

**elf atochem**



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(A)

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Subject: TSCA Section 8(e) Submission



**88970000138**

Dear Sir/Madam:

Elf Atochem North America, Inc. (Elf Atochem) has received the final report of a repeated dose inhalation study in rats and is submitting this report to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). Preliminary results from this study were submitted to the Agency by Elf Atochem on August 29, 1996. This study provides information on isopropylaminoethanol (CAS Registry Number 109-56-8) and does not involve effects in humans.

Nothing in this letter or the enclosed study report is considered confidential business information of Elf Atochem.

Further questions regarding this submission may be directed to me at (215) 419-5890.

Best Regards,

*Debra Randall*

Debra Randall, DABT  
Product Safety Manager

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**FINAL REPORT**

**VOLUME 1 OF 3**  
Text and Summary Tables

**STUDY TITLE**

**A COMBINED REPEATED DOSE 28-DAY ORAL  
AND REPRODUCTION/DEVELOPMENTAL TOXICITY  
STUDY OF ISOPROPYLAMINOETHANOL (IPAE) IN RATS**

*CAS Number 109-56-8*

**STUDY DIRECTOR**

Donald G. Stump, Ph.D.

**STUDY INITIATED ON**

March 26, 1996

**STUDY COMPLETED ON**

January 22, 1997

**PERFORMING LABORATORY**

WIL Research Laboratories, Inc.  
1407 George Road  
Ashland, OH 44805-9281

**LABORATORY STUDY NUMBER**

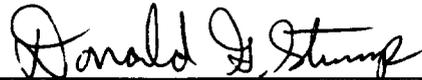
WIL-160046

**SPONSOR**

Elf Atochem North America, Inc.  
2000 Market Street  
Philadelphia, PA 19103-3222

**COMPLIANCE STATEMENT**

This study, designated WIL-160046, was conducted in compliance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations (40 CFR Part 792), October 16, 1989, the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C (81) 30 (Final)], the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol as approved by the sponsor. The protocol was designed and the study was conducted in accordance with the applicable regulations of the OECD Guideline for Testing of Chemicals, Revised Draft Guidelines 407 (28-Day Repeated-Dose Phase) and 421 (Reproduction/Developmental Toxicity Phase), January 1994.



Donald G. Stump, Ph.D.  
Study Director

1/22/97

Date

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## I. SUMMARY

The potential subchronic toxicity (males only) and reproductive toxicity (males and females) related to the administration of the test article were evaluated in this combined repeated-dose study. The test article was administered orally by gavage to four groups of Sprague-Dawley Crl:CD® BR rats once daily at dosage levels of 0.8, 2.5, 7.5 and 37.5 mg/kg/day. Dosage volumes for these groups were 0.53, 1.67, 5 and 5 ml/kg, respectively. The 0.8, 2.5 and 7.5 mg/kg/day groups each consisted of 10 males and 10 females. The 37.5 mg/kg/day group was comprised of 10 males; no females were treated at this dose level. A concurrent control group, comprised of 10 males and 10 females, received the vehicle, deionized water, at a dosage volume of 5 ml/kg. All rats were dosed for 15 days prior to mating and through the day prior to necropsy. The dosing period for the male groups was 35 days. Throughout the study period, all rats were observed at the time of dosing and approximately one hour following dosing. Detailed physical examinations were conducted weekly for all F<sub>0</sub> animals. Parental body weights and food consumption were recorded weekly until confirmation of mating; thereafter, maternal body weights and food consumption were recorded on gestation days 0, 7, 14 and 20, and lactation days 1 and 4. Functional observational battery evaluations were performed on all F<sub>0</sub> males during study weeks -1 and 3. Clinical pathology evaluations (hematology and serum chemistry) were conducted at the time of the scheduled necropsy of F<sub>0</sub> males. All F<sub>0</sub> females were allowed to deliver and rear their pups through lactation day 4. The offspring were also potentially exposed to the test article *in utero* (placental transfer) and through nursing, until euthanization on postnatal day (PND) 4. A complete necropsy was performed on all F<sub>0</sub> animals. Selected organs were weighed from all F<sub>0</sub> animals at the scheduled necropsies and selected tissues were examined microscopically.

In the 37.5 mg/kg/day group, one male died on study day 32 and three males were euthanized *in extremis* on study days 33 or 34. All other animals survived to the scheduled necropsies. Treatment-related clinical findings were limited to the 37.5 mg/kg/day group males (animals found dead, euthanized *in extremis* and surviving to the scheduled necropsy) between study days 32 and 35; these included prostration, body cool to the touch, impaired or no righting reflex, shallow or rapid respiration, decreased

defecation, unkempt or hunched appearance, red material around the nose and/or eyes, drooping (half-closed) eyelids, and animals which rocked, lurched or swayed as they walked or appeared flattened with limbs extended.

Mating and fertility indices and the number of days between pairing and coitus were unaffected by treatment.

Reductions in mean body weight gain or mean body weight losses were observed in the 37.5 mg/kg/day group males during the last three weeks of test article administration. Body weights in this group were also reduced for weeks 3, 4 and 5. Week 5 body weights were also reduced in the 7.5 mg/kg/day group males. Body weight gains were reduced in the 7.5 mg/kg/day group females during gestation days 7-14 and in the 2.5 and 7.5 mg/kg/day group females during gestation days 14-20. Body weights in the 7.5 mg/kg/day group were reduced on gestation days 14 and 20. No treatment-related differences in lactation body weights or lactation body weight gains were observed in the 0.8 and 2.5 mg/kg/day group females. None of the 7.5 mg/kg/day group females delivered litters, therefore, no lactation body weight data were available for this group.

Food consumption was reduced during week 4-5 in the 37.5 mg/kg/day group males. Reductions in food consumption were observed in the 7.5 mg/kg/day group females during gestation days 7-14 and 14-20. Food consumption in the 0.8 and 2.5 mg/kg/day group females was unaffected by treatment throughout gestation and lactation. None of the 7.5 mg/kg/day group females delivered litters, therefore, no lactation food consumption data were available for this group.

No test article-related differences in functional observational battery parameters were apparent in the 0.8, 2.5, 7.5 and 37.5 mg/kg/day group males.

Clinical pathology parameters affected by test article administration were limited to the 37.5 mg/kg/day group males. Effects on hematology parameters included increases in red blood cell and platelet counts, hemoglobin, hematocrit, prothrombin time and activated partial thromboplastin time. A shift in the types of leukocytes present also occurred in the 37.5 mg/kg/day group; the percentage of lymphocytes was decreased, with a corresponding increase in neutrophils. The effects on hematology parameters were indicative of dehydration, stress and decreased liver function, and

correlated with microscopic findings noted for the gastrointestinal tract and liver. Test article-related changes in serum chemistry parameters included decreases in total protein, albumin, globulin and glucose, and increases in total bilirubin, urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, cholesterol, phosphorus and potassium. The changes in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, total bilirubin and cholesterol levels correlated with microscopic findings noted in the liver, while changes in albumin, total protein, globulin, creatinine, urea nitrogen and phosphorus levels correlated with microscopic changes in the kidney.

Treatment-related gross internal findings in the 37.5 mg/kg/day group males included dark red contents in the stomach and/or intestinal tract and small thymus glands. Test article-related decreases in liver and thymus gland weights and increases in mean adrenal gland weight were observed in the 37.5 mg/kg/day group. Microscopic changes were observed in the liver, intestinal tract (primarily cecum and colon), thymus gland and spleen of males in the 37.5 mg/kg/day group and in the kidneys of males in the 7.5 and 37.5 mg/kg/day groups at both the unscheduled and scheduled necropsies. Liver changes in the 37.5 mg/kg/day group males consisted of minimal to moderate bile duct hyperplasia and minimal to mild hepatocellular necrosis. Effects in the kidneys were characterized by bilateral multifocal tubular necrosis (graded mild to moderate) in the 7.5 and 37.5 mg/kg/day group males. Severe, diffuse mucosal necrosis in the cecum (with loss of mucosal epithelium, proprial stromal collapse, infiltration of mononuclear cells and neutrophils) was also observed in the 37.5 mg/kg/day group males. Similar changes (mild to severe) were observed in the colon and/or ileum of several males in this group. Mild to moderate lymphoid depletion was observed in the thymus gland and spleen of several 37.5 mg/kg/day group males.

The scheduled necropsy of F<sub>0</sub> females revealed that one female in the 2.5 mg/kg/day group and all females in the 7.5 mg/kg/day group had entirely resorbed litters (all early resorptions). The difference between the numbers of implantation sites counted at the lactation day 4 necropsy and the numbers of pups born was increased in the 2.5 mg/kg/day group.

Gestation lengths in the 0.8 and 2.5 mg/kg/day group were unaffected by treatment. None of the 7.5 mg/kg/day group females delivered litters (due to entirely resorbed litters), thus precluding assessment of this parameter for this group. No signs of dystocia were noted in any group.

