Study Title

Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats (OECD 422)

Volume 1 of 3

TEST GUIDELINES: Organisation for Economic Cooperation and Development

(OECD), Section 4, (Part 422): Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test, *Guidelines for the Testing of*

Chemicals (1996).

U. S. EPA Health Effects Test Guidelines OPPTS 870.3650

Combined Repeated Dose Toxicity Study With the

Reproduction/Developmental Toxicity Screening Test (2000).

AUTHOR:

STUDY COMPLETED ON: September 19, 2008

PERFORMING LABORATORIES: E.I. du Pont de Nemours and Company

DuPont Haskell Global Centers

for Health & Environmental Sciences

P.O. Box 50

Newark, Delaware 19714

U.S.A.

LABORATORY PROJECT ID: DuPont-18331

WORK REQUEST NUMBER: 16123

SERVICE CODE NUMBER: 1422

SPONSOR: Petroleum HPV Testing Group

American Petroleum Institute (API)

1220 L Street, NW

Washington, D.C. 20005

U.S.A.

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are compatible with current OECD and MAFF (Japan) Good Laboratory Practices, except for the items documented below. The items listed do not impact the validity of the study.

- A sample of the test substance and the original containers will not be retained by the performing laboratory due to the flammability of the test substance and potential explosive hazards. Samples from the same lot in similar containers are retained by the sponsor at another location.
- The test substance was characterized by the sponsor prior to the initiation of this study. Although the characterization was not performed under Good Laboratory Practice Standards, the accuracy of the data is considered sufficient for the purposes of the study.

Applicant / Sponsor: Petroleum HPV Testing Group

American Petroleum Institute (API)

1220 L Street, NW Washington, D.C. 20005

U.S.A.



QUALITY ASSURANCE STATEMENT

Work Request Number: 16123 Study Code Number: 1422

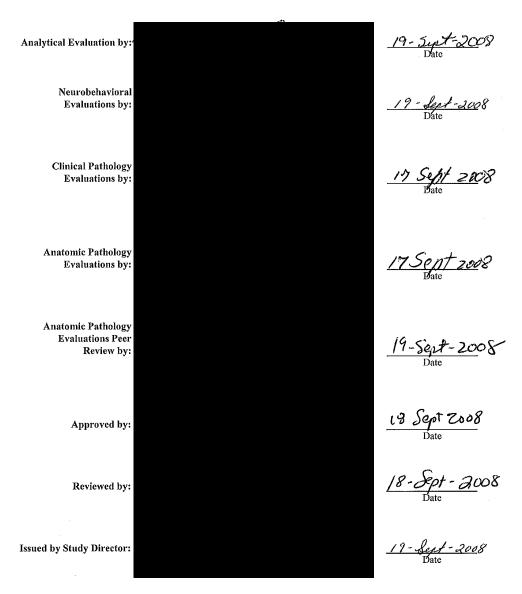
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Reported by:

12 Sep 2008

CERTIFICATION

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



CERTIFICATION (continued)

This report was accepted by the Sponsor.

Accepted by: 9/10/2008

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STUDY INFORMATION

Substance Tested: • Naphtha Petroleum, Heavy Straight-Run

• 64741-41-9 (CAS Number)

Synonyms: • High Naphthenic Naphtha

• Sweet Naphtha

Heavy Hydrocrackate

Haskell Number: 27199

Composition: The test substance contains approximately 225 volatile

hydrocarbons, of which 28 are unidentified.

<u>Purity:</u> The purity of the mixture is 100% (as reported by the

manufacturer)

Physical Characteristics: Colorless liquid

Stability: The test substance appeared to be stable under the

conditions of the study; no evidence of instability was

observed.

Study Initiated/Completed: May 8, 2006 / (see report cover page)

Experimental Start/Termination: May 9, 2006 / (see report cover page)

SUMMARY

Naphtha, petroleum, heavy straight run is a complex mixture of approximately 225 volatile, organic components. The purpose of this study was to evaluate the potential subchronic and reproductive toxicity from repeated inhalation exposure of male and female rats exposed to 0, 100, 500, or 3000 ppm of the test substance.

Concentrations of the test substance vapor were generated by flash evaporation of the test material, and an air control chamber group was also evaluated using a similar generation apparatus, however no test material was supplied to the vapor generator. Vapor concentrations of the test substance were measured by gas chromatography (GC) using the area sum function and integrating all of the eluted peaks. Additional air samples were collected weekly and analyzed for 12 of the larger, most representative components of the test substance using a cryogenic GC method supplied by the sponsor. Measuring these components indicates that all fractions of the test material were adequately vaporized. Temperature, humidity, and airflow were also recorded periodically during each exposure day. Exposures were conducted for 6 hours per day, 7 days per week.

Groups of 12 young, adult, male or nulliparous, non pregnant female Crl:CD(SD) rats were exposed to atmosphere containing 0, 100, 500, or 3000 ppm of the test substance for approximately 28 days. Since pregnancy status could influence the outcome of neurobehavioral, clinical pathology, and organ weight endpoints, separate, satellite groups of 12 young, nulliparous, nonpregnant female rats were exposed to 0, 100, 500, or 3000 ppm during a premating period of approximately 2 weeks, a cohabitation period of approximately 2 weeks, and a gestation period of approximately 3 weeks. The animals were not exposed after gestation day 19, or during the 4 day lactation period. Animals without evidence of mating continued to be exposed for 19 days after the end of the cohabitation period. Body weights, clinical signs, and food consumption were recorded throughout the study. After approximately 28 days, blood samples were collected from all male rats and all subchronic female rats for measurement of hematology and clinical chemistry parameters. An abbreviated neurobehavioral evaluation was conducted on all males, subchronic females, and satellite females prior to test substance administration in order to obtain baseline measurements. This neurobehavioral evaluation was conducted again following approximately 4 weeks of test substance administration for males and subchronic females. Males and subchronic females were sacrificed after approximately 28 days of exposure, selected organs were weighed, and selected tissues were evaluated microscopically.

Following the 2-week premating period, each satellite female was paired with a male of the same respective dosage group during an approximately 2 week cohabitation period. Measurements of body weight, food consumption, and clinical signs of toxicity in females were conducted throughout premating, cohabitation, gestation, and lactation. On postpartum day 4, blood samples were collected from lactating females for hematology and clinical chemistry parameters. In addition, the neurobehavioral evaluation was conducted on lactating females on postpartum day 4, and subsequently, lactating females and offspring were sacrificed, selected organs were weighed, and selected tissues were evaluated microscopically. Offspring were evaluated for external abnormalities.

The mean concentrations, (\pm standard error of the mean) representing the total area for the approximately 225 components contained in the test substance, were 100 ± 0.8 , 500 ± 2.0 , and 3000 ± 8.3 ppm in chambers targeted at 100, 500, and 3000 ppm, respectively. Results from the cryogenic GC analysis indicated that the components were present in the chamber atmosphere within expected concentrations.

Mortality did not occur during the study. Test substance-related increases in the incidence of stained and wet fur in males, subchronic females, and satellite females were observed; however, they did not adversely impact the health of the animals.

Adverse, test substance-related, decreases in body weight, weight gain, and/or food efficiency occurred in 3000 ppm subchronic females and satellite females. Slightly decreased body weight and/or weight gain occurred in 3000 ppm males; however, the magnitude of the effect was not considered to be adverse.

There were no adverse or test substance-related effects on reproductive function, neurobehavioral parameters, hematology and clinical pathology parameters, and no effects on offspring body weight, clinical observations, or survival.

Liver weight parameters were increased in 3000 ppm males and females, which correlated with hepatocellular hypertrophy. Kidney weight parameters were increased in 500 ppm and above males and 3000 ppm females. In males, the increased absolute/relative kidney weights correlated with hyaline droplet accumulation which was observed at 100 ppm and above males. In 3000 ppm females, the increased kidney weight parameters were not associated with any functional or microscopic change, and therefore were considered secondary to non-adverse enzyme induction.

Minimal centrilobular hepatocellular hypertrophy was observed in males and females exposed to 3000 ppm, possibly secondary to enzyme induction. Minimal hypertrophy of thyroid follicular epithelium occurred in 3000 ppm males and females, possibly secondary to the liver enzyme induction. In the kidney, the incidences of hyaline droplets, tubular granular casts, and chronic progressive nephropathy were increased in 100 ppm and above males.

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for systemic toxicity in males was not achieved based on an increased incidence of male-specific hyaline droplet accumulation at 100 ppm and above. However, these findings are generally accepted by U.S. EPA (1991) as a hydrocarbon – induced, male rat nephropathy, and not relevant to human risk assessment. NOAEL for male rats exclusive of the nephropathy is 500 ppm based on hypertrophy of the thyroid follicular epithelium observed in 3000 ppm males. The NOAEL for systemic toxicity in females was 500 ppm based on decreased body weight, weight gain, and food efficiency, and on hypertrophy of the thyroid follicular epithelium observed in 3000 ppm females. The NOAEL for reproductive and neurobehavioral toxicology was 3000 ppm, the highest concentration tested.

INTRODUCTION AND OBJECTIVE

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of the test substance when administered via inhalation to male and female rats. Clinical pathology, neurobehavioral function, gross pathology, histopathology, and reproductive function were evaluated.

SPONSOR

Sponsor: Petroleum HPV Testing Group

American Petroleum Institute (API)

1220 L. Street, NW Washington, DC 20005

U.S.A.

Attention:

EXPERIMENTAL DESIGN

A. Treatment Groups and Exposure Concentrations

Study Groups	Identification ^a					
Subchronic ^b and	Number/					
Satellite (Female) ^c	Sex	Subchronic		Satellite	Targeted Atmospheric	
	Group	Male	Female	Female	Conce	entration (ppm) ^d
1	12	101-112	113-124	125-136	0	Control
2	12	201-212	213-224	225-236	100	Low
3	12	301-312	313-324	325-336	500	Intermediate
4	12	401-412	413-424	425-436	3000	High

a The Identification Number was included on the cage label. The pretest number assigned to each animal was tattooed on the tail during the pretest period and included on the cage label.

B. Treatment Schedule

All exposures were conducted for 6 hours/day, 7 days/week. Lactating dams were not exposed.

Animals	Exposure Duration
Subchronic Males	30 Days
Subchronic Females	31 Days
Satellite Females	Premating: 14 Days Mating: Maximum 14 Days Gestation: 0-19 Days Lactation: Not exposed
Females with no evidence of copulation	54 Days

b Subchronic rats (repeated-treatment, general toxicity, neurotoxicity, clinical pathology, and pathology endpoints).

c Satellite females (reproductive and developmental toxicity, neurotoxicity, clinical pathology, and pathology endpoints).

d The test substance, administered by whole-body inhalation.

C. Study Parameters

Clinical Observations

Daily Animal Health Observations Daily (a.m., pre-exposure) Careful Clinical Observations Daily (p.m., postexposure)

Detailed Clinical Observations Once before first exposure and at least once per week

Clinical Observations During Inhalation Daily, at least 3 times during exposure

Exposures

Body Weights

At least twice/Weekly Quarantine/Pretest

During Study Weekly

Gestation Days 0, 7, 14, 21G Lactation

Days 0, 4L

Food Consumption and Food Efficiency

Weekly During Study

Cohabitation/ Postcohabitation

> (Subchronic Males and Satellite Females) None

Gestation – Satellite Females Days 0, 7, 14, 21G

Lactation – Satellite Females Days 0, 4L

Neurobehavioral Evaluations

Pretest All animals

Subchronic Males and Females Test day 28 (approximate)

Day 4L Satellite Dams with Litters

Clinical Pathology Evaluations

Coagulation All animals at terminal sacrifice

Hematology and Clinical Chemistry

Subchronic Males and Females Test day 28 (approximate)

Satellite Dams with Litters Day 4L

Necropsy

Sacrifice Schedule

Subchronic Males and Females After approximately 28 days of exposure Satellite nonpregnant Dams After approximately 26 days postcohabitation

Satellite Dams with Litters Day 4L Gross Pathology All animals

Offspring – Day 4L Pups – External examination

Organ Weights All animals (excluding offspring)

Histopathology

Subchronic Males and Females Control and high-dose groups (target organs and gross

lesions in intermediate-dose groups, if necessary)

Satellite Females Reproductive organs for rats with reproductive failure

D. Selection of Exposure Concentrations

In a previous range-finding study, (1) male and pregnant female rats were exposed to 0, 250, 1000, or 4000 ppm for 6 hours per day for 14 days (males) or gestation days 6-20 (females). Test substance-related decreases in body weight, weight gain, and food consumption occurred in 4000 ppm males and females. A slightly decreased body weight, food consumption and/or food efficiency were also observed in 250 and 1000 ppm males. Relative liver and kidney weights

were significantly increased in 1000 and 4000 ppm males and in 4000 ppm females; relative testes weights were increased in 1000 and 4000 ppm males. There were no significant differences in absolute kidney, liver, or lung weights in males or females, or testes weights in males. There were no test substance-related effects on clinical signs of toxicity, in adults, number of litters, number of fetuses, number of live fetuses, number of implantations, resorptions, or external fetal observations. At 4000 ppm, fetal weights were slightly lower compared to control values.

Based on these data, exposure concentrations of 0, 100, 500, and 3000 ppm were selected for this study.

E. Route of Administration

The test substance was administered by inhalation as it is a potential route of human exposure.

MATERIALS AND METHODS

A. Regulatory Compliance

The study design complies with the following test guidelines:

- U. S. EPA, OPPTS 870.3650: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test, *Health Effects Test Guidelines* (2000).
- OECD Section 4, (Part 422): Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test, Guidelines for the Testing of Chemicals (1996).

B. Analytical

1. Test Substance

Chemical Name: Naphtha Petroleum Heavy Straight-Run

Other Names Used in this Study: Sweet Naphtha, High Naphthenic Naphtha, Heavy

Hydrocrackate

CAS Number: 64741-41-9 (Appendix A)

Haskell Sample Number: H-27199

Purity: The test substance is a mixture which also contains

numerous volatile hydrocarbons. The purity of the mixture is 100% (as reported by manufacturer)

Color: Colorless Form: Liquid

Supplier: EPL Archives, Inc., Sample #1203-005 Vehicle: Nitrogen (purity > 99.9%) and filtered air.

2. Sample Characterization and Stability

The sponsor provided the purity information, composition of the test substance, physical characteristics of the test substance, and the analytical conditions which were used for the

12 component analysis (see section D.3 below). The weekly 12 component analysis was used to verify that all the components were being delivered to the exposure chambers, and that the test substance composition remained stable over the duration of the study.

C. Inhalation Exposure System

1. Exposure Chambers

Exposures to the test substance were conducted in NYU type 1.4-m³ chambers. The exposure chambers to be used for this study were constructed of stainless steel and glass, and were cubical with square-pyramidal chamber inlets and outlets with a tangential feed at the chamber inlet which promotes uniform chamber distribution of the test substance. The chamber volume was chosen so that the total body volume of the test animals did not exceed 5% of the chamber volume.

2. Atmosphere Generation

(Figure 1)

Chamber atmospheres were generated by flash evaporation of the test substance in nitrogen. The liquid test substance was metered into round-bottom, flash evaporation flasks. A Harvard Apparatus model 22 Syringe Infusion Pump supplied the liquid test material for the 100 ppm chamber, and Cole-Parmer Masterflex model 7521-40 pumps supplied the liquid to the 500 and 3000 ppm chamber evaporation flasks. The flasks were placed in Unimantle heaters that were heated to 185°C for the 0 and 100 ppm chambers, 210°C for the 500 ppm chamber, and 250°C for the 3000 ppm chamber. Brooks model 0154E mass flow controllers supplied approximately 10 L/min of high purity nitrogen (>99.9%) to the evaporation flasks. The resulting vapors were swept into the chambers' HEPA-filtered, conditioned air supply lines. Chamber concentrations of the test substance were controlled by varying the test substance feed rates to the evaporation flasks. The Harvard Apparatus infusion pump, Cole-Parmer Masterflex pumps, Brooks mass flow controllers, and the Unimantle heaters were controlled and monitored by a customized Camile Inhalation Toxicology Automated Data System (CITADS).

The chambers were exhausted by setting the exhaust airflow slightly higher than the incoming chamber air supply so that the exposure chambers would be under slight negative pressure with respect to the surrounding room. Each chamber air supply was set to be at least 240 L/min to achieve a minimum of 10 air changes per hour.

3. Chamber Distribution of the Test Substance

Uniform distribution of the main component of the test substance was determined during the method development study. (2)

4. Exposure Mode

Animals were individually placed in stainless steel wire mesh modules (one/module except during mating) and exposed, whole-body, inside the exposure chamber. The animals were

rotated to a different level within the chamber weekly when there was more than one level of cages, except during cohabitation.

D. Characterization of Chamber Atmosphere

1. Test Substance Sampling and Analysis

Test substance vapor in each of the test chambers was monitored approximately once an hour by drawing a sample of the chamber atmosphere through stainless steel tubing leading to a Hewlett Packard model 6890 GC equipped with a pneumatically operated gas sample valve and a flame-ionization detector (denoted subsequently as the main GC). Samples were automatically injected onto a 30-meter J & W Scientific DB-5 fused silica glass column and were chromatographed using an oven temperature ramp rate of 10°C/min from 40 to 125°C. The atmospheric concentration of the test substance was determined from a standard curve derived from vapor standards that were prepared daily. Gas standards were prepared by injecting 3 known volumes of liquid test substance into Tedlar[®] gas standard bags containing either 5 or 12 liters of air.

Throughout the 6-hour period, GC sample results were automatically transferred to a CITADS unit. Upon completion of the run, a Camile Inhalation Automated Reporting and Analysis System (CIRAS) collated the results of the vapor samples.

Nominal concentrations were calculated daily based on the daily total airflow in a given test chamber, the molecular weight and density of the test substance, and the volume of liquid test substance pumped into the vaporization flask according to the following equation:

$$\frac{\text{Total volume of TS (mL) x TS density (g/mL)}}{\text{mean airflow (L/min) x 360 (min)}} = g/L x \frac{24.450}{\text{MW (g/mole)}} = ppm$$

TS = test substance

MW = molecular weight (111.25 [derived from DuPont-18332])

24.450 = conversion factor

TS density = test substance density, 0.749 g/mL

2. Environmental Monitoring

Chamber temperature was targeted at $19\text{-}25^{\circ}\text{C}$ and chamber relative humidity was targeted at $50 \pm 20\%$. The temperature and humidity were monitored continually with VWR Dial Hygrometer Thermometer Humidity meters and recorded 3 times during each exposure. The airflow was monitored continually with Omega model number FMA-604-V thermoanemometers, and recorded 3 times during each exposure. Chamber oxygen concentration was targeted to be at least 19%. The oxygen concentrations were measured with a Biosystems model 3100R oxygen analyzer and recorded one time during each exposure for each chamber.

3. Twelve Component Analysis

Since the test substance is a mixture of approximately 225 components (Appendix C), 12 components were selected for further analysis in order to verify that all the components in the test substance were being delivered to the chamber. The 12 components were selected from a

cross sample of the components' peak retention times. The analyses were conducted on samples collected from the test chambers approximately weekly.

For this analysis, samples from the 100, 500, and 3000 ppm chambers were collected in Tedlar® gas standard bags and were injected into a separate Hewlett Packard model 6890 Plus GC also equipped with a pneumatically operated gas sample valve and a flame-ionization detector (denoted subsequently as the cryogenic GC). Samples were injected onto a 100-meter Sep Sys SD-009 column and were chromatographed using a cryogenic oven with 3 different oven temperature ramp rates starting from 0°C and ending with a final oven temperature of 262°C. The total run time for one chromatographic analysis was 138 minutes.

Gas standards were prepared by injecting known volumes of the test substance into Tedlar[®] gas standard bags containing known volumes of air. The 12 components' concentrations were calculated by multiplying the percent volume values supplied by the sponsor by the standard concentration. The cryogenic GC was then calibrated for each of the 12 peaks using the individual component concentrations. The standard curve was entered, and an external standard option using a linear curve was selected. The GC Hewlett Packard Chemstation software calculated the concentration of the 12 components in the test substance in parts per million (ppm).

E. Duration of Exposure

Animals were exposed as described in the study design. The starting time of each exposure was defined as the time when the generation system is turned on, and the ending time of each exposure was defined as the time when the generation system was turned off. After each exposure, rats were returned to their home cages.

F. Test Species

Species: Rat

Strain: Crl:CD(SD)

Sex: Male and female, nonsiblings, nulliparous

Source: Charles River Laboratories, Inc

Raleigh, North Carolina

Number of Rats

Requested/Received: 53 males; 105 females

> Age at Arrival: 46 days

Age at Experimental Initiation (First day of

> Exposure): 60 days

> > Weight on Day Approximately 146.5-185.4 grams (males); Approximately 136.8-177.2 grams (females) after Arrival:

> > > The weight range at the time of arrival was not a factor for the purposes of this study since animals were randomly distributed by weight at the time of assignment to groups. Therefore, deviations outside of this range were expected not to have any

impact on the study.

Identification: Number assigned to each animal which was tattooed on the tail

during pretest period and included on cage label.

Selection Criteria: Consistently acceptable health status and extensive experience

with this strain at Haskell Laboratory.

G. Animal Husbandry

Housing - Male

All Phases: Individually (except during cohabitation of mating pairs) in

stainless steel, wire-mesh cages suspended above cage boards;

sexes on separate racks.

Housing – Subchronic

Study Females

All Phases: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Housing – Satellite

Females

Quarantine/Premating: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Cohabitation: Mating pairs (females placed in males' cages) on a 1:1 basis in

stainless steel, wire-mesh cages suspended above cage boards

Days 0–19 of gestation: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Day 19 of gestation -

Day 4 of lactation: After the last exposure on day 19 of gestation, females assumed

pregnant were housed individually in polycarbonate pans with bedding material. Females presumed nonpregnant were housed in the same manner as pregnant females 7 days after the mating

pairs were separated.

Climate: Temperature was maintained at 18-26°C

Relative humidity was maintained at 30%-70%

Illumination: Artificial (fluorescent light) on an approximate 12-hour

light/dark cycle.

Water: Tap water from United Water Delaware ad libitum provided by

an automatic watering system except during exposure.

Feed: PMI[®] Nutrition International, LLC Certified Rodent LabDiet[®]

5002 (pelleted) ad libitum except during exposure and when

fasted.

H. Animal Health and Environmental Monitoring Program (Appendix TT)

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 Screening Tests: Total bacterial counts, and the presence of coliforms, lead, and

other contaminants

Cage and Cage Rack Analyzed for sentinel bacteria to ensure adequate sanitation by

Screening Tests: the cagewashers

Feed: 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.

Program Administration: Laboratory animal veterinarian

Data: Maintained separately from study records

I. Quarantine and Pretest Periods

Pretest Period: 14 days

Quarantine: 6 days (during the pretest period)

Quarantine Release: Test Day -8; performed by the laboratory animal veterinarian or

designee on the basis of adequate body weight gain and absence

of clinical signs of disease or injury.

J. Assignment to Groups

Selection Criteria: Animals without adequate body weight gain and/or with clinical signs

of disease or injury were eliminated from consideration for use in the study; weight variation of individual rats did not exceed $\pm 20\%$ of the

mean weight for each sex.

Randomization: Computerized, stratified randomization so that no statistically

significant group mean body weight differences occur within a sex.

Disposition of Remaining

Animals: Sacrificed by carbon dioxide asphyxiation.

K. In-life Observations of Females

1. Daily Animal Health Observations

Frequency: All animals – At least once daily during quarantine and pretest,

and once daily thereafter. On exposure days, the observations were conducted at the time animals were placed in the exposure

modules.

Scope: Cage-site examination to detect moribund or dead animals.

2. Careful Clinical Observations

Frequency: All animals – once daily after initiation of exposures. On

exposure days, the observations were conducted at the time the animals were returned to their home cages. On non-exposure

days, observations were conducted in the afternoon.

Scope: Acute/systemic toxicity, including but not limited to nervous

system function.

3. Detailed Clinical Observations

Frequency: All animals - Once during pretest (baseline), and weekly

thereafter

Scope: Animals individually handled and examined for abnormal

behavior and appearance in a standardized arena; 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

bizarre behavior.

4. Clinical Observations During Inhalation Exposures

Frequency: All animals visible to the observer through the glass window of

the chamber were observed collectively as a group at least

3 times during each exposure.

Scope: Observations through the window of the chamber for abnormal

behavior or appearance.

5. Body Weight

Quarantine/Pretest: Four weights were collected.

Subchronic Males and

Females: Weekly

Satellite Females: Premating – Weekly.

Cohabitation – Weekly.

Gestation – Days 0, 7, 14, 21G.

Lactation – Days 0, 4L.

Satellite Females without

evidence of copulation:^a Post-cohabitation – Weekly

Neurobehavioral Evaluations: All animals evaluated were weighed on the day of the functional

observational battery (FOB) assessment.

Body Weight Collected at

Terminal Sacrifice All animals.

a Evidence of copulation = intravaginal copulation plug or sperm in the lavage sample.

6. Food Consumption and Food Efficiency

Subchronic Males: Premating – weekly.

Cohabitation and postcohabitation – none.

Subchronic Females: Weekly

Satellite Females: Premating – Weekly.

Cohabitation – None.

Gestation – Days 0, 7, 14, 21G.

Lactation – Days 0, 4L.

Satellite Females without

evidence of copulation: Postcohabitation – None.

Calculation of Food Feeders were weighed at the beginning and end of the interval.

Consumption: The final weight and amount of spillage from the feeder were

subtracted from initial weight.

Calculation of Mean

Daily Food Efficiency: From food consumption and body weight data.

L. Reproductive/Developmental Assessment

Subchronic Male Rats and Satellite Female Rats

1. Cohabitation^a/Pairing

Frequency: Once after approximately 2 weeks of exposure to the test

substance.

Scope: Each satellite female was continually housed on a 1:1 basis with

a randomly selected, nonsibling subchronic male of the same

concentration level.

Duration: Until evidence of copulation was observed or the cohabitation

period ended (Day 14 of cohabitation), at which time the mating

pairs were separated.

Evidence of Copulation: b Daily examination of each female for an intravaginal copulation

plug or sperm in the vaginal lavage sample.

a First day of cohousing = Day 0 of cohabitation; End of cohousing = Day 14 of cohabitation

M. Gestation

After being transferred into polycarbonate pans (on day 19 of gestation for mated females, or 7 days after the mating pairs have been separated for females without evidence of copulation), female rats were observed at least twice daily for signs of delivery and offspring.

N. Lactation

On lactation days 0 and 4, offspring were individually handled and examined for abnormal behavior and appearance; any dead or abnormal pups were recorded.

Day 0:^a Live and dead pups in each litter were counted by sex.

Live pups were individually weighed as soon as possible after delivery was completed.

Dead pups were sent to pathology. The lungs were removed from the pups and placed in saline to determine if they floated.

Day 4:^b Pups in each litter were counted by sex and live pups were individually weighed and a gross external examination was performed.

b Litter Sacrifice

Individual pups that died prior to Day 4 of lactation were examined to the extent possible and discarded.

b Evidence of copulation = Day 0 of gestation

a Day of delivery = Day 0 of lactation

O. Neurobehavioral Evaluation

Pretest: All animals, including spares

During Study: Subchronic Males and Females – Week 4 (test days 26-29), in

the morning, prior to the daily exposure. Satellite Dams with Litters – Day 4L.

Scope: Neurobehavioral test battery consisting of an abbreviated

functional observational battery assessment (FOB) and

motor activity (MA).

Animal Identification: Experimenter was unaware of treatment group of the subchronic

animals. The testing lots were evenly distributed across groups

and days for both the pretest and week 4 assessments.

Acclimation: At least 10 minutes in the FOB laboratory prior to initiation of

assessment.

Order of FOB and MA

Assessments: The parameters were evaluated in the order shown in the table

below.

1. Parameters

Body weights were collected on the day of neurobehavioral assessments.

Phase	Order	Procedure	Parameters or Methods	
FOB	1	Manipulations in Open Field	approach and touch response auditory response	tail pinch response
FOB	2	Fore- and hindlimb grip strength Strain gauge (Chatillion®)	forelimb grip strength	hindlimb grip strength
MA	3	Motor Activity	Duration of movement and nur evaluated in 6 consecutive bloc for the total 60-minute session	cks of 10 minutes each as well as
MA	4	Assessments in MA monitor	diarrhea	polyuria
FOB	5	Pupillary Constriction or Response ^a	Light beam directed to each ey	ve in the darkened MA room

a Conducted at the conclusion of motor activity while the animals were still in the motor activity monitor

2. Test Facility Positive Control Data

Procedures and data describing the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are presented in 5 separate reports. These positive control studies are the basis of training certification for the personnel 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 studies of this type.

P. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all subchronic animals on test days 31 (males) and 32 (females), and on lactating females on test days 42-45. The day before collection of samples for the clinical pathology evaluation for the subchronic part of the study, the animals were allowed to eat for 2 hours after the exposure period, and then were fasted after 3 p.m. for at least 15 hours. Lactating females were not fasted prior to blood collection. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for coagulation parameters were collected at sacrifice from the abdominal *vena cava* of each animal while the animal was under carbon dioxide anesthesia. Additional blood collected from the vena cava was placed in a serum tube, processed to serum, and frozen at approximately -80°C. Serum will be discarded without analysis because further tests were not required to support experimental findings. Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright-Giemsa stain, but analysis was not necessary to support experimental findings. All blood samples were evaluated for quality by visual examination. Results were maintained in the study records and reported only if the sample was analyzed.

1. Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on a Bayer[®] Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-Giemsa-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Coagulation times were determined on a Sysmex[®] CA-1000 Coagulation Analyzer.

The following parameters were determined:

red blood cell count hemoglobin hematocrit mean corpuscular (cell) volume mean corpuscular (cell) hemoglobin mean corpuscular (cell) hemoglobin concentration red cell distribution width absolute reticulocyte count platelet count white blood cell count differential white blood cell count microscopic blood smear examination

prothrombin time activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on an Olympus® AU640 clinical chemistry analyzer.

The following parameters were determined:

aspartate aminotransferase glucose
alanine aminotransferase total protein
sorbitol dehydrogenase albumin
alkaline phosphatase globulin
gamma glutamyl transferase calcium

total bilirubin inorganic phosphorus

urea nitrogen sodium creatinine potassium cholesterol chloride

triglycerides albumin/globulin ratio

Q. Anatomic Pathology Evaluation

1. Quarantine/Pretest

No animals were found dead or sacrificed in extremis during the quarantine/pretest period.

2. Subchronic Males and Females

After 31 (males) or 32 (females) days on study, rats designated for the subchronic toxicity evaluation (12/sex/group) were sacrificed and necropsied. The order of sacrifice for scheduled deaths was stratified across all treatment groups within a sex. Rats were euthanized by carbon dioxide anesthesia and exsanguination. A gross examination was performed on all rats. Final body weights and organ weights were recorded.

All rats designated for subchronic toxicity evaluation survived until the scheduled terminal sacrifice. The following tissues were collected from all rats.

Digestive System	Cardiovascular System	Musculoskeletal System
liver	heart	femur/knee joint
stomach		
duodenum	Hematopoietic System	Reproductive System
jejunum	spleen	Male
ileum	thymus	testes
cecum	mandibular lymph node	epididymides
colon	mesenteric lymph node	prostate
rectum	bone marrow ^a	seminal vesicles
	Peyer's patch ^b	coagulating glands
<u>Urinary System</u>	-	
kidneys	Endocrine System	Female
urinary bladder	thyroid gland	ovaries
-	adrenal glands	oviducts
Respiratory System		uterus
lungs	Nervous System	cervix
trachea	brain (three sections) ^c	vagina
	spinal cord (three levels) ^d	_
	sciatic nerve	Miscellaneous
		Gross observation ^e

- a Bone marrow was collected with the femur.
- b Pever's patches were collected with the intestines.
- c Brain included cerebrum, midbrain, cerebellum, and medullar/pons.
- d Spinal cord included cervical, mid-thoracic, and lumbar sections.
- e Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected.

The following tissues were weighed from all rats at necropsy: liver, kidneys, lungs, adrenal glands, thymus, brain, spleen, heart, testes, epididymides, prostate, ovaries (with oviducts), and uterus (with cervix). Group mean absolute organ weight values and organ weight ratios (% body weight and % brain weight) were calculated.

Testes and epididymides were fixed in modified Davidson's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, sectioned approximately 5-6 microns thick, and stained with hematoxylin and eosin (H&E).

All collected tissues from rats in the control and 3000 ppm exposure groups were processed to slides and evaluated microscopically. Gross lesions, target organs–kidneys (males only), liver, and thyroid gland–were evaluated microscopically from all rats designated for subchronic toxicity evaluation.

3. Satellite Females and Offspring

Procedures for euthanasia, necropsy, gross examination and tissue collection/fixation for satellite females were the same as for subchronic animals. In addition, all satellite females were examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*. Only one mating pair (male 406/female 430 in the 3000 ppm group) failed to produce a litter. Reproductive organs from the animals were processed and evaluated microscopically.

The following tissues were weighed from satellite females at necropsy: liver, kidneys, lungs, ovaries (with oviducts), and uterus (with cervix). Group mean absolute organ weight values and organ weight ratios (% body weight) were calculated.

All offspring surviving to postnatal day 4 were evaluated for external alterations and euthanized by intraperitoneal (i.p.) injection of sodium pentobarbital. Pups found dead or sacrificed in extremis were examined grossly and discarded.

STATISTICAL ANALYSES

A. Reproductive Function Calculations

The following table lists the indices of reproductive function that were calculated for the parental animals.

Reproductive Function Calculations

Mating index (%)	=	number mated ^a number paired	– x 100
Fertility index (%)	=	number pregnant ^b number mated ^a	- x 100
Post-Implantation Loss (%) ^c	=	number of implantation sites - number of pups born number of implantation sites	– x 100
Live Born Index (%) ^c	=	number of pups born alive number of pups born	– x 100
Viability index (%) ^{c,d}	=	number of pups alive Postnatal Day (PND) 4 number of pups born alive	- x 100

Mated = intravaginal copulatory plug, sperm in vaginal lavage, uterine implantation sites, or delivery of a litter.

b Including those found dead pregnant during gestation.

c Determined for each litter.

d Excluding litters sacrificed due to death of dam during lactation.

B. Statistical Methods

		Method of Statistical Analysis (see Appendix A for references) If preliminary test is not	
Parameter	Preliminary Test	significant	significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Precoital Interval Gestation Length Corpora Lutea Implantation Sites Post-Implantation Loss Number of Pups Per Litter Live Born Index Viability Index Clinical Pathology Parameters Organ Weight Parameters	Levene's test for homogeneity ⁽⁸⁾ and Shapiro-Wilk test ⁽⁹⁾ for b normality	One-way analysis of variance ⁽¹⁰⁾ and Dunnett's test ^(11,12,13)	Kruskal-Wallis test ⁽¹⁴⁾ and Dunn's test ⁽¹⁵⁾
FOB Descriptive Parameters Mating Index Fertility Index	None	Sequential application of Cochran-Armitage test for trend ^{(10)c}	
Sex Ratio (Covariate: litter size) Pup Weights (Covariates: litter size, sex ratio)	Levene's test for homogeneity ⁽⁸⁾ and Shapiro-Wilk test ⁽⁹⁾ for d normality	Analysis of covariance ⁽¹⁰⁾ and Dunnett-Hsu ⁽¹⁶⁾	Non-parametric analysis of covariance ⁽¹⁷⁾
Motor Activity ^e Grip Strength	Levene's test for homogeneity ⁽⁸⁾ and Shapiro-Wilk test ⁽⁹⁾ for normality ^d	Repeated measures analysis of variance ⁽¹⁸⁾ followed by Linear contrasts ⁽¹⁹⁾	Sequential application ⁽²⁰⁾ of the Jonckheere-Terpstra trend test ⁽²¹⁾

- a 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 data.
- b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed with Dunn's test.
- c If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽²²⁾ with a Bonferroni correction was used.
- d A normalizing, variance stabilizing transformation was used as needed.
- e Test day and 10-minute interval were used as repeated-measure factors.

Male and female data were evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean were used as the experimental unit for statistical evaluation. (23) The level of significance selected was p < 0.05.

RESULTS

ANALYTICAL

A. Test Substance Concentration

(Table 1, Figure 2, Appendices D-E)

The mean concentrations, (\pm standard error of the mean) representing the total area for the approximately 225 components contained in the test substance, were 100 ± 0.8 , 500 ± 2.0 , and 3000 ± 8.3 ppm in chambers targeted at 100, 500, and 3000 ppm, respectively (note: whenever possible, 2 significant figures were used. Overall daily mean concentrations ranged from 90-110 ppm for the 100 ppm chamber, from 480-560 ppm for the 500 ppm chamber, and from 2800-3100 ppm for the 3000 ppm chamber. The calculated nominal concentrations were generally similar to the actual measured concentrations, with a mean calculation concentration of 101, 584, and 3410 ppm for the 100, 500, and 3000 ppm chambers, respectively (Appendix E). These data demonstrate that the exposure system and analyses were operating as expected.

B. Chamber Environmental Conditions

(Table 2, Appendix F)

The temperatures in the 0, 100, 500, and 3000 ppm chambers ranged from 19-25°C. The chamber temperatures were lower than the targeted range of 21-25°C, however, this difference did not adversely impact the study based on the clinical appearance of the animals.

The relative humidity in the 0, 100, 500, and 3000 ppm chambers was 41%-59%.

The chamber airflows in the 0, 100, 500, and 3000 ppm chambers ranged from 250-400 L/min which was adequate to achieve at least 10 air changes per hour.

The oxygen concentration in the 0, 100, 500, and 3000 ppm chambers was 20%.

C. Twelve Component Analysis

(Table 3, Appendix G)

The concentrations of the 12 selected components indicated small differences between the expected theoretical value and the analytically determined values. However, these differences were most likely due to the low concentration of the components which approached the lower limit for accurate quantification for a flame ionization detector. Therefore, the 12 components evaluated were present in the exposure chamber within the acceptable range of variation from the theoretical values and indicate that the vapor generation method performed as expected.

IN-LIFE TOXICOLOGY

A. Clinical Observations and Mortality

Mortality did not occur during the study. Test substance-related increases in the incidence of stained and wet fur in males, subchronic females, and satellite females were observed. However, they did not adversely impact the health of the animals.

1. During Exposure – All Rats

(Table 4)

Wet fur was observed during exposure in the 3000 ppm animals beginning at the 18th exposure. This observation was consistent with the stained and wet fur observed post-exposure.

2. Subchronic Male Rats

(Tables 5-6, Appendices H-I)

Test substance-related, statistically significant increases in the incidences of red stained facial fur and wet fur were observed in rats following exposure to 3000 ppm. All other post exposure clinical observations and detailed clinical observations had similar incidences across all exposure groups.

3. Subchronic Female Rats

(Tables 7-8, Appendices J-K)

Test substance-related, statistically significant increases in the incidences of red stained facial fur and wet fur were observed in rats following exposure to 3000 ppm, and stained fur was also significantly increased in 500 ppm females. In addition, the incidence of stained fur was significantly increased in 3000 ppm females during detailed observations conducted prior to the daily exposure session. All other post exposure clinical observations and detailed clinical observations had similar incidences across all exposure groups.

4. Satellite Female Rats

(Tables 9-12, Appendices L-O)

<u>Premating</u>: Test substance-related, statistically significant increases in the incidences of red stained facial fur and wet fur were observed in rats following exposure to 3000 ppm, and stained fur was also significantly increased in 500 ppm females. All other post-exposure clinical observations had similar incidences across all exposure groups.

<u>Gestation</u>: Test substance-related, statistically significant increases in the incidences of red stained facial fur and wet fur were observed in rats following exposure to 3000 ppm, and stained fur was also significantly increased in 500 ppm females. All other post-exposure clinical observations had similar incidences across all exposure groups.

<u>Lactation</u>: A test substance-related, statistically significant increase in the incidence of red stained facial fur was observed in rats previously exposed to 3000 ppm.

The incidence of stained fur in satellite females was also evident in 500 and 3000 ppm satellite females during detailed observations conducted prior to the daily exposure session. All other detailed clinical observations had similar incidences across all exposure groups.

B. Body Weights and Body Weight Changes

1. Subchronic Male Rats

(Tables 13-14, Appendices P-Q)

No adverse or statistically significant effects on body weight or weight gain were observed in males for any exposure concentration. On test day 29 (last body weight prior to fasting), body weight of 3000 ppm males was slightly (5%) lower compared to the control mean; and weight gain for the interval of test days 1-29 was 15% lower for 3000 ppm males compared to controls. Since mean body weight on test day 29 was only 5% lower than the control value, it was not considered to be an adverse effect. There were no test substance-related effects or statistically significant differences on weight or weight gain in 100 or 500 ppm males.

2. Subchronic Female Rats

(Tables 15-16, Appendices R-S)

Test substance-related, statistically significant decreases in body weight gain occurred in 3000 ppm females. Body weights and body weight gain values for 3000 ppm females were significantly lower (7% and 70%, respectively) compared to the control group on test day 8 and over test days 1-8, respectively. Body weight for 3000 ppm females was 8% lower compared to the control value on test day 29 (final body weight prior to fasting); and weight gain was 35% lower compared to the control value on test days 1-29. These decreases were considered to be test substance related and adverse. There were no test substance-related effects or statistically significant differences on weight or weight gain in 100 or 500 ppm females.

3. Satellite Female Rats

(Tables 17-22, Appendices T-Y)

<u>Premating</u>: No adverse or statistically significant effects on body weight or weight gain were observed in females for any exposure concentration during the 2-week premating period. On test day 15, body weight of 3000 ppm females was slightly (4%) lower compared to the control mean; and weight gain for the interval of test days 1-15 was 29% lower for 3000 ppm females compared to controls. As was observed in subchronic females, body weight gain was decreased during the first week of exposure at 3000 ppm. However, the magnitude of the change (26% lower than controls) was not sufficient to be statistically significant. Since mean body weight on test day 15 was only 4% lower than the control value, it was not considered to be an adverse effect. There were no test substance-related effects or statistically significant differences on weight or weight gain during the premating period in 100 or 500 ppm females.

Gestation: Test substance-related effects on body weight and weight gain were observed in 3000 ppm females during the 3-week gestation period. On GD21, body weight of 3000 ppm females was slightly (7%) lower compared to the control mean; and weight gain for the interval of GD 0-21 was 14% lower for 3000 ppm females compared to controls. The lower body weight on GD 21 correlates with the lower weight on LD 0 and was considered to be an adverse effect. There were no test substance-related effects or statistically significant differences on weight or weight gain during the gestation period in 100 or 500 ppm females.

<u>Lactation</u>: Test substance-related, statistically significant decreases in body weight occurred in 3000 ppm females. Body weight for 3000 ppm females was 7% lower compared to the control value on Lactation Day (LD) 0; however, weight gain for the interval of LD 0-4 was similar to the control value. The significantly lower body weight on LD 0 for 3000 ppm females suggests an effect on the maternal body weight gain during gestation, and correlates with the lower weight on GD 21 and lower weight gain over the interval of GDs 0-21. There were no test substance-related effects or statistically significant differences on weight or weight gain in 100 or 500 ppm satellite females.

C. Food Consumption and Food Efficiency

1. Subchronic Male Rats

(Tables 23-24, Appendix Z)

Test substance-related, statistically significant decreases in food consumption occurred in males exposed to 3000 ppm of the test substance. Food consumption for 3000 ppm males was significantly lower on test days 1-8, and 1-15, and was 11% lower compared to the control value for test days 1-15. The slightly lower food consumption correlates with the slightly lower body weight and weight gain for 3000 ppm males, however, it was not considered to be adverse due to the small magnitude of the effect on body weight. There were no test substance-related effects or statistically significant differences on food consumption or food efficiency in 100 or 500 ppm males, or on food efficiency in 3000 ppm males.

2. Subchronic Female Rats

(Tables 25-26, Appendix AA)

A test substance-related decrease in food efficiency occurred in 3000 ppm females. During test days 1-8, food efficiency was decreased 72% compared to the control value, was decreased 42% during test days 22-29, and was decreased 33% for the interval of test days 1-29. There were no test substance-related effects or statistically significant differences on food consumption in females for any exposure concentration, or on food efficiency for the 100 and 500 ppm groups.

The decreased food efficiency in 3000 ppm females correlates with the decreased body weight, and was considered to be adverse.

3. Satellite Female Rats

(Tables 27-32, Appendices BB-DD)

<u>Premating</u>: There were no statistically significant differences on food consumption or food efficiency in females for any exposure concentration. However, food efficiency was slightly decreased (21%) in 3000 ppm satellite females during test days 1-8, decreased 32% during test days 8-15, and decreased 25% for the interval of test days 1-15.

<u>Gestation</u>: Food consumption was slightly decreased (8-10%) in 3000 ppm satellite females during GD 0-7, 7-14, 14-21, and 0-21.

<u>Lactation</u>: There were no statistically significant differences on food consumption or food efficiency in females for any exposure concentration.

REPRODUCTIVE/DEVELOPMENTAL ASSESSMENT

A. Reproductive Indices in Satellite Female Rats

(Table 33, Appendices EE-FF)

There were no test substance-related or statistically significant differences in mean number of pregnant animals, number of animals delivering, mating index, fertility index, precoital interval, gestation length, number of corpora lutea, number of implantation sites, or percent of post-implantation loss for any exposure concentration. The mating date for Dam #434 could not be determined from the vaginal smears, and as a result, she delivered during exposure.

B. Litter Parameters

1. Litter Size, Sex Ratio, Pup Survival, Clinical Observations, Pup Weights (Tables 34-36, Appendices GG-II)

There were no test substance-related or statistically significant differences in number of fetuses born or born alive, live born index, viability index, sex ratio, incidence of clinical observations, or mean pup body weight on postnatal days 0 or 4. Mean litter weight on PND 0 and PND 4, and mean litter survival on PND 4 were slightly lower for the 3000 ppm group compared to the control value due to one litter (Dam #434) which delivered during exposure and lost 5/12 pups between lactation days 0-4. The mating date for this dam could not be determined. All other 3000 ppm litters had 100% survival on PND 4. PND 0-4 viability index for Dam #434 was omitted from the mean, and the offspring body weights were re-analyzed omitting Dam #434, yielding 3000 ppm group means that were comparable to control.

NEUROBEHAVIORAL EVALUATION

A. Abbreviated Functional Observational Battery

1. Forelimb Grip Strength

(Tables 37-39, Appendices JJ-KK)

There were no test substance-related effects or statistically significant differences on forelimb grip strength in subchronic males, subchronic females or satellite females exposed to any concentration of the test substance.

2. Hindlimb Grip Strength

(Tables 37-39, Appendices JJ-KK)

There were no test substance-related effects or statistically significant differences on hindlimb grip strength in subchronic males, subchronic females, or satellite females exposed to any concentration of the test substance.

3. Open Field Observations

(Tables 40-42, Appendices LL-MM)

There were no test substance-related effects or statistically significant effects for any behavioral parameter evaluated in subchronic males, subchronic females, or satellite females exposed to any concentration of the test substance. At the week 4 evaluation, females exposed to 3000 ppm had a significantly higher incidence of stained facial fur, which is consistent with the post-exposure observations and detailed clinical observations. However, the stained facial fur was not present in the satellite females evaluated on LD 4, since their exposure to the test substance had been discontinued after test day 19. Although the stained facial fur was considered to be test substance-related, and was present at the time of the neurobehavioral evaluation, it is not indicative of an effect on the function of the nervous system.

B. Motor Activity

(Tables 43-48, Appendices NN-QQ)

There were no test substance-related effects on duration of movement or number of movements in subchronic males, subchronic females, or satellite females exposed to any concentration of the test substance. During the baseline and week 4 evaluations, subchronic males in the 3000 ppm group had significantly lower total duration and number of movements compared to the control mean. In addition, duration and number of movements were significantly lower for 3000 ppm males during the 4th and 5th 10-minute interval of the baseline evaluation, and during the 6th 10-minute interval of the week 4 evaluation. Number of movements was also significantly lower for 3000 ppm males during the second 10-minute interval. However, since total duration and number of movements were significantly lower compared to control during both the baseline and week 4 evaluation, and the relative magnitude of the difference was similar for both the baseline and week 4 evaluations, these statistical differences were not considered to be test substance related.

CLINICAL PATHOLOGY EVALUATION

A. Hematology

(Tables 49-50, Appendix RR)

There were no adverse changes in hematology parameters in male or female rats. The following statistically significant changes in mean hematology parameters were not adverse or not related to exposure to the test substance:

- Reticulocytes were statistically but mildly decreased at test days 42-45 in the satellite female rats exposed to 3000 ppm (mean was 77% of the control group mean). The decrease in reticulocyte count was of uncertain relationship to treatment. In this study, there was no effect of the test substance on red cell mass parameters (red blood cell, hemoglobin and hematocrit). Minimally lower reticulocyte counts without any changes in red cell mass parameters have no biological significance. Therefore, this change was considered to be non-adverse.
- Neutrophils were mildly decreased at test days 42-45 in the satellite female rats exposed to 3000 ppm (mean was 73% of the control group mean). The lower limit of individual values was generally similar across all 3 treatment groups, despite the 300-fold difference in concentration, while the upper limit of individual values was higher in rats exposed to 0-500 ppm of the test substance. This change was of uncertain relationship to treatment. However, due to the similar lower range in both control and treated groups, this change was considered to be non-adverse.

B. Coagulation

(Tables 51-52, Appendix RR)

There were no treatment-related changes in coagulation parameters in male or female rats. Statistically significant prolonged activated partial thromboplastin time at test day 31 in male rats exposed to 500 ppm was considered to be unrelated to treatment and non-adverse because it did not occur in a dose-related pattern.

