FINAL REPORT

CRUDE MCHM

HAEL No.: 97-0216 **EAN: 972790**
PM No.: 18717-00

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

AUTHORS

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TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

970216G1

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

STUDY COMPLETION DATE

January 6, 1999

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

STUDY: 97-0216-1 STUDY DIRECTOR: BERNARD, L.G. PAGE 1
12/15/98

ACCESSION NUMBER: 972790

STUDY TYPE: DERMAL TOXICITY (REPEATED DOSE)

M. L. James 12/15/98
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT. WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES.

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
04/09/98	PROTOCOL SUBMISSION 2-WEEK STUDY 2-WEEK REPEATED DOSE	
04/14/98	PROTOCOL AMENDMENT OF 4/13/98 RECEIVED FOR 2-WK DERMAL TOXICITY STUDY	
04/16/98	TEST SUBSTANCE APPLICATION TO TEST SYSTEM CONTROL SUBSTANCE APPLICATION TO TEST SYSTEM DAY 4	04/16/98
04/30/98	NECROPSY SPECIMEN/SAMPLE WEIGHT SPECIMEN COLLECTION INSTRUMENT TESTING INSPECTION HEMATOLOGY PROTOCOL AMENDMENT OF 4/30/98 RECEIVED BONE MARROW COLLECTION AND SLIDE PREPARATION	04/30/98
06/18/98	PATHOLOGY REPORT	06/18/98
06/19/98	RECORDS REVIEW FOR BLOOD ANALYSIS	06/19/98
07/31/98	FINAL REPORT REVIEW 2-WEEK STUDY	08/03/98
08/03/98	FINAL REPORT REVIEW 2-WEEK REPEATED DOSE STUDY	08/03/98
12/15/98	FINAL REPORT REVIEW	12/15/98

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted according to:

United States Environmental Protection Agency, Toxic Substances Control Act, Good Laboratory Practice Standards, 40 CFR Part 792;

Annex 2, Organisation for Economic Cooperation and Development, Guidelines for Testing of Chemicals [C(81)30(Final)].

Lisa Gayle Bernard

Lisa G. Bernard, M.S.
Study Director

January 6, 1999
Month/Day/Year

Karen R. Miller

Karen R. Miller, Ph.D.
Sponsor's Representative

12/22/98
Month/Day/Year

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ABSTRACT

CRUDE MCHM

HAEL No.: 97-0216 EAN: 972790
PM No.: 18717-00

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

Groups of five male and five female Sprague-Dawley rats were treated topically with 2000, 500, 100, or 0 mg/kg of the test substance 6 hours per day for 13 consecutive weekdays. The test substance, a clear liquid, was administered as received under a semi-occlusive wrap. Elizabethan collars were placed around each animal's neck immediately after removal of the test substance and the associated wrapping material. The collars were removed the following morning. No mortality was observed. Animals were observed daily for clinical signs of toxicity. Test substance-related clinical abnormalities were limited to erythema, desquamation, and crust/scale formation at the test substance application site with minimal to moderate severities for the high-dose group and minimal to minor severities for the mid- and low-dose groups. Body weights and feed consumption were measured at least weekly. Mean body weights and mean feed consumption were comparable among the groups. On Day 13, all animals were placed in metabolism cages for the collection of urine. No blood was detected in the urine, and urine sediment was unremarkable. At study termination, animals were anesthetized with carbon dioxide, and blood was obtained from the posterior vena cava for clinical chemistry and hematology analyses. Fasted body weight and liver, kidney and spleen weights were measured at necropsy. The mean serum phosphorus level was lower ($p \leq 0.05$) for the high-dose male group, and the mean serum triglyceride level was higher ($p \leq 0.05$) for the high-dose female group when compared with the control group. There were no other differences in hematology or clinical chemistry parameters between treated and control groups. Mean relative (to body weight) liver weights were elevated ($p \leq 0.05$) for the high-dose female group when compared with the control group. The mean terminal body weights and all other organ weights for male and female rats were comparable among the groups. The liver, kidneys, spleen, sternum (with bone marrow), and gross lesions were collected in 10% formalin. All tissues collected, except gross lesions of the skin, from the high-dose and control groups were examined microscopically. In addition, all gross lesions, except skin, were examined microscopically for the mid- and low-dose groups. Test substance-related lesions observed at the time of necropsy were limited to erythema and desquamation of the skin at the application site for the high-dose group and desquamation of the skin at the application site for the mid- and low-dose groups. All other lesions were considered incidental to exposure to the test substance. No treatment-related microscopic changes were observed.