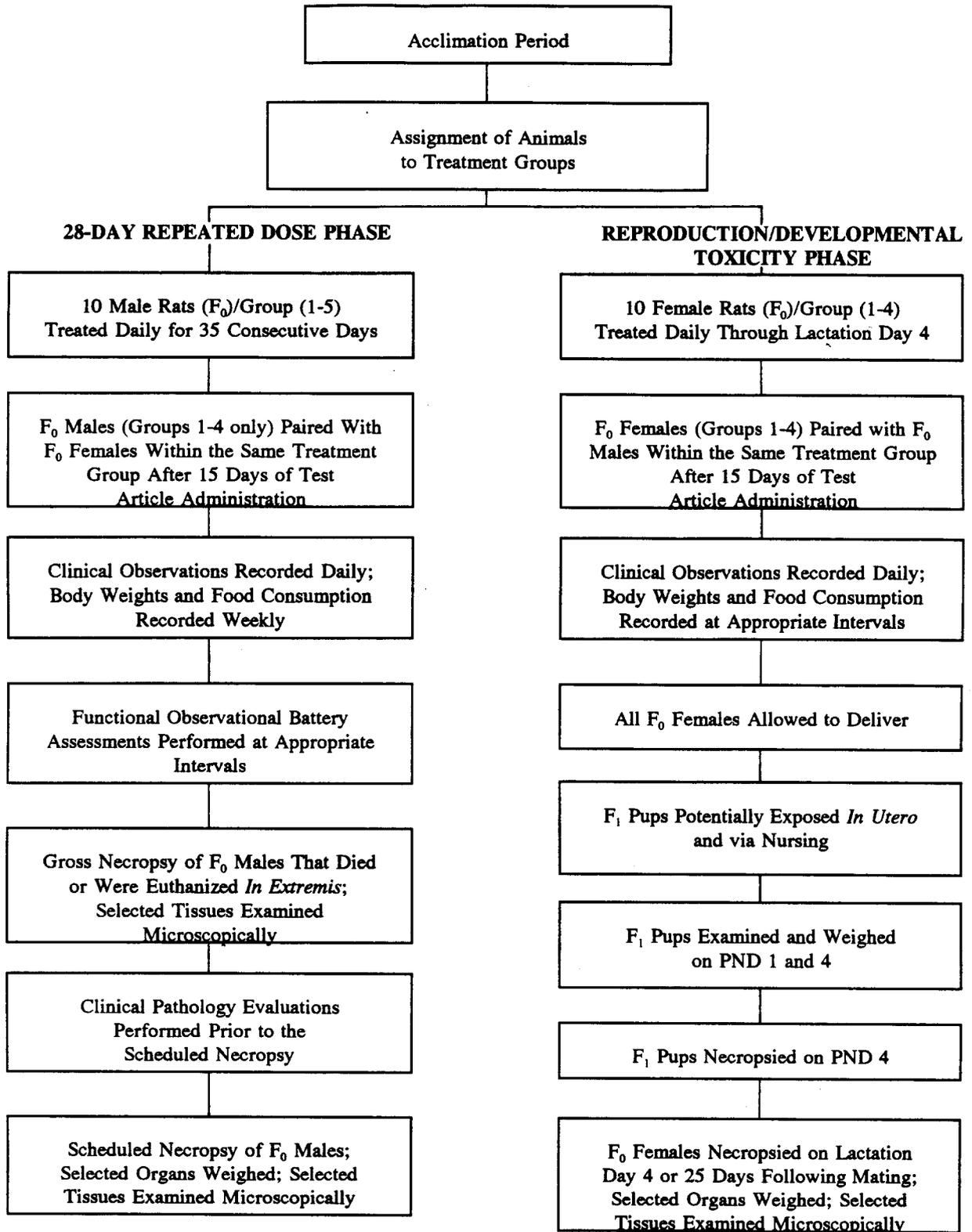
F<sub>1</sub> live litter size in the 2.5 mg/kg/day group was reduced in comparison to the concurrent control group and the WIL historical control data. No adverse effects on F<sub>1</sub> pup viability indices, numbers of dead pups on lactation day 0, stillbirths per litter, pup sex ratios, live births, gestational survival indices, the general physical condition of the pups and pup body weights were observed at dosage levels of 0.8 and 2.5 mg/kg/day. F<sub>0</sub> females in the 7.5 mg/kg/day group did not deliver litters, thus precluding evaluation of F<sub>1</sub> litter data for this group.

In conclusion, oral administration of the test article resulted in F<sub>0</sub> male toxicity at a dose level of 37.5 mg/kg/day, as evidenced by mortality, changes in the clinical condition of the animals, inhibition of body weight gain and food consumption, changes in clinical pathologic parameters, gross and microscopic findings, and changes in organ weights. F<sub>0</sub> male toxicity was also observed at a dose level of 7.5 mg/kg/day, as evidenced by decreased body weight and microscopic findings in the kidneys. No F<sub>0</sub> male toxicity was observed at dose levels of 0.8 and 2.5 mg/kg/day. F<sub>0</sub> female toxicity was expressed at dose levels of 2.5 and 7.5 mg/kg/day by inhibition of body weight gain and/or food consumption during the latter part of gestation. No F<sub>0</sub> female toxicity was observed at a dose level of 0.8 mg/kg/day. F<sub>0</sub> mating and fertility indices were not affected by treatment at any dose level. F<sub>1</sub> prenatal toxicity was exhibited at a dose level of 7.5 mg/kg/day by postimplantation loss (completely resorbed litters) and at a dose level of 2.5 mg/kg/day by decreased live litter size. No indications of prenatal or neonatal toxicity were observed at the 0.8 mg/kg/day dose level. Based on the data obtained, the NOAEL (no observed adverse effect level) for F<sub>0</sub> male subchronic toxicity was considered to be 2.5 mg/kg/day. The NOAEL for F<sub>0</sub> female reproductive toxicity and F<sub>1</sub> prenatal toxicity was considered to be 0.8 mg/kg/day.

II. OBJECTIVE

The objective of the study was to provide information on the potential adverse effects of the test article on male rats following daily oral administration for four weeks and on male and female reproduction. Reproductive parameters evaluated included gonadal function, mating behavior, conception, parturition and lactation of the F<sub>0</sub> generation and the development of offspring from conception through day 4 of postnatal life. The animal model, the Sprague-Dawley Crl:CD®BR rat, is recognized as appropriate for subchronic and developmental/reproductive toxicity studies, and was selected based on the availability of historical control data.

### III. STUDY DESIGN



IV. EXPERIMENTAL PROCEDURES

A. STUDY SCHEDULE

F <sub>0</sub> Male Dose Administration:	April 30, 1996 - June 3, 1996
F <sub>0</sub> Female Dose Administration:	April 30, 1996 - June 22, 1996
F <sub>0</sub> Breeding Period:	May 15-29, 1996
F <sub>0</sub> Male Scheduled Necropsy:	June 4, 1996
F <sub>0</sub> Female Lactation Day 4 Necropsies:	June 9-23, 1996
F <sub>1</sub> Pup Postnatal Day 4 Necropsies:	June 9-23, 1996
Experimental Termination Date (Last histopathological examination):	October 16, 1996

For computer entry purposes, F<sub>0</sub> male data were designated WIL-160046M, and F<sub>0</sub> female and F<sub>1</sub> litter data were designated WIL-160046F.

Dose levels for this study were selected based on the results of a previous toxicity study of the test article in female rats (WIL-160036<sup>1</sup>). In that study, all females dosed at 100 mg/kg/day died between post-mating days 10 and 12. Body weight gain was reduced in the 30 mg/kg/day group. All females in the 100 mg/kg/day group and 2/5 females in the 30 mg/kg/day group were nongravid. All gravid females in the 30 mg/kg/day group and 4/5 gravid females in the 10 mg/kg/day group had entirely resorbed litters. No adverse effects were observed at dose level of 3 mg/kg/day.

Due to spacing constraints, the study title on the report tables was limited to "A Reproduction/Developmental Toxicity Study of IPAE in Rats."

B. TEST AND CONTROL ARTICLES

1. TEST ARTICLE IDENTIFICATION

The test article was received from the sponsor on March 29, 1996. Purity and stability data for the test article were the responsibility of the sponsor. The test article was 99.8% pure, but was considered to be 100% pure for the purpose of dose calculations. The test article was considered stable when stored at room temperature. A 1.04-gram reserve sample of the

bulk test article was collected on April 2, 1996, and stored in the Archives at WIL Research Laboratories, Inc.

2. VEHICLE CONTROL ARTICLE IDENTIFICATION

The vehicle control article utilized in the preparation of the test mixtures and for administration to the control group was deionized water (prepared on-site).

3. PREPARATION

For administration to the control group, a sufficient volume of the vehicle, deionized water, was dispensed into a labeled storage container. The vehicle was stirred continuously throughout the sampling and dosing procedures using a magnetic stir bar and stir plate.

The test article formulations were prepared as follows. The appropriate amount of the test article was weighed for each dosage concentration (1.5 and 7.5 mg/ml) into labeled, precalibrated storage containers. A sufficient amount of vehicle was added to each container to bring the volume of the preparation to the calibration mark. A magnetic stir bar was added and the preparations were stirred continuously on a magnetic stir plate throughout the sampling and dosing procedures. The dosing formulations were prepared biweekly and were stored at room temperature, with the following exception. The 1.5 mg/ml dosing formulation prepared on June 11, 1996 was not within specifications according to initial analytical results. Consequently, the 1.5 mg/ml dosing solution was reformulated on June 13, 1996. It was later discovered that the low analytical results were due to an equipment malfunction in the Analytical Chemistry Department. The June 11, 1996 preparation was reanalyzed and found to be within specifications. The test article preparations were visually inspected by the study director on April 30, 1996, and were found to be acceptable for use.

4. ADMINISTRATION

The dosing formulations were administered orally using a 16-gauge stainless steel gavage cannula (Popper and Sons, Inc., New Hyde Park, New York), as a single daily dose. All animals were dosed for 15 days prior to

mating and through the day prior to necropsy (35 days for males and through lactation day 3 for females). Dosage volumes of 0.53, 1.67, 5 and 5 ml/kg were used for the 0.8, 2.5, 7.5 and 37.5 mg/kg/day groups, respectively. The control group animals received the vehicle, deionized water, on a comparable regimen of 5 ml/kg. Individual dosages were based on the most recently recorded body weights to provide the correct mg/kg/day dose. It should be noted that on June 12, 1996, one control group animal (no. 49795) received 1.7 ml of vehicle rather than the correct dose of 1.6 ml due to a rounding error. This deviation from the protocol had no impact on the outcome of the study. The following table presents the study design.

