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ORIGINAL

B

R.T. Vanderbilt Company, Inc.
INDUSTRIAL MINERALS AND CHEMICALS

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CERTIFIED MAIL

November 15, 1994

OTS Document Processing Center (TS-790)
Attn.: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Contains No CBI

Subject: Notice of Substantial Risk under TSCA Sec. 8(e)
Zinc dimethyldithiocarbamate

Dear Sir:

R. T. Vanderbilt hereby submits this Notice in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA).

R. T. Vanderbilt is a member of a task force that sponsored "An acute neurotoxicity study of ziram in rats" and "A subchronic (13-week) neurotoxicity study of ziram in rats".

A Notice of the preliminary report of the acute toxicity was submitted on December 17, 1993.

The two attached reports were received by R. T. Vanderbilt on November 2, 1994.

The final report of the acute neurotoxicity describes essentially the same symptoms as reported previously.

The subchronic study was conducted at dose levels of 72, 207 and 540 ppm for 91 days. The NOEL was considered to be 207 ppm for systemic toxicity and 540 ppm for neurotoxicity. The NOEL for brain neurotoxic esterase inhibition was considered to be 207 ppm. The NOEL for plasma red blood cell and brain cholinesterase inhibition was considered to be 540 ppm.

The report of the subchronic study is submitted without the Tables of individual experimental values of the test animals, but will be submitted upon request by the Agency.

8EHQ-93-12806
SP001 11/22/94

1/2/95

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The recommendations for use of our materials are based upon tests believed to be reliable. However we do not guarantee the results to be obtained.

If you require additional information on this submission, please contact Rasma Balodis, telephone (203) 853-1400.

Very truly yours,

R. T. VANDERBILT COMPANY, INC.

Jaime D. Lathrop
Executive Vice President

JDL/dap

FINAL REPORT

Contains No CBI

VOLUME 1 OF 4
(Text and Summary Data)

A SUBCHRONIC (13-WEEK) NEUROTOXICITY STUDY OF ZIRAM IN RATS

DATA REQUIREMENT

Guideline #82-7

STUDY DIRECTOR

Mark D. Nemec, B.S.

STUDY INITIATION DATE

September 17, 1993

STUDY COMPLETION DATE

October 7, 1994

PERFORMING LABORATORY

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

LABORATORY STUDY NUMBER

WIL-223004

SPONSOR

The Ziram Task Force
NPC, Incorporated
22636 Glenn Drive
Suite 304
Sterling, VA 22170

266 pages attend volumes 2-3 and 4 Please call submitter

A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10 (d) (1) (A), (B), or (C).

Company: Ziram Task Force

Company Agent: Vincent J. Piccirillo Date: 10/12/94

Chairman, Ziram Task Force
Title

Vincent Piccirillo
Signature

A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

COMPLIANCE STATEMENT

This study, WIL-223004, was designed and conducted in compliance with the following regulatory instruments:

- United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations, 40 CFR Part 160 (October 16, 1989)

- United States EPA/FIFRA Test Guidelines for a Neurotoxicity Screening Battery (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Addendum 10; Neurotoxicity: Series 82-7; October, 1982 and March, 1991)

- Standard Operating Procedures of WIL Research Laboratories, Inc.

- the protocol as approved by the sponsor

Three deviations from the protocol or Standard Operating Procedures are listed as follows; none of the deviations were considered to adversely affect the scientific validity of this study.

1. Section III.B.11. - Relative humidity ranged from 36% to 78% during the study; this was outside the protocol specified range of 30% to 70%.

2. Section III.B.11. - On study days -1 and 0, the lights in the animal room were off approximately 10 minutes longer than the protocol specified 12-hour dark photoperiod.

3. Section III.I.5. - During the study week 3 evaluation of female no. 17962 in the 540 ppm group, hindlimb footsplay was inadvertently evaluated following, not prior to, Locomotor Activity data collection as per Standard Operating Procedures.

Mark D. Nemec, B.S. Study Director	10/7/94 Date
Vincent Piccirillo Sponsor Representative	10/12/94 Date
Vincent Piccirillo Applicant/Submitter	10/12/94 Date

A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

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A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

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A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

I. SUMMARY:

The potential neurotoxicity related to the administration of Ziram in the Sprague-Dawley Crl:CD®BR rat was evaluated in this subchronic study. This study is intended for submission to the U.S. EPA (FIFRA). The test article was administered by the oral route (dietary) for at least 91 consecutive days to all animals (10/sex/group). Test article concentrations in the diet were 72, 207 and 540 ppm. A concurrent control group received the vehicle, basal diet, on a comparable regimen. In each group, 5 animals/sex/group were allocated to cholinesterase/neurotoxic esterase (NTE) evaluations and 5 animals/sex/group were allocated to a neuropathology evaluation. Experimental parameters recorded for all animals included viability, clinical signs, body weights and food consumption. Functional Observational Battery and Locomotor Activity data were recorded for all animals during study weeks 3, 7 and 12 (corresponding to the 4th, 8th and 13th week of exposure). A complete gross necropsy was performed on the animal that died during the study period. At the week 13 necropsy, whole brain weights were recorded for each of the cholinesterase/NTE animals and whole brain weights and brain dimensions were recorded for neuropathology animals. In addition, *in situ* tissue perfusion was performed on all neuropathology animals and a subsequent neuropathological evaluation was conducted on all animals in the control and 540 ppm groups.

Dietary administration of Ziram in rats at concentrations of 72, 207 and 540 ppm for at least 91 days resulted in the following:

A. One male (no. 17859) in the 72 ppm group was found dead on study day 14. Prior to death, this animal displayed hypoactivity and labored respiration. A gross necropsy revealed a large mass on the thymus gland. As no mortality was observed at higher dose levels, this death was not considered to be test article related. All other animals survived to the scheduled euthanization.

B. There were no apparent test article related clinical signs observed for the animals that survived to the scheduled euthanization.

C. Mean body weights in the 540 ppm group males and females were lower than the control group beginning at week 1 and throughout the study period (week 13). The differences from the control group ranged from 8% to 10% for the 540 ppm group males and from 7% to 11% for the females in this group. The lower mean body weights were mainly due to lower mean body weight gains in the 540 ppm group males and females for week 0 to 1. Weekly mean body weight gains were generally comparable to the control group means throughout the remainder of the study. The mean cumulative body weight gains (week 0 to 1 through weeks 0 to 13) were lower than the control group means in the 540 ppm group males and females. The overall (weeks 0 to 13) differences from the control group for mean

body weight gain were 18% and 32% in the 540 ppm group males and females, respectively. No effects on mean body weights or body weight gains were apparent in the 72 and 207 ppm groups.

D. Mean food consumption (evaluated as g/animal/day and g/kg/day) was remarkably reduced in the 540 ppm group males and females during the initial week of test article administration (study week 0 to 1). Furthermore, g/animal/day means for these animals were generally slightly lower than the control group means throughout the remainder of the study period (study weeks 1 to 2 through 12 to 13). As the g/kg/day food consumption values were comparable to control group values, these differences in the g/animal/day values were attributed to the reduced body weights observed in these animals. Food consumption in the 72 and 207 ppm group males and females was unaffected by test article administration throughout the study. The average amounts of test article consumed in the 72, 207, 540 ppm groups were 5, 14 and 34 mg/kg/day for males and 6, 16 and 40 mg/kg/day for females, respectively.

E. No test article related effects indicative of neurotoxicity were apparent between treated and control group animals when Functional Observational Battery and Locomotor Activity evaluations were performed. These observations collectively involved home cage, handling, open field, sensorimotor, neuromuscular and physiological observations and an assessment of total and ambulatory motor activity.

F. No remarkable differences from the control group were observed in mean plasma, red blood cell and brain cholinesterase values at any dietary concentration of Ziram during study weeks 3, 7 and 13.

G. Mean brain neurotoxic esterase values were 47% and 38% lower than the control group values in the 540 ppm group males and females, respectively, at study termination. No test article related effects on mean brain neurotoxic esterase values were observed in the 72 and 207 ppm groups.

H. No effects were observed at any concentration on absolute brain weights or brain weights relative to final body weights in non-perfused animals.

I. No remarkable differences were observed in brain weights or dimensions for animals perfused at the scheduled euthanization.

J. No treatment related neuropathological lesions were observed at the microscopic examination of perfused tissues for 5 animals/sex in the 540 ppm group.

The NOEL (no observable effect level) was considered to be 207 ppm for systemic toxicity and 540 ppm for neurotoxicity. The NOEL for brain neurotoxic esterase inhibition was considered to be 207 ppm. The NOEL for plasma, red blood cell and brain cholinesterase inhibition was considered to be 540 ppm.

II. STUDY OBJECTIVES:

The objectives of this study were to evaluate: a. the potential of the test article to produce gross functional deficits, alterations in motor activity and structural alterations to the nervous system, b. the potential of the test article to affect whole brain neurotoxic esterase (NTE) and red blood cell, plasma and brain cholinesterase when administered to the rat for 13 weeks.

III. MATERIALS AND METHODS:

A. Experimental Schedule and Sponsor Information:

1. Experimental Start Date: October 19, 1993

2. Experimental Termination Date: February 27, 1994

3. Study Sponsor: The Ziram Task Force
c/o NPC, Incorporated
22636 Glenn Drive
Suite 304
Sterling, VA 22107

4. Study Monitor: Vincent Piccirillo, Ph.D., D.A.B.T.
NPC, Incorporated

B. Test System:

1. Species: Rat

2. Strain: Sprague-Dawley Crl:CD®BR

3. Justification for Selection: This species and strain of animal was selected because it is recognized to be appropriate for neurotoxicity studies[1,2].

4. Source: The Charles River Breeding Laboratories, Inc., Portage, Michigan 49081

5. Number on Study: 40 males and 40 females (nulliparous and non-pregnant)

6. Body Weight Range at Initiation of Dosing: Males, 207g - 271g; Females, 151g - 190g

7. Age at Initiation of Dosing: Young adult, 50 days old.

8. Method of Identification: Animals were uniquely identified by a Monel® metal eartag displaying the animal number. Individual cage cards were affixed to each cage and displayed the study number, group number, animal number, dosage level, sex, date of animal arrival and initiation of dosing.

9. Housing: Weanling animals were housed 3 per cage, by sex, in suspended, stainless steel wire-mesh cages for approximately 3 days following receipt. Thereafter, all animals were housed individually. The animals were housed in general accordance with the NIH "Guide for the Care and Use of Laboratory Animals"[3]. The animal facilities are accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

10. Quarantine: The animals were acclimated to laboratory conditions for 19 days prior to dosing initiation. The acclimation period included a pretest period. Due to a delay in the initiation of dosing, the period was extended from one week to two weeks. The animals were observed twice daily for mortality and moribundity.

11. Environmental Conditions: Environmental controls in the animal room were set to maintain temperature at 68-76°F (20.0 - 24.4°C), relative humidity between 30-70%, and a photoperiod of 12 hours light (6 a.m. - 6 p.m.)/12 hours dark. Actual temperature and humidity ranges were 68-75°F (20.0 - 23.9°C) and 36-78%, respectively, during the course of the study. In addition, on study days -1 and 0, the lights were off approximately 10 minutes longer than the specified 12-hour dark photoperiod. These slight deviations from the set humidity level and photoperiod did not apparently affect the outcome of the study.

12. Food and Water: Purina® Certified Rodent Chow® #5002 and municipal water were provided *ad libitum*. Analyses of feed and water used during the study period are maintained at WIL Research Laboratories, Inc.

C. Test Article Data:

1. Identification:	Ziram (Zinc Dimethyldithiocarbamate)
2. Source:	UCB Chemical Organical Division Pantserschipstrast 207 B-900 Gent Belgium 9000
3. Date Received:	March 1, 1993
4. Quantity Received:	1 Bag; gross weight 5300.9 g
5. CAS Number:	137-30-4
6. Lot Number:	V528/8331AA
7. Purity:	97.87%; a correction factor of 1.022 was utilized for dose calculation purposes. A certificate of analysis is located in Appendix B.
8. Physical Description:	White Powder
9. Stability and Storage Conditions:	Stable when stored at room temperature.
10. Retention Sample:	1 g was collected March 9, 1993 and stored under ambient conditions in the Archives at WIL Research Laboratories, Inc.

D. Vehicle Control Data:

1. Identification:	Purina® Certified Rodent Meal #5002
2. Source:	Purina Mills Richmond, Indiana

E. Test Article Preparation:

For the control group, 7.5 kg of feed was weighed out each week and stored in a properly labeled storage bag.

For dose calculation purposes, a correction factor of 1.022 was utilized. For each dose group, the appropriate amount of test article, Ziram, was weighed out into a

tared glass container. After weighing out 1 kg of feed and placing it into a Hobart mixing bowl, the test article was added to the bowl. A small amount of feed was added to the glass container, then the container was scraped to ensure the transference of all of the test article. The preparation was mixed for 5 minutes. The premix was transferred to a V-twin shell mixer and mixed for 10 minutes with enough feed to achieve a total batch of 7.5 kg. An intensifier bar was used during the first and last three minutes of the mixing procedure. Each test diet was prepared approximately weekly, subdivided into seven separate bags for daily administration and stored refrigerated, due to the limited stability of the test article in the diet. One bag of each test diet was withdrawn from refrigeration on a daily basis and released for administration.

F. Sampling:

1. Analytical Tests: Homogeneity, stability and test article concentration analyses were conducted on Ziram diet preparations. The results are presented in Appendix C.

2. Strata Sampled: The top, middle and bottom of the Ziram preparations were sampled for homogeneity. The middle of a test diet was sampled for stability and/or concentration.

3. Sample Size: 100 g

4. Sampling Schedule: Samples were collected prior to study initiation (homogeneity, stability and concentration analyses) and approximately weekly during the study (concentration analyses conducted on samples collected study weeks 0, 1, 2, 3, 7 and 11).

5. Performing Laboratory: Analytical Chemistry Department
WIL Research Laboratories, Inc.

G. Route and Rationale of Test Article Administration:

The oral (dietary) route of administration was utilized. This is a potential route of exposure for the general human population. The test article was administered as a constant concentration (ppm) in the diet.

Test and control articles were administered *ad libitum* and supplied fresh daily, 7 days a week for at least 91 consecutive days prior to necropsy.

Dose levels were selected after consultation with the sponsor based on the results of a previous 6-week dietary range-finding study of Ziram in rats (WIL-160014)[4] and

were consistent with the dose levels selected for the chronic rat study with Ziram. In the 6-week dietary range-finding study, treatment related changes in the clinical condition of the animals (abnormal defecation and/or gait alterations), decreased body weight gains and decreased food consumption were observed at dose levels of 300, 500 and 1000 ppm.

H. Experimental Design:

Animals used on study were determined to be of normal health, weighed and assigned to groups using a computer-based randomization procedure which ensured homogeneity of group means and variances for body weight. (Weight variation did not exceed ± 20% of group mean for each sex.) At randomization, 10 males and 10 females were placed into each group. Within each dose group, 5 animals/sex were allocated for cholinesterase and brain neurotoxic esterase (NTE) determinations. The remaining 5/animals/sex/group were allocated for the neuropathology evaluation at study termination. The five animals/sex/group from the cholinesterase/NTE evaluations were combined with those animals (5 animals/sex/group) for the neuropathology evaluation for the purposes of conducting the Functional Observational Battery (FOB) and Locomotor Activity assessments. Following randomization into study groups, the animals were then randomized into four study replicates (Appendix D) to allow sufficient time for the reasonable conduct of the FOB and the Locomotor Activity assessments. Each dose group and sex were approximately equally represented within a study replicate. On October 15, 1993 (study day -4) control group female no. 17944 (Replicate 1) had an apparent mechanical injury to the left eye and was replaced with female no. 17914. A pretest Functional Observational Battery and a Locomotor Activity evaluation were performed for female no. 17914 on this date. Consequently, no food consumption data was recorded for this animal during the pretest period. This had no impact on the outcome of this study. The following diagram presents the study group assignment:

Group Number	Test Article	Dosage (ppm) Level	Number of Animals Males	Females
1	Basal Diet	0	10	10
2	Ziram	60 (72)	10	10
3	Ziram	180 (207)	10	10
4	Ziram	540	10	10

In order to ensure that concentrations of 60 and 180 ppm for Groups 2 and 3, respectively, were maintained over the course of offering the test diets to the study animals for a period of 16 hours at room temperature, the diets were prepared at concentrations of 72 and 207 ppm, respectively. Information from previous stability analyses indicated that the test article at dosage levels of 60 ppm and 180 ppm was unstable at room temperature, in the selected vehicle; basal diet, for a period of 24 hours. In order to ensure that a concentration of 60 ppm and 180 ppm was

maintained over the course of offering the test diets to the study animals for a period of 16 hours at room temperature, the dosage levels for Groups 2 and 3 were increased by twenty and fifteen percent, respectively.

I. Experimental Observations:

1. Viability:

Adults were observed twice daily (morning and afternoon) for mortality and/or moribundity.

2. Clinical Signs:

Detailed clinical observations were recorded daily for all animals. On study days when the FOB was conducted, no additional clinical signs were recorded with the following exception. All animals in Replicate 1 and 2 were inadvertently examined in addition to the FOB evaluation during week 3. These additional observations were not considered to affect the scientific integrity of the study.

3. Individual Body Weights:

Individual body weights were recorded weekly, beginning approximately two weeks prior to treatment. Body weights were also recorded on treatment days when the FOB and Locomotor Activity evaluations were conducted on animals undergoing these evaluations. Body weights were recorded for all animals prior to the scheduled necropsy (week 13). In addition, a body weight was recorded for the Group 2 male (no. 17859) that died when it was found in that condition.

4. Individual Food and Test Article Consumption:

Individual food consumption was measured daily, beginning two weeks prior to test article administration, and the weekly averages were reported. Food intake was calculated as g/animal/day and g/kg/day.

The mean amounts of Ziram consumed (mg/kg/day) by each sex per group were calculated from the mean food consumed (g/kg/day) and the appropriate nominal concentration of Ziram in the food (ppm).

5. Functional Observational Battery [FOB]:

Observations on 10 animals/sex/group (5 animals/sex/group each from the cholinesterase/NTE group and the neuropathology group) were made pre-study (study week -2) and then during the 4th, 8th and 13th weeks of the test article exposure period (study weeks 3, 7 and 12, respectively) prior to dose administration. Testing was performed by the same technicians, wherever

possible, 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 ± 10db with one exception; home cage observations were performed in the animal room. During the study week 3 evaluation of 540 ppm group female no. 17962, hindlimb footsplay was inadvertently evaluated following, not prior to, Locomotor Activity data collection as per Standard Operating Procedures (SOP). This SOP deviation had no apparent impact on the outcome of the study. All animals were observed for the following parameters as described below (refer to Appendix E for a detailed description of the scoring criteria used for each observation):

a. Home Cage Observations

Posture	Biting
Convulsions/Tremors	Palpebral (eyelid) closure
Feces consistency	

b. 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

c. 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)	

d. Sensory Observations

Approach response	Touch response
Startle response	Tail pinch response
Pupil response	Eyeblink response
Forelimb extension	Hindlimb extension
Air righting reflex	Olfactory orientation

e. Neuromuscular Observations

Hindlimb extensor strength	Grip strength-hind and forelimb
Hindlimb foot splay	Rotarod performance

f. Physiological Observations

Catalepsy	Body weight
Body temperature	

6. Locomotor Activity:

Observations were made on 10 animals/sex/group (5 animals/sex/group each from the cholinesterase/NTE group and the neuropathology group) pre-study (study week -2) and during the 4th, 8th and 13th weeks of the test article exposure period (study weeks 3, 7 and 12, respectively) prior to dose administration. Locomotor Activity, recorded after the completion of the FOB, was measured automatically using the Digiscan 'Micro' Animal Activity System (Omnitech Electronics, Inc., Columbus, OH 43228). This personal computer-controlled system utilizes a series of infrared photobeams surrounding a clear plastic, rectangular cage to quantify an individual animal's motor activity. The testing of treatment groups was done according to replicate sequence. Each animal was tested separately. The activity system was operated in the Stagger Start mode of operation. Data were collected in one minute epochs (print intervals) and the test session duration was 41 minutes. Animal placement into the activity cage in the Stagger Start mode of operation initiated the data collection process. The first epoch was often incomplete due to the placement of the animal in the activity cage. For this reason, the first minute of data was deleted for each animal. The remaining 40 minutes of data collection (divided into 10-minute subsessions) were compiled for data presentation.

Data for ambulatory and total motor activity were tabulated. Total motor activity was defined as a combination of fine motor skills (i.e. grooming; interruption of one or two adjacent photobeams) and ambulatory motor activity (interruption of three or more consecutive photobeams). Refer to Appendix G for additional details on the motor activity methodology.

7. Clinical Pathology (Neurotoxic Esterase and Cholinesterase Animals Only):

Plasma cholinesterase (Cholin) and red blood cell (RBC) cholinesterase (Ache) evaluations were conducted on 5 animals/sex/group pre-study, during the 4th and 8th weeks of test article exposure (corresponding to study weeks 3 and 7, respectively) and at study termination (week 13). Blood samples were collected from the caudal (tail) vein for the intervals prior to study termination and from the inferior vena cava at the time of necropsy. For study weeks 3 and 7, blood

collections followed the completion of the FOB and Locomotor Activity evaluations. The plasma and red blood cell cholinesterase evaluations were conducted at WIL Research Laboratories, Inc. Specific methods, procedures and references used during these analyses are provided in Appendix H.

Following euthanization and exsanguination, whole brain cholinesterase (Cholin) and neurotoxic esterase (NTE) evaluations were conducted for each of the 5 animals/sex/group in this study component. These evaluations were conducted by AniLytics, Incorporated, Gaithersburg, Maryland. The values were then entered into the WIL Toxicology Data Management System (WTDMS™) for statistical analysis.

8. Scheduled Necropsy Examinations:

a. Unscheduled Death:

A complete necropsy was conducted on the animal that was found dead during the study. The necropsy included an examination of the external surface, all orifices, and the cranial, thoracic, abdominal and pelvic cavities including the viscera. Tissues and organs were retained in 10% neutral buffered formalin for possible future histological examination only as deemed necessary by the gross findings.

b. Brain Weights:

At study termination, the 5 animals/sex/group allocated for cholinesterase/NTE evaluations were anesthetized with carbon dioxide and exsanguinated. The brain was excised from the skull for each animal. After weighing each brain, the tissue was prepared, frozen and then shipped on dry ice to AniLytics, Incorporated for evaluation of brain cholinesterase and neurotoxic esterase levels. Whole brain weight to final body weight ratios were calculated.

c. Neuropathology (Neuropathology Animals Only):

At study termination, the 5 animals/sex/group allocated for neuropathological examination were euthanized by carbon dioxide inhalation and then perfused *in situ* with a buffered sodium nitrite solution followed by a solution of 1.5% glutaraldehyde-4.0% formaldehyde. The central and peripheral tissues were dissected and preserved. Brain weight (excluding olfactory bulbs) and brain dimensions (length and width) were recorded. Any observable gross changes, abnormal coloration or lesions of the brain and spinal cord were recorded. The nerve tissues were embedded in plastic or paraffin, as appropriate, sectioned, then stained with hematoxylin and eosin. The following nerve tissues were sampled for a qualitative histopathological examination from

animals in the control and 540 ppm groups:

Central Nervous System tissues[a]
Brain - forebrain, center of cerebrum, midbrain, cerebellum and pons, and the medulla oblongata
Spinal cord - at cervical swellings C_3 - C_8 and at lumbar swellings T_{13} - L_4
Gasserian ganglion/Trigeminal nerves
Lumbar dorsal root ganglion at T_{13} - L_4
Lumbar dorsal root fibers at T_{13} - L_4
Lumbar ventral root fibers at T_{13} - L_4
Cervical dorsal root ganglion at C_3 - C_8
Cervical dorsal root fibers at C_3 - C_8
Cervical ventral root fibers at C_3 - C_8
Optic Nerves
Eyes

a - embedded in paraffin

Peripheral Nervous System tissues[b]
Sciatic nerve (mid-thigh region and at sciatic notch)
Sural nerve
Tibial nerve
Peroneal nerve
Forelimbs[c]
Tail[c]

b - embedded in plastic
c - preserved for potential future examinations

J. Statistical Methods:

All statistical tests for data other than the FOB and Locomotor Activity were performed by a Digital® MicroVAX® 3400 computer with appropriate programming[5]. All analyses were two-tailed (except as noted) for significance levels of 5% and 1%. Each mean was presented with the standard deviation (S.D.) and the number of animals (N) used to calculate the mean. Body weights, body weight changes, food consumption, cholinesterase and neurotoxic esterase values, absolute and relative brain weights and brain dimensions were analyzed by a one-way analysis of variance (ANOVA). If significant differences were indicated by the ANOVA, Dunnett's test[5] was used to compare the control and treated groups. Histopathological findings in the treated groups were compared to the control group data by the one-tailed Kolmogorov-Smirnov test[6].

Statistical tests for the FOB and Locomotor Activity data were performed using a personal computer installed with SAS/STAT statistical software[7]. Each mean was presented with the standard deviation and the number of animals used to calculate the

mean. The animal that died on study was not included in the calculation of the means for any test period. Continuous FOB and Locomotor Activity data were analyzed using a two-way repeated measures ANOVA. If significant treatment or treatment-time interactions occurred, a one-way ANOVA was conducted at each time point. If significant treatment effects were observed at a time point, Dunnett's multiple T-test[6] was conducted to determine significant treatment differences from the control group ($p < 0.05$). FOB parameters yielding scalar (ordinal) or descriptive data were analyzed using the repeated measures SAS CATMOD procedure[7, 8]. If significant treatment or treatment-time interactions occurred, Fisher's Exact test[5] or Dunnett's test[5] were conducted to determine significant treatment differences from the control group. (These tests were performed by a Digital® MicroVAX® 3400 computer with appropriate programming.)

K. 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 protocol.

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

IV. RESULTS AND DISCUSSION:

A. Analysis of Control and Test Article Samples:

Data - Appendix C

The diet formulations were homogeneous with respect to Ziram. There was significant loss of test article in Groups 2 (60 ppm) and 3 (180 ppm) (73.8% and 75.8% of target concentrations, respectively) after 16 hours at room temperature. The Group 4 (540 ppm) diet formulation remained within stability requirements after 16 hours at room temperature (86.1% of target concentration). When Groups 2 and 3 were fortified to 72 and 207 ppm, respectively, the Ziram concentrations decreased to the desired dosage levels [92.0% and 98.9% of the target concentrations (60 and 180 ppm), respectively] after 16 hours of room temperature storage. The diet formulations used for dose administration contained the specified amounts of test article. Mean concentrations (percent of target fortified concentration) for the six diet preparations analyzed were 69.4 ppm (Group 2, 96.3%), 204 ppm (Group 3, 98.5%) and 543 ppm (Group 4, 101%).

B. Survival:

Summary Data - Table 1

Individual Data - Appendix A (Table 1)

One male (no. 17859) in the 72 ppm group was found dead on study day 14. All other animals in the 72 ppm group and all animals in the control, 207 and 540 ppm groups survived through to the scheduled euthanization.

C. Clinical Observations:

Summary Data - Table 1

Individual Data - Appendix F

Male no. 17859 in the 72 ppm group was hypoactive and had labored respiration and red material around the nose on study day 13, the day prior to death. A gross necropsy of this animal revealed a large mass (30 mm x 15 mm x 14 mm) on the thymus gland.

No apparent test article related clinical signs were observed for the animals that survived to the scheduled euthanization. The clinical signs observed in the treated group animals were observed at a similar incidence in the control group, were present in a non dose-related manner, were limited to single animals in various groups, and/or were those commonly observed in laboratory rats.

D. Body Weights:

Summary Data - Tables 2, 3, 3A

Individual Data - Appendix A (Tables 2, 3, 3A)

Mean body weights in the 540 ppm group males and females were lower than the control group beginning at week 1 and continuing throughout the study period (week 13). The differences from the control group ranged from 8% to 10% for the 540 ppm group males and from 7% to 11% for the females in this group. The mean body weight values were significantly ($p<0.05$ or $p<0.01$) lower than the control group values at weeks 1 through 8 for the males and at weeks 1 through 3 and weeks 5 through 13 for the females in the 540 ppm group. The lower mean body weights were mainly due to lower ($p<0.01$) body weight gains in the 540 ppm group males and females for week 0 to 1. In general, weekly mean body weight gains were comparable to the control group means throughout the remainder of the study. A significantly ($p<0.05$) lower body weight gain was observed for the 540 ppm group females for week 9 to 10. The mean cumulative body weight gains (weeks 0 to 1 through weeks 0 to 13) were lower than the control group means in the 540 ppm group males and females. All cumulative gain values were statistically significant ($p<0.05$ or $p<0.01$). The overall (weeks 0 to 13) differences from the control group for mean body weight gain were 18% and 32% in the 540 ppm group males and females, respectively. No test article related effects were observed in the body weight data for the 72 or 207 ppm group males and females.

E. Food Consumption:

Summary Data - Tables 4, 4A, 5

Individual Data - Appendix A (Tables 4, 4A)

Mean food consumption (evaluated as g/animal/day and g/kg/day) was remarkably reduced ($p<0.01$) in the 540 ppm group males and females during the initial week of test article administration (study week 0 to 1). In addition, g/animal/day means for these animals were generally slightly lower than the control group means throughout the remainder of the study period (study weeks 1 to 2 through 12 to 13). The values were statistically significant for weeks 3 to 4, 4 to 5, 5 to 6 and 12 to 13 for the males and for weeks 1 to 2, 2 to 3, 5 to 6, 9 to 10, 10 to 11, 11 to 12 and 12 to 13 for the females. Food consumption in the 72 and 207 ppm group males and females was unaffected by test article administration throughout the study. The only statistically significant ($p<0.05$) difference from the control group was a slightly lower g/kg/day value in the 207 ppm group females for week 0 to 1. However, the g/animal/day value in these females for week 0 to 1 was similar to the control group value. Therefore, the lower g/kg/day value was attributed to a slight difference in mean body weights.

The average amounts of test article consumed weekly (mg/kg/day) were as follows:

Theoretical Dietary Level (ppm)	Average Amount of Test Article Consumed (mg/kg/day)	
	Males	Females
72	5	6
207	14	16
540	34	40

F. Functional Observational Battery [FOB]:

1. Home Cage Observations:

Summary Data - Tables 6 through 13

Individual Data - Appendix A (Tables 5 through 8)

Historical Control Data - Appendix I

No remarkable differences were apparent between the control and treated groups when the home cage observations were evaluated during the pretest period and during study weeks 3, 7 and 12 (4th, 8th and 13th weeks of dose administration, respectively).

2. Handling Observations:

Summary Data - Tables 14 through 21

Individual Data - Appendix A (Tables 9 through 12)

Historical Control Data - Appendix I

No remarkable differences were apparent between the control and treated groups when the handling observations were evaluated during the pretest period and during study weeks 3, 7 and 12.

3. Open Field Observations:

Summary Data - Tables 22 through 29

Individual Data - Appendix A (Tables 13 through 16)

Historical Control Data - Appendix I

No test article related differences were apparent between the control and treated groups when the open field observations were evaluated during the pretest period and during study weeks 3, 7 and 12. One female and one male in the 540 ppm group displayed a gait alteration (walks on tiptoes) at study weeks 3 and 7, respectively. In each case, the alteration was graded as slight but definite. However, these were isolated occurrences for single animals. In addition, this finding has been previously observed in females in the WIL historical control data and no gait alterations were observed during the week 12 open field observations or during the daily clinical examinations at any dose level. Therefore, these isolated occurrences of gait alteration in two animals was not attributed to the test article. No other remarkable differences between the control and treated groups were observed in open field parameters.

4. Sensory Observations:

Summary Data - Tables 30 through 37

Individual Data - Appendix A (Tables 17 through 20)

Historical Control Data - Appendix I

No remarkable differences were apparent between the control and treated groups when the sensorimotor responses were evaluated during the pretest period and during study weeks 3, 7 and 12.

5. Neuromuscular Observations:

Summary Data - Tables 38 through 45

Individual Data - Appendix A (Tables 21 through 24)

Historical Control Data - Appendix I

At the study week 7 neuromuscular evaluation, only the mean forelimb grip strength in the 540 ppm group females was significantly ($p < 0.05$) lower than the control group mean. A similar reduction was not observed in the 540 ppm group males. In addition, mean forelimb grip strength in these females was similar to

the control group means at the other evaluation periods (weeks 3 and 12). Therefore, the difference was not attributed to treatment. No other remarkable differences were apparent between the control and treated groups when the neuromuscular observations were evaluated during the pretest period and study weeks 3, 7 and 12.

6. Physiological Observations:

Summary Data - Tables 46 through 49

Individual Data - Appendix A (Tables 25 through 28)

Historical Control Data - Appendix I

Test article administration had no adverse effects on catalepsy or body temperature at dietary concentrations of 72, 207 and 540 ppm. Mean body weights in the 540 ppm group males and females were reduced during study weeks 3, 7 and 12 when compared to the control group values. With the exception of the week 12 value for the males, all of these means were statistically significant ($p<0.05$ or $p<0.01$). These findings were consistent with those noted for the weekly body weight data (see Section IV.C.). No effects on mean body weights were apparent in the 72 or 207 ppm group males and females when evaluated during the pretest period and during study weeks 3, 7 and 12.

G. Locomotor Activity:

Summary Data - Tables 50 through 53

Individual Data - Appendix A (Tables 29 through 32)

Historical Control Data - Appendix J

Mean ambulatory and total motor activity values in the 72, 207 and 540 ppm group males and females were similar to the control group values during the pretest period and during study weeks 3, 7 and 12 (4th, 8th and 13th weeks of dose administration, respectively). Animals in all study groups during each evaluation period showed normal habituation profiles to the test chambers during the Locomotor Activity sessions.

H. Cholinesterase Determinations:

Summary Data - Tables 54 through 56

Individual Data - Appendix A (Tables 34 through 38)

No remarkable differences from the control group were observed in mean plasma and red blood cell cholinesterase values at any dietary concentration of Ziram during study weeks 3, 7 and 13.

No apparent effect on mean brain cholinesterase was observed at any dietary concentration of Ziram. No significant differences from the control group were observed in the treated groups.

Mean brain neurotoxic esterase values were significantly ($p<0.05$ or $p<0.01$) lower in the 540 ppm group males and females when compared to the control group values at week 13. The differences from the control group were 47% and 38% for the males and females, respectively, and were attributed to the test article. No remarkable differences from the control group were apparent in the 72 or 207 ppm group males and females.

I. Pathology:

1. Non-Perfused Animals:

a. Unscheduled Death:

Summary Data - Table 57

Individual Data - Appendix A (Table 39)

One male in the 72 ppm group died on study day 14. On the day prior to death, this male was hypoactive and had labored respiration. Macroscopic examination of this animal revealed a large mass (30 mm x 15 mm x 14 mm) on the thymus gland. The only other gross lesions observed for this animal were enlarged lymph nodes (mediastinal and bronchial).

b. Brain Weights:

Summary Data - Tables 58, 59

Individual Data - Appendix A (Tables 40, 41)

No test article related changes were apparent in mean absolute brain weights or mean brain weights relative to final body weights at any dietary

concentration tested. All values in the treated groups were comparable to the control group values.

2. Perfused Animals:

a. Brain Weight and Dimensions:

Summary Data - Table 60

Individual Data - Appendix A (Table 42)

No adverse effects were apparent on mean absolute brain weights or brain length and width measurements at dietary concentrations of 72, 207 and 540 ppm. The values in the treated groups were similar to those observed in the control group.

b. Microscopic Examination:

Summary Data - Table 61

Individual Data - Appendix A (Table 43)

Historical Control Data - Appendix K

No microscopic lesions were observed in any central or peripheral nervous system tissues upon histopathological examination of the 5 neuropathology animals/sex in the 540 ppm group. The only lesions observed were limited to one male and one female in the control group. Digestion chambers were noted in the sciatic nerve for both the male and the female and in the peroneal nerve for the female.

V. CONCLUSIONS:

Dietary administration of Ziram in rats at a concentration of 72, 207 and 540 ppm for at least 91 days resulted in the following:

A. One male (no. 17859) in the 72 ppm group was found dead on study day 14. This animal displayed hypoactivity and labored respiration prior to death. A gross necropsy revealed a large mass on the thymus gland. As no mortality was observed at higher dose levels, this death was not considered to be test article related. All other animals survived to the scheduled euthanization.

B. There were no apparent test article related clinical signs observed for the animals that survived to the scheduled euthanization.

C. Mean body weights in the 540 ppm group males and females were lower than the control group beginning at week 1 and throughout the study period (week 13). The differences from the control group ranged from 8% to 10% for the 540 ppm group males and from 7% to 11% for the females in this group. The lower mean body weights were mainly due to lower mean body weight gains in the 540 ppm group males and females for week 0 to 1. Weekly mean body weight gains were generally comparable to the control group means throughout the remainder of the study. The mean cumulative body weight gains (week 0 to 1 through weeks 0 to 13) were lower than the control group means in the 540 ppm group males and females. The overall (weeks 0 to 13) differences from the control group for mean body weight gain were 18% and 32% in the 540 ppm group males and females, respectively. No effects on mean body weights or body weight gains were apparent in the 72 and 207 ppm groups.

D. Mean food consumption (evaluated as g/animal/day and g/kg/day) was remarkably reduced in the 540 ppm group males and females during the initial week of test article administration (study week 0 to 1). Furthermore, g/animal/day means for these animals were generally slightly lower than the control group means throughout the remainder of the study period (study weeks 1 to 2 through 12 to 13). As the g/kg/day food consumption values were comparable to control group values, these differences in the g/animal/day values were attributed to the reduced body weights observed in these animals. Food consumption in the 72 and 207 ppm group males and females was unaffected by test article administration throughout the study. The average amounts of test article consumed in the 72, 207, 540 ppm groups were 5, 14 and 34 mg/kg/day for males and 6, 16 and 40 mg/kg/day for females, respectively.

E. No test article related effects indicative of neurotoxicity were apparent between treated and control animals when Functional Observational Battery and Locomotor Activity evaluations were performed. These observations collectively involved home cage, handling, open field, sensorimotor, neuromuscular and physiological observations and an assessment of total and ambulatory motor activity.

F. No remarkable differences from the control group were observed in mean plasma, red blood cell and brain cholinesterase values at any dietary concentration of Ziram during study weeks 3, 7 and 13.

G. Mean brain neurotoxic esterase values were 47% and 38% lower than the control group values in the 540 ppm group males and females, respectively, at study termination. No test article related effects on mean brain neurotoxic esterase values were observed in the 72 and 207 ppm groups.

H. No effects were observed at any concentration on absolute brain weights or brain weights relative to final body weights in non-perfused animals.

I. No remarkable differences were observed in brain weights or dimensions for animals perfused at the scheduled euthanization.

J. No treatment related neuropathological lesions were observed at the microscopic examination of perfused tissues for 5 animals/sex in the 540 ppm group.

The NOEL (no observable effect level) was considered to be 207 ppm for system toxicity and 540 ppm for neurotoxicity. The NOEL for brain neurotoxic esterase inhibition was considered to be 207 ppm. The NOEL for plasma, red blood cell and brain cholinesterase inhibition was considered to be 540 ppm.

Mark D. Nemec, B.S.
Study Director

10/7/94
Date

VI. KEY STUDY PERSONNEL AND REPORT SUBMISSION:

Pathologist of Record:

Robert R. Dahlgren, D.V.M., Ph.D. — 10-7-94 Date
Diplomate A.C.V.P.
Director of Pathology

Submitted By:

Mark D. Nemec, B.S. — 10/7/94 Date
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Report Prepared By:

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Lisa A. Simon, M.B.A., B.S., M.T. (ASCP)	Supervisor of Clinical Pathology

VII. QUALITY ASSURANCE UNIT STATEMENT:

Date(s) of Inspection(s)	Phase Inspected	Date(s) Findings Reported to Study Director	Date(s) Findings Reported to Management
10/15/93	Test Material Preparation/Analysis	10/18/93	11/24/93
10/21/93	Animal Care/Equipment	10/22/93	11/24/93
11/9/93	Functional Observational Battery	11/9/93	12/27/93
12/7/93	Blood Collection/Analysis	12/8/93	1/27/94
1/18/94	Necropsy	1/19/94	2/24/94
2/10/94	Trimming (Histology)	2/10/94	3/21/94
2/19/94	Brain NTE and Che*	7/18/94	8/31/94
3/15-16/94	Study Records (I-2)	3/16/94	4/27/94
3/16/94	Study Records (I-3)	3/17/94	4/27/94
3/31/94	Study Records (I-4)	3/31/94	4/27/94
3/31 and 4/5/94	Study Records (I-5)	4/5/94	5/27/94
4/1,5/94	Study Records (I-6)	4/5/94	5/27/94
4/5-6/94	Study Records (I-7)	4/6/94	5/27/94
4/6-7/94	Study Records (I-8)	4/7/94	5/27/94
4/7/94	Study Records (I-9)	4/7/94	5/27/94
4/7-8,15/94	Study Records (I-1)	4/19/94	5/27/94
4/13-14/94	Study Records (N-1,H-1/P-1)	4/14/94	5/27/94
4/13-15/94	Study Records (C-1,C-2)	4/15/94	5/27/94
4/15,19/94	Study Records (Rx-1)	4/19/94	5/27/94
5/27,31 & 6/1-3/94	Draft Report (without Appendix B)	6/6/94	7/27/94
6/2/94	Study Records (I-10)	6/2/94	7/27/94
6/28,30 & 7/11-12/94	Draft Report (Appendix B)	7/12/94	8/31/94
7/19, 21/94	Study Records (SAS - FOB/MA)	7/21/94	8/31/94
10/6/94	Study Records (Supplemental)	10/6/94	11/94

* = conducted by AniLytics, Incorporated

This study was conducted and inspected in accordance with all current Good Laboratory Practice Regulations for the United States EPA FIFRA, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol and protocol amendments as approved by the sponsor with one exception. Mean whole brain cholinesterase and neurotoxic esterase values were audited by AniLytics, Incorporated, Gaithersburg, MD. Quality Assurance inspections during the conduct of the study and findings from review of the final report were documented and reported to the study director. A status report is submitted to management monthly.

Raw data in magnetic form, retention samples of the test article and the original final report will be retained at WIL Research Laboratories, Inc.

Deborah L. Little — 10/7/94

Deborah L. Little
Manager of Quality Assurance

Date

VIII. REFERENCES:

1. Moser, V.C., McDaniel, K.L. and Phillips, P.M. (1991) Rat strain and stock comparisons using a functional observational battery: Baseline values and effects of Amitraz. Toxicol. Appl. Pharmacol. 108: 267-283.

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3. NIH (1985) Guide for the Care and Use of Laboratory Animals. United States Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 86-23, 83 pages.

4. WIL-160014, A 6-Week Dietary Range-Finding Study of Ziram in Rats, WIL Research Laboratories, Inc.

5. BMDP (1979) Biomedical Computer Programs (Dixon, W.J. and Brown, M.B., eds.) University of California Press, Berkeley, CA, pp. 612, 780, 781.

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8. Creason, J.P. (1989) Data evaluation and statistical analysis of functional observational battery data. J. Am. Coll. Toxicol. 8: 157-169.