Based on the dermal irritation observed at all treatment levels, a no-observed-effect level (NOEL) was not determined. However, based on the absence of significant histopathologic and serum clinical chemistry changes, 2000 mg/kg was considered to be the no-observed-adverse-effect level (NOAEL) for systemic toxicity.

STUDY AND TEST SUBSTANCE INFORMATION

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

Project Participants

Study Director:	Lisa G. Bernard, M.S.
Study Technician:	Stephen D. Jessup, A.A.S.
Hematologist/Clinical Chemist:	Robert E. Emmons, B.S.
Histopathologist:	Robert H. Garman, D.V.M., DACVP, Consultants in Veterinary Pathology
Report Authors:	Stephen D. Jessup, A.A.S. Lisa G. Bernard, M.S.

Sponsor

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

Authorized Representative:	Karen R. Miller, Ph.D.

Test Substance Characterization

Test Substance Name:	Crude MCHM
HAEL No.:	97-0216
EAN:	972790
PM No.:	18717-00
SRID No.:	6-97
Physical State and Appearance:	Liquid, clear and colorless
Source of Test Substance:	Eastman Chemical Company, Kingsport, TN
Laboratory Project ID:	970216G1

ly Dates

ly Initiation Date:	April 2, 1998
erimental Start Date:	April 13, 1998
erimental Completion Date:	December 12, 1998

PURPOSE

e purpose of this study was to evaluate the toxicity of the test substance when repeatedly plied to the skin of rats for approximately two weeks.

MATERIALS AND METHODS

est system

ive male and five female Sprague-Dawley rats (CD(SD)BR/VAF Plus) obtained from Charles iver Laboratories, Raleigh, NC were randomly assigned to each group. The male and female ats were 58 or 78 days of age and weighed 276 ± 11 or 233 ± 8 grams (mean ± SD), espectively, at the start of the study. Rats were chosen for this study because they are a common epresentative species for toxicity studies. The rat is one of the two primary rodent species ecommended for use in USEPA and OECD test guidelines.

Husbandry

Housing

Animals were housed in an American Association for Accreditation of Laboratory Animal Care-accredited vivarium in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). The rats were singly housed in suspended, stainless-steel mesh cages. A group of rats assigned to a training study, in which no test substance was used, was housed in the same room as this study. Cages and racks were washed once a week. Absorbent paper, used to collect excreta, was changed daily.

Environmental Conditions

The study room was maintained at 20 - 25°C and 39 - 53% relative humidity. A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained.

Husbandry, continued

Acclimation Period

The animals were isolated upon arrival and allowed to acclimate for a period of five days prior to assignment to this study. Animals were judged to be healthy prior to testing.

Feed

Certified Rodent Diet (Purina Rodent Chow #5002, ground chow) was available *ad libitum*. Feed containers were cleaned and refilled at least once a week. No known contaminants which would interfere with the outcome of this study were present in the feed. Analyses of feed are maintained on file within the testing laboratory.

Water

Water was available *ad libitum* through an automatic watering system. The source of the water was the local public water system. There have been no contaminants identified in periodic water analyses that would be expected to interfere with the conduct of the study. Semiannual analyses of water are maintained on file within the testing laboratory.

Identification

Upon arrival, all rats were identified by uniquely-numbered metal ear tags. During randomization, study-specific animal numbers were assigned to each animal. Cage cards, color-coded for each group, contained the study-specific animal number and the ear tag number.

Experimental Design

Randomization

The test animals were culled from the stock population based on body weight and were randomly assigned to groups using computer-generated lists. The body weights of individual animals in the culled population did not vary more than 20% from the mean for each sex. Following randomization, the body weights of all groups were compared by analysis of variance to insure that there were no statistically significant differences prior to initiation of exposure.

Test Guideline

There are no guidelines for a two-week dermal toxicity study.

Experimental Design, continued

Determination of Dose Levels

Dose levels were selected by the Sponsor based on the results of an acute dermal toxicity study.

Test Substance Exposure

Prior to the first application, the hair was removed from the back of each animal with an electric clipper. Rats were treated topically with doses of 2000, 500, 100, or 0 mg/kg of the test substance 6 hours each day for thirteen consecutive weekdays. The test substance was administered as received and was applied directly to the skin. A patch approximately 5 cm square was then placed on the exposure site of each animal and secured using a semi-occlusive elastic wrap. Control animals received volumes of distilled water equivalent to volumes administered to the 2000 mg/kg group. Approximately 6 hours after initiation of exposure, the wraps and patches were removed and any residual test substance was gently wiped away with gauze pads moistened with physiological saline. Immediately after removal of the test substance, an Elizabethan collar was placed around each animal's neck to restrict the ability to groom the area; the collar was removed the following morning.

