY 93	5.38 0.47(10)	5.28 0.50(10)	5.24 0.26(10)	5.23 0.28(10)	5.11 0.25(10)
DAY 122	5.31 0.54(9)	^b	^b	^b	5.39 0.32(9)
DAY 183	5.45 0.12(4)	^b	5.21 0.52(4)	5.62 0.52(4)	5.39 0.25(5)
CL (mmol/L)					
DAY 39	99.8 2.6(10)	99.6 1.9(10)	99.7 1.6(10)	99.7 1.4(10)	100.5 1.9(10)
DAY 93	100.2 1.9(10)	99.7 2.0(10)	100.8 2.1(10)	100.6 1.7(10)	100.6 2.0(10)
DAY 122	100.1 2.7(9)	^b	^b	^b	101.3 1.8(9)
DAY 183	99.3 1.7(4)	^b	100.2 1.7(4)	99.6 2.7(4)	99.3 1.7(5)
PFLU (μg/mL)					
DAY 93	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)
DAY 122	0.1 0.0(9)	^b	^b	^b	0.1 0.0(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 32

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
VOL (mL)					
DAY 38	12.5 6.7(10)	13.5 7.8(10)	10.3 2.7(10)	10.8 5.0(10)	16.0 9.7(10)
DAY 92	7.1 3.6(9)	6.0 4.4(10) _b	8.7 4.8(10) _b	7.0 3.5(10) _b	13.6 8.8(10)
DAY 122	8.3 6.7(10)				11.6 10.5(9)
DAY 183	7.7 7.0(5)	_b	9.8 6.8(5)	8.1 4.9(5)	11.7 4.9(5)
UOSM (mOsm)					
DAY 38	764 324(9)	697 262(10)	816 180(10)	795 279(10)	664 372(10)
DAY 92	1031 333(8)	1324 485(9) _b	1102 429(9) _b	1116 329(10) _b	830 344(10)
DAY 122	1183 457(8)				952 447(7)
DAY 183	1404 956(4)	_b	1319 739(5)	1539 989(5)	820 264(5)
SG					
DAY 38	1.028 0.015(10)	1.023 0.009(10)	1.026 0.006(10)	1.026 0.009(10)	1.022 0.012(10)
DAY 92	1.036 0.014(9)	1.046 0.018(10) _b	1.039 0.018(10) _b	1.036 0.011(10) _b	1.026 0.011(10)
DAY 122	1.045 0.020(10)				1.040 0.022(9)
DAY 183	1.047 0.028(5)	_b	1.039 0.022(5)	1.044 0.023(5)	1.025 0.007(5)
pH					
DAY 38	7.2 0.2(10)	7.1 0.4(10)	7.1 0.3(10)	7.2 0.6(10)	7.3 0.4(10)
DAY 92	6.7 0.4(9)	6.5 0.3(10) _b	6.4 0.3(10) _b	6.8 0.4(10) _b	6.4 0.5(10)
DAY 122	6.7 0.5(10)				6.2@ 0.4(9)

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
URO (EU/dL)					
DAY 38	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 92	0.2 0.0(9)	0.2 0.0(10) _b	0.2 0.0(10) _b	0.2 0.0(10) _b	0.2 0.0(10)
DAY 122	0.2 0.0(10)				0.2 0.0(9)
UFLU (µg)					
DAY 92	7.8 2.8(8)	8.7 2.9(7) _b	19.1 5.9(9) _b	50.1@ 11.4(10) _b	159.2@ 56.8(10)
DAY 122	12.0 7.2(9)				26.1* 8.9(7)
DAY 183	12.8 3.7(4)	_b	14.0 2.9(5)	16.0 5.2(4)	19.4 3.6(5)
UMTP (mg/dL)					
DAY 38	64 43(9)	57 37(10)	49 30(10)	46 18(10)	49 58(10)
DAY 92	105 83(9)	122 52(9) _b	77 72(9) _b	89 47(10) _b	48 40(10)
DAY 122	132 78(10)				77 72(9)
DAY 183	117 69(5)	_b	83 46(5)	255 225(5)	35 24(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 33

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
VOL (mL)					
DAY 39	9.4 5.1(10)	5.8 2.8(10)	4.6 2.4(10)	8.0 5.5(10)	12.3 6.7(10)
DAY 93	4.3 3.2(9)	4.0 2.0(9) _b	4.3 5.3(9) _b	7.6 7.4(10) _b	5.1 2.1(10)
DAY 122	5.8 3.4(10)				7.1 3.3(9)
DAY 183	4.4 4.6(5)	_b	6.4 3.2(4)	6.8 3.8(5)	6.2 1.7(5)
UOSM (mOsm)					
DAY 39	897 518(10)	1198 562(10)	1276 461(10)	925 432(10)	796 484(10)
DAY 93	1241 579(6)	1160 301(7) _b	1147 490(5) _b	890 390(7) _b	1298 485(9)
DAY 122	1046 415(9)				890 317(9)
DAY 183	1257 561(4)	_b	937 318(4)	861 138(4)	956 230(5)
SG					
DAY 39	1.027 0.015(10)	1.036 0.016(10)	1.039 0.013(10)	1.028 0.013(10)	1.025 0.014(10)
DAY 93	1.043 0.015(9)	1.043 0.016(9) _b	1.046 0.020(9) _b	1.037 0.018(10) _b	1.040 0.012(10)
DAY 122	1.036 0.017(10)				1.028 0.010(9)
DAY 183	1.044 0.025(5)	_b	1.027 0.007(4)	1.036 0.027(5)	1.027 0.006(5)
pH					
DAY 39	7.3 0.7(10)	6.8 0.4(10)	6.8 0.4(10)	7.0 0.3(10)	6.8 0.3(10)
DAY 93	5.8 0.4(9)	5.6 0.4(9) _b	5.7 0.5(9) _b	5.8 0.4(10) _b	5.9 0.3(9)
DAY 122	6.0 0.5(10)				5.9 0.5(9)

TABLE 33 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
URO (EU/dL)					
DAY 39	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 93	0.2 0.0(9)	0.2 0.0(9) _b	0.2 0.0(9) _b	0.2 0.0(10) _b	0.2 0.0(9)
DAY 122	0.2 0.0(10)				0.2 0.0(9)
UFLU (µg)					
DAY 93	8.1 2.5(3)	6.6 1.3(6) _b	9.3 1.9(3) _b	30.4 8.3(7) _b	87.0@ 16.2(8)
DAY 122	8.8 1.6(9)				11.7 4.5(9)
DAY 183	9.1 3.1(3)	_b	7.8 1.1(4)	11.1 1.5(4)	10.9 2.4(5)
UMTP (mg/dL)					
DAY 39	21 16(10)	31 18(10)	30 20(10)	21 10(10)	22 13(10)
DAY 93	50 47(6)	41 23(7) _b	29 17(5) _b	22 14(7) _b	63 92(10)
DAY 122	90 113(10)				20@ 11(9)
DAY 183	47 22(4)	_b	108 165(4)	29 33(4)	40 39(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

- a. H-24678 is [REDACTED]
b. Measurements for this group at this timepoint were not taken or not performed.

@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 34
SUMMARY OF HEPATIC BETA-OXIDATION ACTIVITY IN MALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)			
		10-Day Time Point	90-Day Time Point	1-Month Recovery	3-Month Recovery
I	0	7.7 ± 1.7 ^a	9.6 ± 0.5	13.5 ± 2.0	14.5 ± 3.5
III ^b	60 (isopropanol)	8.0 ± 3.2	8.4 ± 1.4	-----	-----
V ^{c,d}	10	7.2 ± 1.1	10.0 ± 1.8	-----	15.6 ± 2.8
VII ^{c,d}	60	5.3 ± 0.9	13.8 ± 1.6*	-----	18.0 ± 3.9
IX	300	13.9 ± 4.4	19.8 ± 3.4*	22.6 ± 1.8*	22.2 ± 4.0*

a. Mean ± standard deviation. The n = 5 for each group.

b. Samples were not prepared for analysis from group III at the 1- and 3-month recovery time points

c. H-24678 is [REDACTED]

d. Samples were not prepared for analysis from groups V and VII at 1-month recovery time point.