A Subchronic (13-Week)
Neurotoxicity Study of Ziram in Rats

Summary Data
(Tables 1-61)

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS/DISPOSITIONS)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE:	10-19-93 TO 01-21-94			
GROUP:	1	2	3	4
NORMAL				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	776/ 10	663/ 10	853/ 10	780/ 10
DISPOSITION				
-FOUND DEAD	0/ 0	1/ 1	0/ 0	0/ 0
-TERMINAL NECROPSY	10/ 10	9/ 9	10/ 10	10/ 10
BEHAVIOR/CNS				
-HYPOACTIVE	0/ 0	1/ 1	0/ 0	0/ 0
BODY/INTEGUMENT				
-SCABBING DORSAL HEAD	0/ 0	21/ 1	0/ 0	16/ 1
-HAIR LOSS DORSAL HEAD	0/ 0	34/ 1	0/ 0	15/ 1
-MOIST SCABBING DORSAL HEAD	0/ 0	5/ 1	0/ 0	1/ 1
-HAIR LOSS RIGHT FORELIMB	75/ 1	66/ 3	1/ 1	58/ 1
-HAIR LOSS LEFT FORELIMB	79/ 2	59/ 1	0/ 0	2/ 1
-DRIED RED MATERIAL PREPUCE AREA	0/ 0	0/ 0	1/ 1	0/ 0
-WET RED MATERIAL PREPUCE AREA	0/ 0	1/ 1	0/ 0	0/ 0
CARDIO-PULMONARY				
-LABORED RESPIRATION	0/ 0	1/ 1	0/ 0	0/ 0
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND NOSE	7/ 4	6/ 2	0/ 0	8/ 4

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 1 (DAILY CLINICAL OBSERVATIONS/DISPOSITIONS)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE:	10-19-93 TO 01-21-94			
GROUP:	1	2	3	4
EYES/EARS/NOSE				
-SCABBING RIGHT EAR	18/ 1	13/ 2	0/ 0	14/ 1
-RIGHT EAR APPEARS SWOLLEN	3/ 1	1/ 1	27/ 1	0/ 0
-DRIED RED MATERIAL AROUND LEFT EYE	0/ 0	23/ 1	0/ 0	0/ 0
-SCABBING AROUND LEFT EYE	0/ 0	2/ 1	0/ 0	4/ 1
-SCABBING LEFT EAR	0/ 0	3/ 1	0/ 0	0/ 0
-DRIED RED MATERIAL AROUND RIGHT EYE	0/ 0	18/ 1	0/ 0	2/ 1
-LACRIMATION RIGHT EYE	0/ 0	2/ 1	0/ 0	0/ 0
-LACRIMATION LEFT EYE	0/ 0	5/ 1	0/ 0	0/ 0
-LEFT EAR APPEARS SWOLLEN	0/ 0	1/ 1	0/ 0	0/ 0
-HAIR LOSS AROUND LEFT EYE	0/ 0	8/ 1	0/ 0	0/ 0
EXCRETA				
-URINE APPEARS CRYSTALLINE ON CAGE PAPER	30/ 8	20/ 9	27/ 10	31/ 9
ORAL/DENTAL				
-DRIED RED MATERIAL AROUND MOUTH	1/ 1	1/ 1	1/ 1	0/ 0
-UPPER INCISORS MALALIGNED	0/ 0	38/ 1	0/ 0	0/ 0
-TEETH LONG, TRIMMED	0/ 0	7/ 1	0/ 0	0/ 0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

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TABLE 1 (DAILY CLINICAL OBSERVATIONS/DISPOSITIONS)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE:	10-19-93 TO 01-21-94			
GROUP:	1	2	3	4
NORMAL				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	814/ 10	760/ 10	780/ 10	835/ 10
DISPOSITION				
-TERMINAL NECROPSY	10/ 10	10/ 10	10/ 10	10/ 10
BODY/INTEGUMENT				
-HAIR LOSS RIGHT FORELIMB	24/ 1	52/ 2	4/ 1	0/ 0
-HAIR LOSS LEFT FORELIMB	42/ 1	64/ 2	0/ 0	0/ 0
-SCABBING RIGHT FORELIMB	0/ 0	11/ 2	0/ 0	0/ 0
-DRIED RED MATERIAL RIGHT FORELIMB	0/ 0	2/ 2	0/ 0	0/ 0
-SCABBING LEFT FORELIMB	0/ 0	7/ 2	0/ 0	0/ 0
-DRIED BROWN STAINING RIGHT FORELIMB	0/ 0	15/ 1	0/ 0	0/ 0
-DRIED BROWN STAINING LEFT FORELIMB	0/ 0	14/ 1	0/ 0	0/ 0
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND NOSE	2/ 2	0/ 0	0/ 0	0/ 0
-SCABBING RIGHT EAR	5/ 1	0/ 0	0/ 0	0/ 0
-RIGHT EAR APPEARS SWOLLEN	1/ 1	5/ 1	57/ 1	0/ 0
-DRIED RED MATERIAL AROUND LEFT EYE	0/ 0	11/ 1	0/ 0	0/ 0
-SCABBING LEFT EAR	0/ 0	6/ 1	0/ 0	0/ 0
-HAIR LOSS AROUND LEFT EAR	0/ 0	2/ 1	0/ 0	0/ 0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 1 (DAILY CLINICAL OBSERVATIONS/DISPOSITIONS)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE: 10-19-93 TO 01-21-94

GROUP:	1	2	3	4
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND RIGHT EYE	1/ 1	0/ 0	0/ 0	0/ 0
-HAIR LOSS AROUND NOSE	18/ 1	0/ 0	0/ 0	0/ 0
-LEFT EAR APPEARS SWOLLEN	0/ 0	5/ 1	0/ 0	0/ 0
-HAIR LOSS AROUND LEFT EYE	0/ 0	2/ 1	0/ 0	0/ 0
EXCRETA				
-FECES APPEAR SMALL IN SIZE	0/ 0	1/ 1	0/ 0	3/ 1
-DECREASED DEFECATION	0/ 0	1/ 1	0/ 0	1/ 1
-URINE APPEARS CRYSTALLINE ON CAGE PAPER	30/ 8	32/ 9	71/ 10	70/ 8
ORAL/DENTAL				
-DRIED RED MATERIAL AROUND MOUTH	0/ 0	0/ 0	1/ 1	0/ 0
-TEETH LONG, TRIMMED	0/ 0	1/ 1	0/ 0	0/ 0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2					
	MEAN	119.	118.	119.	118.
	S.D.	5.1	4.7	4.4	4.7
	N	10	10	10	10
-1					
	MEAN	183.	181.	185.	186.
	S.D.	5.9	12.9	8.6	8.2
	N	10	10	10	10
0					
	MEAN	242.	239.	244.	245.
	S.D.	12.4	17.6	13.5	11.9
	N	10	10	10	10
1					
	MEAN	292.	290.	291.	264.**
	S.D.	15.2	22.1	17.9	11.6
	N	10	10	10	10
2					
	MEAN	332.	330.	333.	300.*
	S.D.	20.8	26.4	25.0	16.9
	N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3					
	MEAN	365.	362.	368.	334.*
	S.D.	26.8	24.9	25.4	18.4
	N	10	9	10	10
4					
	MEAN	386.	385.	392.	349.*
	S.D.	32.3	27.0	26.3	20.6
	N	10	9	10	10
5					
	MEAN	411.	410.	421.	371.*
	S.D.	36.6	28.1	32.1	23.4
	N	10	9	10	10
6					
	MEAN	431.	434.	436.	389.*
	S.D.	37.5	32.3	36.0	25.6
	N	10	9	10	10
7					
	MEAN	448.	455.	456.	407.*
	S.D.	38.8	36.6	37.7	28.0
	N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8	MEAN	455.	455.	466.	413.*
	S.D.	38.7	37.1	39.2	29.4
	N	10	9	10	10
9	MEAN	463.	466.	474.	422.
	S.D.	39.7	38.9	39.9	30.1
	N	10	9	10	10
10	MEAN	483.	489.	490.	439.
	S.D.	44.2	38.6	45.3	34.2
	N	10	9	10	10
11	MEAN	497.	503.	508.	453.
	S.D.	44.7	41.3	44.5	34.8
	N	10	9	10	10
12	MEAN	506.	511.	508.	464.
	S.D.	47.0	43.8	46.8	33.9
	N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

	----- M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 13				
MEAN	507.	508.	510.	463.
S.D.	49.4	38.5	51.7	34.6
N	10	9	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2					
	MEAN	106.	106.	106.	106.
	S.D.	4.4	4.6	4.2	4.4
	N	10	10	10	10
-1					
	MEAN	144.	144.	147.	145.
	S.D.	4.2	6.0	5.2	8.2
	N	9	10	10	10
0					
	MEAN	163.	163.	170.	167.
	S.D.	6.3	9.5	9.0	12.9
	N	10	10	10	10
1					
	MEAN	181.	183.	184.	169.*
	S.D.	7.0	9.7	9.2	12.1
	N	10	10	10	10
2					
	MEAN	196.	197.	196.	183.*
	S.D.	8.1	8.4	11.2	15.0
	N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3					
	MEAN	210.	211.	211.	192.**
	S.D.	9.9	10.3	13.4	14.7
	N	10	10	10	10
4					
	MEAN	211.	215.	218.	197.
	S.D.	13.3	13.3	12.4	15.7
	N	10	10	10	10
5					
	MEAN	227.	228.	227.	208.**
	S.D.	10.8	12.8	14.3	14.4
	N	10	10	10	10
6					
	MEAN	234.	236.	232.	211.**
	S.D.	11.1	14.0	18.1	14.2
	N	10	10	10	10
7					
	MEAN	239.	242.	239.	217.**
	S.D.	15.2	12.7	14.6	13.9
	N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8					
	MEAN	242.	246.	241.	220.**
	S.D.	12.9	13.7	15.8	12.8
	N	10	10	10	10
9					
	MEAN	241.	246.	242.	222.*
	S.D.	19.6	14.1	15.0	13.0
	N	10	10	10	10
10					
	MEAN	253.	254.	250.	227.**
	S.D.	19.2	14.8	19.4	14.0
	N	10	10	10	10
11					
	MEAN	261.	260.	254.	232.**
	S.D.	19.1	15.8	19.2	13.9
	N	10	10	10	10
12					
	MEAN	264.	265.	261.	234.**
	S.D.	20.6	18.6	16.1	13.3
	N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 2
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 13				
MEAN	261.	262.	258.	234.**
S.D.	19.3	17.5	17.5	12.7
N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3

PROJECT NO.:WIL-223004 | A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS | PAGE 1

SPONSOR:ZIRAM TASK FORCE | BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	65.	63.	66.	68.
S.D.	5.9	9.7	7.4	5.5
N	10	10	10	10
-1 TO 0				
MEAN	59.	58.	59.	59.
S.D.	7.2	6.2	5.8	5.2
N	10	10	10	10
0 TO 1				
MEAN	50.	51.	47.	19.**
S.D.	4.5	8.1	6.0	11.8
N	10	10	10	10
1 TO 2				
MEAN	40.	41.	42.	36.
S.D.	7.3	11.1	8.1	9.2
N	10	9	10	10
2 TO 3				
MEAN	33.	32.	35.	33.
S.D.	6.7	9.0	4.0	6.2
N	10	9	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 3
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3 TO 4					
	MEAN	21.	23.	24.	16.
	S.D.	7.7	6.6	4.3	4.5
	N	10	9	10	10
4 TO 5					
	MEAN	25.	25.	29.	22.
	S.D.	5.2	6.8	9.6	6.8
	N	10	9	10	10
5 TO 6					
	MEAN	20.	24.	15.	18.
	S.D.	3.8	11.3	10.5	7.7
	N	10	9	10	10
6 TO 7					
	MEAN	18.	21.	20.	19.
	S.D.	5.6	7.9	6.3	6.8
	N	10	9	10	10
7 TO 8					
	MEAN	6.	0.	10.	6.
	S.D.	4.5	21.3	6.1	5.1
	N	10	9	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 3
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9					
	MEAN	8.	10.	8.	9.
	S.D.	5.3	6.1	8.3	6.1
	N	10	9	10	10
9 TO 10					
	MEAN	20.	24.	16.	18.
	S.D.	6.1	6.4	11.0	7.9
	N	10	9	10	10
10 TO 11					
	MEAN	14.	14.	18.	14.
	S.D.	4.1	4.8	4.4	4.1
	N	10	9	10	10
11 TO 12					
	MEAN	9.	8.	0.	11.
	S.D.	5.0	5.4	14.0	2.8
	N	10	9	10	10
12 TO 13					
	MEAN	1.	-3.	2.	-1.
	S.D.	8.3	9.6	16.0	6.6
	N	10	9	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 3
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	37.	38.	40.	39.
S.D.	2.3	2.7	4.7	6.1
N	9	10	10	10
-1 TO 0				
MEAN	20.	19.	23.	22.
S.D.	4.0	6.3	5.3	6.6
N	9	10	10	10
0 TO 1				
MEAN	18.	20.	14.	2.**
S.D.	5.1	6.0	5.6	6.1
N	10	10	10	10
1 TO 2				
MEAN	15.	13.	12.	14.
S.D.	5.1	4.5	6.6	5.6
N	10	10	10	10
2 TO 3				
MEAN	14.	14.	15.	9.
S.D.	6.7	4.9	5.2	3.6
N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3 TO 4				
MEAN	1.	4.	7.	5.
S.D.	8.8	11.3	6.0	6.6
N	10	10	10	10
4 TO 5				
MEAN	16.	13.	9.	10.
S.D.	8.1	10.6	5.4	3.7
N	10	10	10	10
5 TO 6				
MEAN	7.	8.	5.	3.
S.D.	4.9	5.7	8.1	4.5
N	10	10	10	10
6 TO 7				
MEAN	5.	7.	7.	6.
S.D.	6.7	5.1	5.3	6.8
N	10	10	10	10
7 TO 8				
MEAN	3.	3.	3.	3.
S.D.	5.8	3.3	5.9	3.7
N	10	10	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 3
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9					
	MEAN	-1.	0.	1.	2.
	S.D.	7.7	4.0	4.7	2.8
	N	10	10	10	10
9 TO 10					
	MEAN	11.	9.	7.	5.*
	S.D.	4.9	4.9	6.7	2.7
	N	10	10	10	10
10 TO 11					
	MEAN	9.	6.	5.	5.
	S.D.	3.7	5.6	5.8	3.4
	N	10	10	10	10
11 TO 12					
	MEAN	3.	5.	6.	3.
	S.D.	5.8	6.3	6.0	4.0
	N	10	10	10	10
12 TO 13					
	MEAN	-3.	-3.	-2.	0.
	S.D.	5.0	5.1	4.8	3.3
	N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- MALE -----			
GROUP:		0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 1				
	MEAN	50.	51.	47.	19.**
	S.D.	4.5	8.1	6.0	11.8
	N	10	10	10	10
	0 TO 2				
	MEAN	90.	92.	89.	56.**
	S.D.	10.9	17.0	13.5	14.1
	N	10	9	10	10
	0 TO 3				
	MEAN	123.	124.	125.	89.**
	S.D.	17.2	12.0	13.5	17.6
	N	10	9	10	10
	0 TO 4				
	MEAN	144.	147.	148.	104.**
	S.D.	23.7	16.2	15.4	20.1
	N	10	9	10	10
	0 TO 5				
	MEAN	169.	172.	177.	126.**
	S.D.	27.6	16.6	21.9	23.9
	N	10	9	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 6				
	MEAN	189.	196.	192.	144.**
	S.D.	29.1	22.4	27.1	24.1
	N	10	9	10	10
	0 TO 7				
	MEAN	207.	217.	212.	163.**
	S.D.	30.2	27.9	29.4	26.8
	N	10	9	10	10
	0 TO 8				
	MEAN	213.	217.	223.	168.**
	S.D.	30.4	29.0	30.6	28.8
	N	10	9	10	10
	0 TO 9				
	MEAN	221.	228.	231.	177.**
	S.D.	31.6	30.1	32.1	29.4
	N	10	9	10	10
	0 TO 10				
	MEAN	242.	251.	246.	194.*
	S.D.	36.0	30.7	37.7	32.9
	N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 11				
	MEAN	256.	265.	264.	208.*
	S.D.	36.1	33.6	37.2	32.5
	N	10	9	10	10
	0 TO 12				
	MEAN	264.	273.	264.	219.*
	S.D.	38.4	37.0	41.1	32.0
	N	10	9	10	10
	0 TO 13				
	MEAN	266.	270.	266.	218.*
	S.D.	41.0	33.8	46.5	31.3
	N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 1				
	MEAN	18.	20.	14.	2.**
	S.D.	5.1	6.0	5.6	6.1
	N	10	10	10	10
	0 TO 2				
	MEAN	33.	34.	26.	16.**
	S.D.	6.3	5.0	9.6	6.9
	N	10	10	10	10
	0 TO 3				
	MEAN	47.	48.	41.	25.**
	S.D.	5.8	5.9	10.1	8.2
	N	10	10	10	10
	0 TO 4				
	MEAN	48.	52.	48.	30.**
	S.D.	11.1	13.2	9.0	6.4
	N	10	10	10	10
	0 TO 5				
	MEAN	64.	65.	57.	41.**
	S.D.	8.9	9.2	13.3	6.2
	N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 6				
	MEAN	70.	73.	62.	44.**
	S.D.	9.1	9.8	14.2	6.8
	N	10	10	10	10
	0 TO 7				
	MEAN	76.	79.	69.	50.**
	S.D.	11.8	10.4	11.8	8.9
	N	10	10	10	10
	0 TO 8				
	MEAN	79.	83.	71.	53.**
	S.D.	11.2	10.6	13.6	7.6
	N	10	10	10	10
	0 TO 9				
	MEAN	78.	83.	72.	55.**
	S.D.	17.1	12.7	13.0	7.7
	N	10	10	10	10
	0 TO 10				
	MEAN	89.	91.	80.	60.**
	S.D.	16.8	14.0	16.2	9.0
	N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 11				
	MEAN	98.	97.	84.	65.**
	S.D.	16.1	15.4	16.0	8.5
	N	10	10	10	10
	0 TO 12				
	MEAN	101.	102.	91.	67.**
	S.D.	18.2	17.5	14.6	7.0
	N	10	10	10	10
	0 TO 13				
	MEAN	98.	99.	88.	67.**
	S.D.	17.2	17.6	16.4	7.2
	N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 4

PROJECT NO.:WIL-223004 A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS

SPONSOR:ZIRAM TASK FORCE WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	21.	22.	22.	22.
S.D.	1.5	1.7	1.3	1.3
N	10	10	10	10
-1 TO 0				
MEAN	24.	24.	24.	25.
S.D.	2.5	2.3	2.1	1.8
N	10	10	10	10
0 TO 1				
MEAN	26.	26.	25.	18.**
S.D.	1.8	2.5	2.5	2.2
N	10	10	10	10
1 TO 2				
MEAN	27.	27.	27.	24.
S.D.	2.3	4.8	2.7	3.0
N	10	10	10	10
2 TO 3				
MEAN	27.	28.	27.	25.
S.D.	2.6	2.7	2.2	1.8
N	10	9	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 4

PROJECT NO.:WIL-223004 A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS

SPONSOR:ZIRAM TASK FORCE WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

	----- M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3 TO 4				
MEAN	26.	26.	27.	23.*
S.D.	2.9	2.3	2.2	1.6
N	10	9	10	10
4 TO 5				
MEAN	27.	28.	27.	24.*
S.D.	2.7	2.2	2.3	1.7
N	10	9	10	10
5 TO 6				
MEAN	26.	27.	27.	23.*
S.D.	2.2	2.4	2.8	1.9
N	10	9	10	10
6 TO 7				
MEAN	26.	28.	26.	24.
S.D.	2.7	2.7	2.9	1.5
N	10	9	10	10
7 TO 8				
MEAN	26.	25.	26.	23.
S.D.	2.3	4.6	2.3	1.4
N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 4
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9				
MEAN	27.	27.	27.	24.
S.D.	2.7	2.4	3.2	1.9
N	10	9	10	10
9 TO 10				
MEAN	26.	27.	26.	24.
S.D.	2.5	1.6	2.8	1.7
N	10	9	10	10
10 TO 11				
MEAN	26.	27.	27.	24.
S.D.	2.0	1.6	3.0	1.8
N	10	9	10	10
11 TO 12				
MEAN	26.	26.	26.	24.
S.D.	2.4	2.2	2.3	1.3
N	10	9	10	10
12 TO 13				
MEAN	25.	25.	27.	23.*
S.D.	2.6	2.8	2.4	1.6
N	10	9	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

TABLE 4
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	16.	17.	17.	17.
S.D.	1.1	1.1	0.7	1.1
N	9	10	10	10
-1 TO 0				
MEAN	17.	17.	17.	17.
S.D.	1.3	1.0	1.4	1.4
N	9	10	10	10
0 TO 1				
MEAN	17.	17.	16.	13.**
S.D.	1.3	1.1	1.1	1.4
N	10	10	10	10
1 TO 2				
MEAN	18.	19.	18.	16.**
S.D.	1.2	1.0	1.1	2.1
N	10	10	10	10
2 TO 3				
MEAN	18.	19.	18.	16.*
S.D.	1.9	1.1	1.1	1.6
N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 4
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	3 TO 4				
	MEAN	17.	17.	18.	15.
	S.D.	2.4	1.6	1.8	1.1
	N	10	10	10	10
	4 TO 5				
	MEAN	18.	18.	18.	17.
	S.D.	2.6	1.7	1.6	1.5
	N	10	10	10	10
	5 TO 6				
	MEAN	17.	18.	17.	16.*
	S.D.	2.0	1.4	1.2	1.5
	N	10	10	10	10
	6 TO 7				
	MEAN	17.	19.	18.	16.
	S.D.	3.2	1.4	0.7	1.8
	N	10	10	10	10
	7 TO 8				
	MEAN	17.	18.	17.	16.
	S.D.	2.0	0.7	0.7	1.4
	N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

TABLE 4
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/ANIMAL/DAY) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9				
MEAN	18.	18.	18.	16.
S.D.	2.4	2.3	2.2	1.3
N	10	10	10	10
9 TO 10				
MEAN	18.	18.	17.	15.**
S.D.	1.9	1.7	1.3	1.3
N	10	10	10	10
10 TO 11				
MEAN	19.	18.	17.	16.**
S.D.	1.8	1.9	1.4	1.1
N	10	10	10	10
11 TO 12				
MEAN	18.	18.	17.	15.**
S.D.	2.0	0.9	1.4	1.3
N	10	10	10	10
12 TO 13				
MEAN	17.	16.	16.	15.**
S.D.	1.6	1.8	1.0	1.2
N	10	10	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	140.	146.	141.	143.
S.D.	9.0	6.4	9.3	6.6
N	10	10	10	10
-1 TO 0				
MEAN	114.	115.	114.	114.
S.D.	8.5	4.0	6.8	6.0
N	10	10	10	10
0 TO 1				
MEAN	97.	98.	93.	69.**
S.D.	3.7	4.7	6.5	7.9
N	10	10	10	10
1 TO 2				
MEAN	86.	91.	87.	85.
S.D.	4.0	6.0	4.7	7.7
N	10	9	10	10
2 TO 3				
MEAN	77.	80.	76.	78.
S.D.	2.9	3.9	3.6	3.0
N	10	9	10	10

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	3 TO 4				
	MEAN	69.	69.	70.	68.
	S.D.	3.9	4.5	4.0	2.9
	N	10	9	10	10
	4 TO 5				
	MEAN	67.	69.	67.	65.
	S.D.	2.3	1.2	2.8	2.9
	N	10	9	10	10
	5 TO 6				
	MEAN	62.	64.	62.	60.
	S.D.	1.5	2.3	3.7	3.4
	N	10	9	10	10
	6 TO 7				
	MEAN	60.	62.	58.	61.
	S.D.	4.5	3.0	4.9	2.3
	N	10	9	10	10
	7 TO 8				
	MEAN	58.	54.	56.	56.
	S.D.	3.4	8.4	2.5	2.4
	N	10	9	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9				
MEAN	58.	59.	57.	57.
S.D.	2.4	1.2	4.6	2.2
N	10	9	10	10
9 TO 10				
MEAN	55.	57.	54.	56.
S.D.	2.6	3.8	3.0	2.3
N	10	9	10	10
10 TO 11				
MEAN	54.	55.	55.	54.
S.D.	2.5	2.7	3.3	3.3
N	10	9	10	10
11 TO 12				
MEAN	52.	52.	52.	52.
S.D.	3.1	4.0	2.3	2.8
N	10	9	10	10
12 TO 13				
MEAN	50.	49.	53.	49.
S.D.	2.7	3.7	7.0	3.4
N	10	9	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK -2 TO -1				
MEAN	131.	135.	135.	131.
S.D.	9.6	9.1	7.2	7.4
N	9	10	10	10
-1 TO 0				
MEAN	109.	107.	109.	110.
S.D.	9.4	4.0	6.5	6.0
N	9	10	10	10
0 TO 1				
MEAN	101.	100.	91.*	74.**
S.D.	9.1	6.2	6.6	7.0
N	10	10	10	10
1 TO 2				
MEAN	96.	98.	94.	91.
S.D.	6.0	5.8	4.3	7.2
N	10	10	10	10
2 TO 3				
MEAN	89.	93.	88.	87.
S.D.	7.0	5.0	6.4	7.4
N	10	10	10	10

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 3 TO 4				
MEAN	81.	80.	83.	78.
S.D.	11.6	6.8	8.4	4.0
N	10	10	10	10
4 TO 5				
MEAN	82.	80.	80.	82.
S.D.	10.8	7.4	5.9	6.4
N	10	10	10	10
5 TO 6				
MEAN	75.	77.	75.	75.
S.D.	6.0	6.1	5.1	4.9
N	10	10	10	10
6 TO 7				
MEAN	72.	77.	75.	74.
S.D.	10.8	5.3	5.4	8.1
N	10	10	10	10
7 TO 8				
MEAN	70.	72.	70.	74.
S.D.	8.3	4.1	3.2	6.3
N	10	10	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

----- F E M A L E -----			
0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
76. 11.0 10	74. 8.6 10	72. 8.7 10	73. 5.2 10
74. 6.5 10	72. 6.2 10	70. 3.2 10	68. 5.5 10
72. 3.6 10	71. 6.7 10	67. 4.3 10	68. 4.7 10
70. 5.6 10	68. 4.3 10	66. 4.2 10	65. 4.7 10
66. 4.7 10	62. 4.9 10	63. 2.1 10	64. 5.3 10

NT USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 4A
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
WEEKLY FOOD CONSUMPTION (GRAMS/KG/DAY) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 8 TO 9				
MEAN	76.	74.	72.	73.
S.D.	11.0	8.6	8.7	5.2
N	10	10	10	10
9 TO 10				
MEAN	74.	72.	70.	68.
S.D.	6.5	6.2	3.2	5.5
N	10	10	10	10
10 TO 11				
MEAN	72.	71.	67.	68.
S.D.	3.6	6.7	4.3	4.7
N	10	10	10	10
11 TO 12				
MEAN	70.	68.	66.	65.
S.D.	5.6	4.3	4.2	4.7
N	10	10	10	10
12 TO 13				
MEAN	66.	62.	63.	64.
S.D.	4.7	4.9	2.1	5.3
N	10	10	10	10

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

		----- M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 1				
	MEAN	0.	7.	19.	37.
	S.D.	0.0	0.3	1.5	4.3
	N	10	10	10	10
	1 TO 2				
	MEAN	0.	7.	18.	46.
	S.D.	0.0	0.5	1.2	4.2
	N	10	9	10	10
	2 TO 3				
	MEAN	0.	6.	16.	42.
	S.D.	0.0	0.4	0.7	1.6
	N	10	9	10	10
	3 TO 4				
	MEAN	0.	5.	14.	36.
	S.D.	0.0	0.3	1.0	1.4
	N	10	9	10	10
	4 TO 5				
	MEAN	0.	5.	14.	35.
	S.D.	0.0	0.0	0.7	1.7
	N	10	9	10	10

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 5 TO 6				
MEAN	0.	5.	13.	33.
S.D.	0.0	0.4	0.7	1.9
N	10	9	10	10
6 TO 7				
MEAN	0.	4.	12.	33.
S.D.	0.0	0.5	0.9	1.5
N	10	9	10	10
7 TO 8				
MEAN	0.	4.	12.	30.
S.D.	0.0	0.7	0.5	1.4
N	10	9	10	10
8 TO 9				
MEAN	0.	4.	12.	31.
S.D.	0.0	0.0	1.0	1.1
N	10	9	10	10
9 TO 10				
MEAN	0.	4.	12.	30.
S.D.	0.0	0.3	0.5	1.3
N	10	9	10	10

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 10 TO 11				
MEAN	0.	4.	12.	29.
S.D.	0.0	0.0	0.7	1.7
N	10	9	10	10
11 TO 12				
MEAN	0.	4.	11.	28.
S.D.	0.0	0.4	0.6	1.6
N	10	9	10	10
12 TO 13				
MEAN	0.	3.	11.	26.
S.D.	0.0	0.5	1.5	1.9
N	10	9	10	10
GRAND MEAN	0.	5.	14.	34.
TEST PERIODS	13	13	13	13

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	0 TO 1				
	MEAN	0.	7.	19.	40.
	S.D.	0.0	0.4	1.4	3.8
	N	10	10	10	10
	1 TO 2				
	MEAN	0.	7.	19.	49.
	S.D.	0.0	0.5	0.8	3.8
	N	10	10	10	10
	2 TO 3				
	MEAN	0.	7.	18.	47.
	S.D.	0.0	0.5	1.2	4.0
	N	10	10	10	10
	3 TO 4				
	MEAN	0.	6.	17.	42.
	S.D.	0.0	0.3	1.7	2.0
	N	10	10	10	10
	4 TO 5				
	MEAN	0.	6.	16.	44.
	S.D.	0.0	0.5	1.3	3.4
	N	10	10	10	10

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

		----- F E M A L E -----			
	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK	5 TO 6				
	MEAN	0.	6.	15.	40.
	S.D.	0.0	0.5	1.2	2.7
	N	10	10	10	10
	6 TO 7				
	MEAN	0.	6.	16.	40.
	S.D.	0.0	0.5	1.3	4.5
	N	10	10	10	10
	7 TO 8				
	MEAN	0.	5.	14.	40.
	S.D.	0.0	0.4	0.7	3.2
	N	10	10	10	10
	8 TO 9				
	MEAN	0.	5.	15.	40.
	S.D.	0.0	0.7	1.7	2.8
	N	10	10	10	10
	9 TO 10				
	MEAN	0.	5.	15.	37.
	S.D.	0.0	0.6	0.7	2.8
	N	10	10	10	10

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

TABLE 5
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CALCULATED COMPOUND CONSUMPTION (MG/KG/DAY)

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
WEEK 10 TO 11				
MEAN	0.	5.	14.	37.
S.D.	0.0	0.6	1.0	2.6
N	10	10	10	10
11 TO 12				
MEAN	0.	5.	14.	35.
S.D.	0.0	0.0	0.9	2.7
N	10	10	10	10
12 TO 13				
MEAN	0.	5.	13.	35.
S.D.	0.0	0.5	0.4	2.9
N	10	10	10	10
GRAND MEAN	0.	6.	16.	40.
TEST PERIODS	13	13	13	13

MEAN CONSUMPTION CALCULATED FROM INDIVIDUAL CONSUMPTIONS

TABLE 6 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	7	3	5	6
ASLEEP, LYING ON SIDE OR CURLED UP	3	6	5	4
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
BITING				
NONE	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	7	3	5	6
EYELIDS SLIGHTLY DROOPING	0	1	0	0
DROOPING EYELIDS (HALF-CLOSED)	0	0	0	1
EYELIDS COMPLETELY SHUT	3	5	5	3
FECES CONSISTENCY				
PELLETS	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 6 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	5	4	5	6
ASLEEP, LYING ON SIDE OR CURLED UP	4	6	5	4
ALERT, ORIENTED TOWARD OBSERVER	1	0	0	0
CONVULSIONS - CLONIC				
ABSENT	10	10	10	10
CONVULSIONS - TONIC				
ABSENT	10	10	10	10
TREMORS				
NONE	10	10	10	10
BITING				
NONE	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	6	4	6	6
EYELIDS SLIGHTLY DROOPING	1	2	0	0
DROOPING EYELIDS (HALF-CLOSED)	1	2	0	1
EYELIDS COMPLETELY SHUT	2	2	4	3
FECES CONSISTENCY				
PELLETS	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 7 (PRETEST EVALUATION)

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SPONSOR:ZIRAM TASK FORCE — FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	70.0	33.3	50.0	60.0
ASLEEP, LYING ON SIDE OR CURLED UP	30.0	66.7	50.0	40.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	70.0	33.3	50.0	60.0
EYELIDS SLIGHTLY DROOPING	0.	11.1	0.	0.
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	0.	10.0
EYELIDS COMPLETELY SHUT	30.0	55.6	50.0	30.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 7 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	50.0	40.0	50.0	60.0
ASLEEP, LYING ON SIDE OR CURLED UP	40.0	60.0	50.0	40.0
ALERT, ORIENTED TOWARD OBSERVER	10.0	0.	0.	0.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	60.0	40.0	60.0	60.0
EYELIDS SLIGHTLY DROOPING	10.0	20.0	0.	0.
DROOPING EYELIDS (HALF-CLOSED)	10.0	20.0	0.	10.0
EYELIDS COMPLETELY SHUT	20.0	20.0	40.0	30.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 8 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	4	7	5	8
ASLEEP, LYING ON SIDE OR CURLED UP	2	2	3	1
ALERT, ORIENTED TOWARD OBSERVER	4	0	2	1
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
BITING				
NONE	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	8	7	9
DROOPING EYELIDS (HALF-CLOSED)	1	0	3	0
EYELIDS COMPLETELY SHUT	1	1	0	1
FECES CONSISTENCY				
PELLETS	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 8 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	7	9	7	5
ASLEEP, LYING ON SIDE OR CURLED UP	2	0	0	3
ALERT, ORIENTED TOWARD OBSERVER	1	1	3	2
CONVULSIONS - CLONIC				
ABSENT	10	10	10	10
CONVULSIONS - TONIC				
ABSENT	10	10	10	10
TREMORS				
NONE	10	10	10	10
BITING				
NONE	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	9	10	10	7
DROOPING EYELIDS (HALF-CLOSED)	1	0	0	1
EYELIDS COMPLETELY SHUT	0	0	0	2
FECES CONSISTENCY				
PELLETS	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 9 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	40.0	77.8	50.0	80.0
ASLEEP, LYING ON SIDE OR CURLED UP	20.0	22.2	30.0	10.0
ALERT, ORIENTED TOWARD OBSERVER	40.0	0.	20.0	10.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	80.0	88.9	70.0	90.0
DROOPING EYELIDS (HALF-CLOSED)	10.0	0.	30.0	0.
EYELIDS COMPLETELY SHUT	10.0	11.1	0.	10.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 9 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	70.0	90.0	70.0	50.0
ASLEEP, LYING ON SIDE OR CURLED UP	20.0	0.	0.	30.0
ALERT, ORIENTED TOWARD OBSERVER	10.0	10.0	30.0	20.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	90.0	100.	100.	70.0
DROOPING EYELIDS (HALF-CLOSED)	10.0	0.	0.	10.0
EYELIDS COMPLETELY SHUT	0.	0.	0.	20.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 10 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	3	2	2	3
ASLEEP, LYING ON SIDE OR CURLED UP	5	4	7	5
ALERT, ORIENTED TOWARD OBSERVER	2	3	1	2
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
BITING				
NONE	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	7	5	7
EYELIDS COMPLETELY SHUT	2	2	5	3
FECES CONSISTENCY				
PELLETS	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 10 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	1	1	2	1
ASLEEP, LYING ON SIDE OR CURLED UP	2	3	2	3
ALERT, ORIENTED TOWARD OBSERVER	7	6	6	6
CONVULSIONS - CLONIC				
ABSENT	10	10	10	10
CONVULSIONS - TONIC				
ABSENT	10	10	10	10
TREMORS				
NONE	10	10	10	10
BITING				
NONE	10	9	10	10
BITING OF CAGE	0	1	0	0
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	9	8	10
EYELIDS COMPLETELY SHUT	2	1	2	0
FECES CONSISTENCY				
PELLETS	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 11 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	30.0	22.2	20.0	30.0
ASLEEP, LYING ON SIDE OR CURLED UP	50.0	44.4	70.0	50.0
ALERT, ORIENTED TOWARD OBSERVER	20.0	33.3	10.0	20.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	80.0	77.8	50.0	70.0
EYELIDS COMPLETELY SHUT	20.0	22.2	50.0	30.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 11 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	10.0	10.0	20.0	10.0
ASLEEP, LYING ON SIDE OR CURLED UP	20.0	30.0	20.0	30.0
ALERT, ORIENTED TOWARD OBSERVER	70.0	60.0	60.0	60.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	90.0	100.	100.
BITING OF CAGE	0.	10.0	0.	0.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	80.0	90.0	80.0	100.
EYELIDS COMPLETELY SHUT	20.0	10.0	20.0	0.
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 12 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	3	2	6	3
ASLEEP, LYING ON SIDE OR CURLED UP	6	6	3	5
ALERT, ORIENTED TOWARD OBSERVER	1	1	1	2
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
BITING				
NONE	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	6	7	6
EYELIDS COMPLETELY SHUT	2	3	3	4
FECES CONSISTENCY				
PELLETS	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 12 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	2	4	1	2
ASLEEP, LYING ON SIDE OR CURLED UP	2	2	1	1
ALERT, ORIENTED TOWARD OBSERVER	6	4	8	7
CONVULSIONS - CLONIC				
ABSENT	10	10	10	10
CONVULSIONS - TONIC				
ABSENT	10	10	10	10
TREMORS				
NONE	10	10	10	10
BITING				
NONE	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	9	9	10
EYELIDS COMPLETELY SHUT	2	1	1	0
FECES CONSISTENCY				
PELLETS	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 13 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
POSTURE				
SITTING OR STANDING NORMALLY	30.0	22.2	60.0	30.0
ASLEEP, LYING ON SIDE OR CURLED UP	60.0	66.7	30.0	50.0
ALERT, ORIENTED TOWARD OBSERVER	10.0	11.1	10.0	20.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	80.0	66.7	70.0	60.0
EYELIDS COMPLETELY SHUT	20.0	33.3	30.0	40.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 13 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
POSTURE				
SITTING OR STANDING NORMALLY	20.0	40.0	10.0	20.0
ASLEEP, LYING ON SIDE OR CURLED UP	20.0	20.0	10.0	10.0
ALERT, ORIENTED TOWARD OBSERVER	60.0	40.0	80.0	70.0
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	80.0	90.0	90.0	100.
EYELIDS COMPLETELY SHUT	20.0	10.0	10.0	0.
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	3	4	3	3
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	7	5	7	7
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	9	7	10	8
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	1	2	0	2
LACRIMATION				
NONE	10	9	10	10
CHROMODACRYORRHEA				
ABSENT	10	9	10	10
SALIVATION				
NONE	10	9	10	10
PILOERECTION				
NONE	10	9	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	9	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	10	9	10	10
RED DEPOSITS - eyes				
ABSENT	10	9	10	10
RED DEPOSITS - nose				
PRESENT	1	0	1	1
ABSENT	9	9	9	9
RED DEPOSITS - mouth				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - eyes				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	9	10	10
MUCOUS MEMBRANES - color				
PINK	10	9	10	10
EYES - color				
PINK	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
SKIN - color				
PINK	10	9	10	10
EYE PROMINENCE				
NORMAL	10	9	10	10
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	4	1	2	2
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	6	7	8	7
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0	2	0	1
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	7	9	8	8
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	3	1	2	2
LACRIMATION				
NONE	10	10	10	10
CHROMODACRYORRHEA				
ABSENT	10	10	10	10
SALIVATION				
NONE	10	10	10	10
PILOERECTION				
NONE	10	10	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	10	10	10
RESPIRATORY CHARACTER				
NORMAL	10	10	10	10
RED DEPOSITS - eyes				
PRESENT	0	0	1	0
ABSENT	10	10	9	10
RED DEPOSITS - nose				
PRESENT	0	1	0	0
ABSENT	10	9	10	10
RED DEPOSITS - mouth				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - eyes				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	10	10	10
MUCOUS MEMBRANES - color				
PINK	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color				
PINK	10	10	10	10
SKIN - color				
PINK	10	10	10	10
EYE PROMINENCE				
NORMAL	10	10	10	10
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	30.0	44.4	30.0	30.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	70.0	55.6	70.0	70.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	90.0	77.8	100.	80.0
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	10.0	22.2	0.	20.0
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose				
PRESENT	10.0	0.	10.0	10.0
ABSENT	90.0	100.	90.0	90.0
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.
EYES - color				
PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	40.0	10.0	20.0	20.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	60.0	70.0	80.0	70.0
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0.	20.0	0.	10.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	70.0	90.0	80.0	80.0
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	30.0	10.0	20.0	20.0
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
PRESENT	0.	0.	10.0	0.
ABSENT	100.	100.	90.0	100.
RED DEPOSITS - nose				
PRESENT	0.	10.0	0.	0.
ABSENT	100.	90.0	100.	100.
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 15 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	8	9	10	9
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	2	0	0	1
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	9	7	8	7
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	1	2	2	3
LACRIMATION				
NONE	10	9	10	10
CHROMODACRYORRHEA				
ABSENT	10	9	10	10
SALIVATION				
NONE	10	9	10	10
PILOERECTION				
NONE	10	9	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	9	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	10	9	10	10
RED DEPOSITS - eyes				
ABSENT	10	9	10	10
RED DEPOSITS - nose				
ABSENT	10	9	10	10
RED DEPOSITS - mouth				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - eyes				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	9	10	10
MUCOUS MEMBRANES - color				
PINK	10	9	10	10
EYES - color				
PINK	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
SKIN - color				
PINK	10	9	10	10
EYE PROMINENCE				
NORMAL	10	9	10	10
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	9	8	9	7
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	1	2	1	3
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	7	9	9
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0	3	1	1
LACRIMATION				
NONE	10	9	10	10
SLIGHT	0	1	0	0
CHROMODACRYORRHEA				
ABSENT	10	10	10	10
SALIVATION				
NONE	10	10	10	10
PILOERECTION				
NONE	10	10	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	10	10	10
RESPIRATORY CHARACTER				
NORMAL	10	10	10	10
RED DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	10	9	10	10
RED DEPOSITS - nose				
ABSENT	10	10	10	10
RED DEPOSITS - mouth				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - eyes				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	10	10	10
MUCOUS MEMBRANES - color				
PINK	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color PINK	10	10	10	10
SKIN - color PINK	10	10	10	10
EYE PROMINENCE NORMAL	10	10	10	10
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	80.0	100.	100.	90.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	20.0	0.	0.	10.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	90.0	77.8	80.0	70.0
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	10.0	22.2	20.0	30.0
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.
EYES - color				
PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
SKIN - color PINK	100.	100.	100.	100.
EYE PROMINENCE NORMAL	100.	100.	100.	100.
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	90.0	80.0	90.0	70.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	10.0	20.0	10.0	30.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	70.0	90.0	90.0
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0.	30.0	10.0	10.0
LACRIMATION				
NONE	100.	90.0	100.	100.
SLIGHT	0.	10.0	0.	0.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
PRESENT	0.	10.0	0.	0.
ABSENT	100.	90.0	100.	100.
RED DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 17 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	5	5	7	5
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	5	4	3	5
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	9	9	10	10
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	1	0	0	0
LACRIMATION				
NONE	10	9	10	10
CHROMODACRYORRHEA				
ABSENT	10	9	10	10
SALIVATION				
NONE	10	9	10	10
PILOERECTION				
NONE	10	9	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	4	2	3	3
SLIGHTLY SOILED	6	7	7	7
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	10	9	10	10
RED DEPOSITS - eyes				
ABSENT	10	9	10	10
RED DEPOSITS - nose				
PRESENT	0	0	1	1
ABSENT	10	9	9	9
RED DEPOSITS - mouth				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - eyes				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	9	10	10
MUCOUS MEMBRANES - color				
PINK	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EYES - color PINK	10	9	10	10
SKIN - color PINK	10	9	10	10
EYE PROMINENCE NORMAL	10	9	10	10
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	8	8	9	7
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	2	2	1	3
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	10	10	10
LACRIMATION				
NONE	10	10	9	10
SLIGHT	0	0	1	0
CHROMODACRYORRHEA				
ABSENT	10	10	10	10
SALIVATION				
NONE	10	10	10	10
PILOERECTION				
NONE	10	10	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	10	9	10
SLIGHTLY SOILED	0	0	1	0
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	10	10	10
RESPIRATORY CHARACTER				
NORMAL	10	10	10	10
RED DEPOSITS - eyes				
PRESENT	0	0	1	0
ABSENT	10	10	9	10
RED DEPOSITS - nose				
PRESENT	1	0	1	1
ABSENT	9	10	9	9
RED DEPOSITS - mouth				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	10	9	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	10	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
MUCOUS MEMBRANES - color				
PINK	10	10	10	10
EYES - color				
PINK	10	10	10	10
SKIN - color				
PINK	10	10	10	10
EYE PROMINENCE				
NORMAL	10	9	10	10
EXOPHTHALMUS	0	1	0	0
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	50.0	55.6	70.0	50.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	50.0	44.4	30.0	50.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	90.0	100.	100.	100.
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	10.0	0.	0.	0.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	40.0	22.2	30.0	30.0
SLIGHTLY SOILED	60.0	77.8	70.0	70.0
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose PRESENT	0.	0.	10.0	10.0
ABSENT	100.	100.	90.0	90.0
RED DEPOSITS - mouth ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	80.0	80.0	90.0	70.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	20.0	20.0	10.0	30.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	100.	100.
LACRIMATION				
NONE	100.	100.	90.0	100.
SLIGHT	0.	0.	10.0	0.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	90.0	100.
SLIGHTLY SOILED	0.	0.	10.0	0.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
PRESENT	0.	0.	10.0	0.
ABSENT	100.	100.	90.0	100.
RED DEPOSITS - nose				
PRESENT	10.0	0.	10.0	10.0
ABSENT	90.0	100.	90.0	90.0
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
PRESENT	0.	10.0	0.	0.
ABSENT	100.	90.0	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 19 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	90.0	100.	100.
EXOPHTHALMUS	0.	10.0	0.	0.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	6	9	8	8
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	4	0	2	2
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	9	9	10
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0	0	1	0
LACRIMATION				
NONE	10	9	10	10
CHROMODACRYORRHEA				
ABSENT	10	9	10	10
SALIVATION				
NONE	10	9	10	10
PILOERECTION				
NONE	10	9	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	9	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	9	10	10
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	10	9	10	10
RED DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	10	8	10	10
RED DEPOSITS - nose				
PRESENT	0	0	0	2
ABSENT	10	9	10	8
RED DEPOSITS - mouth				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	10	8	10	10
CRUSTY DEPOSITS - nose				
ABSENT	10	9	10	10
CRUSTY DEPOSITS - mouth				
ABSENT	10	9	10	10
MUCOUS MEMBRANES - color				
PINK	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EYES - color				
PINK	10	9	10	10
SKIN - color				
PINK	10	9	10	10
EYE PROMINENCE				
NORMAL	10	9	10	10
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	9	8	9	10
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	1	2	0	0
MODERATELY DIFFICULT: ANIMAL REARS, OFTEN FOLLOWING INVESTIGATOR'S HAND	0	0	1	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	10	9	9
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0	0	1	1
LACRIMATION				
NONE	10	10	10	10
CHROMODACRYORRHEA				
ABSENT	10	10	10	10
SALIVATION				
NONE	10	10	10	10
PILOERECTION				
NONE	10	10	10	10
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	10	10	10	10
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	10	10	10	10
RESPIRATORY CHARACTER NORMAL	10	10	10	10
RED DEPOSITS - eyes ABSENT	10	10	10	10
RED DEPOSITS - nose ABSENT	10	10	10	10
RED DEPOSITS - mouth ABSENT	10	10	10	10
CRUSTY DEPOSITS - eyes ABSENT	10	10	10	10
CRUSTY DEPOSITS - nose ABSENT	10	10	10	10
CRUSTY DEPOSITS - mouth ABSENT	10	10	10	10
MUCOUS MEMBRANES - color PINK	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 20 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color PINK	10	10	10	10
SKIN - color PINK	10	10	10	10
EYE PROMINENCE NORMAL	10	10	10	10
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	60.0	100.	80.0	80.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	40.0	0.	20.0	20.0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	90.0	100.
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0.	0.	10.0	0.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
PRESENT	0.	11.1	0.	0.
ABSENT	100.	88.9	100.	100.
RED DEPOSITS - nose				
PRESENT	0.	0.	0.	20.0
ABSENT	100.	100.	100.	80.0
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
PRESENT	0.	11.1	0.	0.
ABSENT	100.	88.9	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
EYES - color PINK	100.	100.	100.	100.
SKIN - color PINK	100.	100.	100.	100.
EYE PROMINENCE NORMAL	100.	100.	100.	100.
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	90.0	80.0	90.0	100.
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	10.0	20.0	0.	0.
MODERATELY DIFFICULT: ANIMAL REARS, OFTEN FOLLOWING INVESTIGATOR'S HAND	0.	0.	10.0	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	90.0	90.0
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0.	0.	10.0	10.0
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose ABSENT	100.	100.	100.	100.
RED DEPOSITS - mouth ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color PINK	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 21 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 22 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.3	0.4	0.3
S.D.	0.06	0.07	0.05	0.05
MOBILITY NORMAL	10	9	10	10
GAIT NORMAL	10	9	10	10
CONVULSIONS - CLONIC ABSENT	10	9	10	10
CONVULSIONS - TONIC ABSENT	10	9	10	10
TREMORS NONE	10	9	10	10
GAIT SCORE NORMAL	10	9	10	10
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	10	9	10	10
BIZARRE/STEREOTYPIC BEHAVIOR NONE	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 22 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	7.3	6.2	9.3	5.1
	S.D.	2.58	2.17	3.92	2.77
BACKING	: MEAN	0.1	0.0	0.0	0.0
	S.D.	0.32	0.00	0.00	0.00
GROOMING	: MEAN	0.2	0.8	0.2	0.1
	S.D.	0.63	0.67	0.42	0.32
URINATION	: MEAN	0.6	0.7	0.4	0.6
	S.D.	0.52	0.87	0.52	0.52
DEFECATION	: MEAN	0.7	1.2	1.3	2.0
	S.D.	0.95	1.79	1.34	2.16

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 22 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.4	0.3	0.4	0.3
	S.D.	0.13	0.03	0.08	0.05
MOBILITY					
NORMAL		10	10	10	10
GAIT					
NORMAL		10	10	10	10
CONVULSIONS - CLONIC					
ABSENT		10	10	10	10
CONVULSIONS - TONIC					
ABSENT		10	10	10	10
TREMORS					
NONE		10	10	10	10
GAIT SCORE					
NORMAL		10	10	10	10
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		10	10	10	10
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 22 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	7.7	8.1	5.9	7.8
	S.D.	3.65	2.85	3.38	3.19
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.2	0.1	0.4	0.1
	S.D.	0.42	0.32	0.70	0.32
URINATION	: MEAN	0.1	0.6	0.4	0.2
	S.D.	0.32	0.84	0.52	0.63
DEFECATION	: MEAN	0.2	0.7	0.5	0.0
	S.D.	0.42	1.64	1.27	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 23 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.3	0.4	0.3
S.D.	0.06	0.07	0.05	0.05
MOBILITY NORMAL	100.	100.	100.	100.
GAIT NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC ABSENT	100.	100.	100.	100.
TREMORS NONE	100.	100.	100.	100.
GAIT SCORE NORMAL	100.	100.	100.	100.
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR NONE	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 23 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	7.3	6.2	9.3	5.1
	S.D.	2.58	2.17	3.92	2.77
BACKING	: MEAN	0.1	0.0	0.0	0.0
	S.D.	0.32	0.00	0.00	0.00
GROOMING	: MEAN	0.2	0.8	0.2	0.1
	S.D.	0.63	0.67	0.42	0.32
URINATION	: MEAN	0.6	0.7	0.4	0.6
	S.D.	0.52	0.87	0.52	0.52
DEFECATION	: MEAN	0.7	1.2	1.3	2.0
	S.D.	0.95	1.79	1.34	2.16

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 23 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.4	0.3	0.4	0.3
	S.D.	0.13	0.03	0.08	0.05
MOBILITY NORMAL		100.	100.	100.	100.
GAIT NORMAL		100.	100.	100.	100.
CONVULSIONS - CLONIC ABSENT		100.	100.	100.	100.
CONVULSIONS - TONIC ABSENT		100.	100.	100.	100.
TREMORS NONE		100.	100.	100.	100.
GAIT SCORE NORMAL		100.	100.	100.	100.
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS		100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR NONE		100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 23 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	7.7	8.1	5.9	7.8
	S.D.	3.65	2.85	3.38	3.19
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.2	0.1	0.4	0.1
	S.D.	0.42	0.32	0.70	0.32
URINATION	: MEAN	0.1	0.6	0.4	0.2
	S.D.	0.32	0.84	0.52	0.63
DEFECATION	: MEAN	0.2	0.7	0.5	0.0
	S.D.	0.42	1.64	1.27	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 24 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.4	0.4	0.3	0.4
	S.D.	0.09	0.24	0.10	0.26
MOBILITY NORMAL		10	9	10	10
GAIT NORMAL		10	9	10	10
CONVULSIONS - CLONIC ABSENT		10	9	10	10
CONVULSIONS - TONIC ABSENT		10	9	10	10
TREMORS NONE		10	9	10	10
GAIT SCORE NORMAL		10	9	10	10
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS		10	9	10	10
BIZARRE/STEREOTYPIC BEHAVIOR NONE		10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 24 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	7.0	6.1	6.9	5.3
	S.D.	2.79	2.76	2.81	3.80
BACKING	: MEAN	0.1	0.0	0.0	0.0
	S.D.	0.32	0.00	0.00	0.00
GROOMING	: MEAN	0.1	0.2	0.1	0.0
	S.D.	0.32	0.44	0.32	0.00
URINATION	: MEAN	1.3	1.0	0.6	0.8
	S.D.	1.06	1.00	0.84	0.63
DEFECATION	: MEAN	1.5	0.7	0.2	0.0
	S.D.	2.27	1.12	0.63	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 24 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.3	0.3	0.4	0.3
	S.D.	0.07	0.05	0.08	0.07
MOBILITY					
NORMAL		10	10	10	10
GAIT					
NORMAL		10	10	10	9
WALKS ON TIPTOES		0	0	0	1
CONVULSIONS - CLONIC					
ABSENT		10	10	10	10
CONVULSIONS - TONIC					
ABSENT		10	10	10	10
TREMORS					
NONE		10	10	10	10
GAIT SCORE					
NORMAL		10	10	10	9
SLIGHT IMPAIRMENT, BUT DEFINITE		0	0	0	1
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		10	10	10	10
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 24 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	10.7	10.0	7.1	9.4
	S.D.	3.50	4.11	3.14	4.77
BACKING	: MEAN	0.0	0.1	0.0	0.0
	S.D.	0.00	0.32	0.00	0.00
GROOMING	: MEAN	0.1	0.1	0.0	0.3
	S.D.	0.32	0.32	0.00	0.67
URINATION	: MEAN	0.1	0.3	0.3	0.2
	S.D.	0.32	0.67	0.95	0.42
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 25 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.4	0.4	0.3	0.4
S.D.	0.09	0.24	0.10	0.26
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 25 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	7.0	6.1	6.9	5.3
	S.D.	2.79	2.76	2.81	3.80
BACKING	: MEAN	0.1	0.0	0.0	0.0
	S.D.	0.32	0.00	0.00	0.00
GROOMING	: MEAN	0.1	0.2	0.1	0.0
	S.D.	0.32	0.44	0.32	0.00
URINATION	: MEAN	1.3	1.0	0.6	0.8
	S.D.	1.06	1.00	0.84	0.63
DEFECATION	: MEAN	1.5	0.7	0.2	0.0
	S.D.	2.27	1.12	0.63	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 25 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.3	0.3	0.4	0.3
	S.D.	0.07	0.05	0.08	0.07
MOBILITY					
NORMAL		100.	100.	100.	100.
GAIT					
NORMAL		100.	100.	100.	90.0
WALKS ON TIPTOES		0.	0.	0.	10.0
CONVULSIONS - CLONIC					
ABSENT		100.	100.	100.	100.
CONVULSIONS - TONIC					
ABSENT		100.	100.	100.	100.
TREMORS					
NONE		100.	100.	100.	100.
GAIT SCORE					
NORMAL		100.	100.	100.	90.0
SLIGHT IMPAIRMENT, BUT DEFINITE		0.	0.	0.	10.0
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 25 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	10.7	10.0	7.1	9.4
	S.D.	3.50	4.11	3.14	4.77
BACKING	: MEAN	0.0	0.1	0.0	0.0
	S.D.	0.00	0.32	0.00	0.00
GROOMING	: MEAN	0.1	0.1	0.0	0.3
	S.D.	0.32	0.32	0.00	0.67
URINATION	: MEAN	0.1	0.3	0.3	0.2
	S.D.	0.32	0.67	0.95	0.42
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 26 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.5	0.4	0.6	0.4
S.D.	0.08	0.15	0.22	0.16
MOBILITY				
NORMAL	10	9	10	9
SLIGHTLY IMPAIRED	0	0	0	1
GAIT				
NORMAL	10	9	10	9
WALKS ON TIPTOES	0	0	0	1
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
GAIT SCORE				
NORMAL	10	9	10	9
SLIGHT IMPAIRMENT, BUT DEFINITE	0	0	0	1
AROUSAL				
LOW: SOMEWHAT STUPOROUS	0	0	1	0
NORMAL: ALERT, EXPLORATORY MOVEMENTS	10	9	9	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 26 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		10	9	10	10
REARING	: MEAN	9.4	8.8	8.9	8.0
	S.D.	2.80	3.19	3.87	5.14
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.1	0.1	0.1	0.2
	S.D.	0.32	0.33	0.32	0.63
URINATION	: MEAN	2.9	1.2	1.7	1.4
	S.D.	1.45	1.64	1.49	2.22
DEFECATION	: MEAN	0.0	0.6	0.4	0.2
	S.D.	0.00	1.13	0.84	0.42