<u>Group Number</u>	<u>Article</u>	<u>Dosage Level</u>	<u>Dosage Concentration</u>	<u>Dosage Volume</u>	<u>Number of Animals</u>	
		<u>(mg/kg/day)</u>	<u>(mg/ml)</u>	<u>(ml/kg)</u>	<u>Male</u>	<u>Female</u>
1	Vehicle	0	0	5	10	10
2	Test Article	0.8	1.5	0.53	10	10
3	Test Article	2.5	1.5	1.67	10	10
4	Test Article	7.5	1.5	5	10	10
5	Test Article	37.5	7.5	5	10	0

#### 5. ANALYSES OF DOSING PREPARATIONS

On April 15, 1996, two 10-ml aliquots from the control group preparation and two 10-ml aliquots from the top, middle and bottom strata of each test article formulation (1.5 and 7.5 mg/ml solutions) were removed while the formulations were being stirred. One sample from each dosage concentration and stratum was analyzed to determine homogeneity. The remaining sample from each dosage concentration and stratum was stored under normal laboratory conditions for 14 days and was analyzed to verify the stability of the test article in the vehicle. One 10-ml sample was collected from the middle of each biweekly dosing formulation and was analyzed for concentration.

The methodology and results of the analyses are presented in Appendix A. Data from these analyses confirmed that the dosing formulations were homogeneous, stable for at least 14 days, and contained the designated amounts of test article specified in the protocol.

C. ANIMAL RECEIPT AND ACCLIMATION

Sixty-five male and fifty-five female Sprague-Dawley Crl:CD®BR rats were received in good health from Charles River Laboratories, Inc., Portage, Michigan, on April 18, 1996. Upon receipt, the males and females were approximately 60 and 70 days old, respectively. All animals were examined by qualified technicians and weighed the day following receipt. Animals were uniquely identified by Monel metal eartags displaying the permanent identification number. During the 12-day acclimation period, individual body weights were recorded twice (following receipt and at randomization) and the rats were observed twice daily for changes in general appearance and behavior. For computer entry, pretest data were assigned to computer protocol numbers WIL-160046P and WIL-160046Q for males and females, respectively. Pretest clinical observations are presented in Appendix B.

D. ANIMAL HOUSING

Upon arrival and until pairing, all rats were individually housed in clean, wire-mesh cages suspended above cage-board, with the following exceptions. The rats in Groups 1-4 were paired for mating (1 male:1 female) in the home cage of the male. Following positive identification of mating or at the conclusion of the breeding period, the females were individually housed in clean plastic maternity cages containing ground corn cob nesting material (Bed-O'Cobs®; The Andersons, Industrial Products Division, Maumee, Ohio). Animals were maintained in accordance with the National Research Council "Guide for the Care and Use of Laboratory Animals<sup>2</sup>." The animal facilities at WIL Research Laboratories, Inc., are accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

E. DIET, DRINKING WATER AND MAINTENANCE

The basal diet used in this study was PMI Feeds, Inc.® Certified Rodent LabDiet® 5002. This diet is a certified feed with appropriate analyses performed by the manufacturer and provided to WIL Research Laboratories, Inc. Municipal water supplying the facility is sampled for contaminants according to Standard Operating Procedures. The results of these analyses are maintained at WIL Research Laboratories, Inc. Contaminants were not present in animal feed or water

at concentrations expected to interfere with the objectives of this study. Drinking water delivered by an automatic watering system and the basal diet were provided *ad libitum* throughout the acclimation period and during the study.

F. ENVIRONMENTAL CONDITIONS

All animals were housed throughout the acclimation period and during the study in an environmentally-controlled room. Controls were set to maintain a temperature of  $72^{\circ} \pm 4^{\circ}\text{F}$  and a relative humidity between 30% and 70%. Room temperature and relative humidity were recorded once daily. Temperature ranged from  $71.4^{\circ}$  to  $72.4^{\circ}$  F and relative humidity ranged from 28.0% to 61.6% during the study period. The slight deviation from the protocol-specified humidity range on one day had no impact on the outcome of the study. Light timers were calibrated to provide a 12-hour light/12-hour dark photoperiod. Air handling units were set to provide approximately 10 fresh air changes per hour.

G. ASSIGNMENT OF ANIMALS TO TREATMENT GROUPS

On April 29, 1996 (the day prior to test article administration), all available rats were weighed and examined in detail for physical abnormalities. Animals judged to be suitable for testing, as decided by the study director, were selected for use in the computer randomization procedure. The individual body weights were entered into the WIL Toxicology Data Management System (WTDMS™). A printout containing the animal numbers, corresponding body weights and individual group assignments was generated based on body weight stratification in a block design. The animals then were arranged according to the printout. The control, 0.8, 2.5 and 7.5 mg/kg/day groups each consisted of 10 males and 10 females. The 37.5 mg/kg/day group consisted of 10 males only. After randomization into study groups, the males were then randomized into two study replicates to allow for the reasonable conduct of the functional observational battery assessments. Each dose group was equally represented within each study replicate. The selected animals were approximately 11 weeks old at the initiation of dosing; body weight values ranged from 326 to 384 grams for the males and from 217 to 265 grams for the females. Several females weighed more than the protocol-specified maximum weight of 250 grams. This deviation had no impact on the outcome of the study

as the differences were slight and all female body weights were within  $\pm 20\%$  of the mean, as required by protocol.

#### H. BREEDING PROCEDURES

Following 15 days of dose administration, F<sub>0</sub> males were paired on a 1:1 with F<sub>0</sub> females from the same treatment group (Groups 1-4) on May 15, 1996. A breeding record containing the male and female identification numbers and the date of cohabitation was generated. Positive evidence of mating was confirmed by the presence of sperm in a vaginal smear or a copulatory plug. Each mating pair was examined daily. The day when evidence of mating was identified was termed day 0 of gestation. If evidence of copulation was not detected after 10 days, a female was placed with a proven male from the same treatment group for a maximum of five additional days.

Mating and fertility indices were calculated as follows:

$$\text{Male Mating Index (\%)} = \frac{\text{No. of Males With Evidence of Mating}}{\text{Total No. of Males Used for Mating}} \times 100$$

$$\text{Female Mating Index (\%)} = \frac{\text{No. of Females With Evidence of Mating}}{\text{Total No. of Females Used for Mating}} \times 100$$

$$\text{Male Fertility Index (\%)} = \frac{\text{No. of Males Siring at Least 1 Litter}}{\text{Total No. of Males Used for Mating}} \times 100$$

$$\text{Female Mating Index (\%)} = \frac{\text{No. of Females with Confirmed Pregnancy}}{\text{Total No. of Females Used for Mating}} \times 100$$

#### I. F<sub>0</sub> GENERATION

##### 1. OBSERVATIONS

##### a. CLINICAL OBSERVATIONS AND SURVIVAL

All rats were observed twice daily for moribundity and mortality. Detailed clinical examinations were performed weekly (prior to dosing during the treatment period). Animals were observed for signs of toxicity at the time of dosing and approximately 1-2 hours following dosing (designated one hour post-dosing for reporting purposes); all significant findings were recorded. Females were also observed twice

daily during the period of expected parturition for dystocia (prolonged or delayed labor) or other difficulties.

b. BODY WEIGHTS

Individual male body weights were recorded weekly, beginning with the initiation of treatment, and are presented for weeks 0 through 5. Mean body weights for each of these weeks and corresponding mean weekly body weight changes for each weekly interval were calculated.

Individual female body weights were recorded weekly, beginning with the initiation of dosing and continuing until evidence of copulation was observed, and are presented for weeks 0 through 2 (the last recorded weekly body weight of all females prior to pairing). Once evidence of mating was observed, female body weights were recorded on gestation days 0, 7, 14 and 20, and on lactation days 1 and 4. Mean body weights for each of these periods and corresponding mean body weight changes for each weekly, gestation and lactation interval were calculated.

c. FOOD CONSUMPTION

Individual food consumption was recorded on the days of the corresponding weekly, gestation and lactation body weight measurement, with the following exception. Food consumption measurement was suspended during the breeding period as the males and females were cohabitated at that time. Although the 37.5 mg/kg/day group males were not mated, it should be noted that food consumption was not measured for these animals during the regular breeding period (weeks 2-4). This was done so all groups would be treated equally. Food consumption was reported as g/animal/day and g/kg/day.

2. FUNCTIONAL OBSERVATIONAL BATTERY

A functional observational battery (FOB) screening evaluation was performed on all F<sub>0</sub> males once prior to the initiation of dosing and once during the fourth week of test article administration (study week 3). Testing was performed by the same technicians without knowledge of the animal group assignment. The FOB was performed in a sound-proofed room equipped with

a white noise generator set to operate at  $70 \pm 10$ dB. All animals were observed for the following parameters as described below (refer to Appendix C for a detailed description of the scoring criteria used for each observation):

a. HANDLING OBSERVATIONS

Ease of removal from cage	Ease of handling animal in hand
Lacrimation/chromodacryorrhea	Salivation
Piloerection	Fur appearance
Palpebral closure	Respiratory rate/character
Red/crusty deposits	Mucous membranes/eye/skin color
Eye prominence	Muscle tone

b. OPEN FIELD OBSERVATIONS (evaluated over a 2-minute observation period)

Mobility	Gait
Rearing	Arousal
Convulsions/tremors	Urination/defecation
Grooming	Gait score
Bizarre/stereotypic behavior	Backing
Time to first step (seconds)	

c. SENSORY OBSERVATIONS

Startle response

3. CLINICAL PATHOLOGY

Blood samples for clinical pathologic evaluation were collected from the vena cava of all surviving (nonfasted) males at the scheduled necropsy. Clinical pathology methods, procedures and references are presented in Appendix D. The following parameters were evaluated:

a. HEMATOLOGY

Total Leukocyte Count (White Cell)	Prothrombin Time (Pro Time)
Erythrocyte Count (Red Cells)	Activated Partial Thromboplastin Time (APTT)
Hemoglobin	Differential Leukocyte Count
Hematocrit	-Neutrophil
Mean Corpuscular Volume (MCV)	-Lymphocyte
Mean Corpuscular Hemoglobin Concentration (MCHC)	-Monocyte
Platelet Count	-Eosinophil
Platelet Estimate <sup>a</sup>	-Basophil
RBC Morphology <sup>a</sup>	

a = Presented only on individual tables  
 ( ) = Designates tabular abbreviation

b. SERUM CHEMISTRY

Albumin	Serum Aspartate Aminotransferase (Aspartat Transfer)
Total Protein	Gamma Glutamyltransferase (Glutamyltransfer)
Globulin	Glucose
Albumin/Globulin Ratio (A/G Ratio)	Total Cholesterol
Total Bilirubin (Total Bili)	Calcium
Blood Urea Nitrogen	Chloride
Blood Creatinine	Phosphorus
Serum Alkaline Phosphatase (AlkalinePhos'tse)	Potassium
Serum Alanine Aminotransferase (Alanine Transfer)	Sodium