* Statistically significant difference from control (p < 0.05) by Dunnett's test.

TABLE 35
SUMMARY OF HEPATIC BETA-OXIDATION ACTIVITY IN FEMALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Time Point	90-Day Time Point	3-Month Recovery
II	0	12.9 ± 2.1 ^a	18.3 ± 2.5	17.8 ± 2.2
IV ^b	60 (isopropanol)	8.6 ± 2.2*	17.4 ± 2.8	18.1 ± 3.1
VI ^{c,d}	10	14.3 ± 1.1	17.8 ± 1.0	16.8 ± 1.7 ^e
VIII ^{c,d}	60	16.6 ± 2.8*	17.7 ± 2.1	23.6 ± 2.9*
X	300	19.9 ± 2.5*	23.8 ± 3.1*	24.0 ± 3.5*

- a. Mean ± standard deviation. The n = 5 for each group unless otherwise noted.
b. Samples were not prepared for analysis from group IV at the 1- and 3-month recovery time points
c. H-24678 i [REDACTED]
d. Samples were not prepared for analysis from groups VI and VIII at 1-month recovery time point.
e. n = 4.

* Statistically significant difference from untreated control (*) by Dunnett's test (p < 0.05).

TABLE 36
MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
LIVER	15.08189 0.83853 (9)	15.26610 1.25088 (10)	15.65400 1.72811 (10)	16.10800 2.54757 (10)	19.33890# 2.66904 (10)
KIDNEYS	3.81011 0.25835 (9)	3.97040 0.30793 (10)	4.01810 0.42819 (10)	4.27590# 0.31916 (10)	4.61410# 0.48195 (10)
HEART	1.64289 0.07568 (9)	1.80590# 0.21061 (10)	1.82460 0.33901 (10)	1.76490 0.16277 (10)	1.78100 0.24031 (10)
SPLEEN	0.84122 0.05199 (9)	0.87600 0.14426 (10)	0.84790 0.09991 (10)	0.83750 0.12432 (10)	0.82690 0.11316 (10)
BRAIN	2.10433 0.06112 (9)	2.15380 0.08665 (10)	2.15320 0.04886 (10)	2.13610 0.09297 (10)	2.25230 0.28855 (10)
THYMUS	0.37367 0.10616 (9)	0.36980 0.04806 (10)	0.33350 0.09733 (10)	0.40390 0.08918 (10)	0.40350 0.11397 (10)
ADRENAL GLANDS	0.05933 0.00630 (9)	0.05420 0.00625 (10)	0.05510 0.00840 (10)	0.05000# 0.00794 (10)	0.05290# 0.01042 (10)
THYROID GLAND	0.02422 0.00441 (9)	0.02300 0.00753 (10)	0.02660 0.00636 (10)	0.02670 0.00683 (10)	0.02210 0.00722 (10)
TESTES	3.41756 0.38267 (9)	3.58280 0.20377 (10)	3.48710 0.25185 (10)	3.77130# 0.35601 (10)	3.62650# 0.38068 (10)
EPIDIDYMIDES	1.43944 0.12571 (9)	1.50580 0.09056 (10)	1.50700 0.14321 (10)	1.57190 0.12840 (10)	1.41580 0.12522 (10)
FINAL BODY WEIGHT	557.28889 29.74413 (9)	562.01999 41.82330 (10)	573.62000 50.99172 (10)	553.52000 63.77206 (10)	526.30000 63.47923 (10)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.71144 0.18792 (9)	2.71625 0.09724 (10)	2.73278 0.23034 (10)	2.90036# 0.18283 (10)	3.67045# 0.14199 (10)
KIDNEYS/ FINAL BODY*100	0.68483 0.05169 (9)	0.70699 0.03181 (10)	0.70318 0.07445 (10)	0.78006# 0.09026 (10)	0.88232# 0.08555 (10)
HEART/ FINAL BODY*100	0.29529 0.01657 (9)	0.32196 0.03472 (10)	0.31851 0.05249 (10)	0.32100# 0.03164 (10)	0.33937# 0.03477 (10)
SPLEEN/ FINAL BODY*100	0.15134 0.01216 (9)	0.15584 0.02296 (10)	0.14838 0.01741 (10)	0.15225 0.02226 (10)	0.15838 0.02229 (10)
BRAIN/ FINAL BODY*100	0.37840 0.01980 (9)	0.38518 0.03262 (10)	0.37764 0.02908 (10)	0.39016 0.04291 (10)	0.43344# 0.07621 (10)
THYMUS/ FINAL BODY*100	0.06730 0.01992 (9)	0.06599 0.00864 (10)	0.05847 0.01812 (10)	0.07312 0.01440 (10)	0.07698 0.02196 (10)
ADRENAL GLANDS/ FINAL BODY*100	0.01067 0.00124 (9)	0.00970 0.00138 (10)	0.00974 0.00215 (10)	0.00905 0.00115 (10)	0.01011 0.00195 (10)
THYROID GLAND/ FINAL BODY*100	0.00437 0.00091 (9)	0.00414 0.00144 (10)	0.00468 0.00120 (10)	0.00483 0.00116 (10)	0.00419 0.00129 (10)
TESTES/ FINAL BODY*100	0.61558 0.08312 (9)	0.64118 0.06476 (10)	0.61069 0.05318 (10)	0.69070 0.11565 (10)	0.69381# 0.07389 (10)
EPIDIDYMIDES/ FINAL BODY*100	0.25905 0.02773 (9)	0.26886 0.01973 (10)	0.26447 0.03486 (10)	0.28735 0.04058 (10)	0.27110 0.02702 (10)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)				
	Group I 0 mg/kg/day	Group III 60 mg/kg/day Isopropanol	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
LIVER/ BRAIN*100	717.64202 51.69105(9)	709.42857 60.31705(10)	726.64682 74.71493(10)	754.49609 119.56178(10)	868.64363# 148.28634(10)
KIDNEYS/ BRAIN*100	181.04111 10.71936(9)	184.40956 13.49349(10)	186.67962 20.24034(10)	200.32932# 14.41936(10)	207.38365# 30.76367(10)
HEART/ BRAIN*100	78.15965 4.80593(9)	83.93581 10.16850(10)	84.80677 16.37083(10)	82.64902 7.07642(10)	80.09919 13.94435(10)
SPLEEN/ BRAIN*100	39.97797 2.20162(9)	40.74231 6.80788(10)	39.39784 4.75126(10)	39.23224 5.89183(10)	37.26524 7.26970(10)
THYMUS/ BRAIN*100	17.73973 4.98509(9)	17.22085 2.52732(10)	15.51057 4.66942(10)	18.83530 3.75089(10)	18.11717 5.68768(10)
ADRENAL GLANDS/ BRAIN*100	2.81686 0.26250(9)	2.51585* 0.27170(10)	2.56454 0.42604(10)	2.33989# 0.35437(10)	2.37171# 0.54223(10)
THYROID GLAND/ BRAIN*100	1.15187 0.20968(9)	1.07123 0.35467(10)	1.23482 0.28919(10)	1.25019 0.31721(10)	0.97974 0.30882(10)
TESTES/ BRAIN*100	162.64373 19.82149(9)	166.54741 10.80923(10)	162.02295 12.29517(10)	177.27617 22.50748(10)	163.01471 23.89849(10)
EPIDIDYIMIDES/ BRAIN*100	68.51800 6.94988(9)	69.99758 4.82806(10)	70.03002 6.94203(10)	73.82834 7.98932(10)	63.73639 9.43188(10)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group I 0 mg/kg/day	Group IX 300 mg/kg/day ^a
LIVER	15.81280 1.89401(10)	17.71611 2.77443(9)
KIDNEYS	4.10070 0.51303(10)	4.53367 0.56052(9)
HEART	1.93330 0.23361(10)	1.80000 0.15538(9)
SPLEEN	0.83820 0.08562(10)	0.77667 0.11221(9)
BRAIN	2.14400 0.09869(10)	2.18933 0.10357(9)
THYMUS	0.33390 0.06640(10)	0.42211 0.12042(9)
ADRENAL GLANDS	0.04800 0.00812(10)	0.04522 0.00766(9)
THYROID GLAND	0.02160 0.00597(10)	0.02222 0.00429(9)
TESTES	3.51750 0.17968(10)	3.66511 0.26334(9)
EPIDIDYMIDES	1.54360 0.05685(10)	1.50078@ 0.16784(9)
FINAL BODY WEIGHT	595.10000 51.11742(10)	568.42222 39.71186(9)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group I 0 mg/kg/day	Group IX 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.65213 0.14226(10)	3.10558* 0.32569(9)
KIDNEYS/ FINAL BODY*100	0.68817 0.04775(10)	0.79659* 0.06928(9)
HEART/ FINAL BODY*100	0.32582 0.03845(10)	0.31789 0.03445(9)
SPLEEN/ FINAL BODY*100	0.14132 0.01403(10)	0.13674 0.01864(9)
BRAIN/ FINAL BODY*100	0.36293 0.03916(10)	0.38643 0.02669(9)
ADRENAL GLANDS/ FINAL BODY*100	0.00808 0.00135(10)	0.00799 0.00145(9)
THYMUS/ FINAL BODY*100	0.05636 0.01155(10)	0.07358* 0.01695(9)
THYROID GLAND/ FINAL BODY*100	0.00363 0.00101(10)	0.00394 0.00087(9)
TESTES/ FINAL BODY*100	0.59385 0.04398(10)	0.64663* 0.05279(9)
EPIDIDYMIDES/ FINAL BODY*100	0.26109 0.02384(10)	0.26508 0.03403(9)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)		
	Group I 0 mg/kg/day	Group IX 300 mg/kg/day ^a
LIVER/ BRAIN*100	739.01373 94.03186(10)	808.12266 113.30466(9)
KIDNEYS/ BRAIN*100	191.47131 24.00495(10)	207.09056 23.83624(9)
HEART/ BRAIN*100	90.25849 10.98188(10)	82.25375 6.57906(9)
SPLEEN/ BRAIN*100	39.12067 3.81317(10)	35.50236 5.01238(9)
ADRENAL GLANDS/ BRAIN*100	2.23668 0.35142(10)	2.06323 0.31688(9)
THYMUS/ BRAIN*100	15.55432 2.84614(10)	19.23278 5.27550(9)
THYROID GLAND/ BRAIN*100	1.01216 0.28837(10)	1.01566 0.19728(9)
TESTES/ BRAIN*100	164.34666 10.80786(10)	167.56032 11.78020(9)
EPIDIDYMIDES/ BRAIN*100	72.17039 4.90211(10)	68.63487 7.71067(9)