Disposition of Groups

Animals were distributed into groups as follows:

Group	Dose Level	Number of Animals	Animal Numbers	
			Males	Females
1	Control / 0 mg/kg	5 Males & 5 Females	451 - 455	471 - 475
2	Low / 100 mg/kg	5 Males & 5 Females	456 - 460	476 - 480
3	Mid / 500 mg/kg	5 Males & 5 Females	461 - 465	481 - 485
4	High / 2000 mg/kg	5 Males & 5 Females	466 - 470	486 - 490

Animals were exposed to the test substance six hours per day for 13 consecutive weekdays. The first day the animals were exposed to the test substance was designated as Day 0. All animals were necropsied on Day 17.

Experimental Design, continued

Clinical Observations

Clinical examinations (hands on) were conducted immediately after termination of each exposure and on weekend mornings. Each weekday morning, animals were observed for moribundity and mortality. On weekends, afternoon observations were not performed. Clinical observations included, but were not limited to, examination of the hair, skin, eyes, mucous membranes, motor activity, feces, urine, respiratory system, circulatory system, autonomic nervous system, central nervous system, and behavior patterns.

Body Weight and Feed Consumption

Body weights were measured on Days 0, 4, 7, and 14. Feed consumption was determined on Days 4, 7, and 14. Animals were fasted the day prior to necropsy. Terminal body weights were measured after exsanguination, but prior to necropsy.

Urinalysis

On Day 13, all animals were placed in metabolism cages for approximately 24 hours for urine collection on Day 14. Water and feed were available *ad libitum* during the collection period. The urine was tested for the presence of blood using N-Multistix Reagent Strips for Urinalysis. Microscopic examination was conducted on urinary sediment for the presence of red blood cells, white blood cells, epithelial cells, triple phosphate crystals, amorphous sediment, sperm, and bacteria.

Blood Collection and Euthanasia

Animals were fasted overnight beginning in the afternoon of the last day of treatment. The following day, animals were anesthetized with carbon dioxide and blood was collected from the posterior vena cava. The blood was placed in vacutainer tubes and allowed to clot for serum analysis. Other tubes containing an anticoagulant were used for analyses of whole blood samples. Blood smears were also prepared for blood cell counts. Following blood collection, the animals were exsanguinated. Animals were bled and humanely killed in a random order based on a computer-generated list.

Experimental Design, continued

Hematology and Clinical Chemistry Examinations

Clinical pathology assays were conducted using the following instruments: Roche Analytical Instruments Cobas Fara II serum chemistry analyzer, Technicon H•1 System hematology analyzer, Helena Laboratories Titan Gel Electrophoresis System (A/G ratio and albumin), BBL Fibrosystems analyzer (prothrombin times), and Corning Flame 480 Photometer (sodium and potassium). Hematology tests included: hemoglobin concentration, hematocrit, red blood cell count, white blood cell count, red blood cell indices, prothrombin time and platelet count. Slides containing blood smears were examined for cellular morphology and differential white blood cell counts. Clinical chemistry tests included: alanine aminotransferase, sorbitol dehydrogenase, creatinine, urea nitrogen, glucose, total bilirubin, total protein, albumin, albumin/globulin ratio, total cholesterol, triglycerides, calcium, phosphorus, sodium and potassium.

Necropsy

Following exsanguination, the animals were weighed and necropsied. The following tissues were fixed in 10% neutral buffered formalin: liver, kidneys, spleen, sternum (with bone marrow), and gross lesions.

The femurs from each animal were removed, the adhering muscle and connective tissue was removed, and the femurs were placed in small, sealed plastic tubes containing 5 mL of fetal bovine serum (FBS).

Organ Weights

The liver, kidneys, and spleen were weighed. Paired organs were weighed together.

Histopathology

For the control and high-dose groups, the liver, kidneys, spleen, sternum (with bone marrow), and gross lesions, except skin, were embedded in paraffin and sectioned at 5 μm. The sternum was decalcified prior to being embedded and sectioned. The resulting tissue sections were stained with hematoxylin and eosin (H&E) stains and examined for histopathology. All gross lesions, except skin, from the low-and mid-dose groups were also examined microscopically.