( ) = Designates tabular abbreviation

4. ANATOMIC PATHOLOGY

a. MACROSCOPIC EXAMINATION

A complete necropsy was conducted on all animals that died spontaneously, or were euthanized *in extremis* or at the scheduled necropsies. All surviving animals were euthanized by carbon dioxide inhalation. All surviving F<sub>0</sub> males were euthanized following the conclusion of the breeding period and/or a minimum of 28 days of test article administration. All F<sub>0</sub> females that delivered were necropsied on lactation day 4 and the numbers of former implantation sites were

recorded. F<sub>0</sub> females which failed to deliver were necropsied 25 days after positive detection of mating. Uteri without macroscopic evidence of implantation, if present, were opened and placed in 10% ammonium sulfide solution for detection of implantation sites as described by Salewski<sup>3</sup>. Females with no evidence of mating were examined in the same manner 25 days following the conclusion of the mating period. The necropsy included, but was not limited to, examination of the external surface, all orifices and the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal and pelvic cavities, including viscera. At the time of necropsy, the following tissues and organs were collected and preserved in 10% neutral buffered formalin:

Adrenals (2)	Lungs <sup>a</sup> (including bronchi, fixed by inflation with fixative)
Bone with marrow <sup>a</sup> (sternbrae)	Lymph nodes <sup>a</sup> (mesenteric and submandibular)
Brain <sup>a</sup> (forebrain, mid-brain, hindbrain)	Ovaries with oviducts <sup>b</sup> (2)
Coagulating gland <sup>a</sup>	Peripheral nerve (sciatic)
Gastrointestinal tract <sup>a</sup>	Pituitary
Esophagus	Prostate <sup>a</sup>
Stomach	Seminal vesicles <sup>a</sup> (2)
Duodenum	Spinal cord <sup>a</sup> (cervical)
Jejunum	Spleen
Ileum	Testes with epididymides <sup>a, c</sup> (2) and vas deferens <sup>a</sup>
Cecum	Thymus <sup>a</sup>
Colon	Trachea <sup>a</sup>
Rectum	Urinary bladder <sup>a</sup>
Heart	Uterus with vagina <sup>b</sup>
Kidneys (2)	All gross lesions
Liver (sections of two lobes)	

<sup>a</sup> = Males only

<sup>b</sup> = Females only

<sup>c</sup> = The testes and epididymides were preserved in Bouin's solution.

b. ORGAN WEIGHTS

The following organs from animals euthanized at study termination were weighed:

Adrenals	Lungs (prior to inflation with fixative)
Brain	Ovaries
Epididymides	Pituitary
Heart	Spleen
Kidneys	Testes
Liver	Thymus

All paired organs were weighed together. Organ to final body weight and organ to brain weight ratios were calculated.

c. HISTOPATHOLOGIC PROCEDURES AND MICROSCOPIC EXAMINATION

After fixation, specified tissues were trimmed as described by Thompson<sup>4</sup>. Trimmed specimens were placed in appropriately labeled and numbered cassettes. The tissue samples were processed and then embedded in paraffin blocks. The labeled paraffin blocks were sectioned at five to eight microns. The tissue sections were placed on clean glass microscope slides and labeled with the appropriate study, animal, group and cassette number. Coverslips were placed on the slides upon completion of staining with hematoxylin and eosin (AFIP Manual of Histologic Staining Methods<sup>5</sup>), with the following exception. The testes and epididymides were stained using PAS and hematoxylin.

All tissues listed in Section IV.I.4.a. were examined microscopically for all males in the control and 37.5 mg/kg/day groups. Microscopic examination of the PAS/hematoxylin-stained sections of the seminiferous tubules (a minimum of 10 tubules examined per animal) of the testes was performed to assess spermatogenesis. Effects on spermatogenesis, if present, were classified as early (Stages 1-8) or late (Stages 9-14). Sections of the cecum, kidneys, liver, spleen and thymus gland were examined from all males in the 0.8, 2.5 and 7.5 mg/kg/day groups based on treatment-related findings in these organs in the high dose group males. Sections of the cervix, ovaries, pituitary gland, uterus, vagina and all gross internal lesions were examined from all females in the control and 7.5 mg/kg/day groups. The examinations

were performed by Chandikumar S. Elangbam, M.V.Sc., Ph.D., Senior Pathologist, WIL Research Laboratories, Inc.

J. F<sub>1</sub> LITTER DATA

1. LITTER VIABILITY AND DEATHS

Each litter was observed daily for survival and all deaths were recorded. All pups were individually identified by the application of tattoo markings on the digits (AIMS® Identification Systems, Piscataway, New Jersey) on lactation day 0. A daily record of litter size was maintained. Stillborn pups and pups dying between birth and PND 4 were necropsied using a modification of the Stuckhardt and Poppe<sup>6</sup> fresh dissection technique (including the brain, examined by a mid-coronal slice, and the heart). If a skeletal anomaly was suspected, the carcasses were eviscerated and fixed in 100% ethyl alcohol. Following fixation, the fetus was macerated in potassium hydroxide and stained with Alizarin Red S by a method similar to that described by Dawson<sup>7</sup>.

2. CLINICAL OBSERVATIONS AND SEX DETERMINATION

Litters were examined daily for any adverse changes in appearance and behavior. Each pup received a detailed clinical examination on PND 1 and 4. Any abnormalities in nesting and nursing behavior were recorded. Each pup was sexed on lactation days 0 and 4.

3. BODY WEIGHTS

Pups were individually weighed on PND 1 and 4.

4. POSTNATAL DAY 4 NECROPSY

All surviving pups were euthanized and necropsied on PND 4 with emphasis placed on developmental morphology. Tissues were preserved in 10% neutral buffered formalin for possible future histopathologic examination only as deemed necessary by the gross findings. The carcasses were then discarded.

K. STATISTICAL ANALYSES

All analyses were conducted using two-tailed tests for a minimum significance level of 5%, comparing each treated group to the vehicle control group. Means were presented with the standard deviation (S.D.) and the number of animals (N)

used to calculate the mean. Data obtained from nonpregnant females were excluded from statistical analysis following the mating period. Clinical laboratory values for cell types that occur at a low incidence (e.g., monocytes, eosinophils and basophils) were not subjected to statistical analysis. The following statistical tests were performed by a Digital® MicroVAX® 3400 computer (with appropriate programming) in this laboratory and are referenced on the report tables:

<u>STATISTICAL TEST</u>	<u>PARAMETER</u>
- Chi-Square test <sup>8</sup> with Yates' correction factor	Parental Reproductive Indices, Numbers of Stillborn and Dead Pups, Pup Sex Ratios, Pup Viability Indices
- One-way ANOVA with Dunnett's test <sup>8</sup>	Parental Body Weights, Body Weight Changes, Food Consumption, Clinical Pathology Values, Organ Weights, Gestation Length, Implantation Sites, Pup Body Weights
- Kolmogorov-Smirnov test <sup>9</sup>	Histopathological findings

#### L. DATA RETENTION

The sponsor will have title to all documentation records, raw data, specimens or other work product generated during the performance of the study. All work product including raw paper data and specimens will be retained in the Archives at WIL Research Laboratories, Inc., as specified in the study protocol.

Raw data in magnetic form, a retention sample of the test article and the original final report will be retained in the Archives at WIL Research Laboratories, Inc., in compliance with regulatory requirements.

V. RESULTS

A. F<sub>0</sub> MALES

1. CLINICAL OBSERVATIONS AND SURVIVAL

Summary Data: Tables 1, 2, 3, 4, 5

Individual Data: Table 63, Appendix E

In the 37.5 mg/kg/day group, one male died and three males were euthanized *in extremis* during study week 4. Male no. 49701 died on study day 32. Clinical findings noted for this animal on the day of death included prostration, no righting reflex, body cool to the touch, shallow respiration, yellow matting on the urogenital area and decreased defecation. Male nos. 49711, 49715 and 49741 were euthanized *in extremis* between study days 33 and 34. One day prior to and/or on the day of euthanization, at least two of these three males had unkempt or hunched appearance, an impaired righting reflex, body cool to the touch, shallow or rapid respiration, red material around the nose and/or eyes, drooping (half-closed) eyelids, brown matting on the anogenital area, decreased defecation, diarrhea, the animal appeared to rock, lurch or sway while walking, and the animal appeared flattened with limbs extended. Several of these findings were noted one hour following dosing. However, the majority of the clinical signs were observed at the daily examinations prior to dosing.

All other animals survived to the scheduled necropsy on study day 35 (week 5). Test article-related clinical signs were observed only in the 37.5 mg/kg/day group between study days 32 and 35, primarily at the daily examinations prior to dosing. These consisted of frequent occurrences of decreased defecation and infrequent occurrences of unkempt or hunched appearance, body cool to the touch, rapid respiration, red material around the nose and/or eyes, drooping (half-closed) eyelids, and the animal appeared to rock, lurch or sway while walking.

## 2. REPRODUCTIVE PERFORMANCE

Summary Data: Table 2

Individual Data: Table 82

Reproductive performance was unaffected by test article administration at dose levels of 0.8, 2.5 and 7.5 mg/kg/day. (Males dosed at 37.5 mg/kg/day were not mated as no females were administered this dose level.) Fertility and mating indices for the F<sub>0</sub> males were both 100%, 90%, 90% and 100% in the control, 0.8, 2.5 and 7.5 mg/kg/day groups, respectively. One male in each of the 0.8 and 2.5 mg/kg/day groups did not sire a litter.