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 26 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.4	0.3	0.3	0.3
	S.D.	0.19	0.08	0.08	0.06
MOBILITY					
NORMAL		10	10	10	10
GAIT					
NORMAL		10	10	10	10
CONVULSIONS - CLONIC					
ABSENT		10	10	10	10
CONVULSIONS - TONIC					
ABSENT		10	10	10	10
TREMORS					
NONE		10	10	10	10
GAIT SCORE					
NORMAL		10	10	10	10
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		7	6	8	9
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING		3	4	2	1
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 26 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	13.3	14.4	13.2	12.3
	S.D.	4.24	5.02	5.57	4.37
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.6	0.2	0.4	0.3
	S.D.	0.97	0.42	0.70	0.67
URINATION	: MEAN	0.2	0.4	0.3	0.2
	S.D.	0.42	0.97	0.95	0.42
DEFECATION	: MEAN	0.1	0.2	0.1	0.0
	S.D.	0.32	0.63	0.32	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 27 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.5	0.4	0.6	0.4
	S.D.	0.08	0.15	0.22	0.16
MOBILITY					
NORMAL		100.	100.	100.	90.0
SLIGHTLY IMPAIRED		0.	0.	0.	10.0
GAIT					
NORMAL		100.	100.	100.	90.0
WALKS ON TIPTOES		0.	0.	0.	10.0
CONVULSIONS - CLONIC					
ABSENT		100.	100.	100.	100.
CONVULSIONS - TONIC					
ABSENT		100.	100.	100.	100.
TREMORS					
NONE		100.	100.	100.	100.
GAIT SCORE					
NORMAL		100.	100.	100.	90.0
SLIGHT IMPAIRMENT, BUT DEFINITE		0.	0.	0.	10.0
AROUSAL					
LOW: SOMEWHAT STUPOROUS		0.	0.	10.0	0.
NORMAL: ALERT, EXPLORATORY MOVEMENTS		100.	100.	90.0	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 27 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		100.	100.	100.	100.
REARING	: MEAN	9.4	8.8	8.9	8.0
	S.D.	2.80	3.19	3.87	5.14
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.1	0.1	0.1	0.2
	S.D.	0.32	0.33	0.32	0.63
URINATION	: MEAN	2.9	1.2	1.7	1.4
	S.D.	1.45	1.64	1.49	2.22
DEFECATION	: MEAN	0.0	0.6	0.4	0.2
	S.D.	0.00	1.13	0.84	0.42

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 27 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.4	0.3	0.3	0.3
S.D.	0.19	0.08	0.08	0.06
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	70.0	60.0	80.0	90.0
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING	30.0	40.0	20.0	10.0
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 27 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	13.3	14.4	13.2	12.3
	S.D.	4.24	5.02	5.57	4.37
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.6	0.2	0.4	0.3
	S.D.	0.97	0.42	0.70	0.67
URINATION	: MEAN	0.2	0.4	0.3	0.2
	S.D.	0.42	0.97	0.95	0.42
DEFECATION	: MEAN	0.1	0.2	0.1	0.0
	S.D.	0.32	0.63	0.32	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 28 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.7	0.8	0.8
S.D.	0.23	0.41	0.37	0.41
MOBILITY				
NORMAL	10	9	10	10
GAIT				
NORMAL	10	9	10	10
CONVULSIONS - CLONIC				
ABSENT	10	9	10	10
CONVULSIONS - TONIC				
ABSENT	10	9	10	10
TREMORS				
NONE	10	9	10	10
GAIT SCORE				
NORMAL	10	9	10	10
AROUSAL				
VERY LOW: STUPOR, COMA, LITTLE OR NO RESPONSIVENESS	0	0	1	0
NORMAL: ALERT, EXPLORATORY MOVEMENTS	10	9	9	10
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 28 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	4.9	4.9	5.8	4.5
	S.D.	2.23	2.71	4.87	4.65
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.3	0.0
	S.D.	0.00	0.67	0.48	0.00
URINATION	: MEAN	1.9	0.8	1.6	0.9
	S.D.	1.66	1.09	1.43	1.20
DEFECATION	: MEAN	0.3	0.7	0.2	0.2
	S.D.	0.67	1.32	0.63	0.42

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 28 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
TIME TO FIRST STEP (seconds)	: MEAN	0.8	0.7	0.6	0.4
	S.D.	0.35	0.37	0.40	0.15
MOBILITY					
NORMAL		10	10	10	10
GAIT					
NORMAL		10	10	10	10
CONVULSIONS - CLONIC					
ABSENT		10	10	10	10
CONVULSIONS - TONIC					
ABSENT		10	10	10	10
TREMORS					
NONE		10	10	10	10
GAIT SCORE					
NORMAL		10	10	10	10
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		10	10	10	10
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 28 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	9.3	9.5	9.6	10.0
	S.D.	7.07	5.64	3.86	6.43
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.7	0.1	0.3	0.6
	S.D.	1.34	0.32	0.67	1.07
URINATION	: MEAN	0.3	0.4	0.4	0.8
	S.D.	0.48	0.70	0.97	1.40
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 29 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.7	0.8	0.8
S.D.	0.23	0.41	0.37	0.41
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
VERY LOW: STUPOR, COMA, LITTLE OR NO RESPONSIVENESS	0.	0.	10.0	0.
NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	90.0	100.
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 29 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
REARING	: MEAN	4.9	4.9	5.8	4.5
	S.D.	2.23	2.71	4.87	4.65
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.3	0.0
	S.D.	0.00	0.67	0.48	0.00
URINATION	: MEAN	1.9	0.8	1.6	0.9
	S.D.	1.66	1.09	1.43	1.20
DEFECATION	: MEAN	0.3	0.7	0.2	0.2
	S.D.	0.67	1.32	0.63	0.42

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 29 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
TIME TO FIRST STEP (seconds) : MEAN	0.8	0.7	0.6	0.4
S.D.	0.35	0.37	0.40	0.15
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 29 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
REARING	: MEAN	9.3	9.5	9.6	10.0
	S.D.	7.07	5.64	3.86	6.43
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.7	0.1	0.3	0.6
	S.D.	1.34	0.32	0.67	1.07
URINATION	: MEAN	0.3	0.4	0.4	0.8
	S.D.	0.48	0.70	0.97	1.40
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 30 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	9	9	10
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0	0	1	0
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	8	7	8	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	2	2	1
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	7	8	8	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	1	2	3
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	8	7	8	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	2	2	2
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	9	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	9	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	9	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 30 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	9	10	10
AIR RIGHTING REFLEX				
NORMAL	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 30 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	10	10	10
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	10	10	9	10
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0	0	1	0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	8	8	6	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	2	4	3
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	7	6	5	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	4	5	1
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	10	10	10
PUPIL RESPONSE				
NO PUPIL RESPONSE	0	0	0	1
PUPIL RESPONSE PRESENT	10	10	10	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	10	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 30 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	10	10	10
AIR RIGHTING REFLEX				
NORMAL	10	9	10	10
SLIGHTLY UNCOORDINATED	0	1	0	0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 31 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	100.	100.	90.0	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0.	0.	10.0	0.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	80.0	77.8	80.0	90.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	20.0	22.2	20.0	10.0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	70.0	88.9	80.0	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	30.0	11.1	20.0	30.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	80.0	77.8	80.0	80.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	20.0	22.2	20.0	20.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 31 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
HINDLIMB EXTENSION HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX NORMAL	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 31 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	100.	100.	100.	100.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	100.	100.	90.0	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0.	0.	10.0	0.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	80.0	80.0	60.0	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	20.0	20.0	40.0	30.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	70.0	60.0	50.0	90.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	30.0	40.0	50.0	10.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
NO PUPIL RESPONSE	0.	0.	0.	10.0
PUPIL RESPONSE PRESENT	100.	100.	100.	90.0
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 31 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	90.0	100.	100.
SLIGHTLY UNCOORDINATED	0.	10.0	0.	0.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 32 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	9	10	10
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	9	8	9	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	1	1	1
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	7	7	8	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	2	2	2
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	9	7	10	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	2	0	3
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	9	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	9	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	9	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	9	10	10
AIR RIGHTING REFLEX				
NORMAL	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	8	10	9	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	0	1	1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	8	8	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	2	2	2
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	8	5	6	5
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	5	4	5
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	4	6	5
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	6	4	5
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	10	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	10	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	10	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	10	10	10
AIR RIGHTING REFLEX				
NORMAL	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 33 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	100.	100.	100.	100.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	90.0	88.9	90.0	90.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	10.0	11.1	10.0	10.0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	70.0	77.8	80.0	80.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	30.0	22.2	20.0	20.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	90.0	77.8	100.	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	10.0	22.2	0.	30.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 33 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 33 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	80.0	100.	90.0	90.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	20.0	0.	10.0	10.0
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	80.0	80.0	80.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	40.0	20.0	20.0	20.0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	80.0	50.0	60.0	50.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	20.0	50.0	40.0	50.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	40.0	60.0	50.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	40.0	60.0	40.0	50.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 33 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 34 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	9	10	10
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	10	9	10	10
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	10	9	10	10
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	7	8	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	2	2	3
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	9	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	9	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	9	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	9	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 34 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
AIR RIGHTING REFLEX				
NORMAL	8	6	7	4
SLIGHTLY UNCOORDINATED	2	3	3	5
LANDS ON SIDE	0	0	0	1

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 34 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	10	10	10
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	10	10	10	10
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	10	9	10	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0	1	0	1
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	7	7	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	3	3	2
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	10	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	10	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	10	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 34 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
AIR RIGHTING REFLEX				
NORMAL	10	10	9	10
SLIGHTLY UNCOORDINATED	0	0	1	0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 35 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	100.	100.	100.	100.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	100.	100.	100.	100.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	100.	100.	100.	100.
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	77.8	80.0	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	40.0	22.2	20.0	30.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
AIR RIGHTING REFLEX				
NORMAL	80.0	66.7	70.0	40.0
SLIGHTLY UNCOORDINATED	20.0	33.3	30.0	50.0
LANDS ON SIDE	0.	0.	0.	10.0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	100.	100.	100.	100.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	100.	100.	100.	100.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	100.	90.0	100.	90.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0.	10.0	0.	10.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	70.0	70.0	80.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	40.0	30.0	30.0	20.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
AIR RIGHTING REFLEX				
NORMAL	100.	100.	90.0	100.
SLIGHTLY UNCOORDINATED	0.	0.	10.0	0.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 36 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
NO REACTION	0	0	0	2
SLOW APPROACH, SNIFFING OR TURNING AWAY	9	9	10	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	0	0	0
TOUCH RESPONSE				
NO REACTION	1	0	2	1
ANIMAL MAY SLOWLY TURN, WALK AWAY	9	8	7	8
FREEZES, ACTUAL MUSCLE CONTRACTION	0	1	1	1
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	10	9	10	10
TAIL PINCH RESPONSE				
NO REACTION	2	0	1	0
ANIMAL MAY SLOWLY TURN, WALK AWAY	5	6	7	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	2	2	2
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	0	1	0	1
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	9	10	10
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	9	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 36 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	9	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	9	10	10
AIR RIGHTING REFLEX				
NORMAL	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 36 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
NO REACTION	1	0	1	0
SLOW APPROACH, SNIFFING OR TURNING AWAY	9	9	9	10
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0	1	0	0
TOUCH RESPONSE				
NO REACTION	2	0	0	0
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	8	7	7
FREEZES, ACTUAL MUSCLE CONTRACTION	2	2	3	3
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	10	10	10	10
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	6	5	6	7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	5	4	3
OLFACTORY ORIENTATION				
NO REACTION PRESENT	0	0	0	1
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	10	10	10	9
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	10	10	10	10
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 36 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	10	10	10	10
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	10	10	10	10
AIR RIGHTING REFLEX				
NORMAL	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 37 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
APPROACH RESPONSE				
NO REACTION	0.	0.	0.	20.0
SLOW APPROACH, SNIFFING OR TURNING AWAY	90.0	100.	100.	80.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	10.0	0.	0.	0.
TOUCH RESPONSE				
NO REACTION	10.0	0.	20.0	10.0
ANIMAL MAY SLOWLY TURN, WALK AWAY	90.0	88.9	70.0	80.0
FREEZES, ACTUAL MUSCLE CONTRACTION	0.	11.1	10.0	10.0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	100.	100.	100.	100.
TAIL PINCH RESPONSE				
NO REACTION	20.0	0.	10.0	0.
ANIMAL MAY SLOWLY TURN, WALK AWAY	50.0	66.7	70.0	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	30.0	22.2	20.0	20.0
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	0.	11.1	0.	10.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 37 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	9	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 37 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
APPROACH RESPONSE				
NO REACTION	10.0	0.	10.0	0.
SLOW APPROACH, SNIFFING OR TURNING AWAY	90.0	90.0	90.0	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	0.	10.0	0.	0.
TOUCH RESPONSE				
NO REACTION	20.0	0.	0.	0.
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	80.0	70.0	70.0
FREEZES, ACTUAL MUSCLE CONTRACTION	20.0	20.0	30.0	30.0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	100.	100.	100.	100.
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	60.0	50.0	60.0	70.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	40.0	50.0	40.0	30.0
OLFACTORY ORIENTATION				
NO REACTION PRESENT	0.	0.	0.	10.0
REACTION PRESENT: ANIMAL APPROACHES SWAB, MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	90.0
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 37 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	10	10	10	10
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 38 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	9	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	572.4	608.1	569.0	592.3
	S.D.	61.62	109.64	80.75	58.64
	HIND: MEAN	427.4	434.6	436.0	432.3
	S.D.	80.45	32.86	34.02	55.55
ROTAROD PERFORMANCE (seconds)	: MEAN	68.4	41.9	80.3	45.6
	S.D.	54.59	45.17	52.41	51.75
HINDLIMB FOOTSPLAY (mm)	: MEAN	61.6	65.2	58.9	63.8
	S.D.	13.99	13.68	9.86	8.30

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 38 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		10	10	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	560.4	586.7	568.2	568.0
	S.D.	49.66	74.52	74.06	59.00
	HIND: MEAN	387.0	461.9	433.8	384.7
	S.D.	107.68	74.18	52.04	61.83
ROTAROD PERFORMANCE (seconds)	: MEAN	39.4	34.6	57.4	25.2
	S.D.	40.80	45.29	54.30	38.84
HINDLIMB FOOTSPLAY (mm)	: MEAN	61.4	56.6	62.6	60.0
	S.D.	10.07	11.08	13.52	11.67

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 39 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	572.4	608.1	569.0	592.3
	S.D.	61.62	109.64	80.75	58.64
	HIND: MEAN	427.4	434.6	436.0	432.3
	S.D.	80.45	32.86	34.02	55.55
ROTAROD PERFORMANCE (seconds)	: MEAN	68.4	41.9	80.3	45.6
	S.D.	54.59	45.17	52.41	51.75
HINDLIMB FOOTSPLAY (mm)	: MEAN	61.6	65.2	58.9	63.8
	S.D.	13.99	13.68	9.86	8.30

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 39 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	560.4	586.7	568.2	568.0
	S.D.	49.66	74.52	74.06	59.00
	HIND: MEAN	387.0	461.9	433.8	384.7
	S.D.	107.68	74.18	52.04	61.83
ROTAROD PERFORMANCE (seconds)	: MEAN	39.4	34.6	57.4	25.2
	S.D.	40.80	45.29	54.30	38.84
HINDLIMB FOOTSPLAY (mm)	: MEAN	61.4	56.6	62.6	60.0
	S.D.	10.07	11.08	13.52	11.67

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 40 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		10	9	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	438.1	451.4	471.2	486.9
	S.D.	142.02	133.18	89.56	106.02
	HIND: MEAN	439.0	410.2	397.7	377.5
	S.D.	125.49	176.98	138.87	82.65
ROTAROD PERFORMANCE (seconds)	: MEAN	97.6	79.2	62.2	67.3
	S.D.	33.73	49.73	47.32	40.86
HINDLIMB FOOTSPLAY (mm)	: MEAN	75.5	75.2	72.9	69.5
	S.D.	19.34	12.51	15.92	14.39

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 40 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	10	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	410.0	345.6	377.8	370.7
	S.D.	122.47	101.75	91.10	128.83
	HIND: MEAN	377.4	334.1	372.6	303.3
	S.D.	92.77	73.77	96.08	64.81
ROTAROD PERFORMANCE (seconds)	: MEAN	93.7	86.1	101.1	96.2
	S.D.	45.83	45.11	39.91	38.87
HINDLIMB FOOTSPLAY (mm)	: MEAN	58.4	59.8	59.4	63.7
	S.D.	15.25	19.66	11.78	15.57

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 41 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	438.1	451.4	471.2	486.9
	S.D.	142.02	133.18	89.56	106.02
	HIND: MEAN	439.0	410.2	397.7	377.5
	S.D.	125.49	176.98	138.87	82.65
ROTAROD PERFORMANCE (seconds)	: MEAN	97.6	79.2	62.2	67.3
	S.D.	33.73	49.73	47.32	40.86
HINDLIMB FOOTSPLAY (mm)	: MEAN	75.5	75.2	72.9	69.5
	S.D.	19.34	12.51	15.92	14.39

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 41 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	410.0	345.6	377.8	370.7
	S.D.	122.47	101.75	91.10	128.83
	HIND: MEAN	377.4	334.1	372.6	303.3
	S.D.	92.77	73.77	96.08	64.81
ROTAROD PERFORMANCE (seconds)	: MEAN	93.7	86.1	101.1	96.2
	S.D.	45.83	45.11	39.91	38.87
HINDLIMB FOOTSPLAY (mm)	: MEAN	58.4	59.8	59.4	63.7
	S.D.	15.25	19.66	11.78	15.57

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 42 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	9	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1210.9	1132.3	1269.9	1128.3
	S.D.	207.42	179.43	160.74	204.47
	HIND: MEAN	545.0	545.3	524.3	545.8
	S.D.	87.93	104.16	121.95	60.27
ROTAROD PERFORMANCE (seconds)	: MEAN	93.6	82.8	78.0	89.5
	S.D.	30.91	55.74	53.70	43.01
HINDLIMB FOOTSPLAY (mm)	: MEAN	78.5	84.6	74.5	79.2
	S.D.	13.90	13.03	21.39	14.35

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 42 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	10	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1100.0	917.5	994.1	860.9+
	S.D.	239.48	180.88	164.79	117.34
	HIND: MEAN	525.9	478.4	458.3	422.5
	S.D.	168.65	97.45	104.13	84.67
ROTAROD PERFORMANCE (seconds)	: MEAN	98.4	97.4	120.0	75.1
	S.D.	45.47	47.75	0.00	49.38
HINDLIMB FOOTSPLAY (mm)	: MEAN	70.7	64.8	69.5	69.8
	S.D.	12.18	16.63	10.02	10.52

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 43 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1210.9	1132.3	1269.9	1128.3
	S.D.	207.42	179.43	160.74	204.47
	HIND: MEAN	545.0	545.3	524.3	545.8
	S.D.	87.93	104.16	121.95	60.27
ROTAROD PERFORMANCE (seconds)	: MEAN	93.6	82.8	78.0	89.5
	S.D.	30.91	55.74	53.70	43.01
HINDLIMB FOOTSPLAY (mm)	: MEAN	78.5	84.6	74.5	79.2
	S.D.	13.90	13.03	21.39	14.35

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 43 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1100.0	917.5	994.1	860.9
	S.D.	239.48	180.88	164.79	117.34
	HIND: MEAN	525.9	478.4	458.3	422.5
	S.D.	168.65	97.45	104.13	84.67
ROTAROD PERFORMANCE (seconds)	: MEAN	98.4	97.4	120.0	75.1
	S.D.	45.47	47.75	0.00	49.38
HINDLIMB FOOTSPLAY (mm)	: MEAN	70.7	64.8	69.5	69.8
	S.D.	12.18	16.63	10.02	10.52

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 44 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	9	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1356.7	1336.1	1304.3	1334.9
	S.D.	111.88	139.92	134.09	112.15
	HIND: MEAN	755.8	720.4	737.5	733.3
	S.D.	76.75	95.41	133.15	125.36
ROTAROD PERFORMANCE (seconds)	: MEAN	85.1	84.1	68.4	75.7
	S.D.	49.88	54.15	51.54	40.66
HINDLIMB FOOTSPLAY (mm)	: MEAN	72.4	76.8	70.3	68.6
	S.D.	16.81	15.42	16.74	14.77

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 44 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		10	10	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1008.4	973.5	1063.3	981.8
	S.D.	112.13	123.45	154.66	54.72
	HIND: MEAN	588.2	554.2	555.0	537.4
	S.D.	106.74	76.46	57.31	101.32
ROTAROD PERFORMANCE (seconds)	: MEAN	99.5	100.6	120.0	82.6
	S.D.	43.83	40.92	0.00	50.52
HINDLIMB FOOTSPLAY (mm)	: MEAN	60.4	61.1	63.5	57.8
	S.D.	17.15	19.30	9.20	14.68

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 45 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1356.7	1336.1	1304.3	1334.9
	S.D.	111.88	139.92	134.09	112.15
	HIND: MEAN	755.8	720.4	737.5	733.3
	S.D.	76.75	95.41	133.15	125.36
ROTAROD PERFORMANCE (seconds)	: MEAN	85.1	84.1	68.4	75.7
	S.D.	49.88	54.15	51.54	40.66
HINDLIMB FOOTSPLAY (mm)	: MEAN	72.4	76.8	70.3	68.6
	S.D.	16.81	15.42	16.74	14.77

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 45 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	1008.4	973.5	1063.3	981.8
	S.D.	112.13	123.45	154.66	54.72
	HIND: MEAN	588.2	554.2	555.0	537.4
	S.D.	106.74	76.46	57.31	101.32
ROTAROD PERFORMANCE (seconds)	: MEAN	99.5	100.6	120.0	82.6
	S.D.	43.83	40.92	0.00	50.52
HINDLIMB FOOTSPLAY (mm)	: MEAN	60.4	61.1	63.5	57.8
	S.D.	17.15	19.30	9.20	14.68

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

TABLE 46 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
CATALEPSY (seconds)	: MEAN	0.4	0.7	0.5	0.4
	S.D.	0.38	0.54	0.24	0.41
	N	10	9	10	10
BODY TEMPERATURE (degrees C)	: MEAN	38.5	38.2	38.3	38.3
	S.D.	0.25	0.46	0.24	0.18
	N	10	9	10	10
BODY WEIGHT (g)	: MEAN	134.8	135.3	135.0	136.2
	S.D.	11.66	14.57	9.25	9.88
	N	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 46 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
CATALEPSY (seconds)	: MEAN	0.3	0.3	1.1	0.5
	S.D.	0.09	0.15	2.21	0.43
	N	10	10	10	10
BODY TEMPERATURE (degrees C)	: MEAN	38.5	38.4	38.7	38.5
	S.D.	0.40	0.28	0.39	0.34
	N	10	10	10	10
BODY WEIGHT (g)	: MEAN	122.8	117.4	119.9	117.0
	S.D.	10.30	8.64	6.76	6.15
	N	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST.

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 47 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
CATALEPSY (seconds)	: MEAN	0.5	0.4	0.5	0.5
	S.D.	0.12	0.12	0.20	0.12
	N	10	9	10	10
BODY TEMPERATURE (degrees C)	: MEAN	38.4	38.2	38.1	38.0
	S.D.	0.73	0.56	0.64	0.49
	N	10	9	10	10
BODY WEIGHT (g)	: MEAN	364.8	360.7	366.5	333.0+
	S.D.	26.21	28.12	22.05	17.97
	N	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

TABLE 47 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
CATALEPSY (seconds)	: MEAN	0.4	0.5	0.4	0.5
	S.D.	0.07	0.11	0.08	0.08
	N	10	10	10	10
BODY TEMPERATURE (degrees C)	: MEAN	38.6	38.6	38.6	38.5
	S.D.	0.51	0.54	0.38	0.54
	N	10	10	10	10
BODY WEIGHT (g)	: MEAN	209.5	207.9	209.7	191.0++
	S.D.	10.58	12.06	12.29	12.57
	N	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 48 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
CATALEPSY (seconds)	: MEAN	1.1	0.6	0.6	0.8
	S.D.	1.63	0.67	0.36	1.16
	N	10	9	10	10
BODY TEMPERATURE (degrees C)	: MEAN	39.2	39.1	38.9	39.1
	S.D.	0.36	0.26	0.67	0.31
	N	10	9	10	10
BODY WEIGHT (g)	: MEAN	445.5	451.2	451.7	406.0+
	S.D.	39.46	36.34	34.60	28.24
	N	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

TABLE 48 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
CATALEPSY (seconds)	: MEAN	0.5	0.4	0.4	0.6
	S.D.	0.43	0.35	0.25	0.43
	N	10	10	10	10
BODY TEMPERATURE (degrees C)	: MEAN	39.8	39.7	39.6	39.6
	S.D.	0.24	0.45	0.27	0.39
	N	10	10	10	10
BODY WEIGHT (g)	: MEAN	236.9	238.7	234.7	215.6++
	S.D.	15.13	14.60	14.30	12.98
	N	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 49 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	9	10	10
CATALEPSY (seconds)	: MEAN	0.8	1.4	1.2	0.6
	S.D.	0.33	1.19	1.58	0.33
	N	10	9	10	10
BODY TEMPERATURE (degrees C)	: MEAN	38.5	38.4	38.3	38.6
	S.D.	0.46	0.50	0.41	0.59
	N	10	9	10	10
BODY WEIGHT (g)	: MEAN	500.1	503.9	505.4	457.8
	S.D.	47.93	39.52	41.66	33.68
	N	10	9	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 49 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		10	10	10	10
CATALEPSY (seconds)	: MEAN	0.6	0.9	0.5	0.5
	S.D.	0.29	1.07	0.22	0.17
	N	10	10	10	10
BODY TEMPERATURE (degrees C)	: MEAN	39.4	39.2	39.2	39.0
	S.D.	0.41	0.44	0.38	0.34
	N	10	10	10	10
BODY WEIGHT (g)	: MEAN	260.3	259.2	254.5	230.4++
	S.D.	20.55	17.87	17.22	13.41
	N	10	10	10	10

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 50 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	588	315	281	94	1278
	SD	149.1	130.5	178.8	91.6	422.0
	N	10	10	10	10	10
72.0 PPM	MEAN	592	299	220	193	1304
	SD	149.5	54.8	173.3	138.0	233.7
	N	9	9	9	9	9
207.0 PPM	MEAN	620	292	285	126	1324
	SD	204.3	159.8	113.3	142.6	350.3
	N	10	10	10	10	10
540.0 PPM	MEAN	535	250	250	136	1171
	SD	136.0	116.8	104.0	111.5	304.8
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNET'S TEST

TABLE 50 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	346	167	176	39	729
	SD	91.0	62.0	170.8	38.7	278.2
	N	10	10	10	10	10
72.0 PPM	MEAN	320	150	126	81	677
	SD	57.4	41.9	114.2	64.6	120.9
	N	9	9	9	9	9
207.0 PPM	MEAN	357	166	152	57	732
	SD	116.7	94.8	79.4	70.2	219.0
	N	10	10	10	10	10
540.0 PPM	MEAN	296	123	123	70	611
	SD	97.0	63.6	61.0	62.8	165.2
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNET'S TEST

TABLE 50 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	677	318	237	287	1519
	SD	249.3	115.6	169.0	204.7	309.0
	N	10	10	10	10	10
72.0 PPM	MEAN	615	376	303	261	1555
	SD	194.0	153.2	206.2	202.9	625.0
	N	10	10	10	10	10
207.0 PPM	MEAN	542	210	281	191	1223
	SD	208.7	142.9	248.0	148.7	584.5
	N	10	10	10	10	10
540.0 PPM	MEAN	676	320	193	114	1303
	SD	96.9	126.5	145.5	80.2	315.0
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNET'S TEST

TABLE 50 (PRETEST EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	351	175	137	185	848
	SD	125.6	67.2	99.6	168.3	168.3
	N	10	10	10	10	10
72.0 PPM	MEAN	347	212	148	139	846
	SD	125.6	84.7	107.7	130.6	368.2
	N	10	10	10	10	10
207.0 PPM	MEAN	295	117	150	114	676
	SD	125.3	86.6	146.4	111.7	327.0
	N	10	10	10	10	10
540.0 PPM	MEAN	373	166	100	51	691
	SD	49.6	74.0	82.0	39.9	192.5
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNET'S TEST

TABLE 51 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	719	415	305	258	1698
	SD	121.2	189.0	214.9	158.6	518.6
	N	10	10	10	10	10
72.0 PPM	MEAN	751	437	247	213	1648
	SD	182.7	144.2	155.3	163.4	479.1
	N	9	9	9	9	9
207.0 PPM	MEAN	684	537	421	285	1926
	SD	116.2	127.8	169.0	160.9	346.0
	N	10	10	10	10	10
540.0 PPM	MEAN	730	357	204	259	1549
	SD	178.7	176.4	173.4	170.3	493.9
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 51 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	462	266	202	170	1100
	SD	70.6	125.5	132.1	114.9	333.4
	N	10	10	10	10	10
72.0 PPM	MEAN	470	290	165	147	1071
	SD	107.1	87.3	117.1	116.7	322.8
	N	9	9	9	9	9
207.0 PPM	MEAN	455	344	263	176	1238
	SD	82.4	92.8	91.9	82.6	181.4
	N	10	10	10	10	10
540.0 PPM	MEAN	454	210	125	178	967
	SD	112.9	102.3	106.4	109.5	294.7
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 51 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	855	512	327	315	2009
	SD	186.4	206.8	231.5	170.0	641.3
	N	10	10	10	10	10
72.0 PPM	MEAN	873	560	459	241	2132
	SD	168.5	74.3	129.2	119.4	283.3
	N	10	10	10	10	10
207.0 PPM	MEAN	817	504	326	349	1996
	SD	164.0	179.0	214.1	117.0	540.3
	N	10	10	10	10	10
540.0 PPM	MEAN	844	471	277	238	1831
	SD	113.2	210.7	158.6	192.3	505.7
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 51 (WEEK 3 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	547	314	217	208	1286
	SD	99.9	117.2	152.6	115.8	387.2
	N	10	10	10	10	10
72.0 PPM	MEAN	540	322	289	154	1305
	SD	86.8	48.8	67.9	94.5	161.6
	N	10	10	10	10	10
207.0 PPM	MEAN	499	309	195	213	1216
	SD	121.0	122.7	125.9	68.7	319.7
	N	10	10	10	10	10
540.0 PPM	MEAN	499	298	179	158	1135
	SD	77.4	129.8	95.1	129.8	318.2
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 52 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	653	320	215	180	1368
	SD	144.8	140.2	166.0	197.5	548.1
	N	10	10	10	10	10
72.0 PPM	MEAN	660	344	192	119	1315
	SD	142.6	165.0	154.8	92.2	453.5
	N	9	9	9	9	9
207.0 PPM	MEAN	545	289	194	195	1222
	SD	191.9	136.9	119.1	160.6	493.4
	N	10	10	10	10	10
540.0 PPM	MEAN	504	217	185	156	1061
	SD	149.8	121.2	153.2	127.0	275.0
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 52 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	433	212	150	129	923
	SD	96.9	98.4	116.6	138.1	372.0
	N	10	10	10	10	10
72.0 PPM	MEAN	435	228	136	88	887
	SD	101.2	128.8	111.5	73.9	342.1
	N	9	9	9	9	9
207.0 PPM	MEAN	375	195	132	142	843
	SD	127.9	94.4	85.5	117.3	348.7
	N	10	10	10	10	10
540.0 PPM	MEAN	331	143	129	112	715
	SD	91.9	80.8	102.3	90.3	201.4
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 52 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	699	322	179	172	1372
	SD	192.4	156.6	199.6	175.8	487.2
	N	10	10	10	10	10
72.0 PPM	MEAN	720	461	296	185	1662
	SD	141.3	180.9	177.0	167.8	510.3
	N	10	10	10	10	10
207.0 PPM	MEAN	706	401	212	218	1536
	SD	203.2	188.3	173.3	166.1	549.2
	N	10	10	10	10	10
540.0 PPM	MEAN	638	288	196	115	1237
	SD	182.8	151.2	159.3	93.1	423.1
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 52 (WEEK 7 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	432	199	112	109	853
	SD	117.8	96.5	119.4	105.6	305.9
	N	10	10	10	10	10
72.0 PPM	MEAN	459	283	185	121	1047
	SD	96.2	114.2	114.6	111.0	352.1
	N	10	10	10	10	10
207.0 PPM	MEAN	428	249	154	135	966
	SD	117.8	121.8	129.4	111.8	309.7
	N	10	10	10	10	10
540.0 PPM	MEAN	384	191	121	78	773
	SD	116.9	94.3	93.4	61.4	269.4
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 53 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	720	286	208	123	1336
	SD	131.7	130.0	106.5	147.6	338.4
	N	10	10	10	10	10
72.0 PPM	MEAN	623	271	166	136	1197
	SD	168.8	134.3	110.6	94.6	403.8
	N	9	9	9	9	9
207.0 PPM	MEAN	705	329	170	101	1305
	SD	155.0	95.3	97.4	82.9	288.8
	N	10	10	10	10	10
540.0 PPM	MEAN	668	270	150	169	1256
	SD	149.9	136.3	103.4	103.2	346.3
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 53 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	466	190	149	90	895
	SD	94.4	97.8	73.0	104.4	240.7
	N	10	10	10	10	10
72.0 PPM	MEAN	416	185	113	97	810
	SD	101.4	101.4	73.3	72.6	310.0
	N	9	9	9	9	9
207.0 PPM	MEAN	453	220	129	68	870
	SD	66.0	67.2	75.7	59.5	160.3
	N	10	10	10	10	10
540.0 PPM	MEAN	432	165	98	104	799
	SD	97.1	91.7	72.7	78.7	269.4
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 53 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	847	341	252	263	1703
	SD	163.4	203.8	127.2	124.5	523.4
	N	10	10	10	10	10
72.0 PPM	MEAN	792	433	366	204	1794
	SD	138.7	186.0	261.2	206.6	668.4
	N	10	10	10	10	10
207.0 PPM	MEAN	837	398	270	238	1743
	SD	129.7	114.8	135.3	188.2	326.0
	N	10	10	10	10	10
540.0 PPM	MEAN	826	359	214	149	1548
	SD	153.5	140.1	138.6	141.2	472.2
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 53 (WEEK 12 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0.0 PPM	MEAN	519	234	157	185	1095
	SD	97.1	147.9	93.3	103.9	374.2
	N	10	10	10	10	10
72.0 PPM	MEAN	491	280	229	139	1140
	SD	72.9	123.7	176.4	150.1	441.2
	N	10	10	10	10	10
207.0 PPM	MEAN	540	246	185	172	1143
	SD	79.1	72.3	85.7	135.1	220.7
	N	10	10	10	10	10
540.0 PPM	MEAN	494	227	145	100	966
	SD	64.5	74.7	91.8	101.6	261.8
	N	10	10	10	10	10

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 54

PROJECT NO.:WIL-223004 A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS

SPONSOR:ZIRAM TASK FORCE PLASMA AND RED BLOOD CELL CHOLINESTERASE DETERMINATIONS - SUMMARY OF MEANS

ANALYSIS	GROUP:	----- M A L E ----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
PLASMA CHOLIN (U/L)					
PRETEST	MEAN	502.	534.	473.	500.
	S.D.	61.6	49.2	79.6	62.2
	N	5	5	5	5
WEEK 3	MEAN	424.	498.	461.	426.
	S.D.	65.4	86.7	144.3	43.9
	N	5	5	5	5
WEEK 7	MEAN	410.	533.	438.	443.
	S.D.	78.9	73.7	147.5	49.8
	N	5	4	5	5
WEEK 13	MEAN	388.	408.	391.	362.
	S.D.	79.7	53.9	154.4	40.3
	N	5	5	5	5
RBC ACHE (U/L)					
PRETEST	MEAN	2367.	2320.	2404.	2252.
	S.D.	229.4	227.6	176.1	164.7
	N	5	5	5	5
WEEK 3	MEAN	2087.	2265.	1492.	1929.
	S.D.	592.9	307.8	1117.8	457.5
	N	5	5	5	5

U/L = INTERNATIONAL UNIT/LITER, U/gt = Units/Gram Tissue, NM/MN/MG = NANAMOLES/MIN/MG PROTEIN

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 54

PROJECT NO.:WIL-223004 A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS

SPONSOR:ZIRAM TASK FORCE PLASMA AND RED BLOOD CELL CHOLINESTERASE DETERMINATIONS - SUMMARY OF MEANS

		----- M A L E -----			
ANALYSIS	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
RBC ACHE (U/L)					
WEEK 7	MEAN	2022.	1982.	2031.	1973.
	S.D.	212.4	246.7	199.6	248.9
	N	5	4	5	5
WEEK 13	MEAN	1950.	2016.	2104.	2138.
	S.D.	278.3	331.9	195.7	128.7
	N	5	5	5	5

U/L = INTERNATIONAL UNIT/LITER

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 54
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
PLASMA AND RED BLOOD CELL CHOLINESTERASE DETERMINATIONS - SUMMARY OF MEANS

ANALYSIS	GROUP:	-----F E M A L E----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
PLASMA CHOLIN (U/L)					
PRETEST	MEAN	684.	655.	654.	669.
	S.D.	99.2	174.5	95.8	125.0
	N	5	5	5	5
WEEK 3	MEAN	1564.	1689.	1768.	1459.
	S.D.	501.3	698.4	536.0	383.2
	N	5	5	5	5
WEEK 7	MEAN	2090.	2271.	2467.	1890.
	S.D.	739.9	981.7	774.0	711.0
	N	5	5	5	5
WEEK 13	MEAN	2235.	2531.	2642.	2075.
	S.D.	646.4	1171.7	828.6	608.3
	N	5	5	5	5
RBC ACHE (U/L)					
PRETEST	MEAN	2100.	2272.	2350.	2355.
	S.D.	150.7	253.6	139.0	307.4
	N	5	5	5	5
WEEK 3	MEAN	1634.	1830.	1650.	1900.
	S.D.	594.8	671.5	693.2	635.8
	N	4	5	5	5

U/L = INTERNATIONAL UNIT/LITER

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 54

PROJECT NO.:WIL-223004 A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS

SPONSOR:ZIRAM TASK FORCE PLASMA AND RED BLOOD CELL CHOLINESTERASE DETERMINATIONS - SUMMARY OF MEANS

		-----F E M A L E-----			
ANALYSIS	GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
RBC ACHE (U/L)					
WEEK 7	MEAN	1751.	1963.	1821.	1870.
	S.D.	372.9	328.9	322.1	234.0
	N	5	5	5	5
WEEK 13	MEAN	1802.	1543.	1859.	1849.
	S.D.	290.6	520.2	178.2	496.4
	N	5	5	5	5

U/L = INTERNATIONAL UNIT/LITER

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 55 (WEEK 13 EVALUATION)

PROJECT NO.:WIL-223004 — A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS — PAGE 1

SPONSOR:ZIRAM TASK FORCE — SUMMARY OF BRAIN CHOLINESTERASE DETERMINATIONS — WEEK 13

ANALYSIS GROUP:	----- MALE ----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN CHOLIN (U/gt)				
MEAN	1.55	1.66	1.58	1.30
S.D.	0.334	0.588	0.314	0.556
N	5	5	5	5

U/gt = Units/Gram Tissue

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 55 (WEEK 13 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BRAIN CHOLINESTERASE DETERMINATIONS

ANALYSIS GROUP:	-----F E M A L E----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN CHOLIN (U/gt)				
MEAN	1.75	1.75	1.48	1.35
S.D.	0.630	0.829	0.490	0.270
N	5	5	5	5

U/gt = Units/Gram Tissue

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 56 (WEEK 13 EVALUATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BRAIN NEUROTOXIC ESTERASE DETERMINATIONS

ANALYSIS GROUP:	----- MALE ----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN NTE (NM/MN/MG)				
MEAN	16.5	13.9	14.0	8.7**
S.D.	2.27	3.34	2.56	1.85
N	5	5	5	5

NM/MN/MG = NANAMOLES/MIN/MG PROTEIN

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 56 (WEEK 13 EVALUATION)

PROJECT NO.:WIL-223004 — A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS — PAGE 2

SPONSOR:ZIRAM TASK FORCE — SUMMARY OF BRAIN NEUROTOXIC ESTERASE DETERMINATIONS — WEEK 13

ANALYSIS GROUP:	-----FEMALE----- 0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN NTE(NM/MN/MG)				
MEAN	15.5	11.3	11.8	9.6*
S.D.	2.05	4.13	3.56	1.39
N	5	5	5	5

NM/MN/MG = NANAMOLES/MIN/MG PROTEIN

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 57 (NON-PERFUSED ANIMAL - UNSCHEDULED DEATH)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROSS NECROPSY OBSERVATIONS INCIDENCE SUMMARY

FOUND DEAD OR EUTHANIZED MORIBUND OR IN EXTREMIS

	MALE				FEMALE			
GROUP:	1	2	3	4	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10	10	10	10	10
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND/IN EXTREMIS	0	1	0	0	0	0	0	0
THYMUS GLAND								
-MASS(ES)	0	1	0	0	0	0	0	0
EXTERNAL SURFACE								
-RED MATTING	0	1	0	0	0	0	0	0
LYMPH NODE								
-MEDIASTINAL- ENLARGED	0	1	0	0	0	0	0	0
-BRONCHIAL- ENLARGED	0	1	0	0	0	0	0	0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 58 (NON-PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- M A L E -----		
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN				
MEAN	2.0831	1.9960	2.0415	2.0285
S.D.	0.06598	0.06208	0.12490	0.16033
N	5	5	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 58 (NON-PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS (GRAMS) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN				
MEAN	1.8129	1.8387	1.8673	1.8563
S.D.	0.07377	0.06176	0.03864	0.03404
N	5	5	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 59 (NON-PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS RELATIVE TO FINAL BODY WEIGHTS (GRAMS/100 GRAMS)

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
FINAL BODY WT(G)				
MEAN	509.	523.	546.	469.
S.D.	53.6	35.2	35.8	43.7
N	5	5	5	5
BRAIN				
MEAN	0.412	0.383	0.375	0.434
S.D.	0.0334	0.0167	0.0230	0.0201
N	5	5	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 59 (NON-PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS RELATIVE TO FINAL BODY WEIGHTS (GRAMS/100 GRAMS)

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
FINAL BODY WT(G)				
MEAN	254.	260.	269.	240.
S.D.	17.1	12.4	15.6	11.5
N	5	5	5	5
BRAIN				
MEAN	0.717	0.708	0.697	0.775
S.D.	0.0452	0.0530	0.0436	0.0350
N	5	5	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 60 (PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS AND BRAIN MEASUREMENTS

	----- MALE -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN				
MEAN	2.0740	1.9850	1.9700	1.9560
S.D.	0.05128	0.04796	0.05431	0.13722
N	5	4	5	5
BRAIN LENGTH(MM)				
MEAN	20.6	21.0	21.0	20.7
S.D.	0.47	0.46	0.68	0.76
N	5	4	5	5
BRAIN WIDTH(MM)				
MEAN	14.5	15.1	14.4	15.0
S.D.	0.79	0.20	1.13	0.29
N	5	4	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 60 (PERFUSED ANIMALS - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS AND BRAIN MEASUREMENTS

	----- F E M A L E -----			
GROUP:	0.0 PPM	72.0 PPM	207.0 PPM	540.0 PPM
BRAIN				
MEAN	1.8020	1.8220	1.7720	1.7740
S.D.	0.10826	0.09602	0.09935	0.06877
N	5	5	5	5
BRAIN LENGTH(MM)				
MEAN	19.7	20.3	19.8	19.7
S.D.	0.49	0.49	0.35	0.38
N	5	5	5	5
BRAIN WIDTH(MM)				
MEAN	14.6	14.5	14.2	14.3
S.D.	0.29	0.30	0.15	0.61
N	5	5	5	5

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 61 (PERFUSED TISSUES - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
BRAIN				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-CERV.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-LUMB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
GASSERIAN GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TRIGEMINAL NER.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR DOR. GANG				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 61 (PERFUSED TISSUES - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
LUMBAR DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR VENT. FIB				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. VENT. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SCIATIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	4	NA	NA	5
-DIGESTION CHAMBERS	1	NA	NA	0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

PROJECT NO.:WIL-223004
SPONSOR:ZIRAM TASK FORCE

TABLE 61 (PERFUSED TISSUES - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
SURAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TIBIAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
PERONEAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
OPTIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
EYES				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 61 (PERFUSED TISSUES - SCHEDULED EUTHANIZATION)
A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
BRAIN				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-CERV.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-LUMB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
GASSERIAN GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TRIGEMINAL NER.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR DOR. GANG				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

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A SUBCHRONIC NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
LUMBAR DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR VENT. FIB				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. VENT. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SCIATIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	4	NA	NA	5
-DIGESTION CHAMBERS	1	NA	NA	0

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

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HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	10	10	10	10
NUMBER OF ANIMALS EXAMINED WEEK 13	5	0	0	5
SURAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TIBIAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
PERONEAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	4	NA	NA	5
-DIGESTION CHAMBERS	1	NA	NA	0
OPTIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
EYES				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0.0 PPM 2- 72.0 PPM 3- 207.0 PPM 4- 540.0 PPM
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

FINAL REPORT

Contains No CBI

VOLUME 1 OF 3
(Text and Summary Data)

AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS

DATA REQUIREMENT

Guideline 81-8-SS

STUDY DIRECTOR

Ian C. Lamb, Ph.D.

STUDY INITIATION DATE

July 28, 1993

STUDY COMPLETION DATE

August 25, 1994

PERFORMING LABORATORY

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

LABORATORY STUDY NUMBER

WIL-223001

SPONSOR

The Ziram Task Force
NPC, Incorporated
22636 Glenn Drive
Suite 304
Sterling, VA 22107

262 for Volumes 2 + 3 Call Submitter

An Acute Neurotoxicity Study of Ziram in Rats

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10 (d) (1) (A), (B), or (C).