TABLE 36(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
LIVER	14.14780 2.06533 (5)	16.20120 0.88601 (5)	17.57700 4.50755 (5)	16.89200 2.68111 (5)
KIDNEYS	3.68740 0.36504 (5)	3.98560 0.38329 (5)	5.63980 4.24687 (5)	4.55400 0.86744 (5)
THYROID GLAND	0.02240 0.00288 (5)	0.02460 0.00251 (5)	0.02420 0.00789 (5)	0.02140 0.00422 (5)
TESTES	3.72720 0.25474 (5)	3.42680 0.30835 (5)	3.37320 0.28733 (5)	3.66560 0.19962 (5)
FINAL BODY WEIGHT	562.24000 62.85940 (5)	596.67999 49.44883 (5)	588.96001 86.66663 (5)	610.57999 65.35249 (5)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group I 0 mg/kg/day	Group V 10 mg/kg/day ^a	Group VII 60 mg/kg/day ^a	Group IX 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.50898 0.09046 (5)	2.73184 0.29663 (5)	3.00723 0.83617 (5)	2.75690 0.19853 (5)
KIDNEYS/ FINAL BODY*100	0.65875 0.06087 (5)	0.67421 0.11256 (5)	1.02047 0.91632 (5)	0.74167 0.07355 (5)
THYROID GLAND/ FINAL BODY*100	0.00399 0.00040 (5)	0.00413 0.00043 (5)	0.00409 0.00105 (5)	0.00349 0.00052 (5)
TESTES/ FINAL BODY*100	0.66898 0.08212 (5)	0.57994 0.09309 (5)	0.57830 0.05782 (5)	0.60532 0.06755 (5)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group III (isopropanol control) was excluded from trend comparisons.

* Statistically significant difference from control (Group I) at $p < 0.05$ by Dunnett's test.

@ Statistically significant difference from control (Group I) at $p < 0.05$ by Dunn's test.

TABLE 37
MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
LIVER	8.67870 1.09243 (10)	8.73520 0.70672 (10)	8.05260 0.82624 (10)	9.25420 1.14428 (10)	9.83900# 1.04012 (10)
KIDNEYS	2.21880 0.19422 (10)	2.23970 0.17790 (10)	2.24860 0.09961 (10)	2.35160 0.22373 (10)	2.46620# 0.15020 (10)
HEART	1.21850 0.17648 (10)	1.14930 0.08638 (10)	1.05620@ 0.07636 (10)	1.15300 0.15320 (10)	1.18580 0.17369 (10)
SPLEEN	0.53030 0.05220 (10)	0.51640 0.06933 (10)	0.50260 0.07997 (10)	0.56440 0.07812 (10)	0.53740 0.10276 (10)
BRAIN	1.92630 0.11686 (10)	1.93330 0.07293 (10)	1.88920 0.08708 (10)	1.97520 0.06380 (10)	1.99550# 0.07710 (10)
THYMUS	0.30630 0.04060 (10)	0.27560 0.04608 (10)	0.29080 0.05258 (10)	0.32300 0.10464 (10)	0.33710 0.07626 (10)
ADRENAL GLANDS	0.06530 0.01117 (10)	0.06580 0.00873 (10)	0.06770 0.01065 (10)	0.06950 0.01126 (10)	0.07290 0.01343 (10)
THYROID GLAND	0.01790 0.00303 (10)	0.01730 0.00245 (10)	0.01730 0.00380 (10)	0.01880 0.00336 (10)	0.02020 0.00518 (10)
OVARIES	0.11690 0.01969 (10)	0.13130 0.03323 (10)	0.13120 0.03156 (10)	0.13950 0.03332 (10)	0.12300 0.01913 (10)
UTERUS	0.79250 0.30595 (10)	0.64090 0.17783 (10)	0.71740 0.24541 (10)	0.77330 0.16970 (10)	0.76020 0.21547 (10)
FINAL BODY WEIGHT	309.18000 22.67685 (10)	305.93000 15.19658 (10)	293.97000 25.01995 (10)	316.11000 42.21386 (10)	322.79000 28.80534 (10)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.80290 0.22742 (10)	2.85766 0.22340 (10)	2.74618 0.25686 (10)	2.93782 0.21812 (10)	3.04854# 0.16311 (10)
KIDNEYS/ FINAL BODY*100	0.72035 0.07489 (10)	0.76919 0.05935 (10)	0.73299 0.06493 (10)	0.74948 0.07153 (10)	0.76636 0.03813 (10)
HEART/ FINAL BODY*100	0.39486 0.05513 (10)	0.36064 0.02409 (10)	0.37584 0.02933 (10)	0.36563 0.02579 (10)	0.36836 0.05197 (10)
SPLEEN/ FINAL BODY*100	0.17174 0.01463 (10)	0.16826 0.01561 (10)	0.17107 0.02278 (10)	0.17944 0.02011 (10)	0.16566 0.02256 (10)
BRAIN/ FINAL BODY*100	0.62456 0.03881 (10)	0.63299 0.03219 (10)	0.64733 0.06918 (10)	0.63381 0.07811 (10)	0.62202 0.05301 (10)
THYMUS/ FINAL BODY*100	0.09911 0.01138 (10)	0.09022 0.01493 (10)	0.09944 0.01938 (10)	0.10177 0.03006 (10)	0.10384 0.01859 (10)
ADRENAL GLANDS/ FINAL BODY*100	0.02112 0.00342 (10)	0.02159 0.00331 (10)	0.02314 0.00392 (10)	0.02220 0.00402 (10)	0.02253 0.00323 (10)
THYROID GLAND/ FINAL BODY*100	0.00581 0.00105 (10)	0.00566 0.00082 (10)	0.00587 0.00104 (10)	0.00601 0.00122 (10)	0.00631 0.00182 (10)
OVARIES/ FINAL BODY*100	0.03802 0.00693 (10)	0.04290 0.01064 (10)	0.04453 0.00980 (10)	0.04463 0.01054 (10)	0.03824 0.00590 (10)
UTERUS/ FINAL BODY*100	0.25572 0.09172 (10)	0.20960 0.05628 (10)	0.24650 0.08894 (10)	0.24753 0.06125 (10)	0.24161 0.09408 (10)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

	MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)				
	Group II 0 mg/kg/day	Group IV 60 mg/kg/day Isopropanol	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
LIVER/ BRAIN*100	450.97784 53.57531(10)	452.29062 38.89301(10)	426.50556 41.38126(10)	468.17896 52.62215(10)	493.15457# 49.08503(10)
KIDNEYS/ BRAIN*100	115.52074 11.85912(10)	116.09064 11.41802(10)	119.32911 8.73265(10)	119.14585 11.59916(10)	123.56578 5.28399(10)
HEART/ BRAIN*100	63.28631 8.38153(10)	59.51655 4.82343(10)	56.03737 4.94241(10)	58.40968 7.72237(10)	59.31338 7.27454(10)
SPLEEN/ BRAIN*100	27.57986 2.76124(10)	26.72732 3.61594(10)	26.70644 4.67721(10)	28.57337 3.83565(10)	26.88685 4.78189(10)
THYMUS/ BRAIN*100	15.90487 1.91689(10)	14.31295 2.68467(10)	15.38581 2.61279(10)	16.46200 5.62151(10)	16.84635 3.51737(10)
ADRENAL GLANDS/ BRAIN*100 *	3.38997 0.55983(10)	3.40764 0.46746(10)	3.58773 0.57406(10)	3.51049 0.51452(10)	3.65099 0.62860(10)
THYROID GLAND/ BRAIN*100	0.93019 0.15195(10)	0.89548 0.12478(10)	0.92130 0.23195(10)	0.95325 0.17695(10)	1.01745 0.28439(10)
UTERUS/ BRAIN*100	41.05732 15.22120(10)	33.23672 9.22236(10)	38.15598 13.70562(10)	39.32106 9.46924(10)	38.22284 11.32543(10)
OVARIES/ BRAIN*100	6.10926 1.18806(10)	6.80055 1.70454(10)	6.96446 1.70819(10)	7.05801 1.65752(10)	6.17057 0.97247(10)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group II 0 mg/kg/day	Group X 300 mg/kg/day ^a
LIVER	9.56067 1.85565 (9)	9.24544 1.16496 (9)
KIDNEYS	2.37811 0.29487 (9)	2.30067 0.30399 (9)
HEART	1.22056 0.12026 (9)	1.19378 0.13361 (9)
SPLEEN	0.53100 0.06307 (9)	0.54144 0.06944 (9)
BRAIN	1.98367 0.07833 (9)	1.93756 0.08583 (9)
THYMUS	0.32078 0.06797 (9)	0.30778 0.07416 (9)
ADRENAL GLANDS	0.06422 0.01278 (9)	0.06011 0.01574 (9)
THYROID GLAND	0.01811 0.00203 (9)	0.02089 0.00434 (9)
OVARIES	0.12333 0.02183 (9)	0.11756 0.01663 (9)
UTERUS	0.72178 0.23775 (9)	0.70022 0.28483 (9)
FINAL BODY WEIGHT	356.77778 62.97787 (9)	325.14444 31.49080 (9)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

	MEAN RELATIVE ORGAN WEIGHTS	
	Group II 0 mg/kg/day	Group X 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.67851 0.18233 (9)	2.84290 0.20658 (9)
KIDNEYS/ FINAL BODY*100	0.67295 0.05276 (9)	0.70699 0.05197 (9)
HEART/ FINAL BODY*100	0.34703 0.03754 (9)	0.36817 0.03426 (9)
SPLEEN/ FINAL BODY*100	0.15137 0.02313 (9)	0.16828 0.02967 (9)
BRAIN/ FINAL BODY*100	0.56997 0.09306 (9)	0.59971 0.04942 (9)
THYMUS/ FINAL BODY*100	0.09040 0.01484 (9)	0.09493 0.02238 (9)
ADRENAL GLANDS/ FINAL BODY*100	0.01866 0.00604 (9)	0.01842 0.00372 (9)
THYROID GLAND/ FINAL BODY*100	0.00515 0.00063 (9)	0.00644* 0.00123 (9)
OVARIES/ FINAL BODY*100	0.03550 0.00850 (9)	0.03636 0.00569 (9)
UTERUS/ FINAL BODY*100	0.20693 0.07187 (9)	0.21760 0.09061 (9)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)

	Group II 0 mg/kg/day	Group X 300 mg/kg/day ^a
LIVER/ BRAIN*100	481.85190 90.04451 (9)	476.69219 50.80728 (9)
KIDNEYS/ BRAIN*100	119.93033 14.50344 (9)	118.44874 11.51039 (9)
HEART/ BRAIN*100	61.57367 6.04114 (9)	61.56573 5.83283 (9)
SPLEEN/ BRAIN*100	26.73712 2.67330 (9)	28.01959 4.05704 (9)
THYMUS/ BRAIN*100	16.14120 3.23004 (9)	15.94323 4.06477 (9)
ADRENAL GLANDS/ BRAIN*100	3.22922 0.59413 (9)	3.08901 0.69960 (9)
THYROID GLAND/ BRAIN*100	0.91335 0.09895 (9)	1.07557* 0.20505 (9)
OVARIES/ BRAIN*100	6.22973 1.12355 (9)	6.06376 0.79569 (9)
UTERUS/ BRAIN*100	36.20586 11.14940 (9)	36.25603 15.19679 (9)

TABLE 37(CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
LIVER	8.71380 0.93073 (5)	9.73575 1.11897 (4)	9.42960 1.66419 (5)	10.41600 2.13378 (5)
KIDNEYS	2.30900 0.18728 (5)	2.42400 0.43082 (4)	2.43420 0.39420 (5)	2.44660 0.28291 (5)
THYROID GLAND	0.01540 0.00434 (5)	0.01925 0.00350 (4)	0.01660 0.00288 (5)	0.02040 0.00467 (5)
FINAL BODY WEIGHT	317.02000 32.07768 (5)	356.72499 19.20909 (4)	359.40000 32.90624 (5)	353.60001 40.09009 (5)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
	Group II 0 mg/kg/day	Group VI 10 mg/kg/day ^a	Group VIII 60 mg/kg/day ^a	Group X 300 mg/kg/day ^a
LIVER/ FINAL BODY*100	2.76925 0.36928 (5)	2.73048 0.28605 (4)	2.61172 0.27937 (5)	2.92797 0.34079 (5)
KIDNEYS/ FINAL BODY*100	0.73735 0.12031 (5)	0.67915 0.10778 (4)	0.67461 0.06254 (5)	0.69425 0.06904 (5)
THYROID GLAND/ FINAL BODY*100	0.00486 0.00122 (5)	0.00541 0.00103 (4)	0.00461 0.00057 (5)	0.00574 0.00092 (5)

Data summarized as: Mean
Standard Deviation (n)

a. H-24678 is [REDACTED]

- # Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test. Group IV (isopropanol control) was excluded from trend comparisons.
- * Statistically significant difference from control (Group II) at $p < 0.05$ by Dunnett's test.
- @ Statistically significant difference from control (Group II) at $p < 0.05$ by Dunn's test.