## 3. BODY WEIGHTS

Summary Data: Tables 6, 7

Individual Data: Tables 64, 65

Mean body weight gains in the 37.5 mg/kg/day group were comparable to the control group values during the first two weeks of dosing (weeks 0-1 and 1-2). Throughout the remainder of the study, a reduced mean body weight gain (week 2-3) or mean body weight losses (weeks 3-4 and 4-5) were observed in this group. The differences from the control group values were statistically significant ( $p < 0.01$ ). Mean body weights in the 37.5 mg/kg/day group were also lower than the control group values for weeks 3, 4 ( $p < 0.01$ ) and 5 ( $p < 0.01$ ). The week 5 mean body weight in the 37.5 mg/kg/day group was 23% lower than the concurrent control group value.

Mean body weights in the 7.5 mg/kg/day group were comparable to the control group for weeks 0 through 4. Mean body weight in this group was slightly reduced (not statistically significant) on week 5. Mean body weight gains in the 7.5 mg/kg/day group were comparable to the control group throughout the study.

Mean body weights and body weight gains in the 0.8 and 2.5 mg/kg/day group males were unaffected by test article administration throughout the study. All values in these treated groups were similar to the control group values; no statistically significant differences were observed.

4. FOOD CONSUMPTION

Summary Data: Tables 8, 9

Individual Data: Tables 66, 67

Food consumption, evaluated as g/animal/day and g/kg/day, in the 37.5 mg/kg/day group was comparable to that in the control group during the first two weeks of dosing (weeks 0-1 and 1-2). Following the breeding period (week 4-5), food consumption in this group was markedly reduced. The differences from the control group were statistically significant at  $p < 0.01$ .

In the 0.8, 2.5 and 7.5 mg/kg/day groups, food consumption was unaffected by test article administration. Differences from the control group were slight and not statistically significant.

5. FUNCTIONAL OBSERVATIONAL BATTERY

Summary Data: Tables 10, 11, 12, 13, 14, 15, 16, 17

Individual Data: Tables 68, 69, 70, 71

Historical Control Data: Appendix F

No test article-related differences were observed between the control and treated groups when handling observations, open field observations and startle response were compared during week 3. The only statistically significant difference from the control group was a slight increase in grooming ( $p < 0.05$ ) in the 0.8 mg/kg/day group. Similar increases were not observed at the higher dose levels, and the difference was attributed to biological variation.

6. CLINICAL PATHOLOGY

a. HEMATOLOGY

Summary Data: Tables 18, 19, 20

Individual Data: Tables 72, 73, 74

Test article-related changes in hematology parameters were observed at a dose level of 37.5 mg/kg/day. Mean red blood cell count, hemoglobin and hematocrit means in the 37.5 mg/kg/day group were markedly increased when compared to the control group values. The differences were statistically significant at  $p < 0.01$ . Mean platelet count in this group was also significantly increased ( $p < 0.01$ ) when compared to the control group

value. Prothrombin time and activated partial thromboplastin time means in the 37.5 mg/kg/day group were significantly higher ( $p < 0.05$  and  $p < 0.01$ , respectively) than those in the control group. A shift in the types of leukocytes present also occurred in the 37.5 mg/kg/day group; the percentage of lymphocytes was decreased ( $p < 0.01$ ) with a corresponding increase in neutrophils.

Hematology parameters in the 0.8, 2.5 and 7.5 mg/kg/day groups were unaffected by treatment. The only statistically significant ( $p < 0.01$ ) difference from the control group observed in these groups was an increase in mean platelet count in the 2.5 mg/kg/day group. However, this difference could not be attributed to the test article in the absence of a similar increase in the 7.5 mg/kg/day group. No other statistically significant differences from the control group were observed.

b. SERUM CHEMISTRY

Summary Data: Table 21

Individual Data: Table 75

Numerous test article-related changes in serum chemistry parameters were observed in the 37.5 mg/kg/day group. These consisted of the following. Significant ( $p < 0.01$ ) decreases were observed in mean total protein, albumin, globulin and glucose values. Significant ( $p < 0.01$ ) increases were noted in mean total bilirubin, urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, cholesterol, phosphorus and potassium.

No test article-related effects on serum chemistry parameters were noted at dose levels of 0.8, 2.5 or 7.5 mg/kg/day. Differences from the control group were slight and not statistically significant.

## 7. ANATOMIC PATHOLOGY

### a. MACROSCOPIC EXAMINATION

Summary Data: Tables 22, 23

Individual Data: Tables 76, 77

In the 37.5 mg/kg/day group, one male died and three males were euthanized *in extremis* during study week 4. The predominant finding in all four animals was dark red contents in the stomach and/or intestinal tract. Other internal findings in these animals were single occurrences (such as reddened adrenal glands, dilated renal pelves, etc.).

At the scheduled necropsy, four of six males in the 37.5 mg/kg/day group had small thymus glands. No other test article-related internal findings were observed. Other findings in the treated groups were limited to single occurrences in various dose groups (such as enlarged submandibular lymph nodes and small coagulating glands) or did not occur in a dose-related manner (enlarged mediastinal lymph nodes).

### b. ORGAN WEIGHTS

Summary Data: Tables 24, 25, 26

Individual Data: Tables 78, 79, 80

Test article-related changes in organ weight data were observed in the liver, thymus gland and adrenal gland in the 37.5 mg/kg/day group. Mean absolute liver weight in the 37.5 mg/kg/day group was 51% lower than the control group value; the difference was statistically significant at  $p < 0.01$ . Mean liver weight relative to final body weight and mean liver weight relative to brain weight ratios in this group were also significantly reduced ( $p < 0.01$ ) when compared to the control group values. Mean absolute and relative (to final body weight and to brain weight) thymus gland weights in the 37.5 mg/kg/day group were markedly reduced and statistically significant ( $p < 0.01$ ) when compared to the control group values. The mean absolute thymus gland weight in this group was 70% lower than the control group value. Mean absolute and relative (to final body weight and to brain weight) adrenal gland weights in the 37.5 mg/kg/day group were

increased (27% for absolute weight) in comparison to the control group values. The differences were statistically significant at  $p < 0.01$ .

No other test article-related effects on organ weight data were observed at any dose level. Numerous statistically significant differences were observed between the control and 37.5 mg/kg/day groups in kidney, heart, spleen, lung, epididymal, testes, brain and pituitary gland weights. In most cases, mean absolute and relative (to brain weight) organ weights were reduced in comparison to those in the control group, while corresponding mean relative (to final body weight) organ weights were either comparable to or increased when compared to the control group values. Therefore, these differences were attributed to the differences observed in final body weights between the control and 37.5 mg/kg/day groups (the high dose group mean final body weight was 23% lower than the control group value).

c. MICROSCOPIC EXAMINATION

Summary Data: Tables 27, 28

Individual Data: Tables 76, 77

For the 37.5 mg/kg/day group animal that died, the cause of death was related to severe gastric ulceration. The cause of moribundity for the three high dose group males that were euthanized *in extremis* was severe intestinal changes.

Test article-related microscopic changes were observed in the liver, intestinal tract (primarily cecum and colon), thymus gland and spleen of males in the 37.5 mg/kg/day group. In addition, test article-related microscopic changes were observed in the kidneys of the 7.5 and 37.5 mg/kg/day group males. These changes were observed in males at both the unscheduled and scheduled necropsies.

Liver changes in the 37.5 mg/kg/day group males attributed to the test article consisted of the following. Minimal to moderate bile duct hyperplasia was noted in the animal that died, in the three moribund animals and in 5/6 animals at the scheduled necropsy (9/10 animals). The increased incidence of this finding at the scheduled necropsy was statistically

significant ( $p < 0.05$ ) in comparison to the control group. Hepatocellular necrosis (minimal to mild) occurred in the animal that died, in one moribund animal and in 1/6 males at the scheduled necropsy (3/10 animals).

Test article-related effects in the kidneys of the 7.5 and 37.5 mg/kg/day group males were characterized by multifocal tubular necrosis, mostly confined to the corticomedullary tubules. This change was bilateral and was often accompanied by tubular dilatation, occasionally with luminal accumulation of eosinophilic proteinaceous material. Both findings were graded minimal to mild and mild to moderate in the 7.5 and 37.5 mg/kg/day groups, respectively, and were significantly ( $p < 0.05$ ) different in comparison to the control group. Kidney changes were observed in 9/10 males in the 7.5 mg/kg/day group at the scheduled necropsy and in the three moribund males and in all six males in the 37.5 mg/kg/day group at the scheduled necropsy (9/10 animals).

In the 37.5 mg/kg/day group, test article-related changes in the cecum consisted of severe, diffuse mucosal necrosis with loss of mucosal epithelium, proprial stromal collapse, infiltration of mononuclear cells and neutrophils, and dilatation of crypts containing necrotic cellular debris, submucosal edema and submucosal infiltration of mononuclear cells and neutrophils. These findings were noted in the three males that were euthanized *in extremis* and in 3/6 males at the scheduled necropsy (6/10 animals). Similar changes (mild to severe) were observed in the colon and/or ileum of the three moribund males and 2/6 males in the 37.5 mg/kg/day group at the scheduled necropsy (5/10 animals).

Also in the 37.5 mg/kg/day group, mild to moderate lymphoid depletion was observed in the thymus gland of one moribund male and 4/6 males at the scheduled necropsy (5/10 animals). The increased incidence of this finding at the scheduled necropsy was statistically significant ( $p < 0.05$ ) in comparison to the control group. Similar lymphoid changes were noted in the spleen of the male that died, two moribund males and 1/6

males in the 37.5 mg/kg/day group at the scheduled necropsy (4/10 animals).

No treatment-related effects on spermatogenesis were observed in the 37.5 mg/kg/day group males.

All other histopathological findings in the treated groups occurred with similar frequency in the control group, in a limited number of animals and/or in a manner which was not dose-related.