Company: Ziram Task Force

Company Agent: Vincent J. Piccirillo Date: Sept. 7 1994

Chairman, Ziram Task Force
Title

Signature

An Acute Neurotoxicity Study of Ziram in Rats

COMPLIANCE STATEMENT

This study, WIL-223001, was designed and conducted in compliance with the following regulatory instruments:

- United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations, 40 CFR Part 160 (October 16, 1989)
- United States EPA Test Guidelines for a Neurotoxicity Screening Battery (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Addendum 10; Neurotoxicity: Series 81-8; March, 1991)
- Standard Operating Procedures of WIL Research Laboratories, Inc.
- the protocol as approved by the sponsor

Ian Lamb — 8-25-94
Ian C. Lamb, Ph.D.
Study Director — Date

Vincent Piccirillo — Sept 7 1994
Sponsor Representative — Date

Vincent Piccirillo — Sept. 7 1994
Applicant/Submitter — Date

An Acute Neurotoxicity Study of Ziram in Rats

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An Acute Neurotoxicity Study of Ziram in Rats

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An Acute Neurotoxicity Study of Ziram in Rats

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An Acute Neurotoxicity Study of Ziram in Rats

I. SUMMARY:

The potential acute neurotoxicity related to the administration of Ziram in the Sprague-Dawley Crl:CD®BR rat was evaluated using a neurotoxicity screening battery. The test article was administered by the oral route (gavage) as a single dose at dosage levels of 15, 300 and 600 mg/kg. The 15 and 300 mg/kg groups each consisted of 12 males and 12 females, and the 600 mg/kg group consisted of 16 males and 16 females. A concurrent control group (consisting of 12 males and 12 females) received the vehicle, Mazola® Corn Oil, on a comparable regimen. A dose volume of 7.5 ml/kg was used for all groups. Experimental parameters recorded for all animals included viability, clinical signs, body weights and Functional Observational Battery and Motor Activity evaluations. Functional Observational Battery and Motor Activity evaluations were performed during pretest, at the time of peak effect (approximately 4-hours post-dosing on day 0) and on days 7 and 14. At the scheduled necropsy, brain weights and brain dimensions were determined for all animals. In addition, all animals were perfused *in situ*; 5 animals/sex/group were randomly selected for subsequent neuropathological evaluation in the control and 600 mg/kg groups.

A single oral administration of Ziram in rats at dosage levels of 15, 300 and 600 mg/kg resulted in:

A. Four males (25% mortality) and seven females (44% mortality) died following dose administration with 600 mg/kg Ziram. All of the males and three of the females died on study day 1. The deaths of the other females in the 600 mg/kg group occurred on study day 2, 4 or 5. One female (8% mortality) in the 300 mg/kg group died on study day 2. White contents in the stomach and/or intestine were observed at necropsy for the single 300 mg/kg group female that died and for three of the males and five of the females in the 600 mg/kg group that died. Distention of the stomach and/or intestine was observed for the female in the 300 mg/kg group and for one male and three females in the 600 mg/kg group. Two of the 600 mg/kg group females that died were emaciated (no abdominal adipose tissue present). All other internal findings were considered to be normal background changes or were limited to single animals.

B. Several treatment related clinical signs were observed in the 300 and 600 mg/kg group males and females that survived to study termination. The most remarkable of these findings often were limited to or occurred most frequently in two males (no. 15355 and 15387) in the 300 mg/kg group. Those clinical signs observed for these two males only included cyanosis, hypothermia (cool to touch), enophthalmus and unkempt appearance. The aforementioned clinical signs were observed on study day 8 or later (last week of study) on one to three occasions. Other remarkable clinical signs observed for males no. 15355 and 15387 throughout the study included abnormal respiration, abnormal excreta, gait alterations, abdomen

appearing distended, hypoactivity, ptosis and red, tan, orange and/or brown staining/material.

As mentioned above, several remarkable clinical signs were observed in the 300 and 600 mg/kg group males and females. Those signs observed in the 300 mg/kg (excluding males no. 15355 and 15387) and 600 mg/kg groups included gait alterations (rocking, lurching or swaying and/or high carriage), abnormal respiration (rales, labored respiration and/or gasping), abnormal excreta (soft stool, diarrhea, mucoid feces, decreased defecation and urination and small feces) and abdomen appearing distended. In general, the occurrence of these findings was limited to the first week of study. In addition, tan, red, orange and/or brown staining/material was observed for some males and females in the 300 and 600 mg/kg group generally during the first week of study.

C. Transient reductions in mean body weight gain were apparent in the 300 and 600 mg/kg group males and females for study days 0 to 7. The differences from the control group were 63% and 55% in the 300 mg/kg group and 67% and 45% in the 600 mg/kg group for males and females, respectively. Even though mean body weight gains in the 300 mg/kg group females and the 600 mg/kg group males and females were similar to or greater than the control group for study days 7 to 14 and 14 to 15, the mean cumulative gains were slightly lower than the control group means for study days 0 to 14 and 0 to 15. Mean body weight gain was reduced in the 300 mg/kg group males for study days 7 to 14; this was mainly due to 2/12 of these animals (no. 15355 and 15387). As a result, all mean cumulative gains (study days 0 to 7, 0 to 14 and 0 to 15) in the 300 mg/kg group males were remarkably lower than the control group means. Mean body weight values were remarkably lower for study days 7, 14 and 15 in the 300 mg/kg group males and for study day 7 in the 600 mg/kg group males.

D. Remarkable differences from the control group were observed for animals that received Ziram at dose levels of 300 and 600 mg/kg when the Functional Observational Battery was performed. In general, responses occurred approximately 4-hours following treatment on study day 0, and were transient in nature (several signs were observed at the daily clinical examinations generally during the first week of study; none of these persisted to study day 7). Specific test results included:

1. altered posture, palpebral closure and feces consistency in the 300 and 600 mg/kg group males and females during the home cage observations on study day 0;

2. lacrimation, salivation, changes in fur appearance, altered palpebral closure, changes in respiratory rate and/or character, red deposits around the mouth and crusty deposits around the nose and mouth in the 300 and 600 mg/kg group males and females during the handling observations on study day 0.

In addition, decreased muscle tone was observed in the 600 mg/kg group males on study day 0;

3. impaired mobility and altered gait in the 300 and 600 mg/kg group males and females during the open field observations on study day 0;

4. absent tail pinch and olfactory responses and a slighter startle response in the 300 and 600 mg/kg group males and females, absent startle response in the 600 mg/kg group males and females, absent forelimb and/or hindlimb extension in the 300 and 600 mg/kg group females during the sensory observations on study day 0;

5. decreased body temperatures in the 300 and 600 mg/kg group males and females during the physiological observations on study day 0, and reduced body weights in the 300 and 600 mg/kg group males on study day 7.

E. Remarkable signs observed during the study day 14 FOB evaluation were generally limited to two males (no. 15355 and 15387) in the 300 mg/kg group. It should be noted that these findings were generally not observed during the study day 7 FOB evaluation. Moreover, some of these signs were not even observed at the day 0 FOB evaluation for these animals or the 600 mg/kg group males and females at any evaluation period.

F. The only possible effects on FOB parameters in the 15 mg/kg group were transient in nature and were observed only during the study day 0 evaluation. These possible effects included altered posture for one male during the home cage observations and slight impairment of gait for two males and one female during the open field observations.

G. Reductions in mean ambulatory and total motor activity counts were observed in the 300 and 600 mg/kg group males and females on study day 0. The values for all four subsessions, especially the first three, were remarkably reduced in the 300 and 600 mg/kg group males and females when compared to the control group. Reductions in mean ambulatory and total motor activity counts in the 600 mg/kg group males persisted through to study day 7; however, full recovery was apparent for these males by study day 14. Even though the mean counts were not affected in the 300 mg/kg male group on study day 14, the ambulatory and total motor activity counts for males no. 15355 and 15387 were reduced when compared to the control group at this time period and when compared to their study day 7 values.

H. No treatment related effects on mean absolute brain weights or dimensions were apparent at any dose level.

I. No treatment related microscopic lesions were observed in any of the central or peripheral nervous system tissues examined from the 5 animals/sex in the 600 mg/kg group.

Based on the results of the Functional Observational Battery and Motor Activity evaluations, transient effects [i.e. on study day 0 and 7 (motor activity) only] were observed on one or more parameters in each of the following functional domains described by Moser[1] by a single oral administration of Ziram at 300 and 600 mg/kg: autonomic, neuromuscular, sensorimotor, CNS activity and physiological. Slight, transient effects were observed on the neuromuscular and CNS activity domains at a dose level of 15 mg/kg on study day 0 only.

Based upon the results of this study, the 15 mg/kg dose level was considered to be the minimum effect level for acute neurotoxicity.

II. STUDY OBJECTIVES:

The objectives of this study were to evaluate:

A. the potential of the test article to produce systemic adverse effects when administered to the rat as a single oral dose;

B. the potential of the test article to produce gross functional deficits, alterations in motor activity, and structural alterations to the nervous system when administered to the rat as a single oral dose.

III. MATERIALS AND METHODS:

A. Experimental Schedule and Sponsor Information:

1. Experimental Start Date:	August 2, 1993
2. Experimental Termination Date:	December 22, 1993
3. Study Sponsor:	The Ziram Task Force c/o NPC, Incorporated 22636 Glenn Drive Suite 304 Sterling, VA 22107
4. Sponsor Representative:	Vincent Piccirillo, Ph.D., D.A.B.T. NPC, Incorporated

B. Test System:

1. Species:	Rat
2. Strain:	Sprague-Dawley, Crl:CD®BR
3. Justification for Selection:	This species and strain of animal was selected because it is recognized to be appropriate for neurotoxicity studies[2, 3].
4. Source:	The Charles River Breeding Laboratories, Inc., Portage, Michigan 49081
5. Number on Study:	Fifty-two males and fifty-two females (nulliparous and non-pregnant)

6. Body Weight Range At Initiation of Dosing: Males, 189g - 253g; Females, 138g - 190g

7. Age at Initiation of Dosing: Young adult, 43 days old.

8. Method of Identification: Animals were uniquely identified by a Monel® metal eartag displaying the animal number. Individual cage cards were affixed to each cage and displayed the study number, group number, animal number, dosage level, sex, date of animal arrival and study initiation.

9. Housing: Weanling animals were housed 3 per cage, by sex, in suspended, stainless steel wire-mesh cages for approximately 3 days following receipt. Thereafter, all animals were housed individually. The animals were housed in general accordance with the NIH "Guide for the Care and Use of Laboratory Animals"[4]. The animal facilities are accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

10. Quarantine: The animals were acclimated to laboratory conditions for at least 18 days prior to initiation of dosing. The acclimation period included a one week pretest period. The animals were observed twice daily for mortality and moribundity.

11. Environmental Conditions: Environmental controls in the animal room were set to maintain temperature at 68-76°F (20.0 - 24.4°C), relative humidity between 30-70% and a photoperiod of 12 hours light (6 a.m. to 6 p.m.)/12 hours dark. Actual temperature and humidity ranges were 70-74°F (21.1 - 23.3°C) and 60-85%, respectively, during the course of the study. The occasional deviations from set humidity levels did not apparently affect the outcome of the study. Air handling units were set to provide approximately 10 fresh air changes per hour.

12. Food and Water: Purina® Certified Rodent Chow #5002 and municipal water were provided *ad libitum*. Feed and water analyses are maintained at WIL Research Laboratories, Inc.

C. Test Article Data:

1. Identification: Ziram (Zinc Dimethyldithiocarbamate)

2. Date Received: March 1, 1993

3. Shipped From: UCB Chemicals
Organical Division
Pantserschipstraat 207
B-9000 Gent
Belgium

4. Quantity Received: 1 Bag; gross weight 5300.9 g

5. CAS Number: 137-30-4

6. Lot Number: V528/8331AA

7. Purity: 97.8%; a correction factor of 1.02 was used for the dose calculations. A certificate of analysis is presented in Appendix C.

8. Physical Description: White powder.

9. Stability and Storage Conditions: Stable when stored at room temperature.

10. Retention Sample: Approximately 1 g collected March 9, 1993 and stored at WIL Research Laboratories, Inc.

D. Vehicle Control Data:

1. Identification: Mazola® Corn Oil

2. Manufacturer: Best Foods
CPC International, Inc.
General Offices
Engelwood Cliffs, NJ 07632

3. Dates Received: May 26, 1993 and June 8, 1993

4. Quantity Received: 5-48 fl. oz. bottles (May 26, 1993 shipment)
5-64 fl. oz. bottles (June 8, 1993 shipment)

5. Expiration Dates: September 5, 1994 (May 26, 1993 shipment)
January 27, 1994 (June 8, 1993 shipment)

6. Physical Description: Clear yellow viscous liquid.

E. Vehicle Control and Test Article Preparation:

The appropriate volume of Mazola® Corn Oil to dose the control group animals was dispensed into a properly labeled storage container. The Mazola® Corn Oil was stirred throughout the sampling and dosing procedures using a magnetic stir bar and plate.

Each dosing admixture was prepared in the following manner. A sufficient amount of test article, Ziram, was weighed into a tared precalibrated storage container. An appropriate amount of Mazola® Corn Oil was added to attain the required volume and concentration. The container was then placed on a Polytron® PT 6000 and the contents mixed for approximately 5 minutes. Each preparation was stirred continuously throughout the sampling and dosing procedures using a magnetic stir bar and plate.

All preparations were made on the day of dosing.

The dosing formulations were visually inspected by the study director prior to administration for homogeneity. All formulations were homogeneous and satisfactory for administration.

F. Sampling of Test Article Preparations:

1. Analytical Tests: Homogeneity, stability and test article concentration analyses were conducted on Ziram preparations. The results are presented in Appendix B.

2. Strata Sampled/ Sampling Schedule: Prior to initiation of dosing, the top, middle and bottom of the Ziram preparations were sampled for homogeneity; the middle of the preparations were sampled for stability. On the day of dosing for Replicate 1 (August 2, 1993), the middle of each preparation was sampled for concentration. In addition, samples from the

middle of each preparation were collected on each day of dosing and stored refrigerated. The results are presented in Appendix B.

3. Performing Laboratory: Analytical Chemistry Department
WIL Research Laboratories, Inc.

G. Route and Rationale of Test Article Administration:

The oral route of administration was utilized. This is a potential route of exposure for the general human population. A 16-gauge stainless steel gavage cannula (Popper and Sons, Inc., New Hyde Park, New York 11040) was used for dose administration. Individual animal doses were calculated based on the animal body weight recorded prior to administration.

The test and control articles were administered to non-fasted animals as a single dose on study day 0. Animals were not fasted prior to dose administration in order to avoid any potential confounding effects of inanition on the behavior of the test subjects.

Dose levels were selected based on the results of a range-finding acute study with Ziram (WIL-160013)[5]. Dose levels used in the preliminary study were 10, 20, 25, 50, 150, 300, 500, 600, 700, 800, 1250, 1500, 1750 and 2000 mg/kg. The mortality rate was 2/8, 2/2, 1/2, 2/2, 2/2, 1/1 and 0/1 for males and 3/8, 2/2, 1/2, 1/2, 1/2, 1/1 and 1/1 for females in the 600, 700, 800, 1250, 1500, 1750 and 2000 mg/kg groups, respectively. With the exception of one 600 mg/kg group female that died on study day 3, all of these animals died or were euthanized *in extremis* within approximately 24-hours following dose administration with Ziram. No deaths occurred at dose levels of 10-500 mg/kg. The predominant clinical signs observed in this range-finding study included gait alterations at dose levels of 25 mg/kg and above, hypoactivity at dose levels of 50 mg/kg and above (except 500 mg/kg), lacrimation at 50 mg/kg and at 300 to 1500 mg/kg, and salivation at 150 mg/kg and above (except 500 mg/kg). No remarkable clinical signs were observed in the 10 or 20 mg/kg groups. The estimated time of peak effect of the treatment related clinical signs was approximately 4-hours post-dosing.

H. Experimental Design:

Animals used on study were determined to be of normal health, weighed and assigned to groups using a computer-based randomization procedure which ensured homogeneity of group means and variances for body weight. (Weight variation did not exceed ± 20% of group mean for each sex.) After randomization (July 23, 1993) into study groups, animals were then randomized into four study replicates (Appendix D) to allow for the reasonable conduct of all necessary study functions.

Each dose group and sex were equally represented within a study replicate. During the conduct of the pretest Functional Observational Battery and Motor Activity evaluations, control group male no. 15381 demonstrated a marked impairment in gait. This animal was replaced with male no. 15347 at the study director's request. The following diagram presents the study group assignment:

Group Number	Test Article	Dosage Level (mg/kg)	Dosage Concentration (mg/ml)	Dosage Volume (ml/kg)	Number of Animals Males	Number of Animals Females
1	Mazola® Corn Oil	0	0	7.5	12	12
2	Ziram	15	2	7.5	12	12
3	Ziram	300	40	7.5	12	12
4	Ziram	600	80	7.5	16	16

I. Experimental Observations:

1. Viability:

Animals were observed twice daily (morning and afternoon) for mortality and/or moribundity.

2. Clinical Signs:

Detailed clinical observations were recorded daily for all animals. On study days when the Functional Observational Battery was conducted, no additional clinical signs were recorded.

3. Individual Body Weights:

Individual body weights were recorded pre-study (July 23, 1993) and are presented on the report tables as day -10 body weights. In addition, individual body weights were recorded on study days 0, 7 and 14. Body weights were also recorded during the Functional Observational Battery procedures and prior to necropsy (study day 15). Animals found dead were weighed prior to necropsy with the following exceptions. Final body weights were inadvertently not recorded for 600 mg/kg group male no. 15352 and female no. 15411 found dead on August 3, 1993. These deviations had no impact on the outcome of the study.

4. Functional Observational Battery [FOB]:

Observations on all animals (Groups 1-3, 12/sex/group; Group 4, 16/sex/group) were made pre-study, at the approximate time of "peak effect" (approximately 4-hours after dosage administration) and on study days 7 and 14. 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 ± 10db. with one exception; home cage observations were performed in the animal room. All animals were observed for the following parameters as described below (refer to Appendix E for a detailed description of the scoring criteria used for each observation):

a. Home Cage Observations

Posture
Convulsions/tremors
Feces consistency
Biting
Palpebral (eyelid) closure

b. Handling Observations

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

c. Open Field Observations (evaluated over a 2 minute observation period)

Mobility
Rearing
Convulsions/Tremors
Grooming
Bizarre/Stereotypic behavior
Time to first step (seconds)
Gait
Arousal
Urination/Defecation
Gait score
Backing

d. Sensory Observations

Approach response
Startle response
Pupil response
Forelimb extension
Air righting reflex
Touch response
Tail pinch response
Eyeblink response
Hindlimb extension
Olfactory orientation

e. Neuromuscular Observations

Hindlimb extensor strength
Hindlimb foot splay
Grip strength-hind and forelimb
Rotarod performance

f. Physiological Observations

Catalepsy
Body temperature
Body weight

5. Locomotor Activity:

Observations were made on all animals (Groups 1-3, 12/sex/group; Group 4, 16/sex/group) during the pretest period, at the approximate time of "peak effect" (approximately 4-hours after dosage administration) and on study days 7 and 14. Locomotor Activity, recorded after the completion of the FOB, was measured automatically using the Digiscan 'Micro' Animal Activity System (Omnitech Electronics, Inc., Columbus, OH 43228). This is a personal computer-controlled system consisting of individual test chambers which utilize a series of infrared photobeams surrounding a clear plastic, rectangular cage to quantify an animal's motor activity. The testing of treatment groups was done according to replicate sequence. The activity system was operated in the Stagger Start mode of operation. Data were collected in one minute epochs and the test session was 41 minutes in duration for each animal. Animal placement into the activity cage in the Stagger Start mode of operation initiated the data collection process. The first epoch was often incomplete due to the placement of the animal in the activity cage. For this reason, the first minute of data was deleted. The remaining 40 minutes of data collection (4, 10 minute subsessions) were compiled for tabular presentation.

During the study day 14 Motor Activity data collection, there was an apparent malfunction of the monitor housing 15 mg/kg group male no. 15378. This was discovered following the necropsy of male no. 15378. At the study director's request, these data were not tabulated in the group mean for this interval. This isolated incident had no impact on the scientific integrity, validity or outcome of the study.

Locomotor Activity was divided into two categories; total and ambulatory activity. Total motor activity was defined as a combination of fine motor skills (i.e. grooming; interruption of one or two adjacent photobeams) and ambulatory motor activity (interruption of three or more consecutive photobeams). Data for ambulatory and total motor activity were tabulated. Refer to Appendix J for additional details on the motor activity methodology.

6. Scheduled Necropsy Examinations:

a. Unscheduled Deaths:

A complete necropsy examination was conducted on all animals found dead during the study. The necropsy included an examination of the external

surface, all orifices, and the cranial, thoracic, abdominal and pelvic cavities including the viscera. All gross lesions were collected and preserved in 10% neutral buffered formalin. The carcasses were then discarded.

b. Neuropathology:

After at least 14 days of observation, all surviving animals in each group were euthanized by carbon dioxide inhalation and then perfused *in situ*. The central and peripheral tissues were preserved. Brain weight (excluding olfactory bulbs) and brain dimensions (length and width) were recorded. Any observable gross changes, abnormal coloration or lesions of the brain and spinal cord were recorded. Even though not required by the protocol, it was also recorded when no gross lesions were observed for the brain and spinal cord. In addition, remarkable gross lesions observed internally/externally during the perfusion/dissection processes were also recorded. These deviations from the protocol had no apparent impact on the outcome of the study. The following nerve tissues were dissected and prepared for a qualitative histopathological examination (embedded in paraffin or plastic, sectioned and then stained with hematoxylin and eosin) from five animals per sex in the control and 600 mg/kg groups:

Central Nervous System tissues[a]
Brain - forebrain, center of cerebrum, midbrain, cerebellum and pons, and the medulla oblongata
Spinal cord - at cervical swellings C3 - C8 and at lumbar swellings T13 - L4
Gasserian ganglion/Trigeminal nerves
Lumbar dorsal root ganglion at T13 - L4
Lumbar dorsal root fibers at T13 - L4
Lumbar ventral root fibers at T13 - L4
Cervical dorsal root ganglion at C3 - C8
Cervical dorsal root fibers at C3 - C8
Cervical ventral root fibers at C3 - C8
Optic Nerves
Eyes
[a] - embedded in paraffin

Peripheral Nervous System tissues[b]
Sciatic nerves (mid-thigh region and at sciatic notch)
Sural nerves
Tibial nerves
Peroneal nerves
Forelimbs[c]
Tail[c]
[b] - embedded in plastic
[c] - preserved for possible future neuropathological evaluation

Microscopic examinations were conducted by Robert R. Dahlgren, D.V.M., Ph.D., Diplomate A.C.V.P., Director of Pathology and Veterinary Medicine, WIL Research Laboratories, Inc.

J. Statistical Methods:

Statistical tests for body weight, histopathological and brain data were performed by a Digital® MicroVAX® 3400 computer with appropriate programming[6]. All analyses were two-tailed for a significance level of 5% and 1%. Each mean was presented with the standard deviation (S.D.) and the number of animals (N) used to calculate the mean. Body weight and body weight change data were subjected to a one-way analysis of variance (ANOVA). If significant differences were indicated by the ANOVA, Dunnett's test[6] was used to compare the control and treated groups. Histopathological findings of the 600 mg/kg group were compared to the control group data by the Kolmogorov-Smirnov test[9]. Brain weights and dimensions were analyzed by one-way ANOVA. If significant differences were indicated by the ANOVA, Dunnett's test[6] was used to compare the control and treated groups.

Statistical tests for the Functional Observational Battery and Locomotor Activity data were performed using a personal computer installed with SAS/STAT statistical software[7]. Each mean was presented with the standard deviation and the number of animals used to calculate the mean. Animals that died on study were not included in the calculation of the means for any test period. Continuous FOB data were analyzed using a two-way repeated measures ANOVA. If significant treatment or treatment-time interactions occurred, a one-way ANOVA was conducted at each time point. If significant treatment effects were observed at a time point, Dunnett's multiple T-test[7] was conducted to determine significant treatment differences from the control group ($p<0.05$). FOB parameters yielding scalar (ordinal) or descriptive data were analyzed using the repeated measures SAS CATMOD procedure[7, 8]. If significant treatment or treatment-time effects occurred, Fisher's Exact test or Dunnett's test[6] were conducted to determine significant treatment differences from the control group. (These tests were performed by a Digital® MicroVAX® 3400 computer with appropriate programming).

K. 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 protocol.

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

were evident on study day 7 for these animals during the handling observations (section IV.E.2.). Therefore, the differences in palpebral closure were not attributed to treatment. No other remarkable differences from the control group were observed at any dose level during home cage observations during the study day 7 evaluation.

On study day 14, 300 mg/kg group males no. 15355 and 15387 had altered posture (rearing and sitting with head held low, respectively). In addition, male no. 15355 also had altered palpebral closure (slightly drooping) on study day 14.

The only statistically significant ($p<0.05$) difference from the control group on study day 14 was a decreased number of 600 mg/kg group males that were alert, oriented toward the observed when posture was evaluated. However, the distribution of day 14 posture observations within this group were identical to the pretest distribution and were not attributed to treatment. No other remarkable differences from the control group in home cage parameters were apparent at any dose level on study day 14.

2. Handling Observations:

Summary Data - Tables 12 through 19; Figure 2

Individual Data - Appendix A (Tables 8 through 11)

Historical Control Data - Appendix G

Handling observations in the 15, 300 and 600 mg/kg groups were comparable to the control group values during the pretest evaluation for both sexes.

Administration of Ziram on study day 0 produced treatment related signs of toxicity in males and females that received 300 and 600 mg/kg. These signs included lacrimation, salivation, changes in fur appearance, altered palpebral closure, changes in respiratory rate and/or character, red deposits around the mouth and crusty deposits around the nose and mouth. Decreased muscle tone observed in the 600 mg/kg group on study day 0 was also attributed to Ziram.

Lacrimation was observed for 25% of the males (slight) and 45% (slight) of the females in the 300 mg/kg group and for 11% (1/9) of the females (slight) in the 600 mg/kg group on study day 0. The number of females in the 300 mg/kg group that had lacrimation was statistically significant ($p<0.05$) when compared to the control group. The percentages of 300 mg/kg group males and females and 600 mg/kg group females with lacrimation were outside the WIL FOB historical control data.

Salivation was observed for 58% of the males (slight) and 73% of the females (slight) in the 300 mg/kg group and 50% of the males (42% slight; 8% severe) and 33% of the females (22% slight; 11% severe) in the 600 mg/kg group on study day 0. The numbers of 300 mg/kg group males and females and 600 mg/kg group males that had salivation were statistically significant ($p < 0.05$) when compared to the control group. The percentages of 300 and 600 mg/kg group males and females that had salivation were outside the WIL FOB historical control data.

Changes in fur appearance were noted for 42% of the males (33% slightly soiled; 8% very soiled, crusty) and 45% of the females (36% slightly soiled; 9% very soiled, crusty) in the 300 mg/kg group and for 50% of the males (33% slightly soiled; 17% very soiled, crusty) and 44% of the females (22% slightly soiled; 22% very soiled, crusty) in the 600 mg/kg group on study day 0. The numbers of 300 and 600 mg/kg group males and females that had changes in fur appearance were statistically significant ($p < 0.05$) when compared to the control group.

Alterations in palpebral closure were observed for 50% of the males (eyelids slightly drooping) and 45% of the females (eyelids slightly drooping) in the 300 mg/kg group and for 67% of the males (eyelids slightly drooping) and 67% females (56% eyelids slightly drooping; 11% drooping eyelids, half-closed) in the 600 mg/kg group on study day 0. The numbers of 300 and 600 mg/kg group males and females that had altered palpebral closure were statistically significant ($p < 0.05$) when compared to the control group.

Decreased respiratory rate was observed for 25% of the males and 18% of the females in the 300 mg/kg group and for 42% of the males and 22% of the females in the 600 mg/kg group on study day 0. The number of males in the 600 mg/kg group that had decreased respiration was statistically significant ($p < 0.05$) when compared to the control group. The numbers of males and females in the 300 and 600 mg/kg groups that had decreased respiration were outside the WIL FOB historical control data. In addition, rales were observed for 17% (2/12) of the males in the 300 mg/kg group. Since this finding was not observed in the WIL historical control data, it was attributed to treatment with Ziram.

Red deposits around the mouth were observed for 50% of the males and 9% of the females in the 300 mg/kg group and for 17% of the males and 22% of the females in the 600 mg/kg group. The number of 300 mg/kg group males that had red deposits around the mouth was statistically significant ($p < 0.05$) when compared to the control group. The numbers of males and females in the 300 and 600 mg/kg groups that had red deposits around the mouth were outside the WIL FOB historical control data.

Crusty deposits around the nose were observed for 17% of the males and 27% of the females in the 300 mg/kg group and for 42% of the males and 33% of the females in the 600 mg/kg group on study day 0. The number of 600 mg/kg group males that had crusty deposits around the nose was statistically significant ($p<0.05$) when compared to the control group. The numbers of 300 and 600 mg/kg group males and females with crusty deposits around the nose were outside the WIL FOB historical control data.

Crusty deposits around the mouth were noted for 33% of the males and 54% of the females in the 300 mg/kg group and for 67% of the males and 78% of the females in the 600 mg/kg group on study day 0. The numbers of 300 mg/kg group females and 600 mg/kg group males and females that had crusty deposits around the mouth were statistically significant ($p<0.05$) when compared to the control group. The numbers of 300 and 600 mg/kg group males and females with crusty deposits around the mouth were outside the WIL FOB historical control data.

Changes in muscle tone were observed for 17% (2/12) of the males in the 600 mg/kg group on study day 0. This number was outside the WIL FOB historical control data.

No other treatment related changes in handling observations were apparent on day 0. Red deposits around the eyes were observed for some males in the 15, 300 and 600 mg/kg groups, and red deposits around the nose were observed for some males and/or females in the 15, 300 and 600 mg/kg groups. Even though the numbers were increased when compared to the control group ($p<0.05$ for 300 mg/kg group males, red deposits around the nose), they were either lower than or similar to the WIL FOB historical control data and not attributed to treatment. One female in the 300 mg/kg group had a change in muscle tone (soft and flabby). However, this sign has been observed in the WIL FOB historical control data (one female) and, therefore, could not be directly attributed to the test article. No other remarkable handling observations were noted on study day 0.

On study day 7, two males (no. 15355 and 15387) in the 300 mg/kg group had a change in respiratory character (rales). No other possible treatment related effects on handling parameters were observed on study day 7 at any dose level. One male (no. 15406) in the 600 mg/kg group had a change in fur appearance (slightly soiled) on study day 7. However, this was a single occurrence for this animal (not seen at the clinical observations or during the study day 14 FOB evaluation) and was not attributed to treatment with Ziram. No other remarkable differences from the control group in handling observations were apparent at any dose level on study day 7.

The only remarkable findings observed during the study day 14 handling evaluation were limited to two males (no. 15355 and 15387) in the 300 mg/kg

group. Findings noted for both of these males included altered palpebral closure (no. 15355, drooping eyelids, half-closed; no. 15387, eyelids slightly drooping), a change in respiratory character (gasping) and changes in mucous membrane and skin color (pale). Male no. 15387 also had a change in fur appearance (very soiled, crusty), crusty deposits around the nose and mouth and a change in eye color (pale) on study day 14. A change in eye prominence (enophthalmus) was noted for male no. 15355 on study day 14. No other remarkable differences from the control group in handling observations were apparent at any dose level on study day 14.

3. Open Field Observations:

Summary Data - Tables 20 through 27; Figure 3

Individual Data - Appendix A (Tables 12 through 15)

Historical Control Data - Appendix G

At the pretest evaluation, the mean defecation count in the 300 mg/kg group males was significantly ($p < 0.05$) above the control group mean. All other open field observations in the 15, 300 and 600 mg/kg group were similar to the control group values during the pretest evaluation for both sexes.

Administration of Ziram on study day 0 produced treatment related signs of toxicity in the males and females that received 300 and 600 mg/kg. These signs consisted of impaired mobility and altered gait.

On study day 0, impaired mobility was noted for 33% of the males (25% slight; 8% moderate) and 45% of the females (36% slight; 9% moderate) in the 300 mg/kg group and for 42% of the males (33% slight; 8% moderate) and 33% of the females (22% slight; 11% moderate) in the 600 mg/kg group. The numbers of 300 mg/kg group females and 600 mg/kg group males with impaired mobility were statistically significant ($p < 0.05$) when compared to the control group. The numbers of males and females in the 300 and 600 mg/kg groups that had impairment of mobility were outside the WIL FOB historical control data.

Impaired gait was observed for 67% of the males (33% walks on tiptoes; 33% ataxia) and 73% of the females (64% walks on tiptoes; 9% ataxia) in the 300 mg/kg group and for 75% of the males (58% walks on tiptoes; 17% ataxia) and 78% of the females (56% walks on tiptoes; 22% ataxia) in the 600 mg/kg group on study day 0. The alterations in gait in the 300 and 600 mg/kg group males and females were statistically significant ($p < 0.05$) when compared to the control group. At the 300 mg/kg dose level, gait scores indicated that 58% of the males and 36% of the females had slight impairment and that 8% of the males and 36% of the females had considerable impairment. At the 600 mg/kg dose level, gait

scores indicated that 25% of the males and 33% of the females had slight impairment and that 50% of the males and 44% of the females had considerable impairment. Gait scores in the 300 and 600 mg/kg group males and females were statistically significant ($p < 0.05$) when compared to the control group.

Gait alterations observed for 17% (2/12) of the males and 8% (1/12) of the females in the 15 mg/kg group on study day 0 were considered to be possible effects of treatment. Both males were ataxic and the female walked on tiptoes. The number of males was outside the WIL FOB historical control range. The gait scores indicated that all of these animals had slight impairment.

No other changes in open field parameters on study day 0 could be directly attributed to treatment with Ziram. Single males and females in the 300 and 600 mg/kg groups had altered arousal on study day 0. However, all of these numbers were similar to or below that of the WIL FOB historical control data, and therefore, were not attributed to treatment. The mean time to first step was significantly ($p < 0.01$) increased in the 600 mg/kg group females on study day 0. However, the difference from the control group was slight, and the value was similar to that observed in the WIL FOB historical control data. Therefore, this increase was not attributed to the test article. The grooming count for the 300 mg/kg group females was significantly ($p < 0.05$) above the control group value on study day 0. However, a similar increase was not observed in the 300 mg/kg group males or the 600 mg/kg group males and females. Therefore, this increased grooming count was not considered to be treatment related. No other remarkable differences from the control group were observed in the Ziram treated groups on study day 0.

No treatment related effects on open field parameters were observed on study day 7 at any dose level. The mean urination count for the 300 mg/kg group males was significantly ($p < 0.01$) increased when compared to the control group value on study day 7. These increases were isolated occurrences (not observed on study days 0 and 14) for one sex in highly variable parameters, and therefore, they were not considered to be related to treatment. No other remarkable differences from the control group were observed in the treated groups for open field parameters on study day 7.

On study day 14, 300 mg/kg group males no. 15355 and 15387 had impaired gait (walks on tiptoes). The gait scores indicated that the impairment was considerable (without falling) for both of these males. In addition, male no. 15355 also had impaired mobility (moderate) on study day 14.

On study day 14, the time to first step means for the 15 and 600 mg/kg group males were significantly ($p < 0.05$) lower than the control group mean. However, the differences were slight. In addition, higher times to first step, not lower, are usually considered to be an adverse effect. Therefore, the lower times to first

step were not considered to be related to treatment. Mean urination counts in the 600 mg/kg group males were significantly ($p<0.05$) increased when compared to the control group on study day 14. However, these values were similar to those observed in the WIL FOB historical control data and were not attributed to Ziram administration. No other remarkable differences from the control group were observed at any dose level for open field parameters on study 14.

4. Sensory Observations:

Summary Data - Tables 28 through 35; Figure 4

Individual Data - Appendix A (Tables 16 through 19)

Historical Control Data - Appendix G

Sensorimotor observations in the 15, 300 and 600 mg/kg groups were comparable to the control group values during the pretest evaluation for both sexes.

Administration of Ziram on study day 0 produced treatment related signs of toxicity in the 300 and 600 mg/kg groups. Test article related effects in the 300 and 600 mg/kg group males and females included absent tail pinch and olfactory responses. An absent startle response in the 600 mg/kg group males and females and a slighter startle response in the 300 and 600 mg/kg group males and females were considered to be related to the test article. In addition, absent forelimb and/or hindlimb extension observed in the 300 and 600 mg/kg group females were attributed to treatment.

On study day 0, the absence of a tail pinch response was noted for 8% (1/12) of the males in the 300 mg/kg group and for 11% (1/9) of the females in the 600 mg/kg group. This sign was not observed in the WIL FOB historical control data, and therefore, it was attributed to treatment.

The absence of an olfactory response was observed for 8% (1/12) of the males and 18% (2/11) of the females in the 300 mg/kg group and for 17% (2/12) of the males and 22% (2/9) of the females in the 600 mg/kg group on study day 0. The percentages of males and females affected in the 300 and 600 mg/kg groups were outside the WIL FOB historical control data, and therefore, its presence was considered to be treatment related.

The absence of a startle response was noted for 8% (1/12) of the males and 11% (1/9) of the females in the 600 mg/kg group on study day 0. This finding has not been observed in the WIL FOB historical control data. In addition, the percentages of males and females in the 300 and 600 mg/kg groups that displayed a slighter startle response on study day 0 were increased when compared to the control group values, the pretest and the WIL FOB historical control data values.

The differences were statistically significant ($p < 0.05$) in the 300 and 600 mg/kg group females.

The absence of forelimb extension and the absence of hindlimb extension were observed for 11% (1/9) of the 600 mg/kg group females on study day 0. The absence of hindlimb extension was also observed for 18% (2/11) of the 300 mg/kg group females. These signs were not observed in the WIL FOB historical control data and were attributed to the test article.

No other changes in sensory parameters could be attributed to the administration of Ziram on study day 0. The absence of an approach response was observed for 9% (1/11) of the females in the 300 mg/kg group and for 17% (2/12) of the males and 11% (1/9) of the females in the 600 mg/kg group on study day 0. However, these percentages were lower than or similar to those observed in the WIL FOB historical control data. Therefore, this finding was not attributed to the test article. The absence of a pupil response was observed for 8% (1/12) of the males in the each of the 15 and 300 mg/kg groups on study day 0. However, this sign was not observed in the 600 mg/kg group. In addition, the percentages in the 15 and 300 mg/kg group males were lower than that observed in the WIL FOB historical control data. The absence of a touch response was observed for 11% (1/9) of the 600 mg/kg group females. However, this number was within the WIL FOB historical control data. Therefore, this finding was not attributed to treatment. No other remarkable differences from the control group for sensory observations were observed at any dose level on study day 0.

No treatment related effects on sensorimotor parameters were observed on study day 7 at any dose level. The number of 600 mg/kg group males that had a more energetic tail pinch response was significantly ($p < 0.05$) increased when compared to the control group on study day 7. However, this value for the 600 mg/kg group males was similar to the pretest value, and therefore, it was not considered to be an effect of treatment. No other remarkable differences from the control group for sensory observations were observed in the Ziram treated groups at any dose level on study day 7.

On study day 14, the absence of a startle response and impaired air righting reflex (lands on side) were observed for 300 mg/kg group male no. 15387. The absence of hindlimb extension was noted for 300 mg/kg group male no. 15355 on study 14.

On study day 14, the numbers of 600 mg/kg group females that had slow approach and touch responses were significantly increased ($p < 0.05$) when compared to the control group. However, these values were identical or similar to the pretest values and were not considered to be related to Ziram administration. No other remarkable differences from the control group for sensorimotor parameters were observed on study day 14.

5. Neuromuscular Observations:

Summary Data - Tables 36 through 43

Individual Data - Appendix A (Tables 20 through 23)

Historical Control Data - Appendix G

Pretest neuromuscular values for the 15, 300 and 600 mg/kg group males and females were comparable to the control group values.

Neuromuscular values in the 15, 300 and 600 mg/kg groups were comparable to the control group values during the study day 0 evaluation for both sexes.

No apparent treatment related effects on neuromuscular parameters were observed in the Ziram treated groups during the study day 7 evaluation. Mean rotarod performance was decreased in the 600 mg/kg group males on study day 7. However, the difference was not statistically significant, and the day 7 value for the 600 mg/kg group males was similar to the pretest value. In addition, similar decreases were not observed at the study day 0 and 14 evaluations. No other remarkable differences from the control group in neuromuscular observations were apparent on study day 7 at any dose level.

No apparent treatment related effects on neuromuscular parameters were observed at any dose level on study day 14. Mean forelimb grip strength for the 600 mg/kg group males was significantly increased ($p < 0.01$) when compared to the control group mean on study day 14. However, decreases, not increases, in grip strength are generally considered to be an adverse effect of treatment. Therefore, the increased forelimb grip strength in the 600 mg/kg group males was attributed to biological variation. No other remarkable differences from the control group in neuromuscular observations were apparent on study day 14 at any dose level.

6. Physiological Observations:

Summary Data - Tables 44 through 47; Figure 5

Individual Data - Appendix A (Tables 24 through 27)

Historical Control Data - Appendix G

Physiological observations in the 15, 300 and 600 mg/kg dose groups were comparable to the control group values during the pretest evaluation for both sexes.

Administration of Ziram on study day 0 produced treatment related reductions in body temperature in the 300 and 600 mg/kg group males and females. These differences from the control group were statistically significant ($p<0.01$). Slightly decreased mean body temperatures ($p<0.05$, 600 mg/kg group males) in the 300 and 600 mg/kg group males on study day 7 were not attributed to Ziram administration since these values were similar ($\leq$ 1% difference) to pretreatment values. On study day 14, 300 mg/kg group males no. 15355 and 15387 had markedly decreased body temperatures (34.9°C and 33.2°C, respectively) when compared to the control group mean (38.8°C). No other remarkable differences from the control group were observed in mean body temperatures.

Mean body weights were significantly lower ($p<0.01$) for study days 7 and 14 for the 300 mg/kg group males and for study day 7 in the 600 mg/kg group males. These significant differences from the control group were similar to those discussed in section IV.D.; the mean body weight for the 300 mg/kg group males was decreased on study day 14 due to two males. The study day 14 body weights (157.5 g and 159.5 g, respectively) for 300 mg/kg group males no. 15355 and 15387 were markedly lower than the control group mean (314.4 g). No other remarkable differences in mean body weights were observed.

No treatment related effects on mean catalepsy values were observed in the 300 and 600 mg/kg group males and females on study days 0, 7 and 14.

No effects on mean catalepsy, body temperature or body weight values in the 15 mg/kg group were apparent on study days 0, 7 and 14 in either sex.

F. Locomotor Activity:

Summary Data - Tables 48 through 51; Figures 6, 7

Individual Data - Appendix A (Tables 28 through 31)

Historical Control Data - Appendix H

Locomotor Activity in the 15, 300 and 600 mg/kg dose groups was comparable to the control group values during the pretest evaluation for both sexes.

Treatment with Ziram produced decreases in mean ambulatory and total motor activity counts in the 300 and 600 mg/kg group males and females on study day 0. Full recovery was apparent in the 300 mg/kg group males and females and the 600 mg/kg group females by study day 7 and in the 600 mg/kg group males by study day 14.

When compared to the control group values, overall mean ambulatory activity counts were reduced by 87% and 80% in the 300 and 600 mg/kg group males, respectively, and by 76% and 87% in the 300 and 600 mg/kg group females, respectively, on study day 0. The values for all four subsessions, especially the first three, were remarkably reduced in the 300 and 600 mg/kg group males and females when compared to the control group. Subsessions 1, 2 and 3 in the 300 and 600 mg/kg group males and subsessions 1 and 2 in the 300 and 600 mg/kg group females were statistically significant ($p<0.05$) when compared to the control group.

When compared to the control group values, overall mean total motor activity counts were reduced by 86% and 82% in the 300 and 600 mg/kg group males, respectively, and by 79% and 87% in the 300 and 600 mg/kg group females, respectively, on study day 0. The values for all four subsessions, especially the first three, were remarkably reduced in the 300 and 600 mg/kg group males and females when compared to the control group. Subsessions 1, 2 and 3 in the 300 and 600 mg/kg group males and subsessions 1, 2 and 4 in the 300 and 600 mg/kg group females were statistically significant ($p<0.05$) when compared to the control group.

In the 15 mg/kg group females on study day 0, the subsession 2 mean total motor activity count was significantly ($p<0.05$) lower than the control group mean. However, all other subsession values for day 0 in these females were comparable to the control group values. In addition, the subsession 2 mean ambulatory count in the 15 mg/kg group females was not significantly decreased. Therefore, this lower subsession mean was not considered to be test article related.

On study day 7, the mean ambulatory and total motor activity counts in the 600 mg/kg group males were reduced ($p<0.05$, subsession 4) by 24% and 20%, respectively, when compared to the control group values. On study day 7, the subsession 1 mean ambulatory activity count in the 15 mg/kg group males was significantly ($p<0.05$) increased when compared to the control group. However, decreases, not increases, in locomotor activity are usually considered to be an adverse effect of treatment. Therefore, this increase was not attributed to the test article. All other mean ambulatory and total motor activity counts were comparable to the control group values on study days 7 and 14.

Even though the means were not affected in the 300 mg/kg group on study day 14, the ambulatory and total motor activity counts for two males (no. 15355 and 15387) in this group were reduced when compared to the control group at this time period and when compared to their pretest and study day 7 values.

G. Pathology:

1. Unscheduled Deaths:

Summary Data - Table 52

Individual Data - Appendix A (Table 32)

A total of one female in the 300 mg/kg group and four males and seven females in the 600 mg/kg group died on study. White contents in the stomach and/or intestine were observed for the single 300 mg/kg group female that died and for three of the males and five of the females in the 600 mg/kg group that died. Distention of the stomach and/or intestine was observed for the female in the 300 mg/kg group and for one male and three females in the 600 mg/kg group. Two of the 600 mg/kg group females that died were emaciated (no abdominal adipose tissue present). All other internal findings were considered to be normal background changes (i.e., reddened adrenal glands and reddened renal cortico-medullary junctions) or were limited to single animals (i.e., mottled lungs and a hemorrhagic thymus gland) and were not considered to be related to treatment with Ziram.

2. Brain Weight and Dimensions:

Summary Data - Table 53

Individual Data - Appendix A (Table 33)

No treatment related effects on mean absolute brain weights or dimensions were apparent at any dose level. The mean absolute brain weights for the 300 and 600 mg/kg group males were significantly ($p<0.01$) lower than the control group mean. However, the differences were small (6% or 7%) and no remarkable differences between these males and the control group were apparent in brain dimensions. In addition, no similar differences from the control group in mean absolute brain weights were observed for the 300 and 600 mg/kg group females. Therefore, the slightly lower brain weights for the 300 and 600 mg/kg group males were not attributed to Ziram administration. No other remarkable differences were observed in brain weights or dimensions.

3. Microscopic Examination:

Summary Data - Table 54

Individual Data - Appendix A (Table 34)

Historical Control Data - Appendix I

No treatment related microscopic lesions were observed in any of the central or peripheral nervous system tissues examined from the 5 animals/sex in the 600 mg/kg group. A limited incidence of digestion chambers in central nervous system tissues in the control and 600 mg/kg groups and peripheral nervous system tissue in the control group were observed. In the central nervous system, digestion chambers were noted in the lumbar root of one control group male, in the lumbar ventral root fibers for another control group male and in the lumber dorsal root fibers for one 600 mg/kg group male. In the peripheral nervous system, digestion chambers were noted in the sciatic nerve of one control group male. Spontaneous nerve fiber degeneration, characterized by digestion chambers, has been noted in the central and peripheral nervous systems of control and treated rats[10] and should not be considered uncommon. No other lesions were observed.

V. CONCLUSIONS:

A single oral administration of Ziram in rats at dosage levels of 15, 300 and 600 mg/kg resulted in:

A. Four males (25% mortality) and seven females (44% mortality) died following dose administration with 600 mg/kg Ziram. All of the males and three of the females died on study day 1. The deaths of the other females in the 600 mg/kg group occurred on study day 2, 4 or 5. One female (8% mortality) in the 300 mg/kg group died on study day 2. White contents in the stomach and/or intestine were observed at necropsy for the single 300 mg/kg group female that died and for three of the males and five of the females in the 600 mg/kg group that died. Distention of the stomach and/or intestine was observed for the female in the 300 mg/kg group and for one male and three females in the 600 mg/kg group. Two of the 600 mg/kg group females that died were emaciated (no abdominal adipose tissue present). All other internal findings were considered to be normal background changes or were limited to single animals.

B. Several treatment related clinical signs were observed in the 300 and 600 mg/kg group males and females that survived to study termination. The most remarkable of these findings were often limited to or occurred most frequently in two males (no. 15355 and 15387) in the 300 mg/kg group. Those clinical signs observed only for these two males included cyanosis, hypothermia (cool to touch), enophthalmus and unkempt appearance. The aforementioned clinical signs were observed on study day 8 or later (last week of study) on one to three occasions. The other remarkable clinical signs observed for males no. 15355 and 15387 included abnormal respiration (rales, gasping and labored respiration), abnormal excreta (decreased defecation and urination, feces small in size, diarrhea and mucoid feces), gait alterations (rocking, lurching or swaying, high carriage and/or prostration), abdomen appearing distended, hypoactivity and ptosis. Abnormal respiration was first observed on study day 1 and persisted through to the scheduled euthanization (study day 15) for one male. The other male had abnormal respiration on study days 1 and 2 and not again until study day 6. Abnormal respiration then generally persisted through to study termination. In general, the other clinical signs were observed on study days 1, 2 and/or 3 and not again until study day 10, 11 or 12. These signs then usually persisted through to study termination on study day 15. Findings of red, tan, orange and/or brown staining/material were also observed for males no. 15355 and 15387 on study days 1, 2 and/or 3. The staining/material was not observed again until study day 9 for one male (no. 15387) and persisted through to study termination.