C. Clinical Chemistry

(Tables 53-54, Appendix RR)

There were no adverse changes in clinical chemistry parameters in male or female rats. The following statistically significant changes in mean clinical chemistry parameters were not adverse:

• Glucose was minimally decreased at test days 31/32 in males and females exposed to 3000 ppm (means were 84% and 92% of the respective control group means for males and females). In males, the decrease in glucose was primarily due to one control male (animal 112) with a moderately high glucose concentration. With the exception of 2 rats with high glucose concentrations (animal 112 and 212 at 100 ppm), all groups of males had similar glucose concentrations; this change was considered to be unrelated to treatment. For

females, there was less variability in glucose concentrations among individual animals, compared to males, and therefore the decrease in glucose may have been related to treatment. However, the degree of change in glucose was very small for both males and females and had no adverse consequences; therefore the decreases in glucose were considered to be non-adverse.

• Cholesterol and triglycerides were mildly increased at test day 32 in females exposed to 3000 ppm (means were 132% and 129% of the respective control group means). Six females exposed to 3000 ppm had cholesterol concentrations that were higher than most individual values for other females on this study; this change was likely related to treatment. For triglycerides, the range of concentrations for individual females was similar in all groups, including controls. The statistical difference in triglyceride concentration was unlikely to be related to treatment. Regardless, the changes in triglycerides and cholesterol were minimal and were considered to be non-adverse due to the small magnitude of the changes.

The following statistically significant changes in mean clinical chemistry parameters were considered to be unrelated to treatment and non-adverse because they did not occur in a dose-related pattern:

- Transiently increased sorbitol dehydrogenase activity at test day 32 in female rats exposed to 100 ppm
- Increased glucose at test days 42-45 in female rats exposed to 500 ppm.

ANATOMIC PATHOLOGY EVALUATION

A. Subchronic Male and Female Rats

1. Cause of Death

There were no test substance-related deaths. All rats survived until the scheduled terminal sacrifice.

2. Organ Weights

(Tables 55-56, Appendix SS)

Exposure-related organ weight effects were present in the liver and kidney of male and female rats, and are summarized below.

Mean Liver and Kidney Weights (Relative to Body Weight) in Male and Female Rats^a

		Male			Female			
Concentration (ppm):	100	500	3000	100	500	3000		
Liver wt/body wt	97%	105%	128%*	100%	104%	128%*		
Kidney/body wt	107%	115%*	125%*	99%	104%	<u>114%*</u>		

a values are given as percent of control group mean.

Liver

Liver weight parameters were increased in male and female rats exposed to 3000 ppm of the test substance. The magnitude of the liver weight increase was similar between males and females. For example, liver weight/body weight ratio was 128% of the control group mean for both males and females at 3000 ppm. In some animals, increased liver weight was associated with microscopic hepatocellular hypertrophy. Liver weight changes were consistent with the non-adverse pharmacological induction of hepatic enzymes. (24)

Kidneys

Kidney weights were increased in male rats at 500 and 3000 ppm and in female rats at 3000 ppm. In males only, increased kidney weights correlated with the dose-related hyaline droplet accumulation (and associated secondary changes) observed microscopically at all dose levels.

In the 3000 ppm females, there were no gross or microscopic anatomic correlates, and no clinical chemistry changes associated with the increased kidney weight parameters. The kidney weight effects in females were therefore interpreted to be the result of non-adverse enzyme induction. (25) Although microscopic hypertrophy of renal tubular epithelium may occur in enzyme induction, small increases in kidney weight are often not associated with a morphological change.

Other

Statistically significant increases in testes weight relative to body weight in 3000 ppm males, and in adrenal weight relative to body weight in 3000 ppm females, were not associated with changes in other weight parameters or with microscopic changes in the respective organs. These weight changes were secondary to the slight decreases in final body weight at this exposure level and thus were not considered to be primary effects of the test substance.

All other individual and mean organ weight differences were considered to be spurious and unrelated to exposure to the test substance.

^{*} Statistically significant (alpha = 0.05) by Dunnett/Tamhane-Dunnett pair-wise test (parametric) or by Dunn's pair-wise test (nonparametric).

Underlined values were interpreted to be test substance-related weight effects

3. Gross Observations

(Tables 58-59)

There were no test substance-related gross observations.

4. Microscopic Findings

(Tables 61-62, Appendices TT-UU)

Test substance-related microscopic findings were present in the liver (centrilobular hypertrophy) and thyroid gland (follicular cell hypertrophy) of males and females and the kidneys (hyaline droplet accumulation, granular casts, and increased chronic progressive nephropathy) of males.

Incidences and Severity of Test Substance-Related Microscopic Findings in Male and Female Rats

in Male and Female Kats										
		Fen	nale							
Concentration (ppm):	0	100	500	3000	0	100	500	3000		
Number of Rats:	12	12	12	12	12	12	12	12		
Liver										
Hypertrophy, centrilobular										
Minimal	0	0	0	2	0	0	0	9		
Tot al	0	0	0	2 <u>2</u>	0	0	0	<u>9</u>		
Thyroid gland										
Hypertrophy, follicular cell										
Minimal	0	0	0	2	0	0	0	2		
Tot al	0	0	0	2 <u>2</u>	0	0	0	<u>2</u>		
Kidney										
Hyaline droplets, increased										
Minimal	1	10	4	0	0	0	0	0		
Mild	0	0	8	12	0	0	0	0		
Total	1	<u>10</u>	<u>12</u>	<u>12</u>	0	0	0	0		
Granular casts, tubular,										
Minimal	0	2	5	2	0	0	0	0		
Mild	0	1	2	$\frac{2}{0}$	0	0	0	0		
Total	0	<u>3</u>	2 <u>7</u>	<u>2</u>	0	0	0	0		
Chronic progressive nephropathy										
Minimal	7	9	9	11	0	0	0	2		
Mild	0	1	3	1	0	0	0	0		
Total	7	<u>10</u>	<u>12</u>	<u>12</u>	0	0	0	2		

Underlined values for total incidences were interpreted to be test-substance related increases in microscopic observations.

Liver

Centrilobular hepatocellular hypertrophy was observed in male and female rats exposed to 3000 ppm of the test substance and occurred in greater incidences in females compared to males.

The hepatocellular hypertrophy in all animals was minimal and was characterized by an increase in the size of centrilobular hepatocytes due to an increase in nuclear and cytoplasmic area.

Hepatocellular hypertrophy is a common microscopic finding associated with the non-adverse xenobiotic induction of hepatocellular enzymes. Such was also the case in this study as increased liver weights, and microscopic hepatocellular hypertrophy were not associated with microscopic or clinical pathology changes indicative of liver toxicity.

Thyroid

Low incidences (2/12 in both males and females) of minimal hypertrophy of thyroid follicular epithelium were present in male and female rats in the 3000 ppm exposure groups.

Thyroid hypertrophy is a common finding in rats in association with induction of hepatic microsomal enzymes, and in this study was seen only at doses that also produced liver hypertrophy consistent with enzyme induction. Increased activity of the enzyme UDP-glucuronyltransferase, as part of a spectrum of induced cytochrome P450 isoenzymes, leads to increased biliary excretion of the thyroid hormone, T_4 . This results in elevation of thyroid stimulating hormone (TSH) which produces hypertrophy of follicular cells. Due to the species-specific short half life for T_4 in rodents, rats are uniquely sensitive to thyroid hormone perturbation in association with induction of liver enzymes. Thyroid follicular cell hypertrophy in the current study was considered potentially adverse in the species tested. However, this response is likely not relevant to nonrodent species.

Kidneys

An increase in hyaline droplet accumulation within the epithelium of the proximal convoluted tubule (PCT) of the kidneys was observed in male rats at all exposure concentrations.

Small quantities of hyaline droplets are a normal finding in the cytoplasm of the renal proximal convoluted tubular epithelium in male rats. They consist of phagolysosomes containing the poorly hydrolysable low molecular weight protein, $\alpha_{2\mu}$ globulin. Normally, approximately 50 mg of this globulin are produced daily in the male rat liver and passed into the glomerular filtrate. More than half of the globulin is reabsorbed by the lining cells of the PCT. Several xenobiotics have been reported to increase the accumulation of hyaline droplets in the PCT by binding to the $\alpha_{2\mu}$ globulin. Since female rats, and most other species including mice, dogs, monkeys and humans, do not produce significant quantities of the $\alpha_{2\mu}$ globulin, experimental findings related to hyaline droplet accumulation in male rats are not relevant to other species. (27)

Additional findings in the kidneys of all exposed male groups were the presence of granular casts in renal tubules and slight increases in the incidence and severity of chronic progressive nephropathy (CPN). These changes tended to occur in rats with more prominent accumulation of hyaline droplets, especially at the 500 and 3000 ppm exposure concentrations.

Granular casts were graded as minimal to mild, but did not occur in a clear dose-related manner with respect to either incidence or severity. Granular casts consisted of multiple focal accumulations of lightly eosinophilic granular material in the tubular lumen near the junction of

the inner and outer stripes of the renal outer medulla. The tubular epithelium of affected tubules was often attenuated. Tubular cast may be indicative of renal tubular damage. Urinalysis was not conducted in this study, so the presence or absence of casts in the urine correlative to the casts seen microscopically could not be assessed.

The incidence and severity of chronic progressive nephropathy (CPN) were slightly increased in male rats in all exposed groups compared to the control group. However, as with casts, there was no clear dose response for this observation. CPN is a common background lesion of laboratory rats and is characterized by multifocal tubular epithelial degeneration and regeneration with peritubular fibrosis. Minimal (grade 1) CPN is commonly seen in about half the male rats of this age and strain. The presence of a slight increase in incidence and severity of CPN in the exposed groups suggests that the increased hyaline droplet accumulation contributed to an increase in this naturally occurring degenerative condition in the kidneys and was not a primary effect of the test substance.

In individual animals from the exposed male groups, the presence of tubular casts and more severe CPN were usually associated with more severe accumulation of hyaline droplets, especially at the two higher concentrations. Furthermore, in female rats that did not have increased hyaline droplet accumulation, tubular casts were not observed and incidences and severity of nephropathy was similar to that commonly seen in female rats of this strain and age. Therefore, tubular casts and the increase in CPN noted in all male exposure groups were likely secondary to the increase in tubular hyaline droplets in these groups.

Other

All other microscopic observations in this study were consistent with normal background lesions in rats of this age and strain.

B. Satellite Female Rats

1. Organ Weights

(Table 57, Appendix SS)

There were no test substance-related or statistically significant changes in organ weights in exposed female satellite groups compared to controls. The absence of organ weight changes in 3000 ppm satellite females compared to the 3000 ppm subchronic females may be due to recovery since their last exposure occurred on GD 19.

2. Gross Observations

(Table 60, Appendix TT)

There were no test substance-related gross findings in exposed female satellite groups compared to controls.

3. Microscopic Findings

(Table 60, Appendix UU)

One mating pair (male 406/female 430 in the 3000 ppm group) failed to produce a litter. There were no microscopic changes in the reproductive organs of these animals.

ANATOMIC PATHOLOGY CONCLUSIONS

Following subchronic inhalation exposure of male and female rats to the test substance at concentrations of up to 3000 ppm, test substance-related effects were present in the kidneys, liver and thyroid gland.

In male rats, kidney weights were increased in the 500 and 3000 ppm groups, and increased hyaline droplet accumulation in renal tubules was present at all exposure concentrations. Additional microscopic changes in the kidneys of male rats were likely secondary to hyaline droplet accumulation. These included granular casts within renal tubules and slight increases in the incidence and severity of CPN. The kidney changes in male rats were considered adverse for the species tested. However, hyaline droplet accumulation, and thus the associated secondary effects, is species and sex specific and not predictive of effects in other species.

Kidney weights were also increased in females at 3000 ppm. However, in females the kidney weight changes were not associated with evidence of renal toxicity, based on the lack of correlative microscopic or clinical chemistry findings. Therefore, the kidney weight changes in females were considered non-adverse.

Other exposure-related findings were limited to the 3000 ppm male and female groups. These included increased liver weight and microscopic hepatocellular hypertrophy. These liver effects were considered non-adverse, adaptive responses to metabolism of a xenobiotic. Low incidences of minimal hypertrophy of thyroid follicular epithelium were also present in 3000 ppm males and females and were likely secondary to liver enzyme induction.

DISCUSSION AND CONCLUSIONS

Test substance-related increases in the incidence of stained and wet fur were observed at ≥ 500 ppm, however, they did not adversely impact the health of the animals.

Test substance-related decreases in body weight, weight gain, and food efficiency occurred in 3000 ppm subchronic and satellite females. Slightly decreased body weight and/or weight gain occurred in 3000 ppm males; however, the magnitude of the effect in males was not considered to be adverse. There were no adverse or test substance-related effects on reproductive function, and no effects on offspring body weight, clinical observations, or survival.

There were no adverse or test substance-related effects on neurobehavioral parameters in males, subchronic females, or in satellite females. The range of mean values for forelimb grip strength measurement in satellite females evaluated on lactation day 4 was slightly greater (0.70-0.83 kg) compared to the forelimb grip strength of subchronic females measured during week 4 (0.68-0.78 kg). This small difference likely reflects the slight difference s in range of mean values for body weight between the satellite females and subchronic females (306.9-331.5 g for satellite females and 251.9-269.4 for subchronic females). With respect to hindlimb grip strength, there was no difference between the range of mean values for satellite females compared to subchronic females. In addition, there were no differences in neurobehavioral endpoints evaluated in an open field arena or the motor activity monitor (responses to approach, touch, auditory stimulus, tail pinch; and pupillary response) between satellite females and subchronic females.). With respect to motor activity, there was no difference between the range of mean values for satellite females compared to subchronic females. Therefore, the neurobehavioral data for subchronic females were similar to the data for satellite females evaluated on lactation day 4, indicating that pregnancy status did not affect evaluation of these neurobehavioral parameters.

There were no adverse or test substance-related effects on hematology and clinical pathology parameters. As expected, clinical chemistry parameters were affected by pregnancy status, resulting in differences between subchronic females when compared to lactating females. There were no adverse or biologically significant differences in these parameters between the control and treated females within the subchronic or lactating females group. Thus, there were no unique, test substance-related effects in lactating females. Therefore, lactating females were not more sensitive to the test substance compared to subchronic females.

Liver weight parameters were increased in 3000 ppm males and females, which correlated with hepatocellular hypertrophy. Kidney weight parameters were increased in 500 ppm and above males and 3000 ppm females. In males, the increased absolute/relative kidney weights correlated with hyaline droplet accumulation which was observed at 100 ppm and above males. In 3000 ppm females, the increased kidney weight parameters were not associated with any functional or microscopic change, and therefore were considered secondary to non-adverse enzyme induction. Similar to the changes in clinical chemistry parameters, lactating females had increased liver weights compared to subchronic females. However, there were no unique, test substance-related effects on organ weight in lactating females.

Minimal centrilobular hepatocellular hypertrophy was observed in males and females exposed to 3000 ppm, possibly secondary to enzyme induction. Minimal hypertrophy of thyroid follicular epithelium occurred in 3000 ppm males and females, possibly secondary to the liver enzyme induction. In the kidney, the incidences of hyaline droplets, tubular granular casts, and chronic progressive nephropathy consistent with male and species specific hydrocarbon nephropathy were increased in 100 ppm and above males.

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for systemic toxicity in males was not achieved based on an increased incidence of male-specific hyaline droplet accumulation at 100 ppm and above. However, these findings are generally accepted by US EPA⁽²⁸⁾ as a hydrocarbon-induced male rat nephropathy, and are not relevant to human risk assessment. The NOAEL for male rats exclusive of the nephropathy is 500 ppm based on hypertrophy of the thyroid follicular epithelium observed in 3000 ppm males. The NOAEL for systemic toxicity in females was 500 ppm based on decreased body weight, weight gain, and food efficiency; and on hypertrophy of the thyroid follicular epithelium observed in 3000 ppm females. The NOAEL for reproductive and neurobehavioral toxicology was 3000 ppm, the highest concentration tested.

RECORDS AND SAMPLE STORAGE

Specimens, all raw data, the protocol, amendments, and the final report will be retained in the archives of Haskell Laboratory for ten years following the issuance of the final report. After that period, arrangements will be made to either return all materials to the Sponsor or archive them longer at Haskell Laboratory.

Laboratory-specific raw data such as personnel files, instrument, equipment, refrigerator and/or freezer raw data will be retained at the facility where the work was done.

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EXPLANATORY NOTES

Notes

Due to rounding differences, values in tables may be slightly different than appendices.

Abbreviations

BW =Body weight = Body weight gain **BWG** FC =Food consumption FE =Food efficiency G =Gestation GD =Gestation day Kg =Kilogram L =Lactation LD =Lactation day Mg =Milligram N/n

N/n = Number in group/Number of values used in calculation of mean

PND = Postnatal day
Ppm = parts per million

Wt = Weight

-/---/.../Blank space = No data/Data could not be calculated

INHALATION DATA

Chamber Concentrations of High Naphthenic Naphtha Chamber Environmental Conditions

n - number of samplesppm - parts per million

S.E.M. - standard error of the mean

Summary of Observations in Rats During Exposure

NAD - no abnormalities detected

NOTES:

Chamber Concentrations of High Naphthenic Naphtha Chamber Environmental Conditions

Values are reported to 2 significant figures.

Calculations were performed prior to rounding values.

EXPLANATORY NOTES (Continued)

CLINICAL PATHOLOGY DATA

ABBREVIATIONS:

Summary of Hematology Values

RBC - red blood cell count

HGB - hemoglobin

HCT - hematocrit

MCV - mean corpuscular (cell) volume

MCH - mean corpuscular (cell) hemoglobin

MCHC - mean corpuscular (cell) hemoglobin concentration

RDW - red cell distribution width

ARET - absolute reticulocyte count

PLT - platelet count

WBC - white blood cell count

ANEU - absolute neutrophil

ALYM - absolute lymphocyte

AMON - absolute monocyte

AEOS - absolute eosinophil

ABAS - absolute basophil

ADAS - absolute basopiiii

ALUC - absolute large unstained cell

ABAN - absolute neutrophil band

AHSN - absolute hypersegmented neutrophil

AAL - absolute atypical lymphocyte

- - no data

NC - not calculated or not calculable

Summary of Coagulation Values

PT - prothrombin time

APTT - activated partial thromboplastin time

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Summary of Clinical Chemistry Values

AST - aspartate aminotransferase

ALT - alanine aminotransferase

SDH - sorbitol dehydrogenase

ALKP - alkaline phosphatase

GGT - gamma glutamyltransferase

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

A/G - albumin/globulin ratio

NOTES:

Summary of Hematology Values

Summary of Coagulation Values

Summary of Clinical Chemistry Values

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

Table 1 Chamber Concentrations of Test Substance

DESIGN	MEASURED CONCENTRATION					
CONCENTRATION	(ppm) ^a					
(ppm)	MEAN	S.E.M.	RANGE	n		
0	0	0	0	38		
100	100	0.77	90 - 110	38		
500	500	2.0	480 - 560	38		
3000	3000	8.3	2800 - 3100	48^{b}		

a Values represent the mean, standard error of the mean (S.E.M.), and range of the daily mean values obtained from n exposures.

b Two rats without evidence of copulation were exposed for 19 days post cohabitation.

Table 2 Chamber Environmental Conditions

DESIGN	TEMPERATURE			RELA			
CONCENTRATION	(°C) ^a						
(ppm)	MEAN	S.E.M.	RANGE	MEAN	S.E.M.	RANGE	n
0	23	0.16	20 - 24	51	0.58	41 - 57	38
100	22	0.16	19 - 24	53	0.53	45 - 58	38
500	22	0.18	19 - 24	53	0.56	43 - 59	38
3000	22	0.19	20 - 25	54	0.46	43 - 59	48 ^b

DESIGN	AIRFLOW			OXYGEN			
CONCENTRATION		(L/min) ^a	l		(%) ^a		
(ppm)	MEAN	S.E.M.	RANGE	MEAN	S.E.M.	RANGE	n
0	300	3.48	260 - 400	20	0.017	20	38
100	290	3.41	270 - 390	20	0.024	20	38
500	290	3.23	260 - 370	20	0.015	20	38
3000	280	3.22	250 - 390	20	0.015	20	48 ^b

a Values represent the mean, standard error of the mean (S.E.M.), and range of the daily mean values obtained from n exposures.

b Two rats without evidence of copulation were exposed for 19 days post cohabitation.

Table 3
Mean Measured Concentration (ppm) of 12 Selected Components of
Naphtha, Petroleum, Heavy Straight-Run

Peak	Peak ID	100 ppm ^a	500 ppm ^a	3000 ppm ^b
1	2-MethylC6+C7-Olefin	4.7(0.6)	22.2 (0.5)	128.3 (12.6)
2	3-Methylhexane	3.6 (0.4)	17.2 (0.4)	100.2 (9.7)
3	t-1,3-DimethylcyC5	1.5 (0.3)	7.1 (0.2)	41.4 (4.0)
4	t-1,2-DimethylcycloC5	1.7(0.2)	7.9(0.3)	45.9 (4.3)
5	n-Heptane	7.3 (0.9)	34.4 (0.8)	203.2 (18.4)
6	Methylcyclohexane	6.8(0.8)	32.0 (0.8)	170.1 (17.4)
7	Toluene	3.5 (0.4)	15.9 (0.4)	95.9 (8.4)
8	2-Methylheptane	3.3 (0.4)	14.7 (0.6)	89.5 (7.9)
9	n-Octane	5.7 (0.7)	25.8 (1.1)	158.5 (14.0)
10	Ethylcyclohexane	2,0 (0.2)	8.7 (0.3)	53.2 (4.5)
11	m-Xylene	1.8 (0.2)	7.4(0.3)	45.7 (4.1)
_12	n-Nonane	4.5 (0.7)	19.1 (1.2)	118.3 (10.1)

a Mean and (standard deviation) of 6 measurements.

b Mean and (standard deviation) of 7 measurements.

Table 4
Summary of Observations in Rats During Exposure

	OBSERVATIONS DURING EXPOSURE						
	Group 1	Group 2	Group 3	Group 4			
EXPOSURE	0 ppm	100 ppm	500 ppm	3000 ppm			
1	NAD^{a}	NAD	NAD	NAD			
2	NAD	NAD	NAD	NAD			
3	NAD	NAD	NAD	NAD			
4	NAD	NAD	NAD	NAD			
5	NAD	NAD	NAD	NAD			
6	NAD	NAD	NAD	NAD			
7	NAD	NAD	NAD	NAD			
8	NAD	NAD	NAD	NAD			
9	NAD	NAD	NAD	NAD			
10	NAD	NAD	NAD	NAD			
11	NAD	NAD	NAD	NAD			
12	NAD	NAD	NAD	NAD			
13	NAD	NAD	NAD	NAD			
14	NAD	NAD	NAD	NAD			
15	NAD	NAD	NAD	NAD			
16	NAD	NAD	NAD	NAD			
17	NAD	NAD	NAD	NAD			
18	NAD	NAD	NAD	Wet Fur ^b			
19	NAD	NAD	NAD	Wet Fur			
20	NAD	NAD	NAD	Wet Fur			
21	NAD	NAD	NAD	Wet Fur			
22	NAD	NAD	NAD	Wet Fur			
23	NAD	NAD	NAD	Wet Fur			
24	NAD	NAD	NAD	Wet Fur			
25	NAD	NAD	NAD	Wet Fur			
26	NAD	NAD	NAD	Wet Fur			

Table 4
Summary of Observations in Rats During Exposure (Continued)

_	OBSE	RVATIONS I	DURING EXP	OSURE ^a					
	Group 1	Group 2	Group 3	Group 4					
EXPOSURE	0 ppm	100 ppm	500 ppm	3000 ppm					
27	NAD	NAD	NAD	Wet Fur					
28	NAD	NAD	NAD	Wet Fur					
29	NAD	NAD	NAD	Wet Fur					
30	NAD	NAD	NAD	Wet Fur					
31	NAD	NAD	NAD	Wet Fur					
32	NAD	NAD	NAD	Wet Fur					
33	NAD	NAD	NAD	Wet Fur					
34	NAD	NAD	NAD	Wet Fur					
35	NAD	NAD	NAD	Wet Fur					
36	NAD	NAD	NAD	Wet Fur					
37	NAD	NAD	NAD	Wet Fur					
38	NAD	NAD	NAD	Wet Fur					
39	С	С	c	Wet Fur					
40	С	С	c	Wet Fur					
41	С	С	c	Wet Fur					
42	С	С	c	Wet Fur					
43	С	С	c	Wet Fur					
44	c	С	c	Wet Fur					
45	c	c	c	Wet Fur					
46	c	С	c	Wet Fur					
47	c	С	С	Wet Fur					
48	c	С	С	Wet Fur					

a NAD = no abnormalities detected in animals visible through the chamber window.

b At least one animal visible though the chamber window had wet fur.

c Chamber was not run during this exposure.

Table 5 Summary of Post-Exposure Clinical Observations in Subchronic Male Rats

Group Concent N	eration(ppm)	1 0 12	2 100 12	3 500 12	4 3000 12
Hair Lo	oss Number of Animals	1	1	1	0
Schedul	ed Sacrifice Number of Animals	12	12	12	12
Stained	d Skin/Fur - Red - Face Number of Animals	0	0	0	11#
Wet fur	- Chest, Face, Perineum Number of Animals	0	0	0	7#
Wound -	- Superficial - Forelimb Le Number of Animals	eft 1	0	0	0

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 6 Summary of Detailed Clinical Observations in Subchronic Male Rats Evaluated Prior to Daily Exposure

Group Concent: N	ration(ppm)	1 0 12	2 100 12	3 500 12	4 3000 12
Hair los	ss - Forelimb Bilateral Number of Animals	1	1	1	0
Stained	Skin/Fur - Red - Face Number of Animals	0	0	0	1
Wound -	Superficial - Forelimb Number of Animals	Left 1	0	0	0

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 7 Summary of Post-Exposure Clinical Observations in Subchronic Female Rats

Group Concentration(ppm) N	1 0 12	2 100 12	3 500 12	4 3000 12
Discharge - Black - Eye Right Number of Animals	0	0	1	0
Discharge - Red - Eye Right Number of Animals	0	0	1	0
Hair Loss - Forelimb Bilateral Number of Animals	2	0	1	0
Scab - Tail Number of Animals	1	0	0	0
Scheduled Sacrifice Number of Animals	12	12	12	12
Stained Skin/Fur - Red - Face Number of Animals	7	10	12#	12#
Stained Skin/Fur - Tan - Face Number of Animals	0	0	0	1
Wet Fur - Chest, Chin, Face, Pe Number of Animals	rineum O	0	0	12#
Wound - Deep - End of Tail Number of Animals	1	0	0	0
Wound - Superficial - Tail Number of Animals	1	0	0	0

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 8 Summary of Detailed Clinical Observations in Subchronic Female Rats

Evaluated Prior to Daily Exposure

Group Concentration(ppm) N	1 0 12	2 100 12	3 500 12	4 3000 12
Hair Loss - Forelimb Bilateral Number of Animals	2	0	1	0
Stained Skin/Fur - Red - Face Number of Animals	0	1	1	11#
Wound - Superficial - Tail Number of Animals	1	0	0	0

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 9 Summary of Post-Exposure Clinical Observations in Satellite Female Rats During Premating

Group Concentra N	ation(ppm)	1 0 12	2 100 12	3 500 12	4 3000 12
	s - Forelimb Bilateral Number of Animals	1	0	0	0
	Skin/Fur - Red - Face Jumber of Animals	0	4	9#	12#
	Skin/Fur - Tan - Face Number of Animals	0	1	0	0
	- Chest, Chin, Face Jumber of Animals	0	0	0	11#

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 10 Summary of Post-Exposure Clinical Observations in Satellite Female Rats During Gestation

Group Concentra N	ation(ppm)	1 0 12	2 100 12	3 500 12	4 3000 9
	s - Forelimb Bilateral Number of Animals	5	2	2	1
_	– Tip of Tail Number of Animals	0	0	1	0
	Skin/Fur - Red - Face Number of Animals	1	4	12*	9*
	Skin/Fur - Tan - Face Number of Animals	0	1	0	0
	- Chest, Chin, Face, Perin Number of Animals	eum O	0	0	9#

Note: This table contains data from animals with confirmed mating.

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 11 Summary of Post-Exposure Clinical Observations in Satellite Female Rats During Lactation

Group Concentration(ppm) N	1 0 12	2 100 12	3 500 12	4 3000 11
Hair Loss - Forelimb Bilateral,	Hindquart	ers Left		
Number of Animals	5	2	3	1
Missing - Tip of Tail				
Number of Animals	0	0	1	0
Scheduled Sacrifice				
Number of Animals	12	12	12	11
Stained Skin/Fur - Red - Face				
Number of Animals	0	0	0	5#

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 12 Summary of Detailed Clinical Observations in Satellite Female Rats

Evaluated Prior to Daily Exposure

Group Concentration(ppm) N	1 0 12	2 100 12	3 500 12	4 3000 12
Hair loss - Forelimb Bilateral, Number of Animals	HindQuarters 5	s Left 2	3	1
Missing - Tip of Tail Number of Animals	0	0	1	0
Stained Skin/Fur - Red - Face Number of Animals	0	0	2	9#

^{*} Comparison to control (Fisher's Exact test) significant

[#] Trend test (Cochran-Armitage) significant

Table 13 Mean Body Weights (grams) of Subchronic Male Rats

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000	
BW:DAY1	301.0 14.8(12)	295.5 13.4(12)	293.6 17.6(12)	301.0 14.9(12)	
BW:DAY8	345.0 23.4(12)	341.0 22.1(12)	326.3 35.7(12)	333.0 18.3(12)	
BW:DAY15	381.2 33.6(12)	369.6 29.5(12)	358.2 41.8(12)	363.4 20.8(12)	
BW:DAY22	405.6 37.5(12)	396.9 31.5(12)	381.6 42.2(12)	387.2 24.2(12)	
BW:DAY29	433.7 42.8(12)	422.5 33.7(12)	413.6 47.1(12)	413.7 29.1(12)	
BW:DAY31	408.1 40.6(12)	395.0 29.9(12)	384.6 43.9(12)	384.4 27.7(12)	

Standard Deviation (n)

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 14 Mean Body Weight Gains (grams) of Subchronic Male Rats

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
BWG:DAY1-DAY8	44.0	45.5	32.7	32.0
	12.9(12)	11.7(12)	25.3(12)	8.6(12)
BWG:DAY8-DAY15	36.2	28.6	31.9	30.4
	13.3(12)	9.5(12)	8.8(12)	6.3(12)
BWG:DAY15-DAY22	24.5	27.3	23.4	23.8
	10.8(12)	4.9(12)	8.0(12)	7.6(12)
BWG:DAY22-DAY29	28.1	25.6	31.9	26.4
	11.4(12)	7.9(12)	10.3(12)	8.2(12)
BWG:DAY1-DAY15	80.2	74.1	64.6	62.4
	25.2(12)	19.1(12)	31.8(12)	11.0(12)
BWG:DAY1-DAY29a	132.7	127.0	120.0	112.6
	35.2(12)	24.7(12)	39.5(12)	16.8(12)

Standard Deviation (n)

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

a Body weight gain values for the rats after fasting (on test day 32) were not used for the calculation of mean weight gain over the interval.

Table 15
Mean Body Weights (grams) of Subchronic Female Rats

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000	
BW:DAY1	218.5 13.1(12)	216.8 7.6(12)	218.0 10.3(12)	214.9 10.5(12)	
BW:DAY8	235.9 17.7(12)	231.6 9.8(12)	236.0 14.5(12)	220.3* 16.1(12)	
BW:DAY15	243.3 18.1(12)	241.7 16.5(12)	244.9 19.5(12)	230.0 16.4(12)	
BW:DAY22	258.1 21.4(12)	251.9 20.7(12)	255.1 20.8(12)	241.4 17.7(12)	
BW:DAY29	269.5 23.0(12)	263.7 18.5(12)	266.7 27.2(12)	248.1 22.7(12)	
BW:DAY32	251.2 22.2(12)	246.6 19.4(12)	248.2 25.4(12)	229.5 20.9(12)	

Standard Deviation (n)

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 16 Mean Body Weight Gains (grams) of Subchronic Female Rats

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
BWG:DAY1-DAY8	17.5	14.8	18.0	5.4*
	6.8(12)	4.6(12)	7.5(12)	8.6(12)
BWG:DAY8-DAY15	7.3	10.1	8.8	9.7
	5.6(12)	11.5(12)	7.8(12)	5.2(12)
BWG:DAY15-DAY22	14.8	10.2	10.2	11.5
	7.0(12)	17.7(12)	7.3(12)	17.8(12)
BWG:DAY22-DAY29	11.4	11.8	11.6	6.7
	6.3(12)	6.2(12)	7.6(12)	15.9(12)
BWG:DAY1-DAY15	24.8	24.9	26.9	15.1
	6.5(12)	13.8(12)	11.1(12)	10.3(12)
BWG:DAY1-DAY29a	51.1	46.9	48.7	33.3*
	11.4(12)	13.3(12)	18.7(12)	16.2(12)

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

a Body weight gain values for the rats after fasting (on test day 32) were not used for the calculation of mean weight gain over the interval.

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 17
Mean Body Weights (grams) of Satellite Female Rats During Premating

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
BW:DAY1	219.1	218.8	215.4	217.7
	9.8(12)	15.1(12)	13.2(12)	16.5(12)
BW:DAY8	236.0	237.0	234.4	230.3
	14.5(12)	16.1(12)	14.6(12)	15.1(12)
BW:DAY15	245.1	248.9	242.9	236.2
	14.4(12)	19.9(12)	16.8(12)	13.4(12)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 18
Mean Body Weight Gains (grams) of Satellite Female Rats During Premating

Group:	1	2	3	4
Concentration(ppm)		100	500	3000
BWG:DAY1-DAY8	17.0	18.2	18.9	12.6
	6.8(12)	6.7(12)	8.3(12)	5.3(12)
BWG:DAY8-DAY15	9.1	12.0	8.5	5.9
	6.8(12)	6.7(12)	6.6(12)	6.2(12)
BWG:DAY1-DAY15	26.1	30.1	27.5	18.5
	7.8(12)	10.9(12)	9.8(12)	9.8(12)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 19 Mean Body Weights (grams) of Satellite Female Rats During Gestation

<pre>Group: Concentration(ppm)</pre>	1 0	2 100	3 500	4 3000	
BW:DAY0	252.9 17.7(12)	252.8 17.8(12)	249.9 12.2(12)	247.3 15.3(9)	
BW:DAY7	287.3 19.7(12)	290.7 26.0(12)	287.6 20.1(12)	276.3 20.5(9)	
BW:DAY14	326.5 26.6(12)	329.7 26.1(12)	329.0 24.5(12)	310.1 23.3(9)	
BW:DAY21	424.1 31.6(12)	426.2 34.0(11)	421.2 32.6(11)	394.0 29.3(9)	

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

Note: This table contains data from animals with confirmed mating.

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 20 Mean Body Weight Gains (grams) of Satellite Female Rats During Gestation

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000	
BWG:DAY0-DAY7	34.5 5.5(12)	37.9 11.1(12)	37.7 11.5(12)	29.0 8.1(9)	
BWG:DAY7-DAY14	39.1 10.4(12)	39.0 6.2(12)	41.4 9.0(12)	33.8 5.0(9)	
BWG:DAY14-DAY21	97.6 10.8(12)	96.4 12.6(11)	93.2	83.9 14.6(9)	
BWG:DAY0-DAY21	171.2 19.8(12)	173.4 22.7(11)	171.6 23.7(11)	146.8	

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

Note: This table contains data from animals with confirmed mating.

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 21
Mean Body Weights (grams) of Satellite Female Rats During Lactation

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000	
BW:DAY0	307.3 21.9(12)	313.6 22.3(12)	305.9 22.3(12)	285.6* 13.5(11)	
BW:DAY4	318.7 25.1(12)	319.0 25.9(12)	319.4 17.5(12)	296.5 18.1(11)	

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 22 Mean Body Weight Gains (grams) of Satellite Female Rats During Lactation

Group: Concentration(ppm)	1	2	3	4
	0	100	500	3000
BWG:DAY0-DAY4	11.4	5.4	13.5	10.9
	10.5(12)	12.5(12)	15.2(12)	12.1(11)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 23
Mean Food Consumption (grams/day) by Subchronic Male Rats

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000
FC:DAY1-DAY8	29.9	28.7	27.1	26.1*
	2.5(12)	3.1(12)	4.5(12)	2.5(12)
FC:DAY8-DAY15	30.1	28.2	27.2	27.1
	2.7(12)	3.4(12)	3.9(12)	2.3(12)
FC:DAY1-DAY15	30.0	28.4	27.2	26.6*
	2.4(12)	3.2(12)	4.1(12)	2.2(12)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 24 Mean Food Efficiency (grams weight gain/grams food consumed) by Subchronic Male Rats

Group:	1 0	2	3	4
Concentration(ppm)		100	500	3000
FE:DAY1-DAY8	0.208	0.223	0.158	0.174
	0.051(12)	0.044(12)	0.128(12)	0.044(12)
FE:DAY8-DAY15	0.169	0.143	0.166	0.160
	0.054(12)	0.036(12)	0.033(12)	0.031(12)
FE:DAY1-DAY15	0.189	0.184	0.163	0.167
	0.050(12)	0.031(12)	0.072(12)	0.025(12)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 25
Mean Food Consumption (grams/day) by Subchronic Female Rats

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000
FC:DAY1-DAY8	20.9 2.3(12)	21.1 1.9(12)	21.1 2.9(12)	19.7 2.9(12)
FC:DAY8-DAY15	21.0 1.9(12)	20.9 1.7(12)	21.0 3.0(12)	20.0 2.2(12)
FC:DAY15-DAY18a	21.8 2.6(12)	21.5 7.5(12)	21.5 3.4(12)	21.0 2.4(12)
FC:DAY18-DAY22a	20.9 2.0(12)	21.5 2.4(12)	20.8 3.6(12)	20.5 1.9(12)
FC:DAY22-DAY29	22.6 2.9(12)	22.4 1.8(12)	22.1 3.6(12)	21.1 1.8(12)
FC:DAY1-DAY29	21.4 2.0(12)	21.5 1.9(12)	21.4 3.1(12)	20.4 2.1(12)

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

a In error, the food consumption period was ended on test day 18, rather than test day 22. The 2 intervals for days 15-18 and 18-22 are reported rather than the 7-day interval of days 15-22.

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 26
Mean Food Efficiency (grams weight gain/grams food consumed) by Subchronic Female Rats

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
FE:DAY1-DAY8	0.117	0.100	0.119	0.033*
	0.040(12)	0.028(12)	0.037(12)	0.055(12)
FE:DAY8-DAY15a	0.050	0.069	0.058	0.071
	0.040(12)	0.076(12)	0.047(12)	0.038(12)
FE:DAY22-DAY29	0.073	0.077	0.071	0.042
	0.038(12)	0.041(12)	0.047(12)	0.101(12)
FE:DAY1-DAY29	0.084	0.077	0.079	0.057*
	0.014(12)	0.019(12)	0.021(12)	0.024(12)

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

a In error, the food consumption period was ended on test day 18, rather than test day 22. The 2 intervals for days 15-18 and 18-22 could not be reported for food efficiency because body weights were not collected on test day 18.

Table 27
Mean Food Consumption (grams/day) by Satellite Female Rats During Premating

Group: Concentration(ppm)	1	2 100	3 500	4 3000	
FC:DAY1-DAY8	21.5 1.6(12)	21.6 2.0(12)	20.6 (12)	20.3	
FC:DAY8-DAY15	21.1 1.5(12)	21.5 2.2(12)	20.5 1.7(12)	20.1	
FC:DAY1-DAY15	21.3 1.5(12)	21.5 2.0(12)	20.5	20.2 1.7(12)	

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 28
Mean Food Efficiency (grams weight gain/grams food consumed) by Satellite Female Rats During Premating

Group: Concentration(ppm)	1	2	3	4
	0	100	500	3000
FE:DAY1-DAY8	0.112	0.119	0.128	0.089
	0.042(12)	0.042(12)	0.056(12)	0.036(12)
FE:DAY8-DAY15	0.060	0.077	0.057	0.041
	0.045(12)	0.044(12)	0.046(12)	0.042(12)
FE:DAY1-DAY15	0.087	0.099	0.094	0.065
	0.024(12)	0.032(12)	0.030(12)	0.034(12)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 29
Mean Food Consumption (grams/day) by Satellite Female Rats During Gestation

Group: Concentration(ppm)	1 0	2 100	3 500	4 3000	
FC:DAY0-DAY7	25.3 1.6(12)	26.5 3.5(12)	25.7 2.9(12)	22.7 2.6(9)	
FC:DAY7-DAY14	27.8 2.4(12)	29.2 3.4(12)	27.9 4.7(12)	25.4 3.1(9)	
FC:DAY14-DAY21	28.9 2.3(12)	29.5 2.4(12)	28.9 3.7(12)	26.6 2.5(9)	
FC:DAY0-DAY21	27.3 2.0(12)	28.4 2.8(12)	27.5 3.5(12)	24.9 2.7(9)	

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

Note: This table contains data from animals with confirmed mating.

[^] Cochran-Armitage test for trend

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[#] Trend test (Jonckheere-Terpstra) significant

[~] next to control mean indicates no analyses were performed

Table 30 Mean Food Efficiency (grams weight gain/grams food consumed) by Satellite Female Rats During Gestation

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
FE:DAY0-DAY7	0.194	0.202	0.207	0.181
	0.027(12)	0.044(12)	0.047(12)	0.046(9)
FE:DAY7-DAY14	0.200	0.193	0.212	0.191
	0.042(12)	0.038(12)	0.030(12)	0.021(9)
FE:DAY14-DAY21	0.483	0.469	0.464	0.452
	0.044(12)	0.045(11)	0.036(11)	0.070(9)
FE:DAY0-DAY21	0.298	0.292	0.300	0.281
	0.025(12)	0.033(11)	0.017(11)	0.033(9)

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with confirmed mating.

Table 31 Mean Food Consumption (grams/day) by Satellite Female Rats During Lactation

Group: Concentration(ppm)	1	2	3	4
	0	100	500	3000
FC:DAY0-DAY4	37.8	34.1	37.0	33.9
	5.6(12)	4.8(12)	4.7(12)	6.3(11)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 32 Mean Food Efficiency (grams weight gain/grams food consumed) by Satellite Female Rats During Lactation

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
FE:DAY0-DAY4	0.068	0.031	0.083	0.070
	0.066(12)	0.094(12)	0.096(12)	0.078(11)

Standard Deviation (n)

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Table 33 Summary of Reproductive Outcome

	Group 1 0 ppm	Group 2 100 ppm	Group 3 500 ppm	Group 4 3000 ppm
No. of females paired	12	12	12	12
No. of females mated	12	12	12	11
No. of females pregnant ^a	12	12	12	11
No. of females that littered	12	12	12	11
Mating Index (%) b	100.0	100.0	100.0	91.7
Fertility Index (%) ^c	100.0~	100.0	100.0	100.0
Pre-coital Interval (Days)	3.2 ^d	2.7	3.0	2.9
	0.9(12)	0.7(12)	1.0(12)	1.2(9)
Gestation Length (Days)	22.0	21.9	21.9	21.9
Corpora Lutea	0.0(12) 16.0	0.3(12) 15.3	0.3(12) 15.9	0.3(9) 15.1
	1.6(12)	1.9(12)	1.3(12)	2.5(11)
Implantation Sites	15.9	15.3	15.9	15.0
	1.8(12)	1.9(12)	1.3(12)	2.6(11)
Post-Implantation Loss (%) ^e	3.5	6.2	5.3	7.5
	4.7(12)	6.3(12)	6.0(12)	7.1(11)

a Pregnant = uterine implantation sites

Standard Deviation (n)

b No. of females mated ÷ No. of females paired X 100

c No. of females pregnant \div No. of females mated X 100

d Data summarized as: Mean

e (No. of implantation sites - No. of Pups Born) \div No. of implantation sites X 100.

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

 $^{{\}scriptstyle \sim}$ next to control mean indicates no analyses were performed

Table 34
Summary of Pup Survival

		-	Group 2 100 ppm	Group 3 500 ppm	_
No. of viable litters					
	PND 0	12	12	12	11
	PND 4	12	12	12	11
No. of pups					
Born		15.3 ^a	14.3	15.1	13.8
		1.7(12)	2.1(12)	1.7(12)	2.4(11)
Born Alive		15.3	14.3	15.1	13.8
		1.7(12)	2.1(12)	1.7(12)	2.4(11)
No. of pups alive on:					
	PND 4	15.3	14.3	15.1	13.4
,		1.6(12)	2.1(12)	1.7(12)	3.1(11)
Live Born Index (%) b					
		100.0~	100.0	100.0	100.0
		0.0(12)	0.0(12)	0.0(12)	0.0(11)
Viability Index (%) C					
-		99.5 ^d	99.5 ^d	100.0	100.0°
		1.7(12)	1.8(12)	0.0(12)	0.0(10)
Sex Ratio (%) ^f					
	PND 0	55.8	46.0	51.4	45.9
		14.2(12)	14.7(12)	11.2(12)	9.7(11)

a Data summarized as: Mean Standard

Deviation (n)

b Number of pups born alive ÷ Number of pups born X 100

c Number of pups alive on day $4 \div$ Number of pups born alive X 100

d Groups 1 and 2 lost one female pup in one litter each by day 4, which did not change the average rounded pups/litter but did reduce the Viability Index. Actual values were 15.33 born alive and 15.25 alive on PND 4 in Group 1; and 14.33 born alive and 14.25 alive on PND 4 in Group 2.

e The offspring of dam #434 were excluded because they were delivered during exposure, in the exposure chamber.

f Number of male fetuses ÷ total number fetuses X 100

^{*} Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

[@] Nonparametric comparison to control (Dunn's) significant

[!] Analysis of Covariance and Dunnett-Hsu

[~] next to control mean indicates no analyses were performed

Table 35
Summary of Pup Clinical Observations

Group:	1	2	3	4
Concentration(ppm)	0	100	500	3000
No. of Litters/Pups Affected	0	0	0	0

Table 36 Mean Pup Weights (grams)

Group: Concentr	ation(ppm)	1 0	2 100	3 500	4 3000
PND 0	(Combined)	6.5 0.3(12)	6.6 0.4(12)	6.4 0.5(12)	6.2 0.6(11)
	(Males)	6.7 0.3(12)	6.8 0.4(12)	6.7 0.4(11)a	6.3 0.6(11)
	(Females)	6.3 0.4(12)	6.4 0.5(12)	6.4 0.4(11)a	6.2 0.7(11)
PND 4	(Combined)	10.3 0.5(12)	10.6	10.0 0.8(12)	9.7 1.2(11)
	(Males)	10.5 0.5(12)	10.8	10.3 0.9(12)	9.9 1.3(11)
	(Females)	9.9 0.6(12)	10.4 0.8(12)	9.8 0.9(12)	9.6 1.2(11)

Data summarized as:

Mean of individual pup weights

Standard Deviation (number of litters)

Statistical Analysis: Data were statistically evaluated for the combined means only. Statistical significance is indicated by the following (p < 0.05):

^{*} Analysis of Covariance and Dunnett-Hsu

[#] Nonparametric Analysis of Covariance

a = The data for dam #333 were excluded from the mean values because one pup was missexed on PND 0.

Table 37
Mean Forelimb and Hindlimb Grip Strength for Subchronic Male Rats
(Mean of Three Trials)

Assessment Period	Group Number	ppm	Mean Body Weight (g)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)	
Baseline						
	1	0	236.8 (15.2)	0.64 (0.07)	0.45 (0.08)	
	2	100	235.7 (13.5)	0.64 (0.12)	0.42 (0.09)	
	3	500	234.8 (16.4)	0.62 (0.08)	0.39 (0.09)	
	4	3000	230.2 (35.1)	0.63 (0.07)	0.46 (0.11)	
Week 4						
	1	0	432.5 (41.6)	0.94 (0.26)	0.65 (0.13)	
	2	100	422.7 (31.9)	0.80 (0.22)	0.53 (0.10)	
	3	500	413.7 (48.2)	0.78 (0.33)	0.57 (0.11)	
	4	3000	416.6 (30.0)	0.92 (0.20)	0.60 (0.10)	

Number in Group (N) = 12.

Table 38
Mean Forelimb and Hindlimb Grip Strength for Subchronic Female Rats
(Mean of Three Trials)

Assessment Period	Group Number	Mean Body ppm Weight (g)		Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)	
Baseline						
	1	0	194.0 (10.4)	0.72 (0.12)	0.40 (0.08)	
	2	100	197.5 (9.4)	0.67 (0.13)	0.41 (0.08)	
	3	500	194.3 (11.9)	0.71 (0.16)	0.43 (0.07)	
	4	3000	201.9 (30.9)	0.69 (0.07)	0.43 (0.10)	
Week 4						
	1	0	269.4 (25.8)	0.68 (0.19)	0.51 (0.09)	
	2	100	255.5 (34.4)	0.78 (0.16)	0.49 (0.07)	
	3	500	268.0 (24.9)	0.77 (0.19)	0.48 (0.11)	
	4	3000	251.9 (20.4)	0.68 (0.22)	0.50 (0.09)	

Number in Group (N) = 12.

Table 39
Mean Forelimb and Hindlimb Grip Strength for Satellite Female Rats
(Mean of Three Trials)

Assessment Period	Group Number	nnm	Mean Body Weight (g)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
renou	Nullibei	ppm	weight (g)	Orip Suengui (kg)	Orip Sueligiii (kg)
Baseline					
	1	0	204.6 (7.2)	0.70(0.07)	0.47 (0.06)
	2	100	202.9 (12.2)	0.79 (0.14)	0.50 (0.06)
	3	500	202.1 (10.7)	0.77 (0.10)	0.50 (0.07)
	4	3000	205.2 (14.2)	0.69 (0.11)	0.41 (0.09)
Lactation I	<u> Day 4</u>				
	1	0	330.3 (27.0)	0.70 (0.17)	0.52 (0.08)
	2	100	330.2 (25.2)	0.83 (0.12)	0.54 (0.12)
	3	500	331.5 (20.1)	0.78 (0.16)	0.48 (0.07)
	4	3000	306.9 (21.2)	0.76 (0.15)	0.50 (0.11)

Number in Groups 1, 2, and 3 (N) = 12.

Number in Group 4 (N) = 11 (due to non-pregnant rat #430).