TABLE 38

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)							
		Males							
		0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX			
LIVER		(10)	(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	10	11			
KIDNEYS		(10)	(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	10	11			
LUNGS		(10)	(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	10	11			
FLUID, CLEAR, DIFFUSE.		(10)	(10)	(10)	(10)	(11)			
HEART		10	10	10	10	10			1
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(11)			
SKELETAL MUSCLE		10	10	10	10	11			
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(11)			
SPLEEN		10	10	10	10	11			
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(11)			
AORTA		10	10	10	10	11			
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(11)			
BRAIN		10	10	10	10	11			
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(11)			

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

[REDACTED]

TABLE 38(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Males					
		0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
SPINAL CORD		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
STOMACH		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
DUODENUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
JEJUNUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
ILEUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
PANCREAS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
CECUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
COLON		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678

TABLE 38(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)						
	TREATMENT	Males					
		0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
RECTUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
SALIVARY GLANDS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
THYMUS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
ADRENAL GLANDS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
SCIATIC NERVE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
PITUITARY GLAND		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 38(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
	TREATMENT	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX
THYROID GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
TRACHEA NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
ESOPHAGUS NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
SKIN NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
PROSTATE NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

TABLE 38(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)							
	TREATMENT	Males						
		0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX		
SEMINAL VESICLES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
URINARY BLADDER NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
TESTES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
EPIDIDYMIDES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
STERNUM NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
NOSE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		
POPLITEAL LYMPH NODE MASS, LEFT.		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11		

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 38(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)		Males	
	TREATMENT	0 mg/kg/day ^a IX	300 mg/kg/day ^a IX	
LIVER		(10) 9 1	(9) 9	
NO ABNORMALITY DETECTED HERNIA.				
KIDNEYS		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
LUNGS		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
HEART		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
SKELETAL MUSCLE		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
SPLEEN		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
AORTA		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
BRAIN		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)		Males	
	TREATMENT	0 mg/kg /day I	300 mg/kg /day IX	
SPINAL CORD		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
STOMACH		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
DUODENUM		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
JEJUNUM		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
ILEUM		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
PANCREAS		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
CECUM		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
COLON		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)	
	Males	
	TREATMENT	0 300 mg/kg mg/kg /day ^a /day ^a I IX
RECTUM		(10) (9) 10 9
NO ABNORMALITY DETECTED		
MESENTERIC LYMPH NODE		(10) (9) 10 9
NO ABNORMALITY DETECTED		
SALIVARY GLANDS		(10) (9) 10 9
NO ABNORMALITY DETECTED		
MANDIBULAR LYMPH NODE		(10) (9) 10 9
NO ABNORMALITY DETECTED		
THYMUS		(10) (9) 10 9
NO ABNORMALITY DETECTED		
ADRENAL GLANDS		(10) (9) 10 9
NO ABNORMALITY DETECTED		
SCIATIC NERVE		(10) (9) 10 9
NO ABNORMALITY DETECTED		
PITUITARY GLAND		(10) (9) 10 9
NO ABNORMALITY DETECTED		

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is [REDACTED]

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)	
	TREATMENT	Males
	0 mg/kg/day ^a	300 mg/kg/day ^a
	I	IX
THYROID GLAND	(10)	(9)
NO ABNORMALITY DETECTED	10	9
PARATHYROID GLANDS	(10)	(9)
NO ABNORMALITY DETECTED	10	9
TRACHEA	(10)	(9)
NO ABNORMALITY DETECTED	10	9
ESOPHAGUS	(10)	(9)
NO ABNORMALITY DETECTED	10	9
PHARYNX/LARYNX	(10)	(9)
NO ABNORMALITY DETECTED	10	9
EYE(S) WITH OPTIC NERVE	(10)	(9)
NO ABNORMALITY DETECTED	10	9
SKIN	(10)	(9)
NO ABNORMALITY DETECTED	10	9
PROSTATE	(10)	(9)
NO ABNORMALITY DETECTED	10	9

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDENCE (Numeric)	Males	
	TREATMENT	0 300 mg/kg /day ^a IX
SEMINAL VESICLES NO ABNORMALITY DETECTED	(10) 10	(9) 9
URINARY BLADDER NO ABNORMALITY DETECTED	(10) 10	(9) 9
TESTES NO ABNORMALITY DETECTED	(10) 10	(9) 9
EPIDIDYIMIDES NO ABNORMALITY DETECTED	(10) 10	(9) 9
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED	(10) 10	(9) 9
STERNUM NO ABNORMALITY DETECTED	(10) 10	(9) 9
NOSE NO ABNORMALITY DETECTED	(10) 10	(9) 9

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0 mg/kg /day I	10 mg/kg /day ^a V	60 mg/kg /day ^a VII	300 mg/kg /day ^a IX
LIVER					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 4	(5) 5	
DISCOLORATION, PALE.			1		
KIDNEYS					
NO ABNORMALITY DETECTED	(5) 5	(5) 4	(5) 4	(5) 5	
DISCOLORATION, MOTTLED, BILATERAL.		1			
CHRONIC PROGRESSIVE NEPHROPATHY, BILATERAL.			1		
LUNGS					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
HEART					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SKELETAL MUSCLE					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SPLEEN					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
AORTA					
NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

TREATMENT	LESION INCIDENCE (Numeric)				
	Males				
	0 mg/kg /day I	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
BRAIN NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SPINAL CORD NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
STOMACH NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
DUODENUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
JEJUNUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
ILEUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PANCREAS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
CECUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 i

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)				
	Males				
TREATMENT	0 mg/kg /day I	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
COLON NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
RECTUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
MESENTERIC LYMPH NODE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SALIVARY GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
MANDIBULAR LYMPH NODE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
THYMUS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
ADRENAL GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SCIATIC NERVE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	INCIDENCE (Numeric)				
	Males				
TREATMENT	0 mg/kg /day I	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
PITUITARY GLAND NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
THYROID GLAND NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
TRACHEA NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
ESOPHAGUS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SKIN NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is [REDACTED]

TABLE 38(CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)			
	Males			
	TREATMENT	0 mg/kg /day I	10 mg/kg /day V	60 mg/kg /day VII
PROSTATE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
SEMINAL VESICLES NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
URINARY BLADDER NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
TESTES NO ABNORMALITY DETECTED DISCOLORATION, OPAQUE, LEFT.	(5) 4 1	(5) 5	(5) 5	(5) 5
EPIDIDYMIDES NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
STERNUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5
NOSE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg /day II	60 mg/kg /day ^a IV	10 mg/kg /day ^b VI	60 mg/kg /day ^b VIII	300 mg/kg /day ^b X	
LIVER							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 9 1	(11) 10 1	
HERNIA.							
DISCOLORATION, DARK, RAISED, LEFT, MIDDLE.							
KIDNEYS							
NO ABNORMALITY DETECTED		(10) 10	(10) 9 1	(10) 10 10	(10) 10 10	(11) 11 11	
CYST, RIGHT.							
LUNGS							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10 10	(10) 10 10	(11) 11 11	
HEART							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10 10	(10) 10 10	(11) 11 11	
SKELETAL MUSCLE							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10 10	(10) 10 10	(11) 11 11	
SPLEEN							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10 10	(10) 10 10	(11) 11 11	
AORTA							
NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10 10	(10) 10 10	(11) 11 11	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678

TABLE 39(CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (Numeric)					
	Females					
	0 mg/kg /day II	60 mg/kg /day ^a IV	10 mg/kg /day ^b VI	60 mg/kg /day ^b VIII	300 mg/kg /day ^b X	
BRAIN NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
SPINAL CORD NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
STOMACH NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
DUODENUM NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
JEJUNUM NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
ILEUM NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
PANCREAS NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	
CECUM NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(10) 10	(11) 11	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isotripropanol
^b H-24678 is [REDACTED]