As mentioned above, several remarkable clinical signs were observed in the 300 and 600 mg/kg group males and females. Those signs observed in the 300 mg/kg (excluding males no. 15355 and 15387) and 600 mg/kg groups included gait alterations (rocking, lurching or swaying and/or high carriage), abnormal respiration (rales, labored respiration and/or gasping), abnormal excreta (soft stool, diarrhea,

mucoid feces, decreased defecation and urination and small feces) and abdomen appearing distended. In general, the occurrence of these findings was limited to the first week of study. In addition, tan, red, orange and/or brown staining/material was observed for some males and females in the 300 and 600 mg/kg group generally during the first week of study.

C. Transient reductions in mean body weight gain were apparent in the 300 and 600 mg/kg group males and females for study days 0 to 7. The differences from the control group were 63% and 55% in the 300 mg/kg group and 67% and 45% in the 600 mg/kg group for males and females, respectively. Even though mean body weight gains in the 300 mg/kg group females and the 600 mg/kg group males and females were similar to or greater than the control group for study days 7 to 14 and 14 to 15, the mean cumulative gains were slightly lower than the control group means for study days 0 to 14 and 0 to 15. Mean body weight gain was reduced in the 300 mg/kg group males for study days 7 to 14; this was mainly due to 2/12 of these animals (no. 15355 and 15387). As a result, all mean cumulative gains (study days 0 to 7, 0 to 14 and 0 to 15) in the 300 mg/kg group males were remarkably lower than the control group means. Mean body weight in the 600 mg/kg group males was remarkably lower than the control group on study day 7. Mean body weight values were remarkably lower for study days 7, 14 and 15 in the 300 mg/kg group males.

D. Remarkable differences from the control group were observed for animals that received Ziram at dose levels of 300 and 600 mg/kg when the Functional Observational Battery was performed. In general, responses occurred approximately 4-hours following treatment on study day 0, and were transient in nature (several signs were observed at the daily clinical examinations generally during the first week of study; none of these persisted to study day 7). Specific test results included:

1. altered posture, palpebral closure and feces consistency in the 300 and 600 mg/kg group males and females during the home cage observations on study day 0;

2. lacrimation, salivation, changes in fur appearance, altered palpebral closure, changes in respiratory rate and/or character, red deposits around the mouth and crusty deposits around the nose and mouth in the 300 and 600 mg/kg group males and females during the handling observations on study day 0. In addition, decreased muscle tone was observed in the 600 mg/kg group males on study 0;

3. impaired mobility and altered gait in the 300 and 600 mg/kg group males and females during the open field observations on study day 0;

4. absent tail pinch and olfactory responses and a slighter startle response in the 300 and 600 mg/kg group males and females, absent startle response in the 600 mg/kg group males and females, absent forelimb and/or hindlimb extension in the 300 and 600 mg/kg group females during the sensory observations on study day 0;

5. decreased body temperatures in the 300 and 600 mg/kg group males and females during the physiological observations on study day 0, and reduced body weights in the 300 and 600 mg/kg group males on study day 7.

E. Remarkable signs observed during the study day 14 FOB evaluation were generally limited to two males (no. 15355 and 15387) in the 300 mg/kg group. Those signs observed for one or both males included: altered posture and palpebral closure during the home cage observations; altered palpebral closure, changes in respiratory character, changes in mucous membrane, skin and eye color, a change in fur appearance, crusty deposits around the nose and mouth and a change in eye prominence during the handling observations; impaired gait and mobility during the open field observations; absent startle response and impaired righting reflex during the sensory observations; markedly decreased body temperatures and body weights (which affected the mean) during the physiological observations. It should be noted that these findings were not observed during the study day 7 FOB evaluation with the exception of a change in respiratory character (rales) for both males and altered palpebral closure for one male. Moreover, some of these signs were not even observed at the day 0 FOB evaluation for these animals or the 600 mg/kg group males and females at any evaluation period.

F. The only possible effects on FOB parameters in the 15 mg/kg group were transient in nature and were observed only during the study day 0 evaluation. These possible effects included altered posture for one male during the home cage observations and slight impairment of gait for two males and one female during the open field observations.

G. Reductions in mean ambulatory and total motor activity counts were observed in the 300 and 600 mg/kg group males and females on study day 0. The values for all four subsessions, especially the first three, were remarkably reduced in the 300 and 600 mg/kg group males and females when compared to the control group. Reductions in mean ambulatory and total motor activity counts in the 600 mg/kg group males persisted through to study day 7; however, full recovery was apparent for these males by study day 14. Even though the mean counts were not affected in the 300 mg/kg male group on study day 14, the ambulatory and total motor activity counts for males no. 15355 and 15387 were reduced when compared to the control group at this time period and when compared to their study day 7 values.

H. No treatment related effects on mean absolute brain weights or dimensions were apparent at any dose level.

I. No treatment related microscopic lesions were observed in any of the central or peripheral nervous system tissues examined from the 5 animals/sex in the 600 mg/kg group.

Based on the results of the Functional Observational Battery and Motor Activity evaluations, transient effects [i.e. on study day 0 and 7 (motor activity) only] were observed on one or more parameters in each of the following functional domains described by Moser[1] by a single oral administration of Ziram at 300 and 600 mg/kg: autonomic, neuromuscular, sensorimotor, CNS activity and physiological. Slight, transient effects were observed on the neuromuscular and CNS activity domains at a dose level of 15 mg/kg on study day 0 only.

Based upon the results of this study, the 15 mg/kg dose level was considered to be the minimum effect level for acute neurotoxicity.

Ian Lamb — 8-25-94

Ian C. Lamb, Ph.D.
Study Director

Date

VI. KEY STUDY PERSONNEL AND REPORT SUBMISSION:

Submitted By:

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Study Director

Pathologist of Record:

Robert R. Dahlgren, D.V.M., Ph.D. — 8-25-94 Date
Diplomate A.C.V.P.
Director of Pathology

Report Prepared By:

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President, Director

Mark D. Nemec, B.S. — 8/25/94 Date
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	Ian C. Lamb, Ph.D.	Manager of Pharmacy
	Kerin Clevidence, B.S.	Section Head II - Pathology and Developmental Toxicology Laboratory

VII. QUALITY ASSURANCE UNIT STATEMENT:

Date(s) of Inspection(s)	Phase Inspected	Date(s) Findings Reported to Study Director	Date(s) Findings Reported to Management
8/2/93	Animal Care/Equipment	8/3/93	9/15/93
1/13, 20-21/94	Study Records (I-2)	1/21/94	2/24/94
1/14, 20-21, 24/94	Study Records (I-3)	1/24/94	2/24/94
1/17-18, 20, 25/94	Study Records (I-4)	1/25/94	2/24/94
1/18-20, 25/94	Study Records (I-5)	1/26/94	2/24/94
1/26-27/94	Study Records (I-1)	1/27/94	2/24/94
1/27/94	Study Records (N-1)	1/27/94	2/24/94
1/27-28/94	Study Records (A-1, A-2)	1/28/94	2/24/94
1/28/94	Study Records (I-1 Supplemental)	1/28/94	2/24/94
1/28/94	Study Records (H-1/P-1)	1/28/94	2/24/94
3/9-11, 14-15/94 and 4/3-6, 19-21, 25-28/94	Draft Report (w/out Appendix B)	5/2/94	6/23/94
3/22-23/94	Study Records (SAS-FOB and MA)	3/23/94	4/27/94
4/19, 28/94	Draft Report (Appendix B)	5/2/94	6/23/94
8/4-5/94	Draft Report (figures)	8/5/94	9/94

This study was conducted and inspected in accordance with all current Good Laboratory Practice Regulations for the United States EPA (FIFRA), the Standard Operating Procedures of WIL Research Laboratories, Inc., and the sponsor's protocol and protocol amendments. Quality Assurance inspections, derived from the inspection during the conduct of the study and from inspections of the raw data and final report, are documented and reported to the study director. A status report is submitted to management monthly.

Raw data in magnetic form, retention sample(s) and the original final report will be retained at WIL Research Laboratories, Inc., or another location specified by the sponsor.

Deborah L Little — 8-25-94

Deborah L. Little
Manager of Quality Assurance

Date

VIII. REFERENCES:

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An Acute Neurotoxicity Study of Ziram in Rats

Summary Data
(Tables 1-54)

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE:	08-02-93 TO 08-20-93			
GROUP:	1	2	3	4
-NO SIGNIFICANT CLINICAL OBSERVATIONS	154/ 11	179/ 12	154/ 12	166/ 16
-FOUND DEAD	0/ 0	0/ 0	0/ 0	4/ 4
-TERMINAL NECROPSY	12/ 12	12/ 12	12/ 12	12/ 12
-HYPOACTIVE	0/ 0	0/ 0	6/ 2	4/ 1
-ANIMAL ROCKS, LURCHES, OR SWAYS AS IT WALKS	0/ 0	0/ 0	10/ 3	8/ 5
-HIGH CARRIAGE	0/ 0	0/ 0	8/ 2	2/ 2
-PROSTRATE	0/ 0	0/ 0	1/ 1	0/ 0
-WET YELLOW MATERIAL UROGENITAL AREA	0/ 0	0/ 0	0/ 0	1/ 1
-HAIR LOSS RIGHT FORELIMB	1/ 1	0/ 0	0/ 0	1/ 1
-HAIR LOSS LEFT FORELIMB	6/ 1	0/ 0	0/ 0	0/ 0
-MOIST SCABBING VENTRAL NECK	14/ 1	0/ 0	0/ 0	0/ 0
-HAIR LOSS VENTRAL NECK	12/ 1	0/ 0	0/ 0	0/ 0
-SCABBING LEFT FORELIMB	3/ 1	0/ 0	0/ 0	0/ 0
-WET TAN STAINING VENTRAL NECK	0/ 0	0/ 0	0/ 0	2/ 2
-WET TAN STAINING VENTRAL THORACIC AREA	0/ 0	0/ 0	0/ 0	2/ 2
-WET TAN STAINING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	2/ 2
-WET TAN STAINING UROGENITAL AREA	0/ 0	0/ 0	0/ 0	3/ 3
-WET TAN STAINING ANOGENITAL AREA	0/ 0	0/ 0	0/ 0	2/ 2
-DRIED TAN STAINING ANOGENITAL AREA	0/ 0	0/ 0	1/ 1	8/ 5
-DRIED TAN STAINING VENTRAL THORACIC AREA	0/ 0	0/ 0	1/ 1	1/ 1
-DRIED TAN STAINING UROGENITAL AREA	0/ 0	0/ 0	0/ 0	4/ 2
-ABDOMEN APPEARS DISTENDED	0/ 0	0/ 0	10/ 2	7/ 3
-DRIED TAN STAINING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	1/ 1	2/ 1

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE: 08-02-93 TO 08-20-93

GROUP:	1	2	3	4
-COOL TO TOUCH	0/ 0	0/ 0	3/ 2	2/ 2
-DRIED TAN STAINING RIGHT FORELIMB	0/ 0	0/ 0	3/ 1	1/ 1
-DRIED TAN STAINING LEFT FORELIMB	0/ 0	0/ 0	3/ 1	1/ 1
-DRIED TAN STAINING VENTRAL NECK	0/ 0	0/ 0	1/ 1	0/ 0
-DRIED RED MATERIAL LEFT FORELIMB	0/ 0	0/ 0	3/ 2	3/ 1
-RALES	0/ 0	2/ 2	20/ 3	6/ 3
-LABORED RESPIRATION	0/ 0	0/ 0	10/ 2	4/ 3
-GASPING	0/ 0	0/ 0	13/ 2	1/ 1
-DRIED RED MATERIAL AROUND NOSE	6/ 4	4/ 4	6/ 2	5/ 2
-PTOSIS RIGHT EYE	0/ 0	0/ 0	1/ 1	1/ 1
-SCABBING RIGHT EAR	0/ 0	1/ 1	0/ 0	1/ 1
-PTOSIS LEFT EYE	0/ 0	0/ 0	2/ 2	1/ 1
-WET RED MATERIAL AROUND NOSE	0/ 0	0/ 0	1/ 1	0/ 0
-ENOPHTHALMUS	0/ 0	0/ 0	3/ 2	0/ 0
-SOFT STOOL	1/ 1	0/ 0	2/ 2	7/ 5
-DIARRHEA	0/ 0	0/ 0	2/ 1	7/ 7
-MUCOID FECES	0/ 0	0/ 0	1/ 1	9/ 8
-DECREASED DEFECATION	0/ 0	0/ 0	14/ 3	6/ 3
-DECREASED URINATION	0/ 0	0/ 0	14/ 3	6/ 3
-FECES APPEAR SMALL IN SIZE	0/ 0	0/ 0	6/ 3	3/ 2
-DRIED RED MATERIAL RIGHT FORELIMB	0/ 0	0/ 0	3/ 2	2/ 1
-DRIED ORANGE MATERIAL VENTRAL THORACIC AREA	0/ 0	0/ 0	3/ 1	1/ 1
-DRIED ORANGE MATERIAL VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	3/ 1	1/ 1

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE: 08-02-93 TO 08-20-93

GROUP:	1	2	3	4
-DRIED ORANGE MATERIAL ANOGENITAL AREA	0/ 0	0/ 0	1/ 1	4/ 2
-DRIED RED MATERIAL VENTRAL TAIL	2/ 1	0/ 0	0/ 0	0/ 0
-DRIED BROWN MATERIAL ANOGENITAL AREA	0/ 0	0/ 0	0/ 0	3/ 1
-CYANOTIC	0/ 0	0/ 0	6/ 2	0/ 0
-UNKEMPT APPEARANCE	0/ 0	0/ 0	3/ 2	0/ 0
-WET BROWN MATERIAL ANOGENITAL AREA	0/ 0	0/ 0	1/ 1	0/ 0
-DRIED TAN STAINING AROUND MOUTH	0/ 0	0/ 0	4/ 4	5/ 3
-WET TAN STAINING AROUND MOUTH	0/ 0	0/ 0	0/ 0	1/ 1
-DRIED RED MATERIAL AROUND MOUTH	0/ 0	0/ 0	7/ 2	3/ 1

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE:	08-02-93 TO 08-20-93			
GROUP:	1	2	3	4
-NO SIGNIFICANT CLINICAL OBSERVATIONS	155/ 12	182/ 12	143/ 12	134/ 16
-FOUND DEAD	0/ 0	0/ 0	1/ 1	7/ 7
-TERMINAL NECROPSY	12/ 12	12/ 12	11/ 11	9/ 9
-HYPOACTIVE	0/ 0	0/ 0	0/ 0	2/ 1
-ANIMAL ROCKS, LURCHES, OR SWAYS AS IT WALKS	0/ 0	0/ 0	2/ 2	17/ 8
-HIGH CARRIAGE	0/ 0	0/ 0	1/ 1	12/ 5
-WET YELLOW MATERIAL VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	1/ 1
-WET YELLOW MATERIAL UROGENITAL AREA	0/ 0	0/ 0	0/ 0	5/ 4
-HAIR LOSS RIGHT FORELIMB	24/ 3	0/ 0	0/ 0	0/ 0
-HAIR LOSS LEFT FORELIMB	27/ 3	0/ 0	7/ 1	0/ 0
-MOIST SCABBING VENTRAL NECK	0/ 0	0/ 0	4/ 1	0/ 0
-HAIR LOSS VENTRAL NECK	0/ 0	0/ 0	4/ 1	0/ 0
-SCABBING LEFT FORELIMB	2/ 1	0/ 0	10/ 1	0/ 0
-WET TAN STAINING VENTRAL NECK	0/ 0	0/ 0	0/ 0	2/ 1
-WET TAN STAINING VENTRAL THORACIC AREA	0/ 0	0/ 0	0/ 0	2/ 1
-WET TAN STAINING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	2/ 1
-WET TAN STAINING UROGENITAL AREA	0/ 0	0/ 0	0/ 0	3/ 2
-WET TAN STAINING ANOGENITAL AREA	0/ 0	0/ 0	0/ 0	4/ 2
-DRIED TAN STAINING ANOGENITAL AREA	0/ 0	0/ 0	1/ 1	4/ 3
-DRIED TAN STAINING VENTRAL THORACIC AREA	0/ 0	0/ 0	0/ 0	9/ 6
-DRIED TAN STAINING UROGENITAL AREA	0/ 0	0/ 0	1/ 1	9/ 7
-ABDOMEN APPEARS DISTENDED	0/ 0	0/ 0	0/ 0	6/ 4
-DRIED TAN STAINING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	8/ 6

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE: 08-02-93 TO 08-20-93

GROUP:	1	2	3	4
-DRIED TAN STAINING RIGHT FORELIMB	0/ 0	0/ 0	1/ 1	6/ 5
-DRIED TAN STAINING LEFT FORELIMB	0/ 0	0/ 0	1/ 1	6/ 5
-WET YELLOW STAINING ANOGENITAL AREA	0/ 0	0/ 0	0/ 0	3/ 3
-DRIED TAN STAINING VENTRAL NECK	0/ 0	0/ 0	0/ 0	4/ 4
-DRIED RED MATERIAL VENTRAL THORACIC AREA	0/ 0	0/ 0	0/ 0	1/ 1
-DRIED RED MATERIAL LEFT FORELIMB	0/ 0	0/ 0	0/ 0	6/ 3
-RALES	0/ 0	0/ 0	1/ 1	6/ 3
-LABORED RESPIRATION	0/ 0	0/ 0	0/ 0	6/ 3
-GASPING	0/ 0	0/ 0	0/ 0	2/ 1
-DRIED RED MATERIAL AROUND NOSE	1/ 1	1/ 1	1/ 1	10/ 6
-PTOSIS RIGHT EYE	0/ 0	0/ 0	1/ 1	1/ 1
-PTOSIS LEFT EYE	0/ 0	0/ 0	1/ 1	1/ 1
-SOFT STOOL	0/ 0	0/ 0	4/ 3	6/ 5
-DIARRHEA	0/ 0	0/ 0	0/ 0	5/ 4
-MUCOID FECES	0/ 0	0/ 0	1/ 1	10/ 7
-DECREASED DEFECATION	0/ 0	0/ 0	2/ 2	9/ 6
-DECREASED URINATION	0/ 0	0/ 0	0/ 0	9/ 5
-FECES APPEAR SMALL IN SIZE	1/ 1	3/ 2	9/ 5	6/ 4
-DRIED RED MATERIAL RIGHT FORELIMB	0/ 0	0/ 0	0/ 0	6/ 3
-DRIED ORANGE MATERIAL VENTRAL THORACIC AREA	0/ 0	0/ 0	1/ 1	4/ 2
-DRIED ORANGE MATERIAL VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	1/ 1	4/ 2
-DRIED ORANGE MATERIAL ANOGENITAL AREA	0/ 0	0/ 0	0/ 0	3/ 2
-DRIED RED MATERIAL VENTRAL NECK	0/ 0	0/ 0	0/ 0	4/ 3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 1 (DAILY CLINICAL OBSERVATIONS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE: 08-02-93 TO 08-20-93

GROUP:	1	2	3	4
-DRIED TAN STAINING AROUND MOUTH	0/ 0	0/ 0	3/ 3	11/ 8
-DRIED RED MATERIAL AROUND MOUTH	1/ 1	0/ 0	0/ 0	6/ 3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- MALE -----			
	GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY -10	MEAN	122.	122.	122.	124.
	S.D.	6.2	6.3	5.8	7.0
	N	12	12	12	16
0	MEAN	221.	222.	220.	227.
	S.D.	15.1	9.9	11.6	15.5
	N	12	12	12	16
7	MEAN	273.	272.	239.**	248.**
	S.D.	23.3	10.5	15.6	23.1
	N	12	12	12	12
14	MEAN	321.	322.	271.**	314.
	S.D.	28.8	14.4	56.6	25.8
	N	12	12	12	12
15	MEAN	327.	328.	275.**	321.
	S.D.	28.8	15.3	60.7	24.6
	N	12	12	12	12

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----			
	GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY -10					
	MEAN	106.	106.	106.	109.
	S.D.	4.7	4.9	4.7	6.5
	N	12	12	12	16
0					
	MEAN	154.	156.	158.	164.*
	S.D.	10.1	10.2	9.0	9.8
	N	12	12	12	16
7					
	MEAN	176.	174.	168.	177.
	S.D.	10.1	15.8	9.5	9.4
	N	12	12	11	9
14					
	MEAN	195.	191.	190.	199.
	S.D.	12.0	18.0	13.5	14.4
	N	12	12	11	9
15					
	MEAN	196.	192.	192.	200.
	S.D.	11.7	17.4	12.7	14.1
	N	12	12	11	9

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 3
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

	----- M A L E -----			
GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY -10 TO 0				
MEAN	100.	100.	98.	102.
S.D.	14.2	7.5	9.7	12.6
N	12	12	12	16
0 TO 7				
MEAN	51.	50.	19.**	17.**
S.D.	10.3	6.2	17.1	17.2
N	12	12	12	12
7 TO 14				
MEAN	48.	51.	32.	66.
S.D.	6.3	5.8	46.3	7.3
N	12	12	12	12
14 TO 15				
MEAN	6.	5.	4.	7.
S.D.	3.4	3.5	5.7	3.2
N	12	12	12	12

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 3
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
BODY WEIGHT GAINS (GRAMS) - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY -10 TO 0				
MEAN	48.	50.	52.	55.
S.D.	7.3	7.5	9.0	8.3
N	12	12	12	16
0 TO 7				
MEAN	22.	18.	10.**	12.*
S.D.	8.8	7.6	6.3	5.2
N	12	12	11	9
7 TO 14				
MEAN	19.	17.	23.	23.
S.D.	4.5	7.8	6.7	7.0
N	12	12	11	9
14 TO 15				
MEAN	1.	2.	2.	1.
S.D.	4.9	4.4	5.3	4.8
N	12	12	11	9

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 3A
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

		----- MALE -----			
	GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY	0 TO 7				
	MEAN	51.	50.	19.**	17.**
	S.D.	10.3	6.2	17.1	17.2
	N	12	12	12	12
	0 TO 14				
	MEAN	100.	100.	51.**	83.
	S.D.	15.5	10.7	61.1	20.1
	N	12	12	12	12
	0 TO 15				
	MEAN	106.	106.	55.**	90.
	S.D.	15.6	13.0	65.3	19.2
	N	12	12	12	12

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 3A
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SUMMARY OF BODY WEIGHT CHANGES FROM INTERVAL 0 (GRAMS)

	----- F E M A L E -----			
GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
DAY 0 TO 7				
MEAN	22.	18.	10.**	12.*
S.D.	8.8	7.6	6.3	5.2
N	12	12	11	9
0 TO 14				
MEAN	41.	35.	33.	35.
S.D.	9.6	13.0	7.1	9.3
N	12	12	11	9
0 TO 15				
MEAN	41.	37.	35.	36.
S.D.	11.1	11.7	6.1	7.4
N	12	12	11	9

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 4 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	9	8	7	7
ASLEEP, LYING ON SIDE OR CURLED UP	3	4	5	5
CONVULSIONS - CLONIC				
ABSENT	12	12	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
BITING				
NONE	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	9	8	9	7
EYELIDS SLIGHTLY DROOPING	0	0	1	0
DROOPING EYELIDS (HALF-CLOSED)	0	2	0	0
EYELIDS COMPLETELY SHUT	3	2	2	5
FECES CONSISTENCY				
PELLETS	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 4 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	8	6	8	4
ASLEEP, LYING ON SIDE OR CURLED UP	4	6	3	4
ALERT, ORIENTED TOWARD OBSERVER	0	0	0	1
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
BITING				
NONE	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	6	9	5
EYELIDS SLIGHTLY DROOPING	1	0	0	0
EYELIDS COMPLETELY SHUT	3	6	2	4
FECES CONSISTENCY				
PELLETS	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 5 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	75.0	66.7	58.3	58.3
ASLEEP, LYING ON SIDE OR CURLED UP	25.0	33.3	41.7	41.7
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	75.0	66.7	75.0	58.3
EYELIDS SLIGHTLY DROOPING	0.	0.	8.3	0.
DROOPING EYELIDS (HALF-CLOSED)	0.	16.7	0.	0.
EYELIDS COMPLETELY SHUT	25.0	16.7	16.7	41.7
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 5 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	66.7	50.0	72.7	44.4
ASLEEP, LYING ON SIDE OR CURLED UP	33.3	50.0	27.3	44.4
ALERT, ORIENTED TOWARD OBSERVER	0.	0.	0.	11.1
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	66.7	50.0	81.8	55.6
EYELIDS SLIGHTLY DROOPING	8.3	0.	0.	0.
EYELIDS COMPLETELY SHUT	25.0	50.0	18.2	44.4
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 6 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	5	4	3	2
ASLEEP, LYING ON SIDE OR CURLED UP	7	7	3	4
SITTING, HEAD HELD LOW	0	1	4	5*
REARING	0	0	2	1
CONVULSIONS - CLONIC				
ABSENT	12	12	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
BITING				
NONE	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	5	4	0	1
EYELIDS SLIGHTLY DROOPING	0	1	2	0
DROOPING EYELIDS (HALF-CLOSED)	0	0	1	3
EYELIDS COMPLETELY SHUT	7	7	9	8
FECES CONSISTENCY				
PELLETS	12	12	11	6*
PELLETS, PARTIALLY FORMED	0	0	1	2
UNFORMED, DIARRHEA	0	0	0	4

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 6 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	3	5	4	2
ASLEEP, LYING ON SIDE OR CURLED UP	9	7	3*	3
SITTING, HEAD HELD LOW	0	0	3	2
FLATTENED, LIMBS MAY BE EXTENDED	0	0	1	0
REARING	0	0	0	2
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
BITING				
NONE	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	4	5	2	0
EYELIDS SLIGHTLY DROOPING	0	0	0	1
DROOPING EYELIDS (HALF-CLOSED)	0	0	2	1
EYELIDS COMPLETELY SHUT	8	7	7	7
FECES CONSISTENCY				
PELLETS	12	12	10	6
UNFORMED, DIARRHEA	0	0	1	3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 7 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	41.7	33.3	25.0	16.7
ASLEEP, LYING ON SIDE OR CURLED UP	58.3	58.3	25.0	33.3
SITTING, HEAD HELD LOW	0.	8.3	33.3	41.7
REARING	0.	0.	16.7	8.3
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	41.7	33.3	0.	8.3
EYELIDS SLIGHTLY DROOPING	0.	8.3	16.7	0.
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	8.3	25.0
EYELIDS COMPLETELY SHUT	58.3	58.3	75.0	66.7
FECES CONSISTENCY				
PELLETS	100.	100.	91.7	50.0
PELLETS, PARTIALLY FORMED	0.	0.	8.3	16.7
UNFORMED, DIARRHEA	0.	0.	0.	33.3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 7 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	25.0	41.7	36.4	22.2
ASLEEP, LYING ON SIDE OR CURLED UP	75.0	58.3	27.3	33.3
SITTING, HEAD HELD LOW	0.	0.	27.3	22.2
FLATTENED, LIMBS MAY BE EXTENDED	0.	0.	9.1	0.
REARING	0.	0.	0.	22.2
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	33.3	41.7	18.2	0.
EYELIDS SLIGHTLY DROOPING	0.	0.	0.	11.1
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	18.2	11.1
EYELIDS COMPLETELY SHUT	66.7	58.3	63.6	77.8
FECES CONSISTENCY				
PELLETS	100.	100.	90.9	66.7
UNFORMED, DIARRHEA	0.	0.	9.1	33.3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 8 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	4	6	7	2
ASLEEP, LYING ON SIDE OR CURLED UP	7	5	5	10
ALERT, ORIENTED TOWARD OBSERVER	1	1	0	0
CONVULSIONS - CLONIC				
ABSENT	12	12	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
BITING				
NONE	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	5	8	7	2
EYELIDS SLIGHTLY DROOPING	1	0	1	2
DROOPING EYELIDS (HALF-CLOSED)	0	0	2	2
EYELIDS COMPLETELY SHUT	6	4	2	6
FECES CONSISTENCY				
PELLETS	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 8 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	4	4	4	2
ASLEEP, LYING ON SIDE OR CURLED UP	3	5	4	6
ALERT, ORIENTED TOWARD OBSERVER	5	3	3	1
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
BITING				
NONE	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	9	7	7	2
EYELIDS SLIGHTLY DROOPING	0	0	1	1
DROOPING EYELIDS (HALF-CLOSED)	0	1	0	1
EYELIDS COMPLETELY SHUT	3	4	3	5
FECES CONSISTENCY				
PELLETS	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 9 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	33.3	50.0	58.3	16.7
ASLEEP, LYING ON SIDE OR CURLED UP	58.3	41.7	41.7	83.3
ALERT, ORIENTED TOWARD OBSERVER	8.3	8.3	0.	0.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	41.7	66.7	58.3	16.7
EYELIDS SLIGHTLY DROOPING	8.3	0.	8.3	16.7
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	16.7	16.7
EYELIDS COMPLETELY SHUT	50.0	33.3	16.7	50.0
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 9 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	33.3	33.3	36.4	22.2
ASLEEP, LYING ON SIDE OR CURLED UP	25.0	41.7	36.4	66.7
ALERT, ORIENTED TOWARD OBSERVER	41.7	25.0	27.3	11.1
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	75.0	58.3	63.6	22.2
EYELIDS SLIGHTLY DROOPING	0.	0.	9.1	11.1
DROOPING EYELIDS (HALF-CLOSED)	0.	8.3	0.	11.1
EYELIDS COMPLETELY SHUT	25.0	33.3	27.3	55.6
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 10 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	2	3	2	7
ASLEEP, LYING ON SIDE OR CURLED UP	5	6	4	5
ALERT, ORIENTED TOWARD OBSERVER	5	3	4	0*
SITTING, HEAD HELD LOW	0	0	1	0
REARING	0	0	1	0
CONVULSIONS - CLONIC				
ABSENT	12	12	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
BITING				
NONE	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	6	7	8
EYELIDS SLIGHTLY DROOPING	0	1	1	0
EYELIDS COMPLETELY SHUT	4	5	4	4
FECES CONSISTENCY				
PELLETS	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 10 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	2	3	2	0
ASLEEP, LYING ON SIDE OR CURLED UP	4	2	3	5
ALERT, ORIENTED TOWARD OBSERVER	6	7	6	4
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
BITING				
NONE	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	8	11	8	6
EYELIDS SLIGHTLY DROOPING	1	0	0	0
DROOPING EYELIDS (HALF-CLOSED)	0	0	1	0
EYELIDS COMPLETELY SHUT	3	1	2	3
FECES CONSISTENCY				
PELLETS	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 11 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HOME CAGE OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
POSTURE				
SITTING OR STANDING NORMALLY	16.7	25.0	16.7	58.3
ASLEEP, LYING ON SIDE OR CURLED UP	41.7	50.0	33.3	41.7
ALERT, ORIENTED TOWARD OBSERVER	41.7	25.0	33.3	0.
SITTING, HEAD HELD LOW	0.	0.	8.3	0.
REARING	0.	0.	8.3	0.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	66.7	50.0	58.3	66.7
EYELIDS SLIGHTLY DROOPING	0.	8.3	8.3	0.
EYELIDS COMPLETELY SHUT	33.3	41.7	33.3	33.3
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 11 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

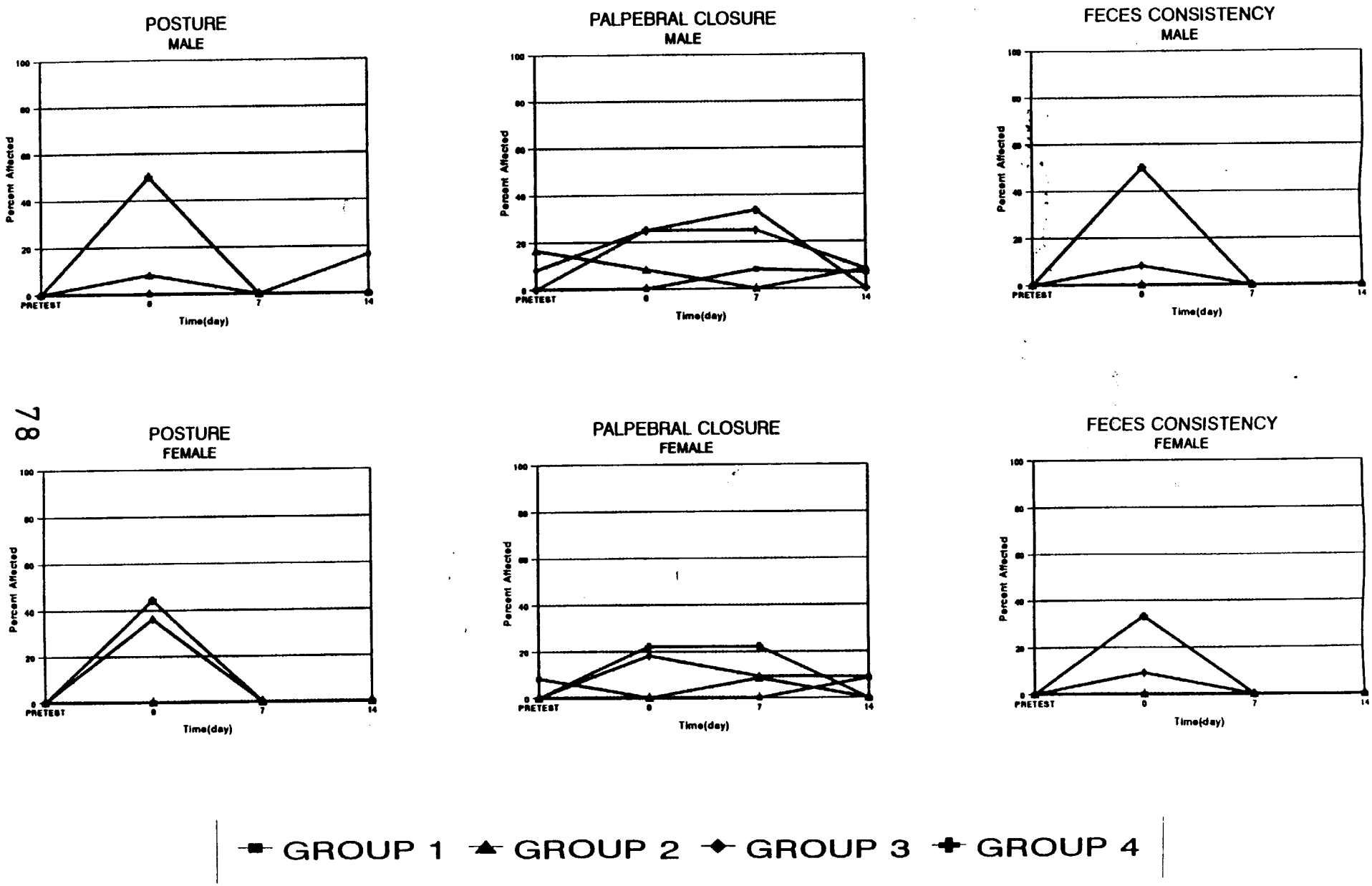
HOME CAGE OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
POSTURE				
SITTING OR STANDING NORMALLY	16.7	25.0	18.2	0.
ASLEEP, LYING ON SIDE OR CURLED UP	33.3	16.7	27.3	55.6
ALERT, ORIENTED TOWARD OBSERVER	50.0	58.3	54.5	44.4
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
BITING				
NONE	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	66.7	91.7	72.7	66.7
EYELIDS SLIGHTLY DROOPING	8.3	0.	0.	0.
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	9.1	0.
EYELIDS COMPLETELY SHUT	25.0	8.3	18.2	33.3
FECES CONSISTENCY				
PELLETS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 1
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HOME CAGE OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	4	5	4	3
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	8	5	7	9
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0	2	1	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	12	12	12	11
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0	0	0	1
LACRIMATION				
NONE	12	12	12	12
CHROMODACRYORRHEA				
ABSENT	12	12	12	12
SALIVATION				
NONE	12	12	12	12
PILOERECTION				
NONE	12	12	12	12
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	12	12
RESPIRATORY CHARACTER NORMAL	12	12	12	12
RED DEPOSITS - eyes ABSENT	12	12	12	12
RED DEPOSITS - nose PRESENT	0	1	1	1
ABSENT	12	11	11	11
RED DEPOSITS - mouth ABSENT	12	12	12	12
CRUSTY DEPOSITS - eyes ABSENT	12	12	12	12
CRUSTY DEPOSITS - nose ABSENT	12	12	12	12
CRUSTY DEPOSITS - mouth ABSENT	12	12	12	12
MUCOUS MEMBRANES - color PINK	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EYES - color				
PINK	12	12	12	12
SKIN - color				
PINK	12	12	12	12
EYE PROMINENCE				
NORMAL	12	12	12	12
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	5	3	3	4
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	5	7	7	3
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	2	2	1	2
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	11	12	11	9
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	1	0	0	0
LACRIMATION				
NONE	12	12	11	9
CHROMODACRYORRHEA				
ABSENT	12	12	11	9
SALIVATION				
NONE	12	12	11	9
PILOERECTION				
NONE	12	12	11	9
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	11	9
RESPIRATORY CHARACTER NORMAL	12	12	11	9
RED DEPOSITS - eyes ABSENT	12	12	11	9
RED DEPOSITS - nose ABSENT	12	12	11	9
RED DEPOSITS - mouth ABSENT	12	12	11	9
CRUSTY DEPOSITS - eyes ABSENT	12	12	11	9
CRUSTY DEPOSITS - nose ABSENT	12	12	11	9
CRUSTY DEPOSITS - mouth ABSENT	12	12	11	9
MUCOUS MEMBRANES - color PINK	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 12 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color PINK	12	12	11	9
SKIN - color PINK	12	12	11	9
EYE PROMINENCE NORMAL	12	12	11	9
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	33.3	41.7	33.3	25.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	66.7	41.7	58.3	75.0
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0.	16.7	8.3	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	100.	91.7
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0.	0.	0.	8.3
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose				
PRESENT	0.	8.3	8.3	8.3
ABSENT	100.	91.7	91.7	91.7
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	41.7	25.0	27.3	44.4
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	41.7	58.3	63.6	33.3
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	16.7	16.7	9.1	22.2
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	91.7	100.	100.	100.
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	8.3	0.	0.	0.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose ABSENT	100.	100.	100.	100.
RED DEPOSITS - mouth ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color PINK	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 13 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	10	10	8	11
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	2	2	4	1
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	11	12	12
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	2	1	0	0
LACRIMATION				
NONE	12	12	9	12
SLIGHT	0	0	3	0
CHROMODACRYORRHEA				
ABSENT	12	12	12	12
SALIVATION				
NONE	12	11	5*	6*
SLIGHT	0	1	7*	5*
SEVERE	0	0	0	1
PILOERECTION				
NONE	12	12	12	12
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	11	7*	6*
SLIGHTLY SOILED	0	1	4	4
VERY SOILED, CRUSTY	0	0	1	2

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	6*	4*
EYELIDS SLIGHTLY DROOPING	0	0	6*	8*
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	9	7*
DECREASED: BELOW 80/MIN.	0	0	3	5*
RESPIRATORY CHARACTER				
NORMAL	12	12	10	12
RALES: ABNORMAL SOUND ACCOMPANYING BREATHING	0	0	2	0
RED DEPOSITS - eyes				
PRESENT	0	1	3	1
ABSENT	12	11	9	11
RED DEPOSITS - nose				
PRESENT	0	2	5*	2
ABSENT	12	10	7*	10
RED DEPOSITS - mouth				
PRESENT	0	0	6*	2
ABSENT	12	12	6*	10
CRUSTY DEPOSITS - eyes				
ABSENT	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
CRUSTY DEPOSITS - nose				
PRESENT	0	0	2	5*
ABSENT	12	12	10	7*
CRUSTY DEPOSITS - mouth				
PRESENT	0	0	4	8*
ABSENT	12	12	8	4*
MUCOUS MEMBRANES - color				
PINK	12	12	12	12
EYES - color				
PINK	12	12	12	12
SKIN - color				
PINK	12	12	12	12
EYE PROMINENCE				
NORMAL	12	12	12	12
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	12	10
MUSCLE IS SOFT AND FLABBY	0	0	0	2

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	8	7	11	8
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	4	3	0	1
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0	2	0	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	10	11	10	9
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	2	1	1	0
LACRIMATION				
NONE	12	12	6*	8
SLIGHT	0	0	5*	1
CHROMODACRYORRHEA				
ABSENT	12	12	11	9
SALIVATION				
NONE	12	12	3*	6
SLIGHT	0	0	8*	2
SEVERE	0	0	0	1
PILOERECTION				
NONE	12	12	11	9
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	6*	5*
SLIGHTLY SOILED	0	0	4*	2
VERY SOILED, CRUSTY	0	0	1	2

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	6*	3*
EYELIDS SLIGHTLY DROOPING	0	0	5*	5*
DROOPING EYELIDS (HALF-CLOSED)	0	0	0	1
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	9	7
DECREASED: BELOW 80/MIN.	0	0	2	2
RESPIRATORY CHARACTER				
NORMAL	12	12	11	9
RED DEPOSITS - eyes				
ABSENT	12	12	11	9
RED DEPOSITS - nose				
PRESENT	0	0	2	1
ABSENT	12	12	9	8
RED DEPOSITS - mouth				
PRESENT	0	0	1	2
ABSENT	12	12	10	7
CRUSTY DEPOSITS - eyes				
ABSENT	12	12	11	9
CRUSTY DEPOSITS - nose				
PRESENT	0	0	3	3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 14 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
CRUSTY DEPOSITS - nose (CONTINUED)				
ABSENT	12	12	8	6
CRUSTY DEPOSITS - mouth				
PRESENT	0	0	6*	7*
ABSENT	12	12	5*	2*
MUCOUS MEMBRANES - color				
PINK	12	12	11	9
EYES - color				
PINK	12	12	11	9
SKIN - color				
PINK	12	12	11	9
EYE PROMINENCE				
NORMAL	12	12	11	9
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	10	9
MUSCLE IS SOFT AND FLABBY	0	0	1	0

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	83.3	83.3	66.7	91.7
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	16.7	16.7	33.3	8.3
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	83.3	91.7	100.	100.
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	16.7	8.3	0.	0.
LACRIMATION				
NONE	100.	100.	75.0	100.
SLIGHT	0.	0.	25.0	0.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	91.7	41.7	50.0
SLIGHT	0.	8.3	58.3	41.7
SEVERE	0.	0.	0.	8.3
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	91.7	58.3	50.0
SLIGHTLY SOILED	0.	8.3	33.3	33.3
VERY SOILED, CRUSTY	0.	0.	8.3	16.7

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	50.0	33.3
EYELIDS SLIGHTLY DROOPING	0.	0.	50.0	66.7
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	75.0	58.3
DECREASED: BELOW 80/MIN.	0.	0.	25.0	41.7
RESPIRATORY CHARACTER				
NORMAL	100.	100.	83.3	100.
RALES: ABNORMAL SOUND ACCOMPANYING BREATHING	0.	0.	16.7	0.
RED DEPOSITS - eyes				
PRESENT	0.	8.3	25.0	8.3
ABSENT	100.	91.7	75.0	91.7
RED DEPOSITS - nose				
PRESENT	0.	16.7	41.7	16.7
ABSENT	100.	83.3	58.3	83.3
RED DEPOSITS - mouth				
PRESENT	0.	0.	50.0	16.7
ABSENT	100.	100.	50.0	83.3
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
CRUSTY DEPOSITS - nose				
PRESENT	0.	0.	16.7	41.7
ABSENT	100.	100.	83.3	58.3
CRUSTY DEPOSITS - mouth				
PRESENT	0.	0.	33.3	66.7
ABSENT	100.	100.	66.7	33.3
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	83.3
MUSCLE IS SOFT AND FLABBY	0.	0.	0.	16.7

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

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TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	66.7	58.3	100.	88.9
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	33.3	25.0	0.	11.1
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0.	16.7	0.	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	83.3	91.7	90.9	100.
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	16.7	8.3	9.1	0.
LACRIMATION				
NONE	100.	100.	54.5	88.9
SLIGHT	0.	0.	45.5	11.1
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	27.3	66.7
SLIGHT	0.	0.	72.7	22.2
SEVERE	0.	0.	0.	11.1
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	54.5	55.6
SLIGHTLY SOILED	0.	0.	36.4	22.2
VERY SOILED, CRUSTY	0.	0.	9.1	22.2