Table 40 Summary of Abbreviated Functional Observational Battery Findings for Subchronic Male Rats

	BASELINE			WEEK 4				
GROUP:	1	2 3		4	1	2 3		4
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000
NUMBER EXAMINED:	12	12	12	12	12	12	12	12
MANIPULATIONS IN OPEN FIELD: APPROACH & TOUCH:								
no reaction	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:								
no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	12	12	12	12	12	12	12	12
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0
TAIL PINCH:								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	12	12	12	12	10	11	12
exaggerated response	0	0	0	0	0	2	1	0

Table 40 Summary of Abbreviated Functional Observational Battery Findings for Subchronic Male Rats (Continued)

		BASE	LINE			WE	EK 4	
GROUP:	1	2	3	4	1	2	3	4
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000
NUMBER EXAMINED:	12	12	12	12	12	12	12	12
IN MOTOR ACTIVITY MONITOR:								
PUPILLARY RESPONSE:								
present	12	12	12	12	12	12	12	12
absent	0	0	0	0	0	0	0	0
DIARRHEA:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
POLYURIA:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
ADDITIONAL SIGNS:								
MISSING TOE(S):								
absent	12	12	12	12	12	11	12	12
present	0	0	0	0	0	1	0	0
STAIN PERINEUM, BROWN:								
absent	12	12	12	12	12	12	12	11
present	0	0	0	0	0	0	0	1
Present			0	U		0	0	1

Table 41 Summary of Abbreviated Functional Observational Battery Findings for Subchronic Female Rats

		BASE	LINE			WEI	EK 4	
GROUP:	1	2 3		4	1	2 3		4
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000
NUMBER EXAMINED:	12	12	12	12	12	12	12	12
MANIPULATIONS IN OPEN FIELD: APPROACH & TOUCH:								
no reaction	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:								
no reaction	0	0	0	0	1	0	0	0
normal reaction (rat flinches or flicks ear)	12	12	12	12	11	12	12	12
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0
TAIL PINCH:								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	12	12	12	10	12	12	12
exaggerated response	0	0	0	0	2	0	0	0

Table 41 Summary of Abbreviated Functional Observational Battery Findings for Subchronic Female Rats (Continued)

	BASELINE					WEEK 4				
GROUP:	1	2	3	4		1	2	3	4	
CONCENTRATION (ppm):	0	100	500	3000		0	100	500	3000	
NUMBER EXAMINED:	12	12	12	12	1	2	12	12	12	
IN MOTOR ACTIVITY MONITOR:										
PUPILLARY RESPONSE:										
present	12	12	12	12	1	2	12	12	12	
absent	0	0	0	0		0	0	0	0	
DIARRHEA:										
absent	12	12	12	12	1	2	12	12	12	
present	0	0	0	0	-	0	0	0	0	
POLYURIA:										
absent	12	12	12	12	1	2	12	12	12	
present	0	0	0	0		0	0	0	0	

Table 41 Summary of Abbreviated Functional Observational Battery Findings for Subchronic Female Rats (Continued)

		BASE	LINE			WEI	EK 4	
GROUP:	1	2	3	4	1	2	3	4
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000
NUMBER EXAMINED:	12	12	12	12	12	12	12	12
ADDITIONAL SIGNS:								
SWOLLEN TOES(S) AND/OR PAW(S):								
absent	12	12	12	12	10	12	12	12
present	0	0	0	0	2	0	0	0
EAR FLICKS, DURING MANIPULATIONS:								
absent	12	12	12	12	11	12	12	12
present	0	0	0	0	1	0	0	0
END OF TAIL MISSING:								
absent	12	12	12	12	11	12	12	12
present	0	0	0	0	1	0	0	0
STAIN FACE, RED:								
absent	12	12	12	12	12	12	12	2
present	0	0	0	0	0	0	0	10*

^{*} Statistically significant trend compared to the control group at p < 0.05 by Cochran Armitage test for trend.

Table 42 Summary of Abbreviated Functional Observational Battery Findings for Satellite Female Rats

		BASE	LINE	\mathbf{L}_{t}	LACTATION DAY 4				
GROUP:	1	2 3		4	1	2 3		4	
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000	
NUMBER EXAMINED:	12	12	12	11 ^a	12	12	12	11 ^a	
MANIPULATIONS IN OPEN FIELD: APPROACH & TOUCH:									
no reaction	0	0	0	0	0	0	0	0	
normal	12	12	12	11	12	12	12	11	
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	
AUDITORY STIMULUS:									
no reaction	0	0	0	0	0	0	0	0	
normal reaction (rat flinches or flicks ear)	12	12	12	11	12	12	12	11	
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	
TAIL PINCH:									
no response	0	1	0	1	1	0	0	0	
normal (turns toward site)	12	11	12	10	11	12	12	11	
exaggerated response	0	0	0	0	0	0	0	0	

Table 42 Summary of Abbreviated Functional Observational Battery Findings for Satellite Female Rats (Continued)

		BASE	LINE	\mathbf{L}_{L}	LACTATION DAY 4				
GROUP:	1	2	3	4	1	2	3	4	
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000	
NUMBER EXAMINED:	12	12	12	11 ^a	12	12	12	11 ^a	
IN MOTOR ACTIVITY MONITOR: PUPILLARY RESPONSE: present	12	12	12	11	12	12	12	11	
absent	0	0	0	0	0	0	0	0	
DIARRHEA: absent present	12 0	12 0	12 0	11 0	12	12	12 0	11	
POLYURIA: absent present	12	12	12	11	12	12	12	11	
present	0	0	0	0	0	0	0	0	

Table 42
Summary of Abbreviated Functional Observational Battery Findings for Satellite Female Rats (Continued)

		BASE	LINE		LA	CTATI	ON DAY	Y 4
GROUP:	1	2	3	4	1	2	3	4
CONCENTRATION (ppm):	0	100	500	3000	0	100	500	3000
NUMBER EXAMINED:	12	12	12	11 ^a	12	12	12	11 ^a
ADDITIONAL SIGNS.								
ADDITIONAL SIGNS: SWOLLEN TOE(S) AND/OR PAW(S):								
absent	12	12	12	11	11	12	12	11
present	0	0	0	0	1	0	0	0
END OF TAIL MISSING:								
absent	12	12	11	11	12	12	11	11
present	0	0	1	0	0	0	1	0
EAR FLICKS:								
absent	12	12	12	10	12	12	12	12
present	0	0	0	1	0	0	0	0

a One rat did not produce a litter. Baseline data were excluded from the summary table and statistics.

Table 43
Motor Activity Assessment: Mean Duration of Movement (Sec) for Subchronic Male Rats

ASSESSMENT PERIOD	GROUP Number	ppm			SUCCESS	IVE 10-MINUT	E INTERVALS		
BASELINE			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	440 (46)	355 (62)	323 (64)	285 (97)	196 (93)	97 (128)	1697 (3 52)
	2	100	429 (37)	363 (45)	288 (65)	266 (109)	201 (128)	116 (120)	1663 (416)
	3	500	425 (38)	343 (46)	281 (80)	230 (135)	190 (144)	108 (98)	1577 (444)
	4	3000	400 (64)	300 (84)	265 (93)	179* (146)	87* (113)	27 (39)	1258* (388)
WEEK 4			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	398 (63)	310 (62)	271 (55)	241 (63)	220 (57)	222 (96)	1660 (2 75)
	2	100	388 (56)	322 (43)	278 (67)	270 (72)	233 (81)	226 (60)	1717 (292)
	3	500	394 (67)	335 (70)	254 (101)	226 (71)	230 (85)	175 (85)	1612 (302)
	4	3000	348 (46)	250 (74)	220 (49)	162 (84)	156 (91)	108* (97)	1243* (295)

Data arranged as: Mean (Standard Deviation). Number in Group (N) = 12.

^{*} Statistically significant by repeated measures analysis of variance p < 0.05.

Table 44
Motor Activity Assessment: Mean Duration of Movement (Sec) for Subchronic Female Rats

ASSESSMENT PERIOD	GROUP Number	ppm			SUCCESSI	VE 10-MINUT	E INTERVALS		
BASELINE			1	2	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	390 (56)	259 (113)	168 (112)	191 (135)	179 (98)	157 (124)	1344 (448)
	2	100	394 (49)	219 (83)	149 (103)	183 (96)	199 (70)	172 (92)	1315 (365)
	3	500	375 (72)	268 (149)	258 (107)	191 (109)	168 (115)	186 (96)	1445 (464)
	4	3000	403 (25)	276 (98)	223 (87)	250 (83)	226 (103)	174 (94)	1551 (330)
WEEK 4			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	391 (61)	254 (61)	194 (68)	197 (76)	175 (62)	171 (69)	1380 (238)
	2	100	373 (55)	251 (74)	215 (100)	201 (71)	192 (74)	170 (76)	1401 (370)
	3	500	389 (62)	282 (61)	227 (83)	200 (80)	198 (67)	177 (79)	1473 (334)
	4	3000	376 (46)	287 (58)	210 (99)	223 (82)	183 (73)	161 (111)	1440 (367)

Number in Group (N) = 12.

Table 45
Motor Activity Assessment: Mean Duration of Movement (Sec) for Satellite Female Rats

ASSESSMENT	GROUP								
PERIOD	NUMBER	ppm			SUCCESS	IVE 10-MINUT	E INTERVALS		
BASELINE			1	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	TOTAL
	1	0	384 (53)	293 (68)	233 (53)	202 (95)	137 (96)	143 (95)	1392 (3 14)
	2	100	382 (38)	258 (91)	206 (74)	171 (125)	215 (91)	192 (93)	1422 (369)
	3	500	387 (73)	298 (113)	207 (77)	144 (124)	95 (86)	90 (84)	1221 (388)
	4	3000	370 (48)	281 (68)	188 (90)	145 (113)	114 (87)	130 (78)	1229 (442)
LACTATION DAY 4			1	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	TOTAL
	1	0	359 (47)	246 (78)	210 (87)	174 (72)	126 (97)	159 (91)	1274 (3 96)
	2	100	371 (71)	282 (67)	226 (71)	197 (64)	191 (65)	159 (54)	1426 (319)
	3	500	381 (70)	266 (78)	205 (95)	186 (86)	151 (103)	156 (88)	1344 (395)
	4	3000	351 (59)	266 (51)	206 (45)	176 (49)	190 (63)	169 (44)	1359 (225)

Number in Groups 1, 2, and 3(N) = 12.

Number in Group 4 (N) = 11 (due to non-pregnant rat #430).

Table 46 Motor Activity Assessment: Mean Number of Movements for Subchronic Male Rats

ASSESSMENT	GROUP								
PERIOD	NUMBER	ppm			SUCCESSIVE	E 10-MINUTE	INTERVALS		
BASELINE			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	TOTAL
	1	0	127 (17)	137 (13)	142 (18)	135 (27)	108 (38)	54 (59)	703 (103)
	2	100	123 (14)	132 (12)	129 (14)	118 (24)	101 (47)	68 (61)	671 (102)
	3	500	129 (18)	141 (14)	133 (14)	110 (53)	91 (60)	66 (59)	670 (154)
	4	3000	135 (18)	129 (17)	122 (33)	88# (55)	39# (42)	20 (27)	532* (100)
WEEK 4			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	TOTAL
	1	0	131 (14)	136 (18)	123 (22)	122 (26)	125 (20)	120 (36)	757 (84)
	2	100	128 (17)	135 (16)	125 (17)	122 (16)	122 (29)	108 (15)	740 (79)
	3	500	131 (20)	137 (18)	117 (40)	122 (32)	113 (27)	101 (46)	721 (94)
	4	3000	133 (13)	119# (15)	116 (19)	98 (41)	98 (49)	66# (51)	630* (139)

Number in Group (N) = 12.

Statistically significant by repeated measures analysis of variance p < 0.05. Statistically significant by Jonckheere-Terpstra trend test at p < 0.05.

Table 47
Motor Activity Assessment: Mean Number of Movements for Subchronic Female Rats

ASSESSMENT PERIOD	GROUP NUMBER	ppm			SUCCESSIV	E 10-MINUTE	INTERVALS		
BASELINE			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	133 (13)	118 (39)	97 (55)	93 (54)	92 (40)	91 (57)	623 (183)
	2	100	139 (14)	117 (28)	87 (47)	106 (45)	116 (29)	110 (46)	674 (126)
	3	500	130 (11)	107 (45)	123 (21)	110 (52)	93 (53)	107 (46)	669 (149)
	4	3000	136 (14)	123 (27)	116 (37)	126# (34)	111 (43)	97 (39)	709 (98)
WEEK 4			1	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
	1	0	132 (21)	130 (14)	112 (26)	114 (27)	115 (42)	108 (26)	710 (82)
	2	100	138 (15)	133 (24)	113 (23)	115 (28)	117 (35)	104 (24)	719 (90)
	3	500	131 (17)	130 (22)	121 (22)	113 (29)	119 (34)	106 (37)	721 (102)
	4	3000	126 (17)	131 (16)	109 (33)	113 (30)	102 (32)	92 (54)	672 (134)

Data arranged as: Mean (Standard Deviation). Number in Group (N) = 12.

[#] Statistically significant by Jonckheere-Terpstra trend test at p < 0.05.

Table 48
Motor Activity Assessment: Mean Number of Movements for Satellite Female Rats

ASSESSMENT PERIOD	GROUP Number	ppm	ppm SUCCESSIVE 10-MINUTE INTERVALS							
BASELINE			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>	
	1	0	135 (15)	131 (14)	123 (21)	111 (40)	86 (51)	87 (51)	672 (1 02)	
	2	100	138 (13)	126 (34)	115 (27)	88 (57)	123 (37)	115 (36)	705 (131)	
	3	500	137 (21)	128 (27)	116 (32)	74 (51)	62 (49)	65 (51)	581 (122)	
	4	3000	134 (15)	131 (13)	99 (28)	90 (52)	69 (53)	85 (43)	607 (163)	
LACTATION DAY 4			<u>1</u>	<u>2</u>	<u>3</u>	4	<u>5</u>	<u>6</u>	<u>TOTAL</u>	
	1	0	134 (19)	124 (16)	116 (27)	96 (33)	75 (45)	90 (40)	635 (1 08)	
	2	100	131 (7)	125 (17)	119 (18)	114 (19)	115 (26)	99 (27)	703 (70)	
	3	500	130 (19)	124 (22)	107 (45)	103 (44)	84 (50)	86 (45)	635 (157)	
	4	3000	133 (17)	130 (23)	114 (21)	103 (28)	114 (38)	108 (26)	702 (114)	

Number in Groups 1, 2, and 3 (N) = 12.

Number in Group 4 (N) = 11 (due to non-pregnant rat #430).

Table 49 Summary of Hematology Values for Subchronic Male Rats

	Group 1	Group 2	Group 3	Group 4	
	0 ppm	100 ppm	500 ppm	3000 ppm	
RBC $(x10^6/\mu L)$					
	0.51	0.50	0.25	8.24	
DAY 31	8.51	8.52	8.35		
HCD (~/4L)	0.40(12)	0.26(12)	0.20(12)	0.35(12)	
HGB (g/dL) DAY 31	15.8	16.0	15.8	15.5	
DA 1 31					
HCT (0/)	0.5(12)	0.5(12)	0.4(12)	0.5(12)	
HCT (%)	40.0	40.6	40.6	40.2	
DAY 31	49.0	49.6	48.6	48.3	
MCV (CL)	1.6(12)	2.0(12)	1.3(12)	2.1(12)	
MCV (fL)	57.7	50.0	50.0	50. C	
DAY 31	57.7	58.2	58.2	58.6	
NGW (1.6(12)	2.0(12)	1.5(12)	2.2(12)	
MCH (pg)	10.6	10.0	10.0	4.0.0	
DAY 31	18.6	18.8	19.0	18.9	
	0.4(12)	0.6(12)	0.4(12)	0.6(12)	
MCHC (g/dL)					
DAY 31	32.3	32.3	32.6	32.2	
	0.4(12)	0.5(12)	0.6(12)	0.5(12)	
RDW (%)					
DAY 31	11.7	11.5	11.5	11.8	
	0.5(12)	0.3(12)	0.4(12)	0.4(12)	
ARET $(x10^3/\mu L)$					
DAY 31	198.3	181.6	191.7	193.4	
	35.7(12)	22.2(12)	29.3(12)	30.2(12)	
PLT $(x10^3/\mu L)$					
DAY 31	1329	1291	1332	1341	
	146(11)	121(12)	245(12)	143(12)	
WBC $(x10^3/\mu L)$					
DAY 31	12.99	13.11	13.07	14.26	
	2.12(12)	3.34(12)	3.64(12)	3.73(12)	
ANEU $(x10^3/\mu L)$					
DAY 31	1.98	1.64	1.99	2.19	
	0.57(12)	0.73(12)	1.19(12)	0.45(12)	
ALYM $(x10^3/\mu L)$					
DAY 31	10.44	10.92	10.55	11.28	
	1.75(12)	2.77(12)	2.77(12)	3.07(12)	
	` /	` /	` '	` /	

Table 49
Summary of Hematology Values for Subchronic Male Rats (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
AMON $(x10^3/\mu L)$				
DAY 31	0.23	0.23	0.25	0.44
	0.12(12)	0.05(12)	0.16(12)	0.47(12)
AEOS $(x10^3/\mu L)$, ,		, ,	,
DAY 31	0.17	0.13	0.13	0.17
	0.11(12)	0.06(12)	0.05(12)	0.08(12)
ABAS $(x10^3/\mu L)$,		, ,	,
DAY 31	0.09	0.10	0.08	0.10
	0.05(12)	0.04(12)	0.03(12)	0.05(12)
ALUC $(x10^3/\mu L)$	()	()	()	()
DAY 31	0.08	0.08	0.08	0.09
	0.04(12)	0.03(12)	0.03(12)	0.04(12)
	\ /	\ /	\ /	\

Standard deviation (Number of values included in calculation)

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

Table 50 Summary of Hematology Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45]

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
RBC $(x10^6/\mu L)$				
DAY 32	8.13	8.36	8.20	8.11
DA 1 32		0.42(12)	0.43(12)	
DAY 42-45	0.27(12) 6.83	6.71	6.97	0.32(12) 6.95
DA1 42-43	0.44(12)	0.40(11)	0.39(12)	0.36(11)
HGB (g/dL)	0.44(12)	0.40(11)	0.57(12)	0.50(11)
DAY 32	15.5	15.8	15.6	15.5
5111 32	0.4(12)	0.6(12)	0.7(12)	0.4(12)
DAY 42-45	12.9	12.8	13.2	13.5
D111 12 13	0.8(12)	0.6(11)	0.6(12)	0.5(11)
HCT (%)	0.0(12)	0.0(11)	0.0(12)	0.5(11)
DAY 32	46.4	47.1	46.8	46.3
5711 32	1.4(12)	1.9(12)	2.2(12)	1.5(12)
DAY 42-45	40.9	40.8	42.1	41.9
D111 12 13	2.3(12)	2.0(11)	1.9(12)	1.9(11)
MCV (fL)	2.3(12)	2.0(11)	1.9(12)	1.5(11)
DAY 32	57.1	56.3	57.1	57.2
5711 32	2.0(12)	1.1(12)	1.8(12)	2.4(12)
DAY 42-45	59.9	61.0	60.4	60.3
D111 12 13	1.7(12)	2.2(11)	2.0(12)	1.6(11)
MCH (pg)	1.7(12)	2.2(11)	2.0(12)	1.0(11)
DAY 32	19.1	18.9	19.1	19.1
D/11 32	0.5(12)	0.5(12)	0.5(12)	0.8(12)
DAY 42-45	19.0	19.1	19.0	19.4
D111 12 13	0.6(12)	0.7(11)	0.7(12)	0.4(11)
MCHC (g/dL)	0.0(12)	0.7(11)	0.7(12)	0.1(11)
DAY 32	33.3	33.6	33.4	33.4
D111 32	0.6(12)	0.5(12)	0.5(12)	0.5(12)
DAY 42-45	31.6	31.3	31.5	32.3
DITT 42 43	0.6(12)	0.7(11)	0.7(12)	0.8(11)
RDW (%)	0.0(12)	0.7(11)	0.7(12)	0.0(11)
DAY 32	11.6	11.4	11.4	11.9
	0.5(12)	0.3(12)	0.4(12)	0.4(12)
DAY 42-45	16.7	17.0	16.0	15.2
2111 12 10	1.6(12)	2.1(11)	1.1(12)	1.4(11)
	1.0(12)	2.1(11)	1.1(12)	1.1(11)

Table 50 Summary of Hematology Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45] (Continued)

	C 1			C 4
	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
ARET $(x10^3/\mu L)$				
DAY 32	174.0	168.4	169.6	204.7
DA1 32	40.3(12)	36.8(12)	24.9(12)	49.9(12)
DAY 42-45	465.9	510.4	450.0	360.6*
DA1 42-43	71.7(12)	129.7(11)	69.5(12)	89.7(11)
PLT $(x10^3/\mu L)$	/1./(12)	129.7(11)	09.3(12)	09.7(11)
DAY 32	1283	1331	1387	1192
DA 1 32				
DAY 42 45	175(11)	198(11)	172(10)	261(12)
DAY 42-45	1553	1455	1313	1697
WDC (~103/I)	214(10)	337(6)	194(7)	284(8)
WBC $(x10^3/\mu L)$	10.22	12.07	12.04	12 (0
DAY 32	12.33	12.87	12.94	12.69
DAY 40 45	1.62(12)	2.34(12)	3.25(12)	2.82(12)
DAY 42-45	12.86	13.47	12.51	12.82
ANDII (102 / T)	1.64(12)	3.85(11)	2.68(12)	4.06(11)
ANEU $(x10^3/\mu L)$	1.00	1 15	1.70	1.20
DAY 32	1.00	1.15	1.72	1.20
D 1 7 7 10 15	0.31(12)	0.57(12)	0.96(12)	0.56(12)
DAY 42-45	3.62	3.74	3.14	2.64@
	0.90(12)	1.55(11)	0.82(12)	0.62(11)
ALYM $(x10^3/\mu L)$				
DAY 32	10.60	10.96	10.41	10.89
	1.59(12)	2.31(12)	2.66(12)	2.67(12)
DAY 42-45	8.75	9.32	8.95	9.73
	1.45(12)	2.51(11)	2.32(12)	3.58(11)
AMON $(x10^3/\mu L)$				
DAY 32	0.34	0.37	0.36	0.26
	0.19(12)	0.14(12)	0.15(12)	0.12(12)
DAY 42-45	0.27	0.19	0.20	0.23
	0.08(12)	0.11(11)	0.07(12)	0.14(11)
AEOS $(x10^3/\mu L)$				
DAY 32	0.19	0.18	0.19	0.16
	0.09(12)	0.06(12)	0.08(12)	0.06(12)
DAY 42-45	0.11	0.11	0.12	0.10
	0.03(12)	0.05(11)	0.07(12)	0.06(11)

Table 50
Summary of Hematology Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45] (Continued)

_	Group 1	Group 2	Group 3	Group 4
·	0 ppm	100 ppm	500 ppm	3000 ppm
ABAS $(x10^3/\mu L)$				
DAY 32	0.11	0.11	0.09	0.11
	0.06(12)	0.05(12)	0.05(12)	0.04(12)
DAY 42-45	0.07	0.07	0.06	0.07
	0.03(12)	0.04(11)	0.04(12)	0.04(11)
ALUC $(x10^3/\mu L)$,	()		()
DAY 32	0.08	0.07	0.06	0.08
5111 32	0.05(12)	0.03(12)	0.04(12)	0.02(12)
DAY 42-45	0.05	0.05	0.05	0.05
D111 12 13	0.01(12)	0.03(11)	0.02(12)	0.04(11)
ABAN $(x10^3/\mu L)^a$	0.01(12)	0.03(11)	0.02(12)	0.04(11)
DAY 32			0.35	
DA 1 32	-	-		-
ATION (103/ T)			NC(1)	
AHSN $(x10^3/\mu L)^a$			0.00	
DAY 32	-	-	0.23	-
			NC(1)	
$AAL (x10^3/\mu L)^a$				
DAY 32	0.13	0.14	0.35	-
	NC(1)	NC(1)	0.33(2)	
	. ,	,	. /	

a Statistics were unable to be performed due to low number of observations.

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

[@] Statistically significant difference from control at p < 0.05 by Dunn's test.

Table 51 Summary of Coagulation Values for Subchronic Male Rats

	Group 1 0 ppm	Group 2 100 ppm	Group 3 500 ppm	Group 4 3000 ppm
PT (sec)				
DAY 31	14.4	14.5	14.6	15.2
	1.1(12)	0.7(12)	1.1(12)	1.6(12)
APTT (sec)			,	,
DAY 31	15.0	15.5	16.5*	16.1
	1.3(12)	1.1(12)	1.5(12)	1.3(12)

Standard deviation (Number of values included in calculation)

Table 52 Summary of Coagulation Values for Subchronic Female Rats [Day 32] and Satellite Female Rats (Days 42-45]

	Group 1	roup 1 Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
PT (sec)				
DAY 32	13.6	13.8	13.8	13.6
	0.4(12)	0.3(12)	0.4(12)	0.5(12)
DAY 42-45	15.5	15.6	15.4	15.6
	0.3(12)	0.5(12)	0.3(12)	0.4(11)
APTT (sec)		` ,	` ,	, ,
DAY 32	13.6	13.7	14.6	13.6
	1.7(12)	1.5(12)	1.1(12)	1.6(12)
DAY 42-45	15.7	14.8	15.4	15.4
	2.0(12)	1.5(12)	1.6(12)	1.8(11)

Data arranged as: Mean

Standard deviation (Number of values included in calculation)

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

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

Table 53
Summary of Clinical Chemistry Values for Subchronic Male Rats

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
A CTP (TI/T)				
AST (U/L)	7.4	7.6	72	71
DAY 31	74	76	73	71
	16(12)	13(12)	7(12)	18(12)
ALT (U/L)				
DAY 31	27	25	25	32
	4(12)	5(12)	4(12)	14(12)
SDH (U/L)				
DAY 31	16.6	17.5	18.1	18.3
	4.6(12)	3.6(12)	4.7(12)	7.0(12)
ALKP(U/L)				
DAY 31	156	159	147	132
	34(12)	18(12)	38(12)	24(12)
GGT (U/L)				
DAY 31	0	0	0	1
	0(12)	0(12)	0(12)	2(12)
BILI (mg/dL)	,	. ,	,	,
DAY 31	0.14	0.14	0.15	0.16
	0.02(12)	0.03(12)	0.02(12)	0.02(12)
BUN (mg/dL)				,
DAY 31	13	13	13	13
	2(12)	2(12)	1(12)	2(12)
CREA (mg/dL)	2(12)	2(12)	1(12)	2(12)
DAY 31	0.35	0.36	0.37	0.34
D/11 31	0.03(12)	0.03(12)	0.03(12)	0.03(12)
CHOL (mg/dL)	0.03(12)	0.03(12)	0.03(12)	0.03(12)
DAY 31	50	47	56	56
DAT JI	18(12)	13(12)	12(12)	12(12)
TRIG (mg/dL)	10(12)	13(12)	12(12)	12(12)
	6.1	15	44	<i>1</i> .1
DAY 31	64	45		41
CLUC (ma/dL)	31(12)	20(12)	13(12)	12(12)
GLUC (mg/dL)	110	102	00	026
DAY 31	110	102	98	92@
TD (/1I)	22(12)	20(12)	10(12)	7(12)
TP (g/dL)	<i>(</i> 1	C 1	<i>C</i> 1	6.2
DAY 31	6.1	6.1	6.1	6.2
	0.3(12)	0.2(12)	0.2(12)	0.3(12)

Table 53
Summary of Clinical Chemistry Values for Subchronic Male Rats (Continued)

	Group 1 0 ppm	Group 2	Group 3	Group 4 3000 ppm
		100 ppm	500 ppm	
ALD (/III)				
ALB (g/dL)				
DAY 31	3.4	3.4	3.3	3.4
	0.1(12)	0.1(12)	0.1(12)	0.2(12)
GLOB (g/dL)				
DAY 31	2.7	2.7	2.8	2.8
	0.2(12)	0.1(12)	0.1(12)	0.2(12)
CALC (mg/dL)	· /	` /	\ /	, ,
DAY 31	10.7	10.6	10.5	10.8
	0.3(12)	0.3(12)	0.4(12)	0.3(12)
IPHS (mg/dL)	()	()	···()	()
DAY 31	7.9	7.6	7.6	7.8
	0.8(12)	0.5(12)	0.5(12)	0.4(12)
NA (mmol/L)				
DAY 31	147.1	146.5	146.1	146.2
-	1.5(12)	1.7(12)	1.0(12)	1.7(12)
K (mmol/L)	1.5(12)	1.7(12)	1.0(12)	1.7(12)
DAY 31	5.74	5.73	5.69	5.66
DR1J1	0.35(12)	0.30(12)	0.35(12)	0.31(12)
CL (mmol/L)	0.55(12)	0.30(12)	0.55(12)	0.31(12)
DAY 31	100.4	100.0	100.4	99.1
DAY 31		100.8		
	2.6(12)	2.1(12)	2.7(12)	1.8(12)
A/G				
DAY 31	1.3	1.3	1.2	1.2
	0.1(12)	0.1(12)	0.1(12)	0.1(12)

[@] Statistically significant difference from control at p < 0.05 by Dunn's test.

Table 54
Summary of Clinical Chemistry Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45]

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
. CT (T. (T.)				
AST (U/L)				
DAY 32	64	68	70	57
	7(12)	8(12)	18(12)	6(12)
DAY 42-45	117	97	105	86
	46(12)	15(12)	43(12)	11(11)
ALT (U/L)				
DAY 32	23	23	26	25
	4(12)	4(12)	11(12)	5(12)
DAY 42-45	100	82	96	87
	22(12)	15(12)	27(12)	21(11)
SDH (U/L)				
DAY 32	14.7	17.5@	15.0	13.8
	2.0(12)	3.3(12)	5.2(12)	1.6(12)
DAY 42-45	17.1	14.2	14.7	12.1
	6.9(12)	2.7(12)	7.1(12)	3.0(11)
ALKP (U/L)	, ,	, ,	, ,	` ,
DAY 32	85	82	77	78
	26(12)	19(12)	17(12)	18(12)
DAY 42-45	293	343	316	271
	138(12)	140(12)	125(12)	112(11)
GGT (U/L)	,	\	()	
DAY 32	0~	0~	0~	0~
	0(12)	0(12)	0(12)	0(12)
DAY 42-45	0~	0~	0~	0~
	0(12)	0(12)	0(12)	0(11)
BILI (mg/dL)	,	\	()	
DAY 32	0.18	0.19	0.18	0.19
	0.02(12)	0.02(12)	0.02(12)	0.02(12)
DAY 42-45	0.18	0.16	0.16	0.16
	0.03(12)	0.03(12)	0.01(12)	0.02(11)
BUN (mg/dL)	0.05(12)	0.05(12)	0.01(12)	0.02(11)
DAY 32	15	15	15	15
	2(12)	2(12)	2(12)	2(12)
DAY 42-45	20	20	19	21
DIII 12 13	3(12)	2(12)	2(12)	2(11)
	5(12)	2(12)	2(12)	2(11)

Table 54
Summary of Clinical Chemistry Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45] (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
		• •	• •	•
CREA (mg/dL)				
DAY 32	0.37	0.40	0.38	0.35
	0.03(12)	0.03(12)	0.03(12)	0.04(12)
DAY 42-45	0.38	0.40	0.39	0.39
	0.03(12)	0.02(12)	0.03(12)	0.03(11)
CHOL (mg/dL)				
DAY 32	74	72	80	98*
	15(12)	12(12)	20(12)	18(12)
DAY 42-45	79	81	82	84
	10(12)	13(12)	12(12)	13(11)
TRIG (mg/dL)				
DAY 32	35	39	41	45@
	8(12)	13(12)	19(12)	10(12)
DAY 42-45	60	57	63	67
	20(12)	7(12)	21(12)	19(11)
GLUC (mg/dL)				
DAY 32	97	94	93	89*
	5(12)	7(12)	5(12)	5(12)
DAY 42-45	98	101	109@	105
	8(12)	14(12)	14(12)	8(11)
TP (g/dL)				
DAY 32	6.6	6.7	6.7	6.7
	0.4(12)	0.3(12)	0.5(12)	0.3(12)
DAY 42-45	6.6	6.7	6.6	6.7
	0.2(12)	0.3(12)	0.3(12)	0.4(11)
ALB (g/dL)				
DAY 32	3.7	3.8	3.7	3.7
	0.2(12)	0.2(12)	0.3(12)	0.2(12)
DAY 42	3.5	3.5	3.5	3.5
	0.1(12)	0.2(12)	0.1(12)	0.2(11)
GLOB (g/dL)				
DAY 32	2.9	2.9	3.0	3.0
	0.2(12)	0.2(12)	0.2(12)	0.2(12)
DAY 42-45	3.1	3.2	3.2	3.2
	0.2(12)	0.2(12)	0.2(12)	0.2(11)

Table 54
Summary of Clinical Chemistry Values for Subchronic Female Rats [Day 32] and Satellite Female Rats [Days 42-45] (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
CALC (mg/dL)				
DAY 32	11.1	11.1	11.1	11.1
	0.3(12)	0.3(12)	0.3(12)	0.2(12)
DAY 42-45	10.9	11.0	11.0	11.1
	0.3(12)	0.3(12)	0.4(12)	0.5(11)
IPHS (mg/dL)				
DAY 32	7.0	7.0	6.9	6.8
	0.6(12)	0.7(12)	0.7(12)	0.5(12)
DAY 42-45	5.3	5.9	5.9	6.2
	1.3(12)	0.9(12)	1.6(12)	1.7(11)
NA (mmol/L)	` ,		. ,	, ,
DAY 32	144.1	144.8	144.4	145.0
	1.3(12)	2.1(12)	0.7(12)	1.3(12)
DAY 42-45	148.2	148.6	148.4	148.9
	3.3(12)	2.2(12)	2.1(12)	1.4(11)
K (mmol/L)	` ,	, ,		, ,
DAY 32	5.61	5.76	5.69	5.58
	0.36(12)	0.49(12)	0.49(12)	0.29(12)
DAY 42-45	5.92	5.68	5.66	5.63
	0.46(12)	0.55(12)	0.46(12)	0.54(11)
CL (mmol/L)	` ,	` ,	` ,	, ,
DAY 32	101.5	101.8	101.8	101.4
	1.8(12)	2.5(12)	1.9(12)	1.6(12)
DAY 42-45	102.4	103.7	104.4	103.0
	1.9(12)	2.5(12)	2.4(12)	2.5(11)
A/G	` ,	, ,		, ,
DAY 32	1.3	1.3	1.3	1.3
	0.1(12)	0.1(12)	0.1(12)	0.1(12)
DAY 42-45	1.1	1.1	1.1	1.1
	0.1(12)	0.1(12)	0.1(12)	0.1(11)

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

[@] Statistically significant difference from control at p < 0.05 by Dunn's test.

[~] Due to lack of variability among group means, statistical analyses were unable to be performed.

Table 55 Mean Final Body and Organ Weights from Subchronic Male Rats

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
MEAN FINAL BODY	AND ABSOLUT	E ORGAN WEIC	GHTS (grams)	
LIVER	12.584	11.807	12.392	15.143*
	1.784(12)	1.302(12)	1.727(12)	1.908(12)
KIDNEYS	3.479	3.600	3.782	4.121*
	0.372(12)	0.460(12)	0.627(12)	0.522(12)
LUNGS	1.752	1.749	1.840	1.646
	0.127(12)	0.144(12)	0.264(12)	0.121(12)
HEART	1.500	1.452	1.494	1.443
	0.104(12)	0.143(12)	0.215(12)	0.143(12)
SPLEEN	0.720	0.704	0.692	0.728
	0.102(12)	0.150(12)	0.117(12)	0.130(12)
THYMUS	0.475	0.451	0.528	0.417
	0.142(12)	0.113(12)	0.098(12)	0.066(12)
ADRENAL GLANDS	0.067	0.073	0.070	0.070
	0.009(12)	0.012(12)	0.012(12)	0.009(12)
BRAIN	2.053	2.097	2.038	2.052
	0.071(12)	0.088(12)	0.104(12)	0.114(12)
TESTES	3.411	3.522	3.460	3.569
	0.216(12)	0.225(12)	0.213(12)	0.161(12)
EPIDIDYMIDES	1.218	1.253	1.191	1.249
	0.076(12)	0.095(12)	0.084(12)	0.108(12)
PROSTATE	0.594	0.668	0.661	0.666
	0.150(12)	0.133(12)	0.208(12)	0.106(12)
FINAL BODY WEIGH	IT (grams) 408.1 40.6(12)	395.0 29.9(12)	384.6 43.9(12)	384.4 27.7(12)

Table 55
Mean Final Body and Organ Weights from Subchronic Male Rats (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
MEAN RELATIVE ORG	AN WEIGHTS (%	of body weight)		
LIVER/	3.077	2.986	3.218	3.936*
FINAL BODY * 100	0.232(12)	0.189(12)	0.229(12)	0.344(12)
KIDNEYS/	0.854	0.910	0.979*	1.069*
FINAL BODY * 100	0.056(12)	0.077(12)	0.073(12)	0.081(12)
LUNGS/	0.433	0.444	0.479@	0.429
FINAL BODY * 100	0.049(12)	0.040(12)	0.049(12)	0.024(12)
HEART/	0.370	0.368	0.390	0.375
FINAL BODY * 100	0.040(12)	0.024(12)	0.050(12)	0.018(12)
SPLEEN/	0.177	0.178	0.181	0.189
FINAL BODY * 100	0.022(12)	0.036(12)	0.029(12)	0.026(12)
THYMUS/	0.116	0.114	0.137	0.108
FINAL BODY * 100	0.031(12)	0.023(12)	0.018(12)	0.014(12)
ADRENAL GLANDS/	0.016	0.018	0.018	0.018
FINAL BODY * 100	0.002(12)	0.002(12)	0.002(12)	0.002(12)
BRAIN/	0.507	0.533	0.535	0.536
FINAL BODY * 100	0.052(12)	0.038(12)	0.048(12)	0.042(12)
TESTES/	0.842	0.896	0.914	0.932@
FINAL BODY * 100	0.082(12)	0.077(12)	0.151(12)	0.068(12)
EPIDIDYMIDES/	0.300	0.318	0.314	0.325
FINAL BODY * 100	0.029(12)	0.024(12)	0.047(12)	0.022(12)
PROSTATE/	0.148	0.170	0.173	0.173
FINAL BODY * 100	0.043(12)	0.034(12)	0.053(12)	0.025(12)

Table 55 Mean Final Body and Organ Weights from Subchronic Male Rats (Continued)

	Group 1 0 ppm	Group 2 100 ppm	Group 3 500 ppm	Group 4 3000 ppm
MEAN RELATIVE OR	GAN WEIGHT	S (% organ to brain	n weight)	
LIVER/	614.095	563.561	606.566	737.286*
BRAIN * 100	92.538(12)	63.507(12)	68.688(12)	73.563(12)
KIDNEYS/	169.460	171.850	185.048	201.237*
BRAIN * 100	16.500(12)	22.393(12)	26.746(12)	26.503(12)
LUNGS/	85.490	83.417	90.019	80.371
BRAIN * 100	7.298(12)	6.001(12)	9.764(12)	6.764(12)
HEART/	73.170	69.229	73.095	70.363
BRAIN * 100	5.584(12)	6.146(12)	8.275(12)	6.386(12)
SPLEEN/	35.071	33.555	33.991	35.380
BRAIN * 100	4.631(12)	7.110(12)	5.431(12)	5.219(12)
THYMUS/	23.159	21.497	25.796	20.302
BRAIN * 100	7.022(12)	5.288(12)	4.192(12)	2.816(12)
ADRENAL GLANDS/	3.246	3.484	3.443	3.404
BRAIN * 100	0.430(12)	0.519(12)	0.519(12)	0.430(12)
TESTES/	166.367	168.240	170.242	174.487
BRAIN * 100	12.347(12)	13.391(12)	14.624(12)	14.068(12)
EPIDIDYMIDES/	59.392	59.889	58.650	61.125
BRAIN * 100	4.155(12)	5.624(12)	5.757(12)	7.300(12)
PROSTATE/	28.964	31.988	32.591	32.389
BRAIN * 100	7.293(12)	7.031(12)	10.616(12)	4.546(12)

Data arranged as:

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at p < 0.05 by Dunn's test.

Table 56 Mean Final Body and Organ Weights from Subchronic Female Rats

	Group 1 0 ppm	Group 2 100 ppm	Group 3 500 ppm	Group 4 3000 ppm
MEAN FINAL BODY A	AND ABSOLUT	E ORGAN WEIC	GHTS (grams)	
LIVER	7.737	7.590	7.903	9.026*
	0.866(12)	0.731(12)	0.922(12)	1.086(12)
KIDNEYS	2.058	2.003	2.100	2.125
	0.251(12)	0.256(12)	0.172(12)	0.157(12)
LUNGS	1.447	1.439	1.394	1.364
	0.140(12)	0.176(12)	0.153(12)	0.155(12)
HEART	1.002	0.987	0.993	0.958
	0.071(12)	0.093(12)	0.103(12)	0.102(12)
SPLEEN	0.541	0.558	0.535	0.545
	0.066(12)	0.056(12)	0.104(12)	0.093(12)
THYMUS	0.457	0.444	0.456	0.421
	0.096(12)	0.113(12)	0.114(12)	0.139(12)
ADRENAL GLANDS	0.075	0.075	0.074	0.082
	0.011(12)	0.011(12)	0.011(12)	0.009(12)
BRAIN	1.873	1.896	1.933	1.846
	0.064(12)	0.060(12)	0.076(12)	0.092(12)
OVARIES	0.140	0.145	0.140	0.136
	0.028(12)	0.025(12)	0.019(12)	0.022(12)
UTERUS	0.526	0.617	0.564	0.587
	0.162(12)	0.219(12)	0.159(12)	0.170(12)
FINAL BODY WEIGH	Γ (grams) 251.2 22.2(12)	246.6 19.4(12)	248.2 25.4(12)	229.5 20.9(12)

Table 56
Mean Final Body and Organ Weights from Subchronic Female Rats (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
MEAN RELATIVE ORG	AN WEIGHTS (%	% of body weight)		
LIVER/	3.077	3.079	3.195	3.927@
FINAL BODY * 100	0.159(12)	0.192(12)	0.336(12)	0.217(12)
KIDNEYS/	0.818	0.813	0.849	0.929*
FINAL BODY * 100	0.053(12)	0.091(12)	0.046(12)	0.066(12)
LUNGS/	0.577	0.584	0.564	0.594
FINAL BODY * 100	0.044(12)	0.058(12)	0.054(12)	0.041(12)
HEART/	0.400	0.401	0.401	0.418
FINAL BODY * 100	0.024(12)	0.026(12)	0.031(12)	0.033(12)
SPLEEN/	0.217	0.227	0.216	0.237
FINAL BODY * 100	0.032(12)	0.025(12)	0.040(12)	0.030(12)
THYMUS/	0.181	0.179	0.186	0.183
FINAL BODY * 100	0.031(12)	0.037(12)	0.052(12)	0.059(12)
ADRENAL GLANDS/	0.030	0.030	0.030	0.036*
FINAL BODY * 100	0.005(12)	0.004(12)	0.005(12)	0.006(12)
BRAIN/	0.751	0.773	0.788	0.809
FINAL BODY * 100	0.067(12)	0.063(12)	0.104(12)	0.074(12)
OVARIES/	0.056	0.059	0.057	0.060
FINAL BODY * 100	0.011(12)	0.009(12)	0.008(12)	0.010(12)
UTERUS/	0.211	0.247	0.230	0.257
FINAL BODY * 100	0.065(12)	0.070(12)	0.072(12)	0.073(12)

Table 56
Mean Final Body and Organ Weights from Subchronic Female Rats (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
MEAN RELATIVE OR	GAN WEIGHTS	S (% organ to brain	n weight)	
LIVER/	413.012	400.519	409.803	489.377*
BRAIN * 100	44.418(12)	37.910(12)	52.430(12)	56.471(12)
KIDNEYS/	109.802	105.707	109.053	115.447
BRAIN * 100	12.526(12)	13.867(12)	12.349(12)	10.629(12)
LUNGS/	77.204	75.929	72.352	74.070
BRAIN * 100	6.943(12)	9.247(12)	9.209(12)	9.428(12)
HEART/	53.508	52.119	51.586	52.097
BRAIN * 100	4.128(12)	5.154(12)	6.737(12)	6.616(12)
SPLEEN/	28.910	29.466	27.772	29.524
BRAIN * 100	3.561(12)	3.303(12)	5.823(12)	4.797(12)
THYMUS/	24.316	23.417	23.610	22.839
BRAIN * 100	4.788(12)	5.807(12)	5.673(12)	7.674(12)
ADRENAL GLANDS/	4.015	3.933	3.822	4.424
BRAIN * 100	0.590(12)	0.532(12)	0.536(12)	0.464(12)
OVAIRES/	7.501	7.612	7.292	7.378
BRAIN * 100	1.543(12)	1.221(12)	1.126(12)	1.073(12)
UTERUS/	28.125	32.536	29.259	31.689
BRAIN * 100	8.741(12)	11.446(12)	8.342(12)	8.655(12)

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

[@] Statistically significant difference from control at p < 0.05 by Dunn's test.