**B. F<sub>0</sub> FEMALES**

**1. CLINICAL OBSERVATIONS AND SURVIVAL**

Summary Data: Tables 29, 30, 31, 32, 33

Individual Data: Tables 81, 82

All F<sub>0</sub> females survived to the scheduled necropsy. Clinical findings in the treated groups, such as hair loss on the forelimbs and red material around the nose, occurred infrequently and/or similarly in the control group. No relationship to test article administration was apparent.

**2. REPRODUCTIVE PERFORMANCE**

Summary Data: Table 30

Individual Data: Table 82

Reproductive performance was unaffected by test article administration at dose levels of 0.8, 2.5 and 7.5 mg/kg/day. Fertility and mating indices for the F<sub>0</sub> females were both 100%, 100%, 90% and 100% in the control, 0.8, 2.5 and 7.5 mg/kg/day groups, respectively. One female in the 2.5 mg/kg/day group and all 10 females in the 7.5 mg/kg/day group had evidence of mating but did not deliver; all of these females were found to be gravid upon macroscopic examination. One 2.5 mg/kg/day group female had no evidence of mating and was nongravid.

The mean number of days between pairing and coitus in the treated groups was similar to the control group value.

3. **BODY WEIGHTS**

a. **WEEKLY**

Summary Data: Tables 34, 35

Individual Data: Tables 83, 84

Mean weekly body weights and body weight gains in the 0.8, 2.5 and 7.5 mg/kg/day group females were comparable to the control group values prior to breeding (weeks 0-1 and 1-2). No statistically significant differences were observed.

b. **GESTATION**

Summary Data: Tables 36, 37

Individual Data: Tables 85, 86

Mean body weights in the 7.5 mg/kg/day group females were comparable to the control group values on gestation days 0 and 7. Mean body weights in this group were reduced in comparison to the control group values on gestation days 14 and 20; the difference on gestation day 20 was statistically significant ( $p < 0.01$ ). Mean body weight gain in the 7.5 mg/kg/day group during gestation days 0-7 was comparable to the control group value. A markedly reduced mean body weight gain was observed in this group during gestation days 7-14 and a mean body weight loss occurred during gestation days 14-20. The differences from the control group were statistically significant at  $p < 0.01$ . The reduced mean body weights and body weight gains in this group correlated with the entirely resorbed litters observed for these females.

In the 2.5 mg/kg/day group, a slightly reduced mean body weight gain was observed during gestation days 14-20. The difference from the control group was not statistically significant. This reduction correlated with the decreased live litter size noted for this group. All other mean body weight gains and all mean body weights in the 2.5 mg/kg/day group were comparable to the control group values.

Mean gestation body weights and body weight gains in the 0.8 mg/kg/day group were similar to the control group values.

c. LACTATION

Summary Data: Tables 38, 39

Individual Data: Tables 87, 88

No dams in the 7.5 mg/kg/day group delivered litters, therefore, no lactation body weight data were available for this group. Mean lactation body weights and body weight gains in the 0.8 and 2.5 mg/kg/day groups were comparable to the control group values; none of the differences were statistically significant.

4. FOOD CONSUMPTION

a. WEEKLY

Summary Data: Tables 40, 41

Individual Data: Tables 89, 90

Food consumption, evaluated as g/animal/day and g/kg/day, in the 0.8, 2.5 and 7.5 mg/kg/day groups prior to breeding was unaffected by test article administration. All values in the treated groups were comparable to the control group values; no statistically significant differences were observed.

b. GESTATION

Summary Data: Tables 42, 43

Individual Data: Tables 91, 92

Food consumption (g/animal/day and g/kg/day) in the 7.5 mg/kg/day group was comparable to that in the control group during gestation days 0-7. Throughout the remainder of gestation (days 7-14 and 14-20), food consumption in this group was reduced and statistically significant ( $p < 0.05$  or  $p < 0.01$ ) when compared to the control group. These reductions in food consumption correlated with the reduced body weight gains observed for this group during these intervals.

Food consumption in the 0.8 and 2.5 mg/kg/day groups was comparable to that in the control group throughout gestation; no statistically significant differences occurred.

c. LACTATION

Summary Data: Tables 44, 45

Individual Data: Tables 93, 94

Food consumption could not be evaluated during lactation in the 7.5 mg/kg/day group as no dams delivered. In the 0.8 and 2.5 mg/kg/day groups, food consumption (g/animal/day and g/kg/day) during lactation was either comparable to or slightly higher than ( $p < 0.05$ ) that in the control group.

5. GESTATION LENGTH AND PARTURITION

Summary Data: Table 46

Individual Data: Table 95

The mean lengths of gestation were comparable between the control group and the 0.8 and 2.5 mg/kg/day groups (no dams in the 7.5 mg/kg/day group delivered). The mean gestation lengths in the 0.8 and 2.5 mg/kg/day groups were 21.9 and 22.0 days, respectively, compared to mean gestation lengths of 21.7 days in the concurrent control group and 21.9 days in the WIL reproductive historical control data. No signs of dystocia were noted.

6. NECROPSY DATA

a. FEMALES WHICH FAILED TO DELIVER

Summary Data: Table 47

Individual Data: Table 96

Two females in the 2.5 mg/kg/day group and all 10 females in the 7.5 mg/kg/day group failed to deliver; all of these animals were internally normal. Female no. 49765 in the 2.5 mg/kg/day group was nongravid; all other females were gravid and had entirely resorbed litters (all early resorptions).

b. LACTATION DAY 4

Summary Data: Tables 48, 49

Individual Data: Tables 97, 98

No test article-related internal findings were observed in dams necropsied on lactation day 4. Female no. 49767 in the 0.8 mg/kg/day

group had reddened adrenal glands. All other females were internally normal.

In the 2.5 mg/kg/day group, the mean number of pups born was markedly decreased and the mean number of unaccounted sites was markedly increased when compared to the control group values. The differences were statistically significant at  $p < 0.05$  and  $p < 0.01$ , respectively. These parameters were unaffected by test article administration at a dose level of 0.8 mg/kg/day.

#### 7. ORGAN WEIGHTS

Summary Data: Tables 50, 51, 52, 53, 54, 55

Individual Data: Tables 99, 100, 101, 102, 103, 104

No test article-related effects on organ weight data were observed at any dose level. The only statistically significant differences from the control group were observed at a dose level of 0.8 mg/kg/day. Mean absolute kidney weight, mean liver and kidney weights relative to final body weight and mean liver and kidney weights relative to brain weight in the 0.8 mg/kg/day group were significantly increased ( $p < 0.05$  or  $p < 0.01$ ) when compared to the control group values. Similar increases were not observed at the higher dose levels of 2.5 and 7.5 mg/kg/day, and no relationship to the test article was evident.

#### 8. MICROSCOPIC EXAMINATION

Summary Data: Tables 56, 57

Individual Data: Tables 96, 97

No microscopic lesions attributed to test article administration were observed in the 7.5 mg/kg/day group upon histopathological examination. The lesions observed in this group were noted similarly in the control group.

### C. F<sub>1</sub> LITTER DATA

#### 1. LIVE BIRTH AND VIABILITY INDICES

Summary Data: Table 58

Individual Data: Table 105, 106

The numbers of dead pups on lactation day 0 were not affected by treatment at dose levels of 0.8 and 2.5 mg/kg/day. Pup viability indices in these same

dose groups for lactation days 1 and 4 were comparable to the values in the control group. No statistically significant differences were observed. Live birth and gestational survival indices and mean stillbirth litter size in the 0.8 and 2.5 mg/kg/day groups were unaffected by treatment.

## 2. SEX RATIOS

Summary Data: Table 58

Individual Data: Table 105

F<sub>1</sub> pup sex ratios were not adversely affected at dose levels of 0.8 and 2.5 mg/kg/day. The pup sex ratio in the 2.5 mg/kg/day group was slightly skewed toward males when compared to the control group sex ratio; the difference was statistically significant at  $p < 0.01$ . However, the toxicological significance of this finding is unknown.

## 3. GENERAL PHYSICAL CONDITION AND MORTALITIES

Summary Data: Tables 58, 59, 60

Individual Data: Tables 105, 106, 107, 108

Pups which were found dead between lactation days 0 and 4 numbered 3, 5 and 1 in the control, 0.8 and 2.5 mg/kg/day groups, respectively. In these same dose groups, 0, 4 and 1 pups, respectively, were missing and presumed cannibalized. The general physical condition of the F<sub>1</sub> pups during lactation in the 0.8 and 2.5 mg/kg/day groups was similar to that in the control group.

With the exception of the presence or absence of milk in the stomach, remarkable necropsy findings for pups found dead during the postnatal period were limited to the following. One pup in each of the control and 0.8 mg/kg/day groups (nos. 49795-01 and 49784-15, respectively) had unilateral microphthalmia.

## 4. LIVE LITTER SIZE AND PUP BODY WEIGHTS

Summary Data: Tables 58, 61

Individual Data: Tables 105, 106, 109, 110

Historical Control Data: Appendices G, H

Mean live litter size in the 2.5 mg/kg/day group (10.4 pups) was reduced when compared to the concurrent control group value (13.4 pups); the difference

was not statistically significant. The 2.5 mg/kg/day group value was also lower than the minimum mean value in the WIL reproductive historical control data (11.7 pups). Mean live litter size in the 0.8 mg/kg/day group was comparable to the control group value.

Mean F<sub>1</sub> pup body weights in the 2.5 mg/kg/day group were greater than the control group values for lactation days 1 and 4. The difference on lactation day 4 was statistically significant at  $p < 0.05$ . The increased pup weights on lactation days 1 and 4 in the 2.5 mg/kg/day group correlated with the decreased mean live litter size in this group. Mean pup body weights in the 0.8 mg/kg/day group were comparable to the control group values on lactation days 1 and 4; no statistically significant differences were observed.