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	54.5	33.3
EYELIDS SLIGHTLY DROOPING	0.	0.	45.5	55.6
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	0.	11.1
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	81.8	77.8
DECREASED: BELOW 80/MIN.	0.	0.	18.2	22.2
RESPIRATORY CHARACTER				
NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose				
PRESENT	0.	0.	18.2	11.1
ABSENT	100.	100.	81.8	88.9
RED DEPOSITS - mouth				
PRESENT	0.	0.	9.1	22.2
ABSENT	100.	100.	90.9	77.8
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
PRESENT	0.	0.	27.3	33.3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 15 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
CRUSTY DEPOSITS - nose (CONTINUED)				
ABSENT	100.	100.	72.7	66.7
CRUSTY DEPOSITS - mouth				
PRESENT	0.	0.	54.5	77.8
ABSENT	100.	100.	45.5	22.2
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	90.9	100.
MUSCLE IS SOFT AND FLABBY	0.	0.	9.1	0.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	12	11	11	11
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	0	1	1	1
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	12	12	12	12
LACRIMATION				
NONE	12	12	12	12
CHROMODACRYORRHEA				
ABSENT	12	12	12	12
SALIVATION				
NONE	12	12	12	12
PILOERECTION				
NONE	12	12	12	12
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	12	11
SLIGHTLY SOILED	0	0	0	1
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	12	12
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
RESPIRATORY CHARACTER				
NORMAL	12	12	10	12
RALES: ABNORMAL SOUND ACCOMPANYING BREATHING	0	0	2	0
RED DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	12	11	12	12
RED DEPOSITS - nose				
PRESENT	1	3	2	0
ABSENT	11	9	10	12
RED DEPOSITS - mouth				
PRESENT	0	1	0	0
ABSENT	12	11	12	12
CRUSTY DEPOSITS - eyes				
ABSENT	12	12	12	12
CRUSTY DEPOSITS - nose				
ABSENT	12	12	12	12
CRUSTY DEPOSITS - mouth				
ABSENT	12	12	12	12
MUCOUS MEMBRANES - color				
PINK	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EYES - color				
PINK	12	12	12	12
SKIN - color				
PINK	12	12	12	12
EYE PROMINENCE				
NORMAL	12	12	12	12
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	10	11	10	9
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	1	1	1	0
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	1	0	0	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	12	11	11	8
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0	1	0	1
LACRIMATION				
NONE	12	12	11	9
CHROMODACRYORRHEA				
ABSENT	12	12	11	9
SALIVATION				
NONE	12	12	11	9
PILOERECTION				
NONE	12	12	11	9
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	11	9
RESPIRATORY CHARACTER NORMAL	12	12	11	9
RED DEPOSITS - eyes ABSENT	12	12	11	9
RED DEPOSITS - nose ABSENT	12	12	11	9
RED DEPOSITS - mouth ABSENT	12	12	11	9
CRUSTY DEPOSITS - eyes ABSENT	12	12	11	9
CRUSTY DEPOSITS - nose ABSENT	12	12	11	9
CRUSTY DEPOSITS - mouth ABSENT	12	12	11	9
MUCOUS MEMBRANES - color PINK	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 16 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color				
PINK	12	12	11	9
SKIN - color				
PINK	12	12	11	9
EYE PROMINENCE				
NORMAL	12	12	11	9
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	100.	91.7	91.7	91.7
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	0.	8.3	8.3	8.3
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	100.	100.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	91.7
SLIGHTLY SOILED	0.	0.	0.	8.3
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
RESPIRATORY CHARACTER				
NORMAL	100.	100.	83.3	100.
RALES: ABNORMAL SOUND ACCOMPANYING BREATHING	0.	0.	16.7	0.
RED DEPOSITS - eyes				
PRESENT	0.	8.3	0.	0.
ABSENT	100.	91.7	100.	100.
RED DEPOSITS - nose				
PRESENT	8.3	25.0	16.7	0.
ABSENT	91.7	75.0	83.3	100.
RED DEPOSITS - mouth				
PRESENT	0.	8.3	0.	0.
ABSENT	100.	91.7	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	83.3	91.7	90.9	100.
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	8.3	8.3	9.1	0.
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	8.3	0.	0.	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	91.7	100.	88.9
MODERATELY LOW: SLIGHT RESISTANCE TO BEING HANDLED, WITH/WITHOUT VOCALIZATION	0.	8.3	0.	11.1
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose ABSENT	100.	100.	100.	100.
RED DEPOSITS - mouth ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color PINK	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 17 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color PINK	100.	100.	100.	100.
SKIN - color PINK	100.	100.	100.	100.
EYE PROMINENCE NORMAL	100.	100.	100.	100.
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	11	11	9	9
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	1	1	2	2
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0	0	0	1
VERY DIFFICULT: TAIL AND THROAT RATTLES WITH/WITHOUT VOCALIZATION; MAY ATTACK	0	0	1	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	12	12	11	12
HIGH: SQUIRMS, TWISTS, ATTEMPTS TO BITE, WITH/WITHOUT VOCALIZATION	0	0	1	0
LACRIMATION				
NONE	12	12	12	12
CHROMODACRYORRHEA				
ABSENT	12	12	12	12
SALIVATION				
NONE	12	12	12	12
PILOERECTION				
NONE	12	12	12	12
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	11	12
VERY SOILED, CRUSTY	0	0	1	0
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	10	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
PALPEBRAL CLOSURE (CONTINUED)				
EYELIDS SLIGHTLY DROOPING	0	0	1	0
DROOPING EYELIDS (HALF-CLOSED)	0	0	1	0
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	12	12	12	12
RESPIRATORY CHARACTER				
NORMAL	12	12	10	12
GASPING	0	0	2	0
RED DEPOSITS - eyes				
PRESENT	0	1	0	0
ABSENT	12	11	12	12
RED DEPOSITS - nose				
PRESENT	2	0	0	2
ABSENT	10	12	12	10
RED DEPOSITS - mouth				
ABSENT	12	12	12	12
CRUSTY DEPOSITS - eyes				
ABSENT	12	12	12	12
CRUSTY DEPOSITS - nose				
PRESENT	0	0	1	0
ABSENT	12	12	11	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
CRUSTY DEPOSITS - mouth				
PRESENT	0	0	1	0
ABSENT	12	12	11	12
MUCOUS MEMBRANES - color				
PINK	12	12	10	12
PALE	0	0	2	0
EYES - color				
PINK	12	12	11	12
PALE	0	0	1	0
SKIN - color				
PINK	12	12	10	12
PALE	0	0	2	0
EYE PROMINENCE				
NORMAL	12	12	11	12
ENOPHTHALMUS	0	0	1	0
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	12	9	9	8
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	0	2	2	1
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0	1	0	0
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	12	12	11	9
LACRIMATION				
NONE	12	12	11	9
CHROMODACRYORRHEA				
ABSENT	12	12	11	9
SALIVATION				
NONE	12	12	11	9
PILOERECTION				
NONE	12	12	11	9
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	12	12	11	9
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	12	12	11	9
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	12	11	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE (CONTINUED)				
INCREASED: ABOVE 110/MIN.	0	1	0	0
RESPIRATORY CHARACTER				
NORMAL	12	12	11	9
RED DEPOSITS - eyes				
ABSENT	12	12	11	9
RED DEPOSITS - nose				
PRESENT	1	0	0	1
ABSENT	11	12	11	8
RED DEPOSITS - mouth				
PRESENT	1	0	0	0
ABSENT	11	12	11	9
CRUSTY DEPOSITS - eyes				
ABSENT	12	12	11	9
CRUSTY DEPOSITS - nose				
ABSENT	12	12	11	9
CRUSTY DEPOSITS - mouth				
ABSENT	12	12	11	9
MUCOUS MEMBRANES - color				
PINK	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 18 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color PINK	12	12	11	9
SKIN - color PINK	12	12	11	9
EYE PROMINENCE NORMAL	12	12	11	9
MUSCLE TONE MUSCLE IS FIRM BUT NOT HARD (NORMAL)	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	91.7	91.7	75.0	75.0
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	8.3	8.3	16.7	16.7
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0.	0.	0.	8.3
VERY DIFFICULT: TAIL AND THROAT RATTLES WITH/WITHOUT VOCALIZATION; MAY ATTACK	0.	0.	8.3	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	91.7	100.
HIGH: SQUIRMS, TWISTS, ATTEMPTS TO BITE, WITH/WITHOUT VOCALIZATION	0.	0.	8.3	0.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	91.7	100.
VERY SOILED, CRUSTY	0.	0.	8.3	0.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	83.3	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
PALPEBRAL CLOSURE (CONTINUED)				
EYELIDS SLIGHTLY DROOPING	0.	0.	8.3	0.
DROOPING EYELIDS (HALF-CLOSED)	0.	0.	8.3	0.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	100.	100.	100.
RESPIRATORY CHARACTER				
NORMAL	100.	100.	83.3	100.
GASPING	0.	0.	16.7	0.
RED DEPOSITS - eyes				
PRESENT	0.	8.3	0.	0.
ABSENT	100.	91.7	100.	100.
RED DEPOSITS - nose				
PRESENT	16.7	0.	0.	16.7
ABSENT	83.3	100.	100.	83.3
RED DEPOSITS - mouth				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - eyes				
ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose				
PRESENT	0.	0.	8.3	0.
ABSENT	100.	100.	91.7	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
CRUSTY DEPOSITS - mouth				
PRESENT	0.	0.	8.3	0.
ABSENT	100.	100.	91.7	100.
MUCOUS MEMBRANES - color				
PINK	100.	100.	83.3	100.
PALE	0.	0.	16.7	0.
EYES - color				
PINK	100.	100.	91.7	100.
PALE	0.	0.	8.3	0.
SKIN - color				
PINK	100.	100.	83.3	100.
PALE	0.	0.	16.7	0.
EYE PROMINENCE				
NORMAL	100.	100.	91.7	100.
ENOPHTHALMUS	0.	0.	8.3	0.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EASE OF REMOVAL				
VERY EASY: ANIMAL SITS QUIETLY, ALLOWS INVESTIGATOR TO PICK IT UP	100.	75.0	81.8	88.9
EASY: WITH/WITHOUT VOCALIZATION, WITHOUT RESISTANCE OR SLIGHT RESISTANCE	0.	16.7	18.2	11.1
DIFFICULT: RUNS AROUND CAGE, IS HARD TO GRAB, WITH/WITHOUT VOCALIZATION	0.	8.3	0.	0.
EASE OF HANDLING IN HAND				
LOW: NO RESISTANCE, ANIMAL IS EASY TO HANDLE	100.	100.	100.	100.
LACRIMATION				
NONE	100.	100.	100.	100.
CHROMODACRYORRHEA				
ABSENT	100.	100.	100.	100.
SALIVATION				
NONE	100.	100.	100.	100.
PILOERECTION				
NONE	100.	100.	100.	100.
FUR APPEARANCE				
NORMAL: CLEAN AND GROOMED	100.	100.	100.	100.
PALPEBRAL CLOSURE				
EYELIDS WIDE OPEN	100.	100.	100.	100.
RESPIRATORY RATE				
NORMAL: BY OBSERVATION (80-110/MIN.)	100.	91.7	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
RESPIRATORY RATE (CONTINUED) INCREASED: ABOVE 110/MIN.	0.	8.3	0.	0.
RESPIRATORY CHARACTER NORMAL	100.	100.	100.	100.
RED DEPOSITS - eyes ABSENT	100.	100.	100.	100.
RED DEPOSITS - nose PRESENT	8.3	0.	0.	11.1
ABSENT	91.7	100.	100.	88.9
RED DEPOSITS - mouth PRESENT	8.3	0.	0.	0.
ABSENT	91.7	100.	100.	100.
CRUSTY DEPOSITS - eyes ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - nose ABSENT	100.	100.	100.	100.
CRUSTY DEPOSITS - mouth ABSENT	100.	100.	100.	100.
MUCOUS MEMBRANES - color PINK	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 19 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

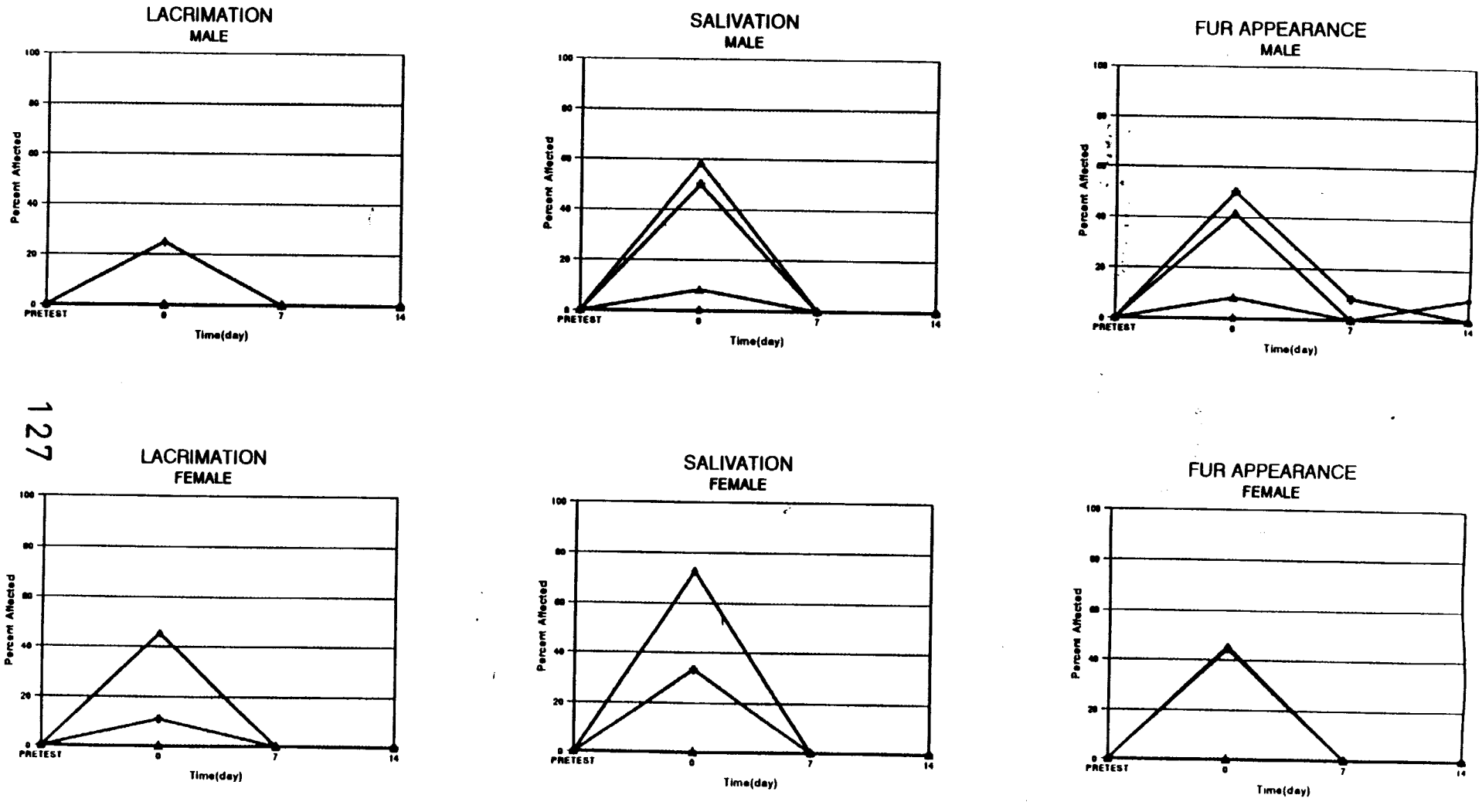
HANDLING OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYES - color				
PINK	100.	100.	100.	100.
SKIN - color				
PINK	100.	100.	100.	100.
EYE PROMINENCE				
NORMAL	100.	100.	100.	100.
MUSCLE TONE				
MUSCLE IS FIRM BUT NOT HARD (NORMAL)	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

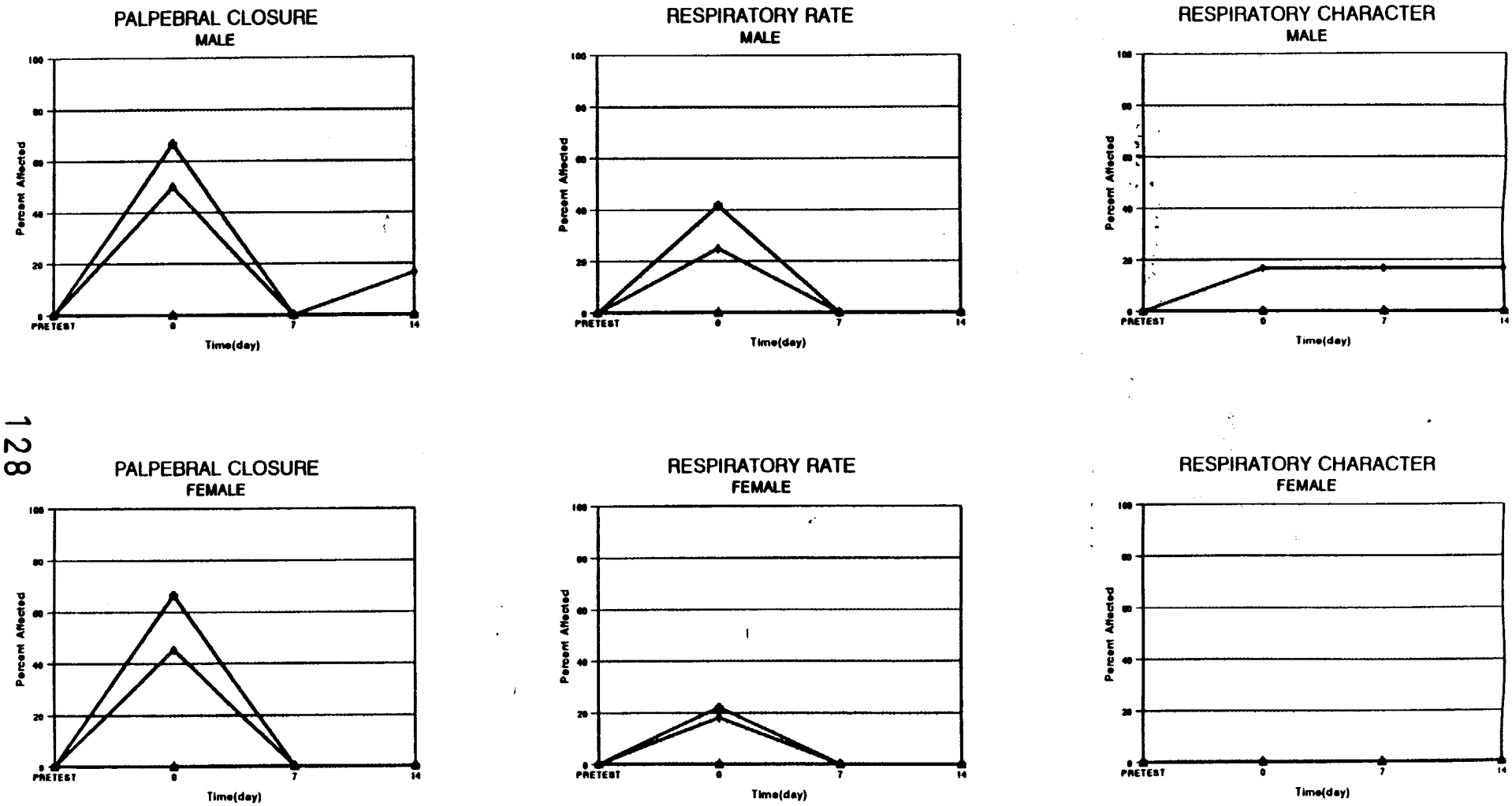
PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HANDLING OBSERVATIONS: DOSE-EFFECT CURVES



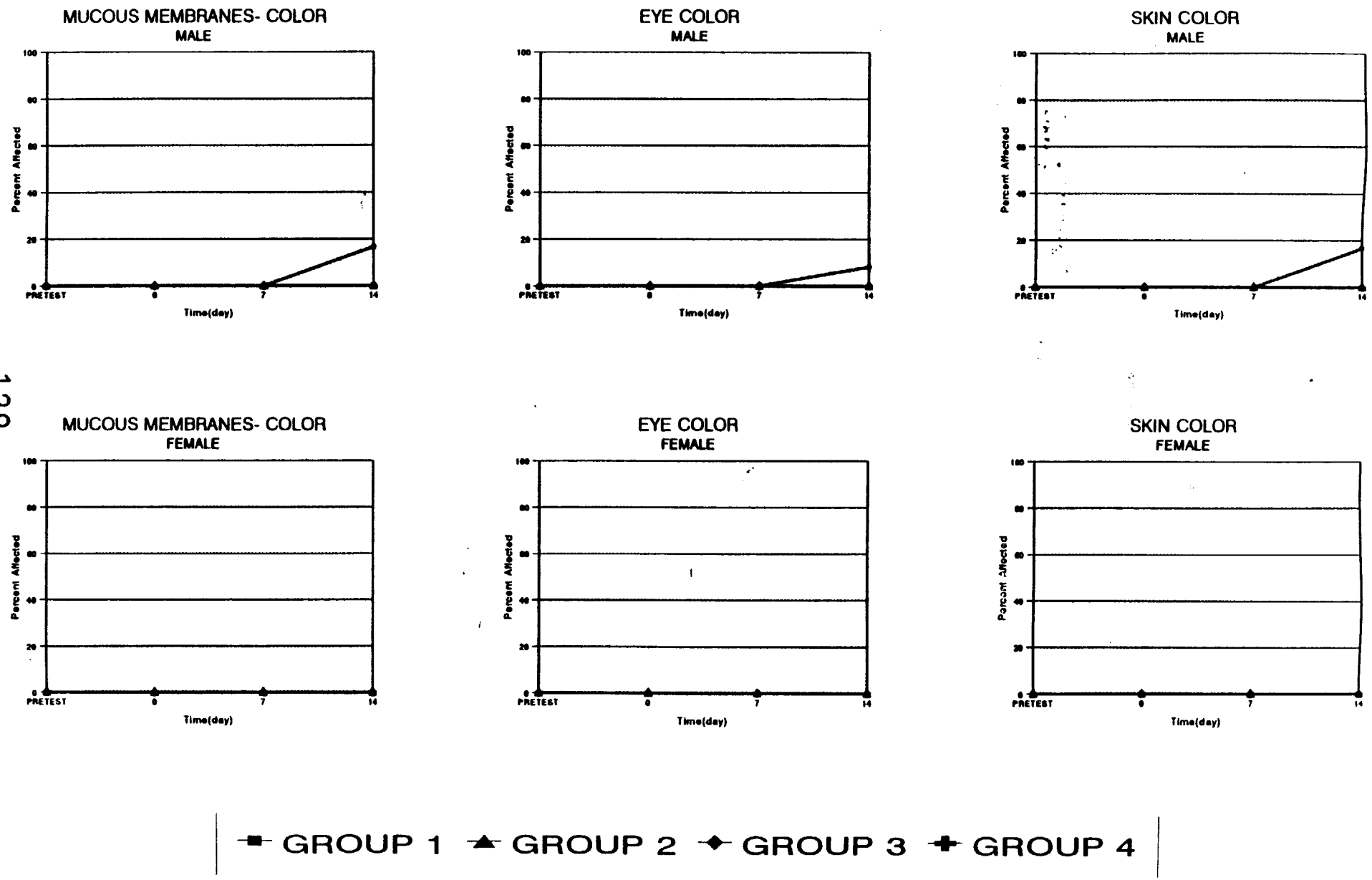
PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HANDLING OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HANDLING OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HANDLING OBSERVATIONS: DOSE-EFFECT CURVES

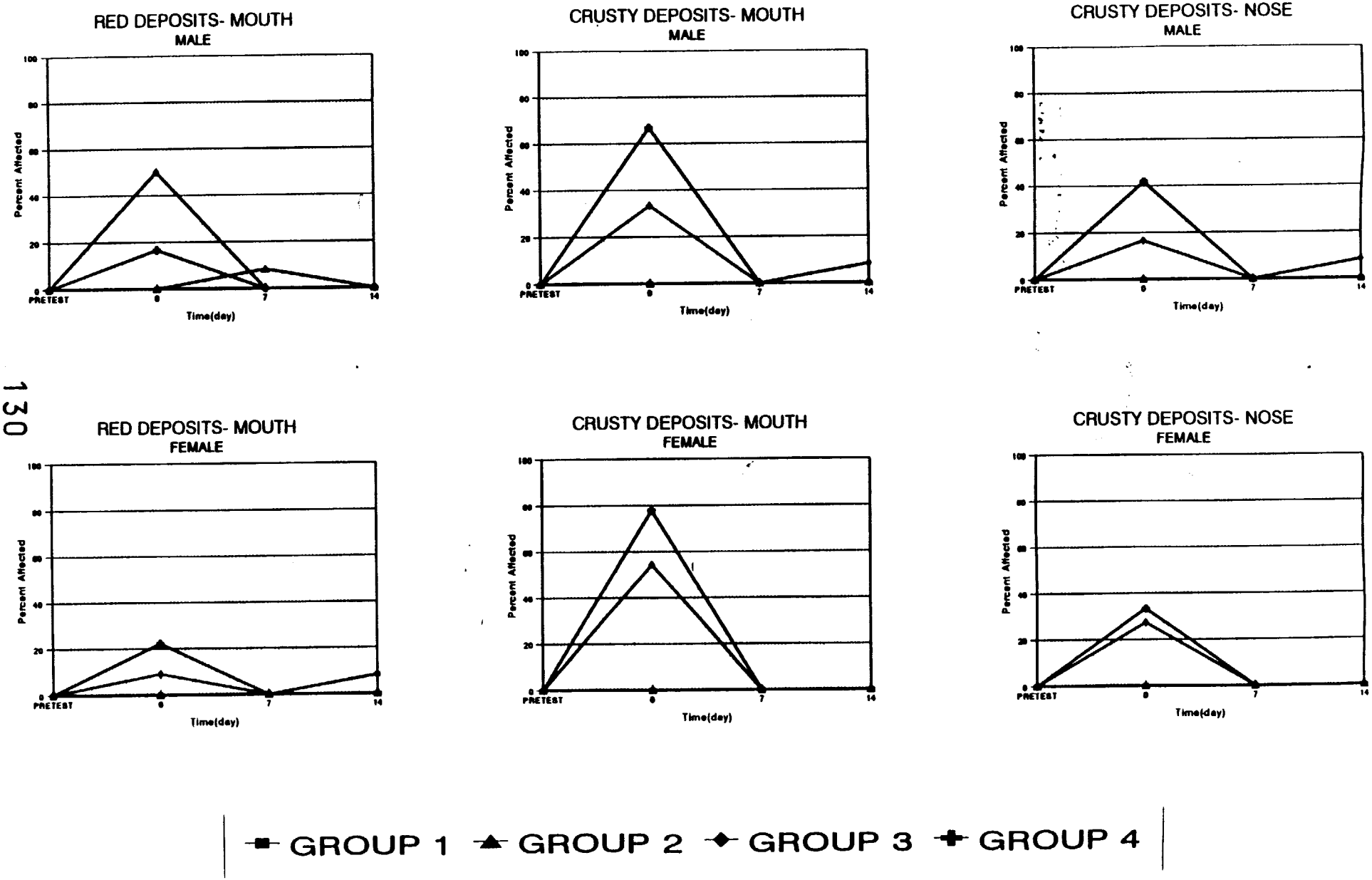
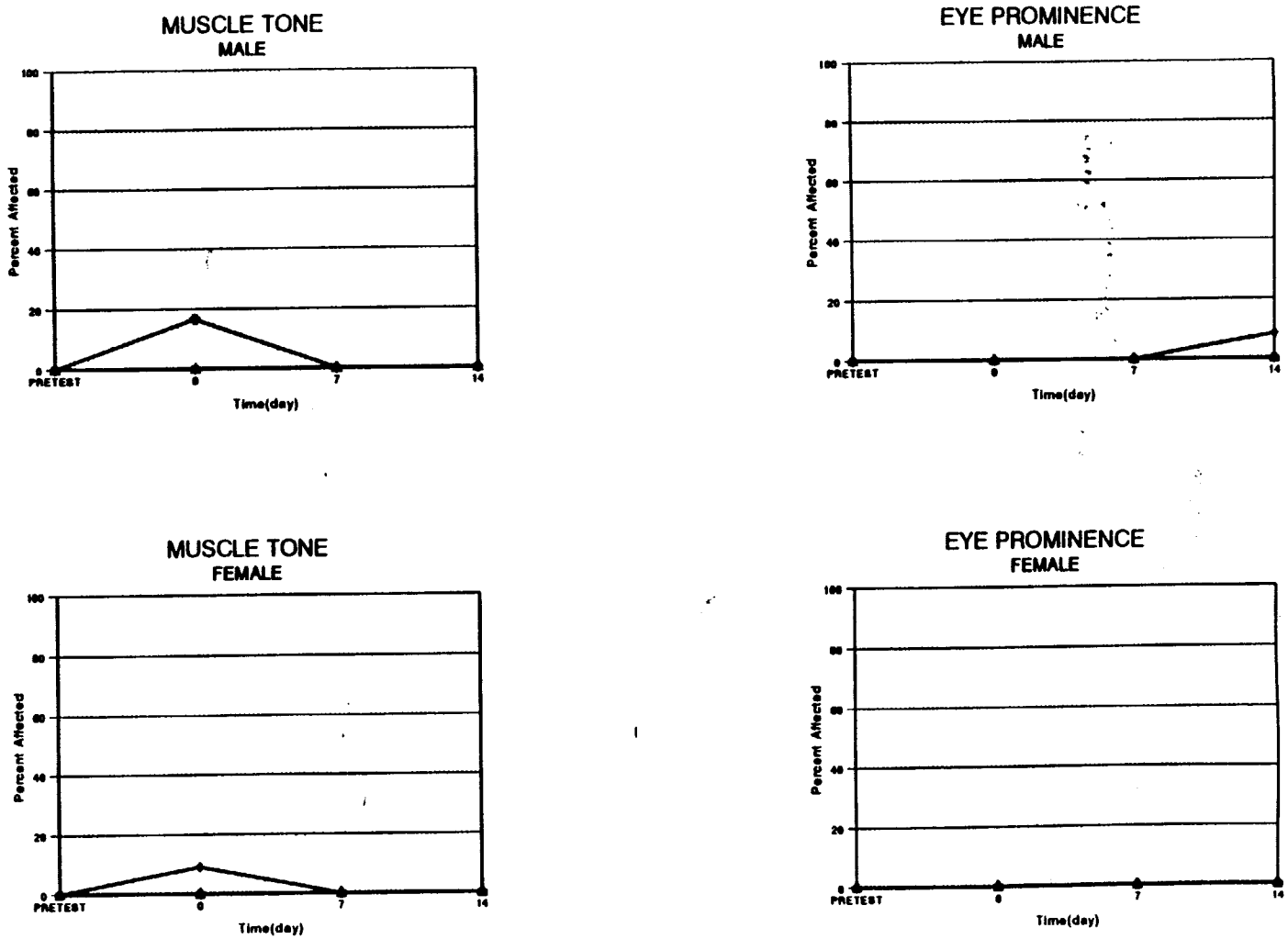


FIGURE 2
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HANDLING OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 20 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.4	0.4	0.6
S.D.	0.05	0.20	0.22	0.87
MOBILITY NORMAL	12	12	12	12
GAIT NORMAL	12	12	12	12
CONVULSIONS - CLONIC ABSENT	12	12	12	12
CONVULSIONS - TONIC ABSENT	12	12	12	12
TREMORS NONE	12	12	12	12
GAIT SCORE NORMAL	12	12	12	12
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	12	12	12	12
BIZARRE/STEREOTYPIC BEHAVIOR NONE	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 20 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
REARING	: MEAN	8.0	7.6	7.6	8.2
	S.D.	3.69	3.96	4.78	2.98
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.3	0.0	0.1	0.0
	S.D.	0.62	0.00	0.29	0.00
URINATION	: MEAN	0.0	0.3	0.3	0.2
	S.D.	0.00	0.87	0.87	0.39
DEFECATION	: MEAN	0.0	0.3	1.3+	0.1
	S.D.	0.00	0.62	2.05	0.29

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 20 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.3	0.3	0.3
S.D.	0.04	0.07	0.04	0.05
MOBILITY NORMAL	12	12	11	9
GAIT NORMAL	12	12	11	9
CONVULSIONS - CLONIC ABSENT	12	12	11	9
CONVULSIONS - TONIC ABSENT	12	12	11	9
TREMORS NONE	12	12	11	9
GAIT SCORE NORMAL	12	12	11	9
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	12	12	11	9
BIZARRE/STEREOTYPIC BEHAVIOR NONE	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 20 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	9.0	9.0	8.4	7.4
	S.D.	6.62	2.86	3.11	1.59
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.1	0.0
	S.D.	0.00	0.39	0.30	0.00
URINATION	: MEAN	0.0	0.0	0.2	0.0
	S.D.	0.00	0.00	0.40	0.00
DEFECATION	: MEAN	0.3	0.1	0.2	0.0
	S.D.	0.87	0.29	0.60	0.00

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 21 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.4	0.4	0.6
S.D.	0.05	0.20	0.22	0.87
MOBILITY NORMAL	100.	100.	100.	100.
GAIT NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC ABSENT	100.	100.	100.	100.
TREMORS NONE	100.	100.	100.	100.
GAIT SCORE NORMAL	100.	100.	100.	100.
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR NONE	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 21 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
REARING	: MEAN	8.0	7.6	7.6	8.2
	S.D.	3.69	3.96	4.78	2.98
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.3	0.0	0.1	0.0
	S.D.	0.62	0.00	0.29	0.00
URINATION	: MEAN	0.0	0.3	0.3	0.2
	S.D.	0.00	0.87	0.87	0.39
DEFECATION	: MEAN	0.0	0.3	1.3	0.1
	S.D.	0.00	0.62	2.05	0.29

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 21 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.3	0.3	0.3
S.D.	0.04	0.07	0.04	0.05
MOBILITY NORMAL	100.	100.	100.	100.
GAIT NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC ABSENT	100.	100.	100.	100.
TREMORS NONE	100.	100.	100.	100.
GAIT SCORE NORMAL	100.	100.	100.	100.
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR NONE	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 21 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	9.0	9.0	8.4	7.4
	S.D.	6.62	2.86	3.11	1.59
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.1	0.0
	S.D.	0.00	0.39	0.30	0.00
URINATION	: MEAN	0.0	0.0	0.2	0.0
	S.D.	0.00	0.00	0.40	0.00
DEFECATION	: MEAN	0.3	0.1	0.2	0.0
	S.D.	0.87	0.29	0.60	0.00

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 22 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.5	0.8	0.6
S.D.	0.46	0.19	0.74	0.31
MOBILITY				
NORMAL	12	12	8	7*
SLIGHTLY IMPAIRED	0	0	3	4
MODERATELY IMPAIRED	0	0	1	1
GAIT				
NORMAL	12	10	4*	3*
WALKS ON TIPTOES	0	0	4	7*
ATAXIA, EXCESSIVE SWAY, ROCKS OR LURCHES AS PROCEEDS FORWARD	0	2	4	2
CONVULSIONS - CLONIC				
ABSENT	12	11	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
GAIT SCORE				
NORMAL	12	10	4*	3*
SLIGHT IMPAIRMENT, BUT DEFINITE	0	2	7*	3
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING	0	0	1	6*

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 22 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
AROUSAL					
LOW: SOMEWHAT STUPOROUS		0	0	1	1
NORMAL: ALERT, EXPLORATORY MOVEMENTS		12	12	11	11
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		12	12	12	12
REARING	: MEAN	5.3	4.7	3.1	3.2
	S.D.	2.42	3.70	3.00	1.80
BACKING	: MEAN	0.0	0.0	0.1	0.2
	S.D.	0.00	0.00	0.29	0.58
GROOMING	: MEAN	0.3	0.5	0.0	0.1
	S.D.	0.62	1.17	0.00	0.29
URINATION	: MEAN	0.2	0.3	0.8	0.2
	S.D.	0.39	0.89	0.87	0.39
DEFECATION	: MEAN	0.6	0.1	0.1	0.2
	S.D.	1.38	0.29	0.29	0.39

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 22 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.4	0.4	0.5	0.6++
S.D.	0.08	0.15	0.09	0.20
MOBILITY				
NORMAL	12	12	6*	6
SLIGHTLY IMPAIRED	0	0	4*	2
MODERATELY IMPAIRED	0	0	1	1
GAIT				
NORMAL	12	11	3*	2*
WALKS ON TIPTOES	0	1	7*	5*
ATAXIA, EXCESSIVE SWAY, ROCKS OR LURCHES AS PROCEEDS FORWARD	0	0	1	2
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
GAIT SCORE				
NORMAL	12	11	3*	2*
SLIGHT IMPAIRMENT, BUT DEFINITE	0	1	4*	3
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING	0	0	4*	4*

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 22 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
AROUSAL					
LOW: SOMEWHAT STUPOROUS		0	0	1	1
NORMAL: ALERT, EXPLORATORY MOVEMENTS		11	12	10	8
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING		1	0	0	0
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		12	12	11	9
REARING	: MEAN	6.6	10.5	3.4	3.4
	S.D.	6.65	3.75	2.16	2.40
BACKING	: MEAN	0.1	0.0	0.2	0.0
	S.D.	0.29	0.00	0.40	0.00
GROOMING	: MEAN	0.2	0.3	1.2+	0.3
	S.D.	0.39	0.89	1.08	0.71
URINATION	: MEAN	0.1	0.2	0.3	0.2
	S.D.	0.29	0.58	0.90	0.44
DEFECATION	: MEAN	0.0	0.0	0.0	0.1
	S.D.	0.00	0.00	0.00	0.33

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 23 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.5	0.8	0.6
S.D.	0.46	0.19	0.74	0.31
MOBILITY				
NORMAL	100.	100.	66.7	58.3
SLIGHTLY IMPAIRED	0.	0.	25.0	33.3
MODERATELY IMPAIRED	0.	0.	8.3	8.3
GAIT				
NORMAL	100.	83.3	33.3	25.0
WALKS ON TIPTOES	0.	0.	33.3	58.3
ATAXIA, EXCESSIVE SWAY, ROCKS OR LURCHES AS PROCEEDS FORWARD	0.	16.7	33.3	16.7
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	83.3	33.3	25.0
SLIGHT IMPAIRMENT, BUT DEFINITE	0.	16.7	58.3	25.0
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING	0.	0.	8.3	50.0

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 23 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
AROUSAL					
LOW: SOMEWHAT STUPOROUS		0.	0.	8.3	8.3
NORMAL: ALERT, EXPLORATORY MOVEMENTS		100.	100.	91.7	91.7
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		100.	100.	100.	100.
REARING	: MEAN	5.3	4.7	3.1	3.2
	S.D.	2.42	3.70	3.00	1.80
BACKING	: MEAN	0.0	0.0	0.1	0.2
	S.D.	0.00	0.00	0.29	0.58
GROOMING	: MEAN	0.3	0.5	0.0	0.1
	S.D.	0.62	1.17	0.00	0.29
URINATION	: MEAN	0.2	0.3	0.8	0.2
	S.D.	0.39	0.89	0.87	0.39
DEFECATION	: MEAN	0.6	0.1	0.1	0.2
	S.D.	1.38	0.29	0.29	0.39

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 23 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.4	0.4	0.5	0.6
S.D.	0.08	0.15	0.09	0.20
MOBILITY				
NORMAL	100.	100.	54.5	66.7
SLIGHTLY IMPAIRED	0.	0.	36.4	22.2
MODERATELY IMPAIRED	0.	0.	9.1	11.1
GAIT				
NORMAL	100.	91.7	27.3	22.2
WALKS ON TIPTOES	0.	8.3	63.6	55.6
ATAXIA, EXCESSIVE SWAY, ROCKS OR LURCHES AS PROCEEDS FORWARD	0.	0.	9.1	22.2
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	91.7	27.3	22.2
SLIGHT IMPAIRMENT, BUT DEFINITE	0.	8.3	36.4	33.3
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING	0.	0.	36.4	44.4

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 23 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
AROUSAL					
LOW: SOMEWHAT STUPOROUS		0.	0.	9.1	11.1
NORMAL: ALERT, EXPLORATORY MOVEMENTS		91.7	100.	90.9	88.9
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING		8.3	0.	0.	0.
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		100.	100.	100.	100.
REARING	: MEAN	6.6	10.5	3.4	3.4
	S.D.	6.65	3.75	2.16	2.40
BACKING	: MEAN	0.1	0.0	0.2	0.0
	S.D.	0.29	0.00	0.40	0.00
GROOMING	: MEAN	0.2	0.3	1.2	0.3
	S.D.	0.39	0.89	1.08	0.71
URINATION	: MEAN	0.1	0.2	0.3	0.2
	S.D.	0.29	0.58	0.90	0.44
DEFECATION	: MEAN	0.0	0.0	0.0	0.1
	S.D.	0.00	0.00	0.00	0.33

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 24 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	1.1	0.8	0.5	0.6
S.D.	0.89	0.83	0.11	0.36
MOBILITY				
NORMAL	12	12	12	12
GAIT				
NORMAL	12	12	12	12
CONVULSIONS - CLONIC				
ABSENT	12	12	12	12
CONVULSIONS - TONIC				
ABSENT	12	12	12	12
TREMORS				
NONE	12	12	12	12
GAIT SCORE				
NORMAL	12	12	12	12
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	12	12	12	12
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 24 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
REARING	: MEAN	7.6	6.3	6.2	8.3
	S.D.	3.73	2.84	4.41	3.89
BACKING	: MEAN	0.0	0.0	0.2	0.0
	S.D.	0.00	0.00	0.58	0.00
GROOMING	: MEAN	0.3	0.4	0.8	0.2
	S.D.	0.62	0.79	1.06	0.39
URINATION	: MEAN	0.0	0.3	1.3++	0.9
	S.D.	0.00	0.87	1.23	1.38
DEFECATION	: MEAN	0.0	0.0	1.1	0.9
	S.D.	0.00	0.00	1.31	2.11

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 24 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.5	0.4	0.4
S.D.	0.50	0.24	0.04	0.04
MOBILITY				
NORMAL	12	12	11	9
GAIT				
NORMAL	12	12	11	9
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
GAIT SCORE				
NORMAL	12	12	11	9
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	11	11	11	9
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING	1	1	0	0
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 24 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	10.3	10.7	11.6	13.6
	S.D.	6.68	4.60	4.25	4.45
BACKING	: MEAN	0.0	0.0	0.1	0.0
	S.D.	0.00	0.00	0.30	0.00
GROOMING	: MEAN	0.0	0.4	0.3	0.2
	S.D.	0.00	0.51	0.65	0.67
URINATION	: MEAN	0.0	0.0	0.1	0.2
	S.D.	0.00	0.00	0.30	0.44
DEFECATION	: MEAN	0.0	0.0	0.2	0.8
	S.D.	0.00	0.00	0.60	1.30

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 25 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	1.1	0.8	0.5	0.6
S.D.	0.89	0.83	0.11	0.36
MOBILITY NORMAL	100.	100.	100.	100.
GAIT NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC ABSENT	100.	100.	100.	100.
TREMORS NONE	100.	100.	100.	100.
GAIT SCORE NORMAL	100.	100.	100.	100.
AROUSAL NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.
BIZARRE/STEREOTYPIC BEHAVIOR NONE	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 25 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
REARING	: MEAN	7.6	6.3	6.2	8.3
	S.D.	3.73	2.84	4.41	3.89
BACKING	: MEAN	0.0	0.0	0.2	0.0
	S.D.	0.00	0.00	0.58	0.00
GROOMING	: MEAN	0.3	0.4	0.8	0.2
	S.D.	0.62	0.79	1.06	0.39
URINATION	: MEAN	0.0	0.3	1.3	0.9
	S.D.	0.00	0.87	1.23	1.38
DEFECATION	: MEAN	0.0	0.0	1.1	0.9
	S.D.	0.00	0.00	1.31	2.11

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 25 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.6	0.5	0.4	0.4
S.D.	0.50	0.24	0.04	0.04
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	91.7	91.7	100.	100.
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING	8.3	8.3	0.	0.
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 25 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	10.3	10.7	11.6	13.6
	S.D.	6.68	4.60	4.25	4.45
BACKING	: MEAN	0.0	0.0	0.1	0.0
	S.D.	0.00	0.00	0.30	0.00
GROOMING	: MEAN	0.0	0.4	0.3	0.2
	S.D.	0.00	0.51	0.65	0.67
URINATION	: MEAN	0.0	0.0	0.1	0.2
	S.D.	0.00	0.00	0.30	0.44
DEFECATION	: MEAN	0.0	0.0	0.2	0.8
	S.D.	0.00	0.00	0.60	1.30

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 26 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
TIME TO FIRST STEP (seconds)	: MEAN	0.8	0.4+	0.5	0.4+
	S.D.	0.68	0.21	0.22	0.07
MOBILITY					
NORMAL		12	12	11	12
MODERATELY IMPAIRED		0	0	1	0
GAIT					
NORMAL		12	12	10	12
WALKS ON TIPTOES		0	0	2	0
CONVULSIONS - CLONIC					
ABSENT		12	12	12	12
CONVULSIONS - TONIC					
ABSENT		12	12	12	12
TREMORS					
NONE		12	12	12	12
GAIT SCORE					
NORMAL		12	12	10	12
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING		0	0	2	0
AROUSAL					
NORMAL: ALERT, EXPLORATORY MOVEMENTS		12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

TABLE 26 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
BIZARRE/STEREOTYPIC BEHAVIOR					
NONE		12	12	12	12
REARING	: MEAN	8.5	8.5	9.3	7.0
	S.D.	3.34	2.47	6.25	5.44
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.3	0.2	0.1
	S.D.	0.00	0.45	0.58	0.29
URINATION	: MEAN	0.1	0.0	0.7	1.1+
	S.D.	0.29	0.00	1.07	1.62
DEFECATION	: MEAN	0.0	0.0	0.2	0.8
	S.D.	0.00	0.00	0.58	1.27

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

TABLE 26 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.4	0.4	0.3
S.D.	0.09	0.16	0.30	0.09
MOBILITY				
NORMAL	12	12	11	9
GAIT				
NORMAL	12	12	11	9
CONVULSIONS - CLONIC				
ABSENT	12	12	11	9
CONVULSIONS - TONIC				
ABSENT	12	12	11	9
TREMORS				
NONE	12	12	11	9
GAIT SCORE				
NORMAL	12	12	11	9
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	10	10	11	8
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING	2	2	0	1
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 26 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	13.1	14.1	11.3	11.3
	S.D.	7.90	5.88	4.73	2.78
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.1	0.0
	S.D.	0.00	0.39	0.30	0.00
URINATION	: MEAN	0.0	0.0	0.0	0.1
	S.D.	0.00	0.00	0.00	0.33
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 27 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
TIME TO FIRST STEP (seconds) : MEAN	0.8	0.4	0.5	0.4
S.D.	0.68	0.21	0.22	0.07
MOBILITY				
NORMAL	100.	100.	91.7	100.
MODERATELY IMPAIRED	0.	0.	8.3	0.
GAIT				
NORMAL	100.	100.	83.3	100.
WALKS ON TIPTOES	0.	0.	16.7	0.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	83.3	100.
CONSIDERABLE IMPAIRMENT, WITHOUT FALLING	0.	0.	16.7	0.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 27 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
BIZARRE/STEREOTYPIC BEHAVIOR NONE		100.	100.	100.	100.
REARING	: MEAN	8.5	8.5	9.3	7.0
	S.D.	3.34	2.47	6.25	5.44
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.3	0.2	0.1
	S.D.	0.00	0.45	0.58	0.29
URINATION	: MEAN	0.1	0.0	0.7	1.1
	S.D.	0.29	0.00	1.07	1.62
DEFECATION	: MEAN	0.0	0.0	0.2	0.8
	S.D.	0.00	0.00	0.58	1.27

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 27 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
TIME TO FIRST STEP (seconds) : MEAN	0.3	0.4	0.4	0.3
S.D.	0.09	0.16	0.30	0.09
MOBILITY				
NORMAL	100.	100.	100.	100.
GAIT				
NORMAL	100.	100.	100.	100.
CONVULSIONS - CLONIC				
ABSENT	100.	100.	100.	100.
CONVULSIONS - TONIC				
ABSENT	100.	100.	100.	100.
TREMORS				
NONE	100.	100.	100.	100.
GAIT SCORE				
NORMAL	100.	100.	100.	100.
AROUSAL				
NORMAL: ALERT, EXPLORATORY MOVEMENTS	83.3	83.3	100.	88.9
SOMEWHAT HIGH: SLIGHT EXCITEMENT, TENSE, SUDDEN DARTING OR FREEZING	16.7	16.7	0.	11.1
BIZARRE/STEREOTYPIC BEHAVIOR				
NONE	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 27 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

OPEN FIELD OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
REARING	: MEAN	13.1	14.1	11.3	11.3
	S.D.	7.90	5.88	4.73	2.78
BACKING	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
GROOMING	: MEAN	0.0	0.2	0.1	0.0
	S.D.	0.00	0.39	0.30	0.00
URINATION	: MEAN	0.0	0.0	0.0	0.1
	S.D.	0.00	0.00	0.00	0.33
DEFECATION	: MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 3
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
OPEN FIELD OBSERVATIONS: DOSE-EFFECT CURVES

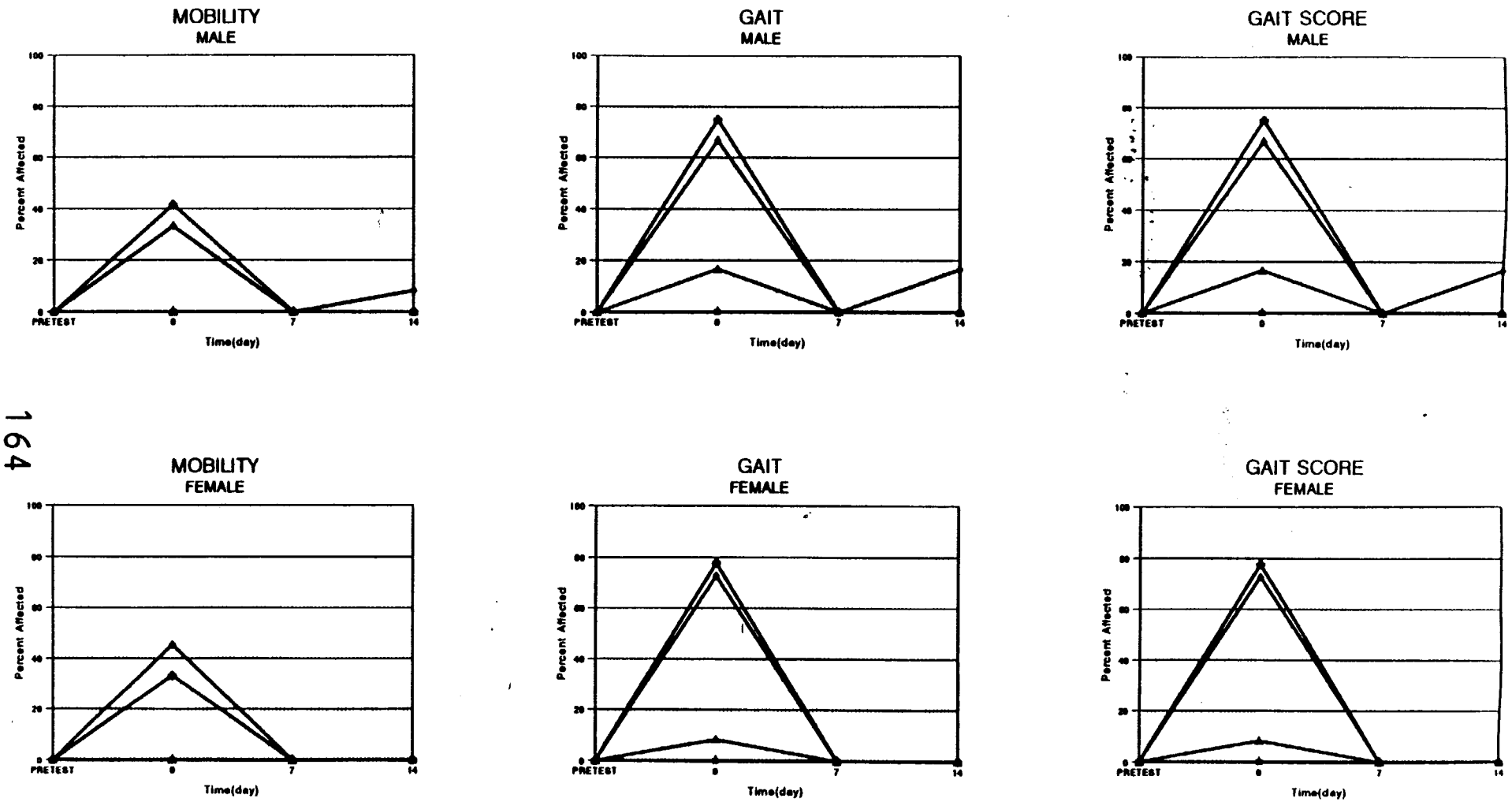


TABLE 28 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	11	10	11
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	1	2	1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	9	11	12	12
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	1	0	0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	1	2	0	0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	11	10	12	12
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	0	4	1	3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	12	8	10	9
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	0	0	1	0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	12	12
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	12	12
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	12	12
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 28 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	12	12	12	12
AIR RIGHTING REFLEX				
NORMAL	12	11	12	12
SLIGHTLY UNCOORDINATED	0	1	0	0

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 28 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	11	11	9	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	1	2	1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	11	12	9	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	0	2	0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	0	1	1	0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	12	11	10	9
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	0	0	0	1
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	12	12	11	8
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	11	9
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	11	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	11	9
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 28 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	12	12	11	9
AIR RIGHTING REFLEX				
NORMAL	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 29 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	83.3	91.7	83.3	91.7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	16.7	8.3	16.7	8.3
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	75.0	91.7	100.	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	25.0	8.3	0.	0.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	8.3	16.7	0.	0.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	91.7	83.3	100.	100.
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	0.	33.3	8.3	25.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	100.	66.7	83.3	75.0
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	0.	0.	8.3	0.
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 29 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	91.7	100.	100.
SLIGHTLY UNCOORDINATED	0.	8.3	0.	0.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 29 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	91.7	91.7	81.8	88.9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	8.3	18.2	11.1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	91.7	100.	81.8	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	0.	18.2	0.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	0.	8.3	9.1	0.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	100.	91.7	90.9	100.
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	0.	0.	0.	11.1
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	100.	100.	100.	88.9
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 29 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 30 (DAY 0 EVALUATION)