Table 57 Mean Final Body and Organ Weights from Satellite Female Rats

	Group 1	Group 2	Group 3	Group 4				
	0 ppm	100 ppm	500 ppm	3000 ppm				
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)								
LIVER	14.415	13.781	14.450	13.774				
	1.482(12)	1.354(12)	0.737(12)	1.528(12)				
KIDNEYS	2.420	2.352	2.428	2.269				
	0.233(12)	0.162(12)	0.188(12)	0.215(12)				
LUNGS	1.529	1.458	1.519	1.471				
	0.095(12)	0.095(12)	0.127(12)	0.160(12)				
OVARIES	0.146	0.146	0.147	0.140				
	0.019(12)	0.014(12)	0.012(12)	0.018(12)				
UTERUS	0.764	0.773	0.742	0.762				
	0.127(12)	0.104(12)	0.117(12)	0.093(12)				
FINAL BODY WEIGHT (grams)								
	318.7	319.0	319.4	294.9*				
	25.1(12)	25.9(12)	17.5(12)	18.1(12)				

Table 57
Mean Final Body and Organ Weights from Satellite Female Rats (Continued)

	Group 1	Group 2	Group 3	Group 4
	0 ppm	100 ppm	500 ppm	3000 ppm
MEAN RELATIVE ORG	AN WEIGHTS (% of body weight)		
LIVER/	4.518	4.323	4.529	4.662
FINAL BODY * 100	0.203(12)	0.279(12)	0.199(12)	0.321(12)
KIDNEYS/	0.760	0.739	0.761	0.770
FINAL BODY * 100	0.049(12)	0.044(12)	0.061(12)	0.058(12)
LUNGS/	0.481	0.458	0.476	0.498
FINAL BODY * 100	0.032(12)	0.020(12)	0.035(12)	0.037(12)
OVARIES/	0.046	0.046	0.046	0.048
FINAL BODY * 100	0.005(12)	0.005(12)	0.004(12)	0.006(12)
UTERUS/	0.240	0.243	0.233	0.259
FINAL BODY * 100	0.033(12)	0.035(12)	0.038(12)	0.033(12)

^{*} Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

Table 58
Incidences of Gross Observations in Subchronic Male Rats

Group : Concentration : Number of Animals on Study :	1 0 ppm 12	2 100 ppm 12	3 500 ppm 12	4 3000 ppm 12
ADRENAL GLANDS; No Visible Lesions	12	12	12	12
BRAIN; No Visible Lesions	12	12	12	12
CECUM; No Visible Lesions	12	12	12	12
COAGULATING GLANDS; No Visible Lesions	12	12	12	12
COLON; No Visible Lesions	12	12	12	12
DUODENUM; No Visible Lesions	12	12	12	12
EPIDIDYMIDES; No Visible Lesions	12	12	12	12
FEMUR/KNEE JOINT; No Visible Lesions	12	12	12	12
HEART; No Visible Lesions	12	12	12	12
ILEUM; No Visible Lesions	12	12	12	12
JEJUNUM; No Visible Lesions	12	12	12	12
KIDNEYS; No Visible Lesions. Dilatation	11 1	12	11 1	12 0

Table 58
Incidences of Gross Observations in Subchronic Male Rats (Continued)

Group : Concentration : Number of Animals on Study :	1 0 ppm 12	2 100 ppm 12	3 500 ppm 12	4 3000 ppm 12
LIVER; No Visible Lesions Discoloration	10 2	12 0	12 0	12 0
LUNGS; No Visible Lesions	12	12	12	12
MANDIBULAR LYMPH NODE; No Visible Lesions	12	12	12	12
MESENTERIC LYMPH NODE; No Visible Lesions	12	12	12	12
PROSTATE; No Visible Lesions	12	12	12	12
RECTUM; No Visible Lesions	12	12	12	12
SCIATIC NERVE; No Visible Lesions	12	12	12	12
SEMINAL VESICLES; No Visible Lesions	12	12	12	12
SPINAL CORD; No Visible Lesions	12	12	12	12
SPLEEN; No Visible Lesions	12	12	12	12
STOMACH; No Visible Lesions	12	12	12	12
TESTES; No Visible Lesions	12	12	12	12

Table 58
Incidences of Gross Observations in Subchronic Male Rats (Continued)

Group : Concentration : Number of Animals on Study :	0 ppm			
THYMUS; No Visible Lesions	12	12	12	12
THYROID GLAND; No Visible Lesions	12	12	12	12
TRACHEA; No Visible Lesions	12	12	12	12
URINARY BLADDER; No Visible Lesions	12	12	12	12

Table 59
Incidences of Gross Observations in Subchronic Female Rats

Group :	1	2	3	4
Concentration : Number of Animals on Study :		100 ppm 12	500 ppm 12	3000 ppm 12
Nambel of Infinate on Study .				
ADRENAL GLANDS; No Visible Lesions	12	12	12	12
BRAIN; No Visible Lesions	12	12	12	12
CECUM; No Visible Lesions	12	12	12	12
CERVIX; No Visible Lesions	12	12	12	12
COLON; No Visible Lesions	12	12	12	12
DUODENUM; No Visible Lesions	12	12	12	12
FEMUR/KNEE JOINT; No Visible Lesions	12	12	12	12
HEART; No Visible Lesions	12	12	12	12
ILEUM; No Visible Lesions	12	12	12	12
JEJUNUM; No Visible Lesions	12	12	12	12
KIDNEYS; No Visible Lesions Dilatation	11 1	12 0	12	12
LIVER; No Visible Lesions.	12	11 1	12	12
Adhesion	U	Τ	U	U

Table 59
Incidences of Gross Observations in Subchronic Female Rats (Continued)

Group : Concentration : Number of Animals on Study :	12	12	12	4 3000 ppm 12
LUNGS; No Visible Lesions	12	12	12	12
MANDIBULAR LYMPH NODE; No Visible Lesions.	12	12	12	12
MESENTERIC LYMPH NODE; No Visible Lesions	12	12	12	12
OVARIES; No Visible Lesions	12	12	12	12
OVIDUCT; No Visible Lesions	12	12	12	12
RECTUM; No Visible Lesions	12	12	12	12
SCIATIC NERVE; No Visible Lesions	12	12	12	12
SPINAL CORD; No Visible Lesions	12	12	12	12
SPLEEN; No Visible Lesions	12	12	12	12
STOMACH; No Visible Lesions	12	12	12	12
THYMUS; No Visible Lesions	12	12	12	12
THYROID GLAND; No Visible Lesions	12	12	12	12
TRACHEA; No Visible Lesions	12	12	12	12

Table 59
Incidences of Gross Observations in Subchronic Female Rats (Continued)

Group : Concentration : Number of Animals on Study :	0 ppm			4 3000 ppm 12
URINARY BLADDER; No Visible Lesions	12	12	12	12
UTERUS; No Visible Lesions	12	12	12	12
VAGINA; No Visible Lesions	12	12	12	12

Table 60 Incidences of Gross Observations in Satellite Female Rats

Group : Concentration : Number of Animals on Study :	12	12	12	4 3000 ppm 12
ADRENAL GLANDS; No Visible Lesions	12	12	12	12
BRAIN; No Visible Lesions	12	12	12	12
CECUM; No Visible Lesions	12	12	12	12
CERVIX; No Visible Lesions	12	12	12	12
COLON; No Visible Lesions	12	12	12	12
DUODENUM; No Visible Lesions	12	12	12	12
FEMUR/KNEE JOINT; No Visible Lesions	12	12	12	12
HEART; No Visible Lesions	12	12	12	12
ILEUM; No Visible Lesions	12	12	12	12
JEJUNUM; No Visible Lesions	12	12	12	12
KIDNEYS; No Visible Lesions	11 1	12	12	12
LIVER; No Visible Lesions.	12	12	12	12
LUNGS; No Visible Lesions	12	12	12	12

Table 60
Incidences of Gross Observations in Satellite Female Rats (Continued)

Group : Concentration : Number of Animals on Study :	12	12	12	4 3000 ppm 12
MANDIBULAR LYMPH NODE; No Visible Lesions	12	12	12	12
MESENTERIC LYMPH NODE; No Visible Lesions	12	12	12	12
OVARIES; No Visible Lesions	12	12	12	12
OVIDUCT; No Visible Lesions	12	12	12	12
RECTUM; No Visible Lesions	12	12	12	12
SCIATIC NERVE; No Visible Lesions	12	12	12	12
SKIN; No Visible Lesions	0 1	0 0	0 0	0 0
SPINAL CORD; No Visible Lesions	12	12	12	12
SPLEEN; No Visible Lesions	12	12	12	12
STOMACH; No Visible Lesions	12	12	12	12
THYMUS; No Visible Lesions	12	12	12	12
THYROID GLAND; No Visible Lesions	12	12	12	12
TRACHEA; No Visible Lesions	12	12	12	12

Table 60
Incidences of Gross Observations in Satellite Female Rats (Continued)

Group : Concentration : Number of Animals on Study :	0 ppm			4 3000 ppm 12
URINARY BLADDER; No Visible Lesions	12	12	12	12
UTERUS; No Visible Lesions	12	12	12	12
VAGINA; No Visible Lesions	12	12	12	12

Table 61
Incidences and Lesion Grades of Microscopic Observations in Subchronic Male Rats

Group : Concentration :	1 0 ppm			4 3000 ppm
Number of Animals on Study:	12	12	12	12
ADRENAL GLANDS; Examined	(12) 12	(O) O	(0)	(12) 12
BONE MARROW; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
BRAIN;				
Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
CECUM;				
Examined	(12) 10 (2) 2	(0) 0 (0) 0	(0) 0 (0) 0	(12) 11 (1) 1
COAGULATING GLANDS; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
COLON;				
Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
DUODENUM;				
Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
EPIDIDYMIDES;				
Examined. Within Normal Limits. Sperm granuloma mild	(12) 12 (0) 0	(0) 0 (0) 0	(0) 0 (0) 0	(12) 11 (1) 1
FEMUR;				
Examined	(12) 12	(0)	(0)	(12) 12

Table 61 Incidences and Lesion Grades of Microscopic Observations in Subchronic Male Rats (Continued)

Group :	1	2	3	4
Concentration :	0 ppm	100 ppm	500 ppm	3000 ppm
Number of Animals on Study :	12	12	12	12
HEART;				
Examined.	(12)	(0)	(0)	(12)
Within Normal Limits	8	0	0	9
Cardiomyopathy	(4)	(0)	(0)	(3)
minimal	4	0	0	3
ILEUM;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
JEJUNUM;				
Examined.	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
WIDNESS				
KIDNEYS; Examined	(12)	(12)	(12)	(12)
Within Normal Limits	4	(12)	(12)	(12)
Chronic progressive nephropathy	(7)	(10)	(12)	(12)
minimal	7	9	9	11
mild	0	1	3	1
Hyaline droplets; increased	(1)	(10)	(12)	(12)
minimal	1	10	4	` o´
mild	0	0	8	12
Dilatation; tubules; focal	(1)	(0)	(0)	(0)
minimal	1	0	0	0
Hydronephrosis; bilateral	(1)	(0)	(0)	(0)
mild	1	0	0	0
Hydronephrosis; unilateral	(1)	(0)	(1)	(0)
minimal	1	0	0	0
mild	0	0	1	0
Casts; tubules	(0)	(3)	(7)	(2)
minimal	0	2	5	2
mild	0	1	2	0
Aggregates; lymphoid	(0)	(0)	(0)	(1)
minimal	0	0	0	1

Table 61
Incidences and Lesion Grades of Microscopic Observations in Subchronic Male Rats (Continued)

Group :	1	 2	3	4
Concentration :	0 ppm			3000 ppm
Number of Animals on Study:	12	100 ppiii 12	12	12
Number of infinite on study .				
LIVER;				
Examined	(12)	(0)	(12)	(12)
Within Normal Limits	2	0	6	1
Inflammation, subacute	(9)	(0)	(6)	(11)
minimal	9	0	6	11
Necrosis, focal	(0)	(0)	(0)	(3)
minimal	0	0	0	2
mild	0	0	0	1
Hypertrophy; centrilobular	(0)	(0)	(0)	(2)
minimal	0	0	0	2
Fatty change; median cleft	(1)	(0)	(0)	(0)
minimal	1	0	0	0
Infarct; lobe	(1)	(0)	(0)	(0)
severe	1	0	0	0
LUNGS;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	9	0	0	9
Histiocytosis; alveolar	(0)	(0)	(0)	(2)
minimal	0	0	0	2
Inflammation, subacute	(2)	(0)	(0)	(1)
minimal	2	0	0	1
Inflammation; perivascular/peribronchiolar	(1)	(0)	(0)	(0)
minimal	1	0	0	0
MANDIBULAR LYMPH NODE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
MESENTERIC LYMPH NODE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	11
Histiocytosis	(0)	(0)	(0)	(1)
minimal	0	0	0	1
PEYERS PATCH;				
Examined .	(10)	(0)	(0)	(9)
Within Normal Limits.	10	0	0	9
Not Examined: MISSING	2	0	0	3
	_	· ·	Ü	9

Table 61
Incidences and Lesion Grades of Microscopic Observations in Subchronic Male Rats (Continued)

Group :	1	2	3	4
Concentration :	0 ppm	100 ppm	500 ppm	3000 ppm
Number of Animals on Study:	12	12	12	12
PROSTATE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	11	0	0	11
Inflammation, subacute	(1)	(0)	(0)	(1)
minimal	1	0	0	1
RECTUM;				
Examined	(11)	(0)	(0)	(12)
Within Normal Limits	11	0	O	12
Not Examined: MISSING	1	0	0	0
SCIATIC NERVE;				
Examined	(11)	(0)	(0)	(11)
Within Normal Limits	11	0	0	9
Not Examined: MISSING	1	0	0	1
Degeneration; axon/myelin	(0)	(0)	(0)	(2)
minimal	0	0	0	2
SEMINAL VESICLES;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
SPINAL CORD;	(10)	(0)	(0)	(10)
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
SPLEEN;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
STOMACH;	44.0:			44.03
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
TESTES;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12

Table 61
Incidences and Lesion Grades of Microscopic Observations in Subchronic Male Rats (Continued)

Group :	1	2	3	4
Concentration :	mqq 0	100 ppm	500 ppm	3000 ppm
Number of Animals on Study :				12
THYMUS;	(4.0)			(4.0)
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
THYROID GLAND;				
Examined	(12)	(0)	(12)	(12)
Within Normal Limits	11	0	12	` 9´
Ectopic thymus tissue	(1)	(0)	(0)	(1)
present	1	0	0	1
Hypertrophy; follicular cell	(0)	(0)	(0)	(2)
minimal	0	0	0	2
MITTIMAL	Ü	· ·	· ·	2
TRACHEA;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
URINARY BLADDER;				
Examined	(12)	(0)	(0)	(11)
Within Normal Limits	12	0	(0)	11
Not Examined: MISSING	0	0	0	1
NOL EXAMITIEG: MISSING	U	U	U	1

Table 62
Incidences and Lesion Grades of Microscopic Observations in Subchronic Female Rats

Group :	1	2	3	4
Concentration:	0 ppm			3000 ppm
Number of Animals on Study:	12	12	12	12
ADRENAL GLANDS:				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
BONE MARROW;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
BRAIN;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
CECUM;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	11
Inflammation, subacute minimal	(0)	(0)	(0)	(1) 1
INITITEMENT	U	U	U	Τ
CERVIX;	(11)	(0)	(0)	(10)
Examined Within Normal Limits	(11) 11	(0) 0	(0)	(12) 11
Not Examined: MISSING	1	0	0	0
Cyst; keratin	(0)	(0)	(0)	(1)
present	0	0	0	1
			-	_
COLON; Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
DUODENUM; Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	(0)	12
NICHIA NOIMAI DIMICO	14	O	O .	12
FEMUR; Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	(0)	12
		•	•	

Table 62
Incidences and Lesion Grades of Microscopic Observations in Subchronic Female Rats (Continued)

Group : Concentration : Number of Animals on Study :	1 0 ppm	2	3	4
				-
Number of Animals on Study:	1 0		1.1	3000 ppm
	12	12	12	12
EART;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	10	0	0	11
Cardiomyopathy	(1)	(0)	(0)	(1)
minimal	1	0	0	1
Inflammation/degeneration; subendocardial	(1)	(0)	(0)	(0)
minimal	1	0	0	0
LEUM; Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
EJUNUM;	(10)	(0)	(0)	(1.0)
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
IDNEYS;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	11	0	0	10
Chronic progressive nephropathy	(0)	(0)	(0)	(2)
minimal	0	0	0	2
Hydronephrosis; unilateral	(1)	(0)	(0)	(0)
mild	1	0	0	0
IVER;				
Examined	(12)	(1)	(12)	(12)
Within Normal Limits	3	0	4	0
Inflammation, subacute	(5)	(1)	(8)	(9)
minimal	5	1	8	9
Necrosis, focal	(0)	(0)	(1)	(0)
minimal	0	0	1	0
Hypertrophy; centrilobular	(0)	(0)	(0)	(9)
minimal	0	0	0	9
Fatty change; median cleft	(4)	(0)	(0)	(2)
minimal	4	0	0	2
Fatty change; periportal	(0)	(0)	(0)	(1)
minimal	0	0	0	1
Fibrosis; capsule	0	1	0	0

Table 62
Incidences and Lesion Grades of Microscopic Observations in Subchronic Female Rats (Continued)

Group : Concentration :	1 0 ppm			4 3000 ppm
Number of Animals on Study:	12	12	12	12
 UNGS;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	10	0	0	11
Histiocytosis; alveolar	(0)	(0)	(0)	(1)
minimal	0	0	0	1
Inflammation; perivascular/peribronchiolar	(2)	(0)	(0)	(0)
minimal	2	0	0	0
ANDIBULAR LYMPH NODE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
ESENTERIC LYMPH NODE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
VARIES;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12
VIDUCT;				
Examined	(12)	(0)	(0)	(11)
Within Normal Limits	12	0	0	11
Not Examined: MISSING	0	0	0	1
EYERS PATCH;				
Examined	(11)	(0)	(0)	(12)
Within Normal Limits	11	0	0	12
Not Examined: MISSING	1	0	0	0
ECTUM;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	11
Inflammation, subacute; tunica muscularis	(0)	(0)	(0)	(1)
minimal	0	0	0	1
CIATIC NERVE;				
Examined	(12)	(0)	(0)	(12)
Within Normal Limits	12	0	0	12

Table 62
Incidences and Lesion Grades of Microscopic Observations in Subchronic Female Rats (Continued)

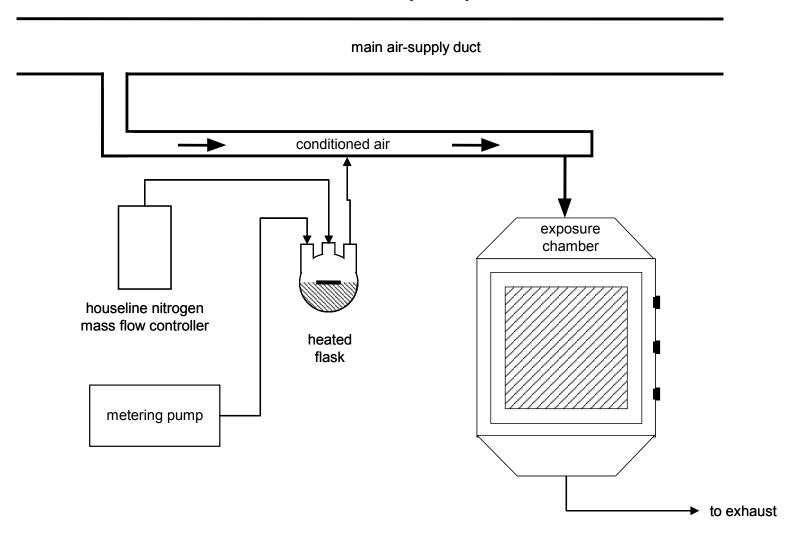
Group : Concentration : Number of Animals on Study :	1 0 ppm 12	2 100 ppm 12	3 500 ppm 12	4 3000 ppm 12
SPINAL CORD; Examined	(12) 12	(0)	(0)	(12) 12
SPLEEN; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
STOMACH; Examined. Within Normal Limits.	(12) 12	(0)	(0)	(12) 12
THYMUS; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
THYROID GLAND; Examined. Within Normal Limits. Hypertrophy; follicular cell minimal Adenoma; c-cell; incidental	(12) 12 (0) 0	(0) 0 (0) 0	(12) 12 (0) 0	(12) 9 (2) 2 1
TRACHEA; Examined	(12) 12	(0)	(0)	(12) 12
URINARY BLADDER; Examined. Within Normal Limits.	(12) 12	(0)	(0)	(12) 12
UTERUS; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12
VAGINA; Examined Within Normal Limits	(12) 12	(0)	(0)	(12) 12

Table 63
Incidences and Lesion Grades of Microscopic Observations in Satellite Female Rats

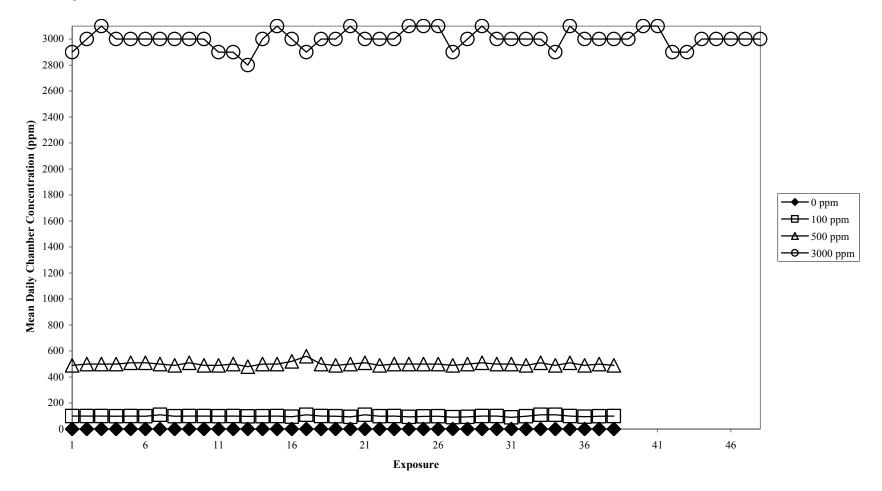
Group : Concentration : 0		2 100 ppm		4 3000 ppm
Number of Animals on Study:				12
CERVIX; Examined Within Normal Limits		(0)	(0)	(1) 1
OVARIES; Examined Within Normal Limits	(0)	(0)	(0)	(1) 1
OVIDUCT; Examined Within Normal Limits	(0)	(0)	(0)	(1) 1
UTERUS; Examined Within Normal Limits	(0)	(0)	(0)	(1) 1
VAGINA; Examined Within Normal Limits	(0)	(0)	(0)	(1) 1

FIGURES

Figure 1 Schematic Of Exposure System



Mean Daily Chamber Concentrations



APPENDICES

APPENDICES

EXPLANATORY NOTES

Notes

Due to rounding differences, values in tables may be slightly different than appendices.

Abbreviations

BW =Body weight **BWG** = Body weight gain FC =Food consumption Food efficiency FE =G =Gestation GD =Gestation day Kilogram Kg =Lactation L =LD =Lactation day Mg =Milligram

N/n = Number in group/Number of values used in calculation of mean

PND = Postnatal day
Ppm = parts per million

Wt = Weight

-/---/.../Blank space = No data/Data could not be calculated

Appendix A
Sample Characterization of High Naphthenic Naphtha:
Chemical Abstract Number Designation

Sample Characterization of High Naphthenic Naphtha: Chemical Abstract Number Designation

The test material used in studies to characterize mammalian toxicity and biodegradation of hydrocarbons in the Naphthenic (cycloparaffin) blending streams category of the HPV Gasoline Blending Stream Test Plan is a high naphthenic naphtha containing approximately 30% naphthenes. Results of studies with this test material can be used for read-across purposes for all CAS numbers identifying high naphthenic gasoline blending streams containing 19 to 30% or more naphthenic components.

This high naphthenic naphtha is derived from hydrogenation and hydrocracking process steps with removal of nitrogen and sulfur (sweetening) that convert low grade gas oils to higher quality components for direct blending of gasoline. Due to the multiple steps in generating this test material, the supplying refinery identified the sample under the broad CAS #64741-41-9, with the Chemical Abstract name of Naphtha, petroleum, heavy straight run, a CAS number which encompasses the more process-specific designations sweet naphtha and heavy crackate. The refinery further indicated that the sample underwent the hydrocracking HUX process that also makes applicable the more narrowly defined designation heavy hydrocrackate. Finally, the CAS #64741-78-2, with the Chemical Abstract name of Naphtha, petroleum, heavy hydrocracked can and has been used to identify this test material and is descriptive of the hydrocracking step employed.

This test sample identified as CAS #64741-41-9 for chain of custody purposes was collected as a single lot from one refinery and was chemically characterized prior to shipping in 3 drums to the sample repository. Contents of each drum were further analyzed to verify compositional uniformity between drums and distributed to the contract laboratories for testing. CAS #64741-41-9 and the name Naphtha, petroleum, heavy straight run will therefore be used officially to designate the test material.

Appendix B Protocol and Protocol Amendments

DuPont-18331

Highly Naphthenic Naphtha: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats (OECD 422)

Work Request Number 16123

Service Code 1422

Protocol

Performing Laboratory: E.I. du Pont de Nemours and Company HaskellSM Laboratory for Health and Environmental Sciences

P.O. Box 50

Newark, Delaware 19714

U.S.A.

Haskell Animal Welfare

Committee Number: DGRT123-GP

DuPont-18331

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DuPont-18331

OBJECTIVE

The objective of this study is to evaluate the potential subchronic and reproductive toxicity of the test substance when administered via inhalation to male and female rats during premating, cohabitation, gestation (G), and to lactation day 4 (day 4L). Clinical pathology, neurobehavioral function, gross pathology, histopathology, and reproductive function will be evaluated.

SPONSOR

Sponsor: Petroleum HPV Testing Group

American Petroleum Institute (API)

1220 L. Street, NW Washington, DC 20005

U.S.A

Sponsor Approval: Will be indicated by sponsor's signature and date on the protocol

REGULATORY COMPLIANCE AND TEST GUIDELINES

This study will be conducted in compliance with the following good laboratory practice(s), which are compatible with current OECD and MAFF (Japan) Good Laboratory Practices:

- U. S. EPA TSCA (40 CFR Part 792) Good Laboratory Practice Standards, except for the items documented below. None of the items listed impact the validity of the study.
 - A sample of the test substance and the original containers will not be retained by the performing laboratory due to the flammability of the test substance and potential explosive hazards. Samples from the same lot in similar containers are retained by the sponsor at another location.
 - A certificate of analysis conducted according to Good Laboratory Practice Standards will not be provided by the sponsor since the test substance is a mixture composed of approximately 225 substances. The sponsor is providing the composition and physical properties of the test substance.

This study will be conducted in compliance with the following testing guidelines:

- U. S. EPA, OPPTS 870.3650: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test, *Health Effects Test Guidelines* (2000).
- OECD Section 4, (Part 422): Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test, Guidelines for the Testing of Chemicals (1996).

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DuPont-18331

EXPERIMENTAL DESIGN

A. Treatment Groups and Exposure Concentrations

Study Groups		Identification ^c				
Subchronic ^a and	Number/					
Satellite (Female) ^b	Sex	Subcl	ronic	Satellite	Target	ed Atmospheric
	Group	Male	Female	Female	Conce	ntration (ppm) ^d
1	12	101-112	113-124	125-136	0	Control
2	12	201-212	213-224	225-236	100	Low
3	12	301-312	313-324	325-336	500	Intermediate
4	12	401-412	413-424	425-436	3000	High

- a Subchronic rats (repeated-treatment, general toxicity, neurotoxicity, clinical pathology, and pathology endpoints).
- b Satellite females (reproductive and developmental toxicity, neurotoxicity, clinical pathology, and pathology endpoints).
- c The Identification Number will be included on the cage label. The pretest number assigned to each animal will be tattooed on the tail during the pretest period and included on the cage label.
- d The test substance, administered by whole-body inhalation.

B. Treatment Schedule

All exposures will be 6 hours/day, 7 days/week. Lactating dams will not be exposed.

Animals/Study Phase	Duration
Premating ^a	14 Days (Approximate)
Subchronic Females	28 Days (Approximate)
Cohabitation ^a	Up to 14 days
Postcohabitation ^a	
Subchronic Males	30 Days (Approximate)
Females with no evidence of copulation	26 Days (Approximate)
Gestation	Day 0-19G

a Subchronic Males and Satellite Females.

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C. Study Parameters

(See appropriate sections in protocol for details).

Clinical Observations

Daily Animal Health Observations

Careful Clinical Observations

Daily (a.m., pre-exposure).

Daily (p.m., postexposure)

Detailed Clinical Observations Once before first exposure and at least once per week

thereafter

Clinical Observations During Inhalation

Daily, at least 3 times during exposure

Exposures Body Weights

Quarantine/Pretest At least twice/Weekly

During Study Weekly

Gestation Days 0, 7, 14, 21G Lactation Days 0, 4L

Food Consumption and Food Efficiency

During Study Weekly

Cohabitation/Postcohabitation

(Subchronic Males and Satellite Females) None

Gestation – Satellite Females Days 0, 7, 14, 21G Lactation – Satellite Females Days 0, 4L

Neurobehavioral Evaluations

Pretest All animals

Subchronic Males and Females Test day 28 (approximate)

Satellite Dams with Litters Day 4L

Clinical Pathology Evaluations

Coagulation

All animals at terminal sacrifice

Hematology and Clinical Chemistry
Subchronic Males and Females
Test day 28 (approximate)

Satellite Dams with Litters Day 4L

Necropsy

Sacrifice Schedule

Subchronic Males and Females After approximately 28 days of exposure Satellite nonpregnant Dams After approximately 26 days postcohabitation

Satellite Dams with Litters Day 4L Gross Pathology All animals

Offspring - Day 4L Pups - External examination

Organ Weights All animals

Histopathology

Subchronic Males and Females

Control and high-dose groups (target organs and gross lesions in intermediate-dose groups, if necessary)

Satellite Females

Reproductive organs for rats with reproductive failure

D. Selection of Exposure Concentrations

In a previous range-finding study, (1) male and pregnant female rats were exposed to 0, 250, 1000, or 4000 ppm for 6 hours per day for 14 days (males) or gestation days 6-20 (females). Test substance-related decreases in body weight, weight gain, and food consumption occurred in

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4000 ppm males and females. Decreased body weight and weight gain were also observed in 250 and 1000 ppm males. Males in the 4000 ppm group had slightly higher liver and testes weights and 4000 ppm females had slightly higher liver weights. There were no test substance-related effects on clinical signs of toxicity, in adults, number of litters, number of fetuses, number of live fetuses, number of implantations, resorptions, or external fetal observations. At 4000 ppm, fetal weights were slightly lower compared to control values.

Based on these data, exposure concentrations of 0, 100, 500, and 3000 ppm were selected for the current study.

F. Route of Administration

The test substance will be administered by inhalation since it is a potential route of exposure.

MATERIALS AND METHODS

A. Test Substance

Chemical Name: Sweet Naphtha

Other Name Used in this Protocol: Highly Naphthenic Naphtha

CAS Number: 64741-41-9

Haskell Sample Number: H-27199

Purity: The test substance is a mixture of approximately 225

volatile hydrocarbons.

Color: Colorless Form: Liquid

Supplier: EPL Archives, Inc., Sample #1203-005

Vehicle: Nitrogen (purity > 99.9%)

Filtered air.

1. Sample Characterization and Stability

The sponsor will provide the composition of the test substance, and a copy will be maintained in the study records. In addition, the sponsor will provide the analytical conditions that were used so the composition of the liquid test substance can be verified at Haskell Laboratory prior to the initial exposure and after the final exposure to establish stability of the liquid test substance.

B. Inhalation Exposure System

1. Exposure Chambers

Exposures to the test substance will be conducted in NYU type 1.4-m³ chambers. The exposure chambers to be used for this study are constructed of stainless steel and glass, and are cubical with square-pyramidal chamber inlets and outlets with a tangential feed at the chamber inlet which promotes uniform chamber distribution of the test substance. The chamber volume has been chosen so that the total body volume of the test animals is not expected to exceed approximately 5% of the chamber volume.

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2. Atmosphere Generation

The target exposure concentrations are 0, 100, 500, and 3000 ppm, with a range of $\pm 10\%$ of the overall target concentration.

The test substance will be vaporized by flash evaporation in a heated glass flask under flowing nitrogen. The resulting vapor will be mixed with conditioned, filtered air leading to the inhalation chambers. The concentration of test substance in each test chamber will be adjusted by varying the amount of the test substance delivered to each flask and/or by varying the amount of filtered air. Test atmospheres will be generated dynamically using airflows needed to achieve at least 10 air changes per hour in the exposure chamber.

All components of the vapor generation systems will be fabricated from stainless steel, glass, Neoprene® or Teflon.® The specific equipment used for atmosphere generation was determined during the method development study. (2)

3. Chamber Distribution of the Test Substance:

Uniform distribution of the main component of the test substance was determined during the method development study. (2)

4. Exposure Mode

Animals will be individually placed in stainless steel wire mesh modules (one/module) and exposed, whole-body, inside the exposure chamber, except during the cohabitation period, when animals will be housed as mating pairs in stainless steel wire mesh modules and exposed in the same manner. The chamber volume was chosen so that the total body volume of the test animals does not exceed 5% of the chamber volume. Animals will be rotated to a different level within the chamber approximately weekly, except during cohabitation.

C. Characterization of Chamber Atmosphere

1. Test Substance Sampling and Analysis

The atmospheric concentration of the test substance will be determined at least once per hour by gas chromatography (GC). Samples of chamber atmosphere will be drawn from the breathing zone of the animals and directly analyzed by a Hewlett Packard gas chromatograph equipped with a flame-ionization detector. Gas standards (ordinarily 3 working standards of different concentrations spanning the range of test substance concentrations) will be prepared prior to each exposure by the quantitative dilution of the test substance in known amounts of air. The samples collected from the chambers will be compared to the standard curve resulting from analyses of the gas standards. The control chamber will also be sampled at least once during the 6-hour exposure period. More frequent samples may be taken at the discretion of the Study Director. Nominal chamber concentrations will be calculated from the chamber air flow and the amount of test substance metered into each chamber.

Since the test substance is a mixture containing approximately 225 individual substances, 12 components of the mixture will be selected for quantification weekly. This analysis will be

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conducted by cryogenic gas chromatography using samples collected from the 100, 500, and 3000 ppm chambers.

Details of the analytical method(s) used will be documented in the study records.

2. Environmental Monitoring

Chamber airflow will be set to achieve at least 10 air changes per hour and will be monitored continually with thermoanemometers. Chamber temperature and relative humidity will be targeted at 19-25°C and 30%-70%, respectively, and will be measured with dial-type hygrometer/thermometers. Airflow, temperature, and relative humidity will be monitored continually and recorded at least 3 times in each exposure chamber during each exposure. Chamber oxygen concentration will be targeted to be at least 19%, will be measured with a Biosystems model 3100R Oxygen Analyzer, and will be recorded at least once in each exposure chamber during each exposure.

D. Duration of Exposure

Animals will be exposed as described in the study design. The starting time of each exposure will be defined as the time when the generation system is turned on. The ending time of each exposure will be defined as the time when the generation system is turned off. Rats will be exposed to the test substance during both the time it takes for the chamber to reach concentration, and the time it takes for the test substance to be purged from the chamber. After each exposure, rats will be returned to their cages.

E. Test Species

Species: Rat

Strain: Crl:CD(SD)

Sex: Male and female, nonsiblings, nulliparous

Source: Charles River Laboratories, Inc

Raleigh, North Carolina

Number of Rats Requested: 53 males; 105 females

Age at Arrival: 52 days

Age at Start of Study: Approximately 66 days

Weight at Arrival: Approximately 201-225 grams (males);

Approximately 176-200 grams (females)

The weight range at the time of arrival is not a factor for the purposes of this study since animals will be randomly distributed by weight at the time of assignment to groups. Therefore, deviations outside of this range are expected not to have any impact on the study. The body weight range will be documented

in the study records and provided in the final report.

Identification: Number assigned to each animal which will be tattooed on the

tail during pretest period and included on cage label.

Selection Criteria: Consistently acceptable health status and extensive experience

with this strain at Haskell Laboratory.

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F. Animal Husbandry

Housing

Subchronic study males:

All Phases: Individually (except during cohabitation of mating pairs) in

stainless steel, wire-mesh cages suspended above cage boards;

sexes on separate racks.

Housing

Subchronic study females:

All Phases: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Housing

Satellite Females:

Quarantine/Premating: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Cohabitation: Mating pairs (females placed in males' cages) on a 1:1 basis in

stainless steel, wire-mesh cages suspended above cage boards

Days 0-19 of gestation: Individually in stainless steel, wire-mesh cages suspended above

cage boards; sexes on separate racks.

Day 19 of gestation -

Day 4 of lactation: After the last exposure on day 19 of gestation, females assumed

pregnant will be housed individually in polycarbonate pans with bedding material. Females presumed nonpregnant will be housed in the same manner as pregnant females 7 days after the mating

pairs are separated.

Cage Rack Positioning: Cage racks will not be relocated within the animal room.

Climate: Temperature of 18-26°C

Relative humidity of 30%-70%

Illumination: Artificial (fluorescent light) on an approximate 12-hour

light/dark cycle.

Water: Tap water from United Water Delaware ad libitum provided by

an automatic watering system except during exposure.

Feed: PMI® Nutrition International, LLC Certified Rodent LabDiet®

5002 (pelleted) ad libitum except during exposure and when

fasted.

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G. Animal Health and Environmental 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 Screening Tests: Total bacterial counts, and the presence of coliforms, lead, and

other contaminants. The water analysis reports will be appended

to the main final report.

Cage and Cage Rack Analyzed for sentinel bacteria to ensure adequate sanitation by

Screening Tests: the cagewashers

Feed: 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 feed analysis reports will be appended

to the main final report.

Program Administration: Laboratory animal veterinarian

Data: Maintained separately from study records and may be included

in the final report at the discretion of the study director

H. Pretest Period/Quarantine

Pretest Period: Approximately 7-14 days (minimum of 5 days)

Quarantine: Approximately 5 days (minimum of 3 days

during the pretest period)

Quarantine Release: Performed by the laboratory animal veterinarian or designee on

the basis of adequate body weight gain and absence of clinical

signs of disease or injury.

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I. Assignment to Groups

Selection Criteria: Animals without adequate body weight gain and/or with clinical signs

of disease or injury may be eliminated from consideration for use in the study; weight variation of individual rats will not exceed \pm 20%

of the mean weight for each sex.

Randomization: Computerized, stratified randomization so that no statistically

significant group mean body weight differences occur within a sex.

Disposition of Remaining

Animals: To be sent to Animal Resources or sacrificed by carbon dioxide

asphyxiation at the discretion of the study director.

J. Clinical Observations

1. Daily Animal Health Observations

Frequency: All animals – At least once daily during quarantine and pretest,

and once daily thereafter. On exposure days, the observations will be conducted at the time animals are placed in the exposure

modules.

Scope: Cage-site examination to detect moribund or dead animals.

2. Careful Clinical Observations

Frequency: All animals – once daily after initiation of exposures. On

exposure days, the observations will be conducted at the time the animals are returned to their home cages. On non-exposure days, observations will be conducted in the afternoon.

Scope: Acute/systemic toxicity, including but not limited to nervous

system function. Clinical observations commonly observed following whole body inhalation exposure, such as alopecia and

yellow stained or wet fur, will not be recorded.

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3. Detailed Clinical Observations

Frequency: All animals - Once during pretest (baseline), and weekly

thereafter

Scope: Animals individually handled and examined for abnormal

behavior and appearance in a standardized arena; observations will include (but are 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

bizarre behavior.

4. Clinical Observations During Inhalation Exposures

Frequency: All animals visible to the observer through the glass window of

the chamber will be observed collectively as a group at least 3

times during each exposure.

Scope: Observations through the window of the chamber for abnormal

behavior or appearance.

K. Body Weight

Quarantine: At least twice.

Pretest: Weekly.

Subchronic Males and

Females: Weekly

Satellite Females: Premating – Weekly.

Cohabitation – Weekly. Gestation – Days 0, 7, 14, 21G.

Lactation - Days 0, 4L.

Satellite Females without

evidence of copulation:^a Post-cohabitation - Weekly

Neurobehavioral Evaluations: All animals evaluated will be weighed on the day of the FOB

assessment.

Body Weight Collected at

Terminal Sacrifice All animals.

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L. Food Consumption and Food Efficiency

Subchronic Males: Premating – weekly.

Cohabitation and postcohabitation – none.

Subchronic Females: Weekly

Satellite Females: Premating – Weekly.

Cohabitation – None.

Gestation - Days 0, 7, 14, 21G.

Lactation - Days 0, 4L.

Satellite Females without

evidence of copulation: Postcohabitation – None.

Calculation of Food Feeders will be weighed at the beginning and end of the interval.

Consumption: The final weight and amount of spillage from the feeder will be

subtracted from initial weight.

Calculation of Mean

Daily Food Efficiency: From food consumption and body weight data.

M. Reproductive/Developmental Assessment

Subchronic Male Rats and Satellite Female Rats

1. Cohabitation^a/Pairing

Frequency: Once after approximately 2 weeks of exposure to the test

substance.

Scope: Each satellite female will be continually housed on a 1:1 basis

with a randomly selected, nonsibling subchronic male of the

same concentration level.

Duration: Until evidence of copulation is observed or the cohabitation

period has ended (Day 14 of cohabitation), at which time the

mating pairs will be separated.

Evidence of Copulation: Daily examination of each female for an intravaginal copulation

plug or sperm in the vaginal lavage sample.

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a First day of cohousing = Day 0 of cohabitation; End of cohousing = Day 14 of cohabitation

b Evidence of copulation = Day 0 of gestation

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N. Gestation

After being transferred into polycarbonate pans (on day 19 of gestation for mated females, or 7 days after the mating pairs have been separated for females without evidence of copulation), female rats will be observed at least twice daily for signs of delivery and offspring.

O. Lactation

On lactation days 0 and 4, offspring will be individually handled and examined for abnormal behavior and appearance; any dead or abnormal pups will be recorded.

- Day 0:^a Live and dead pups in each litter will be counted by sex.

 Live pups will be individually weighed as soon as possible after delivery is completed.

 Dead pups will be sent to pathology. The lungs will be removed from the pups and placed in saline to determine if they float.
- Day 4:^b Pups in each litter will be counted by sex and live pups will be individually weighed and a gross external examination will be performed.
- a Day of delivery = Day 0 of lactation
- b Litter Sacrifice

If litters die prior to Day 4 of lactation, the female will be sacrificed. If the female dies prior to Day 4 of lactation, the litter will be sacrificed. If individual pups die prior to Day 4 of lactation, the pups will be sent to pathology and the carcasses of the pups will be examined to the extent possible and discarded.

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P. Neurobehavioral Evaluation

Pretest: All animals

During Study: Subchronic Males and Females -

Approximately test days 26, 27, 28, and 29 in the morning, prior to the daily exposure. For subchronic males and females,

testing will be counterbalanced by sex and exposure concentration over time to minimize the influence of

uncontrolled factors.

Satellite Dams with Litters – Day 4L.

Scope: Neurobehavioral test battery consisting of an abbreviated

functional observational battery assessment (FOB) and

motor activity (MA).

Animal Identification: Experimenter will be unaware of treatment group of the animals.

Acclimation: At least 10 minutes in the FOB laboratory prior to initiation of

assessment.

Order of FOB and MA

Assessments: The parameters will be evaluated in the order shown in the table

below.

1. Parameters

Body weights will be collected on the day of neurobehavioral assessments and will be reported in the main final report.

Order	Phase	Procedure	Parameters or Methods		
1	FOB	Manipulations in Open Field	approach and touch response auditory response	tail pinch response	
2	FOB	Fore- and hindlimb grip strength Strain gauge (Chatillion®)	forelimb grip strength	hindlimb grip strength	
3	MA	Motor Activity	Duration of movement and number of movements will be evaluated in 6 consecutive blocks of 10 minutes each as wel as for the total 60-minute session.		
4	MA	Assessments in MA monitor	diarrhea	polyuria	
5	FOB	Pupillary Constriction or Response ^a	Light beam directed to each e	ye in the darkened MA room	

a Conducted at the conclusion of motor activity while the animals are still in the motor activity monitor.

2. Test Facility Positive Control Data

Procedures and data describing the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are presented in 5 separate reports. (3,4,5,6,7) These positive control studies are the basis of training certification for the personnel making judgments in the neurobehavioral and

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neuropathology tests. The data also document that the equipment and procedures are capable of detecting effects that maybe seen in studies of this type.

Q. Clinical Pathology Evaluation

Coagulation and additional

saved serum: All animals at terminal sacrifice.

Hematology/Clinical

Chemistry: Subchronic Males and Females – Test day 28 (Approximate)

Satellite Lactating Females with Litters – Day 4L

Fasting: On the day prior to blood collection, subchronic males and

females will be allowed to eat upon return to their home cages following exposure. After approximately 2 hours, feeders will be removed from the cages for at least 15 hours prior to sample

collection.

Anesthesia: Carbon dioxide

1. Collection Sites and Samples

(all blood volumes are approximate)

Hematology: Orbital sinus (0.5 mL into EDTA tube)

Coagulation: Abdominal vena cava at sacrifice

(1.8 mL into sodium citrate tube)

Clinical Chemistry: Orbital sinus (0.75 mL into serum separator tube)

Additional Saved Serum: Abdominal vena cava at sacrifice (all remaining blood into

serum separator tube); processed to serum, and frozen at approximately -80°C. Serum may be used for additional testing as documented by protocol amendment, or will be discarded

when the final report issues

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2. Collection Parameters

All blood samples will be evaluated for quality by visual examination prior to analysis. Results will be maintained in the study records and reported only if the sample is analyzed. The following parameters will be evaluated.

	Hematology		Clinical Chemistry ^b
	red blood cell count		globulin
1	hemoglobin		calcium
1	hematocrit	V	inorganic phosphorus
V	mean corpuscular volume	V	sodium
V	mean corpuscular hemoglobin		potassium
1	mean corpuscular hemoglobin concentration	1	chloride
1	red cell distribution width	V	albumin/globulin ratio
1	absolute reticulocyte count		creatinine kinase
√	platelet count		bicarbonate
	mean platelet volume		high-density lipoprotein cholesterol
1	white blood cell count		low-density lipoprotein cholesterol
1	differential white blood cell count		serum osmolality
	Heinz bodies		total bile acids
	methemoglobin		fluoride (EDTA plasma)
	Wright's-stained, blood smear prepareda		
1	red blood cell, white blood cell, and platelet morphology		
1	new-methylene-blue-stained, blood smear prepareda		Urinalysis
			quality
	Coagulation		color
V	prothrombin time		clarity
V	activated partial thromboplastin time		volume
	thrombin clotting time		osmolality
	fibrinogen		specific gravity
			pН
	Clinical Chemistry ^b		glucose
1	aspartate aminotransferase		ketone
1	alanine aminotransferase		bilirubin
√	sorbitol dehydrogenase		blood
√,	alkaline phosphatase		urobilinogen
√,	gamma glutamyltransferase		protein
√,	total bilirubin		fluoride
1	urea nitrogen		microscopic urine sediment examination
√,	creatinine		
1	cholesterol		Other Determinations
1	triglycerides	√	Bone marrow smears ^a
1	glucose		
√,	total protein		
	albumin		

- a Examined if required to substantiate or clarify the results of hematology findings.
- b All parameters will be analyzed on serum unless indicated.

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R. Anatomic Pathology Evaluation

1. Quarantine/Pretest

Rats that are accidentally killed or removed from study during the quarantine/pretest period will be discarded without necropsy. Rats that are found dead or sacrificed *in extremis* during the pretest period will undergo a gross pathological examination to check for the presence of disease. Dependent upon these findings, further diagnostic procedures may be employed at the discretion of the study director, a pathologist, or the laboratory animal veterinarian. The results will not be reported in the final report unless considered significant to the evaluation of the study.

2. Subchronic Males and Females

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross evaluation. Rats will be euthanized by carbon dioxide asphyxiation and exsanguination. The order of sacrifice for scheduled deaths will be random among all treatment groups within a sex.

Blood samples and bone marrow smears for terminal clinical pathology parameters as described in the Clinical Pathology Evaluation section will be collected from all rats at this time.

The following tissues will be collected:

Digestive System	Cardiovascular System	Musculoskeletal System
liver	heart	Femur
stomach		
duodenum	Hematopoietic System	Reproductive System
jejunum	spleen	Male
ileum	thymus	testes
cecum	mandibular lymph node	epididymides
colon	mesenteric lymph node	prostate
rectum	bone marrow ^a	seminal vesicles
	Peyer's patches ^b	coagulating glands
Urinary System	Endocrine System	Female ^e
kidneys	thyroid gland	ovaries
urinary bladder	adrenal glands	oviducts
-	_	cervix
Respiratory System	Nervous System	uterus
lungs	brain (3 sections) ^e	vagina
trachea	spinal cord (3 levels) ^d	
	sciatic nerve	Miscellaneous
		gross observations ^f

- a Bone marrow will be collected with the femur.
- b Peyer's patches will be collected from sections of the digestive tract.
- c Including cerebrum, midbrain, cerebellum, and brain stem.
- d Including cervical, thoracic, and lumbar sections.
- e All satellite females (including females that do not deliver a litter) will be examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*.
- f Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

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All tissues will be placed in the appropriate fixative. Testes and epididymides will be fixed in modified Davidson's solution. All other tissues will be fixed in 10% neutral buffered formalin.

Histologic examination of all the tissues collected will be conducted for all Subchronic animals in the control and high-concentration groups. Examination of tissues from the remaining groups will be limited to relevant gross lesions and those tissues that demonstrate treatment-related histologic effects in the high-treatment group. Tissues from rats found dead or sacrificed *in extremis* will be histologically examined in a similar manner in an attempt to determine cause of death or morbidity.

Paraffin-embedded tissues will be sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin, and examined microscopically by a veterinary pathologist. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, tail chronic dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinna) will be saved, but will generally not be processed for microscopic evaluation.

Additional procedures to identify and/or clarify histologic features of lesions may be performed at the discretion of the pathologist and will be documented in the final report.

For all Subchronic rats sacrificed by design, the following organs will be trimmed of any adherent tissue, and weighed wet. Group mean and relative organ weights (percent of final body weight; percent of brain weight) will be calculated. Final body weights determined prior to necropsy will be used in the assessment of organ weight changes. Organs from rats found dead, sacrificed *in extremis*, or accidentally killed may be weighed at the discretion of the pathologist or study director.

Organ Weights from all Subchronic Rats Sacrificed by Design

Male	<u>Female</u>	Both Sexes
Testis ^a	Ovaries with oviducts	Liver
Epididymis ^a	Uterus with vagina	Kidneys
Prostate		Lungs
		Adrenal glands
		Thymus
		Spleen
		Brain
		Heart

a The right testis and epididymis will be placed in modified Davidson's solution. All other tissues will be fixed in 10% neutral buffered formalin.

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3. Satellite Females

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross evaluation. Rats will be euthanized by carbon dioxide asphyxiation and exsanguination. The order of sacrifice for scheduled deaths will be random among all treatment groups within a sex.

The following tissues will be collected and preserved from all Satellite females.

Digestive System	Cardiovascular System	Musculoskeletal System
liver stomach	heart	Femur
duodenum	Hematopoietic System	Reproductive System
jejunum	spleen	=== <u></u>
ileum	thymus	Female ^e
cecum	mandibular lymph node	ovaries
colon	mesenteric lymph node	oviducts
rectum	bone marrow ^a	cervix
	Peyer's patches ^b	uterus
		vagina
<u>Urinary System</u>	Endocrine System	
kidneys	thyroid gland	<u>Miscellaneous</u>
urinary bladder	adrenal glands	gross observations f
Respiratory System	Nervous System	
lungs	brain (3 sections) ^e	
trachea	spinal cord (3 levels) ^d	
	sciatic nerve	

- a Bone marrow will be collected with the femur.
- b Peyer's patches will be collected from sections of the digestive tract.
- c Including cerebrum, midbrain, cerebellum, and brain stem.
- d Including cervical, thoracic, and lumbar sections.
- e All satellite females (including females that do not deliver a litter) will be examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*.
- f Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

The following tissues will be trimmed of any adherent tissue and weighed wet.

Tissues Collected from Satellite Female Rats Sacrificed by Design

Ovaries with oviducts Uterus with vagina Liver Kidneys Lungs

The uteri of all Satellite females (including females that do not deliver a litter) will be examined for the number of implantation sites and the ovaries will be examined for the number of *corpora lutea*. The uterus of each apparently "nonpregnant" female will be stained with ammonium sulfide⁽⁸⁾ to detect very early resorptions; the number of implantation sites will be recorded.

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Histologic examination of the reproductive tissues collected from Satellite females with reproductive failure will be conducted.

4. Pups

All pups found dead on lactation day 0 will be sent to pathology. The lungs will be removed from the pups and placed in saline to determine if they float.

All offspring surviving to postnatal day 4 will be evaluated for external alterations and euthanized by intraperitoneal (i.p.) injection of sodium pentobarbital. Pups found dead or sacrificed *in extremis* will be examined to the extent possible and discarded.

S. Reproductive Function Calculations

The following table lists the indices of reproductive function that will be calculated for the parental animals.

Mating Index (%)	=	Number copulated ^a Number cohabited	- x 100
Fertility Index (%)	=	Number pregnant Number copulated Number copulated	- x 100
Gestation Index (%)	=	Number of litters with at least one live pup Number of litters	_ x 100
Implantation Efficiency (%) ^c	=	Number of pups born Number of implantation sites	- x 100
Pups Born Alive (%)	=	Number of pups born alive Number of pups born	x 100
0-4 Day Viability (%)	=	Number of pups alive day 4 Number of pups born alive	- x 100

a Evidence of copulation = intravaginal copulatory plug, sperm in vaginal lavage, uterine implantation sites, or delivery of a litter.

b Including delivery of a litter or uterine implantation sites.

c To be determined for each litter. Mean and standard deviation for each dose level will be calculated.

d Excluding litters sacrificed due to death of dam during lactation.