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
COLON		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
RECTUM		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
SALIVARY GLANDS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
THYMUS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
ADRENAL GLANDS		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	
SCIATIC NERVE		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	11	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is [REDACTED]

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg /day ^a II	60 mg/kg /day ^a IV	10 mg/kg /day ^a VI	60 mg/kg /day ^a VIII	300 mg/kg /day ^a X
PITUITARY GLAND NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
THYROID GLAND NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
PARATHYROID GLANDS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
TRACHEA NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
ESOPHAGUS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
PHARYNX/LARYNX NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
SKIN NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
OVARIES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
UTERUS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
VAGINA NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
URINARY BLADDER NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
STERNUM NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11
NOSE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10	(11) 11

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)	
	TREATMENT	Females
	0 ng/kg /day II	300 ng/kg /day X
LIVER NO ABNORMALITY DETECTED	(10) 10	(9) 9
KIDNEYS NO ABNORMALITY DETECTED	(10) 10	(9) 9
LUNGS NO ABNORMALITY DETECTED	(10) 10	(9) 9
HEART NO ABNORMALITY DETECTED	(10) 10	(9) 9
SKELETAL MUSCLE NO ABNORMALITY DETECTED	(10) 10	(9) 9
SPLEEN NO ABNORMALITY DETECTED	(10) 10	(9) 9
AORTA NO ABNORMALITY DETECTED	(10) 10	(9) 9
BRAIN NO ABNORMALITY DETECTED	(10) 10	(9) 9

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)		
	Males		Females
	TREATMENT	0 mg/kg/day II	300 mg/kg/day ^a XI
SPINAL CORD NO ABNORMALITY DETECTED		(10) 10	(9) 9
STOMACH NO ABNORMALITY DETECTED		(10) 10	(9) 9
DUODENUM NO ABNORMALITY DETECTED		(10) 10	(9) 9
JEJUNUM NO ABNORMALITY DETECTED		(10) 10	(9) 9
ILEUM NO ABNORMALITY DETECTED		(10) 10	(9) 9
PANCREAS NO ABNORMALITY DETECTED		(10) 10	(9) 9
CECUM NO ABNORMALITY DETECTED		(10) 10	(9) 9
COLON NO ABNORMALITY DETECTED		(10) 10	(9) 9

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)		
	TREATMENT	0 mg/kg/day ^a II	300 mg/kg/day ^a X
RECTUM		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
MESENTERIC LYMPH NODE		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
SALIVARY GLANDS		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
MANDIBULAR LYMPH NODE		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
THYMUS		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
ADRENAL GLANDS		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
SCIATIC NERVE		(10) 10	(9) 9
NO ABNORMALITY DETECTED			
PITUITARY GLAND		(10) 10	(9) 9
NO ABNORMALITY DETECTED			

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is [REDACTED]

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)		Females
	TREATMENT		
	0	300	
	mg/kg	mg/kg	
	/day ^a	/day ^a	
	II	X	
THYROID GLAND	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
PARATHYROID GLANDS	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
TRACHEA	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
ESOPHAGUS	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
PHARYNX/LARYNX	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
EYE(S) WITH OPTIC NERVE	(10)	(9)	
NO ABNORMALITY DETECTED	9	9	
DISCOLORATION, WHITE, LEFT.	1		
SKIN	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	
MAMMARY GLAND (FEMALE)	(10)	(9)	
NO ABNORMALITY DETECTED	10	9	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is [REDACTED]

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)			
	Females			
	TREATMENT	0 mg/kg/day II	300 mg/kg/day ^a X	
OVARIES		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
UTERUS		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
VAGINA		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
URINARY BLADDER		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
FEMUR/KNEE JOINT		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
STERNUM		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				
NOSE		(10) 10	(9) 9	
NO ABNORMALITY DETECTED				

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT	0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
LIVER NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
KIDNEYS NO ABNORMALITY DETECTED DILATATION, LEFT.	(5) 5	(5) 4 1	(5) 5	(5) 5	
LUNGS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
HEART NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SKELETAL MUSCLE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SPLEEN NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
AORTA NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
BRAIN NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)				
	TREATMENT	Females			
		0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
SPINAL CORD		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
STOMACH		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
DUODENUM		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
JEJUNUM		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
ILEUM		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
PANCREAS		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
CECUM		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					
COLON		(5) 5	(5) 5	(5) 5	(5) 5
NO ABNORMALITY DETECTED					

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT	0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
RECTUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
MESENTERIC LYMPH NODE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SALIVARY GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
MANDIBULAR LYMPH NODE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
THYMUS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
ADRENAL GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SCIATIC NERVE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PITUITARY GLAND NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT	0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
THYROID GLAND NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
TRACHEA NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
ESOPHAGUS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
SKIN NO ABNORMALITY DETECTED MASS, PINK, FIRM, INGUEN, RIGHT.	(5) 5	(5) 4	(5) 5	(5) 5	
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT	0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
OVARIES NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
UTERUS NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
URINARY BLADDER NO ABNORMALITY DETECTED CALCULUS\CALCULI.	(5) 5	(5) 4 1	(5) 5	(5) 5	
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
STERNUM NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	
NOSE NO ABNORMALITY DETECTED	(5) 5	(5) 5	(5) 5	(5) 5	

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a H-24678 is

TABLE 40

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (NUMERIC)					
	Males					
	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
LESIONS						
DIGESTIVE SYSTEM	(10)	(10)	(10)	(10)	(11)	
LIVER						
NECROSIS, FOCAL.				4	3	
INFLAMMATION, SUBACUTE/CHRONIC.	10	10	10	10	9	
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.				1	10	
HYPERPLASIA, BILE DUCT.			1		1	
FATTY CHANGE, MEDIAN CLEFT.		3		2		
FATTY CHANGE, CENTRILOBULAR.			3	3	2	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day V	60 mg/kg /day ^b VII	300 mg/kg /day IX
DIGESTIVE SYSTEM						
PANCREAS		(10)				(11)
NO ABNORMALITY DETECTED		6				7
INFLAMMATION, SUBACUTE/CHRONIC.		1				3
HYPERPLASIA, FOCAL, ACINAR CELL.						1
ATROPHY.		4				2
ALTERATION, BASOPHILIC, FOCAL.						1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
DIGESTIVE SYSTEM							
ESOPHAGUS		(10)				(10)	
NO ABNORMALITY DETECTED		10				10	
STOMACH		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
DUODENUM		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
JEJUNUM		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
ILEUM		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX	
DIGESTIVE SYSTEM						
CECUM	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	
COLON	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	
RECTUM	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	
SALIVARY GLANDS	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)						
	Males						
TREATMENT	0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX		
URINARY SYSTEM							
KIDNEYS							
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)	(11)		
NEPHROPATHY, CHRONIC PROGRESSIVE.	5	8	5	5			
HYPERTROPHY, TUBULAR.	5	2	4	4	8		
HYDRONEPHROSIS, UNILATERAL.			1		11		
CYST.							
URINARY BLADDER							
NO ABNORMALITY DETECTED	(10)			1			(11)
	10						11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
RESPIRATORY SYSTEM							
LUNGS		(10)				(11)	
NO ABNORMALITY DETECTED		10				10	
FOREIGN MATERIAL.						1	
EDEMA.						1	
TRACHEA		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
PHARYNX/LARYNX		(10)				(11)	
NO ABNORMALITY DETECTED		9				11	
INFLAMMATION, SUBACUTE/CHRONIC.		1					