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SPONSOR:THE ZIRAM TASK FORCE | FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE | DAY 0

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
NO REACTION	0	0	0	2
SLOW APPROACH, SNIFFING OR TURNING AWAY	11	11	12	10
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	1	0	0
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	12	12	12	12
STARTLE RESPONSE				
NO REACTION	0	0	0	1
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	7	5	11	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	5	7	1	2
TAIL PINCH RESPONSE				
NO REACTION	0	0	1	0
ANIMAL MAY SLOWLY TURN, WALK AWAY	9	9	8	11
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	3	3	1
OLFACTORY ORIENTATION				
NO REACTION PRESENT	0	0	1	2
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	11	10
PUPIL RESPONSE				
NO PUPIL RESPONSE	0	1	1	0
PUPIL RESPONSE PRESENT	12	11	11	12
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 30 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	12	12
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	12	12	12	12
AIR RIGHTING REFLEX				
NORMAL	12	12	12	11
SLIGHTLY UNCOORDINATED	0	0	0	1

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 30 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
NO REACTION	0	0	1	1
SLOW APPROACH, SNIFFING OR TURNING AWAY	11	10	10	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	2	0	0
TOUCH RESPONSE				
NO REACTION	0	0	0	1
ANIMAL MAY SLOWLY TURN, WALK AWAY	11	9	11	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	3	0	0
STARTLE RESPONSE				
NO REACTION	0	0	0	1
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	4	2	10*	8*
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8	10	1*	0*
TAIL PINCH RESPONSE				
NO REACTION	0	0	0	1
ANIMAL MAY SLOWLY TURN, WALK AWAY	4	5	8	4
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	7	7	3	4
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	1	0	0	0
OLFACTORY ORIENTATION				
NO REACTION PRESENT	1	0	2	2
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	11	12	9	7
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 30 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	11	9
FORELIMB EXTENSION				
NO FORELIMB EXTENSION	0	0	0	1
FORELIMB EXTENSION PRESENT	12	12	11	8
HINDLIMB EXTENSION				
NO HINDLIMB EXTENSION	1	0	2	1
HINDLIMB EXTENSION PRESENT	11	12	9	8
AIR RIGHTING REFLEX				
NORMAL	11	11	10	9
SLIGHTLY UNCOORDINATED	1	1	1	0

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 31 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
NO REACTION	0.	0.	0.	16.7
SLOW APPROACH, SNIFFING OR TURNING AWAY	91.7	91.7	100.	83.3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	8.3	0.	0.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	100.	100.	100.	100.
STARTLE RESPONSE				
NO REACTION	0.	0.	0.	8.3
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	58.3	41.7	91.7	75.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	41.7	58.3	8.3	16.7
TAIL PINCH RESPONSE				
NO REACTION	0.	0.	8.3	0.
ANIMAL MAY SLOWLY TURN, WALK AWAY	75.0	75.0	66.7	91.7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	25.0	25.0	25.0	8.3
OLFACTORY ORIENTATION				
NO REACTION PRESENT	0.	0.	8.3	16.7
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	91.7	83.3
PUPIL RESPONSE				
NO PUPIL RESPONSE	0.	8.3	8.3	0.
PUPIL RESPONSE PRESENT	100.	91.7	91.7	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 31 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	91.7
SLIGHTLY UNCOORDINATED	0.	0.	0.	8.3

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 31 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
NO REACTION	0.	0.	9.1	11.1
SLOW APPROACH, SNIFFING OR TURNING AWAY	91.7	83.3	90.9	88.9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	16.7	0.	0.
TOUCH RESPONSE				
NO REACTION	0.	0.	0.	11.1
ANIMAL MAY SLOWLY TURN, WALK AWAY	91.7	75.0	100.	88.9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	25.0	0.	0.
STARTLE RESPONSE				
NO REACTION	0.	0.	0.	11.1
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	33.3	16.7	90.9	88.9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	66.7	83.3	9.1	0.
TAIL PINCH RESPONSE				
NO REACTION	0.	0.	0.	11.1
ANIMAL MAY SLOWLY TURN, WALK AWAY	33.3	41.7	72.7	44.4
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	58.3	58.3	27.3	44.4
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	8.3	0.	0.	0.
OLFACTORY ORIENTATION				
NO REACTION PRESENT	8.3	0.	18.2	22.2
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	91.7	100.	81.8	77.8
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 31 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
NO FORELIMB EXTENSION	0.	0.	0.	11.1
FORELIMB EXTENSION PRESENT	100.	100.	100.	88.9
HINDLIMB EXTENSION				
NO HINDLIMB EXTENSION	8.3	0.	18.2	11.1
HINDLIMB EXTENSION PRESENT	91.7	100.	81.8	88.9
AIR RIGHTING REFLEX				
NORMAL	91.7	91.7	90.9	100.
SLIGHTLY UNCOORDINATED	8.3	8.3	9.1	0.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 32 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	9	11	12	11
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	3	1	0	1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	12	12	12	12
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	7	3	5	6
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	5	9	7	6
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	10	11	5	4*
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	1	7	8*
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	12	12
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	12	12
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	12	12
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	12	12	12	12
AIR RIGHTING REFLEX				
NORMAL	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	10	9	9	8
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	3	2	1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	11	10	9	9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	2	2	0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	1	4	5	3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	11	8	6	6
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	3	4	4	1
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	9	8	7	8
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	11	9
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	11	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	11	9
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 32 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	12	12	11	9
AIR RIGHTING REFLEX				
NORMAL	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 33 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	75.0	91.7	100.	91.7
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	25.0	8.3	0.	8.3
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	100.	100.	100.	100.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	58.3	25.0	41.7	50.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	41.7	75.0	58.3	50.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	83.3	91.7	41.7	33.3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	16.7	8.3	58.3	66.7
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 33 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX NORMAL	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 33 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	83.3	75.0	81.8	88.9
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	16.7	25.0	18.2	11.1
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	91.7	83.3	81.8	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	16.7	18.2	0.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	8.3	33.3	45.5	33.3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	91.7	66.7	54.5	66.7
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	25.0	33.3	36.4	11.1
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	75.0	66.7	63.6	88.9
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 33 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION				
HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 34 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	11	10	9	12
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	1	2	3	0
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	10	11	10	12
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	2	1	2	0
STARTLE RESPONSE				
NO REACTION	0	0	1	0
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	2	3	6	6
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	10	9	5	6
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	7	5	7	3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	5	7	5	9
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	12	12
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	12	12
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	12	12
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 34 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION				
NO HINDLIMB EXTENSION	0	0	1	0
HINDLIMB EXTENSION PRESENT	12	12	11	12
AIR RIGHTING REFLEX				
NORMAL	12	12	11	12
LANDS ON SIDE	0	0	1	0

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

TABLE 34 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	7	6	10	9*
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	5	6	1	0*
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	7	8	10	9*
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	4	4	1	0
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	1	0	0	0
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	2	1	0	2
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	10	11	11	7
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	4	6	2	3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8	6	9	6
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	12	12	11	9
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	12	12	11	9
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	12	12	11	9
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 34 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION HINDLIMB EXTENSION PRESENT	12	12	11	9
AIR RIGHTING REFLEX NORMAL	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 35 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	91.7	83.3	75.0	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	8.3	16.7	25.0	0.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	83.3	91.7	83.3	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	16.7	8.3	16.7	0.
STARTLE RESPONSE				
NO REACTION	0.	0.	8.3	0.
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	16.7	25.0	50.0	50.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	83.3	75.0	41.7	50.0
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	58.3	41.7	58.3	25.0
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	41.7	58.3	41.7	75.0
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	12	12
HINDLIMB EXTENSION				
NO HINDLIMB EXTENSION	0.	0.	8.3	0.
HINDLIMB EXTENSION PRESENT	100.	100.	91.7	100.
AIR RIGHTING REFLEX				
NORMAL	100.	100.	91.7	100.
LANDS ON SIDE	0.	0.	8.3	0.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
APPROACH RESPONSE				
SLOW APPROACH, SNIFFING OR TURNING AWAY	58.3	50.0	90.9	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	41.7	50.0	9.1	0.
TOUCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	58.3	66.7	90.9	100.
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	33.3	33.3	9.1	0.
BIZARRE REACTION: JUMPS, BITES OR ATTACKS	8.3	0.	0.	0.
STARTLE RESPONSE				
SLIGHT REACTION, EAR FLICK OR SOME EVIDENCE THAT SNAP WAS HEARD	16.7	8.3	0.	22.2
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	83.3	91.7	100.	77.8
TAIL PINCH RESPONSE				
ANIMAL MAY SLOWLY TURN, WALK AWAY	33.3	50.0	18.2	33.3
MORE ENERGETIC RESPONSE THAN (2), WITH/WITHOUT VOCALIZATION	66.7	50.0	81.8	66.7
OLFACTORY ORIENTATION				
REACTION PRESENT: ANIMAL APPROACHES SWAB MAKING SNIFFING MOVEMENTS WITH NOSE	100.	100.	100.	100.
PUPIL RESPONSE				
PUPIL RESPONSE PRESENT	100.	100.	100.	100.
EYEBLINK RESPONSE				
EYEBLINK RESPONSE PRESENT	100.	100.	100.	100.
FORELIMB EXTENSION				
FORELIMB EXTENSION PRESENT	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

TABLE 35 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

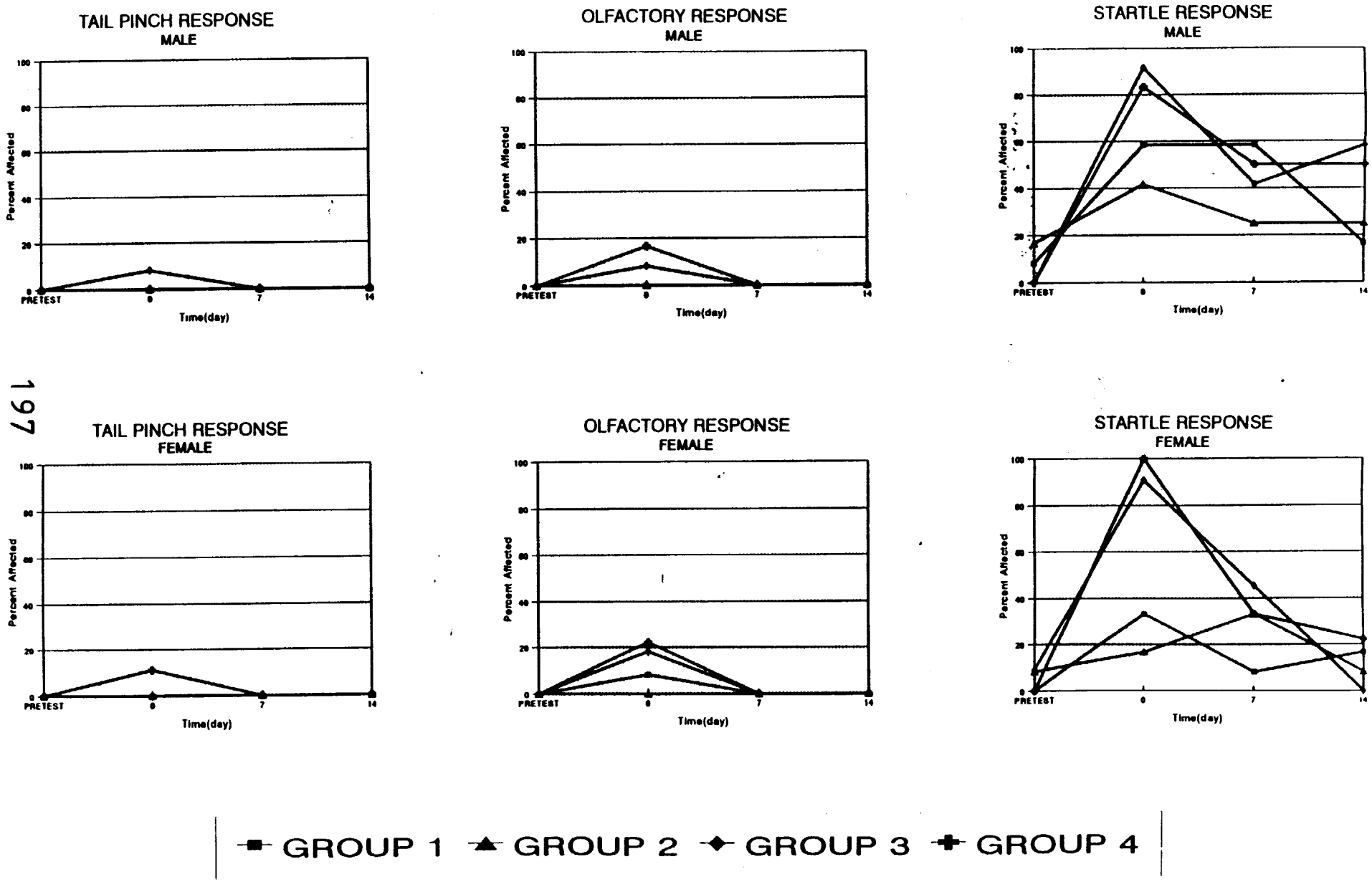
SENSORY OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:	1	2	3	4
NUMBER TESTED:	12	12	11	9
HINDLIMB EXTENSION HINDLIMB EXTENSION PRESENT	100.	100.	100.	100.
AIR RIGHTING REFLEX NORMAL	100.	100.	100.	100.

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
COMPLETE SCORING CRITERIA PRESENTED AS AN APPENDIX

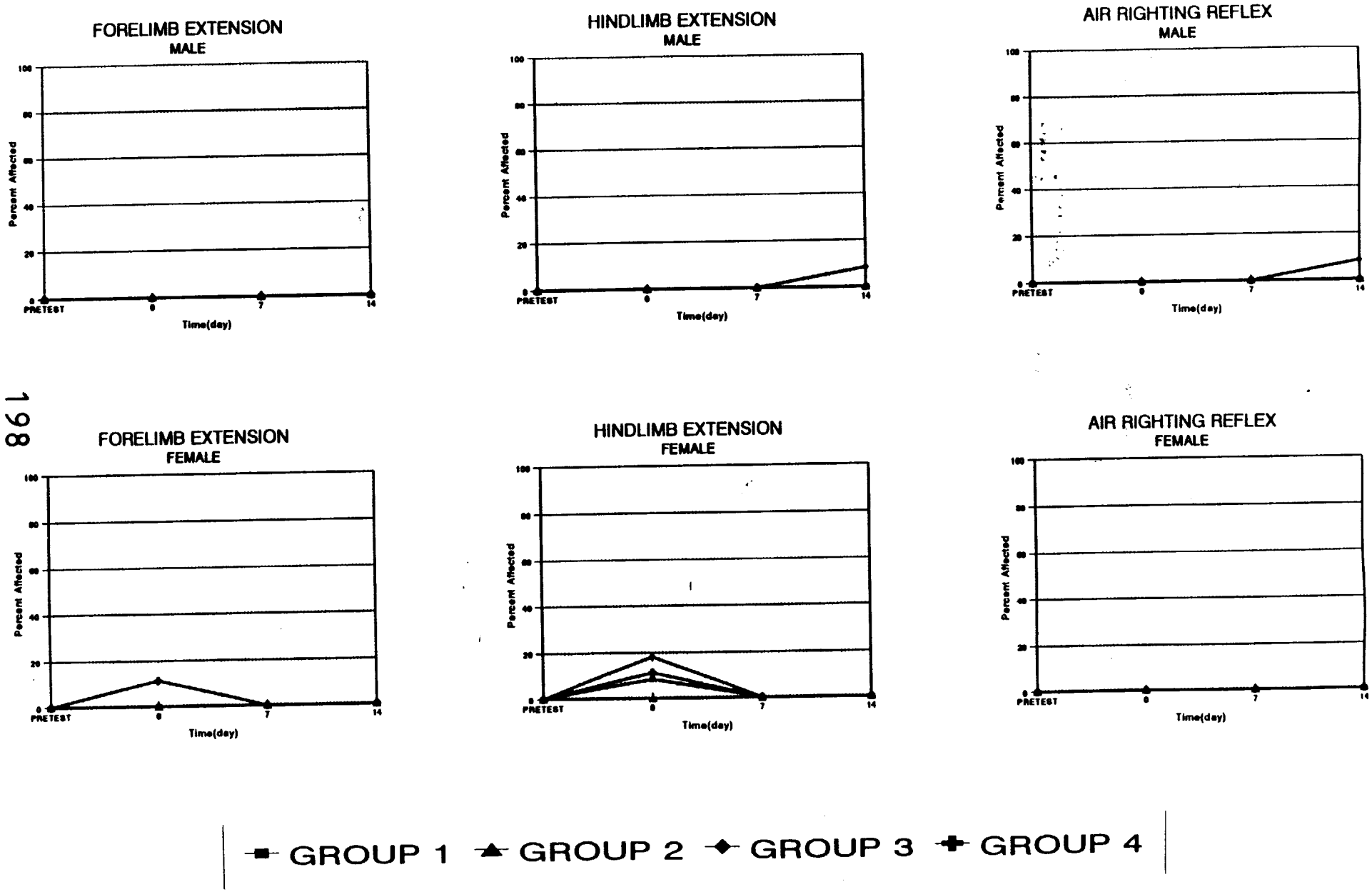
PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 4
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SENSORY OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 4
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
SENSORY OBSERVATIONS: DOSE-EFFECT CURVES



PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 36 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

		1	2	3	4
GROUP:		12	12	12	12
NUMBER TESTED:					
HINDLIMB EXTENSOR STRENGTH		12	12	12	12
HINDLIMB RESISTANCE PRESENT					
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	485.9	482.5	457.9	465.3
	S.D.	69.48	61.96	58.60	61.98
	HIND: MEAN	201.8	216.7	212.3	220.3
	S.D.	30.72	32.89	54.36	64.74
ROTAROD PERFORMANCE (seconds)	: MEAN	71.4	80.6	87.9	69.9
	S.D.	47.65	49.62	40.91	50.82
HINDLIMB FOOTSPLAY (mm)	: MEAN	59.9	61.3	57.5	63.0
	S.D.	15.84	13.69	15.13	14.51

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 36 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		12	12	11	9
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	454.3	430.5	429.4	445.6
	S.D.	46.60	63.17	76.95	74.06
	HIND: MEAN	205.7	196.8	186.0	213.9
	S.D.	45.99	40.62	47.60	25.71
ROTAROD PERFORMANCE (seconds)	: MEAN	65.1	52.9	57.3	56.5
	S.D.	49.36	37.44	51.07	49.68
HINDLIMB FOOTSPLAY (mm)	: MEAN	55.1	49.0	52.6	54.9
	S.D.	13.92	15.39	17.83	12.99

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 37 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	485.9	482.5	457.9	465.3
	S.D.	69.48	61.96	58.60	61.98
	HIND: MEAN	201.8	216.7	212.3	220.3
	S.D.	30.72	32.89	54.36	64.74
ROTAROD PERFORMANCE (seconds)	: MEAN	71.4	80.6	87.9	69.9
	S.D.	47.65	49.62	40.91	50.82
HINDLIMB FOOTSPLAY (mm)	: MEAN	59.9	61.3	57.5	63.0
	S.D.	15.84	13.69	15.13	14.51

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 37 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	454.3	430.5	429.4	445.6
	S.D.	46.60	63.17	76.95	74.06
	HIND: MEAN	205.7	196.8	186.0	213.9
	S.D.	45.99	40.62	47.60	25.71
ROTAROD PERFORMANCE (seconds)	: MEAN	65.1	52.9	57.3	56.5
	S.D.	49.36	37.44	51.07	49.68
HINDLIMB FOOTSPLAY (mm)	: MEAN	55.1	49.0	52.6	54.9
	S.D.	13.92	15.39	17.83	12.99

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 38 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH					
REDUCED HINDLIMB RESISTANCE, ANIMAL SHOWS SOME WEAKNESS		2	1	2	2
HINDLIMB RESISTANCE PRESENT		10	11	10	10
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	575.8	579.1	616.6	642.3
	S.D.	107.10	95.46	76.98	84.96
	HIND: MEAN	259.3	232.3	260.9	233.9
	S.D.	54.97	65.13	67.24	49.38
ROTAROD PERFORMANCE (seconds)	: MEAN	89.0	94.5	91.0	76.0
	S.D.	44.46	46.28	33.28	40.17
HINDLIMB FOOTSPLAY (mm)	: MEAN	62.3	63.5	63.7	67.8
	S.D.	18.86	15.06	15.30	12.80

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 38 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH					
REDUCED HINDLIMB RESISTANCE, ANIMAL SHOWS SOME WEAKNESS		1	1	0	1
HINDLIMB RESISTANCE PRESENT		11	11	11	8
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	521.3	536.1	547.3	562.0
	S.D.	89.65	94.96	56.79	102.61
	HIND: MEAN	242.4	270.6	248.8	242.8
	S.D.	54.98	46.16	47.12	72.02
ROTAROD PERFORMANCE (seconds)	: MEAN	99.4	94.7	108.9	88.8
	S.D.	37.99	45.86	18.63	34.15
HINDLIMB FOOTSPLAY (mm)	: MEAN	63.3	61.8	62.5	69.9
	S.D.	15.69	15.82	16.54	11.54

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 39 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH					
REDUCED HINDLIMB RESISTANCE, ANIMAL SHOWS SOME WEAKNESS		16.7	8.3	16.7	16.7
HINDLIMB RESISTANCE PRESENT		83.3	91.7	83.3	83.3
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	575.8	579.1	616.6	642.3
	S.D.	107.10	95.46	76.98	84.96
	HIND: MEAN	259.3	232.3	260.9	233.9
	S.D.	54.97	65.13	67.24	49.38
ROTAROD PERFORMANCE (seconds)	: MEAN	89.0	94.5	91.0	76.0
	S.D.	44.46	46.28	33.28	40.17
HINDLIMB FOOTSPLAY (mm)	: MEAN	62.3	63.5	63.7	67.8
	S.D.	18.86	15.06	15.30	12.80

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 39 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH					
REDUCED HINDLIMB RESISTANCE, ANIMAL SHOWS SOME WEAKNESS		8.3	8.3	0.	11.1
HINDLIMB RESISTANCE PRESENT		91.7	91.7	100.	88.9
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	521.3	536.1	547.3	562.0
	S.D.	89.65	94.96	56.79	102.61
	HIND: MEAN	242.4	270.6	248.8	242.8
	S.D.	54.98	46.16	47.12	72.02
ROTAROD PERFORMANCE (seconds)	: MEAN	99.4	94.7	108.9	88.8
	S.D.	37.99	45.86	18.63	34.15
HINDLIMB FOOTSPLAY (mm)	: MEAN	63.3	61.8	62.5	69.9
	S.D.	15.69	15.82	16.54	11.54

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 40 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:			1	2	3	4
NUMBER TESTED:			12	12	12	12
HINDLIMB EXTENSOR STRENGTH						
HINDLIMB RESISTANCE PRESENT			12	12	12	12
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE:	MEAN	627.8	597.8	663.6	672.2
		S.D.	113.08	121.90	87.01	92.11
	HIND:	MEAN	335.3	318.9	347.9	372.3
		S.D.	40.80	70.13	42.41	39.75
ROTAROD PERFORMANCE (seconds)	:	MEAN	102.3	94.4	100.7	52.9
		S.D.	38.71	46.25	35.77	46.87
HINDLIMB FOOTSPLAY (mm)	:	MEAN	62.1	56.8	63.1	66.5
		S.D.	18.35	13.32	10.10	13.28

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

TABLE 40 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH					
HINDLIMB RESISTANCE PRESENT		12	12	11	9
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	531.1	534.7	604.3	572.1
	S.D.	111.71	118.96	62.21	84.75
	HIND: MEAN	312.5	304.9	320.1	311.0
	S.D.	66.34	50.03	32.13	44.32
ROTAROD PERFORMANCE (seconds)	: MEAN	90.2	87.1	65.4	83.1
	S.D.	45.42	43.11	53.92	45.86
HINDLIMB FOOTSPLAY (mm)	: MEAN	58.3	58.1	56.1	65.9
	S.D.	12.56	16.51	10.28	12.68

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 41 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	627.8	597.8	663.6	672.2
	S.D.	113.08	121.90	87.01	92.11
	HIND: MEAN	335.3	318.9	347.9	372.3
	S.D.	40.80	70.13	42.41	39.75
ROTAROD PERFORMANCE (seconds)	: MEAN	102.3	94.4	100.7	52.9
	S.D.	38.71	46.25	35.77	46.87
HINDLIMB FOOTSPLAY (mm)	: MEAN	62.1	56.8	63.1	66.5
	S.D.	18.35	13.32	10.10	13.28

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 41 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	531.1	534.7	604.3	572.1
	S.D.	111.71	118.96	62.21	84.75
	HIND: MEAN	312.5	304.9	320.1	311.0
	S.D.	66.34	50.03	32.13	44.32
ROTAROD PERFORMANCE (seconds)	: MEAN	90.2	87.1	65.4	83.1
	S.D.	45.42	43.11	53.92	45.86
HINDLIMB FOOTSPLAY (mm)	: MEAN	58.3	58.1	56.1	65.9
	S.D.	12.56	16.51	10.28	12.68

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 42 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		12	12	12	12
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	548.3	625.8	599.1	703.6++
	S.D.	63.17	88.60	131.86	87.29
	HIND: MEAN	357.5	330.6	333.3	373.8
	S.D.	84.90	63.82	73.21	35.36
ROTAROD PERFORMANCE (seconds)	: MEAN	79.3	85.8	90.8	78.7
	S.D.	51.71	38.39	44.73	49.50
HINDLIMB FOOTSPLAY (mm)	: MEAN	52.8	58.5	55.7	70.9
	S.D.	16.75	8.94	11.76	8.94

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 42 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
NUMBER OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		12	12	11	9
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	543.2	539.1	533.7	601.0
	S.D.	82.08	88.26	73.91	66.68
	HIND: MEAN	342.1	306.3	323.1	338.2
	S.D.	42.26	46.04	30.93	57.01
ROTAROD PERFORMANCE (seconds)	: MEAN	100.3	106.6	69.1	80.3
	S.D.	42.41	33.48	42.38	51.31
HINDLIMB FOOTSPLAY (mm)	: MEAN	57.2	58.0	51.7	59.4
	S.D.	12.90	14.91	12.35	14.59

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING FISHER'S EXACT TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 43 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
MALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	548.3	625.8	599.1	703.6
	S.D.	63.17	88.60	131.86	87.29
	HIND: MEAN	357.5	330.6	333.3	373.8
	S.D.	84.90	63.82	73.21	35.36
ROTAROD PERFORMANCE (seconds)	: MEAN	79.3	85.8	90.8	78.7
	S.D.	51.71	38.39	44.73	49.50
HINDLIMB FOOTSPLAY (mm)	: MEAN	52.8	58.5	55.7	70.9
	S.D.	16.75	8.94	11.76	8.94

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 43 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

NEUROMUSCULAR OBSERVATIONS
FEMALES
PERCENTAGE OF ANIMALS SHOWING EACH OBSERVATION

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
HINDLIMB EXTENSOR STRENGTH HINDLIMB RESISTANCE PRESENT		100.	100.	100.	100.
GRIP STRENGTH (g) - FORE/HINDLIMB	FORE: MEAN	543.2	539.1	533.7	601.0
	S.D.	82.08	88.26	73.91	66.68
	HIND: MEAN	342.1	306.3	323.1	338.2
	S.D.	42.26	46.04	30.93	57.01
ROTAROD PERFORMANCE (seconds)	: MEAN	100.3	106.6	69.1	80.3
	S.D.	42.41	33.48	42.38	51.31
HINDLIMB FOOTSPLAY (mm)	: MEAN	57.2	58.0	51.7	59.4
	S.D.	12.90	14.91	12.35	14.59

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 44 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
CATALEPSY (seconds)	: MEAN	0.4	0.4	0.5	0.4
	S.D.	0.24	0.10	0.22	0.20
	N	12	12	12	12
BODY TEMPERATURE (degrees C)	: MEAN	38.6	38.7	38.8	38.5
	S.D.	0.41	0.23	0.28	0.32
	N	12	12	12	12
BODY WEIGHT (g)	: MEAN	166.2	166.8	165.7	173.0
	S.D.	12.51	9.22	11.73	12.46
	N	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 44 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
CATALEPSY (seconds)	: MEAN	0.4	0.4	0.4	0.3
	S.D.	0.12	0.09	0.16	0.15
	N	12	12	11	9
BODY TEMPERATURE (degrees C)	: MEAN	38.7	38.7	38.8	38.8
	S.D.	0.31	0.35	0.45	0.55
	N	12	12	11	9
BODY WEIGHT (g)	: MEAN	130.0	132.5	132.2	137.0
	S.D.	6.82	8.16	6.99	9.44
	N	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 45 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
CATALEPSY (seconds)	: MEAN	0.7	0.6	0.5	0.6
	S.D.	0.47	0.29	0.28	0.26
	N	12	12	12	12
BODY TEMPERATURE (degrees C)	: MEAN	38.8	38.6	35.1++	35.2++
	S.D.	0.25	0.56	1.02	0.82
	N	12	12	12	12
BODY WEIGHT (g)	: MEAN	214.6	214.0	210.2	219.1
	S.D.	15.29	9.74	11.65	11.57
	N	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 45 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
CATALEPSY (seconds)	: MEAN	0.5	0.5	0.6	0.5
	S.D.	0.20	0.25	0.29	0.33
	N	12	12	11	9
BODY TEMPERATURE (degrees C)	: MEAN	38.9	38.8	35.2++	35.1++
	S.D.	0.42	0.44	0.96	1.20
	N	12	12	11	9
BODY WEIGHT (g)	: MEAN	151.3	153.4	151.7	157.3
	S.D.	8.44	10.61	8.97	10.71
	N	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 46 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
CATALEPSY (seconds)	: MEAN	0.5	0.6	0.5	0.3
	S.D.	0.20	0.59	0.43	0.10
	N	12	12	12	12
BODY TEMPERATURE (degrees C)	: MEAN	38.7	38.8	38.4	38.3+
	S.D.	0.28	0.46	0.42	0.35
	N	12	12	12	12
BODY WEIGHT (g)	: MEAN	267.7	265.9	233.7++	244.5++
	S.D.	22.67	9.84	15.10	21.61
	N	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 46 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
CATALEPSY (seconds)	: MEAN	0.4	0.3	0.3	0.3
	S.D.	0.21	0.12	0.10	0.12
	N	12	12	11	9
BODY TEMPERATURE (degrees C)	: MEAN	39.1	38.9	38.6	38.7
	S.D.	0.43	0.47	0.55	0.49
	N	12	12	11	9
BODY WEIGHT (g)	: MEAN	173.6	171.0	166.7	173.4
	S.D.	9.79	14.43	9.21	9.96
	N	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 47 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

PHYSIOLOGICAL OBSERVATIONS
MALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	12	12
CATALEPSY (seconds)	: MEAN	0.3	0.3	0.3	0.3
	S.D.	0.06	0.10	0.16	0.14
	N	12	12	12	12
BODY TEMPERATURE (degrees C)	: MEAN	38.8	38.7	38.1	38.4
	S.D.	0.39	0.45	1.94	0.36
	N	12	12	12	12
BODY WEIGHT (g)	: MEAN	314.4	315.7	265.5++	305.9
	S.D.	26.54	13.57	54.41	24.87
	N	12	12	12	12

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
++ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING DUNNETT'S TEST

TABLE 47 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
FUNCTIONAL OBSERVATIONAL BATTERY SUMMARY INCIDENCE

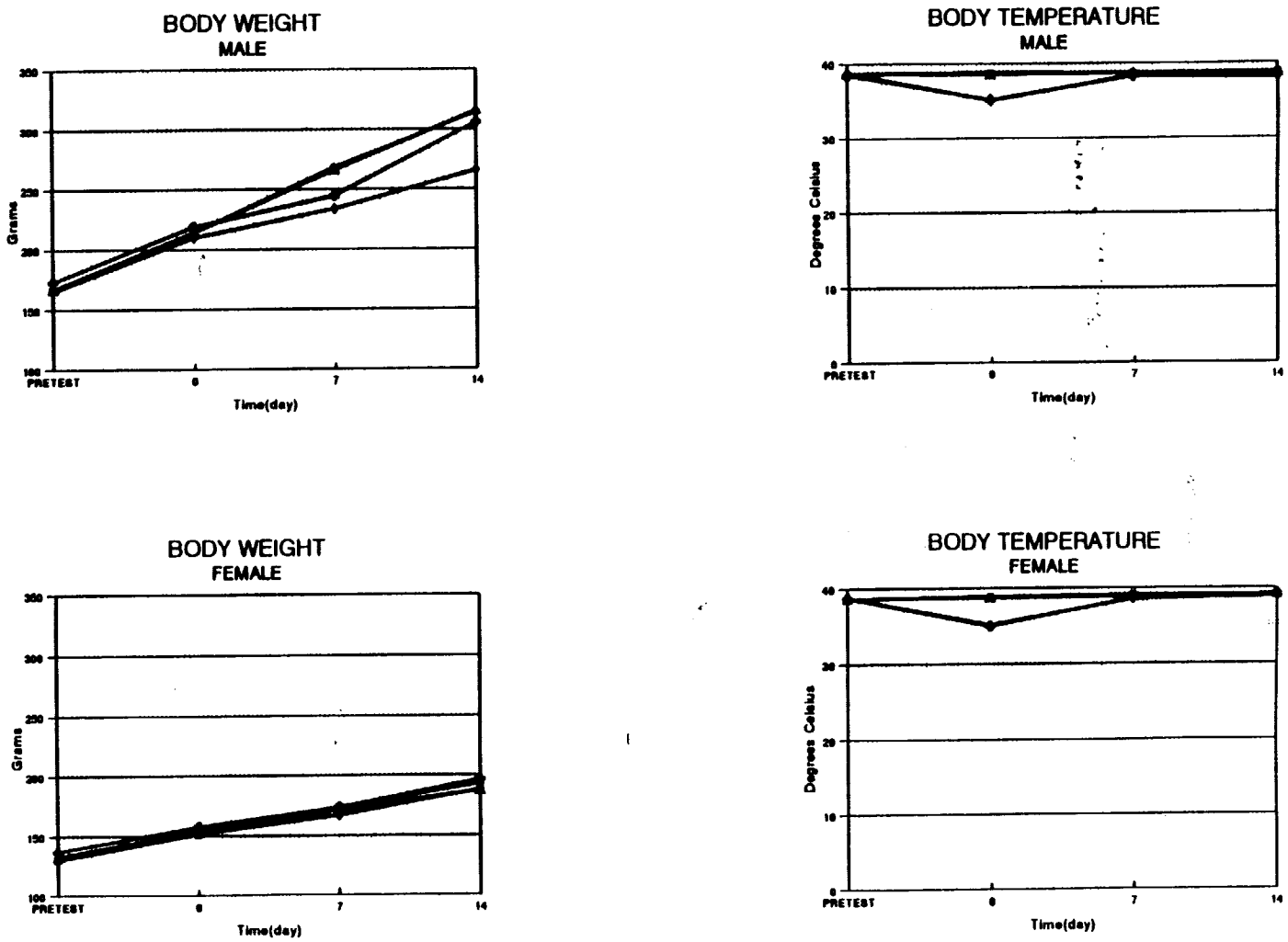
PHYSIOLOGICAL OBSERVATIONS
FEMALES

GROUP:		1	2	3	4
NUMBER TESTED:		12	12	11	9
CATALEPSY (seconds)	: MEAN	0.5	0.4	0.3	0.3
	S.D.	0.64	0.41	0.05	0.05
	N	12	12	11	9
BODY TEMPERATURE (degrees C)	: MEAN	39.1	39.2	39.0	39.2
	S.D.	0.29	0.57	0.48	0.15
	N	12	12	11	9
BODY WEIGHT (g)	: MEAN	193.0	187.5	188.1	196.5
	S.D.	12.05	17.41	12.39	13.32
	N	12	12	11	9

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 5
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
PHYSIOLOGICAL OBSERVATIONS: DOSE-EFFECT CURVES



GROUP 1 GROUP 2 GROUP 3 GROUP 4

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 48 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: PRETEST

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	761	452	316	159	1687
	SD	127.8	234.6	235.4	116.3	548.3
	N	12	12	12	12	12
15 MG/KG	MEAN	793	485	324	208	1811
	SD	145.9	102.5	176.7	187.9	393.0
	N	12	12	12	12	12
300 MG/KG	MEAN	708	471	272	142	1593
	SD	143.2	164.5	129.9	150.3	351.7
	N	12	12	12	12	12
600 MG/KG	MEAN	757	467	340	233	1797
	SD	260.0	254.1	276.0	234.4	818.3
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 48 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: PRETEST

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	370	244	156	78	848
	SD	74.3	119.3	117.1	64.9	290.9
	N	12	12	12	12	12
15 MG/KG	MEAN	376	254	184	120	934
	SD	70.5	62.8	98.8	134.4	227.7
	N	12	12	12	12	12
300 MG/KG	MEAN	341	232	138	62	772
	SD	98.7	96.3	64.7	50.0	217.9
	N	12	12	12	12	12
600 MG/KG	MEAN	404	261	183	113	961
	SD	155.4	145.4	150.7	117.2	447.8
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 48 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: PRETEST

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	863	489	288	172	1812
	SD	199.7	178.0	234.9	171.7	528.6
	N	12	12	12	12	12
15 MG/KG	MEAN	911	463	321	160	1855
	SD	213.6	206.4	209.0	151.2	611.4
	N	12	12	12	12	12
300 MG/KG	MEAN	997	530	410	202	2139
	SD	105.9	194.7	135.0	190.7	432.8
	N	11	11	11	11	11
600 MG/KG	MEAN	882	514	321	144	1861
	SD	248.3	310.3	263.3	122.9	883.9
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 48 (PRETEST EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: PRETEST

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	347	249	148	95	839
	SD	87.7	85.6	112.7	92.7	237.6
	N	12	12	12	12	12
15 MG/KG	MEAN	402	244	173	78	896
	SD	137.6	123.6	123.9	86.3	413.8
	N	12	12	12	12	12
300 MG/KG	MEAN	443	266	214	113	1036
	SD	80.5	118.4	62.4	117.1	295.6
	N	11	11	11	11	11
600 MG/KG	MEAN	426	271	175	79	950
	SD	137.7	175.5	163.5	66.6	506.6
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 49 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 0

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	693	429	234	149	1504
	SD	209.3	190.8	114.0	175.8	333.8
	N	12	12	12	12	12
15 MG/KG	MEAN	649	349	236	141	1375
	SD	272.9	215.9	188.3	142.5	585.9
	N	12	12	12	12	12
300 MG/KG	MEAN	106+	31+	33+	34	205+
	SD	75.9	57.4	27.0	16.8	118.5
	N	12	12	12	12	12
600 MG/KG	MEAN	117+	40+	59+	51	267+
	SD	99.9	30.8	50.1	56.9	159.9
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

STUDY INTERVAL: DAY 0

TABLE 49 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	383	231	100	86	800
	SD	89.1	108.7	53.6	116.1	158.6
	N	12	12	12	12	12
15 MG/KG	MEAN	371	195	124	78	768
	SD	152.8	135.7	111.1	93.4	368.1
	N	12	12	12	12	12
300 MG/KG	MEAN	54+	12+	17+	23	106+
	SD	44.3	17.6	11.7	11.9	56.3
	N	12	12	12	12	12
600 MG/KG	MEAN	71+	23+	36+	31	161+
	SD	70.0	20.0	31.4	32.9	107.0
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

STUDY INTERVAL: DAY 0

TABLE 49 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	803	442	224	234	1703
	SD	184.1	231.4	347.0	192.0	688.8
	N	12	12	12	12	12
15 MG/KG	MEAN	796	266+	161	226	1449
	SD	160.8	160.7	120.8	212.3	326.4
	N	12	12	12	12	12
300 MG/KG	MEAN	156+	60+	71	73+	360+
	SD	166.8	91.3	100.1	58.1	294.9
	N	11	11	11	11	11
600 MG/KG	MEAN	129+	14+	28	57+	228+
	SD	69.2	18.9	34.2	53.0	94.1
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 49 (DAY 0 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 0

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	422	225	115	112	873
	SD	122.5	107.7	160.6	105.0	354.7
	N	12	12	12	12	12
15 MG/KG	MEAN	403	144	87	90	724
	SD	103.4	91.7	77.8	106.2	215.4
	N	12	12	12	12	12
300 MG/KG	MEAN	83+	33+	48	47	212+
	SD	85.8	63.9	73.3	45.8	207.1
	N	11	11	11	11	11
600 MG/KG	MEAN	70+	8+	12	27	117+
	SD	43.5	10.8	12.3	24.2	48.9
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 50 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 7

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	709	492	298	276	1775
	SD	159.2	220.1	194.2	183.1	540.5
	N	12	12	12	12	12
15 MG/KG	MEAN	876	482	376	309	2043
	SD	155.7	105.0	174.3	155.6	487.1
	N	12	12	12	12	12
300 MG/KG	MEAN	785	457	262	138	1642
	SD	140.0	124.7	188.9	126.9	411.3
	N	12	12	12	12	12
600 MG/KG	MEAN	698	358	255	104+	1415
	SD	249.4	153.4	212.0	141.9	638.0
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

STUDY INTERVAL: DAY 7

TABLE 50 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	410	281	185	161	1037
	SD	88.1	111.4	117.4	120.5	295.6
	N	12	12	12	12	12
15 MG/KG	MEAN	522+	297	243	181	1243
	SD	77.2	68.4	120.5	94.8	299.3
	N	12	12	12	12	12
300 MG/KG	MEAN	436	255	140	78	908
	SD	53.0	68.2	85.6	71.3	195.8
	N	12	12	12	12	12
600 MG/KG	MEAN	391	205	133	56+	784
	SD	140.3	94.7	121.9	81.0	372.2
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
+ = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.05 LEVEL USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 50 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 7

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	852	481	366	299	1998
	SD	172.9	155.4	196.4	216.5	555.7
	N	12	12	12	12	12
15 MG/KG	MEAN	887	480	305	340	2012
	SD	146.7	172.1	183.1	200.9	498.1
	N	12	12	12	12	12
300 MG/KG	MEAN	857	511	300	252	1919
	SD	156.8	131.5	164.3	167.7	465.8
	N	11	11	11	11	11
600 MG/KG	MEAN	954	521	352	151	1977
	SD	211.8	276.8	226.8	165.7	766.3
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

STUDY INTERVAL: DAY 7

TABLE 50 (DAY 7 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	479	281	218	169	1147
	SD	111.0	105.5	120.8	137.6	377.8
	N	12	12	12	12	12
15 MG/KG	MEAN	502	292	191	198	1184
	SD	98.2	109.3	114.9	122.6	315.0
	N	12	12	12	12	12
300 MG/KG	MEAN	456	293	166	142	1056
	SD	98.5	82.5	87.0	91.6	293.9
	N	11	11	11	11	11
600 MG/KG	MEAN	526	266	188	74	1054
	SD	147.2	150.6	136.3	89.4	455.2
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 51 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 14

TOTAL ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	726	385	314	234	1659
	SD	180.7	136.9	147.2	167.4	531.3
	N	12	12	12	12	12
15 MG/KG	MEAN	808	457	349	274	1888
	SD	139.8	128.1	176.8	162.1	474.8
	N	11	11	11	11	11
300 MG/KG	MEAN	779	450	325	173	1727
	SD	253.7	153.7	153.6	153.0	607.1
	N	12	12	12	12	12
600 MG/KG	MEAN	738	449	225	177	1589
	SD	261.5	213.5	182.7	153.9	667.2
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 51 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 14

AMBULATORY ACTIVITY (COUNTS)
MALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	433	244	187	141	1004
	SD	85.6	96.7	89.7	101.9	306.7
	N	12	12	12	12	12
15 MG/KG	MEAN	494	288	226	184	1193
	SD	83.7	96.2	121.4	112.9	341.8
	N	11	11	11	11	11
300 MG/KG	MEAN	449	264	202	103	1017
	SD	142.1	87.3	94.0	95.4	353.7
	N	12	12	12	12	12
600 MG/KG	MEAN	415	236	126	97	875
	SD	126.6	134.4	116.1	85.5	392.7
	N	12	12	12	12	12

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 51 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

STUDY INTERVAL: DAY 14

TOTAL ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	892	525	435	403	2255
	SD	215.4	241.6	201.5	235.8	670.1
	N	12	12	12	12	12
15 MG/KG	MEAN	849	493	303	285	1929
	SD	252.4	220.8	180.4	150.5	542.9
	N	12	12	12	12	12
300 MG/KG	MEAN	874	519	416	361	2170
	SD	88.7	196.7	135.3	153.2	335.8
	N	11	11	11	11	11
600 MG/KG	MEAN	902	617	453	192	2165
	SD	255.8	188.8	314.4	226.9	850.0
	N	9	9	9	9	9

SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 51 (DAY 14 EVALUATION)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY COUNTS

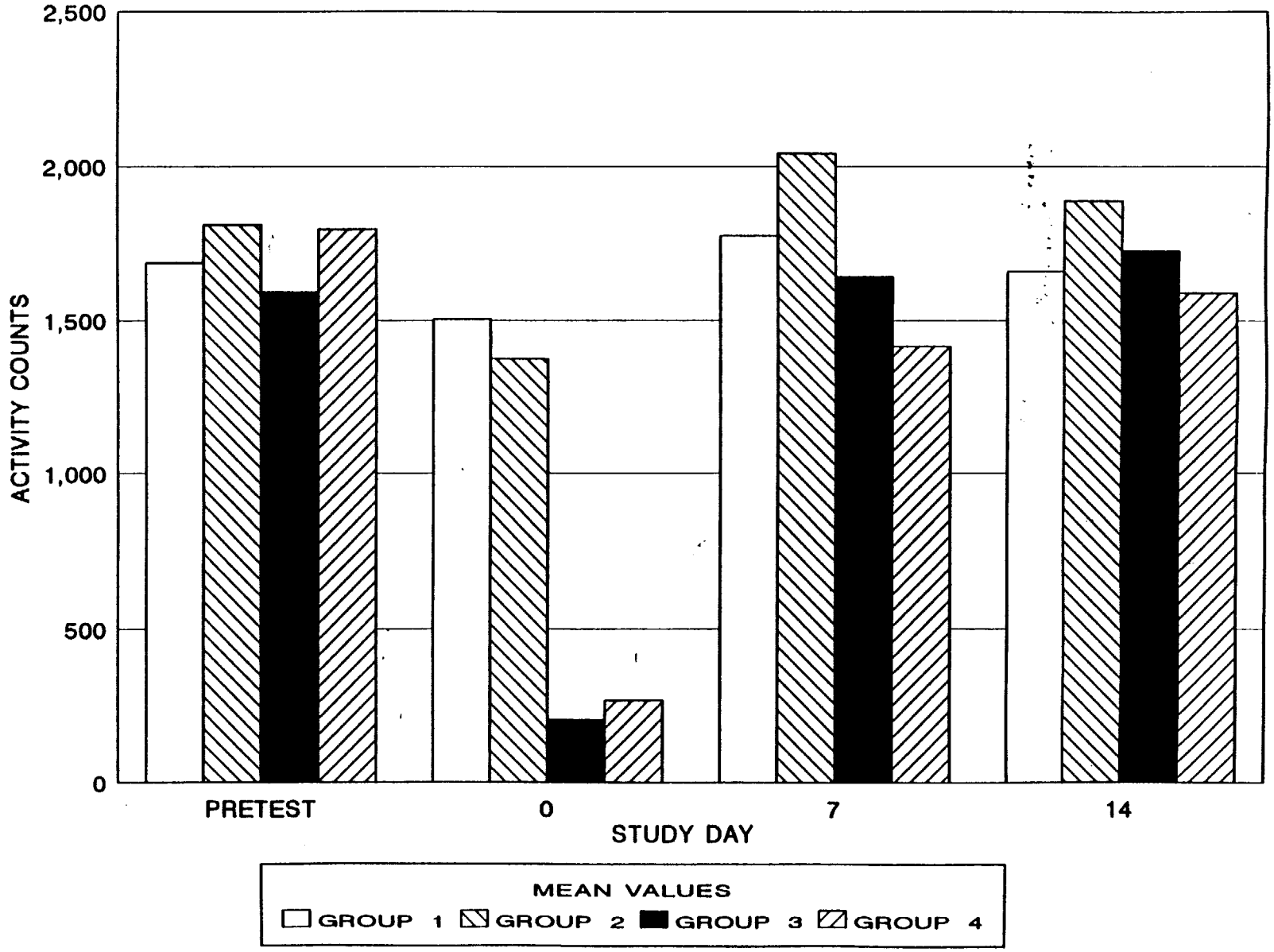
STUDY INTERVAL: DAY 14

AMBULATORY ACTIVITY (COUNTS)
FEMALE

GROUP		SUBSESSION 1	2	3	4	TOTAL
0 MG/KG	MEAN	503	315	268	261	1346
	SD	127.7	161.7	132.8	149.4	433.4
	N	12	12	12	12	12
15 MG/KG	MEAN	486	299	192	164	1140
	SD	109.2	122.5	122.8	98.5	294.9
	N	12	12	12	12	12
300 MG/KG	MEAN	505	299	242	223	1268
	SD	84.7	127.7	98.9	115.1	279.2
	N	11	11	11	11	11
600 MG/KG	MEAN	518	370	266	123	1277
	SD	185.7	127.3	199.4	159.8	604.8
	N	9	9	9	9	9