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T. Statistical Methods

		Method of Statistical Analysis		
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant	
Body Weight Body Weight Gain Food Consumption Food Efficiency Gestation Length Implantation Site Numbers Implantation Efficiency Corpora Lutea Counts Mean Number of Pups Per Litter Percent Born Alive 0-4 Day Viability Clinical Pathology ^a Organ Weight	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for normality	One-way analysis of variance ⁽¹¹⁾ and Dunnett's test ^(12,13,14)	Kruskal-Wallis test ^(I.5) and Dunn's test ^(I.6)	
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend ^{(11)c}		
Sex Ratio (Covariate: litter size) Mean Pup Weights (Covariates: litter size, sex ratio)	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for d normality	Analysis of covariance ⁽¹¹⁾ and Dunnett-Hsu ⁽¹⁷⁾	Non-parametric analysis of covariance ⁽¹⁸⁾	
Motor Activity ^e Grip Strength	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for normality ^d	Repeated measures analysis of variance ⁽¹⁹⁾ followed by Linear contrasts ⁽²⁰⁾	Sequential application ⁽²¹⁾ of the Jonckheere-Terpstra trend test ⁽²²⁾	

- a When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity is reported as >1.083, 1.083 is used for any calculations performed with that data.
- b If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used. If the Shapiro-Wilk test is significant, Kruskal-Wallis test is followed with Dunn's test.
- c If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test⁽²³⁾ with a Bonferroni correction is used.
- d A normalizing, variance stabilizing transformation may be used as needed.
- e Test day and 10-minute interval will be used as repeated-measure factors.

Subchronic male, Subchronic female, and Satellite female data will be evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean will be used as the experimental unit for statistical evaluation. The level of significance selected is p < 0.05. Additional statistical tests will be used, and other parameters analyzed, if deemed necessary.

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SAFETY AND HOUSEKEEPING

Procedures for handling the test substance will be in accordance with the Process Safety Review for this study.

Animal carcasses, feces, and unused food will be incinerated.

RECORDS AND SAMPLE STORAGE

Specimens (if applicable), all raw data, the protocol, amendments (if any), and the final report will be retained in the archives of Haskell Laboratory for ten years following the issuance of the final report. After that period, arrangements will be made to either return all materials to the Sponsor or archive them longer at Haskell Laboratory.

Laboratory-specific raw data such as personnel files, instrument, equipment, refrigerator and/or freezer raw data will be retained at the facility where the work was done.

STUDY DATES

Proposed Experimental Start: May 9, 2006

In-life Completion Date: June 30, 2006 (Approximate)

Proposed Experimental Termination: February 20, 2007

REFERENCES

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SIGNATURES



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Highly Naphthenic Naphtha: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats (OECD 422)

Work Request Number 16123

Service Code 1422

Protocol Amendment 1

The protocol is amended as follows:

Effective June 9, 2006

 Page 19, Materials and Methods, Section R. Anatomic Pathology Evaluation, Subsection 2. Subchronic Males and Females, in the table entitled "Organ Weights from all Subchronic Rats Sacrificed by Design, change "Uterus with vagina" to Uterus with cervix".

Rationale: This change was made to correct a typographical error in the original protocol.

Page 20, Materials and Methods, Section R. Anatomic Pathology Evaluation, Subsection
 Satellite Females, change the title of the table to: "Organ Weights for Satellite Females Sacrificed by Design"

Rationale: This change was made to correct a typographical error in the original protocol.

3. Page 20, Materials and Methods, Section R. Anatomic Pathology Evaluation, Subsection 3. Satellite Females, in the table now entitled Organ Weights for Satellite Females Sacrificed by Design, change "Uterus with vagina" to Uterus with cervix".

Rationale: This change was made to correct a typographical error in the original protocol.

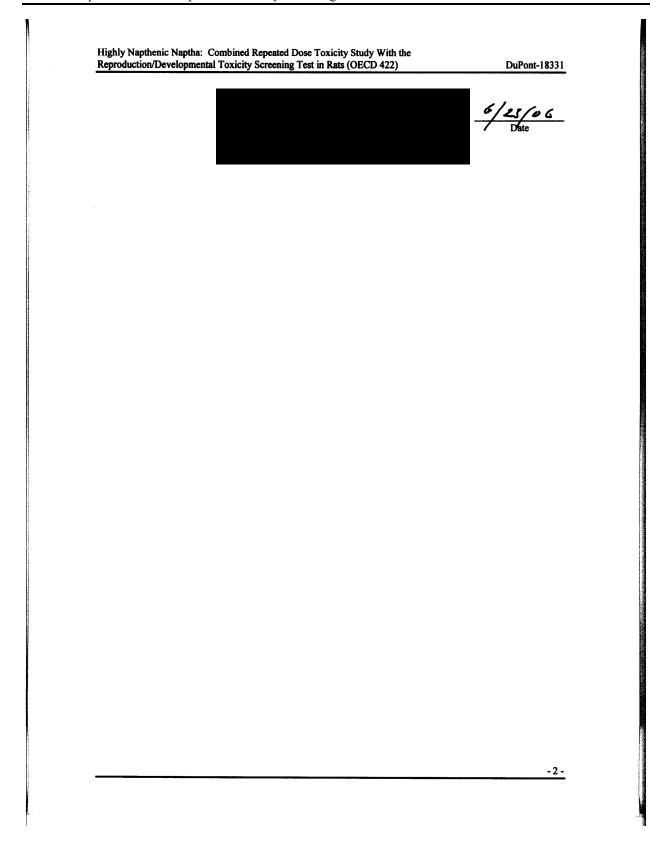
Effective June 19, 2006

4. Page 4, Section B. Treatment Schedule, change the duration of exposure for Females with no evidence of copulation to 19 days after the cohoused male and female have been separated.

Rationale: If the female becomes pregnant on the last day the animals were cohoused, then they should only be exposed for 19 days after the male and female were separated in order to ensure that they receive the same number of exposures as the pregnant, gestating females.



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Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats (OECD 422)

DuPont-18331

Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Study With the Reproduction/Developmental Toxicity Screening Test in Rats (OECD 422)

Work Request Number 16123

Service Code 1422

Protocol Amendment 2

The protocol and amendment #1 is amended as follows:

1. On the title page, change the name of the test substance to: Naphtha, Petroleum, Heavy Straight-Run

Rationale: The change was requested by the sponsor.



Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-18331

Work Request Number 16123 Service Code 1422 Protocol Amendment 3

The protocol is amended as follows:

1. Page 15, Materials and Methods, P. Neurobehavioral Evaluation, Animal Identification, change to the following:

Animal Identification: Experimenter will be unaware of treatment group of the animals for the evaluation of subchronic males and females.

<u>Rationale</u>: Since the order of the animals during the evaluation on lactation day 4 could not be randomized or counterbalanced, the identity of the treatment group on the cage label during the neurobehavioral evaluation will be present.

2. Page 20, Materials and Methods, R. Anatomic Pathology Evaluation, 3. Satellite Females, fourth paragraph, remove the second sentence.

<u>Rationale</u>: Staining of the uterus with ammonium sulfide to detect early resorptions is not used in reproduction studies due to the length of time elapsed between cohabitation and sacrifice.

- 3. Page 21, Materials and Methods, S. Reproductive Function Calculations, replace section with the following:
 - S. Reproductive Function Calculations

The following table lists the indices of reproductive function that will be calculated for the parental animals.

Reproductive Function Calculations

Mating index (%)	= -	number mated ^a number paired	- x 100
Fertility index (%)	= -	number pregnant ^b number mated ^a	- x 100
Post-Implantation Loss (%) ^c Live Born Index (%) ^c		number of implantation sites - number of pups born number of implantation sites	- x 100
		number of pups born alive number of pups born	- x 100
Viability index (%) ^{c,d}	= -	number of pups alive Postnatal Day (PND) 4 number of pups born alive	- x 100

Mated = intravaginal copulatory plug, sperm in vaginal lavage, uterine implantation sites, or delivery of a litter.

- 1 -

b Including those found dead pregnant during gestation.

To be determined for each litter.

d Excluding litters sacrificed due to death of dam during lactation.

Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-18331

Work Request Number 16123 Service Code 1422 Protocol Amendment 3 (Continued)

Rationale: The wording and description of process for reproductive function calculations was updated to be consistent with the new computer data collection program.

4. Page 22, Materials and Methods, T. Statistical Methods, replace section with the following:

T. Statistical Methods

		Method of Statistical Analysis (see Appendix A for references)		
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant	
Body Weight Body Weight Gain Food Consumption Food Efficiency Precoital Interval Gestation Length Corpora Lutea Implantation Sites Post-Implantation Loss Number of Pups Per Litter Live Born Index Viability Index Clinical Pathology Parameters Organ Weight Parameters	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for normality	One-way analysis of variance ⁽¹¹⁾ and Dunnett's test ^(12,13,14)	Kruskal-Wallis test ⁽¹⁵⁾ and Dunn's test ⁽¹⁶⁾	
FOB Descriptive Parameters Mating Index Fertility Index	None		pplication of e test for trend ^{(11)¢}	
Sex Ratio (Covariate: litter size) Pup Weights (Covariates: litter size, sex ratio)	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for normality	Analysis of covariance ⁽¹¹⁾ and Dunnett-Hsu ⁽¹⁷⁾	Non-parametric analysis of covariance ⁽¹⁸⁾	
Motor Activity ^e Grip Strength	Levene's test for homogeneity ⁽⁹⁾ and Shapiro-Wilk test ⁽¹⁰⁾ for normality ^d	Repeated measures analysis of variance ⁽¹⁹⁾ followed by Linear contrasts ⁽²⁰⁾	Sequential application ⁽²¹⁾ of the Jonckheere-Terpstra trend test ⁽²²⁾	

- a When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as < 0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity is reported as > 1.083, 1.083 is used for any calculations performed with that data.
- b If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used. If the Shapiro-Wilk test is significant, Kruskal-Wallis test is followed with Dunn's test.
- c If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test⁽²³⁾ with a Bonferroni correction is used.
- d A normalizing, variance stabilizing transformation may be used as needed.
- e Test day and 10-minute interval will be used as repeated-measure factors.

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Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-18331

Work Request Number 16123 Service Code 1422 Protocol Amendment 3 (Continued)

Male and female data will be evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean will be used as the experimental unit for statistical evaluation. The level of significance selected is p < 0.05. Additional statistical tests will be used and other parameters analyzed, if deemed necessary.

<u>Rationale</u>: The statistical procedures were revised to be consistent with the new computer data collection program.

5. Protocol Amendment 1, Header, correct test substance name to: "Highly Naphthenic Naphtha."

Rationale: To correct typographical error.

6. The protocol and Amendments 1 and 2 are amended as follows:

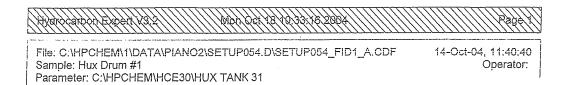
The Sponsor Representative is changed to: Russell D. White, Ph.D., D.A.B.T.®

Rationale: At the Sponsor's request, the Sponsor Representative is changed.



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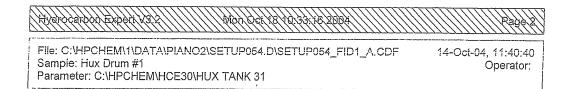


Component List

Pk# 1 2 3 4 5 6 7 8 9 10	Time 27.926 28.974 31.607 35.331 40.127 41.743 42.310 45.102 46.708 46.975	Group Component 16 64 2,3-Dimethylbutane 16 74 2-Methylpentane 16 80 3-Methylpentane P6 96 n-Hexane N6 112 McyC5+2,2DMC5 17 116 2,4-Dimethylpentane 17 118 2,2,3-Trimethylbutane A6 130 Benzene 17 134 33DMC5+5m1C6ene N6 136 Cyclohexane	%Wgt 0.007 0.064 0.085 0.181 0.669 0.140 0.007 0.108 0.046 0.496	%Vol 0.008 0.074 0.095 0.205 0.667 0.156 0.008 0.092 0.049 0.476	%MoI 0.010 0.084 0.110 0.236 0.893 0.157 0.008 0.156 0.051
1 —11	50.221	17 156 2-MethylC6 + C7-Olefin 17 166 3-Methylhexane N7 172 t-1,3-DimethylcyC5 N7 174 c-1,3-DMcyclopentane N7 176 t-1,2-DimethylcycloC5 17 180 3-Ethylpentane 18 186 2,2,4-Trimethylpentane O7 189 C7-Olefin P7 200 n-Heptane N7 222 Methylcyclohexane	4.090	4.500	4.585
2 —13	52.055		3.230	3.517	3.621
14	52.832		1.464	1.450	1.674
15	53.403		1.327	1.323	1.518
16	54.023		1.621	1.613	1.855
17	54.159		0.226	0.241	0.253
18	54.613		0.039	0.042	0.039
19	54.990		0.008	0.008	0.009
19	57.702		6.621 -	7.230	7.421
19	61.065		6.962	6.762	7.964
21	61.883	N8 224 1,1,3-TrimethylcycloC5 18 226 2,2-Dimethylhexane N7 234 Ethylcyclopentane 18 240 2,2,3-Trimethylpentane 18 245 2,5-DMC6 + C8-olefin 18 250 2,4-Dimethylhexane N8 260 t,c-1,2,4-TriMcyC5 18 265 3,3-DMC6 + C8-olefin N8 278 t,c-1,2,3-TriMcycloC5 18 292 2,3,4-Trimethylpentane	0.477	0.477	0.478
22	62.325		0.060	0.065	0.059
23	63.722		1.200	1.170	1.372
24	64.393		0.013	0.013	0.013
25	64.642		0.495	0.530	0.487
26	64.980		0.582	0.622	0.573
27	65.790		0.932	0.932	0.933
28	66.201		0.077	0.081	0.075
29	67.298		0.647	0.642	0.648
30	67.939		0.064	0.067	0.063
7 - 31	68.519	A7 300 Toluene O8 312 C8-Olefin I8 314 2,3-Dimethylhexane I8 316 2-M-3-Epentane I8 326 2-Methylheptane I8 328 4-Methylheptane O7 330 C7-Diolefin + C8-Olefin O8 333 C8-Olefins N8 335 t-1,4-DiMcycloC6	3.997	3.443	4.873
32	69.946		0.196	0.205	0.196
33	70.285		0.393	0.413	0.387
34	70.428		0.163	0.170	0.161
5 - 35	71.674		3.039	3.253	2.989
36	71.885		1.003	1.039	0.986
37	72.056		0.189	0.199	0.189
38	72.190		0.159	0.166	0.159
39	72.738		1.945	1.846	1.947

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Component List

	Pk# 40 41 42 43 44 45 46 47 48 49	72.937 73.079 73.927	Group Component 18 336 3-Methylheptane 18 338 3-Ethylhexane O8 348 C8-Olefin N8 352 c1Ethyl-3-methylcyC5 N8 356 t-1-E-3-McyC5 N8 360 t-1-E-2-McyC5 N8 362 1-M-1-EcycloC5 N8 368 t-1,2-DiMcycloC6 N8 385 t-1,3-DiMcycloC6 N8 390 c-1,4-DiMcycloC6	%Wgt 2.493 1.185 0.248 0.800 0.737 0.703 0.075 0.859 0.069 1.303	%Voi 2.638 1.240 0.260 0.776 0.716 0.680 0.072 0.827 0.066 1.250	%Mol 2.452 1.165 0.248 0.801 0.738 0.704 0.075 0.860 0.069 1.305
· 442	7 —50 51 52 53 54 55 56 57 58	77.537 78.327 78.468 79.056 79.382 79.982 80.451 80.825 81.064 81.343	P8 400 n-Octane O9 410 C9-Olefin O9 412 C9-Olefin I9 418 2,2,4-Trimethylhexane I9 420 2,4,4-Trimethylhexane I9 424 2,3,5-Trimethylhexane I9 428 2,2,3,4-TetraMC5 N8 432 c-1,2-DiMcycloC6 I9 434 2,4-Dimethylheptane O9 436 C9-Olefin	5.463 0.174 0.116 0.025 0.052 0.302 0.056 0.334 0.412 0.069	5.805 0.180 0.120 0.026 0.054 0.313 0.058 0.311 0.431 0.071	5.372 0.155 0.103 0.021 0.046 0.265 0.049 0.334 0.361 0.061
. \$1	60 61 62 63 64 65 66 67 68 69	81.663 81.863 82.029 82.188 82.465 82.797 82.955 83.116 83.235 83.411	N8 440 Ethylcyclohexane 19 444 2-Methyl-4-Ethylhexane 19 446 2,6-Dimethylheptane O9 449 C9-Olefin O9 452 C9-Olefins O9 454 C9-Olefins 19 458 2,5 & 3,5-DMheptane O9 460 C9-Olefins 19 462 3,3-Dimethylheptane ? Unidentified	2.059 0.055 0.811 0.128 0.923 0.170 0.701 0.118 0.205 0.326	1.952 0.057 0.841 0.132 0.950 0.175 0.722 0.122 0.212 0.338	2.061 0.048 0.710 0.114 0.822 0.152 0.614 0.105 0.179 0.285
ⁱ ħ11	70 71 72 73 74 75 76 77 78	83.640 84.232 84.407 84.639 84.892 85.166 85.473 85.603 85.754	19 466 C9-Isoparaffin A8 475 Ethylbenzene N9 480 t-1,2,4-TrimethylcyC6 19 485 2,3,4-Trimethylhexane O9 490 C9-Olefins 19 495 3,3,4-Trimethylhexane? A8 500 m-Xylene A8 502 p-Xylene 19 503 2,3-Dimethylheptane	0.214 1.012 0.347 0.616 0.088 0.153 1.973 0.697 0.508	0.219 0.872 0.332 0.623 0.090 0.153 1.706 0.604 0.520	0.187 1.070 0.309 0.539 0.078 0.134 2.087 0.737 0.445

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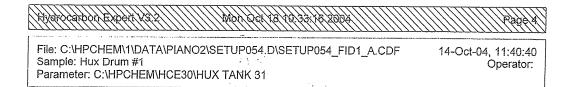


Component List

Pk# 79 80 81 82 83 84 85 86 87 88	86.000 86.191 86.389 86.553 86.831 86.978	Group Component 19 506 3,4-Dimethylheptane O9 508 C9-Olefin 19 510 3-Methyl-3-ethylhexane 19 516 4-Ethylheptane 19 518 4-MC8+C9-Olefin 19 520 2-Methyloctane 19 524 C9-Isoparaffin 19 528 3-Ethylheptane 19 530 3-Methyloctane N9 540 c-1,2,4-TriMcyC6	%Wgt 0.064 0.214 0.242 0.101 0.872 1.187 0.170 0.386 1.520 0.088	%Vol 0.066 0.219 0.244 0.103 0.904 1.247 0.176 0.395 1.566 0.084	%Mol 0.056 0.190 0.212 0.088 0.763 1.039 0.149 0.338 1.331 0.079
89	88.289	N9 545 1,1,2-TriMcycloC6 A8 550 o-Xylene O9 560 C9-Olefin O9 562 C9-Olefin O9 564 C9-Olefin ? Unidentified N9 568 t-1-E-4-M-cyC6? N9 570 c-1-E-4-McyC6? I9 572 C9-Isoparaffin O9 575 1-Nonene	0.138	0.135	0.123
90	88.426		1.175	0.997	1.243
91	88.543		0.083	0.085	0.074
92	88.669		0.149	0.152	0.133
93	88.873		0.021	0.021	0.018
94	88.950		0.022	0.023	0.020
95	89.250		0.527	0.493	0.468
96	89.404		0.805	0.753	0.716
97	89.695		0.423	0.431	0.370
98	90.008		0.101	0.102	0.090
99	90.179	N9 580 Isobutylcyclopentane ? Unidentified O9 590 cis-3-Nonene I9 595 C9-Isoparaffin P9 600 n-Nonane O9 604 trans-2-Nonene N9 606 1-M-1-Ecyclohexane O10 610 C10-Olefin A9 616 Isopropylbenzene O9 618 cis-2-Nonene	0.145	0.138	0.129
100	90.262		0.091	0.087	0.081
101	90.967		0.074	0.076	0.066
102	91.094		0.026	0.026	0.022
103	91.369		4.300	4.474	3.766
104	91.750		0.523	0.529	0.465
105	92.096		0.179	0.166	0.159
106	92.302		0.023	0.023	0.018
107	92.578		0.134	0.116	0.125
108	92.774		0.027	0.027	0.024
109 110 111 112 113 114 115 116	92.906 93.053 93.293 93.565 93.821 93.975 94.068 94.373 94.525	N9 620 tert-Butylcyclopentane O9 622 C9-Olefins O9 624 C9-Olefin N9 626 Isopropylcyclohexane I10 630 2,2-Dimethyloctane ? Unidentified ? Unidentified N10 634 1-M-4-isopropylcyC6? N9 636 sec-Butylcyclopentane	0.125 0.317 0.253 0.233 0.134 0.025 0.021 0.351 0.562	0.118 0.321 0.256 0.217 0.138 0.025 0.021 0.331 0.531	0.111 0.282 0.225 0.207 0.106 0.019 0.016 0.281 0.500

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Component List

Pk# 118 119 120 121 122 123 124 125 126	Time 94.697 94.850 94.957 95.143 95.409 95.547 95.694 95.826 96.016 96.241	Group Component 110 638 2,6-Dimethyloctane 110 640 2,5-Dimethyloctane? N9 642 Butylcyclopentane N9 644 Propylcylohexane 110 646 3,6-Dimethyloctane N9 648 1-M-2-EcycloC6 ? Unidentified O10 650 C10-Olefin A9 651 Propylbenzene 110 652 3,6-Dimethyloctane	%Wgt 0.103 0.111 0.312 0.105 0.726 0.105 0.058 0.140 0.469 0.450	%Vol 0.105 0.112 0.296 0.098 0.734 0.097 0.059 0.141 0.407 0.457	%Mol 0.081 0.087 0.277 0.093 0.573 0.093 0.047 0.112 0.439 0.356
128 129 130 131 132 133 134 135 136 137	96.473 96.612 96.735 96.870 97.099 97.276 97.366 97.707 97.977	I10 653 3-Methyl-5-ethylheptane O10 654 C10-Olefin ? Unidentified A9 655 1-Ethyl-3-methylbenzene A9 656 1-Ethyl-4-methylbenzene ? Unidentified N10 657 C10-Naphthene A9 658 1,3,5-Trimethylbenzene I10 659 2,3-Dimethyloctane ? Unidentified	0.080 0.104 0.040 0.696 0.419 0.019 0.016 0.684 0.062 0.084	0.081 0.105 0.040 0.601 0.363 0.018 0.015 0.591 0.063 0.086	0.063 0.083 0.032 0.650 0.391 0.015 0.013 0.639 0.049 0.067
138	98.215	 110 660 5-Methylnonane 110 661 4-Methylnonane 110 662 2-Methylnonane A9 663 1-Ethyl-2-methylbenzene N10 666 C10-Naphthene ? Unidentified 110 668 3-Methylnonane ? Unidentified O10 670 C10-Olefin I10 671 C10-Isoparaffin 	0.229	0.234	0.181
139	98.409		0.556	0.563	0.439
140	98.685		0.500	0.513	0.395
141	98.785		0.325	0.274	0.303
142	99.050		0.159	0.147	0.128
143	99.231		0.029	0.030	0.023
144	99.380		0.485	0.494	0.383
145	99.555		0.177	0.179	0.142
146	99.706		0.048	0.048	0.038
147	99.853		0.131	0.134	0.104
148	100.159	I10 672 C10-Isoparaffin A9 673 1,2,4-Trimethylbenzene ? Unidentified I10 674 C10-Isoparaffin I10 675 C10-Isoparaffin I10 676 Isobutylcyclohexane ? Unidentified N10 677 C10-Isoparaffin I10 678 C10-Isoparaffin	0.064	0.066	0.051
149	100.415		0.753	0.642	0.704
150	100.582		0.162	0.165	0.128
151	100.749		0.210	0.214	0.166
152	100.900		0.184	0.188	0.146
153	101.051		0.089	0.083	0.070
154	101.241		0.025	0.026	0.020
155	101.341		0.082	0.084	0.066
156	101.493		0.043	0.044	0.034

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Component List

Pk#	Time	Group Component I10 682 C10-Isoparaffin A10 690 Isobutylbenzene I10 694 C10-Isoparaffin P10 700 n-Decane I11 702 C11-Isoparaffin ? Unidentified ? Unidentified ? Unidentified I11 704 C11-Isoparaffin A9 705 1,2,3-Trimethylbenzene	%Wgt	%Vol	%Mol
157	101.616		0.017	0.018	0.014
158	101.815		0.064	0.056	0.054
159	102.017		0.093	0.094	0.073
160	102.329		1.911	1.955	1.508
161	102.601		0.031	0.032	0.023
162	102.675		0.020	0.020	0.014
163	102.813		0.035	0.036	0.025
164	102.871		0.028	0.028	0.020
165	103.061		0.047	0.047	0.033
166	103.258		0.309	0.258	0.289
167	103.453	? Unidentified A10 706 1-M-3-isopropylbenzene A10 708 1-M-4-isopropylbenzene I11 709 C11-Isoparaffin I11 710 C11-Isoparaffin? ? Unidentified A9 712 2,3-Dihydroindene ? Unidentified N10 714 sec-Butylcyclohexane ? Unidentified	0.032	0.028	0.027
168	103.529		0.029	0.026	0.025
169	103.686		0.059	0.052	0.050
170	103.869		0.110	0.111	0.079
171	104.087		0.030	0.030	0.021
172	104.278		0.035	0.027	0.033
173	104.424		0.167	0.130	0.159
174	104.540		0.030	0.023	0.028
175	104.724		0.300	0.274	0.240
176	104.989		0.019	0.016	0.016
177 178 179 180 181 182 183 184 185 186	105.092 105.217 105.328 105.482 105.799 105.988 106.242 106.430 106.601 106.708	 I11 720 3-Ethylnonane Punidentified I11 721 C11-Isoparaffin N10 722 C10-Naphthene I11 723 C11-Isoparaffin A10 724 1,3-Diethylbenzene A10 725 1-M-3-propylbenzene A10 726 1,4-Diethylbenzene A10 727 1-M-4-propylbenzene A10 728 Butylbenzene 	0.017 0.066 0.050 0.128 0.146 0.064 0.216 0.026 0.068 0.068	0.017 0.067 0.050 0.117 0.145 0.055 0.187 0.023 0.060 0.059	0.012 0.048 0.036 0.102 0.129 0.053 0.181 0.022 0.057
187 188 189 190 191 192 193 194	106.833 106.992 107.112 107.367 107.556 107.668 107.819 107.974 108.087	A10 729 3,5-DM-1-Ebenzene ? Unidentified A10 730 1,2-Diethylbenzene? I11 732 C11-Isoparaffin A10 736 C10-Aromatic A10 740 1-M-2-propyl benzene ? Unidentified I11 748 4-Methyldecane	0.075 0.038 0.038 0.042 0.042 0.092 0.071 0.010 0.071	0.065 0.032 0.032 0.042 0.036 0.079 0.060 0.009 0.066	0.063 0.032 0.032 0.030 0.035 0.077 0.059 0.007 0.051

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Component List

Pk#	<u>Time</u>	Group	Cor	nponent	%Wgt	<u>%Vol</u>	%Mol
196	108.388	111	754	C11-Isoparaffin	0.071	0.067	0.051
197	108.526	A10	756		0.064	0.054	0.053
198	108.688	A10	758		0.058	0.049	0.048
199	108.815	111	762	,	0.019	0.020	0.014
200	108.934	?		dentified	0.062	0.062	0.044
201	109.196	A10		1,2-DM-4-Ebenz+C1indan	0.075	0.064	0.063
202	109.387	111	766		0.015	0.014	0.011
203	109.656	?		dentified	0.023	0.019	0.019
204	109.744	A10	768	.,	0.017	0.014	0.014
205	109.877	?	Unic	lentified	0.009	0.008	0.008
206	400.007	?	l Inia	laudenad .	0.040	0.040	0.000
206 207	109.997 110.172	! 111		lentified	0.012 0.023	0.012 0.022	0.009
207	110.172	111	770	C11-Isoparaffin	0.023	0.022	0.017
209	110.507	A11	775 780	C11-Isoparaffin	0.011	0.009	0.008 0.008
	110.657	7		1-M-4-tert-butylbenzene lentified		0.009	
210 211	110.726	A10	785		0.016 0.030	0.014	0.012
212	111.187	P11	800	1,2-DM-3-ethylbenzene	0.030	0.025	0.025
213	111.167	A11	802	n-Undecane	0.156	0.157	0.112
213	111.307	112	804	1-E-4-isopropylbenzene		0.015	0.013
215	111.796	A10	806	C12-Isoparaffin	0.011	0.011	0.008
215	111.790	AIU	000	1,2,4,5-TetraMbenzene	0.014	0.012	0.012
216	112.057	A10	810	1,2,3,5-TetraMbenzene	0.020	0.017	0.017
217	112,400	A11	814	C11-Aromatic	0.009	0.007	0.007
218	112.631	A11	816	C11-Aromatic	0.013	0.011	0.010
219	113.371	A11	826	1-Ethyl-2-propylbenzene	0.015	0.013	0.011
220	113.913	A11	832	C11-Aromatic	0.008	0.007	0.006
221	114,123	A11	834	1-Methyl-3-butylbenzene	0.014	0.012	0.010
222	114.383	A11	836	1,2,3,4-TetraMbz+C11aro	0.013	0.011	0.011
223	114.891	A11	842	C11-Aromatic	0.013	0.011	0.010
224	129.405	A12	970	1,5-Dimethylnaphthalene	0.006	0.005	0.005
225	130.694	A12	976	1,2-Dimethylnaphthalene	0.011	0.008	0.008
				,			

Appendix D
Daily Chamber Concentrations

DAILY CHAMBER CONCENTRATIONS

EXPLANATORY NOTES

ABBREVIATIONS:

n - number of samplesppm - parts per millionS.D. - standard deviation

FOOTNOTES:

- a Value could not be calculated from number of observations.
- b Chamber was not run during this exposure.

NOTES:

Values are reported to 2 significant figures. Calculations were performed prior to rounding values.

Daily Chamber Concentrations (ppm)

		0 p	pm			10	0 ppm			50	0 ppm		3000 ppm			
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
											_				_	
1	0	a	0	1	100	6.6	96 - 120	6	490	20	460 - 510	6	2900	300	2300 - 3200	6
2	0	a	0	1	100	1.8	98 - 100	6	500	14	490 - 520	6	3000	24	3000	6
3	0	a	0	1	100	4.5	97 - 110	6	500	19	480 - 530	6	3100	320	2900 - 3800	6
4	0	a	0	1	98	7.5	84 - 110	6	500	17	480 - 520	6	3000	120	2800 - 3100	6
5	0	a	0	1	100	3.6	97 - 110	6	510	7.4	500 - 520	6	3000	130	2800 - 3100	6
6	0	a	0	1	99	6.2	90 - 110	6	510	21	480 - 530	6	3000	96	2900 - 3200	6
7	0	a	0	1	110	16	93 - 130	6	500	14	480 - 520	6	3000	130	2800 - 3100	6
8	0	a	0	1	98	14	78 - 110	6	490	11	480 - 510	6	3000	80	2900 - 3100	6
9	0	a	0	1	100	4.7	92 - 110	6	510	11	490 - 520	6	3000	56	3000 - 3100	6
10	0	a	0	1	100	3.6	99 - 110	6	490	24	450 - 520	6	3000	31	2900 - 3000	6
11	0	a	0	1	99	8.9	85 - 110	6	490	24	470 - 530	6	2900	120	2800 - 3100	6
12	0	a	0	1	100	5.4	93 - 110	6	500	28	460 - 540	6	2900	190	2600 - 3100	6
13	0	a	0	1	97	7.0	85 - 100	6	480	39	410 - 510	6	2800	170	2600 - 3000	6
14	0	a	0	1	99	3.7	95 - 110	6	500	12	490 - 510	6	3000	67	2900 - 3100	6
15	0	a	0	1	100	2.2	99 - 110	6	500	14	480 - 520	6	3100	100	2800 - 3100	6
16	0	a	0	1	95	5.2	86 - 100	6	520	25	470 - 540	6	3000	56	2900 - 3100	6
17	0	a	0	1	110	15	87 - 130	6	560	190	350 - 820	6	2900	150	2600 - 3100	6
18	0	a	0	1	100	2.2	100 - 110	6	500	100	290 - 550	6	3000	110	2900 - 3100	6
19	0	a	0	1	99	2.4	96 - 100	6	490	21	450 - 510	6	3000	160	2700 - 3100	6
20	0	a	0	1	93	11	76 - 110	6	500	19	470 - 530	6	3100	150	2900 - 3300	6
21	0	a	0	1	110	6.7	100 - 120	6	510	22	490 - 540	6	3000	45	3000 - 3100	6
22	0	a	0	1	98	8.5	91 - 110	6	490	13	480 - 520	6	3000	35	3000	6
23	0	a a	0	1	100	7.9	96 - 120	6	500	22	470 - 520	6	3000	96	2900 - 3100	6
24	0	a	0	1	93	10	77 - 100	6	500	7.3	490 - 510	6	3100	41	3000 - 3100	6
25	0	a	0	1	97	3.9	93 - 100	6	500	19	460 - 520	6	3100	62	3000 - 3100	6
26	0	a	0	1	98	0.47	98 - 99	4	500	10	490 - 510	3	3100	60	3000 - 3100	3
27	0	a	0	1	91	3.0	87 - 94	6	490	7.1	490 - 500	6	2900	68	2800 - 3000	6
28	0	a	0	1	94	5.8	85 - 100	6	500	24	460 - 520	6	3000	72	2900 - 3000	6
29	0	a	0	1	100	2.4	100 - 110	6	510	10	490 - 520	6	3100	66	3000 - 3100	6
30	0	a	0	1	100	7.2	90 - 110	6	500	12	480 - 510	6	3000	200	2600 - 3200	6
31	0	a	0	1	90	15	69 - 110	6	500	13	480 - 510	6	3000	180	2700 - 3200	6
32	0	a	0	1	98	6.3	90 - 110	6	490	18	470 - 510	6	3000	88	2900 - 3100	6
33	0	a	0	1	110	13	95 - 130	6	510	15	500 - 540	6	3000	77	2900 - 3200	6
34	0	a	0	1	110	5.4	100 - 110	6	490	54	420 - 550	6	2900	210	2500 - 3100	6
35	0	a	0	1	100	4.5	96 - 110	6	510	18	500 - 550	6	3100	110	3000 - 3300	6
36	0	a	0	1	95	3.5	89 - 100	6	490	14	470 - 510	6	3000	40	2900 - 3000	6
37	0	a	0	1	99	2.9	96 - 100	6 6	500	36	440 - 540	6	3000	70	2900 - 3100	6
38	0 b		0	1	100	2.2	97 - 100	ь	490 b	10	490 - 510	6	3000	63 78	2900 - 3100	6
39	b				b				b				3000		2900 - 3100	6
40	1								1				3100	200	2900 - 3500	6

Daily Chamber Concentrations (ppm)

	0 ppm			100 ppm				500 ppm				30	000 ppm		
Exposure	Mean	S.D.	Range n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
41	b			b				b				3100	190	2900 - 3400	6
42	b			b				b				2900	82	2800 - 3100	6
43	b			b				b				2900	92	2800 - 3100	6
44	b			b				b				3000	89	2900 - 3100	6
45	b			b				b				3000	180	2700 - 3100	6
46	b			b				b				3000	72	3000 - 3100	6
47	b			b				b				3000	110	2900 - 3200	6
48	b			b				b				3000	45	3000 - 3100	6

Appendix E
Daily Nominal Concentration Calculations

DAILY NOMINAL CONCENTRATION CALCULATIONS

EXPLANATORY NOTES

FOOTNOTES:

a Chamber was not run during this exposure.

Daily Nominal Concentration Calculations for 100 ppm Chamber

-	7	matal 17al af	Manda a 1	Non-i1	71
	Average	Total Volume of	Nominal	Nominal	Analytical
	Air Flow (L/min)	Test Substance	Concentration	Concentration	Concentration
Exposure	(L/MITI)	(mL)	(mg/L)	(ppm)	(ppm)
1	301	68	0.468	103	104
2	272	68	0.518	114	100
3	265	63	0.493	108	104
4	305	68	0.462	102	98
5	283	64	0.469	103	102
6	276	70	0.526	116	99
7					
8	280	49	0.363	80	111
	285	60	0.436	96	98
9	298	62	0.431	95	100
10	285	60	0.436	96	104
11	266	56	0.436	96	99
12	274	50	0.378	83	101
13	304	65	0.443	97	97
14	307	70	0.472	104	99
15	290	68	0.486	107	102
16	297	70	0.488	107	95
17	319	51	0.331	73	108
18	276	47	0.353	78	105
19	278	50	0.373	82	99
20	291	69	0.491	108	93
21	273	65	0.493	108	107
22	288	66	0.475	104	98
23	292	54	0.383	84	105
24	284	63	0.460	101	93
25	277	64	0.479	105	97
26	268	60	0.464	102	98
27	278	65	0.485	106	91
28	294	70	0.493	108	94
29	300	69	0.477	105	103
30	277	70	0.524	115	104
31	288	81	0.583	128	90
32	305	88	0.598	131	98
33	284	66	0.482	106	106
34	391	60	0.318	70	105
35	294	60	0.423	93	102
36	288	64	0.460	101	95
37	280	71	0.525	115	99
38	295	68	0.478	105	100
39	a				
40	a				
41	a				
42	a				
43	a				
44	a				
45	a				
46	a				
47	a				
48	a				

Daily Nominal Concentration Calculations for 500 ppm Chamber

	7	motal Waluma of	Nominal	Nominal	Analytical
	Average Air Flow	Total Volume of Test Substance	Concentration	Concentration	Concentration
Exposure	(L/min)	(mL)	(mg/L)	(ppm)	(ppm)
Exposure	(1/11111)	(11111)	(IIIg/L)	(ррш)	(ррш)
1	283	301	2.20	484	491
2	289	318	2.28	501	504
3	260	278	2.22	487	501
4	299	302	2.09	460	501
5	271	295	2.26	496	506
6	278	295	2.20	483	506
7	267	258	2.00	440	497
8	281	283	2.09	459	491
9	290	284	2.03	446	506
10	268	309	2.39	525	495
11	275	335	2.52	555	491
12	278	333	2.48	546	499
13	313	386	2.56	562	477
14		407		679	502
	273	407	3.09 2.83	623	495
15 16	299 272	437	3.33	732	518
17	332	437 374	2.33	513	558
18	306	381	2.58	567	498
19	310	403	2.69	592	489
20	276	408	3.06	673	502
21	294	381	2.69	590	507
22	283	371	2.72	597	492
23	288	386	2.78	610	501
24	272	376	2.86	630	496
25	291	382	2.72	598	497
26	288	392	2.82	620	502
27	289	413	2.96	651	491
28	281	424	3.13	687	499
29	277	406	3.04	667	509
30	287	412	2.97	654	504
31	275	408	3.07	676	495
32	293	422	2.98	656	491
33	301	420	2.89	635	510
34	371	472	2.64	579	491 514
35	296	411	2.88	632	
36	293	399	2.82	620	489
37	275	409	3.08	677	499
38	297 a	388	2.71	595	495
39	a				
40	a				
41	a				
42	a				
43	a				
44	a				
45	a				
46	a				
47	a				
48	-				

Daily Nominal Concentration Calculations for 3000 ppm Chamber

	Average	Total Volume of	Nominal	Nominal	Analytical
	Air Flow	Test Substance	Concentration	Concentration	Concentration
Exposure	(L/min)	(mL)	(mg/L)	(ppm)	(ppm)
1	261	1963	15.59	3425	2927
2	279	2315	17.19	3779	3016
3	264	1781	13.98	3072	3115
4	309	1895	12.71	2793	2977
5	275	1865	14.05	3089	2959
6	258	1764	14.17	3114	3014
7	258	1665	13.37	2939	2953
8	270	1778	13.65	2999	2985
9	278	1820	13.57	2981	3038
10	265	1811	14.16	3112	2971
11	261	1865	14.81	3254	2946
12	264	1823	14.31	3145	2941
13	280	2186	16.18	3555	2841
14	268	2340	18.09	3976	3044
15	293	2355	16.66	3660	3057
16	265	2413	18.87	4147	3012
17	289	2656	19.04	4185	2919
18	296	2437	17.06	3749	3002
19	293	2448	17.31	3805	2995
20	255	2127	17.28	3799	3063
21	258	2076	16.67	3664	3028
22	263	2056	16.20	3560	3009
23	258	2186	17.56	3859	2975
24	266	2165	16.87	3707	3076
25	276	2191	16.45	3615	3064
26	284	2140	15.61	3432	3080
27	289	2200	15.77	3467	2911
28	303	2329	15.93	3501	2975
29	294	2292	16.15	3550	3073
30	289	2328	16.69	3669	2968
31	284	2273	16.59	3645	3028
32	299	2275	15.77	3465	3015
33	318	2197	14.32	3146	3041
34	390	2651	14.09	3096	2890
35	297	2282	15.92	3499	3078
36	302	2238	15.36	3375	3000
37	289	2162	15.50	3407	2998
38	290	2118	15.13	3326	2977
39	300	2355	16.27	3575	3015
40	306	2133	14.44	3174	3065
41	280	1950	14.43	3172	3108
42	288	2001	14.40	3164	2920
43	286	1997	14.47	3180	2940
44	287	1998	14.43	3170	2972
45	275	1866	14.06	3090	2968
46	284	2054	14.99	3294	3033
47	274	1922	14.54	3195	3012
48	274	1880	14.22	3125	3008
10	2/1	1000	I 1 • 6 6	2123	5500

Appendix F
Daily Chamber Environmental Conditions

DAILY CHAMBER ENVIRONMENTAL CONDITIONS

EXPLANATORY NOTES

ABBREVIATIONS:

- S.D. standard deviation
 - n number of observations

FOOTNOTES:

- a Chamber was not run during this exposure.
- b Value could not be calculated from number of observations.

NOTES:

Values are reported to 2 significant figures. Calculations were performed prior to rounding values.

Daily Chamber Environmental Conditions - Temperature (°C)

		0	ppm			100	ppm			500	ppm			3000	ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
<u>, </u>																
1	22	0.58	21 - 22	3	22	0.58	21 - 22	3	22	0.58	21 - 22	3	23	1.0	22 - 24	3
2	22	1.0	21 - 23	3	22	1.0	21 - 23	3	22	1.0	21 - 23	3	23	0.58	22 - 23	3
3	22	0.58	22 - 23	3	22	0	22	3	22	0.58	22 - 23	3	23	0.58	22 - 23	3
4	23	0.58	22 - 23	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	23	1.0	22 - 24	3
5	23	0.58	22 - 23	3	23	0.58	22 - 23	3	22	0.58	22 - 23	3	23	1.0	22 - 24	3
6	22	0.58	22 - 23	3	22	0.58	22 - 23	3	22	0	22	3	23	1.0	22 - 24	3
7	22	0.58	22 - 23	3	22	0.58	22 - 23	3	22	1.0	21 - 23	3	23	0.58	22 - 23	3
8	23	1.0	22 - 24	3	22	0	22	3	22	0.58	22 - 23	3	23	0.58	22 - 23	3
9	23	0.58	22 - 23	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	23	0	23	3
10	23	1.0	22 - 24	3	23	0.58	22 - 23	3	23	0.58	22 - 23	3	24	0.58	23 - 24	3
11	23	0.58	22 - 23	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	23	0.58	22 - 23	3
12	22	0	22	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3
13	23	0	23	3	23	0	23	3	23	0	23	3	23	0	23	3
14	23	0.58	22 - 23	3	22	0	22	3	22	0	22	3	23	1.0	22 - 24	3
15	23	0.58	23 - 24	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	23	0.58	23 - 24	3
16	23	0.58	22 - 23	3	22	0	22	3	22	0	22	3	23	1.0	22 - 24	3
17	24	0.58	23 - 24	3	23	0.58	22 - 23	3	23	0.58	22 - 23	3	23	0.58	23 - 24	3
18	24	0	24	3	23	0.58	23 - 24	3	23	0.58	23 - 24	3	24	0.58	23 - 24	3
19	24	0.58	23 - 24	3	23	0.58	22 - 23	3	23	0.58	23 - 24	3	24	0.58	24 - 25	3
20	24	1.0	23 - 25	3	23	0.58	22 - 23	3	23	1.0	22 - 24	3	24	1.0	23 - 25	3
21	24	0.58	24 - 25	3	24	0	24	3	24	0	24	3	24	0.58	24 - 25	3
22	24	0.58	24 - 25	3	24	0.58	23 - 24	3	24	0.58	23 - 24	3	25	0.58	24 - 25	3
23	24	0.58	23 - 24	3	23	0.58	22 - 23	3	23	1.0	22 - 24	3	24	1.0	23 - 25	3
24	24	1.0	23 - 25	3	23	1.0	22 - 24	3	23	0.58	23 - 24	3	24	1.2	23 - 25	3
25	24	0.58	23 - 24	3	23	0.58	22 - 23	3	23	0.58	22 - 23	3	24	0.58	23 - 24	3
26	23	0.58	23 - 24	3	23	0.58	23 - 24	3	23	0.58	23 - 24	3	23	0.58	23 - 24	3
27	23	0.58	22 - 23	3	23	0.58	22 - 23	3	23	0.58	22 - 23	3	23	0.58	22 - 23	3
28	23	0	23	3	22	0	22	3	22	0	22	3	23	0	23	3
29	23	0	23	3	22	0.58	22 - 23	3	22	0.58	22 - 23	3	23	0.58	23 - 24	3
30	23	0.58	22 - 23	3	22	0.58	21 - 22	3	22	0.58	21 - 22	3	23	0.58	22 - 23	3
31	22	0.58	22 - 23	3	21	0.58	21 - 22	3	21	0.58	21 - 22	3	22	1.0	21 - 23	3
32	22	0.58	22 - 23	3	21	0.58	21 - 22	3	21	1.0	20 - 22	3	22	1.0	21 - 23	3
33	21	0.58	21 - 22	3	21	0.58	20 - 21	3	20	0.58	20 - 21	3	21	0.58	21 - 22	3
34	20	0.58	20 - 21	3	19	0.58	19 - 20	3	19	0.58	19 - 20	3	20	1.0	19 - 21	3
35	21	0.58	21 - 22	3	20	0.58	20 - 21	3	20	0.58	20 - 21	3	21	1.0	20 - 22	3
36	21	0.58	21 - 22	3	21	0.58	20 - 21	3	20	0.58	20 - 21	3	21	1.0	20 - 22	3
37	21	0.58	21 - 22	3	21	0.58	20 - 21	3	20	0.58	20 - 21	3	21	1.0	20 - 22	3
38	21 a	0.58	20 - 21	3	20 a	0.58	19 - 20	3	20 a	0.58	19 - 20	3	20	0.58	20 - 21	3
39	a				a				a				20	1.0	19 - 21	3
40													20	1.2	19 - 21	3

Daily Chamber Environmental Conditions - Temperature (°C)

		0 p	pm			100	ppm			500	ppm			3000	ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
41	a				a				a				21	1.5	19 - 22	3
42	a				a				a				21	1.0	20 - 22	3
43	a				a				a				21	1.2	20 - 22	3
44	a				a				a				20	1.5	19 - 22	3
45	a				a				a				21	1.2	20 - 22	3
46	a				a				a				21	1.0	20 - 22	3
47	a				a				a				21	0.58	20 - 21	3
48	a				a				a				20	0.58	20 - 21	3

Daily Chamber Environmental Conditions - Relative Humidity (%)

		0	ppm			100	ppm			500	ppm			3000) ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	41	5.0	36 - 46	3	46	1.5	45 - 48	3	46	2.5	43 - 48	3	46	4.6	42 - 51	3
2	46	0.58	46 - 47	3	48	2.3	47 - 51	3	48	2.1	46 - 50	3	47	3.5	45 - 51	3
3	49	3.1	46 - 52	3	55	1.0	54 - 56	3	54	1.0	53 - 55	3	54	2.6	52 - 57	3
4	49	1.0	48 - 50	3	54	3.5	50 - 57	3	53	4.0	49 - 57	3	52	4.0	48 - 56	3
5	50	2.0	48 - 52	3	56	1.5	54 - 57	3	56	1.5	54 - 57	3	55	4.4	52 - 60	3
6	50	1.5	49 - 52	3	56	1.0	55 - 57	3	56	2.1	54 - 58	3	55	3.8	52 - 59	3
7	49	0	49	3	58	1.2	57 - 59	3	58	1.0	57 - 59	3	57	1.2	56 - 58	3
8	46	3.6	43 - 50	3	53	3.2	51 - 57	3	53	3.2	51 - 57	3	53	4.4	50 - 58	3
9	46	2.6	44 - 49	3	55	2.1	53 - 57	3	53	1.5	52 - 55	3	53	4.2	50 - 58	3
10	54	2.1	52 - 56	3	55	2.0	53 - 57	3	54	3.1	51 - 57	3	55	6.2	50 - 62	3
11	52	2.1	50 - 54	3	54	1.5	53 - 56	3	54	1.2	53 - 55	3	56	5.0	51 - 61	3
12	53	2.1	51 - 55	3	53	2.9	50 - 55	3	54	2.6	51 - 56	3	53	2.6	50 - 55	3
13	50	1.0	49 - 51	3	50	0.58	50 - 51	3	50	1.0	49 - 51	3	50	1.0	49 - 51	3
14	45	0.58	45 - 46	3	46	0.58	46 - 47	3	46	0.58	46 - 47	3	47	2.1	45 - 49	3
15	43	0.58	42 - 43	3	45	0.58	44 - 45	3	43	0.58	42 - 43	3	43	1.5	42 - 45	3
16	47	2.1	45 - 49	3	47	1.5	46 - 49	3	46	1.0	45 - 47	3	47	3.6	44 - 51	3
17	53	1.0	52 - 54	3	54	1.5	53 - 56	3	53	1.5	52 - 55	3	53	3.2	51 - 57	3
18	56	2.5	54 - 59	3	58	1.0	57 - 59	3	57	2.0	55 - 59	3	57	3.0	54 - 60	3
19	53	1.0	52 - 54	3	54	1.5	53 - 56	3	54	1.5	52 - 55	3	54	2.1	52 - 56	3
20	54	1.5	52 - 55	3	56	2.3	53 - 57	3	54	2.3	51 - 55	3	57	6.0	51 - 63	3
21	54	2.5	51 - 56	3	54	2.5	52 - 57	3	54	3.0	51 - 57	3	54	2.0	52 - 56	3
22	52	1.5	51 - 54	3	52	1.5	51 - 54	3	52	2.6	50 - 55	3	53	4.9	50 - 59	3
23	51	1.2	50 - 52	3	51	1.0	50 - 52	3	51	1.0	50 - 52	3	53	4.2	50 - 58	3
24	51	1.2	50 - 52	3	52	1.2	51 - 53	3	51	1.5	49 - 52	3	54	3.6	51 - 58	3
25	53	2.1	51 - 55	3	53	2.5	51 - 56	3	53	2.0	51 - 55	3	56	5.3	52 - 62	3
26	52	1.5	51 - 54	3	53	2.0	51 - 55	3	53	1.7	52 - 55	3	54	2.0	52 - 56	3
27	52	2.5	50 - 55	3	53	2.5	51 - 56	3	53	2.6	51 - 56	3	55	4.0	51 - 59	3
28	53	0.58	52 - 53	3	53	0	53	3	52	0	52	3	54	2.6	52 - 57	3
29	52	1.7	51 - 54	3	54	2.9	52 - 57	3	53	2.6	51 - 56	3	54	4.7	50 - 59	3
30	55	1.0	54 - 56	3	57	0.58	56 - 57	3	57	1.0	56 - 58	3	58	3.2	56 - 62	3
31	57	0.58	56 - 57	3	58	0.58	57 - 58	3	59	0	59	3	59	2.9	57 - 62	3
32	55	4.4	52 - 60	3	55	3.5	52 - 59	3	54	4.2	51 - 59	3	56	4.7	52 - 61	3
33	52	1.0	51 - 53	3	53	1.5	52 - 55	3	52	1.2	51 - 53	3	53	2.6	51 - 56	3
34	50	0	50	3	50	0.58	50 - 51	3	50	1.0	49 - 51	3	51	2.1	49 - 53	3
35	53	0.58	53 - 54	3	55	0.58	55 - 56	3	54	0.58	54 - 55	3	56	2.1	54 - 58	3
36	54	2.1	52 - 56	3	56	2.3	53 - 57	3	55	2.6	52 - 57	3	56	3.6	52 - 59	3
37	53	1.5	52 - 55	3	56	1.5	54 - 57	3	55	1.5	54 - 57	3	55	2.0	53 - 57	3
38	54	2.5	52 - 57	3	56	2.0	54 - 58	3	56	3.1	53 - 59	3	55	3.1	52 - 58	3
39	a				a				a				54	2.5	52 - 57	3
40	a				a				a				55	1.5	53 - 56	3