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678: [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0	60	10	60	300	
	mg/kg /day I	mg/kg /day ^a III	mg/kg /day ^b V	mg/kg /day ^b VII	mg/kg /day ^b IX	
RESPIRATORY SYSTEM						
NOSE	(10)				(11)	
NO ABNORMALITY DETECTED	9				7	
ODONTODYSPLASIA.	1					
INFLAMMATION, SUBACUTE/CHRONIC.					2	
FOREIGN MATERIAL.					1	
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (NUMERIC)					
	Males					
	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
CARDIOVASCULAR SYSTEM						
HEART	(10)				(11)	
NO ABNORMALITY DETECTED	9				7	
CARDIOMYOPATHY.	1				4	
AORTA	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)				(11)
NO ABNORMALITY DETECTED		10				11
THYMUS		(10)				(11)
NO ABNORMALITY DETECTED		10				11
MANDIBULAR LYMPH NODE		(10)				(11)
NO ABNORMALITY DETECTED		10				11
MESENTERIC LYMPH NODE		(10)				(11)
NO ABNORMALITY DETECTED		10				11
POPLITEAL LYMPH NODE				(1)		
HEMANGIOSARCOMA [M].				1		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
BONE MARROW	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (NUMERIC)							
	Males							
	0 mg/kg /day I	60 mg/kg /day III	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX			
ENDOCRINE SYSTEM								
PITUITARY GLAND	(10)				(11)			
NO ABNORMALITY DETECTED	10				11			
THYROID GLAND	(10)	(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED	5	2	2	5	1			
HYPERTROPHY, FOLLICULAR. ALTERATION, COLLOID.				2	7			
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.	5	8	8	4	10			
PARATHYROID GLANDS					1			
NO ABNORMALITY DETECTED	(9)				(9)			
ADRENAL GLANDS	9				9			
NO ABNORMALITY DETECTED	(10)				(11)			
NO ABNORMALITY DETECTED	10				11			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Males				
		0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX
NERVOUS SYSTEM						
BRAIN		(10)				(11)
NO ABNORMALITY DETECTED		10				11
SPINAL CORD		(10)				(11)
NO ABNORMALITY DETECTED		10				11
SCIATIC NERVE		(10)				(11)
NO ABNORMALITY DETECTED		10				11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day isopropanol
^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (NUMERIC)				
	Males				
	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE	(10)				(11)
NO ABNORMALITY DETECTED	10				11
FEMUR/KNEE JOINT	(10)				(11)
NO ABNORMALITY DETECTED	10				11
STERNUM	(10)				(11)
NO ABNORMALITY DETECTED	10				11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESION	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX	
REPRODUCTIVE SYSTEM						
TESTES	(10)				(11)	
NO ABNORMALITY DETECTED	10				10	
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, BILATERAL.					1	
EPIDIDYIMIDES	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	
PROSTATE	(10)				(11)	
NO ABNORMALITY DETECTED	7				9	
INFLAMMATION, SUBACUTE/CHRONIC.	3				2	
SEMINAL VESICLES	(10)				(11)	
NO ABNORMALITY DETECTED	10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Males				
		0 mg/kg /day I	60 mg/kg /day ^a III	10 mg/kg /day ^b V	60 mg/kg /day ^b VII	300 mg/kg /day ^b IX
CUTANEOUS SYSTEM						
SKIN		(10)				(11)
NO ABNORMALITY DETECTED		10				11
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE		(10)				(11)
NO ABNORMALITY DETECTED		8				11
FOLD/ROSETTE, RETINAL.		1				
ATROPHY, RETINAL.		1				

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 40 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDENCE (NUMERIC)	Males	
	0 mg/kg/day ^a	300 mg/kg/day ^a
TREATMENT	I	IX
DIGESTIVE SYSTEM	(10)	(9)
LIVER	1	1
NO ABNORMALITY DETECTED		
NECROSIS, FOCAL.	9	9
INFLAMMATION, SUBACUTE/CHRONIC.		
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.	3	6
FATTY CHANGE, MEDIAN CLEFT.	1	1
FATTY CHANGE, CENTRILOBULAR.		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			

	-----		Males	
	TREATMENT	0 mg/kg /day I	300 mg/kg /day ^a IX	

URINARY SYSTEM				

KIDNEYS		(10)	(9)	
NO ABNORMALITY DETECTED		3	4	
NEPHROPATHY, CHRONIC PROGRESSIVE.		7	4	
HYDRONEPHROSIS, UNILATERAL.		1	1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is

TABLE 40 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDENCE (NUMERIC)	Males		
	TREATMENT	0 mg/kg /day ^a I	300 mg/kg /day ^a IX
ENDOCRINE SYSTEM		(10)	(9)
THYROID GLAND		5	6
NO ABNORMALITY DETECTED			
HYPERTROPHY, FOLLICULAR.			
ALTERATION, COLLOID.		5	9
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.			1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678

TABLE 40 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg /day I	10 mg/kg /day V	60 mg/kg /day VII	300 mg/kg /day IX
DIGESTIVE SYSTEM					
LIVER		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		1	1		
NECROSIS, FOCAL.				1	3
INFLAMMATION, SUBACUTE/CHRONIC.		3	4	5	5
HYPERPLASIA, BILE DUCT.			1	1	
FIBROSIS, BILE DUCT.				1	
FATTY CHANGE, MEDIAN CLEFT.		2			1
FATTY CHANGE, CENTRILOBULAR.				1	
ECTASIA, BILE DUCT.				1	
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(5)	(5)	(5)
ALTERATION, COLLOID.		5	5	5	5

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)						
	TREATMENT	Females					
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
DIGESTIVE SYSTEM							
LIVER		(10)				(11)	
NO ABNORMALITY DETECTED						4	
INFLAMMATION, SUBACUTE/CHRONIC.		9				7	
FATTY CHANGE, MEDIAN CLEFT.		3				1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1	
PANCREAS		(10)				(11)	
NO ABNORMALITY DETECTED		7				9	
HYPERPLASIA, FOCAL, ACINAR CELL.		1				2	
DEGENERATION/NECROSIS, ACINAR CELL.		1				1	
ATROPHY.		2				1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
DIGESTIVE SYSTEM						
ESOPHAGUS		(10)				(11)
NO ABNORMALITY DETECTED		9				9
INFLAMMATION, SUBACUTE/CHRONIC.		1				2
STOMACH		(10)				(11)
NO ABNORMALITY DETECTED		10				11
DUODENUM		(10)				(11)
NO ABNORMALITY DETECTED		10				11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1
JEJUNUM		(10)				(11)
NO ABNORMALITY DETECTED		10				11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day isopropanol
^b H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
	0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
DIGESTIVE SYSTEM						
ILEUM	(10)					(11)
NO ABNORMALITY DETECTED	10					11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1
CECUM	(10)					(11)
NO ABNORMALITY DETECTED	10					11
COLON	(10)					(11)
NO ABNORMALITY DETECTED	10					11
RECTUM	(10)					(11)
NO ABNORMALITY DETECTED	10					11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 1^a

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)									
	TREATMENT	0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	Females			
DIGESTIVE SYSTEM										
SALIVARY GLANDS		(10)				(11)				
NO ABNORMALITY DETECTED		10				11				
URINARY SYSTEM										
KIDNEYS		(10)				(11)				
NO ABNORMALITY DETECTED		6				8				
NEPHROPATHY, CHRONIC PROGRESSIVE.		4				3				
INFARCT.		1				1				
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.										
URINARY BLADDER		(10)				(11)				
NO ABNORMALITY DETECTED		10				11				