5. POSTNATAL DAY 4 NECROPSY

Summary Data: Table 62

Individual Data: Table 111

At the postnatal day 4 scheduled necropsy, no treatment-related internal findings were observed in pups at any dose level available for evaluation. Variations were noted in one pup in each of the control and 2.5 mg/kg/day groups. Pup no. 49787-02 in the 2.5 mg/kg/day group had an undeveloped renal papilla. Control group pup no. 49795-04 had a hemorrhagic ring around the iris (unilateral). Malformations were noted in one pup in each of the control and 0.8 mg/kg/day groups. Situs inversus was noted for pup no. 49792-09 in the 0.8 mg/kg/day group. Pup no. 49766-15 in the control group had anophthalmia (bilateral); this pup also had 7th cervical ribs and a vertebral anomaly (an extra site of ossification was adjacent to cervical centrum no. 2).

## VI. DISCUSSION AND CONCLUSIONS

In the 37.5 mg/kg/day group, one male died on study day 32 and three males were euthanized *in extremis* on study days 33 or 34. All other animals survived to the scheduled necropsies. Treatment-related clinical findings were limited to the 37.5 mg/kg/day group males between study days 32 and 35. Findings noted for the animal that died and the animals euthanized *in extremis* or at the scheduled necropsy included body cool to the touch, shallow or rapid respiration, and decreased defecation. Prostration and no righting reflex were also noted for the animal that died. Two of the animals which were euthanized *in extremis* appeared flattened with limbs extended and had an impaired righting reflex and diarrhea. Findings noted for animals that were euthanized *in extremis* and for animals euthanized at the scheduled necropsy included unkempt or hunched appearance, red material around the nose and/or eyes, drooping (half-closed) eyelids, and animals which rocked, lurched or swayed as they walked.

Mating and fertility indices were 90% or greater for males and females in the control, 0.8, 2.5 and 7.5 mg/kg/day groups. Other reproductive parameters (days between pairing and coitus, gestation and parturition) were also unaffected by treatment.

In the 37.5 mg/kg/day group males, statistically significant reductions in mean body weight gain or mean body weight losses were observed during the last three weeks of test article administration (weeks 2-3, 3-4 and 4-5). Mean body weights in this group were also significantly reduced in comparison to the control group values for weeks 3, 4 and 5. Mean body weight in the 7.5 mg/kg/day group males was slightly reduced for week 5. No other remarkable differences in mean weekly body weights were observed at any dose level.

Mean body weight gains in the 7.5 mg/kg/day group females were reduced during gestation days 7-14 and 14-20; the differences from the control group were statistically significant. Reductions in mean body weights were observed in this group on gestation days 14 and 20; the difference between the control and 7.5 mg/kg/day group on gestation day 20 was statistically significant. The reduced mean body weights and body weight gains in this group correlated with the entirely resorbed litters observed for these females. A reduction in mean body weight gain in the 2.5 mg/kg/day group during gestation days 14-20 correlated with the reduced mean live litter size observed in this

group. No other treatment-related differences in gestation or lactation body weights or body weight gains were observed in the 0.8 and 2.5 mg/kg/day group females. None of the 7.5 mg/kg/day group females delivered litters, therefore, no lactation body weight data were available for this group.

Food consumption, evaluated as g/animal/day and g/kg/day, was significantly reduced during week 4-5 in the 37.5 mg/kg/day group males. Weekly food consumption in the 0.8, 2.5 and 7.5 mg/kg/day groups was unaffected by treatment.

Statistically significant reductions in food consumption were observed in the 7.5 mg/kg/day group females during gestation days 7-14 and 14-20. In the 0.8 and 2.5 mg/kg/day group females, food consumption was unaffected by treatment throughout gestation and lactation. None of the 7.5 mg/kg/day group females delivered litters, therefore, no lactation food consumption data were available for this group.

No test article-related differences in functional observational battery parameters were apparent in the 0.8, 2.5, 7.5 and 37.5 mg/kg/day group males. Parameters evaluated included handling and open field observations, and startle response.

Clinical pathology parameters affected by test article administration were limited to the 37.5 mg/kg/day group males. Effects on hematology parameters included statistically significant increases in mean red blood cell and platelet counts, and in hemoglobin, hematocrit, prothrombin time and activated partial thromboplastin time means. A shift in the types of leukocytes present also occurred in the 37.5 mg/kg/day group males; the percentage of lymphocytes was significantly decreased, with a corresponding increase in neutrophils. The effects on hematology parameters were indicative of dehydration, stress and decreased liver function, and correlated with microscopic findings noted for the gastrointestinal tract and liver. Test article-related changes in serum chemistry parameters included statistically significant decreases in mean total protein, albumin, globulin and glucose, and statistically significant increases in mean total bilirubin, urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, cholesterol, phosphorus and potassium. The changes in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin and cholesterol levels correlated with microscopic

findings noted in the liver, while changes in albumin, total protein, globulin, creatinine, urea nitrogen and phosphorous levels correlated with microscopic changes in the kidney.

The predominant internal finding observed at the necropsies of the 37.5 mg/kg/day group males that died or were euthanized *in extremis* was dark red contents in the stomach and/or intestinal tract. At the scheduled necropsy of F<sub>0</sub> males, four of six animals in the 37.5 mg/kg/day group had small thymus glands. No treatment-related gross internal findings were noted in the 0.8, 2.5 and 7.5 mg/kg/day group males.

The scheduled necropsy of F<sub>0</sub> females which failed to deliver revealed that one female in the 2.5 mg/kg/day group and all females in the 7.5 mg/kg/day group were gravid and had entirely resorbed litters (all early resorptions). In the 2.5 mg/kg/day group, the difference between the numbers of implantation sites counted at the lactation day 4 necropsy and the numbers of pups born was significantly increased in comparison to the control group value.

Test article-related changes in organ weights occurred in the 37.5 mg/kg/day group males. These included decreases in mean liver and thymus gland weights and increases in mean adrenal gland weight when evaluated on an absolute basis and relative to final body weights and brain weights. Organ weights were unaffected by treatment in the 0.8, 2.5 and 7.5 mg/kg/day group males and females.

Microscopic examination of the male in the 37.5 mg/kg/day group that died revealed that the cause of death was related to severe gastric ulceration. The cause of moribundity for the three 37.5 mg/kg/day group males that were euthanized *in extremis* was severe intestinal changes. Test article-related microscopic changes were observed in the liver, intestinal tract (primarily cecum and colon), thymus gland and spleen of males in the 37.5 mg/kg/day group and in the kidneys of males in the 7.5 and 37.5 mg/kg/day groups at both the unscheduled and scheduled necropsies. Liver changes in the 37.5 mg/kg/day group males consisted of minimal to moderate bile duct hyperplasia and minimal to mild hepatocellular necrosis. Effects in the kidneys were characterized by bilateral multifocal tubular necrosis (graded mild to moderate) in the 7.5 and 37.5 mg/kg/day group males. Severe, diffuse mucosal necrosis in the cecum (with loss of mucosal epithelium, proprial stromal collapse, infiltration of mononuclear cells and neutrophils) was also observed in the 37.5 mg/kg/day group males. Similar changes

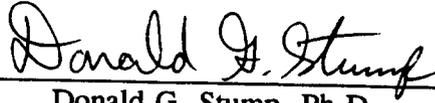
(mild to severe) were observed in the colon and/or ileum of several males in this group. Mild to moderate lymphoid depletion was observed in the thymus gland and spleen of several 37.5 mg/kg/day group males. No treatment-related microscopic findings were observed in the 0.8 and 2.5 mg/kg/day group males. No test article-related microscopic changes in female reproductive organs were observed at any dose level.

Mean lengths of gestation in the 0.8 and 2.5 mg/kg/day group were comparable to the control group values. None of the 7.5 mg/kg/day group females delivered litters (due to entirely resorbed litters), thus precluding assessment of this parameter for this group. No signs of dystocia were noted.

Mean  $F_1$  live litter size in the 2.5 mg/kg/day group was reduced in comparison to the concurrent control group and the WIL historical control data. No adverse effects on  $F_1$  pup viability indices, numbers of dead pups on lactation day 0, stillbirths per litter, pup sex ratios, live births, gestational survival indices, the general physical condition of the pups and pup body weights were observed at dosage level of 0.8 and 2.5 mg/kg/day.  $F_0$  females in the 7.5 mg/kg/day group did not deliver litters, thus precluding evaluation of  $F_1$  litter data.

In conclusion, oral administration of the test article resulted in  $F_0$  male toxicity at a dose level of 37.5 mg/kg/day, as evidenced by mortality, changes in the clinical condition of the animals, inhibition of body weight gain and food consumption, changes in clinical pathologic parameters, gross and microscopic findings, and changes in organ weights.  $F_0$  male toxicity was also observed at a dose level of 7.5 mg/kg/day, as evidenced by decreased body weight and microscopic findings. No  $F_0$  male toxicity was observed at dose levels of 0.8 and 2.5 mg/kg/day.  $F_0$  female toxicity was expressed at dose levels of 2.5 and 7.5 mg/kg/day by inhibition of body weight gain and/or food consumption during the latter part of gestation. No  $F_0$  female toxicity was observed at a dose level of 0.8 mg/kg/day.  $F_0$  mating and fertility indices were not affected by treatment at any dose level.  $F_1$  prenatal toxicity was exhibited at a dose level of 7.5 mg/kg/day by postimplantation loss (completely resorbed litters) and at a dose level of 2.5 mg/kg/day by decreased live litter size. No indications of prenatal or neonatal toxicity were observed at the 0.8 mg/kg/day dose level. Based on the data

obtained, the NOAEL (no observed adverse effect level) for F<sub>0</sub> male subchronic toxicity was considered to be 2.5 mg/kg/day. The NOAEL for F<sub>0</sub> female reproductive toxicity and F<sub>1</sub> prenatal toxicity was considered to be 0.8 mg/kg/day.