Daily Chamber Environmental Conditions - Relative Humidity (%)

		0 p	pm			100	ppm			500	ppm			3000	ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
41	a				a				a				55	2.1	53 - 57	3
42	a				a				a				54	2.5	52 - 57	3
43	a				a				a				56	2.3	53 - 57	3
44	a				a				a				54	2.5	52 - 57	3
45	a				a				a				56	1.5	55 - 58	3
46	a				a				a				54	2.0	52 - 56	3
47	a				a				a				56	1.5	54 - 57	3
48	a				a				a				57	0.58	56 - 57	3

Daily Chamber Environmental Conditions - Airflow (L/min)

-		0	ppm			10	0 ppm			50	0 ppm			300	00 ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	300	6.1	300 - 310	3	300	14	290 - 320	3	280	28	260 - 310	3	260	20	250 - 280	3
2	290	34	260 - 320	3	270	26	250 - 300	3	290	19	270 - 310	3	280	15	260 - 290	3
3	290	7.4	280 - 300	3	270	6	260 - 270	3	260	13	250 - 280	3	260	19	240 - 280	3
4	330	38	310 - 380	3	310	49	270 - 360	3	300	36	270 - 340	3	310	93	250 - 420	3
5	280	19	260 - 300	3	280	20	260 - 300	3	270	23	250 - 300	3	270	19	250 - 290	3
6	280	7.6	270 - 290	3	280	12	260 - 290	3	280	4	270 - 280	3	260	15	250 - 280	3
7	280	19	260 - 290	3	280	7	270 - 290	3	270	6	260 - 270	3	260	17	250 - 280	3
8	300	26	270 - 320	3	280	31	250 - 310	3	280	19	260 - 290	3	270	20	260 - 290	3
9	300	9.2	300 - 310	3	300	4	300	3	290	11	280 - 300	3	280	30	250 - 310	3
10	290	6.1	280 - 290	3	290	1.2	280 - 290	3	270	12	250 - 280	3	260	8.1	260 - 270	3
11	280	22	260 - 310	3	270	17	260 - 290	3	280	33	250 - 310	3	260	19	240 - 280	3
12	300	17	290 - 320	3	270	30	250 - 310	3	280	30	240 - 300	3	260	32	240 - 300	3
13	310	20	290 - 330	3	300	6.5	300 - 310	3	310	16	300 - 330	3	280	37	240 - 310	3
14	300	10	280 - 300	3	310	23	280 - 330	3	270	18	260 - 290	3	270	5.0	260 - 270	3
15	310	8.5	300 - 320	3	290	17	270 - 310	3	300	2.6	300	3	290	10	280 - 300	3
16	300	7.8	290 - 300	3	300	13	280 - 310	3	270	16	250 - 290	3	260	18	250 - 290	3
17	310	14	290 - 320	3	320	20	300 - 340	3	330	12	320 - 340	3	290	14	280 - 310	3
18	290	8.7	280 - 290	3	280	3.8	270 - 280	3	310	4.7	300 - 310	3	300	12	290 - 310	3
19	300	9.5	290 - 310	3	280	13	270 - 290	3	310	10	300 - 320	3	290	21	270 - 310	3
20	310	14	300 - 320	3	290	7.5	280 - 300	3	280	19	260 - 290	3	250	7.8	250 - 260	3
21	310	15	300 - 330	3	270	16	260 - 280	3	290	9.0	290 - 300	3	260	4.4	260	3
22	310	2.5	300 - 310	3	290	12	270 - 300	3	280	12	270 - 300	3	260	10	260 - 270	3
23	300	17	280 - 310	3	290	10	280 - 300	3	290	6.0	280 - 290	3	260	2.5	260	3
24	290	10	280 - 300	3	280	5.3	280 - 290	3	270	16	260 - 290	3	270	7.6	260 - 280	3
25	320	11	300 - 320	3	280	13	270 - 290	3	290	4.5	290 - 300	3	280	20	250 - 290	3
26	310	5.0	300 - 310	3	270	10	260 - 280	3	290	16	270 - 300	3	280	5.2	280 - 290	3
27	260	19	250 - 290	3	280	4.9	280	3	290	11	280 - 300	3	290	6.2	280 - 300	3
28	300	5.3	300 - 310	3	290	16	280 - 310	3	280	8.1	270 - 290	3	300	1.2	300	3
29	310	3.1	310 - 320	3	300	7.0	290 - 310	3	280	16	260 - 290	3	290	9.5	290 - 310	3
30	290	11	280 - 300	3	280	6.8	270 - 290	3	290	14	270 - 300	3	290	17	270 - 300	3
31	290	7.5	280 - 300	3	290	15	270 - 300	3	270	11	260 - 280	3	280	8.5	270 - 290	3
32	300	12	290 - 310	3	300	9.1	300 - 320	3	290	9.1	290 - 300	3	300	17	280 - 310	3
33	310	11	300 - 320	3	280	14	270 - 300	3	300	16	290 - 320	3	320	9.3	310 - 330	3
34	400	11	390 - 410	3	390	4.4	390 - 400	3	370	14	360 - 380	3	390	11	380 - 400	3
35	300	3.0	300	3	290	17	270 - 310	3	300	18	280 - 310	3	300	15	280 - 310	3
36	310	18	290 - 330	3	290	7.0	280 - 300	3	290	5.5	290 - 300	3	300	13	290 - 320	3
37	280	5.7	280 - 290	3	280	5.3	270 - 280	3	280	7.0	270 - 280	3	290	10	280 - 300	3
38	300 a	16	280 - 310	3	300	10	290 - 310	3	300 a	22	280 - 320	3	290	3.5	290	3
39	a				a				a				300	15	280 - 310	3
40	I -				-								310	10	300 - 320	3

Daily Chamber Environmental Conditions - Airflow (L/min)

		0	ppm			100 ppm			500	ppm			300	00 ppm	
Exposure	Mean	S.D.	Range	n	Mean S.1). Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
41	a				a			a				280	12	270 - 290	3
42	a				a			a				290	18	270 - 300	3
43	a				a			a				290	5.6	280 - 290	3
44	a				a			a				290	4.7	280 - 290	3
45	a				a			a				280	3.5	270 - 280	3
46	a				a			a				280	5.0	280 - 290	3
47	a				a			a				270	4.0	270 - 280	3
48	a				a			a				270	2.5	270 - 280	3

Daily Chamber Environmental Conditions - Oxygen (%)

		0 p	pm			100	ppm			500 p	pm			3000	ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
1	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
2	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
3	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
4	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
5	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
6	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
7	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
8	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
9	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
10	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
11	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
12	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
13	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
14	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
15	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
16	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
17	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
18	20	b	20	1	20	b ,	20	1	20	b	20	1	20	b	20	1
19	20	b	20	1	20	b ,	20	1	20	b	20	1	20	b	20	1
20	20	b	20	1	20	b b	20	1	20	b	20	1	20	b	20	1
21	20	b	20	1	20	ь	20	1	20	b	20	1	20	b	20	1
22	20	b	20	1	20		20	1	20	b	20	1	20	b	20	1
23	20	b b	20	1	20	b b	20	1	20	b	20	1	20	b b	20	1
24	20	b	20	1	20	ь	20	1	20	b b	20	1	20	b	20	1
25	20	b	20	1	20	ь	20	1	20	ь	20	1	20	b	20	1
26	20	b	20	1	20	ь	20	1	20	ь	20	1	20	b	20	1
27	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	20	1
28	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	20	1
29	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
30	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	20	1
31	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	2.0	1
32	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
33	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
34	20	b	20	1	20	b	20	1	20	b	20	1	20	b	2.0	1
35	20	b	20	1	20	b	20	1	20	b	20	1	20	b	20	1
36	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	20	1
37	20	b	20	1	20	b	20	1	20	ь	20	1	20	b	20	1
38	20 a	D	20	1	20 a	2	20	1	20	D	20	1	20	b	20	1
39	a				a								20	b	20	1
40	-								I				20	~	20	1

Daily Chamber Environmental Conditions - Oxygen (%)

		0 p	pm			100	ppm			500 r	pm			3000	ppm	
Exposure	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n	Mean	S.D.	Range	n
41 42 43 44 45 46 47 48	a a a a a				a a a a a a				a a a a a a		_		20 20 20 20 20 20 20 20 20	b b b b b b b	20 20 20 20 20 20 20 20 20 20	1 1 1 1 1 1 1

Appendix G Twelve-Component Analysis

TWELVE-COMPONENT ANALYSIS

EXPLANATORY NOTES

FOOTNOTES:

- a Supplied by sponsor.
- b Calculated concentration (ppm) of the components listed based on the actual chamber concentration of total components at the time of sample collection and on the sponsor-supplied volume percent.
- c Actual measured concentration (ppm) of the component listed.

Twelve Component Analysis - 100 ppm Chamber

					Theoreti	cal Conce	entratio	on (ppm) b	
		Volume	Date of Analysis (2006):	May 11	May 18	May 26	May 30	June 9	June 15
Peak	Peak ID	(응) ^a	Concentration:	101 ppm	105 ppm	107 ppm	95 ppm	109 ppm	99 ppm
1	2-MethylC6+C7-Olefin	4.50		4.55	4.73	4.82	4.28	4.91	4.46
2	3-Methylhexane	3.52		3.55	3.69	3.76	3.34	3.83	3.48
3	t-1,3-DimethylcyC5	1.45		1.46	1.52	1.55	1.38	1.58	1.44
4	t-1,2-DimethylcycloC5	1.61		1.63	1.69	1.73	1.53	1.76	1.60
5	n-Heptane	7.23		7.30	7.59	7.74	6.87	7.88	7.16
6	Methylcyclohexane	6.76		6.83	7.10	7.24	6.42	7.37	6.69
7	Toluene	3.44		3.48	3.62	3.68	3.27	3.75	3.41
8	2-Methylheptane	3.25		3.29	3.42	3.48	3.09	3.55	3.22
9	n-Octane	5.81		5.86	6.10	6.21	5.51	6.33	5.75
10	Ethylcyclohexane	1.95		1.97	2.05	2.09	1.85	2.13	1.93
11	m-Xylene	1.71		1.72	1.79	1.83	1.62	1.86	1.69
12	n-Nonane	4.47		4.52	4.70	4.79	4.25	4.88	4.43
		Volume							
Peak	Peak ID	(%) ^a				Results	(ppm)		
1	2-MethylC6+C7-Olefin	4.50		5.10	4.19	5.35	4.05	5.07	4.38
2	3-Methylhexane	3.52		3.75	3.31	4.04	3.08	3.95	3.42
3	t-1,3-DimethylcyC5	1.45		1.65	1.44	1.71	1.06	1.73	1.41
4	t-1,2-DimethylcycloC5	1.61		1.75	1.58	1.88	1.46	1.86	1.66
5	n-Heptane	7.23		7.54	6.71	8.00	5.95	8.26	7.38
6	Methylcyclohexane	6.76		6.96	6.29	7.48	5.50	7.84	6.96
7	Toluene	3.44		3.58	3.19	3.76	2.76	3.92	3.54
8	2-Methylheptane	3.25		3.22	3.05	3.52	2.64	3.72	3.36
9	n-Octane	5.81		5.60	5.28	6.33	4.77	6.53	5.94
10	Ethylcyclohexane	1.95		1.91	1.78	2.06	1.72	2.33	2.01
11	m-Xylene	1.71		1.73	1.64	1.92	1.37	2.05	1.89
12	n-Nonane	4.47		4.26	4.01	4.85	3.63	5.46	4.67

Twelve Component Analysis - 500 ppm Chamber

-					Theoretica	al Concen	tration	(ppm) ^b	
Peak	Peak ID	Volume	Date of Analysis (2006): Concentration:	May 12 475 ppm	May 17 494 ppm	May 27	May 31 466 ppm	June 7	June 13 493 ppm
<u>r can</u>	I Can ID	(- /	concentration.	1,0 ppm	131 pp	101 pp			_
1	2-MethylC6+C7-Olefin	4.50		21.4	22.2	21.8	21.0	22.9	22.2
2	3-Methylhexane	3.52		16.7	17.4	17.0	16.4	17.9	17.3
3	t-1,3-DimethylcyC5	1.45		6.89	7.2	7.0	6.8	7.4	7.1
4	t-1,2-DimethylcycloC5	1.61		7.66	8.0	7.8	7.5	8.2	8.0
5	n-Heptane	7.23		34.3	35.7	35.0	33.7	36.7	35.6
6	Methylcyclohexane	6.76		32.1	33.4	32.7	31.5	34.4	33.3
7	Toluene	3.44		16.4	17.0	16.7	16.0	17.5	17.0
8	2-Methylheptane	3.25		15.5	16.1	15.7	15.2	16.5	16.0
9	n-Octane	5.81		27.6	28.7	28.1	27.1	29.5	28.6
10	Ethylcyclohexane	1.95		9.27	9.6	9.4	9.1	9.9	9.6
11	m-Xylene	1.71		8.10	8.4	8.3	7.9	8.7	8.4
12	n-Nonane	4.47		21.3	22.1	21.7	20.8	22.7	22.1
Peak	Peak ID	Volume				Results (ppm) ^C		
1	2-MethylC6+C7-Olefin	4.50		21.62	21.96	22.36	23.06	22.07	22.34
2	3-Methylhexane	3.52		16.65	17.03	17.20	17.76	17.21	17.27
3	t-1,3-DimethylcyC5	1.45		6.78	6.99	7.31	7.15	7.05	7.06
4	t-1,2-DimethylcycloC5	1.61		7.66	7.72	8.13	8.43	7.68	7.88
5	n-Heptane	7.23		33.71	33.51	35.10	35.43	33.75	34.79
6 7	Methylcyclohexane Toluene	6.76		31.19	31.26	32.90	32.94	31.36	32.18
8		3.44		15.78	15.62	16.53	16.24 14.79	15.47	15.98
8 9	2-Methylheptane n-Octane	3.25 5.81		14.37 25.12	14.15 24.57	15.44 27.23	25.67	14.34 24.94	15.40 27.11
10	Ethylcyclohexane	1.95		8.54	8.30	9.15	8.70	8.34	8.93
11	m-Xylene	1.71		7.33	7.21	8.04	7.36	7.10	0.93 7.56
12	n-Nonane	4.47		18.81	18.22	20.95	18.32	18.04	20.43
14	ii Molialie	7.7/		10.01	10.22	20.93	10.52	10.04	20.43

Twelve Component Analysis - 3000 ppm Chamber

					Th	eoretical	Concentra	ation (ppm	ı) ^b	
		Volume	Date of Analysis (2006):	May 12	May 17	May 24	June 1	June 8	June 16	June 21
		(%) a							2902 ppm	
Peak	Peak ID	(8)	Concentration:	3052 ppm	3062 ppm	2905 ppm	JUTE PPIN		2302 ppm	
	2-MethylC6+C7-									
1	Olefin	4.50		137.3	137.8	130.7	138.2	134.5	130.6	134.5
2	3-Methylhexane	3.52		107.3	107.7	102.2	108.0	105.1	102.1	105.1
3	t-1,3-DimethylcyC5 t-1,2-	1.45		44.3	44.4	42.1	44.5	43.3	42.1	43.3
4	DimethylcycloC5	1.61		49.2	49.4	46.9	49.5	48.2	46.8	48.2
5	n-Heptane	7.23		220.7	221.4	210.0	222.0	216.1	209.8	216.1
6	Methylcyclohexane	6.76		206.4	207.1	196.4	207.7	202.1	196.2	202.1
7	Toluene	3.44		105.1	105.4	100.0	105.7	102.9	99.9	102.9
8	2-Methylheptane	3.25		99.3	99.6	94.5	99.9	97.2	94.4	97.2
9	n-Octane	5.81		177.2	177.7	168.6	178.3	173.5	168.5	173.5
10	Ethylcyclohexane	1.95		59.6	59.8	56.7	59.9	58.3	56.6	58.3
11	m-Xylene	1.71		52.1	52.2	49.6	52.4	51.0	49.5	51.0
12	n-Nonane	4.47		136.5	137.0	130.0	137.4	133.7	129.8	133.7
		Volume								
Peak	Peak ID	Volume (%) a				Re	sults (ppm	n) ^C		
Peak	Peak ID 2-MethylC6+C7-					Re	sults (ppm	n) ^C		
Peak 1				110.6	111.1	141.1	sults (ppm	n) ^C	132.9	131.0
	2-MethylC6+C7- Olefin 3-Methylhexane	(%) a		86.6	87.5	141.1 109.5	140.6 111.1	130.8 102.4	102.3	102.1
1	2-MethylC6+C7- Olefin	(%) ^a				141.1	140.6	130.8		
1 2	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5	(%) ^a 4.50 3.52		86.6	87.5	141.1 109.5	140.6 111.1	130.8 102.4	102.3	102.1
1 2 3 4 5	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane	(%) a 4.50 3.52 1.45 1.61 7.23		86.6 35.8 39.8 178.1	87.5 36.0 40.1 178.0	141.1 109.5 45.4 50.0 219.5	140.6 111.1 45.7 50.4 224.1	130.8 102.4 42.4 46.5 206.8	102.3 42.5 47.4 210.6	102.1 41.9 46.9 205.6
1 2 3 4 5 6	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane	(%) a 4.50 3.52 1.45 1.61 7.23 6.76		86.6 35.8 39.8 178.1 166.2	87.5 36.0 40.1 178.0 166.0	141.1 109.5 45.4 50.0 219.5 205.9	140.6 111.1 45.7 50.4 224.1 208.9	130.8 102.4 42.4 46.5 206.8 193.6	102.3 42.5 47.4 210.6 197.3	102.1 41.9 46.9 205.6 192.7
1 2 3 4 5 6 7	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane Toluene	(%) a 4.50 3.52 1.45 1.61 7.23 6.76 3.44		86.6 35.8 39.8 178.1 166.2 85.2	87.5 36.0 40.1 178.0 166.0 83.6	141.1 109.5 45.4 50.0 219.5 205.9 103.3	140.6 111.1 45.7 50.4 224.1 208.9 104.6	130.8 102.4 42.4 46.5 206.8 193.6 96.6	102.3 42.5 47.4 210.6 197.3 101.0	102.1 41.9 46.9 205.6 192.7 96.7
1 2 3 4 5 6 7 8	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane Toluene 2-Methylheptane	(%) a 4.50 3.52 1.45 1.61 7.23 6.76 3.44 3.25		86.6 35.8 39.8 178.1 166.2 85.2 78.9	87.5 36.0 40.1 178.0 166.0 83.6 78.6	141.1 109.5 45.4 50.0 219.5 205.9 103.3 95.2	140.6 111.1 45.7 50.4 224.1 208.9 104.6 99.0	130.8 102.4 42.4 46.5 206.8 193.6 96.6 90.9	102.3 42.5 47.4 210.6 197.3 101.0 94.2	102.1 41.9 46.9 205.6 192.7 96.7 89.8
1 2 3 4 5 6 7 8 9	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane Toluene 2-Methylheptane n-Octane	(%) a 4.50 3.52 1.45 1.61 7.23 6.76 3.44 3.25 5.81		86.6 35.8 39.8 178.1 166.2 85.2 78.9 141.0	87.5 36.0 40.1 178.0 166.0 83.6 78.6 138.4	141.1 109.5 45.4 50.0 219.5 205.9 103.3 95.2 168.6	140.6 111.1 45.7 50.4 224.1 208.9 104.6 99.0 174.0	130.8 102.4 42.4 46.5 206.8 193.6 96.6 90.9 159.8	102.3 42.5 47.4 210.6 197.3 101.0 94.2 168.7	102.1 41.9 46.9 205.6 192.7 96.7 89.8 159.0
1 2 3 4 5 6 7 8 9	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane Toluene 2-Methylheptane n-Octane Ethylcyclohexane	(%) a 4.50 3.52 1.45 1.61 7.23 6.76 3.44 3.25 5.81 1.95		86.6 35.8 39.8 178.1 166.2 85.2 78.9 141.0 47.6	87.5 36.0 40.1 178.0 166.0 83.6 78.6 138.4 46.6	141.1 109.5 45.4 50.0 219.5 205.9 103.3 95.2 168.6 56.4	140.6 111.1 45.7 50.4 224.1 208.9 104.6 99.0 174.0 57.7	130.8 102.4 42.4 46.5 206.8 193.6 96.6 90.9 159.8 53.5	102.3 42.5 47.4 210.6 197.3 101.0 94.2 168.7 57.4	102.1 41.9 46.9 205.6 192.7 96.7 89.8 159.0 53.1
1 2 3 4 5 6 7 8 9	2-MethylC6+C7- Olefin 3-Methylhexane t-1,3-DimethylcyC5 t-1,2- DimethylcycloC5 n-Heptane Methylcyclohexane Toluene 2-Methylheptane n-Octane	(%) a 4.50 3.52 1.45 1.61 7.23 6.76 3.44 3.25 5.81		86.6 35.8 39.8 178.1 166.2 85.2 78.9 141.0	87.5 36.0 40.1 178.0 166.0 83.6 78.6 138.4	141.1 109.5 45.4 50.0 219.5 205.9 103.3 95.2 168.6	140.6 111.1 45.7 50.4 224.1 208.9 104.6 99.0 174.0	130.8 102.4 42.4 46.5 206.8 193.6 96.6 90.9 159.8	102.3 42.5 47.4 210.6 197.3 101.0 94.2 168.7	102.1 41.9 46.9 205.6 192.7 96.7 89.8 159.0

With the Reproduction/Developmental Toxicity Screening Test in Rats	DuPont-18331
Annondiv H	
Appendix H Individual Clinical Observations and Mortality Data in Subchronic N	Male Rats

Test Day

-	Animal	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 РМ	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
5011	110111001	011111001 01911	5100																
1m	101	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
	102	No Abnormalities Detected		Χ	Χ	Х	Χ	Χ	X	X	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х
		Scheduled sacrifice																	
	103	No Abnormalities Detected		Χ	Χ	X	X	Χ	X	X	X	X	X	X	X	X	X	X	X
		Hair loss	Forelimb bilateral	•					•	•		•			•	•			
		Scheduled sacrifice																	
	104	No Abnormalities Detected		Х	X	Χ	X	Χ	X	X	Х	Х	Х	Х	Χ	X	X	Х	X
		Scheduled sacrifice																	•
	105	No Abnormalities Detected		X	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•		•	•	•	•	•
		Wound - superficial	Forelimb left	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•
	106	No Abnormalities Detected		X	X	X	X	Х	X	X	Х	Х	Х	Х	Х	X	X	Х	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	107	No Abnormalities Detected		Χ	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	X
		Scheduled sacrifice		•	•	٠	•	•	•	•	•	•	•	•	•	•	•	•	•
	108	No Abnormalities Detected		Χ	X	Х	Х	Χ	X	X	Х	Х	Х	Х	Χ	X	X	Х	X
	400	Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	109	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Χ	Х	Χ	Х	Х	Χ	Х	Х	Х	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	110	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Χ	Χ	Χ	Χ	Х	Х	Х	Х	Х	Х
	111	Scheduled sacrifice		•		•	•	•	•	•	•	•	•	•	•			•	•
	111	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
	110	Scheduled sacrifice No Abnormalities Detected		•	•	X	•	•	•	•	•	•	•	•	•	•	•	•	•
	112	Scheduled sacrifice		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		scheduled Sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

X = Present

Test Day

-	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sex	Number	Clinical Sign	Site	PM	AM													
1m	101	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice			•													X
	102	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	X	X	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•		•	•	•	X
	103	No Abnormalities Detected		X	Х	Х	Х	Х	•	•	•	•	Х	Х	Х	X	•	
		Hair loss	Forelimb bilateral	•	•	•	•	•	Х	Х	Х	Χ	•	•	•	X	X	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•		•	•	•	X
	104	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	X	X	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	X
	105	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	•	•	
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•		•	•	•	X
			Forelimb left	•	•	•	•	•	•	•	•	•	•		•	Х	X	X
	106	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х	X	X	X
		Scheduled sacrifice			•				•			•			•			Х
	107	No Abnormalities Detected		Х	Χ	X	X	Х	Χ	X	X	X	Х	Х	Χ	X	X	Х
		Scheduled sacrifice			•				•						•			X
	108	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	Х	X	X	Χ	X
		Scheduled sacrifice			•				•						•			X
	109	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	Χ	Х	X	X	Χ	X
		Scheduled sacrifice																X
	110	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	X	X	Χ	X	X	X	X
		Scheduled sacrifice																X
	111	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	X	X	Χ	X	X	X	X
		Scheduled sacrifice																X
	112	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		Scheduled sacrifice							•									X

X = Present

Test Day

_	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
2m	201	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
	202	No Abnormalities Detected		Χ	Χ	X	X	Χ	Χ	Χ	X	X	Χ	Χ	Χ	X	X	X	X
		Scheduled sacrifice																	
	203	No Abnormalities Detected		Χ	Χ	Χ	X	Х	Х	Χ	X	X	Х	Х	X	Χ	X	X	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	204	No Abnormalities Detected		X	X	Х	Х	Х	X	X	Х	Х	Х	Х	Х	Х	Х	Х	X
		Hair loss	Forelimb bilateral	•	•	•	•		•	•	•	•			•	•	•		
		Scheduled sacrifice		•	•	•	•		•	•	•	•			•	•	•		
	205	No Abnormalities Detected		X	X	Х	Χ	X	X	X	Х	Х	X	Χ	Х	Х	Х	X	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	206	No Abnormalities Detected		Χ	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	X	Χ
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	207	No Abnormalities Detected		X	X	Х	X	X	X	X	Х	Х	Х	X	Х	Х	Х	Х	X
		Scheduled sacrifice		•	•	•	•		•	•					•	•	•		
	208	No Abnormalities Detected		X	Χ	Х	Χ	Х	X	Χ	Х	Х	Χ	Х	Χ	Х	Х	Х	X
		Scheduled sacrifice		•	•	•	•	•	•	•	٠	٠	•	•	•	•	•	•	•
	209	No Abnormalities Detected		Χ	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Χ
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	210	No Abnormalities Detected		Χ	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Χ	Х	Х	Χ
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	211	No Abnormalities Detected		Χ	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	X	Χ
	04.5	Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
	212	No Abnormalities Detected		Χ	Χ	Х	Х	Х	X	Χ	Х	Х	Х	Х	Х	Х	Х	X	Χ
		Scheduled sacrifice		•	•	•	•		•	•	•	•			•	•	•	•	

X = Present

Test Day

Group Sex	Animal Number	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 AM
2m	201	No Abnormalities Detected		Х	Х	Х	Χ	Х	Χ	X	Χ	Χ	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice		•														Х
	202	No Abnormalities Detected		Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	X	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
	203	No Abnormalities Detected		Х	X	Х	Х	Х	Х	Х	Х	X	X	X	Х	Х	X	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
	204	No Abnormalities Detected		Х	X	Х	Х	Х	Х	Х	Х	X	X	X	Χ	•	•	•
		Hair loss	Forelimb bilateral	•	•	•	•	•	•	•	•	•			•	Х	X	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
	205	No Abnormalities Detected		Х	X	Х	Х	Х	X	Х	Х	Χ	X	Χ	Х	Х	X	Х
		Scheduled sacrifice		٠	•	٠	•	•	•	•	•	•	•	•	•	•	•	Х
	206	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х
		Scheduled sacrifice		٠	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
	207	No Abnormalities Detected		Х	X	Х	Х	Х	X	Х	Х	Χ	Χ	Χ	Χ	Х	Х	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
	208	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х
		Scheduled sacrifice		٠	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
	209	No Abnormalities Detected		Χ	Х	Χ	X	Х	Х	Х	X	Х	Х	Х	Χ	Х	Χ	Х
		Scheduled sacrifice		٠	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
	210	No Abnormalities Detected		Х	Х	Χ	X	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	Х
		Scheduled sacrifice		٠	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
	211	No Abnormalities Detected		Х	Х	Χ	X	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	Х
	040	Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	X
	212	No Abnormalities Detected		Χ	Х	Χ	X	Х	Х	Х	X	Х	Х	Х	Χ	Х	Χ	Х
		Scheduled sacrifice		٠	•	•	•	•	•	•	•	•	•	•	•	•	•	Х

X = Present

Test Day

-	Animal			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	Number	Clinical Sign	Site	PM															
3m	301	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
	302	No Abnormalities Detected		X	Χ	X	X	Х	X	X	X	X	X	Χ	Χ	X	X	X	X
		Scheduled sacrifice							•										
	303	No Abnormalities Detected		X	Χ	X	X	Х	X	X	X	X	X	Χ	Χ	X	X	X	X
		Scheduled sacrifice																	
	304	No Abnormalities Detected		X	X	Χ	X	Χ	X	X	X	Χ	X	Χ	X	X	X	X	X
		Scheduled sacrifice																	
	305	No Abnormalities Detected		X	X	Χ	X	Χ	X	X	X	Χ	X	Χ	X	X	X	X	X
		Scheduled sacrifice																	
	306	No Abnormalities Detected		X	X	X	X	Х	Χ	Χ	X	X	X	X	X	Χ	Χ	X	X
		Scheduled sacrifice																	
	307	No Abnormalities Detected		X	X	X	X	Х	Χ	Χ	X	X	X	X	X	Χ	Χ	X	X
		Scheduled sacrifice																	
	308	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	X	X	X	X	X	X	X	Χ
		Scheduled sacrifice																	
	309	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	X	X	X	X	X	X	X	Χ
		Scheduled sacrifice																	
	310	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	X	X	X	X	X	X	X	Χ
		Scheduled sacrifice																	
	311	No Abnormalities Detected		Х	Χ	Х	Χ	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х
		Hair loss	Forelimb bilateral																
		Scheduled sacrifice																	
	312	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
		Scheduled sacrifice																	

X = Present

Test Day

Group	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sex	Number	Clinical Sign	Site	PM	AM													
3m	301	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice		•											•			X
	302	No Abnormalities Detected		X	X	X	X	Х	X	X	Х	X	Х	X	X	Х	X	X
		Scheduled sacrifice																X
	303	No Abnormalities Detected		X	X	X	X	Х	X	X	Х	X	Х	X	X	Х	X	X
		Scheduled sacrifice																X
	304	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	Χ	Χ	X	X	X	X
		Scheduled sacrifice																X
	305	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	Χ	Χ	X	X	X	X
		Scheduled sacrifice																X
	306	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	Χ	X	X	X
		Scheduled sacrifice																X
	307	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	Χ	X	X	X
		Scheduled sacrifice																X
	308	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	Χ	X	X	X	X	Χ	X
		Scheduled sacrifice																X
	309	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	Χ	X	X	X	X	Χ	X
		Scheduled sacrifice																X
	310	No Abnormalities Detected		X	X	X	Χ	X	X	X	X	Χ	X	X	X	X	Χ	X
		Scheduled sacrifice																X
	311	No Abnormalities Detected		Χ	Х	Χ	Χ	Х	Χ	Х	Х	Χ	Χ	Χ	Χ			
		Hair loss	Forelimb bilateral													Х	Χ	X
		Scheduled sacrifice																Х
	312	No Abnormalities Detected		Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																Х

X = Present

Test Day

_	Animal			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	Number	Clinical Sign	Site	PM															
4m	401	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
		Wet fur	Face																
	402	No Abnormalities Detected		X	Χ	Х	Х	Х	Х	Χ		Х	Х	X		Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face								Х				Х				
	403	No Abnormalities Detected		X	Х	Х	Х	Х	Х			Х	Х	Х	Х	Х	Х		
		Scheduled sacrifice																	
		Stained skin/fur - red	Face							Χ	Х							Х	Х
		Wet fur	Face																
		Wet fur	Perineum																
	404	No Abnormalities Detected		X	Х	Х	Х	Х	Х			Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face							Χ	Х								
		Wet fur	Face																
		Wet fur	Perineum																
	405	No Abnormalities Detected		X	Х	Х	Х	Х	Х		Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face							Χ									
		Wet fur	Face																
		Wet fur	Perineum																
	406	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																
		Wet fur	Perineum																
	407	No Abnormalities Detected		X	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Χ	Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																

X = Present

Test Day

Group	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Sex	Number	Clinical Sign	Site	PM	AM													
4m	401	No Abnormalities Detected		Х	Х			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																Х
		Wet fur	Face			X	Χ								•	•		
	402	No Abnormalities Detected		Χ	Χ	Χ	Χ	Х	Χ						Χ	Χ	Χ	Х
		Scheduled sacrifice				•			•		•						•	X
		Stained skin/fur - red	Face			•			•	X	X	Χ	X	Х			•	
	403	No Abnormalities Detected						Х	Χ	Χ	Χ							Х
		Scheduled sacrifice				•			•		•						•	X
		Stained skin/fur - red	Face	X	Х	•			•		•	Χ	X	Х	Χ	X	X	
		Wet fur	Face			X	X		•		•						•	
		Wet fur	Perineum	•	•	•	Х	•	•	•	•	•	•	•	•	•	•	•
	404	No Abnormalities Detected		X	•	•	•	•	•	•	•	•	•	•	•	X	Х	Х
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•	•	•	•	•	•	Х
		Stained skin/fur - red	Face		Х	X	X	Х	X	X	X	Χ	X	Х	Χ		•	
		Wet fur	Face			•	X	Х	•		•						•	
		Wet fur	Perineum			•	X	Х	•		•						•	
	405	No Abnormalities Detected		X	Х	X		Х	X	X	X						•	X
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
		Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	Х	Х	Х	Χ	Х	Х	•
		Wet fur	Face			•	X		•		•						•	
		Wet fur	Perineum			•	X		•		•						•	
	406	No Abnormalities Detected		X	Х	•		Х	X	X	X						•	
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
		Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	Х	Х	X	Χ	Х	Х	Х
		Wet fur	Perineum	•	•	X	Х	•	•	•	•	•			•	•	•	•
	407	No Abnormalities Detected		X	•	•	Х	Х	X	X	X	X	X	X	Χ	X	X	Х
		Scheduled sacrifice			•	•	•	•	•		•				•		•	Х
		Stained skin/fur - red	Face	•	X	X		•	•	•	•	•			•	•	•	•

X = Present

Tе	st.	Da	V

-	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
		3																	
4m	408	No Abnormalities Detected		X	X		X	X	X	X		X			X	Х	X		
		Scheduled sacrifice							•										
		Stained skin/fur - red	Face			X			•		X		X	X				X	X
	409	No Abnormalities Detected		X	X	X	X	X	Χ	X		X	X	X	X	Χ	X	X	X
		Scheduled sacrifice							•										
		Stained skin/fur - red	Face								X								
		Wet fur	Chest						•										
		Wet fur	Face						•										
		Wet fur	Perineum						•										
	410	No Abnormalities Detected		X	X	X	X	X	Χ	X	X	X	X	X	X	Χ	X	X	X
		Scheduled sacrifice							•										
		Stained skin/fur - red	Face						•										
	411	No Abnormalities Detected		X	X	X	X	X	Χ	X	X	X			X	Χ	X		
		Scheduled sacrifice																	
		Stained skin/fur - red	Face										X	X				Х	X
		Wet fur	Face																
		Wet fur	Perineum																
	412	No Abnormalities Detected		X	X	X	X	X	X	X					X	X	X	Х	X
		Scheduled sacrifice																	
		Stained skin/fur - red	Face								Χ	Χ	Χ	Χ					

X = Present

Test Day

Group Sex	Animal Number	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 AM
4m	408	No Abnormalities Detected						Х	Х	Х	Х				Х	Х	Х	Х
	100	Scheduled sacrifice		·	·	·	·					·	·	·				Х
		Stained skin/fur - red	Face	X	X	X	X	•	•	•	·	X	X	X	•	•	·	
	409	No Abnormalities Detected		Х	Х	Х		X	X	X	Х	Х	Х	Х	X	X	X	Х
		Scheduled sacrifice																Х
		Stained skin/fur - red	Face															
		Wet fur	Chest				Х											
		Wet fur	Face				Χ											
		Wet fur	Perineum				X											
	410	No Abnormalities Detected		X	X	X	X	X	X	X	X					X	X	Х
		Scheduled sacrifice																Х
		Stained skin/fur - red	Face									X	Х	Х	X			
	411	No Abnormalities Detected						Х	Х	Х	X					Х	Χ	Х
		Scheduled sacrifice																Х
		Stained skin/fur - red	Face	X	Х							Χ	X	X	Х			
		Wet fur	Face			Χ	Χ		•									
		Wet fur	Perineum				Χ		•									
	412	No Abnormalities Detected		Х	Х	Х	•	•	•	•	•	•	•	•	•	•	•	•
		Scheduled sacrifice		•	•	•	•	•	•	•	•	•			•	•	•	Х
		Stained skin/fur - red	Face				X	X	X	X	X	X	X	X	X	X	X	X

X = Present

						Test Da	У	
Group	Animal			1	8	15	22	29
Sex	Number	Clinical Sign	Site	AM	AM	AM	AM	AM
1m	101	No Abnormalities Detected		Х	Х	Х	Х	Х
	102	No Abnormalities Detected		X	X	X	X	X
	103	No Abnormalities Detected		X	X	X		
		Hair loss	Forelimb bilateral				X	X
	104	No Abnormalities Detected		X	X	X	X	X
	105	No Abnormalities Detected		X	X	X	X	
		Wound - superficial	Forelimb left					X
	106	No Abnormalities Detected		X	X	X	X	X
	107	No Abnormalities Detected		X	X	X	X	X
	108	No Abnormalities Detected		X	X	X	X	X
	109	No Abnormalities Detected		X	X	X	X	X
	110	No Abnormalities Detected		X	X	X	X	X
	111	No Abnormalities Detected		X	X	X	X	X
	112	No Abnormalities Detected		X	X	X	X	X

X = Present

						Test Da	У	
Group	Animal			1	8	15	22	29
Sex	Number	Clinical Sign Si	te	AM	AM	AM	AM	AM
2m	201	No Abnormalities Detected		X	Х	X	X	Х
	202	No Abnormalities Detected		Χ	X	X	X	Х
	203	No Abnormalities Detected		Χ	X	X	X	Х
	204	No Abnormalities Detected		X	X	X	X	
		Hair loss Fo	relimb bilateral					X
	205	No Abnormalities Detected		X	X	X	X	X
	206	No Abnormalities Detected		X	X	X	X	X
	207	No Abnormalities Detected		X	X	X	X	X
	208	No Abnormalities Detected		X	X	X	X	X
	209	No Abnormalities Detected		X	X	X	X	X
	210	No Abnormalities Detected		X	X	X	X	X
	211	No Abnormalities Detected		X	X	X	X	X
	212	No Abnormalities Detected		X	X	X	X	X

X = Present

						Test Da	У	
Group	Animal		-1.	1	8	15	22	29
Sex	Number	Clinical Sign	Site	AM	AM	AM	AM	MA
3m	301	No Abnormalities Detected		Х	X	Х	Х	Х
	302	No Abnormalities Detected		X	X	X	X	X
	303	No Abnormalities Detected		X	X	X	X	X
	304	No Abnormalities Detected		X	X	X	X	X
	305	No Abnormalities Detected		X	X	X	X	X
	306	No Abnormalities Detected		X	X	X	X	X
	307	No Abnormalities Detected		X	X	X	X	X
	308	No Abnormalities Detected		X	X	X	X	X
	309	No Abnormalities Detected		X	X	X	X	X
	310	No Abnormalities Detected		X	X	X	X	X
	311	No Abnormalities Detected		X	X	X	X	
		Hair loss	Forelimb bilateral					X
	312	No Abnormalities Detected		X	X	X	X	X

X = Present

						Test Da	У	
Group	Animal			1	8	15	22	29
Sex	Number	Clinical Sign	Site	AM	AM	AM	AM	AM
4m	401	No Abnormalities Detected		X	Х	Х	Х	Х
	402	No Abnormalities Detected		X	X	X	X	X
	403	No Abnormalities Detected		X	X	X	X	X
	404	No Abnormalities Detected		X	X	X	X	X
	405	No Abnormalities Detected		X	X	X	X	X
	406	No Abnormalities Detected		X	X	X	X	X
	407	No Abnormalities Detected		X	X	X	X	X
	408	No Abnormalities Detected		X	X	X	X	X
	409	No Abnormalities Detected		X	X	X	X	X
	410	No Abnormalities Detected		X	X	X	X	X
	411	No Abnormalities Detected		X	X	X	X	X
	412	No Abnormalities Detected		X	X	X		X
		Stained skin/fur - red	Face				X	

X = Present

ith the Reproduction/Develo	traight-Run: Combined Repeated Dose Toxicity Study opmental Toxicity Screening Test in Rats	DuPont-183
	Annendiy I	
Individual Clinica	Appendix J al Observations and Mortality Data in Subchr	onic Female Rats

Test Day

Group	Animal			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	Number	Clinical Sign	Site	PM															
1f	113	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice			•														
	114	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Χ
		Scheduled sacrifice																	
	115	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																
	116	No Abnormalities Detected		X	Χ	Χ	Х	X	X	X	X	X	X	X	X	Χ	X	X	Х
		Scheduled sacrifice																	
	117	No Abnormalities Detected		Χ	Х	Χ	Х	Х	Х	Χ	X	X	X	X	Χ	X	X	X	Χ
		Scheduled sacrifice			•														
	118	No Abnormalities Detected		Χ	Х	Χ	Х	Х	Х	Χ	X	X	X	X	Χ	X	X	X	X
		Hair loss	Forelimb bilateral		•														
		Scheduled sacrifice		•	•	•						•				•	•		
		Stained skin/fur - red	Face	•	•	•						•				•	•		
	119	No Abnormalities Detected		X	Х	X	Х	X	X	X	Χ	Х	Х	X	Х	Χ	•		
		Scheduled sacrifice		•	•	•						•				•	•		
		Stained skin/fur - red	Face		•												X	X	X
	120	No Abnormalities Detected		Χ	Х														
		Scab	Tail	•	•	X	Х	X	X	X		•				•	•		
		Scheduled sacrifice			•														
		Stained skin/fur - red	Face		•												X	X	X
		Wound - deep	End of tail		•														
		Wound - superficial	Tail		•		Х	Х	Х	Χ	X	X	X	X	Χ	X	X	X	Χ
	121	No Abnormalities Detected		Χ	Х	Χ	Х	Х	Х	Χ	X	X	X	X	Χ	X		X	Χ
		Hair loss	Forelimb bilateral																
		Scheduled sacrifice																	
		Stained skin/fur - red	Face	•	٠	•	•	•	•		•	•	•	•	•	•	X	•	•

X = Present

Test Day

Group	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Sex	Number	Clinical Sign	Site	PM	AM														
1f	113	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	X
	114	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		Scheduled sacrifice																	Χ
	115	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X			
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face														X	X	Х
	116	No Abnormalities Detected		X	X	Χ	X	X	X	X	X	X	X	Χ	X	X	X	X	Χ
		Scheduled sacrifice																	X
	117	No Abnormalities Detected		X	X	Χ	X	X	X	X	X	X	X	Χ	X	X	X	X	Χ
		Scheduled sacrifice																	X
	118	No Abnormalities Detected		X	X	X	X	X											
		Hair loss	Forelimb bilateral						X	X	Χ	X	X	X	X	X	X	X	X
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face																X
	119	No Abnormalities Detected				X	X	X	X	X	X	X	X	X	X	X	X	X	X
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X														
	120	No Abnormalities Detected																	
		Scab	Tail																
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	Х	Χ	Х	Χ	Χ	Χ	Х	Х	Χ	Х	Χ					Χ
		Wound - deep	End of tail			Х	Χ	Χ	Χ	Х	Х	Χ	Х	Χ	Х				
		Wound - superficial	Tail	Х	Χ											X	Χ	Х	Χ
	121	No Abnormalities Detected		Х	Χ	Х	Χ	Χ											
		Hair loss	Forelimb bilateral						Χ	Х	Х	Χ	Х	Χ	Х	X	Χ	Х	Χ
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face									Х	Х	Х					

X = Present

Test Day

_	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM	
1f	122	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	
		Scheduled sacrifice																		
		Stained skin/fur - red	Face														X			
	123	No Abnormalities Detected		Х	X	X	Х	Х	X	Χ	X	Х	Х	Х	Х	Χ	Χ	Х	X	
		Scheduled sacrifice																		
		Stained skin/fur - red	Face							•										
	124	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	
		Scheduled sacrifice																		

X = Present

Test Day

_	Animal Number	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 PM	32 AM
1f	122	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice		•	•					•	•						•		Χ
		Stained skin/fur - red	Face		•	•				•						•			
	123	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X			
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face														X	Χ	X
	124	No Abnormalities Detected		Χ	Χ	Х	Χ	Χ	Χ	Х	Χ	Χ	Х	Χ	Х	Х	Х	Χ	X
		Scheduled sacrifice																	X

X = Present

Test Day

-	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
2.f	213	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	Х	Х	Х	Х	Х	Х	X	Х	Х
		Scheduled sacrifice												-					
		Stained skin/fur - red	Face																
	214	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
	215	No Abnormalities Detected		Х	Χ	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																
	216	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	Х	Х	X	X	X	X	Х
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																
	217	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	Х	X	X	X	Х
		Scheduled sacrifice																	
	218	No Abnormalities Detected		X	X	X	X	Χ	X	X	X	X	Χ	Χ	X	Χ	X	X	Χ
		Scheduled sacrifice																	
		Stained skin/fur - red	Face																
	219	No Abnormalities Detected		X	X	X	X	X	X	X	Х	X	Х	Х	X	X	X		
		Scheduled sacrifice		•						•							•		
		Stained skin/fur - red	Face							•								X	Χ
	220	No Abnormalities Detected		X	X	X	X	X	X	Χ	Х	X	Х	X	Χ	Χ	X	Х	Х
		Scheduled sacrifice								•									
		Stained skin/fur - red	Face							•									
	221	No Abnormalities Detected		X	Х	X	Χ	X	Х	Χ	X	Χ	Х		X	X		Х	Х
		Scheduled sacrifice		•		•				•									
		Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	•	•	Х	•	•	Х	•	•
	222	No Abnormalities Detected		X	X	X	X	X	X	Х	Х	X	Х	X	Х	Х	•	•	
		Scheduled sacrifice		•	•	•			•	•	•				•	•		•	•
		Stained skin/fur - red	Face							•							X	X	Χ

X = Present

Test Day

_	Animal Number	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 PM	32 AM
0011	110111001	011111001 01911	5100																
2f	213	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х			Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face								Х	Х							
	214	No Abnormalities Detected		Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Scheduled sacrifice																	Х
	215	No Abnormalities Detected		Χ	Χ	Х	Х	Χ	Χ	Χ					X	X	Χ	Х	Χ
		Scheduled sacrifice																	Χ
		Stained skin/fur - red	Face								X	X	X	X					
	216	No Abnormalities Detected		X	X	X			X	X	Χ	X	X	X	X	Χ	X	X	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face				X	Х											
	217	No Abnormalities Detected		X	X	X	X	Χ	X	X	X	X	X	X	X	X	X	Χ	Χ
		Scheduled sacrifice																	Χ
	218	No Abnormalities Detected		X	X	Χ		Х	X	X	X	X	Χ	X	X	X	X	Х	Х
		Scheduled sacrifice																	Χ
		Stained skin/fur - red	Face				X												
	219	No Abnormalities Detected				X	Х	X	X	X	X				X	X	X	Х	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	X	X							Χ	X	Х					
	220	No Abnormalities Detected		X		X	Х	X	X	X	X		X	X	X	X	X	Х	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	•	Х						•	X			•	•	•		
	221	No Abnormalities Detected				Χ	X	Х	Х						X	X	X	Х	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	Χ	Χ					Χ	Χ	Χ	Χ	Х					
	222	No Abnormalities Detected		•	•	Х	Х	Х	Х	•			Χ	Х	Χ	Χ	Χ	Х	Х
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	X	X					X	Χ	Χ							