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day isopropanol
^b H-24678

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESION	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Females					
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
RESPIRATORY SYSTEM							
LUNGS		(10)				(11)	
NO ABNORMALITY DETECTED		9				11	
INFLAMMATION, SUBACUTE/CHRONIC.		1					
TRACHEA		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
PHARYNX/LARYNX		(10)				(10)	
NO ABNORMALITY DETECTED		9				10	
INFLAMMATION, SUBACUTE/CHRONIC.		1					
NOSE		(10)				(11)	
NO ABNORMALITY DETECTED		10				10	
REGENERATION, OLFACTORY, EPITHELIUM.						1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)							
	TREATMENT	Females						
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X		
CARDIOVASCULAR SYSTEM								
HEART		(10)				(11)		
NO ABNORMALITY DETECTED		9				9		
CARDIOMYOPATHY.		1				2		
AORTA		(10)				(11)		
NO ABNORMALITY DETECTED		10				11		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)				(11)
NO ABNORMALITY DETECTED		10				11
THYMUS		(10)				(11)
NO ABNORMALITY DETECTED		10				11
MANDIBULAR LYMPH NODE		(10)				(11)
NO ABNORMALITY DETECTED		10				11
MESENTERIC LYMPH NODE		(10)				(11)
NO ABNORMALITY DETECTED		10				11
BONE MARROW		(10)				(11)
NO ABNORMALITY DETECTED		10				11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Females					
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	50 mg/kg /day VIII	300 mg/kg /day X	
ENDOCRINE SYSTEM							
PITUITARY GLAND		(10)				(11)	
NO ABNORMALITY DETECTED		10				10	
CYST.						1	
THYROID GLAND		(10)	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		5	8	7	6	8	
HYPERTROPHY, FOLLICULAR.						1	
ALTERATION, COLLOID.		5	2	3	4	3	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						1	
PARATHYROID GLANDS		(8)				(7)	
NO ABNORMALITY DETECTED		8				7	
ADRENAL GLANDS		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

TREATMENT	LESION INCIDENCE (NUMERIC)				
	Females				
	0 mg/kg /day II	60 mg/kg /day ^a IV	10 mg/kg /day ^b VI	60 mg/kg /day ^b VIII	300 mg/kg /day ^b X
NERVOUS SYSTEM					
BRAIN		(10)			(11)
NO ABNORMALITY DETECTED		10			11
SPINAL CORD		(10)			(11)
NO ABNORMALITY DETECTED		10			11
SCIATIC NERVE		(10)			(11)
NO ABNORMALITY DETECTED		10			11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESION	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(10)				(11)
NO ABNORMALITY DETECTED		10				11
FEMUR/KNEE JOINT		(10)				(11)
NO ABNORMALITY DETECTED		10				11
STERNUM		(10)				(11)
NO ABNORMALITY DETECTED		10				11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
REPRODUCTIVE SYSTEM						
OVARIES		(10)				(11)
NO ABNORMALITY DETECTED		10				11
UTERUS		(10)				(11)
NO ABNORMALITY DETECTED		6				9
DILATATION, GLAND/LUMEN.		4				2
MAMMARY GLAND (FEMALE)		(8)				(11)
NO ABNORMALITY DETECTED		8				11

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol

^b H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)						
	TREATMENT	Females					
		0 mg/kg /day II	60 mg/kg /day IV	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X	
CUTANEOUS SYSTEM							
SKIN		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
SPECIAL SENSES SYSTEM							
EYE(S) WITH OPTIC NERVE		(10)				(11)	
NO ABNORMALITY DETECTED		10				11	
OPTIC NERVE NOT PRESENT.		1				1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.							

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 60 mg/kg/day Isopropanol
^b H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT	Females
	0 mg/kg/day II	300 mg/kg/day ^a X
DIGESTIVE SYSTEM		
LIVER		(1)
FATTY CHANGE, MEDIAN CLEFT.		1
PANCREAS		(1)
NO ABNORMALITY DETECTED		1
ESOPHAGUS		(1)
NO ABNORMALITY DETECTED		1
STOMACH		(1)
NO ABNORMALITY DETECTED		1
DUODENUM		(1)
NO ABNORMALITY DETECTED		1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDENCE (NUMERIC)	Females	
	0 mg/kg/day ^a	300 mg/kg/day ^a
TREATMENT	II	X
DIGESTIVE SYSTEM		
JEJUNUM	(1)	
NO ABNORMALITY DETECTED AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.	1	1
ILEUM	(1)	
NO ABNORMALITY DETECTED AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.	1	1
CECUM	(1)	
NO ABNORMALITY DETECTED	1	
COLON	(1)	
NO ABNORMALITY DETECTED	1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
	TREATMENT	0 ng/kg /day II	300 ng/kg /day X	Females
DIGESTIVE SYSTEM				
RECTUM			(1)	
NO ABNORMALITY DETECTED			1	
SALIVARY GLANDS			(1)	
NO ABNORMALITY DETECTED			1	
URINARY SYSTEM				
KIDNEYS			(1)	
NO ABNORMALITY DETECTED			1	
URINARY BLADDER			(1)	
NO ABNORMALITY DETECTED			1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is



TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT	Females
	0 mg/kg/day ^a	300 mg/kg/day ^a
	II	X
RESPIRATORY SYSTEM		
LUNGS		(1)
NO ABNORMALITY DETECTED		1
TRACHEA		(1)
NO ABNORMALITY DETECTED		1
PHARYNX/LARYNX		(1)
NO ABNORMALITY DETECTED		1
NOSE		(1)
NO ABNORMALITY DETECTED		1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
	Males			Females
	TREATMENT	0 mg/kg/day II	300 mg/kg/day ^a X	
CARDIOVASCULAR SYSTEM				
HEART			(1)	
NO ABNORMALITY DETECTED			1	
AORTA			(1)	
NO ABNORMALITY DETECTED			1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)		
	TREATMENT	0 mg/kg/day II	300 mg/kg/day ^a X
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
SPLEEN		(1)	
NO ABNORMALITY DETECTED		1	
THYMUS		(1)	
NO ABNORMALITY DETECTED		1	
MANDIBULAR LYMPH NODE		(1)	
NO ABNORMALITY DETECTED		1	
MESENTERIC LYMPH NODE		(1)	
NO ABNORMALITY DETECTED		1	
BONE MARROW		(1)	
NO ABNORMALITY DETECTED		1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT	Females
	0 mg/kg/day II	300 mg/kg/day ^a X
ENDOCRINE SYSTEM		
PITUITARY GLAND	(1)	
NO ABNORMALITY DETECTED	1	
THYROID GLAND	(10)	(9)
NO ABNORMALITY DETECTED	8	
ADRENAL GLANDS	2	9
NO ABNORMALITY DETECTED	(1)	
	1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
	TREATMENT	0 mg/kg /day II	300 mg/kg /day X	Females
NERVOUS SYSTEM				
BRAIN			(1)	
NO ABNORMALITY DETECTED			1	
SPINAL CORD			(1)	
NO ABNORMALITY DETECTED			1	
SCIATIC NERVE			(1)	
NO ABNORMALITY DETECTED			1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
	TREATMENT		Females	
	0 mg/kg /day	300 mg/kg /day ^a X	0 mg/kg /day II	300 mg/kg /day X
MUSCULAR AND SKELETAL SYSTEM				
SKELETAL MUSCLE			(1)	
NO ABNORMALITY DETECTED			1	
FEMUR/KNEE JOINT			(1)	
NO ABNORMALITY DETECTED			1	
STERNUM			(1)	
NO ABNORMALITY DETECTED			1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT	Females
	0 mg/kg/day II	300 mg/kg/day ^a X
REPRODUCTIVE SYSTEM		
OVARIES		
NO ABNORMALITY DETECTED	(1)	1
UTERUS		
NO ABNORMALITY DETECTED	(1)	1
MAMMARY GLAND (FEMALE)		
NO ABNORMALITY DETECTED	(1)	1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT	Females 0 mg/kg/day ^a II 300 mg/kg/day ^a X
CUTANEOUS SYSTEM		
SKIN		(1)
NO ABNORMALITY DETECTED		1
SPECIAL SENSES SYSTEM		
EYE(S) WITH OPTIC NERVE		(1)
NO ABNORMALITY DETECTED		1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT	Females			
		0 mg/kg /day II	10 mg/kg /day VI	60 mg/kg /day VIII	300 mg/kg /day X
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED				1	1
ALTERATION, COLLOID.		5	5	4	4
REPRODUCTIVE SYSTEM					
MAMMARY GLAND (FEMALE)			(1)		
FIBROADENOMA [B].			1		

[B] Benign tumour
Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a H-24678 is [REDACTED]