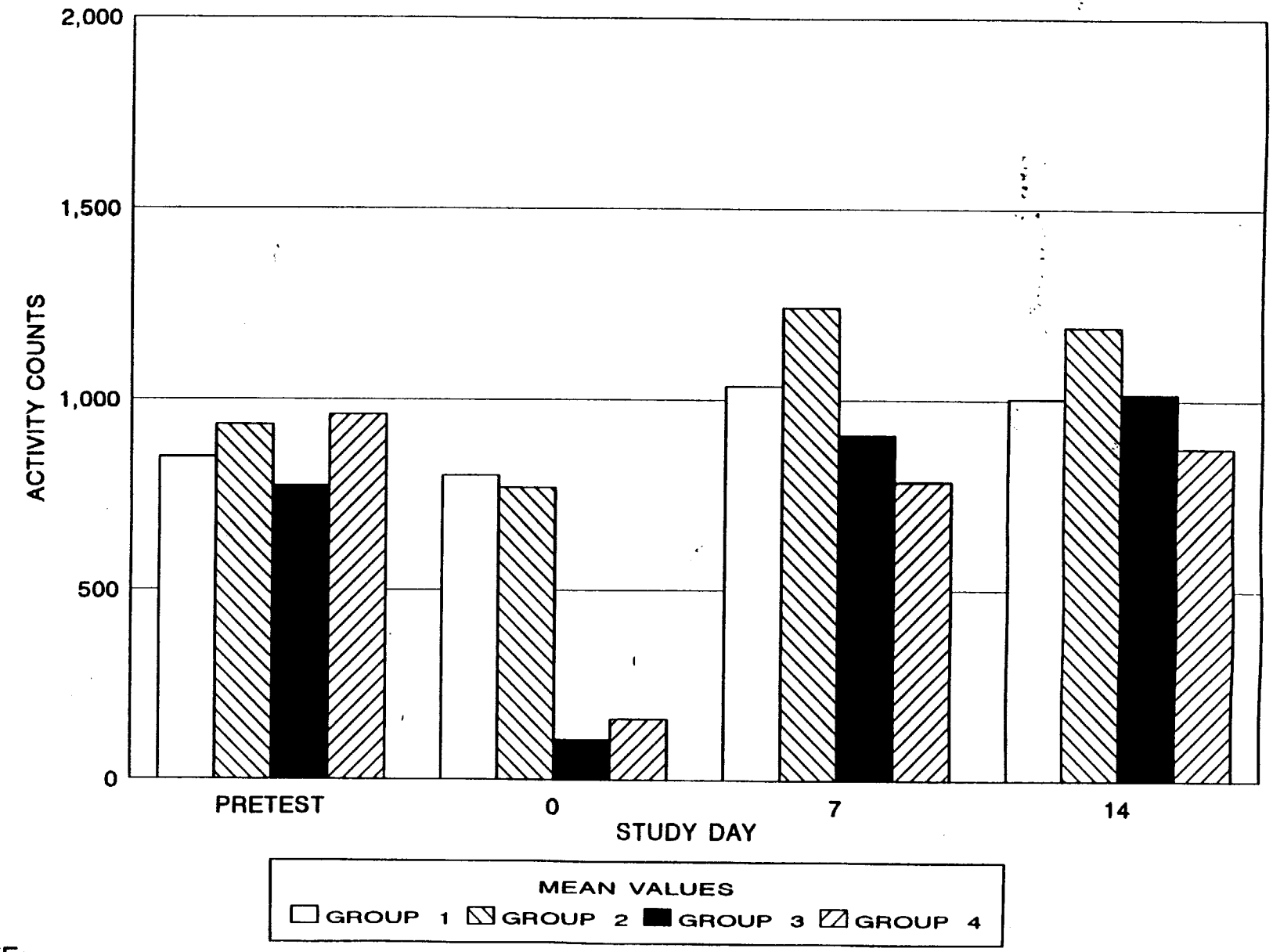
SUBSESSION LENGTH: 10 MIN. SESSION LENGTH: 40 MIN.
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROLS USING DUNNETT'S TEST

FIGURE 6
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
MALE



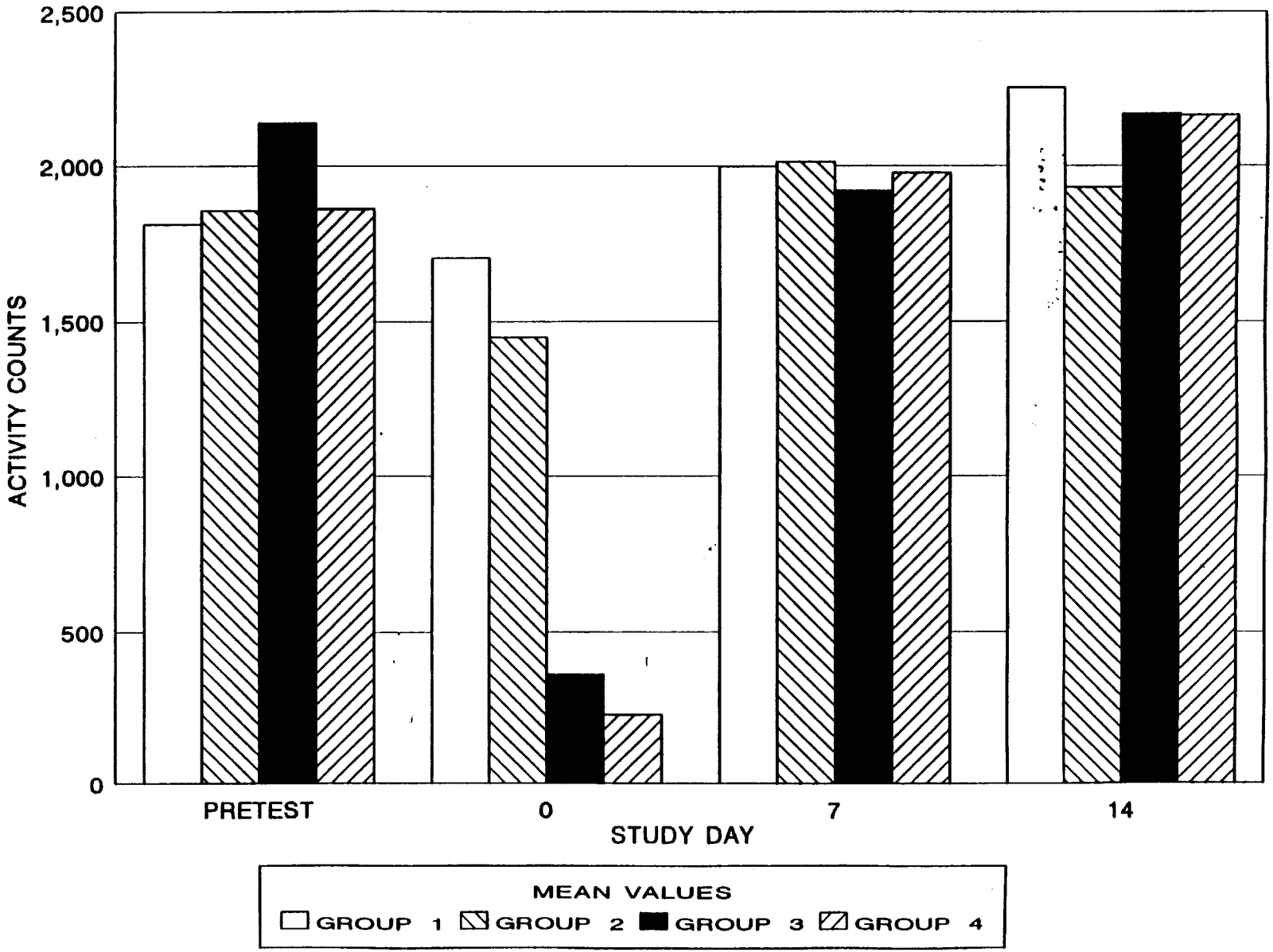
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SEE TEXT FOR EXPLANATION.

FIGURE 6
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
MALE



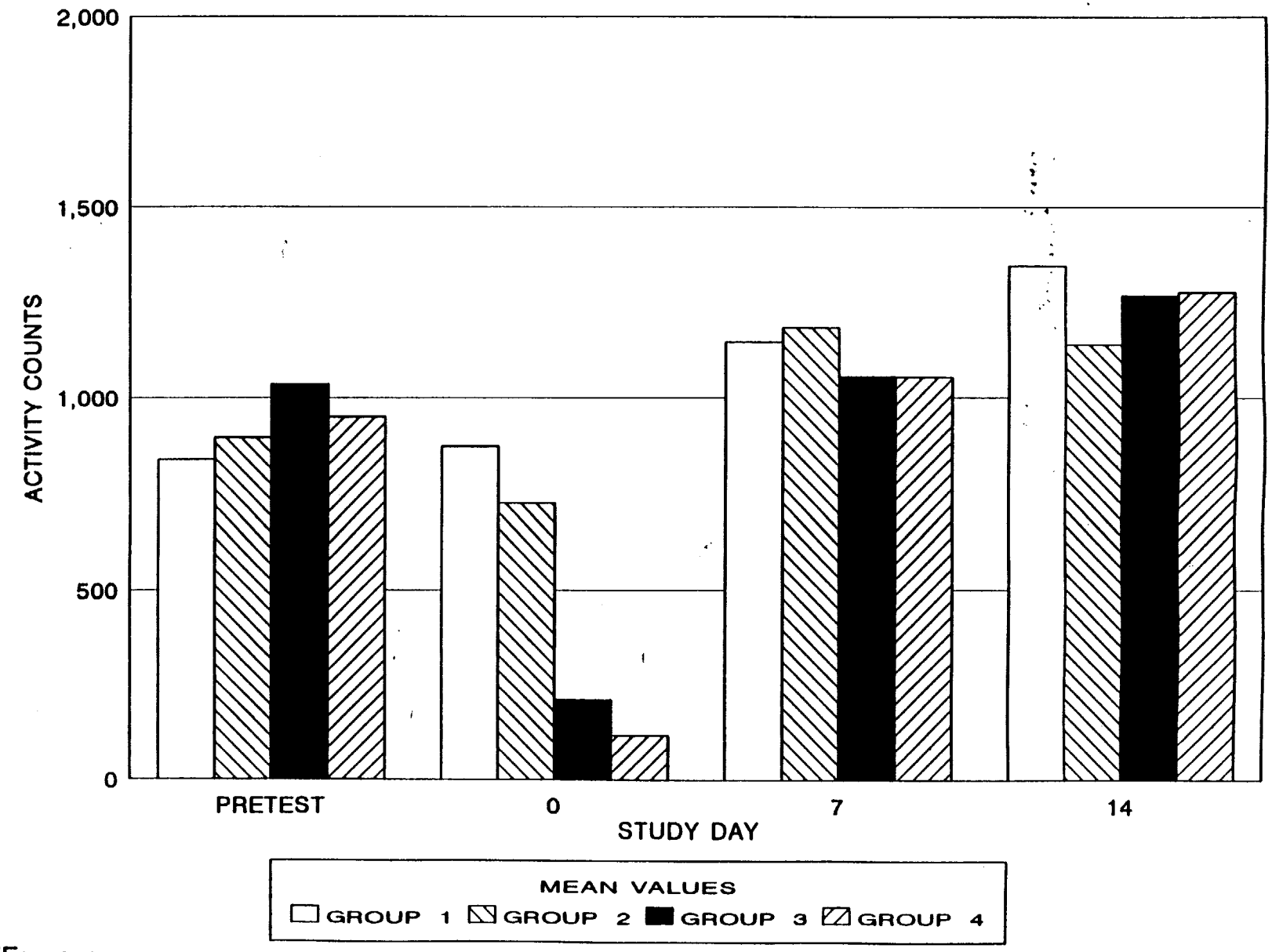
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SEE TEXT FOR EXPLANATION.

FIGURE 6
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
FEMALE



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SEE TEXT FOR EXPLANATION.

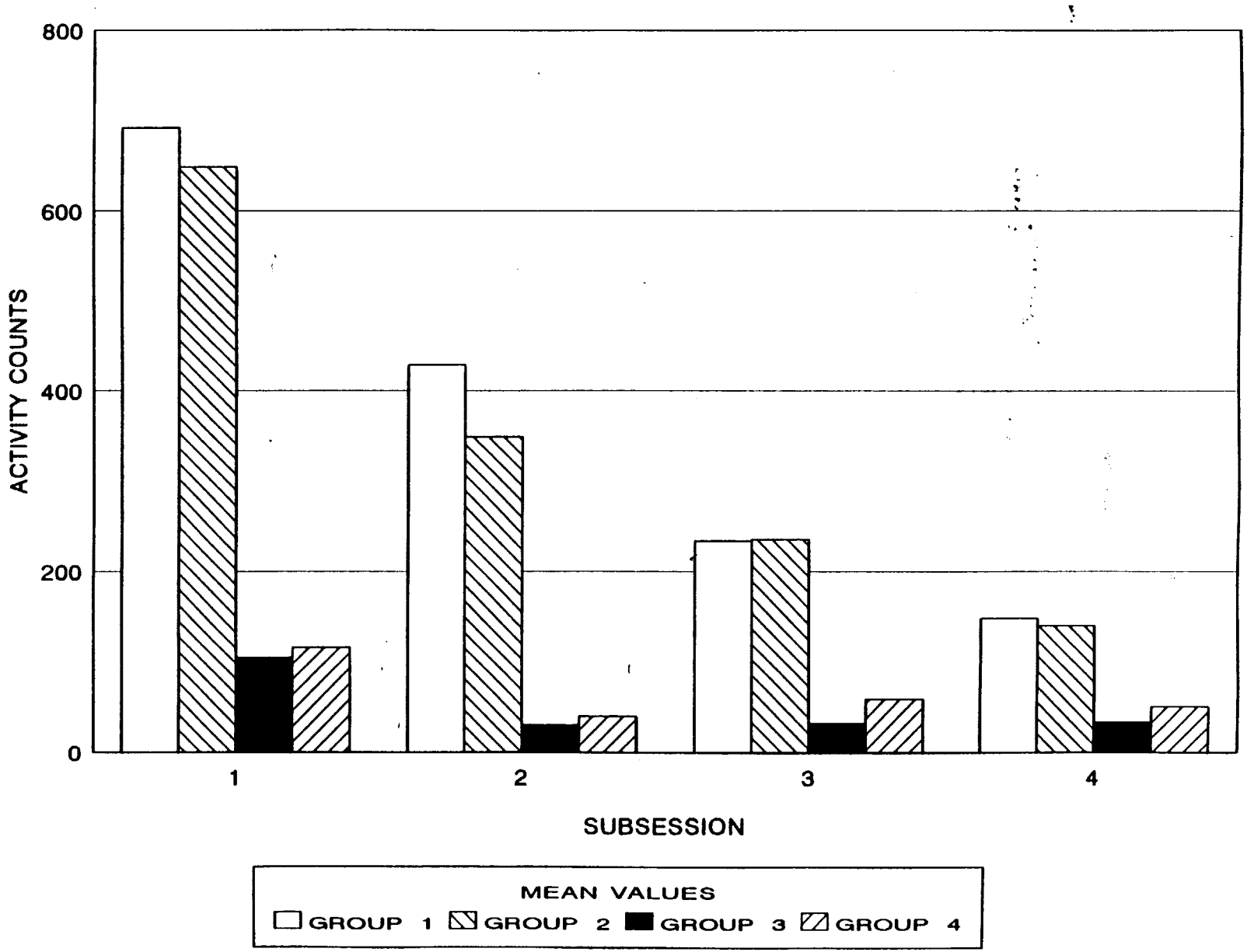
FIGURE 6
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
FEMALE



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SEE TEXT FOR EXPLANATION.

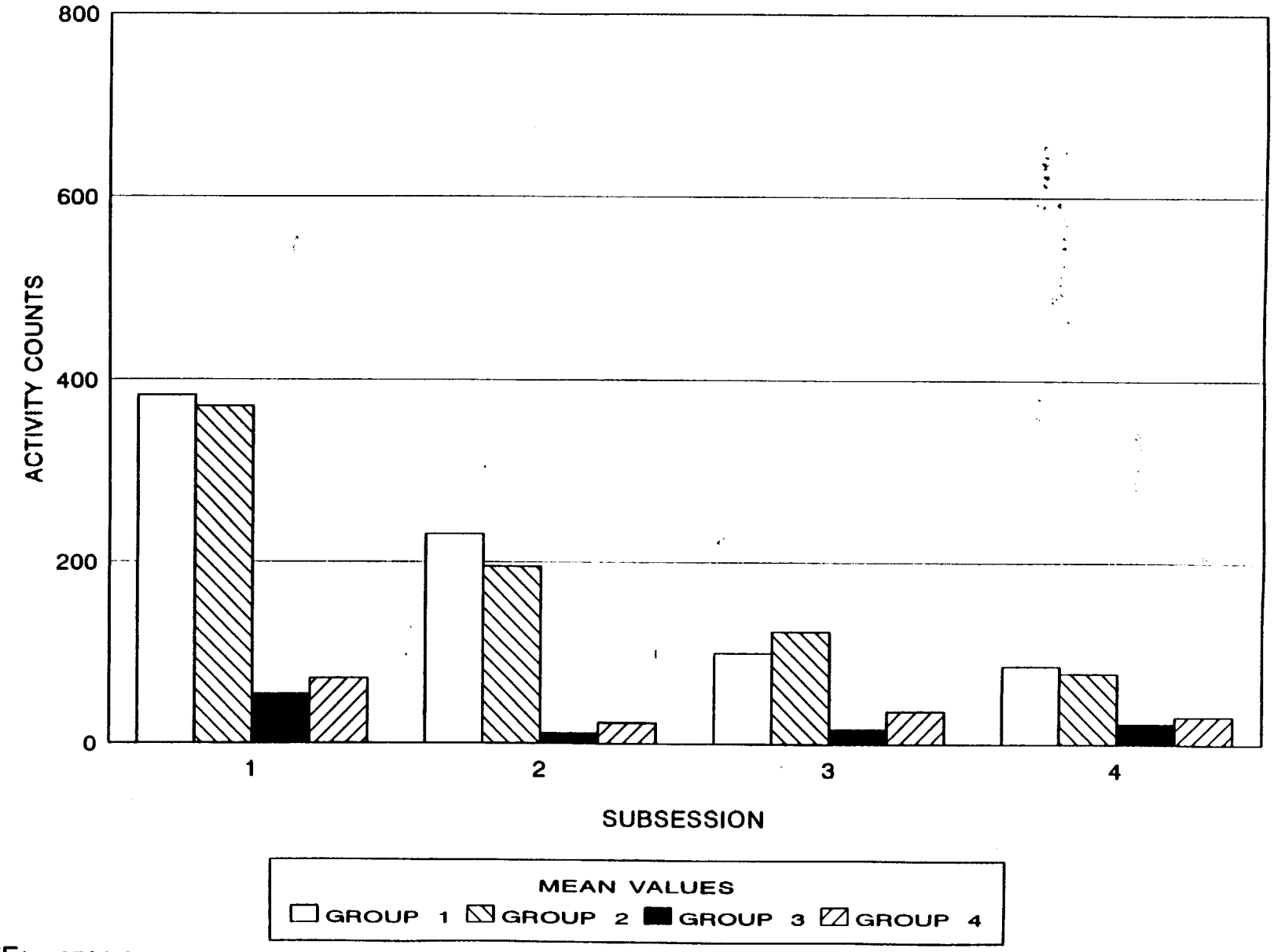
PROJECT NO.: WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 7
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
MALE DAY 0



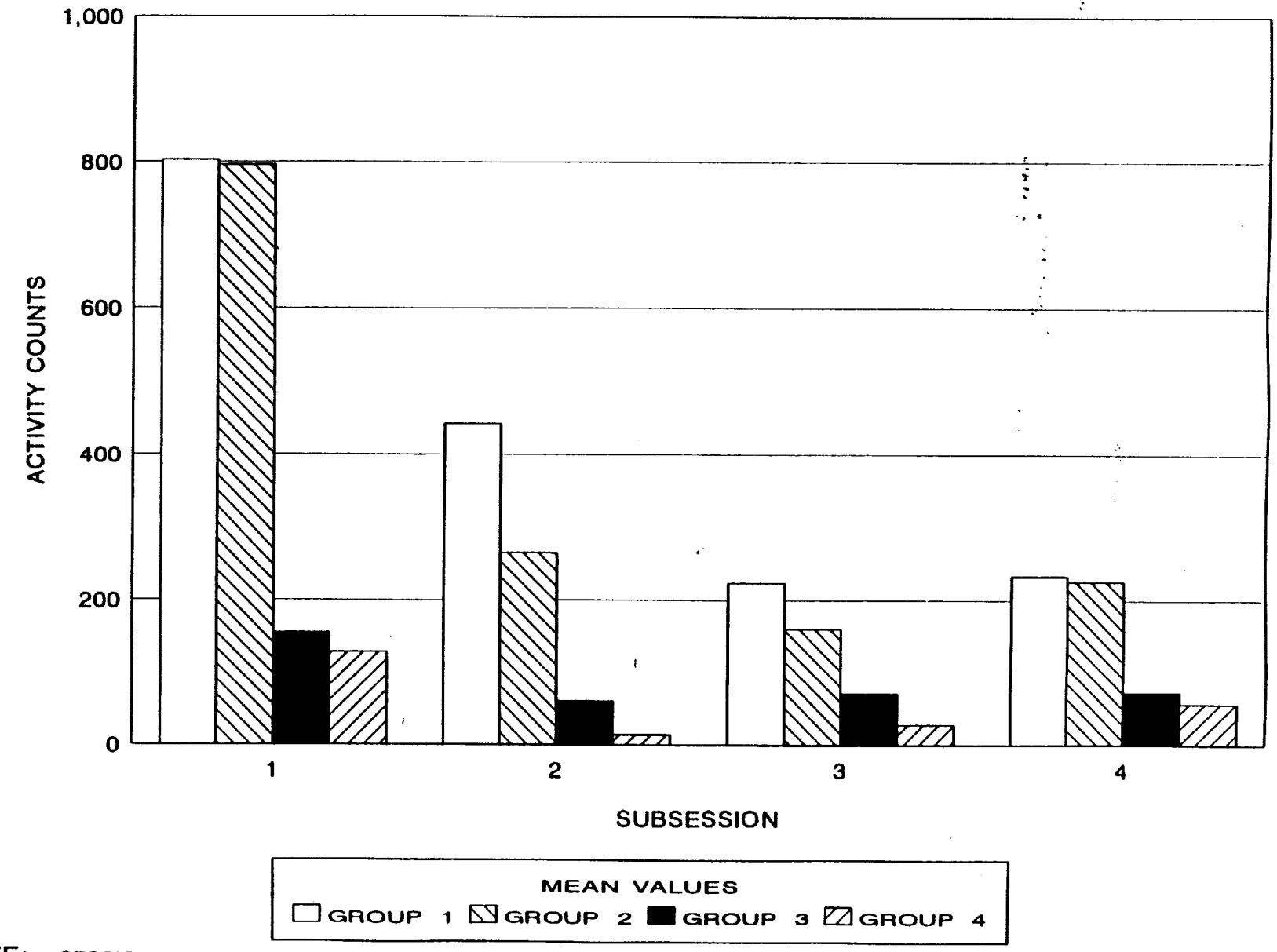
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION.
SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

FIGURE 7
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
MALE DAY 0



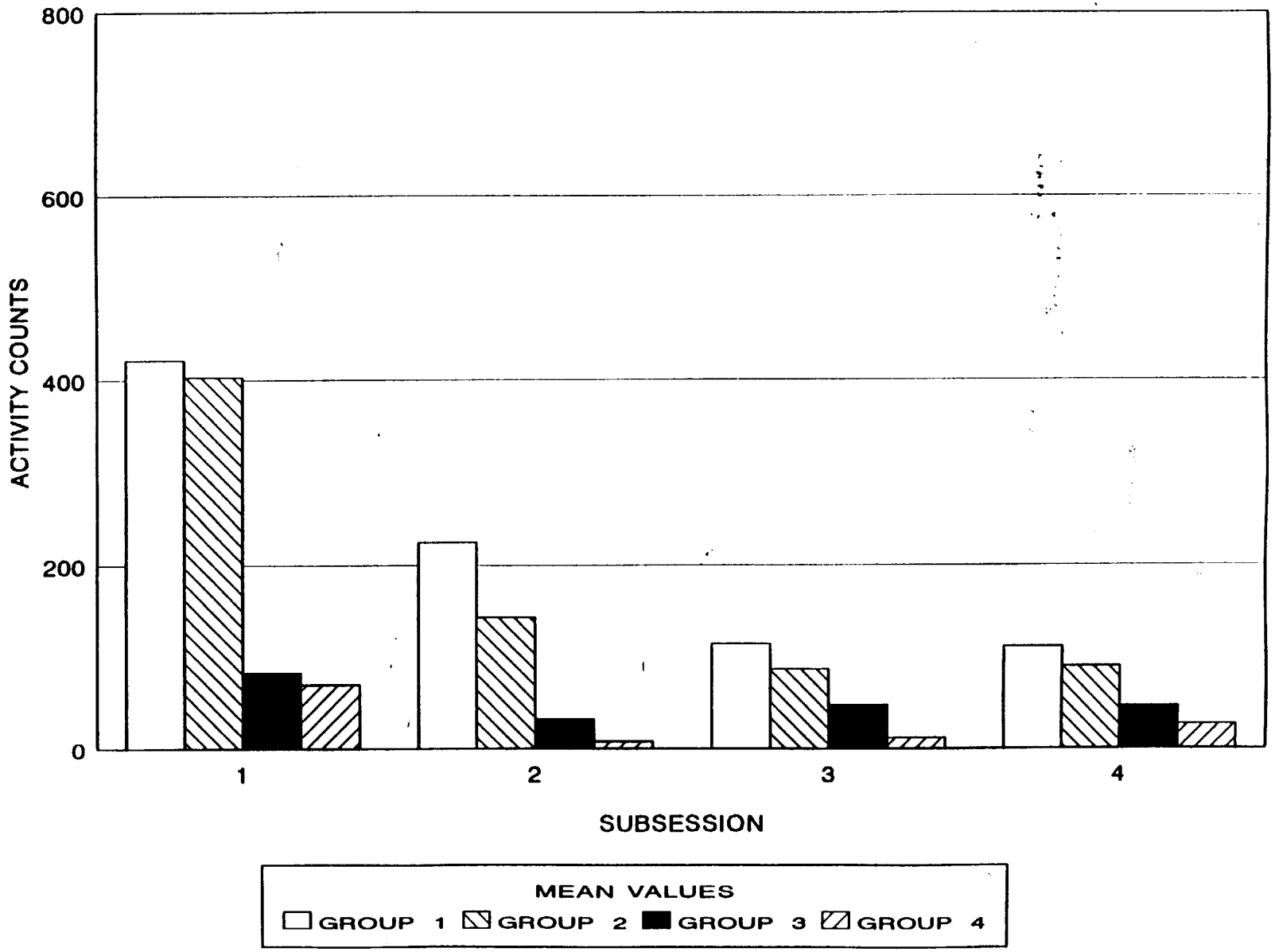
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION.
SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

FIGURE 7
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
FEMALE DAY 0



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION.
SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

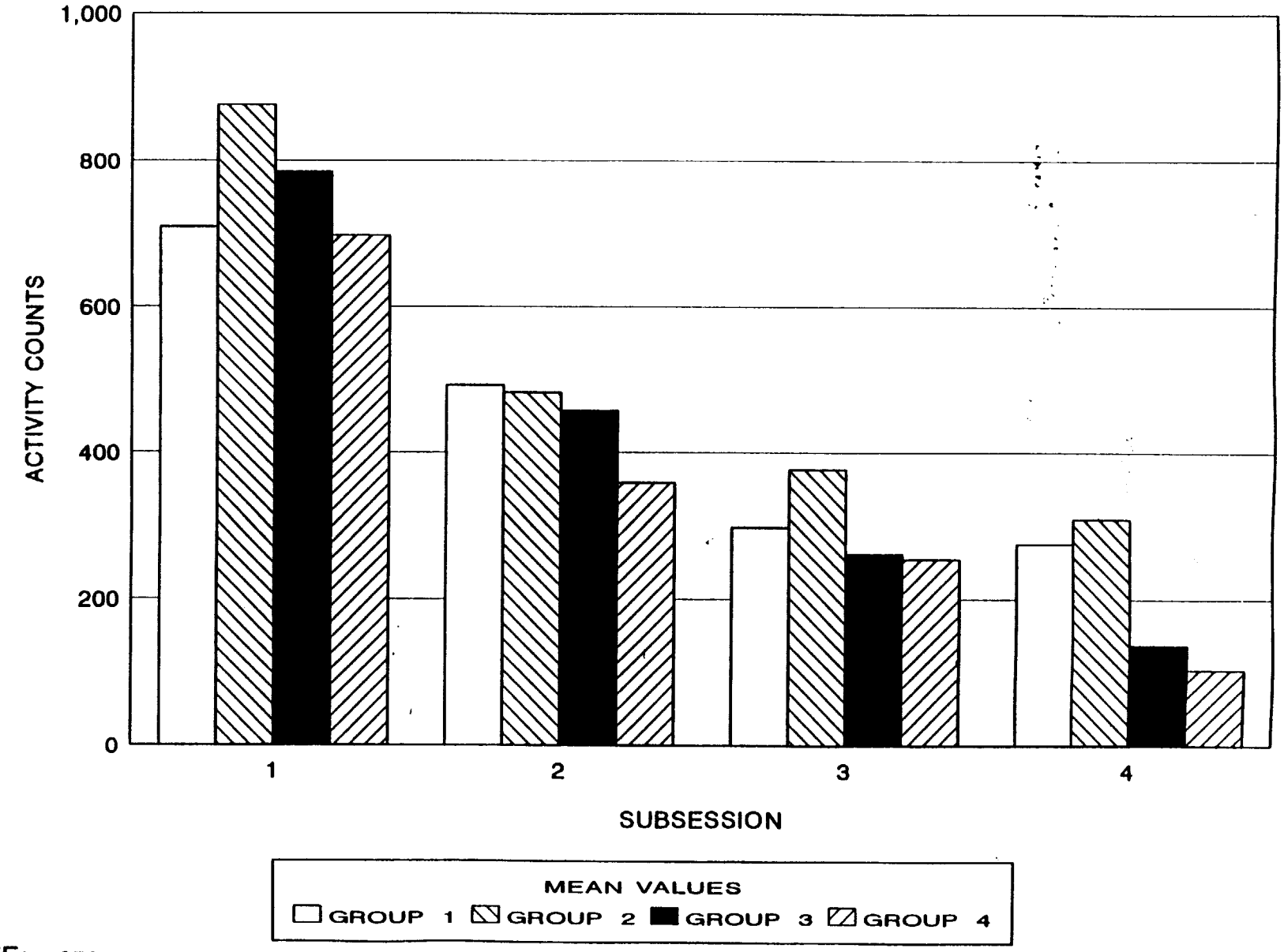
FIGURE 7
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
FEMALE DAY 0



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION.
SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

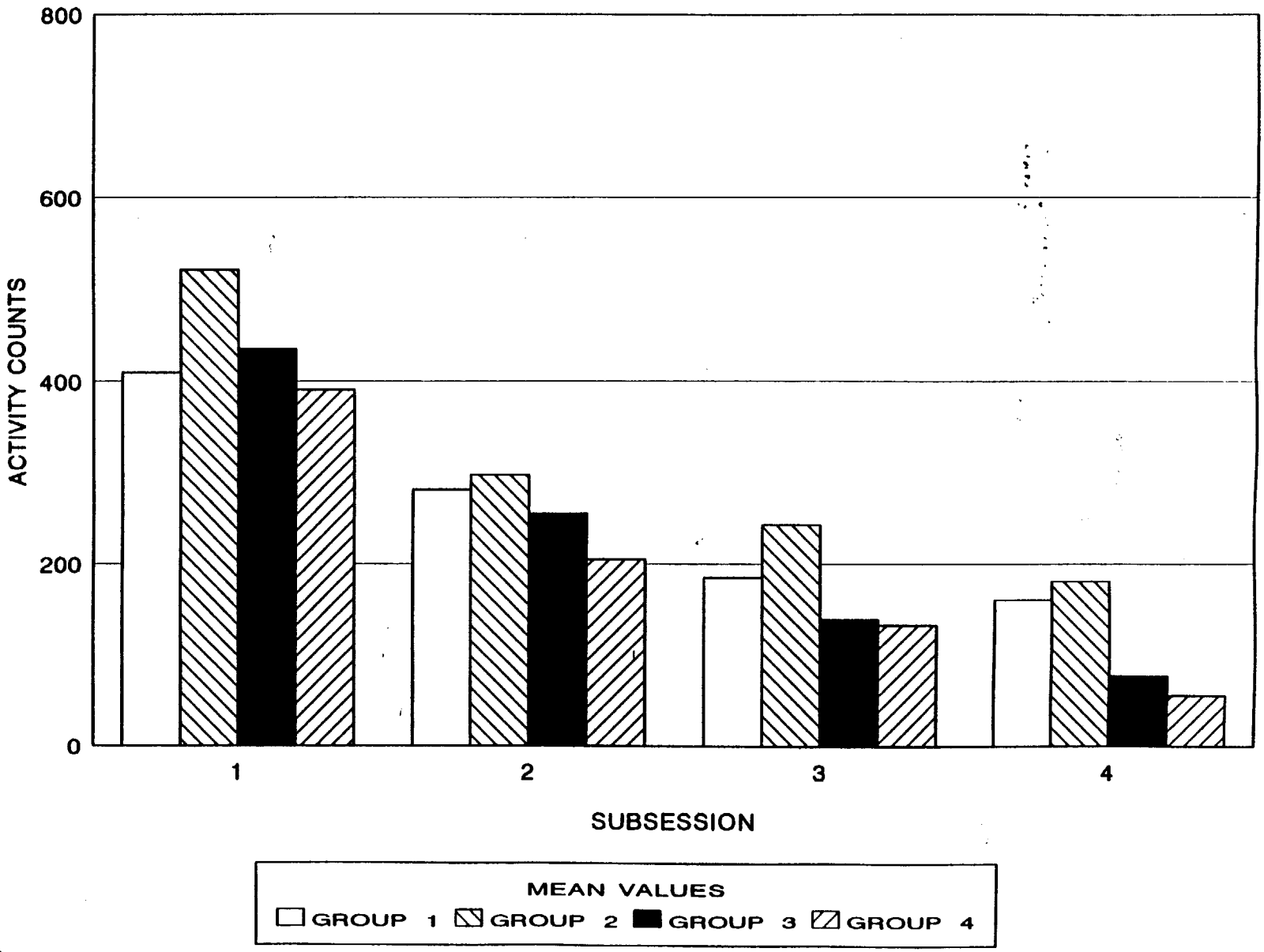
PROJECT NO.: WIL-223001
SPONSOR:ZIRAM TASK FORCE

FIGURE 8
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
MALE DAY 7



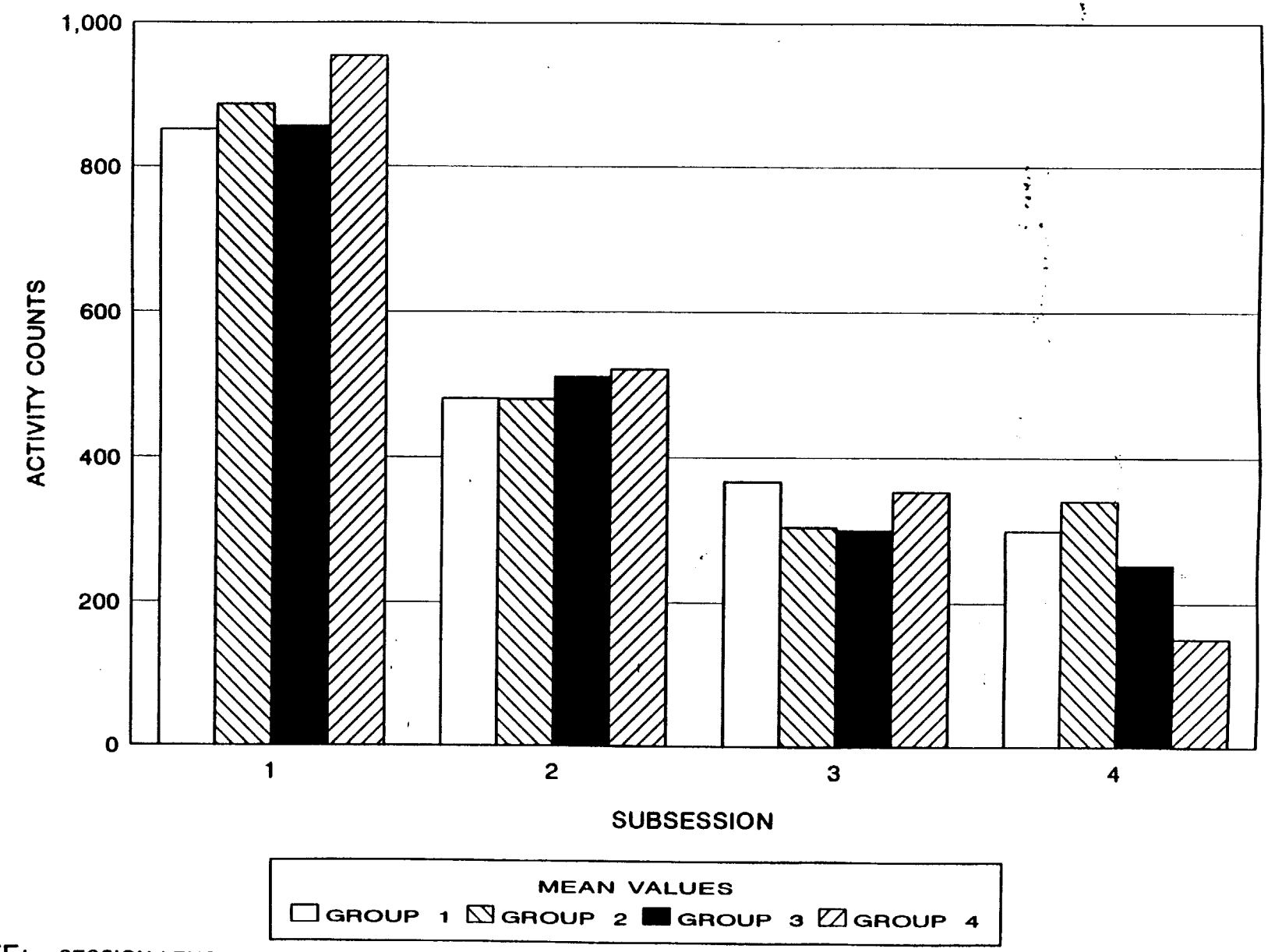
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

FIGURE 8
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
MALE DAY 7



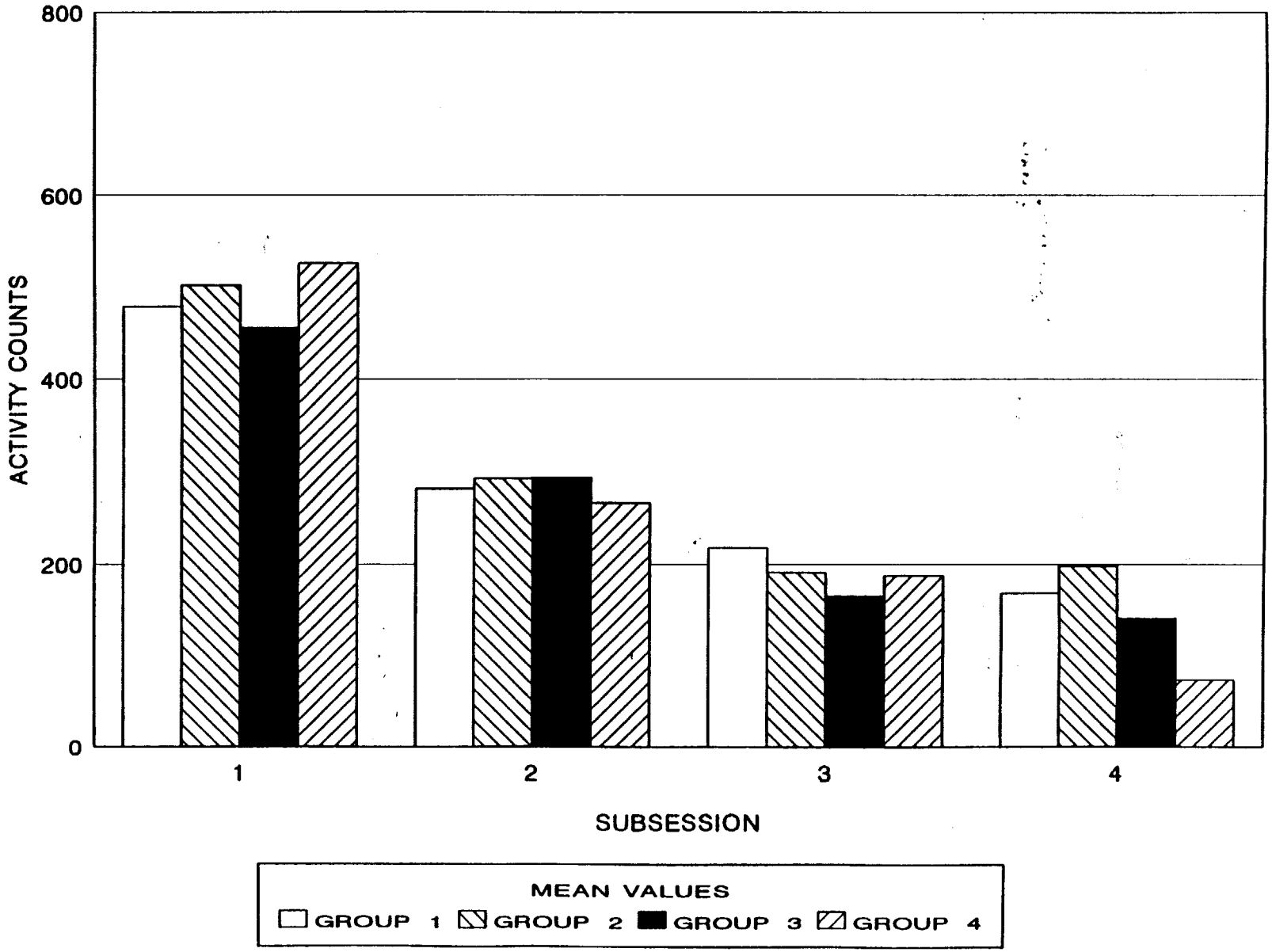
NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

FIGURE 8
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
TOTAL ACTIVITY (COUNTS)
FEMALE DAY 7



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION.
SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

FIGURE 8
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROUP MEAN MOTOR ACTIVITY
AMBULATORY ACTIVITY (COUNTS)
FEMALE DAY 7



NOTE: SESSION LENGTH: 41 MINUTES. SESSION LENGTH TRUNCATED TO 40 MINUTES FOR DATA PRESENTATION. SUBSESSION LENGTH: 10 MINUTES. SEE TEXT FOR EXPLANATION.

TABLE 52 (NON-PERFUSED ANIMALS - UNSCHEDULED DEATHS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROSS NECROPSY OBSERVATIONS INCIDENCE SUMMARY

FOUND DEAD OR EUTHANIZED MORIBUND OR IN EXTREMIS

	MALE				FEMALE			
GROUP:	1	2	3	4	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16	12	12	12	16
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND/IN EXTREMIS	0	0	0	4	0	0	1	7
ADRENAL GLANDS								
-REDDENED	0	0	0	3	0	0	1	3
-DARK RED	0	0	0	0	0	0	0	1
INTESTINE								
-DISTENDED	0	0	0	0	0	0	0	3
-WHITE CONTENTS	0	0	0	0	0	0	0	3
-DARK RED CONTENTS	0	0	0	0	0	0	0	1
KIDNEYS								
-REDDENED CORTICO-MEDULLARY JUNCTION	0	0	0	1	0	0	1	5
LUNGS								
-MOTTLED	0	0	0	0	0	0	0	1
STOMACH								
-DISTENDED	0	0	0	1	0	0	1	3
-WHITE CONTENTS	0	0	0	3	0	0	1	5
-DARK RED CONTENTS	0	0	0	0	0	0	0	1
-DARK RED AREA(S)	0	0	0	0	0	0	0	1
THYMUS GLAND								
-HEMORRHAGIC	0	0	0	1	0	0	0	0
EXTERNAL SURFACE								
-YELLOW MATTING	0	0	0	3	0	0	0	6

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 52 (NON-PERFUSED ANIMALS - UNSCHEDULED DEATHS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
GROSS NECROPSY OBSERVATIONS INCIDENCE SUMMARY

FOUND DEAD OR EUTHANIZED MORIBUND OR IN EXTREMIS

	MALE				FEMALE			
GROUP:	1	2	3	4	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16	12	12	12	16
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND/IN EXTREMIS	0	0	0	4	0	0	1	7
EXTERNAL SURFACE - CONTINUED								
-TAN MATTING	0	0	0	1	0	0	0	3
-RED MATTING	0	0	0	3	0	0	1	7
-BROWN MATTING	0	0	0	0	0	0	1	1
ABDOMINAL CAVITY								
-EMACIATED	0	0	0	0	0	0	0	2

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG

TABLE 53 (PERFUSED ANIMALS)

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SPONSOR:THE ZIRAM TASK FORCE — BRAIN WEIGHTS AND BRAIN MEASUREMENTS - SUMMARY OF MEANS — DAY 15

	----- MALE -----			
GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
BRAIN(G)				
MEAN	1.90	1.83	1.78**	1.77**
S.D.	0.056	0.061	0.054	0.098
N	12	12	12	11
BRAIN LENGTH(MM)				
MEAN	19.9	20.2	20.2	19.9
S.D.	0.51	0.59	0.65	0.24
N	12	12	12	11
BRAIN WIDTH(MM)				
MEAN	14.9	14.9	14.7	14.6
S.D.	0.45	0.43	0.46	0.34
N	12	12	12	11

G = GRAMS, MM = MILLIMETERS

** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING DUNNETT'S TEST

TABLE 53 (PERFUSED ANIMALS)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
BRAIN WEIGHTS AND BRAIN MEASUREMENTS - SUMMARY OF MEANS

	----- F E M A L E -----			
GROUP:	0 MG/KG	15 MG/KG	300 MG/KG	600 MG/KG
BRAIN(G)				
MEAN	1.69	1.67	1.67	1.63
S.D.	0.076	0.066	0.077	0.064
N	12	12	11	9
BRAIN LENGTH(MM)				
MEAN	19.4	19.5	19.6	19.5
S.D.	0.67	0.44	0.38	0.37
N	12	12	11	9
BRAIN WIDTH(MM)				
MEAN	14.4	14.5	14.5	14.5
S.D.	0.37	0.41	0.31	0.13
N	12	12	11	9

G = GRAMS, MM = MILLIMETERS
NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
BRAIN				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-CERV.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-LUMB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
GASSERIAN GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TRIGEMINAL NER.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR ROOT				
TOTAL NUMBER EXAMINED	1	NA	NA	NA
EXAMINED, UNREMARKABLE	0	NA	NA	NA
-DIGESTION CHAMBERS	1	NA	NA	NA

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
LUMBAR DOR. GANG				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	4
-DIGESTION CHAMBERS	0	NA	NA	1
LUMBAR VENT. FIB				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	4	NA	NA	5
-DIGESTION CHAMBERS	1	NA	NA	0
CERV. DOR. GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

PROJECT NO.:WIL-223001
SPONSOR:THE ZIRAM TASK FORCE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
CERV. VENT. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SCIATIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	4	NA	NA	5
-DIGESTION CHAMBERS	1	NA	NA	0
SURAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TIBIAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
PERONEAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
OPTIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- MALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
EYES				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
BRAIN				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-CERV.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SPINAL C.-LUMB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
GASSERIAN GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TRIGEMINAL NER.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR DOR. GANG				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
LUMBAR DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
LUMBAR VENT. FIB				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. GANG.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. DOR. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
CERV. VENT. FIB.				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
SCIATIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE

TABLE 54 (PERFUSED TISSUES)
AN ACUTE NEUROTOXICITY STUDY OF ZIRAM IN RATS
HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

----- FEMALE -----

GROUP:	1	2	3	4
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	16
NUMBER OF ANIMALS EXAMINED DAY 15	5	0	0	5
SURAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
TIBIAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
PERONEAL NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
OPTIC NERVE				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5
EYES				
TOTAL NUMBER EXAMINED	5	NA	NA	5
EXAMINED, UNREMARKABLE	5	NA	NA	5

1- 0 MG/KG 2- 15 MG/KG 3- 300 MG/KG 4- 600 MG/KG
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING THE KOLMOGOROV-SMIRNOV ONE-TAILED TEST.
NA = NOT APPLICABLE