X = Present

Test Day

-	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM		8 PM		10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
2f	223	No Abnormalities Detected Scheduled sacrifice		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	•	•	•
		Stained skin/fur - red	Face				:		•		•		•	•		•	X	X	X
	224	No Abnormalities Detected		X	X	X	X	X	X	X	X	Х	X	X	X	X			
		Scheduled sacrifice																	
		Stained skin/fur - red	Face														X	X	X

X = Present

Test Day

Group	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Sex	Number	Clinical Sign	Site	PM	AM														
2f	223	No Abnormalities Detected			•	X	X	X	X	X	X				X	X	X	X	X
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X							X	X	X					
	224	No Abnormalities Detected				X	X	X	X	X	X		X	X	X	X			
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X							X					Х	Х	Х

X = Present

Test Day

_	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
3f	313	No Abnormalities Detected		Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х			
		Scheduled sacrifice		•	•	•	•		•	•	•		•		•				
		Stained skin/fur - red	Face	•	•	•	•	•	•	٠	•	•	•	•	•	•	Х	X	Х
	314	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	X	Χ	Х	Х	Χ	Χ	Χ	•	•
		Scheduled sacrifice	_	•	•	٠	•	•	•	٠	٠	•	•	•	•	•	•		•
	04.5	Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	•	•	•	•	•	•	X	Х
	315	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х
		Scheduled sacrifice	D	٠	•	٠	•	•	٠	•	•	٠	•	•	٠	٠	٠	•	•
	21.0	Stained skin/fur - red No Abnormalities Detected	Face	X	X	•	•	X	X	X	X	X	X	X	X	X	X	X	·
	310	Scheduled sacrifice		Λ	Λ	Λ	Λ	Λ	Λ	Λ	Λ	Λ	Λ	Λ	Χ	Λ	Λ	Λ	X
		Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	317	No Abnormalities Detected	race	×	·	X	×	X	X	X	X	·	X	X	·	·	X	•	•
	317	Scheduled sacrifice		21	21	21	21	21	21	21	21	21	21	21	21	21	21	•	•
		Stained skin/fur - red	Face	•	•	•	•	•	•	•	•	•	•	•	•	•	•	×	X
	318	No Abnormalities Detected	1400	X	X	×	X	X	X	X	X	X	X	X	×	X	X	X	
	010	Scheduled sacrifice																	
		Stained skin/fur - red	Face																Х
	319	No Abnormalities Detected		Х	Х	Х	Х		Х	Х	Х	Х	Х	Х		Х			
		Scheduled sacrifice																	
		Stained skin/fur - red	Face					Х							Х		Х	Х	X
	320	No Abnormalities Detected		Χ	Χ	Χ	Χ		X	X	Χ	X	Χ	Х		X			
		Discharge - black	Eye right																
		Discharge - red	Eye right																Х
		Scheduled sacrifice		•					•						•				
		Stained skin/fur - red	Face			•	•	Х	•	•	•			•	Χ		Χ	Х	Х

X = Present

Test Day

_	Animal		Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 DM	26 PM	27 PM	28 PM	29 PM	30 PM	31 PM	32 AM
sex	Number	Clinical Sign	Site	PM	АМ														
3f	313	No Abnormalities Detected				Х	Х	Х	Х	Х	Х								
		Scheduled sacrifice		•	•	•	•		•	•	•	•	•	•	•	•	•	•	X
		Stained skin/fur - red	Face	X	X	•	•		•	•	•	Х	X	Х	X	Х	X	Х	X
	314	No Abnormalities Detected		•	•	•	•		•	•	•	•			Х	Х	Х	Х	X
		Scheduled sacrifice		•					•	•					•				X
		Stained skin/fur - red	Face	Х	X	X	Χ	X	X	X	X	X	Х	Х	•				
	315	No Abnormalities Detected				X	Χ	X	Х	Χ	X				Х	X	X		
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	Χ		•					X	X	Х				Х	X
	316	No Abnormalities Detected		X		X	Χ	X	Х	Χ	X								
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face		X							X	X	Х	X	X	X	X	X
	317	No Abnormalities Detected				X	Χ	X	X	X	X				X	X	X	X	X
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X							X	X	X					
	318	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	Х	X	X	X	X	X
	319	No Abnormalities Detected				X	X	X	X	X									
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	Х	Х						Х	Х	Χ	Х	Χ	Х	Χ	Χ	Х
	320	No Abnormalities Detected																	
		Discharge - black	Eye right			Χ	X	Χ	Χ	Х	Х								
		Discharge - red	Eye right	Х	Χ														
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	Х	Х						Х	Х	Х	Х	Х	Х	Х	Х	Х

X = Present

Test Day

-	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM
3f	321	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х									
		Hair loss	Forelimb bilateral								Х	Х	Х	Х	Х				
		Scheduled sacrifice																	
		Stained skin/fur - red	Face												X	X	Χ	Х	X
	322	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	Х	X	X			
		Scheduled sacrifice																	
		Stained skin/fur - red	Face														X	X	X
	323	No Abnormalities Detected		X	X	X	Χ	X	X	X	Χ	X	X	X	X	X			
		Scheduled sacrifice																	
		Stained skin/fur - red	Face														X	X	X
	324	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	Х	X	X	Χ		
		Scheduled sacrifice																	
		Stained skin/fur - red	Face															Х	Х

X = Present

Test Day

-	Animal Number	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 PM	32 AM
3f	321	No Abnormalities Detected																	
		Hair loss	Forelimb bilateral						Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
	322	No Abnormalities Detected				Х	Х	Х	Х	Х					Х	Х	Х	Х	X
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	Х	Х						Х	Х	Х	Х					
	323	No Abnormalities Detected			Х	Х	Х	Х	Х	Х					Х	Х			
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	Х							Х	Х	Х	Х			Х	Х	X
	324	No Abnormalities Detected			Х	Х	Х	Х	Х	Х									
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X							X	X	X	X	X	X	X	X	X

X = Present

Test Day

	Animal	01''1 0'	0'11	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
sex	Number	Clinical Sign	Site	PM															
4 f	413	No Abnormalities Detected		Х	Х							Х	Х	Х	Х	Х	Х		
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X	X	X	X	X							Χ	X
		Wet fur	Chin															Χ	X
		Wet fur	Perineum																
	414	No Abnormalities Detected		X	Χ			X	X										
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X			X	X	X	X	X	X	X	X	X	X
		Wet fur	Chin															X	X
		Wet fur	Perineum																
	415	No Abnormalities Detected		X	X			X	X	X									
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X				X	X	X	X	X	X	X	X	X
		Wet fur	Chest																
		Wet fur	Chin																X
		Wet fur	Perineum																
	416	No Abnormalities Detected		X	X			X	X										
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X			X	X	X	X	X	X	X	X	X	X
		Wet fur	Chin																
		Wet fur	Face																
		Wet fur	Perineum																
	417	No Abnormalities Detected		X	X			X	X										
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			Χ	X			Χ	Χ	Χ	Х	Х	X	Χ	X	Х	Х
		Wet fur	Chest																
		Wet fur	Chin																

X = Present

Test Day

_	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Sex	Number	Clinical Sign	Site	PM	AM														
4 f	413	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
		Wet fur	Chin	X	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Χ	X	Χ	
		Wet fur	Perineum							Χ	Χ	Χ	Χ	Χ	Χ	Χ	X	Χ	
	414	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X	X	Х	X	X	X	X	X	X	Χ	X	X	X
		Wet fur	Chin	X						X	X	X	X	X	X	Χ	X	X	
		Wet fur	Perineum						•	X	X	X	X	X	X	Χ	X	X	
	415	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	Χ	X	Χ	X	X	X	X	Χ	Χ	X	X	X	Χ	X
		Wet fur	Chest						•	X	X	X	X	X	X	Χ	X	X	
		Wet fur	Chin							X	X	X	X	X	X	X	X	X	
		Wet fur	Perineum							X	X	X	X	X	X	X	X	X	
	416	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	Χ	X	Χ	Χ	X	X	X	X	X	Χ	X	X	X
		Wet fur	Chin		X														
		Wet fur	Face													X	X	Χ	
		Wet fur	Perineum														X	X	
	417	No Abnormalities Detected						X											
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X		Χ	X	X	X	Х	Х	Х	X	Х	Х	Χ
		Wet fur	Chest			•	•		X	Х	X	X	X	X	Х	Χ	Х	X	
		Wet fur	Chin		X	•	•		Χ	X	X	X	Х	Х	Х	Х	Х	Х	

X = Present

Test Day

-	Animal			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	Number	Clinical Sign	Site	PM															
4 f	418	No Abnormalities Detected		Х	Х			Х	Х	Х	Х	Х	Х						
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X			•				Χ	Χ	X	Χ	X	X
		Wet fur	Chest															Χ	Χ
		Wet fur	Chin							•								X	X
		Wet fur	Face							•									
		Wet fur	Perineum																
	419	No Abnormalities Detected		X										X	X				
		Scheduled sacrifice								•									
		Stained skin/fur - red	Face		X	X	X	X	X	Χ	Χ	X	X						
		Stained skin/fur - tan	Face							•						X	Χ	X	X
		Wet fur	Chest							•								X	X
		Wet fur	Chin															Х	Х
		Wet fur	Face							•									
	420	No Abnormalities Detected		X						•	Χ	X	X						
		Scheduled sacrifice								•									
		Stained skin/fur - red	Face		X	X	X	X	X	X				X	X	X	X	X	X
		Wet fur	Chest														X	X	X
		Wet fur	Chin							•							Χ	X	X
		Wet fur	Face																
		Wet fur	Perineum																
	421	No Abnormalities Detected		X	X									X	X	X			
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			X	X	X	X	X	X	X	X				X	X	X
		Wet fur	Chest														X	X	X
		Wet fur	Chin														X	Х	Х
		Wet fur	Perineum							•									

X = Present

Test Day

-	Animal	Clinical Sign	Site	17 PM	18 PM	19 PM	20 PM	21 PM	22 PM	23 PM	24 PM	25 PM	26 PM	27 PM	28 PM	29 PM	30 PM	31 PM	32 AM
sex	Number	CIIIIICAI SIGII	Sice	L IM	LIM	E IM	L IM	E IM	E IM	LIM	E M	E IM	E M	E IM	L IM	E IM	E M	E M	AM
4f	418	No Abnormalities Detected																	
		Scheduled sacrifice																	Χ
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	X	X	X	Χ	X	X
		Wet fur	Chest																
		Wet fur	Chin																
		Wet fur	Face		X		X	Х	X	X	X	X	X	Х	X	X	X	X	
		Wet fur	Perineum													X	Χ	X	
	419	No Abnormalities Detected																	
		Scheduled sacrifice																	Χ
		Stained skin/fur - red	Face			X	X	Х	X	X	X	X	X	Х	X	X	X	X	Х
		Stained skin/fur - tan	Face	X	X														
		Wet fur	Chest	X	X														
		Wet fur	Chin	X	X														
		Wet fur	Face			X	X	X	X	X	X	X	X	X	X	X	Χ	X	
	420	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	X	X	X	Χ	X	X
		Wet fur	Chest	X	X														
		Wet fur	Chin	X	X														
		Wet fur	Face			X	X	X	X	X	X	X	X	X	X	X	Χ	X	
		Wet fur	Perineum			X	X	X	X	X	X	X	X	X	X	X	Χ	X	
	421	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	X	X	X	Χ	X	X
		Wet fur	Chest	X	X				X	X	X	X	X	Х	X	X	X	X	
		Wet fur	Chin	X	X				X	X						X	X	X	
		Wet fur	Perineum														X	X	

X = Present

Test Day

Group	Animal			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sex	Number	Clinical Sign	Site	PM															
4 f	422	No Abnormalities Detected		Х	Х									Х	Х				
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			Χ	Χ	X	X	X	X	X	X			Χ	X	X	X
		Wet fur	Chest														X	X	X
		Wet fur	Chin														X	X	X
		Wet fur	Face																
		Wet fur	Perineum																
	423	No Abnormalities Detected		X	Х														
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			Х	Х	Х	Χ	X	Х	Х	Х	Χ	Х	Х	Χ	Х	Х
		Wet fur	Chest														Х	Х	Х
		Wet fur	Chin														Χ	Х	Х
		Wet fur	Face																
		Wet fur	Perineum																
	424	No Abnormalities Detected		Х	Х									Х					
		Scheduled sacrifice																	
		Stained skin/fur - red	Face			Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х	Х	Х
		Wet fur	Chest														Х	Х	Х
		Wet fur	Chin														Х	Х	Х
		Wet fur	Face																
		Wet fur	Perineum																

X = Present

Test Day

Group	Animal			17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Sex	Number	Clinical Sign	Site	PM	AM														
4 f	422	No Abnormalities Detected																	
		Scheduled sacrifice																	Х
		Stained skin/fur - red	Face	X	Χ	X	Χ	X	X	X	X	X	Χ	X	X	Χ	X	X	Χ
		Wet fur	Chest	X	Χ		Χ	X	X	X	X	X	Χ	X	X	Χ	X	X	
		Wet fur	Chin	X	Χ														
		Wet fur	Face				Χ	X	X	X	X	X	Χ	X	X	Χ	X	X	
		Wet fur	Perineum				X	Χ	X	X	X	X	X	X	X	X	X	X	
	423	No Abnormalities Detected				X		X	X										
		Scheduled sacrifice																	Χ
		Stained skin/fur - red	Face	X	Χ		Χ			X	X	X	Χ	X	X	Χ	X	X	Χ
		Wet fur	Chest	X	Χ														
		Wet fur	Chin	X	Χ														
		Wet fur	Face				Χ				X	X	Χ	X	X	Χ	X	X	
		Wet fur	Perineum													Χ	Χ	Χ	
	424	No Abnormalities Detected																	
		Scheduled sacrifice																	X
		Stained skin/fur - red	Face	X	X	X	X	Χ	X	X	X	X	X	X	X	X	X	X	X
		Wet fur	Chest	X	X														
		Wet fur	Chin	X	X														
		Wet fur	Face								Χ	Χ	X	Χ	Χ	Χ	Χ	Χ	
		Wet fur	Perineum				Χ	Χ	Χ	X	Χ	Χ	X	Χ	Χ	Χ	Χ	Χ	

X = Present

						Test Da	У	
Group Sex	Animal Number	Clinical Sign	Site	1 AM	8 AM	15 AM	22 AM	29 AM
1f	113	No Abnormalities Detected		Х	Х	Х	Х	Х
	114	No Abnormalities Detected		Х	X	Х	X	X
	115	No Abnormalities Detected		Х	X	X	Х	X
	116	No Abnormalities Detected		X	X	X	X	X
	117	No Abnormalities Detected		X	X	X	X	X
	118	No Abnormalities Detected		X	X		•	
		Hair loss	Forelimb bilateral			X	X	X
	119	No Abnormalities Detected		Х	X	X	X	X
	120	No Abnormalities Detected		X				
		Wound - superficial	Tail		X	X	X	X
	121	No Abnormalities Detected		X	X	X		
		Hair loss	Forelimb bilateral				X	X
	122	No Abnormalities Detected		X	X	X	X	X
	123	No Abnormalities Detected		X	X	X	X	X
	124	No Abnormalities Detected		X	X	X	X	X

X = Present

Individual Detailed Clinical Observations in Subchronic Female Rats

						Test Da	У	
Group	Animal			1	8	15	22	29
Sex	Number	Clinical Sign	Site	AM	AM	AM	AM	AM
2f	213	No Abnormalities Detected		X	Х	Х	Х	Х
	214	No Abnormalities Detected		X	X	X	X	X
	215	No Abnormalities Detected		X	X	X	X	X
	216	No Abnormalities Detected		X	X	X	X	X
	217	No Abnormalities Detected		X	X	X	X	X
	218	No Abnormalities Detected		X	X	X	X	X
	219	No Abnormalities Detected		X	X	X	X	X
	220	No Abnormalities Detected		X	X	X	X	X
	221	No Abnormalities Detected		X	X	X	X	X
	222	No Abnormalities Detected		X	X		X	X
		Stained skin/fur - red	Face	•		X		
	223	No Abnormalities Detected		X	X	X	X	X
	224	No Abnormalities Detected		X	X	X	X	X

X = Present

Individual Detailed Clinical Observations in Subchronic Female Rats

					,	Test Da	У	
Group	Animal			1	8	15	22	29
Sex	Number	Clinical Sign	Site	AM	AM	AM	AM	AM
3f	313	No Abnormalities Detected		Х	X	X	Х	X
	314	No Abnormalities Detected		X	X	X	X	X
	315	No Abnormalities Detected		X	X	X	Х	X
	316	No Abnormalities Detected		X	X	X	Х	X
	317	No Abnormalities Detected		X	X	X	X	X
	318	No Abnormalities Detected		X	X	X		•
		Stained skin/fur - red	Face				X	X
	319	No Abnormalities Detected		X	X	X	X	X
	320	No Abnormalities Detected		X	X	X	X	X
	321	No Abnormalities Detected		X				•
		Hair loss	Forelimb bilateral		X	X	X	X
	322	No Abnormalities Detected		X	X	X	X	X
	323	No Abnormalities Detected		X	X	X	X	X
	324	No Abnormalities Detected		X	X	X	X	X

X = Present

Individual Detailed Clinical Observations in Subchronic Female Rats

						Test Da	У	
Group Sex	Animal Number	Clinical Sign	Site	1 AM	8 AM	15 AM	22 AM	29 AM
4 f	413	No Abnormalities Detected		X	Х	Х	_	
		Stained skin/fur - red	Face				X	X
	414	No Abnormalities Detected	2400	X	X	X		
		Stained skin/fur - red	Face				X	X
	415	No Abnormalities Detected		X				
		Stained skin/fur - red	Face		X	X	X	X
	416	No Abnormalities Detected		X	-	X		
		Stained skin/fur - red	Face		X		X	X
	417	No Abnormalities Detected		X	X			
		Stained skin/fur - red	Face			X	X	X
	418	No Abnormalities Detected		X	X	Х		
		Stained skin/fur - red	Face				X	X
	419	No Abnormalities Detected		X	X			
		Stained skin/fur - red	Face			Х	Х	Х
	420	No Abnormalities Detected		X	X			
		Stained skin/fur - red	Face			X	X	X
	421	No Abnormalities Detected		X	X			
		Stained skin/fur - red	Face			X	X	X
	422	No Abnormalities Detected		X	X	X		
		Stained skin/fur - red	Face				X	X
	423	No Abnormalities Detected		X	X	X	Х	X
	424	No Abnormalities Detected		X	X	X		
		Stained skin/fur - red	Face				X	X

X = Present

DuPont-18331

Appendix L Individual Clinical Observations in Satellite Female Rats During Premating

Test 1	Day
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-	Animal Number	Clinical Sign		Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM
1f	125	No Abnormalities	Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
	126	No Abnormalities	Detected		Х	Χ	X	Х	Χ	X	Х								
		Hair loss		Forelimb bilateral								X	Χ	Х	Χ	Χ	X	Χ	Х
	127	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	128	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	Х	X	X	X	X	X
	129	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	Х	X	X	X	X	X
	130	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	131	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	132	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	133	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	134	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	135	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х
	136	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X = Present

Test Day

Group Sex	Animal Number	Clinical Sign		Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM
2f	225	No Abnormalities	Detected		Χ	Χ	Χ	X	Χ	Χ	Χ	Χ	Χ	Χ	Χ	X	Χ	Χ	Х
	226	No Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	X	Х	Х	Χ	Х	Χ	X	X	Х	X
	227	No Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	X	Х	Х	Χ	Х	Χ	X	X	Х	
		Stained skin/fur	- red	Face															X
	228	No Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	X	Х	Х	Χ	Х	Χ	X			
		Stained skin/fur	- tan	Face													X	Х	Х
	229	No Abnormalities	Detected		Х	Χ	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Х	Х
	230	No Abnormalities	Detected		Х	Χ	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Х	Х
	231	No Abnormalities	Detected		Х	Χ	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Х	
		Stained skin/fur	- red	Face															X
	232	No Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	X	Х	Х	Χ	Х	Χ	X	X	Х	
		Stained skin/fur	- red	Face															X
	233	No Abnormalities	Detected		Х	Χ	Χ	Χ	Χ	X	Х	Х	Χ	Х	Χ	X	X	Х	
		Stained skin/fur	- red	Face															Х
	234	No Abnormalities	Detected		Х	Χ	Х	Χ	Х	Х	Χ	Х	Х	Х	Х	Х	Χ	Х	Х
	235	No Abnormalities	Detected		Χ	Х	Х	Χ	Х	Χ	Χ	Χ	Х	Х	Х	Х	Х	Х	Х
	236	No Abnormalities	Detected		Χ	Χ	Χ	Х	Χ	Χ	Χ	Х	Χ	Х	Х	Х	Х	Х	X

X = Present

Test Day

-	Animal Number	Clinical Sign		Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM
3f	325	No Abnormalities	Detected		Х	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
		Stained skin/fur		Face															Х
	326	No Abnormalities			Х	X	X	X	Х	Х	X	X	Х	Х	Х	Х	Х	Х	Х
	327	No Abnormalities	Detected		Х	Χ	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Х	Х		
		Stained skin/fur	- red	Face														Х	Х
	328	No Abnormalities	Detected		X	Χ	Χ	Χ	Χ	Χ	Χ	Χ	Х	Χ	Χ	Х	Χ		
		Stained skin/fur	- red	Face														Χ	Χ
	329	No Abnormalities	Detected		X	X	X	X	X	X	X	X	Х	Х	X	X	X		
		Stained skin/fur	- red	Face														X	X
	330	No Abnormalities	Detected		X	X	X	X	Χ	X	X	X	Х	X	X	X	Χ		X
		Stained skin/fur	- red	Face														X	
	331	No Abnormalities	Detected		X	X	X	X	Χ	X	X	X	Х	X	X	X	Χ	X	X
	332	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	X	Χ	X	X	X	Χ
	333	No Abnormalities	Detected		X	X	X	X	Χ	X	X	X	Х	X	X	X	Χ		
		Stained skin/fur	- red	Face														X	Χ
	334	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	Χ	X	X	X		
		Stained skin/fur	- red	Face														X	X
	335	No Abnormalities	Detected		X	Х	Χ	X	X	Х	X	X	Х	Х	X	X	Х		
		Stained skin/fur	- red	Face														X	X
	336	No Abnormalities	Detected		X	X	X	X	X	X	X	X	X	Χ	X	X	X		
		Stained skin/fur	- red	Face														X	X

X = Present

Test Day

-	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM
4 f	425	No Abnormalities Detected		Х	Х						Х	Х						
41	423	Stained skin/fur - red	B	Λ	Λ	•	•	•	•	•	Λ	Λ	•	•	•	•	•	•
	426	No Abnormalities Detected	Face	•	•	Х	Х	Х	Х	Х	•	•	X	X	Х	Х	Χ	Х
	426	Stained skin/fur - red	D	Х	Х	•	•	•	•	•	•	Х	Х	Х	•	•	•	•
		Wet fur	Face	•	•	Х	Х	Х	Х	Х	Х	•	•	•	Х	Х	X	X
		Wet fur	Chest Chin	•	•	•	•	•	•	•	•	•	•	•	•	•	X	X
	405		Cnin	•	•	•	•	•	•	•	•	•	•	•	•	•	Х	Х
	427	No Abnormalities Detected	_	Х	Х	•	•		•	•	•	•		Х	Х	•	•	
		Stained skin/fur - red	Face	•	•	Х	Х	Х	Х	Х	Х	Х	Х	•	•	Χ	X	X
		Wet fur	Chest	•	•	•	•	•	•	•	•	•		•	•	٠	X	X
	400	Wet fur	Chin	•	•	•	•	•	•	•	Х	X	X		•	٠	Х	Х
	428	No Abnormalities Detected	_	Χ	Χ	•	•		•	•	•	Х	Х	Х	•	•	•	
		Stained skin/fur - red	Face	•	•	Х	Х	Х	Χ	Х	Х	•	•	•	Х	Х	Х	Х
		Wet fur	Chest	•	•	•	•	•	•	•	٠	•	•	•	•	٠	X	•
		Wet fur	Chin	•	•	•	•	•	•	•	•	•	•	•	•	•	Х	•
	429	No Abnormalities Detected	_	Х	Х	•	•	•	•	•	•	Х	•	Х	Х	•	•	•
		Stained skin/fur - red	Face	•	•	Х	Х	Х	Х	Х	Χ	•	X	•	•	Х	Х	Х
		Wet fur	Chin	•	•	•	•	•	•	•	•	•	Χ	•	•	•	•	•
	430	No Abnormalities Detected		Х	Х	٠	•	•	•	•	•	•	•	•	•	•	٠	•
		Stained skin/fur - red	Face	•	•	Х	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х
		Wet fur	Chest	•	•	•	•	•	•	•	•	•	•		•	•	Х	Х
		Wet fur	Chin	•	•	•	•	•	•	•	•	•	Χ	Х	•	•	Х	Х
	431	No Abnormalities Detected		X	X	•	•	•	•	•	•	•	•	Х	X	Х	•	•
		Stained skin/fur - red	Face	•	•	Х	X	Х	X	Х	Х	X	Χ		•	•	Х	Х
		Wet fur	Chest	•	•	•	•	•	•	•	•	•	•		•	•	Х	Х
		Wet fur	Chin	•	•	•	•	•	•	•	•	•	•		•	•	Х	Х
	432	No Abnormalities Detected		X	X	•	•	•	•	•	•	•	•	Х	Х	Х	•	•
		Stained skin/fur - red	Face	•	•	Х	X	X	X	Х	Х	X	X			•	Х	X
		Wet fur	Chin	•	•		•	•	•	•	•	•	•		•	•	Х	X
		Wet fur	Face	•	•	•	•	•	•	•	•	•	•	•	•	•	Х	Х

X = Present

Test	Day
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Group Sex	Animal Number	Clinical Sign	Site	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM
		,																
4 f	433	No Abnormalities Detected		Х	Х													
		Stained skin/fur - red	Face			Х	X	Χ	X	Χ	X	Χ	Х	X	Χ	X	X	Х
		Wet fur	Chest														Х	X
		Wet fur	Chin														X	Х
	434	No Abnormalities Detected		X	X													
		Stained skin/fur - red	Face			Х	Χ	Χ	Χ	Χ	Χ	Χ	Х	Χ	Х	X	Х	X
		Wet fur	Chest														Х	Х
		Wet fur	Chin														Х	Х
	435	No Abnormalities Detected		Х	X									Х	X			
		Stained skin/fur - red	Face			Х	Χ	Х	Х	Х	Χ	Х	Х			Х	Х	Х
		Wet fur	Chest														Х	Х
		Wet fur	Chin														Х	Х
	436	No Abnormalities Detected		Х	Х										Х			
		Stained skin/fur - red	Face			Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
		Wet fur	Chest						-								Х	X
		Wet fur	Chin														Х	Х

X = Present

		Annendi	v M		
Individual C	Clinical Observ	vations in Sat	ellite Female	Rats During	Gestation

Gestation Day

Group Sex	Animal Number	Clinical Sign	Site	0 PM	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM
1f	125	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Hair loss	Forelimb bilateral										
	126	Hair loss	Forelimb bilateral	X	Х	Х	Х	Х	Х	X	X	Х	Х
	127	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
	128	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
	129	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
	130	No Abnormalities Detected		X	Х	X	X	X	Х	X	X	Х	X
	131	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
	132	No Abnormalities Detected		X	Х	Х	Х						
		Hair loss	Forelimb bilateral					Х	Х	X	X	Х	Х
	133	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
	134	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	X	Х	Х
		Hair loss	Hind quarters left										
	135	No Abnormalities Detected		X	Х	X	X	X	X	X		Х	Х
		Hair loss	Forelimb bilateral										
		Stained skin/fur - red	Face								X		
	136	No Abnormalities Detected		X	Х	X	X	X	Х	X	X	Х	X

X = Present

Gestation Day

Group Sex	Animal Number	Clinical Sign	Site	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM	17 PM	18 PM	19 PM	20 PM	21 PM
1f	125	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х					
		Hair loss	Forelimb bilateral								Х	Х	X	Х	X
	126	Hair loss	Forelimb bilateral	X	X	X	X	X	X	X	Х	Х	Х	Х	Х
	127	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
	128	No Abnormalities Detected		Х	X	Х	X	Х	X	X	Х	X	Х	X	X
	129	No Abnormalities Detected		Х	X	Х	X	Х	X	X	X	X	Х	X	X
	130	No Abnormalities Detected		Х	X	Х	X	Х	X	X	Х	X	Х	X	X
	131	No Abnormalities Detected		Х	X	Х	X	Х	X	X	Х	X	Х	X	X
	132	No Abnormalities Detected													
		Hair loss	Forelimb bilateral	X	X	Х	X	Х	Х	Х	Х	Х	X	Х	X
	133	No Abnormalities Detected		X	X	Х	Х	Х	X	Х	Х	Х	X	Х	X
	134	No Abnormalities Detected		X	X	Х	Х	Х	X	Х	Х				
		Hair loss	Hind quarters left									Х	X	Х	X
	135	No Abnormalities Detected		X	X	Х	X	Х	Х	Х	Х				
		Hair loss	Forelimb bilateral									Х	X	Х	X
		Stained skin/fur - red	Face												
	136	No Abnormalities Detected		Х	Х	X	Х	X	Х	X	X	X	Х	X	Х

X = Present

236 No Abnormalities Detected

Individual Clinical Observations in Satellite Female Rats During Gestation

 X X X X X X X X X X

									Ges	tatio	n Day		
Group Sex	Animal Number	Clinical Sign	Site	0 PM	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM
2f	225	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
	226	No Abnormalities Detected		Х	X	X	Χ	X	X	Х	X	X	X
		Hair loss	Forelimb bilateral	•			•	•			•		•
	227	No Abnormalities Detected		•	•	Х	X	X	Х	X	X	X	X
		Stained skin/fur - red	Face	X	Х		•	•	•	•	•	•	•
	228	No Abnormalities Detected		•	Х	Х	X	X	Х	X	X	X	X
		Stained skin/fur - tan	Face	X									
	229	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X
	230	No Abnormalities Detected		X	X	X							
		Hair loss	Forelimb bilateral				X	X	X	X	X	X	X
	231	No Abnormalities Detected			X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X									
	232	No Abnormalities Detected				X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X								
	233	No Abnormalities Detected			X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X									
	234	No Abnormalities Detected		X	X	Χ	Χ	X	X	X	Х	Χ	Χ
	235	No Abnormalities Detected		Х	X	X	X	X	X	X	X	X	X

X = Present

Gestation Day

Group Sex	Animal Number	Clinical Sign	Site	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM	17 PM	18 PM	19 PM	20 PM	21 PM
2f	225	No Abnormalities Detected		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
	226	No Abnormalities Detected		X	X	X	X	X	X	X	X	X			
		Hair loss	Forelimb bilateral										X	X	X
	227	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face												
	228	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - tan	Face												
	229	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
	230	No Abnormalities Detected													•
		Hair loss	Forelimb bilateral	X	X	X	X	X	X	X	X	X	X	X	X
	231	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face												•
	232	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face												•
	233	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face												
	234	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
	235	No Abnormalities Detected		X	Х	Χ	Χ	Χ	Χ	Χ	Χ	X	X	Χ	Χ
	236	No Abnormalities Detected		Χ	Х	Х	Χ	Х	Х	Χ	Χ	Χ	Х	Χ	Χ

X = Present

									Gest	tatio:	n Day		
Group	Animal			0	1	2	3	4	5	6	7	8	9
Sex	Number	Clinical Sign	Site	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM
3f	325	No Abnormalities Detected		Х	Х	Х							
		Stained skin/fur - red	Face				X	X	X	X	X	X	X
	326	No Abnormalities Detected		Х	X	Х	X	X	X	Х			
		Stained skin/fur - red	Face								X	X	X
	327	No Abnormalities Detected			X	Х	X						
		Hair loss	Forelimb bilateral										
		Stained skin/fur - red	Face	Х				X	X	Х	X	X	X
	328	No Abnormalities Detected			X	Х	X	X	X	Х			
		Stained skin/fur - red	Face	X							X	X	X
	329	No Abnormalities Detected			X	Х	X						
		Stained skin/fur - red	Face	Х				X	X	Х	X	X	X
	330	No Abnormalities Detected		Х	X	Х	X						X
		Stained skin/fur - red	Face					X	X	Х	X	X	
	331	No Abnormalities Detected		X	X	Х	X	X	X				
		Stained skin/fur - red	Face							Х	X	X	X
	332	No Abnormalities Detected		Х	X	Х	X	X	X	Х	X		
		Stained skin/fur - red	Face									X	X
	333	No Abnormalities Detected											
		Missing	Tip of tail		X	Х	X						
		Stained skin/fur - red	Face	X	X	Х	X	X	X	Х	X	X	X
	334	No Abnormalities Detected		Х	Х	Х	Х	Х	Х				
		Stained skin/fur - red	Face							Х	X	X	X
	335	No Abnormalities Detected				Х	X	X	X	Х	X		
		Stained skin/fur - red	Face	Х	Х							X	X
	336	No Abnormalities Detected						X	X	Х			
			Forelimb bilateral										
		Stained skin/fur - red	Face	Х	Х	Х	Х	•	•		Х	Х	Х

X = Present

Gestation Day

Group	Animal			10	11	12	13	14	15	16	17	18	19	20	21
Sex	Number	Clinical Sign	Site	PM											
3f	325	No Abnormalities Detected						Х	Х	Х	Х	Х	Х	Х	Х
		Stained skin/fur - red	Face	X	X	X	X								
	326	No Abnormalities Detected							X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X							•
	327	No Abnormalities Detected		X											
		Hair loss	Forelimb bilateral		X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face		X	X	X	X	X			X			
	328	No Abnormalities Detected							X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X							•
	329	No Abnormalities Detected							X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X							•
	330	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face												•
	331	No Abnormalities Detected					X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X									
	332	No Abnormalities Detected								X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X	X						
	333	No Abnormalities Detected		X	X	X	X	X	X	X	X				
		Missing	Tip of tail									X	X	X	X
		Stained skin/fur - red	Face												
	334	No Abnormalities Detected						X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X								
	335	No Abnormalities Detected								X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X	X						
	336	No Abnormalities Detected													
		Hair loss	Forelimb bilateral				X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	Χ	Χ	Χ	Х	Χ	Х	Χ	Χ	X	

X = Present

									Ges	tatio	n Day		
Group	Animal			0	1	2	3	4	5	6	7	8	9
Sex	Number	Clinical Sign	Site	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM
4 f	425	Stained skin/fur - red	Face	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Wet fur	Chest										
		Wet fur	Face		X	X	X	X	X	X	X	X	X
	427	No Abnormalities Detected						X	X				
		Stained skin/fur - red	Face	X	X	X				X	X	X	X
		Wet fur	Chest	X	X	X	X				X	X	X
		Wet fur	Chin	X	X	X							
		Wet fur	Face								X	X	X
	428	Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X
		Wet fur	Chest			X	X	X	X	X	X	X	X
		Wet fur	Face			X	X	X	X	X	X	X	X
	429	No Abnormalities Detected					X						
		Hair loss	Forelimb bilateral										
		Stained skin/fur - red	Face	X	X	X		X	X	X	X	X	X
		Wet fur	Chest		•	X				•			
		Wet fur	Chin		•	X				•			
		Wet fur	Face		•					•		X	X
	431	Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X
		Wet fur	Chest		X	X	X	X	X	X	X	X	X
		Wet fur	Chin		X	X	X	X	X	X	X	X	X
	432	No Abnormalities Detected		X	•					•			
		Stained skin/fur - red	Face		X	X	X	X	X	X	X	X	X
		Wet fur	Chest		X	X	X	X	X	X	X	X	X
		Wet fur	Chin										
		Wet fur	Face		X	X	X	X	X	X	X	X	X
		Wet fur	Perineum		X	X	X	X	X	X	X	X	X

X = Present

Gestation Day

Group	Animal			10	11	12	13	14	15	16	17	18	19	20	21
Sex	Number	Clinical Sign	Site	PM											
4 f	425	Stained skin/fur - red	Face	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
4.1	423			Λ									Λ	Λ	Λ
		Wet fur Wet fur	Chest	•	X	X	X	X	X	X	X	X	•	•	•
	407		Face	Х	Χ	Χ	Х	Χ	Χ	Χ	Χ	Χ	•	•	•
	427	No Abnormalities Detected	D	•	•	•	•	•	•	•	•	•	•	•	•
		Stained skin/fur - red	Face	X	X	X	Х	X	X	X	X	X	X	Χ	Χ
		Wet fur	Chest	Χ	Х	Χ	X	Χ	Χ	Χ	Χ	Χ	X	•	•
		Wet fur	Chin	•	•	•	•	•	•	•	•	•	٠	•	•
		Wet fur	Face	X	Х	X	Х	X	Χ	X	Χ	X	Х	•	•
	428	Stained skin/fur - red	Face	X	Х	Х	X	Х	X	X	X	Х	X	X	X
		Wet fur	Chest	Х	Х	X	X	Х	Χ	Х			•	•	•
		Wet fur	Face	X	X	X	X	X	X	X		X	•		•
	429	No Abnormalities Detected													
		Hair loss	Forelimb bilateral				X	X	X	X	X	X	X	X	X
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X			
		Wet fur	Chest												
		Wet fur	Chin												
		Wet fur	Face	X	X	X	X	X	X	X	X	X			
	431	Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	X	X
		Wet fur	Chest	X	X	Х	X	X	X	X	X	Х	X		
		Wet fur	Chin	X	X	Х	Х	Х	X	Х	X	Х			
	432	No Abnormalities Detected													
		Stained skin/fur - red	Face	X	X	Х	X	X	Х	X	Х	Х	Х	X	X
		Wet fur	Chest	Х	Х	Х	Х	Х	Х	Х	Х				
		Wet fur	Chin										X		
		Wet fur	Face	X	X	X	X	X	X	X	X				
		Wet fur	Perineum	X	X	X									
							•	•	-	•	-	-	•	•	•

X = Present

Stained skin/fur - red

Wet fur

Wet fur

Individual Clinical Observations in Satellite Female Rats During Gestation

Χ

Χ

Gestation Day

Χ

Group Sex	Animal Number	Clinical Sign	Site	0 PM	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM
4 f	433	Stained skin/fur - red	Face	X	Х					Х	Х	Х	Х
		Wet fur	Chest	X	X								
		Wet fur	Chin	X	X								
		Wet fur	Face			X	X	X	X	X	X	X	X
	435	No Abnormalities Detected											
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X
		Wet fur	Chest	X						X	X	X	X
		Wet fur	Chin	X						X	X	X	X
	436	No Abnormalities Detected				•			•			•	

X = Present

Nominal Dose: Group 1 - 0 ppm Group 2 - 100 ppm Group 3 - 500 ppm Group 4 - 3000 ppm

Face

Chest

Chin

Gestation Day

Group Sex	Animal Number	Clinical Sign	Site	10 PM	11 PM	12 PM	13 PM	14 PM	15 PM	16 PM	17 PM	18 PM	19 PM	20 PM	21 PM
4 f	433	Stained skin/fur - red	Face	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
		Wet fur	Chest						Х	Х	X	Х	Х		
		Wet fur	Chin												
		Wet fur	Face	X	X	X	X	X	X	X	X	X	X		
	435	No Abnormalities Detected													X
		Stained skin/fur - red	Face	X	X	X	X	X	X	X	X	X	X	X	
		Wet fur	Chest	X	Х	Х	Х	Х	Х	Х	Х	Х			
		Wet fur	Chin												
	436	No Abnormalities Detected												X	X
		Stained skin/fur - red	Face	X	Х	Х	Х	Х	Х	Х	Х	Х	X		
		Wet fur	Chest												
		Wet fur	Chin	X	X	X	X	X	X	X	X	X	X		

X = Present

Appendix N
Individual Clinical Observations and Mortality Data in Satellite Female Rats
During Lactation

Scheduled sacrifice

Individual Clinical Observations and Mortality Data in Satellite Female Rats During Lactation

					Lac	ctation	Day	
Group	Animal			0	1	2	3	4
Sex	Number	Clinical Sign	Site	PM	PM	PM	PM	AM
1f	125	Hair loss	Forelimb bilateral	X	Х	Х	Х	Х
		Scheduled sacrifice						X
	126	Hair loss	Forelimb bilateral	X	X	X	X	X
		Scheduled sacrifice						X
	127	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice						X
	128	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice						X
	129	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice						X
	130	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice						X
	131	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice		•				X
	132	Hair loss	Forelimb bilateral	X	X	X	X	X
		Scheduled sacrifice						X
	133	No Abnormalities Detected		X	X	X	X	X
		Scheduled sacrifice						X
	134	Hair loss	Hind quarters left	X	X	X	X	Х
		Scheduled sacrifice						X
	135	Hair loss	Forelimb bilateral	X	X	X	X	X
		Scheduled sacrifice		•				X
	136	No Abnormalities Detected		X	X	X	X	X

X = Present

Scheduled sacrifice

Individual Clinical Observations and Mortality Data in Satellite Female Rats During Lactation

				Lac	ctation	Day	
Animal	Clinical Sign	Sito	0 DM	1 pm	2 DM	3 DM	4 AM
Number	CIINICAI Sign	2166	E I*I	LIA	L IVI	L Ivi	ΑΨ
225	No Abnormalities Detected		X	X	X	X	Х
	Scheduled sacrifice						X
226	Hair loss	Forelimb bilateral	X	X	X	X	X
	Scheduled sacrifice						X
227	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
228	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
229	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice		•				X
230	Hair loss	Forelimb bilateral	X	X	X	X	X
	Scheduled sacrifice						X
231	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice		•				X
232	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
233	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
234	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
235	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
236	No Abnormalities Detected		X	X	X	X	X
	Number 225 226 227 228 229 230 231 232 233 234 235	Number Clinical Sign 225 No Abnormalities Detected Scheduled sacrifice 226 Hair loss Scheduled sacrifice 227 No Abnormalities Detected Scheduled sacrifice 228 No Abnormalities Detected Scheduled sacrifice 229 No Abnormalities Detected Scheduled sacrifice 230 Hair loss Scheduled sacrifice 231 No Abnormalities Detected Scheduled sacrifice 232 No Abnormalities Detected Scheduled sacrifice 233 No Abnormalities Detected Scheduled sacrifice 234 No Abnormalities Detected Scheduled sacrifice 235 No Abnormalities Detected Scheduled sacrifice 236 No Abnormalities Detected Scheduled sacrifice 237 No Abnormalities Detected Scheduled sacrifice 238 No Abnormalities Detected Scheduled sacrifice	Number Clinical Sign Site 225 No Abnormalities Detected Scheduled sacrifice 226 Hair loss Forelimb bilateral Scheduled sacrifice 227 No Abnormalities Detected Scheduled sacrifice 228 No Abnormalities Detected Scheduled sacrifice 229 No Abnormalities Detected Scheduled sacrifice 230 Hair loss Forelimb bilateral Scheduled sacrifice 231 No Abnormalities Detected Scheduled sacrifice 232 No Abnormalities Detected Scheduled sacrifice 233 No Abnormalities Detected Scheduled sacrifice 234 No Abnormalities Detected Scheduled sacrifice 235 No Abnormalities Detected Scheduled sacrifice 236 No Abnormalities Detected Scheduled sacrifice 237 No Abnormalities Detected Scheduled sacrifice 238 No Abnormalities Detected Scheduled sacrifice 239 No Abnormalities Detected Scheduled sacrifice	Number Clinical Sign Site PM 225 No Abnormalities Detected Scheduled sacrifice . 226 Hair loss Forelimb bilateral X Scheduled sacrifice . 227 No Abnormalities Detected Scheduled sacrifice . 228 No Abnormalities Detected X Scheduled sacrifice . 229 No Abnormalities Detected X Scheduled sacrifice . 229 No Abnormalities Detected X Scheduled sacrifice . 230 Hair loss Forelimb bilateral X Scheduled sacrifice . 231 No Abnormalities Detected X Scheduled sacrifice . 232 No Abnormalities Detected X Scheduled sacrifice . 233 No Abnormalities Detected X Scheduled sacrifice . 234 No Abnormalities Detected X Scheduled sacrifice . 235 No Abnormalities Detected X Scheduled sacrifice . 236 No Abnormalities Detected X Scheduled sacrifice . 237 No Abnormalities Detected X Scheduled sacrifice . 238 No Abnormalities Detected X Scheduled sacrifice . 239 No Abnormalities Detected X X Scheduled sacrifice . 230 No Abnormalities Detected X X Scheduled sacrifice . 231 No Abnormalities Detected X X Scheduled sacrifice .	Animal Number Clinical Sign Site PM PM 225 No Abnormalities Detected Scheduled sacrifice 226 Hair loss Forelimb bilateral X X Scheduled sacrifice 227 No Abnormalities Detected X X X Scheduled sacrifice 228 No Abnormalities Detected X X X Scheduled sacrifice 229 No Abnormalities Detected X X X Scheduled sacrifice 229 No Abnormalities Detected X X X Scheduled sacrifice 230 Hair loss Forelimb bilateral X X Scheduled sacrifice 231 No Abnormalities Detected X X X Scheduled sacrifice 232 No Abnormalities Detected X X X Scheduled sacrifice 233 No Abnormalities Detected X X X Scheduled sacrifice 234 No Abnormalities Detected X X X Scheduled sacrifice 235 No Abnormalities Detected X X X Scheduled sacrifice 236 No Abnormalities Detected X X X Scheduled sacrifice 237 No Abnormalities Detected X X X Scheduled sacrifice 238 No Abnormalities Detected X X X Scheduled sacrifice 239 No Abnormalities Detected X X X Scheduled sacrifice 230 No Abnormalities Detected X X X Scheduled sacrifice 231 No Abnormalities Detected X X X Scheduled sacrifice 232 No Abnormalities Detected X X X Scheduled sacrifice 233 No Abnormalities Detected X X X Scheduled sacrifice 234 No Abnormalities Detected X X X Scheduled sacrifice 235 No Abnormalities Detected X X X Scheduled sacrifice X X X	Animal Number Clinical Sign Site PM PM PM 225 No Abnormalities Detected Scheduled sacrifice 226 Hair loss Forelimb bilateral X X X X Scheduled sacrifice 227 No Abnormalities Detected Scheduled sacrifice 228 No Abnormalities Detected Scheduled sacrifice 229 No Abnormalities Detected Scheduled sacrifice 229 No Abnormalities Detected Scheduled sacrifice 230 Hair loss Forelimb bilateral X X X X Scheduled sacrifice 231 No Abnormalities Detected Scheduled sacrifice 232 No Abnormalities Detected Scheduled sacrifice 233 No Abnormalities Detected Scheduled sacrifice 234 No Abnormalities Detected Scheduled sacrifice 235 No Abnormalities Detected Scheduled sacrifice 236 No Abnormalities Detected Scheduled sacrifice 237 No Abnormalities Detected Scheduled sacrifice Schedule	Number Clinical Sign Site PM PM PM PM PM 225 No Abnormalities Detected X X X X X X X X X X X X X X X X X X X

X = Present

Individual Clinical Observations and Mortality Data in Satellite Female Rats During Lactation

				Lactation Day						
Group Sex	Animal Number	Clinical Sign	Site	0 PM	1 PM	2 PM	3 PM	4 AM		
3f	325	No Abnormalities Detected		X	X	X	X	Х		
31	325	Scheduled sacrifice		X			Λ	X		
	326	No Abnormalities Detected		X	·	X	·	X		
	320	Scheduled sacrifice		Λ	Λ			X		
	327	Hair loss	Forelimb bilateral	· X	×	×	X	X		
	32,	Scheduled sacrifice	rorering brideerar					X		
	328	No Abnormalities Detected		X	X	X	X	X		
		Scheduled sacrifice						X		
	329	No Abnormalities Detected		X	X	X	X	Х		
		Scheduled sacrifice		•				X		
	330	No Abnormalities Detected		X	X	X	X	Х		
		Scheduled sacrifice						X		
	331	No Abnormalities Detected		X	X	X	X	X		
		Scheduled sacrifice		•			•	X		
	332	No Abnormalities Detected		X	X	X	X	X		
		Scheduled sacrifice						X		
	333	Hair loss	Forelimb bilateral	•			•	X		
		Missing	Tip of tail	X	X	X	X	X		
		Scheduled sacrifice		•	•	•	•	Х		
	334	No Abnormalities Detected		X	X	X	Х	Х		
		Scheduled sacrifice		•	•	•	•	Х		
	335	No Abnormalities Detected		X	X	X	X	Х		
	226	Scheduled sacrifice	The condition in 12 and 2	•	•	•	•	X		
	336	Hair loss	Forelimb bilateral	X	X	X	X	X		
		Scheduled sacrifice		•	•	•	•	X		

X = Present

Individual Clinical Observations and Mortality Data in Satellite Female Rats During Lactation