Donald G. Stump, Ph.D.  
Study Director

1/22/97  
Date

VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION

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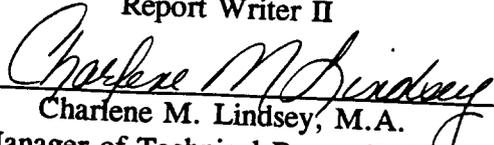
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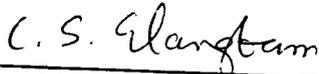
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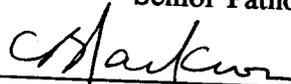
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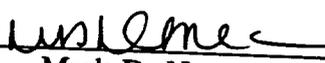
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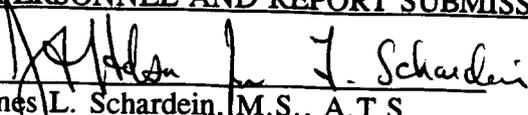
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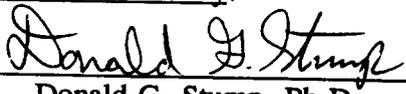
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VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION (continued)

  
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Senior Vice President,      Date  
Director of Research

Approved and Submitted By:

  
\_\_\_\_\_  
Donald G. Stump, Ph.D.      1/22/97  
Staff Toxicologist, Developmental,      Date  
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**VIII. QUALITY ASSURANCE UNIT STATEMENT**

<u>Date(s) of Inspection(s)</u>	<u>Phase Inspected</u>	<u>Date(s) Findings Reported to Study Director</u>	<u>Date(s) Findings Reported to Management</u>
4/30/96	Test Material Preparation/ Analysis	4/30/96	5/28/96
5/9/96	Animal Care/Equipment	5/9/96	6/20/96
5/14, 15/96	Pair Up/Confirmation of Breeding	5/15/96	6/20/96
6/4/96	Blood Collection/Analysis	6/4/96	7/30/96
6/4/96	Necropsy	6/4/96	7/30/96
7/1/96	Trimming of Tissues	7/1/96	8/26/96
9/12-13/96	Study Records (Rx-1)	9/13/96	10/24/96
9/13, 16-17/96	Study Records (I-1)	9/17/96	10/24/96
9/18-20/96	Study Records (I-3)	9/20/96	10/24/96
9/20/96	Study Records (I-1 Supplemental)	9/20/96	10/24/96
9/20, 24/96	Study Records (I-4)	9/25/96	10/24/96
9/25-27/96	Study Records (N-1)	9/27/96	10/24/96
9/27, 30/96	Study Records (N-2)	9/30/96	10/24/96
9/30/96	Study Records (C-1, C-2, C-3)	9/30/96	10/24/96
9/30, 10/1-2/96	Study Records (I-2)	10/2/96	11/26/96
10/2-4/96	Study Records (A-1)	10/09/96	11/26/96
10/3-4/96	Draft Report (Appendix A only)	10/09/96	11/26/96
10/15-18, 29-31, 11/1/96	Draft Report (without Appendix A)	11/4/96	12/27/96
10/29/96	Study Records (H-1/P-1)	10/29/96	11/26/96

The study was conducted and inspected in general accordance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol as approved by the sponsor. Quality Assurance findings, derived from inspections during the conduct of the study and findings from inspections of the raw data and the draft report, are documented and have been reported to the study director. A status report is submitted to management monthly.

The raw data, retention sample(s), if applicable, and the original final report will be stored in the Archives at WIL Research Laboratories, Inc.

*Deborah L. Little*

Deborah L. Little  
Manager of Quality Assurance

*1/22/97*  
Date

**IX. REFERENCES**

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5. American Registry of Pathology (1968) Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology, 3rd Ed., (Luna, L.G., ed.) McGraw Hill Book Co., New York, NY pp. 38-39.
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**TRIAGE of 8(e) Submissions**

Date sent to triage: \_\_\_\_\_

NON-CAP

CAP

Submission number: 13888 ~~X~~ A

TSCA Inventory

Y

N

D

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**STUDY TYPE (circle appropriate):**

**Ernest Falke (E605C)**

ATOX

SBTOX

SEN

CARC

**Gordon Cash (E425)**

ECO

AQUATO

**Katherine Anitole (E613B)**

RTOX/DTOX

**Daljit Sawhney (E611A)**

CTOX

STOX

**Deborah Norris (E606)**

NEUR

**Elizabeth Margosches (E613C)**

EPI

**Michael Cimino (E611D)**

GTOX

**Leonard Keifer (E611C)**

Metabolism/Pharmacokinetics

**OTHER:** \_\_\_\_\_

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**NOTES:**

LEGACY TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8810-0297-13858 SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Elf Atochem North America,

Inc

SUB DATE: 2-18-97

DATE: 2-19-97

CSRAD DATE: 5-6-97

CHEMICAL NAME: Isopropylamine ethanol

CASE: 109-56-8

INFORMATION REQUESTED: ELWP DATE

0501 NO INFO REQUESTED

0502 INFO REQUESTED (TECH)

0503 INFO REQUESTED (VOL ACTIONS)

0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:

0639 REFER TO CHEMICAL SCREENING

0678 CAP NOTICE

VOLUNTARY ACTIONS:

0401 MATERIAL REJECTED

0402 STUDIES PLANNED/IN PROGRESS

0403 INVESTIGATION IN PROGRESS/COMPLETED

0404 LABELING/STUDY (TIA) IS

0405 PROFESSIONAL INQUIRY (TIA) IS

0406 APPAUSE DISCONTINUED

0407 PRODUCTION DISCONTINUED

0408 CONFIDENTIAL

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	BIOAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	ENV. OCCUR/BEH/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAMAGE/FAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	RESPONSE REQUEST DELAY	01 02 04	0248 PRODUCE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	PROD COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	REPORTING RATIONALE	01 02 04	0259 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (HUMAN)	01 02 04		

TRIAL DATA: NON-SEL INVENTORY

YES

CAS SR NO

IN INVENTORY

UNCLASSIFIED

ONGOING REVIEW

YES (DROP/REFER)

NO (CONTINUE)

REFR

SPECIES

RAT

TOXICOLOGICAL CONCERN:

LOW

MED

HIGH

USE: PRODUCTION

*H-repeated subchronic oral toxicity*

"13888A" = " " = "DAILY DOSES OF 0 (DEIONIZED WATER), 0.8, 2.5, OR 7.5 MG/KG/DAY OF ISOPROPYLAMINOETHANOL (CAS# 109-56-8) IN DEIONIZED WATER WERE ADMINISTERED ORALLY BY GAVAGE TO SPRAGUE-DAWLEY CRL:CDBR RATS (10/SEX/DOSE). TEN MALE RATS WERE DOSED AT 37.5 MG/KG/DAY UNDER THE SAME CONDITIONS. ALL RATS WERE DOSED FOR 15 DAYS PRIOR TO MATING THROUGH THE DAY PRIOR TO NECROPSY. THE 37.5 MG/KG/DAY MALE GROUP WAS NECROPSIED ON DAY 35 AND FEMALES ON LACTATION DAY 4. ACTUAL DATA WERE NOT PROVIDED. MALE TOXICITY WAS OBSERVED AT 37.5 MG/KG/DAY. OBSERVATIONS INCLUDED MORTALITY, CHANGES IN THE ANIMALS' CLINICAL CONDITION, INHIBITION OF BODY WEIGHT GAIN AND FOOD CONSUMPTION, CHANGES IN CLINICAL PATHOLOGIC PARAMETERS, GROSS AND MICROSCOPIC FINDINGS, AND CHANGES IN ORGAN WEIGHTS. MALE TOXICITY WAS NOT OBSERVED AT 0.8 AND 2.5 MG/KG/DAY. FEMALE TOXICITY WAS EXPRESSED AT DOSE LEVELS OF 2.5 AND 7.5 MG/KG/DAY BY INHIBITION OF BODY WEIGHT GAIN AND/OR FOOD CONSUMPTION. FEMALE TOXICITY WAS NOT OBSERVED AT 0.8 MG/KG/DAY. THE NOAEL FOR MALE SUB-CHRONIC TOXICITY WAS 2.5 MG/KG/DAY.

ISOPROPYLAMINOETHANOL

109-56-8

*H - reproduction toxicity*

“13888A”=H”=“DAILY DOSES OF 0 (DEIONIZED WATER), 0.8, 2.5, OR 7.5 MG/KG/DAY OF ISOPROPYLAMINOETHANOL (CAS# 109-56-8) IN DEIONIZED WATER WERE ADMINISTERED ORALLY BY GAVAGE TO SPRAGUE-DAWLEY CRL:CDBR RATS (10/SEX/DOSE). ALL RATS WERE DOSED FOR 15 DAYS PRIOR TO MATING THROUGH THE DAY PRIOR TO NECROPSY. MALES WERE NECROPSIED ON DAY 35 AND FEMALES ON LACTATION DAY 4. ACTUAL DATA WERE NOT PROVIDED. MATING AND FERTILITY INDICES AND THE NUMBER OF DAYS BETWEEN PAIRING AND COITUS WERE UNAFFECTED BY TREATMENT. NO CLINICAL SIGNS OF TOXICITY WERE NOTED IN MALES AT ANY DOSE. A SIGNIFICANTLY REDUCED MEAN BODY WEIGHT GAIN WAS OBSERVED IN FEMALES AT 7.5 MG/KG DURING GESTATION DAYS 7-14, AND A MEAN BODY WEIGHT LOSS OCCURRED FROM DAYS 14-20. THESE REDUCTIONS/LOSSES CORRELATED WITH THE ENTIRELY RESORBED LITTERS NOTED FOR THESE FEMALES. NO EFFECTS ON LACTATION, BODY WEIGHT GAIN, FOOD CONSUMPTION, GESTATIONAL LENGTH, OR PARTURITION WERE OBSERVED. AT 2.5 MG/KG, THE MEAN NUMBER OF PUPS BORN WAS SIGNIFICANTLY DECREASED AND THE MEAN NUMBER OF UNACCOUNTED SITES INCREASED WITH RESPECT TO CONTROLS. PUP VIABILITY WAS UNAFFECTED BY TREATMENT, ALTHOUGH SIGNIFICANTLY MORE MALES THAN FEMALES WERE BORN IN 2.5 MG/KG GROUP. MEAN PUP WEIGHTS WERE ALSO SIGNIFICANTLY GREATER AT 2.5 MG/KG. NO OTHER TREATMENT-RELATED EFFECTS WERE NOTED AT NECROPSY.”