				Lac	ctation	Day	
Animal			0	1	2	3	4
Number	Clinical Sign	Site	PM	PM	PM	PM	AM
425	No Abnormalities Detected		Х	Х	Х	Х	Х
	Scheduled sacrifice						X
426	No Abnormalities Detected				X	X	X
	Scheduled sacrifice						X
	Stained skin/fur - red	Face	X	X			
427	No Abnormalities Detected				X	X	X
	Scheduled sacrifice						X
	Stained skin/fur - red	Face	X	X			
428	No Abnormalities Detected			X	X	X	X
	Scheduled sacrifice						X
	Stained skin/fur - red	Face	X				
429	Hair loss	Forelimb bilateral	X	X	X	X	X
	Scheduled sacrifice						X
431	No Abnormalities Detected				X	X	X
	Scheduled sacrifice						X
	Stained skin/fur - red	Face	X	X			
432	No Abnormalities Detected			X	X	X	X
	Scheduled sacrifice						X
	Stained skin/fur - red	Face	X				
433	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
434	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
435	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice						X
436	No Abnormalities Detected		X	X	X	X	X
	Scheduled sacrifice		•				X
	Number 425 426 427 428 429 431 432 433 434 435	Number Clinical Sign 425 No Abnormalities Detected Scheduled sacrifice 426 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red 427 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red 428 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red 429 Hair loss Scheduled sacrifice 431 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red 432 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red 432 No Abnormalities Detected Scheduled sacrifice 434 No Abnormalities Detected Scheduled sacrifice 435 No Abnormalities Detected Scheduled sacrifice 436 No Abnormalities Detected Scheduled sacrifice	Number Clinical Sign Site 425 No Abnormalities Detected Scheduled sacrifice 426 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red Face 427 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red Face 428 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red Face 429 Hair loss Forelimb bilateral Scheduled sacrifice 431 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red Face 432 No Abnormalities Detected Scheduled sacrifice Stained skin/fur - red Face 433 No Abnormalities Detected Scheduled sacrifice 434 No Abnormalities Detected Scheduled sacrifice 435 No Abnormalities Detected Scheduled sacrifice 436 No Abnormalities Detected Scheduled sacrifice 437 No Abnormalities Detected Scheduled sacrifice	Number Clinical Sign Site PM 425 No Abnormalities Detected Scheduled sacrifice	Animal Number Clinical Sign Site PM PM 425 No Abnormalities Detected X X X Scheduled sacrifice	Animal Number Clinical Sign Site PM PM PM PM	Number Clinical Sign Site PM PM PM PM PM 425 No Abnormalities Detected X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X

X = Present

DuPont-18331

Appendix O Individual Weekly Detailed Clinical Observations in Satellite Female Rats

							Tes	t Day			
Group Sex	Animal Number	Clinical Sign	Site	1 AM	8 AM	15 AM	22 AM	29 AM	36 AM	43 AM	50 AM
1f	125	No Abnormalities Detected		Х	Х	Х	Х	X			
		Hair loss	Forelimb bilateral						X	X	
	126	No Abnormalities Detected		X							
		Hair loss	Forelimb bilateral		X	X	X	X	X	X	
	127	No Abnormalities Detected		X	X	X	X	X	X	X	
	128	No Abnormalities Detected		X	X	X	X	X	X	X	
	129	No Abnormalities Detected		X	X	X	X	X	X	X	
	130	No Abnormalities Detected		X	X	X	X	X	X	X	
	131	No Abnormalities Detected		X	X	X	X	X	X		
	132	No Abnormalities Detected		X	X	X					
		Hair loss	Forelimb bilateral	•			X	X	X	X	
	133	No Abnormalities Detected		X	X	X	X	X	X	X	
	134	No Abnormalities Detected		X	X	X	X	X			
		Hair loss	Forelimb bilateral						X		
		Hair loss	Hind quarters left						X	X	
	135	No Abnormalities Detected		X	X	X	X	X			
		Hair loss	Forelimb bilateral						X	X	
	136	No Abnormalities Detected		X	X	X	X	Х	X	X	

X = Present

							Tes	t Day			
Group Sex	Animal Number	Clinical Sign	Site	1 AM	8 AM	15 AM	22 AM	29 AM	36 AM	43 AM	50 AM
2f	225	No Abnormalities Detected		Х	X	X	Х	X	Х	Х	
	226	No Abnormalities Detected		X	X	X	X	X			
		Hair loss	Forelimb bilateral						X	X	
	227	No Abnormalities Detected		X	X	X	X	X	X	X	
	228	No Abnormalities Detected		X	X	X	X	X	X	X	
	229	No Abnormalities Detected		X	X	X	X	X	X	X	
	230	No Abnormalities Detected		X	X	X					
		Hair loss	Forelimb bilateral				X	X	X	X	
	231	No Abnormalities Detected		X	X	X	X	X	X	X	
	232	No Abnormalities Detected		X	X	X	X	X	X	X	
	233	No Abnormalities Detected		X	X	X	X	X	X	X	
	234	No Abnormalities Detected		X	X	X	X	X	X	X	
	235	No Abnormalities Detected		X	X	X	X	X	X	X	
	236	No Abnormalities Detected		X	Χ	X	X	X	Х	Χ	•

X = Present

							Tes	t Day			
Group Sex	Animal Number	Clinical Sign	Site	1 AM	8 AM	15 AM	22 AM	29 AM	36 AM	43 AM	50 AM
3f	325	No Abnormalities Detected		X	Х	Х	Х	Х	Х	X	
	326	No Abnormalities Detected		X	X	X	X	X	X	X	
	327	No Abnormalities Detected		X	X						
		Hair loss	Forelimb bilateral					X	X	X	
		Stained skin/fur - red	Face			Х	X	X	X		
	328	No Abnormalities Detected		X	X	X	X	X	X	X	
	329	No Abnormalities Detected		X	X	Х	X	X	X	X	
	330	No Abnormalities Detected		X	X	X	X	X	X	X	
	331	No Abnormalities Detected		X	X	X	X	X	X	X	
	332	No Abnormalities Detected		X	X	X	X	X	X	X	
	333	No Abnormalities Detected		X	X	X	X	X			
		Hair loss	Forelimb bilateral							X	
		Missing	Tip of tail						X	X	
	334	No Abnormalities Detected		X	X	X	X	X	X	X	
	335	No Abnormalities Detected		X	X	X	X	X	X	X	
	336	No Abnormalities Detected		X	X		X				
		Hair loss	Forelimb bilateral					X	X		
		Stained skin/fur - red	Face		_	X			_		

X = Present

						Tes	t Day			
Group Sex	Animal Number	Clinical Sign Sit	te 1	8 AM	15 AM	22 AM	29 AM	36 AM	43 AM	50 AM
1.5	425	No Aboromolitica Detected	V	7.7	77		37	37	v	
4 f	425	No Abnormalities Detected	X	X	X	•	X	Х	X	•
		Stained skin/fur - red Fac		•	•	X	•	•	•	•
	426	No Abnormalities Detected	X	X	•	•	X	X	•	•
		Stained skin/fur - red Fac			X	X			•	•
	427	No Abnormalities Detected	X	X			X	X	X	
		Stained skin/fur - red Fac	ce .		X	X				
	428	No Abnormalities Detected	X				X	X	X	
		Stained skin/fur - red Fac	ce .	X	X	X				
	429	No Abnormalities Detected	X	X						
		Hair loss For	relimb bilateral .				X	X		
		Stained skin/fur - red Fac	ce .		Х	Х				
	430	No Abnormalities Detected	X	X		X	X	X	X	Х
		Stained skin/fur - red Fac		-	X					
	431	No Abnormalities Detected	X	X	X	X	X	X	•	
	432	No Abnormalities Detected	X	X	X	X	X	X	X	•
	433	No Abnormalities Detected	X	X		21	27	21	X	•
	400	Stained skin/fur - red Fac			X	·	·	·		•
	434	No Abnormalities Detected	X	·	X	X	X	X	·	•
					Χ	X	Λ	Λ		•
	435	No Abnormalities Detected	X	X	•	•	•	•	X	•
		Stained skin/fur - red Fac		•	X	X	X	X	•	•
	436	No Abnormalities Detected	X	X	•	•		•	X	
		Stained skin/fur - red Fac	ce .		X	X	X	X		

X = Present

Appendix P Individual Body Weights of Subchronic Male Rats

Individual Body Weights (grams) of Subchronic Male Rats

Cmain	Animal	Test Day								
Group Sex	Number	1	8	15	22	29	31			
1m	101 102 103 104 105 106 107 108 109 110 111	296.6 290.7 313.7 312.5 284.4 309.8 304.9 300.6 298.6 312.4 267.5 320.2	354.0 340.0 358.7 372.3 324.6 373.7 328.7 348.3 329.9 353.8 292.1 364.3	397.6 381.4 403.8 426.3 356.4 421.6 348.3 400.6 343.2 387.9 315.8 391.4	427.9 398.7 409.5 469.6 366.8 447.5 382.0 433.4 364.2 403.8 341.0 423.4	463.5 443.2 442.4 512.3 382.3 475.6 389.2 447.6 394.1 427.1 369.2 458.1	440.8 410.8 416.0 476.1 356.4 450.0 376.1 433.0 370.0 398.8 341.7 427.5			
	Mean S.D. N	300.99 14.81 12	345.03 23.42 12	381.19 33.56 12	405.65 37.48 12	433.72 42.82 12	408.10 40.63 12			

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Male Rats

Croun	Animal			Test	Day		
Group Sex	Number	1	8	15	22	29	31
2m	201 202 203 204 205 206 207 208 209 210 211 212	289.2 308.2 326.2 294.6 290.7 288.3 288.5 283.0 294.3 277.1 310.4	325.5 354.1 383.2 340.2 344.5 323.2 341.2 334.9 333.4 295.1 361.7	355.5 384.6 425.1 367.1 368.7 363.7 361.6 367.8 316.9 399.6	386.9 415.3 453.8 388.3 431.3 393.5 357.7 394.1 387.4 338.4 426.6	411.3 431.4 475.4 421.5 470.0 420.6 374.4 409.2 420.1 424.9 360.0 451.7	381.0 403.3 439.5 393.2 439.9 392.9 359.0 389.7 391.1 391.5 336.2 422.2
	Mean S.D. N	295.54 13.44 12	341.03 22.07 12	369.64 29.49 12	396.93 31.53 12	422.54 33.74 12	394.96 29.87 12

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Male Rats

C	7 7			Test	Day		
Group Sex	Animal Number	1	8	15	22	29	31
3m	301 302 303 304 305 306 307 308 309 310 311 312	265.4 303.4 292.0 297.2 300.9 301.3 295.3 291.9 317.9 313.3 288.1 256.7	297.1 327.7 333.2 350.6 2350.6 229.2 338.3 327.2 386.1 370.5 319.4 264.9	336.5 361.7 360.9 393.2 2359.7 373.0 349.5 418.8 416.2 355.6 282.5	362.5 368.9 389.8 416.0 3181.0 399.8 384.7 4427.6 385.9 304.5	407.8 408.9 421.1 450.6 323.4 417.9 441.1 400.8 474.8 469.7 416.6 330.1	372.1 380.5 393.4 409.6 297.1 385.5 410.1 381.2 445.2 445.2 397.7 309.2
	Mean S.D. N	293.62 17.57 12	326.30 35.68 12	358.24 41.85 12	381.64 42.23 12	413.57 47.13 12	384.63 43.86 12

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Male Rats

C	7 7			Test	Day		
Group Sex	Animal Number	1	8	15	22	29	31
4m	401 402 403 404 405 406 407 408 409 410 411 412	277.7 293.5 293.2 302.2 280.6 299.8 309.5 333.3 311.7 306.9 295.6 308.3	298.9 333.8 325.8 333.2 305.3 328.8 339.0 362.0 357.0 340.5 327.1	326.3 364.5 360.5 374.1 354.2 368.3 393.6 387.0 359.9 354.6	350.6 385.0 384.8 400.3 379.5 387.9 422.5 407.7 416.7 376.3 394.5	371.4 403.6 399.9 434.6 361.7 409.8 405.6 460.9 445.2 438.0 407.3 426.0	343.0 393.7 375.0 395.3 331.3 369.6 383.1 429.1 411.2 409.0 381.2 391.3
	Mean S.D. N	301.03 14.85 12	332.98 18.27 12	363.40 20.77 12	387.23 24.17 12	413.67 29.09 12	384.40 27.68 12

^{* =} Result to left has an associated comment or marker

Appendix Q Individual Body Weight Gains of Subchronic Male Rats

Individual Body Weight Gains (grams) of Subchronic Male Rats

		Y								
		Base Weight	_			4.5		2.2	Abs Gain	% Gain
Group	Animal	Day	From:	1	8	15	22	29	1	Τ
Sex	Number	1	To:	8	15	22	29	31	31	31
1m	101	296.6		57.4	43.6	30.3	35.6	-22.7	144.2	48.618
	102	290.7		49.3	41.4	17.3	44.5	-32.4	120.1	41.314
	103	313.7		45.0	45.1	5.7	32.9	-26.4	102.3	32.611
	104	312.5		59.8	54.0	43.3	42.7	-36.2	163.6	52.352
	105	284.4		40.2	31.8	10.4	15.5	-25.9	72.0	25.316
	106	309.8		63.9	47.9	25.9	28.1	-25.6	140.2	45.255
	107	304.9		23.8	19.6	33.7	7.2	-13.1	71.2	23.352
	108	300.6		47.7	52.3	32.8	14.2	-14.6	132.4	44.045
	109	298.6		31.3	13.3	21.0	29.9	-24.1	71.4	23.912
	110	312.4		41.4	34.1	15.9	23.3	-28.3	86.4	27.657
	111	267.5		24.6	23.7	25.2	28.2	-27.5	74.2	27.738
	112	320.2		44.1	27.1	32.0	34.7	-30.6	107.3	33.510
	Mean	300.99		44.04	36.16	24.46	28.07	-25.62	107.11	35.473
	S.D.	14.81		12.92	13.27	10.83	11.36	6.63	32.76	10.347
	N	12		12	12	12	12	12	12	12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Subchronic Male Rats

				Test Day									
Group	Animal	Base Weight Day	From:	1	8	15	22	29	Abs Gain 1	% Gain 1 31			
Sex	Number	1	To:	8	15	22	29	31	31	31			
2m	201 202	289.2 308.2		36.3 45.9	30.0 30.5	31.4 30.7	24.4 16.1	-30.3 -28.1	91.8 95.1	31.743 30.857			
	203	326.2		57.0	41.9	28.7	21.6	-35.9	113.3	34.733			
	204	294.6		45.6	26.9	21.2	33.2	-28.3	98.6	33.469			
	205	296.0		59.3	43.4	32.6	38.7	-30.1	143.9	48.615			
	206	290.7		53.8	24.2	24.8	27.1	-27.7	102.2	35.157			
	207	288.3		34.9	10.5	24.0	16.7	-15.4	70.7	24.523			
	208	288.5		52.7	20.4	32.5	15.1	-19.5	101.2	35.078			
	209	283.0		51.9	32.9	20.0	32.3	-29.0	108.1	38.198			
	210	294.3		39.1	23.0	33.0	35.5	-33.4	97.2	33.028			
	211	277.1		18.0	21.8	21.5	21.6	-23.8	59.1	21.328			
	212	310.4		51.3	37.9	27.0	25.1	-29.5	111.8	36.018			
	Mean	295.54		45.48	28.62	27.28	25.62	-27.58	99.42	33.562			
	S.D.	13.44		11.73	9.54	4.86	7.91	5.65	21.20	6.760			
	N	12		12	12	12	12	12	12	12			

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Subchronic Male Rats

							Test Day	•			
Group	Base Weight Animal Day From:			1	8	15	22	29	Abs Gain 1	% Gain 1	
Sex	Number	1	To:	8	15	22	29	31	31	31	
3m	301 302 303 304 305 306 307 308 309 310 311 312	265.4 303.4 292.0 297.2 300.9 301.3 295.3 291.9 317.9 313.3 288.1 256.7		31.7 24.3 41.2 53.4 -29.5 27.9 43.0 35.3 68.2 57.2 31.3 8.2	39.4 34.0 27.7 42.6 19.9 30.5 34.7 22.3 32.7 45.7 36.2 17.6	26.0 7.2 28.9 22.8 19.6 21.3 26.8 35.2 29.3 11.4 30.3 22.0	45.3 40.0 31.3 34.6 12.5 36.9 41.3 16.1 26.7 42.1 30.7 25.6	-35.7 -28.4 -27.7 -41.0 -26.3 -32.4 -31.0 -19.6 -29.6 -35.7 -18.9 -20.9	106.7 77.1 101.4 112.4 -3.8 84.2 114.8 89.3 127.3 120.7 109.6 52.5	40.203 25.412 34.726 37.820 -1.263 27.946 38.876 30.593 40.044 38.525 38.042 20.452	
	Mean S.D.	293.62 17.57		32.68 25.30	31.94 8.80	23.40 7.96	31.93 10.29	-28.93 6.84	91.02 36.48	30.948 12.015	
	N	12		12	12	12	12	12	12	12	

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Subchronic Male Rats

				Test Day										
		Base Weight							Abs Gain	% Gain				
Group	Animal	Day	From:	1	8	15	22	29	1	1				
Sex	Number	1	To:	8	15	22	29	31	31	31				
4m	401	277.7		21.2	27.4	24.3	20.8	-28.4	65.3	23.515				
	402	293.5		40.3	30.7	20.5	18.6	-9.9	100.2	34.140				
	403	293.2		32.6	34.7	24.3	15.1	-24.9	81.8	27.899				
	404	302.2		31.0	40.9	26.2	34.3	-39.3	93.1	30.807				
	405	280.6		24.7	25.9	9.8	20.7	-30.4	50.7	18.068				
	406	299.8		29.0	25.4	25.3	30.3	-40.2	69.8	23.282				
	407	309.5		29.5	29.3	19.6	17.7	-22.5	73.6	23.780				
	408	333.3		28.7	31.6	28.9	38.4	-31.8	95.8	28.743				
	409	311.7		45.3	30.6	20.1	37.5	-34.0	99.5	31.922				
	410	306.9		37.4	41.7	30.7	21.3	-29.0	102.1	33.268				
	411	295.6		44.9	19.4	16.4	31.0	-26.1	85.6	28.958				
	412	308.3		18.8	27.5	39.9	31.5	-34.7	83.0	26.922				
	Mean	301.02		31.95	30.43	23.83	26.43	-29.27	83.38	27.609				
	S.D.	14.85		8.60	6.35	7.59	8.24	8.15	16.02	4.751				
	N	12		12	12	12	12	12	12	12				

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Appendix R Individual Body Weights of Subchronic Female Rats

Individual Body Weights (grams) of Subchronic Female Rats

				Test	Day		
Group Sex	Animal Number	1	8	15	22	29	32
1f	113 114 115 116 117 118 119 120 121 122 123 124	218.0 240.9 202.7 190.9 220.7 207.0 223.4 221.1 217.4 225.2 225.4 229.0	227.1 257.3 215.2 195.8 245.3 223.8 245.6 244.5 233.9 253.8 242.6	236.9 276.6 224.8 208.5 250.6 222.6 256.4 250.3 240.9 247.6 255.0 248.8	245.0 285.4 233.9 222.6 278.0 229.2 274.2 270.8 251.9 251.9 280.7 266.2	255.8 307.0 249.0 227.9 280.5 238.4 278.7 281.7 264.5 273.6 288.5 288.7	239.9 280.3 229.4 211.7 267.0 219.6 264.9 265.2 246.2 250.2 274.6 265.5
	Mean S.D. N	218.48 13.09 12	235.93 17.72 12	243.25 18.08 12	258.09 21.39 12	269.53 23.04 12	251.21 22.20 12

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Female Rats

				Test	Day		
Group Sex	Animal Number	1	8	15	22	29	32
2f	213 214 215 216 217 218 219 220 221 222 223 224	213.0 211.0 207.7 224.3 221.6 223.2 203.1 228.2 218.1 220.0 210.3	217.4 222.1 228.0 238.1 236.4 237.5 218.9 250.3 230.1 240.2 235.1 225.1	217.0 239.6 231.1 240.5 240.9 228.5 277.4 233.5 254.7 225.4 255.7	217.9 254.9 227.6 259.9 259.2 271.0 233.7 286.1 250.0 254.1 276.1 232.1	228.5 271.6 247.3 276.5 263.9 278.0 243.5 292.8 263.8 276.8 247.4	212.9 250.0 226.9 257.2 247.8 255.7 226.1 279.7 243.4 255.7 271.1 232.3
	Mean S.D. N	216.80 7.64 12	231.60 9.75 12	241.73 16.46 12	251.88 20.72 12	263.72 18.46 12	246.57 19.41 12

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Female Rats

					Test	Day		
	oup Sex	Animal Number	1	8	15	22	29	32
3f		313 314 315 316 317 318 319 320 321 322 323 324	210.5 213.9 212.2 211.4 201.2 220.3 208.3 224.5 218.1 229.7 233.3 232.6	232.9 226.0 221.1 224.0 216.1 239.1 223.7 258.4 242.0 248.7 259.9	235.1 229.3 237.0 232.5 218.3 248.4 225.7 272.8 243.0 247.2 276.2 272.8	249.1 228.2 240.5 238.8 227.4 271.1 239.5 288.7 260.6 261.9 281.2 274.1	257.0 237.1 247.6 248.8 221.4 281.1 251.8 307.9 273.4 274.7 301.5 297.6	242.3 218.3 234.4 233.1 205.7 263.4 233.2 293.0 255.0 249.7 275.5 274.4
		Mean S.D.	218.00 10.26	236.03 14.53	244.86 19.52	255.09 20.79	266.66 27.15	248.17 25.40

^{* =} Result to left has an associated comment or marker

Individual Body Weights (grams) of Subchronic Female Rats

				Test	Day		
Group Sex	Animal Number	1	8	15	22	29	32
4f	413 414 415 416 417 418 419 420 421 422 423 424	207.6 212.6 215.9 239.9 221.4 216.2 204.7 207.7 211.7 207.9 227.8	210.5 218.7 216.2 257.0 220.6 240.4 205.0 205.9 207.6 217.4 208.2 235.6	220.2 233.9 223.4 268.0 232.7 246.1 212.5 209.6 214.6 236.3 224.6 237.6	227.2 247.3 276.1 242.5 236.9 216.9 223.1 229.1 249.6 232.1 265.2	234.7 268.3 248.4 281.5 243.2 271.2 213.2 222.3 234.0 248.7 231.7 280.5	219.1 247.5 223.3 258.8 228.7 255.8 196.1 206.6 215.5 213.8 233.4
	Mean S.D.	214.88 10.47	220.26 16.12	229.96 16.38	241.41 17.70	248.14 22.69	229.52 20.89

^{* =} Result to left has an associated comment or marker

Appendix S Individual Body Weight Gains of Subchronic Female Rats 12

Individual Body Weight Gains (grams) of Subchronic Female Rats

			Test Day									
		Base Weight			Abs Gain	% Gain						
Group	Animal	Day	From:	1	8	15	22	29	1	1		
Sex	Number	1	To:	8	15	22	29	32	32	32		
1f	113	218.0		9.1	9.8	8.1	10.8	-15.9	21.9	10.046		
	114	240.9		16.4	19.3	8.8	21.6	-26.7	39.4	16.355		
	115	202.7		12.5	9.6	9.1	15.1	-19.6	26.7	13.172		
	116	190.9		4.9	12.7	14.1	5.3	-16.2	20.8	10.896		
	117	220.7		24.6	5.3	27.4	2.5	-13.5	46.3	20.979		
	118	207.0		16.8	-1.2	6.6	9.2	-18.8	12.6	6.087		
	119	223.4		22.2	10.8	17.8	4.5	-13.8	41.5	18.577		
	120	221.1		23.4	5.8	20.5	10.9	-16.5	44.1	19.946		
	121	217.4		16.5	7.0	11.0	12.6	-18.3	28.8	13.247		
	122	225.2		21.1	1.3	11.6	14.4	-23.4	25.0	11.101		
	123	225.4		28.4	1.2	25.7	7.8	-13.9	49.2	21.828		
	124	229.0		13.6	6.2	17.4	22.5	-23.2	36.5	15.939		
	Mean	218.47		17.46	7.32	14.84	11.43	-18.32	32.73	14.848		
	S.D.	13.09		6.82	5.64	6.95	6.28	4.25	11.66	4.904		

12

12

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12

12

12

Nominal Dose: Group 1 - 0 ppm Group 2 - 100 ppm Group 3 - 500 ppm Group 4 - 3000 ppm

12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Subchronic Female Rats

	Test	Day	
e			Abs

Group Sex	Animal Number	Base Weight Day 1	From: To:	1 8	8 15	15 22	22 29	29 32	Abs Gain 1 32	% Gain 1 32
2f	213	213.0		4.4	-0.4	0.9	10.6	-15.6	-0.1	-0.047
	214	211.0		11.1	17.5	15.3	16.7	-21.6	39.0	18.483
	215	207.7		20.3	3.1	-3.5	19.7	-20.4	19.2	9.244
	216	224.3		13.8	2.4	19.4	16.6	-19.3	32.9	14.668
	217	221.6		14.8	10.0	12.8	4.7	-16.1	26.2	11.823
	218	223.2		14.3	13.4	20.1	7.0	-22.3	32.5	14.561
	219	203.1		15.8	9.6	5.2	9.8	-17.4	23.0	11.324
	220	228.2		22.1	27.1	8.7	6.7	-13.1	51.5	22.568
	221	218.1		12.0	3.4	16.5	13.8	-20.4	25.3	11.600
	222	221.1		19.1	14.5	-0.6	20.4	-18.8	34.6	15.649
	223	220.0		15.1	-9.7	50.7	0.7	-5.7	51.1	23.227
	224	210.3		14.8	30.6	-23.6	15.3	-15.1	22.0	10.461
	Mean	216.80		14.80	10.13	10.16	11.83	-17.15	29.77	13.630
	S.D.	7.64		4.61	11.48	17.72	6.24	4.57	14.13	6.257
	S.D. N	12		12	12.40	17.72	12	12	14.13	12
		12		12	12	12	12	12	12	12

Abs Gain = absolute bodyweight gain between base period and end of the analysis period <math>% Gain = percentage bodyweight gain between base period and end of the analysis period

 $[\]star$ = result to left has an associated comment or marker

Individual Body Weight Gains (grams) of Subchronic Female Rats

				Test Day									
		Base Weight							Abs Gain	% Gain			
Group	Animal	Day	From:	1	8	15	22	29	1	1			
Sex	Number	1	To:	8	15	22	29	32	32	32			
3f	313	210.5		22.4	2.2	14.0	7.9	-14.7	31.8	15.107			
	314	213.9		12.1	3.3	-1.1	8.9	-18.8	4.4	2.057			
	315	212.2		8.9	15.9	3.5	7.1	-13.2	22.2	10.462			
	316	211.4		12.6	8.5	6.3	10.0	-15.7	21.7	10.265			
	317	201.2		14.9	2.2	9.1	-6.0	-15.7	4.5	2.237			
	318	220.3		18.8	9.3	22.7	10.0	-17.7	43.1	19.564			
	319	208.3		15.4	2.0	13.8	12.3	-18.6	24.9	11.954			
	320	224.5		33.9	14.4	15.9	19.2	-14.9	68.5	30.512			
	321	218.1		23.9	1.0	17.6	12.8	-18.4	36.9	16.919			
	322	229.7		10.8	6.7	14.7	12.8	-25.0	20.0	8.707			
	323	233.3		15.4	27.5	5.0	20.3	-26.0	42.2	18.088			
	324	232.6		27.3	12.9	1.3	23.5	-23.2	41.8	17.971			
	Mean	218.00		18.03	8.83	10.23	11.57	-18.49	30.17	13.654			
	S.D.	10.26		7.48	7.85	7.30	7.60	4.18	17.97	7.886			
	з.D. N	10.26		12	12	12	12	12					
		14		14	12	12	12	12	12	12			

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

421

422

423

424

-----Mean

S.D.

Ν

211.7

205.1

207.9

227.8

214.87

10.47

12

1.795

24.622

2.838

2.458

6.821

8.546

12

Individual Body Weight Gains (grams) of Subchronic Female Rats

Test Day

4.9

5.1

-0.4

15.3

6.73

15.91

12

-18.5

-17.9

-47.1

-18.63

12

11.96

6.9

3.8

50.5

5.9

5.6

14.64

17.88

12

		Base Weight							Abs Gain	% Gain
Group	Animal	Day	From:	1	8	15	22	29	1	1
Sex	Number	1	To:	8	15	22	29	32	32	32
4 f	413	207.6		2.9	9.7	7.0	7.5	-15.6	11.5	5.539
	414	212.6		6.1	15.2	13.4	21.0	-20.8	34.9	16.416
	415	215.9		0.3	7.2	52.7	-27.7	-25.1	7.4	3.428
	416	239.9		17.1	11.0	-25.5	39.0	-22.7	18.9	7.878
	417	221.4		-0.8	12.1	4.2	6.3	-14.5	7.3	3.297
	418	216.2		24.2	5.7	10.8	14.3	-15.4	39.6	18.316
	419	204.7		0.3	7.5	4.4	-3.7	-17.1	-8.6	-4.201
	420	207.7		-1.8	3.7	13.5	-0.8	-15.7	-1.1	-0.530

7.0

18.9

16.4

2.0

9.70

5.20

12

-4.1

12.3

0.3

7.8

5.38

8.58

12

14.5

7.3

7.5

27.6

11.45

17.84

12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Appendix T Individual Body Weights of Satellite Female Rats During Premating

		1	Test Day	
Group Sex	Animal Number	1	8	15
1f	125 126 127 128 129 130 131 132 133 134 135	227.0 215.2 207.7 233.5 233.6 216.7 204.9 220.9 219.5 217.1 226.1	248.3 239.1 220.0 250.0 252.8 226.9 217.4 241.3 247.4 247.4 234.7 245.4	257.7 245.6 229.4 261.2 256.8 234.9 221.8 255.7 258.2 229.9 258.0
	Mean S.D. N	219.06 9.76 12	236.02 14.48 12	

^{* =} Result to left has an associated comment or marker

			Test Day	
Group Sex	Animal Number	1	8	15
2f	225 226 227 228 229 230 231 232 233 234 235 236	215.3 205.2 240.3 212.1 240.4 225.4 242.6 205.2 212.3 114.5 215.7	232.4 221.0 260.5 234.6 252.4 242.1 264.1 237.0 222.3 211.9 240.9 224.6	247.7 215.2 270.2 245.3 264.7 281.3 254.6 229.1 221.3 258.8 241.8
	Mean S.D. N	218.82 15.14 12	236.98 16.09 12	248.94 19.91 12

^{* =} Result to left has an associated comment or marker

			Test Day	
Group Sex	Animal Number	1	8	15
3f	325 326 327 328 329 330 331 332 333 334 335 336	199.8 236.9 225.8 203.6 220.3 221.2 207.9 213.9 190.3 224.8 214.5	215.9 255.5 241.2 231.9 246.5 252.7 220.7 224.2 2314.6 249.2 224.0	218.5 255.8 254.4 246.3 257.5 232.8 235.1 259.4 262.0 234.5
	Mean S.D. N	215.44 13.17 12	234.39 14.57 12	

^{* =} Result to left has an associated comment or marker

			Test Day	
Group Sex	Animal Number	1	8	15
4f	425 426 427 428 429 430 431 432 433 434 435	228.4 225.9 215.4 216.6 216.8 204.6 202.8 247.9 204.7 187.0 233.6 228.8	239.7 242.6 234.2 237.1 237.3 219.7 216.0 251.3 210.2 200.8 239.9 239.9	240.6 242.0 252.0 240.6 238.0 232.4 227.3 251.4 213.0 210.8 239.3 247.1
	Mean S.D. N	217.71 16.47 12	230.31 15.15 12	

^{* =} Result to left has an associated comment or marker

DuPont-18331

Appendix U Individual Body Weight Gains of Satellite Female Rats During Premating

Individual Body Weight Gains (grams) of Satellite Female Rats During Premating

					Te	st Day	
		Base Weight				Abs Gain	% Gain
Group	Animal	Day	From:	1	8	1	1
Sex	Number	1	To:	8	15	15	15
1f	125	227.0		21.3	9.4	30.7	13.524
	126	215.2		23.9	6.5	30.4	14.126
	127	207.7		12.3	9.4	21.7	10.448
	128	233.5		16.5	11.2	27.7	11.863
	129	233.6		19.2	4.0	23.2	9.932
	130	216.7		10.2	8.0	18.2	8.399
	131	204.9		12.5	4.4	16.9	8.248
	132	220.9		20.4	14.4	34.8	15.754
	133	219.5		27.9	10.8	38.7	17.631
	134	206.5		2.4	23.6	26.0	12.591
	135	217.1		17.6	-4.8	12.8	5.896
	136	226.1		19.3	12.6	31.9	14.109
	Mean	219.06		16.96	9.13	26.08	11.877
	S.D.	9.76		6.80	6.79	7.76	3.415
	N	12		12	12	12	12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Satellite Female Rats During Premating

					Te	st Day	
		Base Weight				Abs Gain	% Gain
Group	Animal	Day	From:	1	8	1	1
Sex	Number	1	To:	8	15	15	15
2f	225	215.3		17.1	15.3	32.4	15.049
	226	205.2		15.8	-5.8	10.0	4.873
	227	240.3		20.2	9.7	29.9	12.443
	228	212.1		22.5	10.7	33.2	15.653
	229	240.4		12.0	14.9	26.9	11.190
	230	225.4		16.7	12.6	29.3	12.999
	231	242.6		21.5	17.2	38.7	15.952
	232	205.2		31.8	17.6	49.4	24.074
	233	212.3		10.0	6.8	16.8	7.913
	234	196.8		15.1	9.4	24.5	12.449
	235	214.5		26.4	17.9	44.3	20.653
	236	215.7		8.9	17.2	26.1	12.100
	Mean	218.82		18.17	11.96	30.13	13.779
	S.D.	15.14		6.72	6.73	10.88	5.139
	N	12		12	12	12	12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

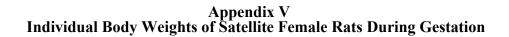
Individual Body Weight Gains (grams) of Satellite Female Rats During Premating

					Te	st Day	
		Base Weight				Abs Gain	% Gain
Group	Animal	Day	From:	1	8	1	1
Sex	Number	1	To:	8	15	15	15
3f	325	199.8		16.1	2.6	18.7	9.359
	326	236.9		18.6	0.3	18.9	7.978
	327	225.8		15.4	13.2	28.6	12.666
	328	203.6		28.3	14.4	42.7	20.972
	329	220.3		26.2	8.5	34.7	15.751
	330	226.3		26.4	4.8	31.2	13.787
	331	221.2		-0.5	12.1	11.6	5.244
	332	207.9		16.3	10.9	27.2	13.083
	333	213.9		22.4	17.1	39.5	18.467
	334	190.3		24.3	-5.2	19.1	10.037
	335	224.8		24.4	12.8	37.2	16.548
	336	214.5		9.5	10.5	20.0	9.324
	Mean	215.44		18.95	8.50	27.45	12.768
	S.D.	13.17		8.32	6.57	9.85	4.618
	N	12		12	12	12	12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

					Te	st Day	
		Base Weight				Abs Gain	% Gain
Group	Animal	Day	From:	1	8	1	1
Sex	Number	1	To:	8	15	15	15
4 f	425	228.4		11.3	0.9	12.2	5.342
	426	225.9		16.7	-0.6	16.1	7.127
	427	215.4		18.8	17.8	36.6	16.992
	428	216.6		15.5	8.5	24.0	11.080
	429	216.8		20.5	0.7	21.2	9.779
	430	204.6		15.1	12.7	27.8	13.587
	431	202.8		13.2	11.3	24.5	12.081
	432	247.9		3.4	0.1	3.5	1.412
	433	204.7		5.5	2.8	8.3	4.055
	434	187.0		13.8	10.0	23.8	12.727
	435	233.6		6.3	-0.6	5.7	2.440
	436	228.8		11.1	7.2	18.3	7.998
	Mean	217.71		12.60	5.90	18.50	8.718
	S.D.	16.47		5.33	6.19	9.79	4.817
	N	12		12	12	12	12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period



Note: This appendix contains data from animals with confirmed mating.

Gestation	Day
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Group Sex	Animal Number	Pregnancy Outcome	0	7	14	21
1f	125 126 127 128 129 130 131 132 133 134 135	PL	268.0 258.6 240.4 272.1 265.1 245.5 225.0 255.5 268.3 226.0 273.9	307.0 299.2 269.3 301.5 291.4 285.9 252.8 296.0 304.1 266.2 311.8	368.4 333.6 313.1 333.2 330.0 314.0 279.7 346.0 352.7 352.7 294.9 352.0	474.4 409.4 423.1 443.6 423.7 402.4 362.2 448.1 454.8 391.9 449.9
	Mean S.D.		252.88 17.71	287.34 19.69	326.48 26.62	424.07 31.63

^{* =} Result to left has an associated comment or marker

[#] = Animal not pregnant and has been excluded from statistics PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

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Group Sex	Animal Number	Pregnancy Outcome	0	7	14	21
2f	225 226 227 228 229 230 231 232 233 234 235 236	PL	252.4 226.0 261.4 251.1 268.2 286.9 256.8 236.9 225.3 263.5 241.0	282.6 248.5 320.1 291.6 304.7 318.5 305.5 263.5 259.7 304.6 266.1	328.0 276.5 358.5 336.9 339.9 358.9 359.0 306.8 299.0 334.0 314.2	337.4a 357.0 477.8 450.6 434.0 440.5 449.5 449.5 449.6 383.1 434.4 419.8
	Mean S.D. N		252.78 17.76 12	290.68 25.98 12	329.70 26.08 12	426.24 33.98 11

a Delivery occurred on GD21 before GD 21 data could be collected; excluded from statistics.

^{* =} Result to left has an associated comment or marker

^{# =} Animal not pregnant and has been excluded from statistics
PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

		Gestation Day					
Group Sex	Animal Number	Pregnancy Outcome	0	7	14	21	
3f	325 326 327 328 329 330 331 332 333 334 335 336	PL PL PL PL PL PL PL PL PL	239.0 256.4 263.6 246.5 258.2 242.3 238.8 253.4 264.9 240.7	273.4 319.0 306.2 281.0 292.8 305.8 281.6 250.3 299.8 299.8 302.1 275.9	311.8 379.5 342.4 333.4 336.2 343.6 317.3 299.0 340.4 290.1 344.5 309.9	406.9 480.1 452.1 439.3 425.2 438.8 403.0 382.7 326.2a 367.4 436.4 401.2	
	Mean S.D. N		249.88 12.20 12	287.60 20.11 12	329.01 24.49 12	421.19 32.59 11	

a Delivery occurred on GD21 before GD 21 data could be collected; excluded from statistics.

^{* =} Result to left has an associated comment or marker

^{# =} Animal not pregnant and has been excluded from statistics
PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

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Group Sex	Animal Number	Pregnancy Outcome	0	7	14	21
4f	425 427 428 429 431 432 433 435	PL PL PL PL PL PL PL PL	267.2 248.5 244.9 236.9 236.0 272.7 223.2 249.6 246.3	300.5 280.9 279.3 275.5 255.4 301.8 235.7 279.4 277.8	343.6 311.4 312.0 306.9 295.5 336.6 262.2 312.2 310.5	417.4 403.1 407.7 400.5 375.6 405.7 323.5 394.6 418.1
	Mean S.D. N		247.26 15.29 9	276.26 20.51 9	310.10 23.32 9	394.02 29.34 9

^{* =} Result to left has an associated comment or marker

^{# =} Animal not pregnant and has been excluded from statistics
PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined



Note: This appendix contains data from animals with confirmed mating.

Gestation Day

Group Sex	Animal Number	Pregnancy Outcome	Base Weight Day O	From: To:	0 7	7 14	14 21	Abs Gain 0 21	% Gain 0 21
1f	125	PL	268.0		39.0	61.4	106.0	206.4	77.015
	126	PL	258.6		40.6	34.4	75.8	150.8	58.314
	127	PL	240.4		28.9	43.8	110.0	182.7	75.998
	128	PL	272.1		29.4	31.7	110.4	171.5	63.028
	129	PL	265.1		26.3	38.6	93.7	158.6	59.826
	130	PL	245.5		40.4	28.1	88.4	156.9	63.910
	131	PL	225.0		27.8	26.9	82.5	137.2	60.978
	132	PL	255.5		40.5	50.0	102.1	192.6	75.382
	133	PL	268.3		35.8	48.6	102.1	186.5	69.512
	134	PL	226.2		36.7	37.3	105.1	179.1	79.178
	135	PL	236.0		30.2	28.7	97.0	155.9	66.059
	136	PL	273.9		37.9	40.2	97.9	176.0	64.257
	Mean		252.88		34.46	39.14	97.58	171.18	67.788
	S.D.		17.71		5.51	10.39	10.82	19.81	7.358
	N		12		12	12	12	12	12

^{# =} Animal not pregnant and has been excluded from statistics

PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

^{* =} result to left has an associated comment or marker

Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Satellite Female Rats During Gestation

Gestati	

Group Sex	Animal Number	Pregnancy Outcome	Base Weight Day O	From: To:	0 7	7 14	14 21	Abs Gain 0 21	% Gain 0 21
2f	225	PL	252.4		30.2	45.4	9.4a		
	226	PL	226.0		22.5	28.0	80.5	131.0	57.965
	227	PL	261.4		58.7	38.4	119.3	216.4	82.785
	228	PL	251.1		40.5	45.3	113.7	199.5	79.450
	229	PL	268.2		36.5	35.2	94.1	165.8	61.820
	230	PL	283.8		38.9	36.2	81.6	156.7	55.215
	231	PL	266.9		51.6	40.5	90.5	182.6	68.415
	232	PL	256.8		48.7	39.2	94.6	182.5	71.067
	233	PL	236.9		26.6	43.3	95.8	165.7	69.945
	234	PL	225.3		34.4	39.3	84.1	157.8	70.040
	235	PL	263.5		41.1	29.4	100.4	170.9	64.858
	236	PL	241.0		25.1	48.1	105.6	178.8	74.191
	Mean		252.77		37.90	39.03	96.38	173.43	68.705
	S.D.		17.76		11.11	6.18	12.61	22.74	8.440
	N		12		12	12	11	11	11

a Delivery occurred on GD21 before GD 21 data could be collected; excluded from statistics.

^{# =} Animal not pregnant and has been excluded from statistics

PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

^{* =} result to left has an associated comment or marker

Abs Gain = absolute bodyweight gain between base period and end of the analysis period

[%] Gain = percentage bodyweight gain between base period and end of the analysis period

Nominal Dose: Group 1 - 0 ppm Group 2 - 100 ppm Group 3 - 500 ppm Group 4 - 3000 ppm

Individual Body Weight Gains (grams) of Satellite Female Rats During Gestation

Gestation Day

Group Sex	Animal Number	Pregnancy Outcome	Base Weight Day O	From: To:	0 7	7 14	14 21	Abs Gain 0 21	% Gain 0 21
3f	325	PL	239.0		34.4	38.4	95.1	167.9	70.251
	326	PL	256.4		62.6	60.5	100.6	223.7	87.246
	327	PL	263.6		42.6	36.2	109.7	188.5	71.510
	328	PL	246.5		34.5	52.4	105.9	192.8	78.215
	329	PL	255.2		37.6	43.4	89.0	170.0	66.614
	330	PL	268.2		37.6	37.8	95.2	170.6	63.609
	331	PL	242.3		39.3	35.7	85.7	160.7	66.323
	332	PL	238.8		11.5	48.7	83.7	143.9	60.260
	333	PL	253.4		46.4	40.6	-14.2a	•	•
	334	PL	229.6		33.7	26.8	77.3	137.8	60.017
	335	PL	264.9		37.2	42.4	91.9	171.5	64.741
	336	PL	240.7		35.2	34.0	91.3	160.5	66.681
	Mean		249.88		37.72	41.41	93.22	171.63	68.679
	S.D.		12.20		11.49	9.02	9.58	23.70	8.044
	N N		12.20		12	12	11	11	11

a Delivery occurred on GD21 before GD 21 data could be collected; excluded from statistics.

^{# =} Animal not pregnant and has been excluded from statistics

PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

^{* =} result to left has an associated comment or marker

Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Gestation Day

_			Base Weight	_				Abs Gain	% Gain
Group	Animal	Pregnancy	Day	From:	0	/	14	0	0
Sex	Number	Outcome	0	To:	7	14	21	21	21
4 f	425	PL	267.2		33.3	43.1	73.8	150.2	56.213
	427	PL	248.5		32.4	30.5	91.7	154.6	62.213
	428	PL	244.9		34.4	32.7	95.7	162.8	66.476
	429	PL	236.9		38.6	31.4	93.6	163.6	69.059
	431	PL	236.0		19.4	40.1	80.1	139.6	59.153
	432	PL	272.7		29.1	34.8	69.1	133.0	48.772
	433	PL	223.2		12.5	26.5	61.3	100.3	44.937
	435	PL	249.6		29.8	32.8	82.4	145.0	58.093
	436	PL	246.3		31.5	32.7	107.6	171.8	69.752
	Mean		247.26		29.00	33.84	83.92	146.77	59.407
	S.D.		15.29		8.08	5.01	14.60	21.34	8.606
	N		9		9	9	9	9	9

^{# =} Animal not pregnant and has been excluded from statistics

PC = Pregnant Caesarian, PL = Pregnant Littered, NP = Not Pregnant, ND = Not Determined

^{* =} result to left has an associated comment or marker

Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Nominal Dose: Group 1 - 0 ppm Group 2 - 100 ppm Group 3 - 500 ppm Group 4 - 3000 ppm

Appendix X
Individual Body Weights of Satellite Female Rats During Lactation

T.a	cta	a t	iο	n	Day	7

Group Sex	Animal Number	0	4
1f	125 126 127 128 129 130 131 132 133 134 135	340.7 317.4 298.6 311.6 329.7 295.6 272.1 322.0 315.7 286.6 274.2 323.7	344.5 333.0 317.6 332.4 321.0 307.7 283.7 334.1 336.3 276.3 351.9
	Mean S.D. N	307.32 21.89	318.73 25.06

* = Result to left has an associated comment or marker

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Lа	Сτ	aт	ı	on	Dav

Group Sex	Animal Number	0	4
2f	225 226 227 228 229 230 231 232 233 234 235 236	337.4 281.7 333.6 329.4 325.2 329.6 321.7 288.5 276.0 322.0 291.4	328.8 271.0 348.9 333.8 4343.5 344.9 336.4 281.1 297.9 309.9 303.4
	Mean S.D. N	313.61 22.30 12	319.00 25.91 12

* = Result to left has an associated comment or marker

Lactation Dav	La	cta	ati	on	Dav	
---------------	----	-----	-----	----	-----	--

Group Sex	Animal Number	0	4
3f	325 326 327 328 329 331 332 333 334 335 336	304.2 342.1 297.8 320.6 317.6 304.9 287.8 296.2 326.2 260.7 327.0 286.0	307.4 358.6 332.2 315.0 317.8 333.5 320.8 310.2 322.3 289.8 323.2 302.0
	Mean S.D. N	305.93 22.26	319.40 17.46

* = Result to left has an associated comment or marker

т -	- 4-	- 4-	•		D
Lа	Сτ	aт	ı	on	Dav

Group Sex	Animal Number	0	4
4f	425 426 427 428 429 431 432 433 434 435 436	299.1 276.6 281.7 297.5 299.4 285.9 300.3 259.8 271.0 292.2 277.6	298.2 301.0 314.1 309.3 304.4 288.6 319.3 260.6 268.1 296.4 301.2
	Mean S.D. N	285.55 13.46 11	296.47 18.05

^{* =} Result to left has an associated comment or marker

Naphtha, Petroleum, Heavy Straight-Run: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-18331

Appendix Y
Individual Body Weight Gains of Satellite Female Rats During Lactation

Individual Body Weight Gains (grams) of Satellite Female Rats During Lactation

Lactation Day

Group Sex		Base Weight Day O	0 4	Abs Gain 0 4	% Gain 0 4
1f	125 126 127 128 129 130 131 132 133 134 135	340.7 317.4 298.6 311.6 329.7 295.6 272.1 322.0 315.7 286.6 274.2 323.7	3.8 15.6 19.0 20.8 -8.7 12.1 11.6 12.1 20.6 -0.3 2.1 28.2	12.1 11.6 12.1 20.6	4.093 4.263 3.758 6.525
	Mean S.D. N	307.32 21.89 12	11.41 10.52 12		

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Lactation Day

Group Sex	Animal Number	Base Weight Day O	From: To:	0 4	Abs Gain 0 4	% Gain 0 4
2f	225 226 227 228 229 230 231 232 233 234 235 236	337.4 281.7 333.6 329.4 326.8 325.2 329.6 321.7 288.5 276.0 322.0 291.4		-8.6 -10.7 15.3 4.4 1.6 18.3 15.3 14.7 -7.4 21.9 -12.1 12.0	-8.6 -10.7 15.3 4.4 1.6 18.3 15.3 14.7 -7.4 21.9 -12.1 12.0	-2.549 -3.798 4.586 1.336 0.490 5.627 4.642 4.569 -2.565 7.935 -3.758 4.118
	Mean S.D. N	313.61 22.30 12		5.39 12.45 12	5.39 12.45 12	1.719 4.081 12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Individual Body Weight Gains (grams) of Satellite Female Rats During Lactation

Lactation Day

Group Sex	Animal Number	Base Weight Day O	From: To:	0 4	Abs Gain 0 4	% Gain 0 4
3f	325 326 327 328 329 330 331 332 333 334 335 336	304.2 342.1 297.8 320.6 317.6 304.9 287.8 296.2 326.2 260.7 327.0 286.0		3.2 16.5 34.4 -5.6 0.2 28.6 33.0 14.0 -3.9 29.1 -3.8 16.0	3.2 16.5 34.4 -5.6 0.2 28.6 33.0 14.0 -3.9 29.1 -3.8 16.0	1.052 4.823 11.551 -1.747 0.063 9.380 11.466 4.727 -1.196 11.162 -1.162 5.594
	Mean S.D. N	305.92 22.26 12		13.48 15.24 12	13.48 15.24 12	4.643 5.245 12

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period

Lactation Day

Group Sex	Animal Number	Base Weight Day O	From: To:	0 4	Abs Gain 0 4	% Gain 0 4
4f	425 426 427 428 429 431 432 433 434 435 436	299.1 276.6 281.7 297.5 299.4 285.9 300.3 259.8 271.0 292.2 277.6		-0.9 24.4 32.4 11.8 5.0 2.7 19.0 0.8 -2.9 4.2 23.6	-0.9 24.4 32.4 11.8 5.0 2.7 19.0 0.8 -2.9 4.2 23.6	-0.301 8.821 11.502 3.966 1.670 0.944 6.327 0.308 -1.070 1.437 8.501
	Mean S.D. N	285.55 13.46 11		10.92 12.05 11	10.92 12.05 11	3.828 4.290 11

^{* =} result to left has an associated comment or marker Abs Gain = absolute bodyweight gain between base period and end of the analysis period % Gain = percentage bodyweight gain between base period and end of the analysis period