Experimental Design, continued

Bone Marrow Slide Preparation

Both ends of each femur were opened and the marrow was flushed into a small (15 mL) centrifuge tube using a syringe and needle filled with FBS. The marrow from both femurs of one animal was collected into one tube. Following centrifugation at approximately 270 x g, the supernatant serum fraction was poured off and portions of the resuspended bone marrow cell pellet prepared as blood films on four separate slides. The slides were then air dried, and briefly fixed in methanol. For each animal, one slide was stained with Wright-Giemsa stain; the other three slides were not stained. All slides were held for possible examination in the future.

Data Storage

The final report, data sheets, all nonperishable raw data, and an aliquot of the test substance have been stored in the testing facility archive managed under GLP-mandated conditions.

Calculations and Statistical Procedures

For body weight, feed consumption, serum chemistries, hematology values, organ weights, and organ-to-body weight ratios, mean values were calculated, homogeneity of data were evaluated using Bartlett's test ($p \leq 0.001$), and the data were evaluated using a one-way analysis of variance (ANOVA) ($p \leq 0.05$) and Duncan's multiple range test ($p \leq 0.05$).

Protocol and Standard Operating Procedure Deviations

On Day 0, animal #474 (ear tag # M4659) was dehydrated. Therefore, this animal was replaced by M4661 and its back was shaved on the Day of the first application instead of the day prior to the first application. During the afternoon on Day 0, the animals were transferred to a different room. The humidity level was not recorded for the new housing room on Day 0. On Day 11, moderate erythema was observed for Rat 488. Therefore, the application site for this animal should have been changed from the back to the left flank. However, at the next test substance application (Day 14) the application site for Rat 486, rather than for Rat 488, was changed to the left flank. These deviations did not affect the outcome of the study.

In consultation with the Sponsor, it was decided that gross lesions observed in the skin would not be examined microscopically. This deviation did not affect the outcome of the study, since the study was conducted to evaluate the toxicity of the test substance and not the irritant nature of the test substance to the skin.

There were no SOP deviations and no other protocol deviations.

RESULTS

Mortality

There was no mortality observed during this study.

Clinical Observations

Clinical observations are summarized on pages 20 - 22 (males) and 23 - 26 (females). Individual animal data are presented in Appendix A.

Erythema, desquamation, and eschar formation were observed at the application site for animals in all treatment groups. For the high-dose group, moderate erythema was observed for two female rats and minimal to minor erythema was observed for the other rats. Moderate desquamation was noted for four female rats and minimal to minor desquamation was noted for four male and the other female high-dose rats. Moderate eschar formation was noted for one female high-dose rat and minimal to minor eschar formation was noted for two male and the other female high-dose rats. For the mid-dose group, minimal to minor erythema was observed for all male and female rats. Minimal to minor desquamation was evident for two male and all female mid-dose rats. Single incidences of minimal eschar formation were noted for two female mid-dose rats. For the low-dose group, minimal to minor erythema was observed for three male and three female rats. Minimal to minor desquamation was evident for all female low-dose rats. Single incidences of minimal eschar formation were noted for three female low-dose rats.

Porphyrin discharges from the eyes and/or nose were observed for animals from all groups throughout the study; these discharges were attributed to the inability of the animals to groom while wearing the Elizabethan collars. Enlargement of the neck and/or head was observed for five control, one low-dose, and one mid-dose male or female rats. These swellings were attributed to the rats' attempts to remove the Elizabethan collars and, in general, the swellings resolved within 24 hours.

Incidental clinical abnormalities included hair which was wet or stained with urine for two control, two mid-dose, and four high-dose female rats. Dehydration was observed for one male and two female high-dose rats; for the male rat, the dehydration was determined to have been caused by a malfunction in the watering system. A single incidence of hematuria and discolored (green) urine was observed for one high-dose female on Day 2. A minor wound, caused by removal of the tape used during the test substance exposure, was observed for one high-dose female rat on Day 4.

Body Weight and Feed Consumption

Mean feed consumption data are presented in graph and tabular forms on page 27 - 28 (males) and 29 - 30 (females). Mean body weights are presented in graph and tabular forms on pages 31 - 32 (males) and 33 - 34 (females). Individual animal data are presented in Appendix A.

There were no significant differences found in mean feed consumption or mean body weights among any of the groups. Body weight loss or small amounts of body weight gain were noted, primarily, between Days 0 - 4 for male and female rats from all groups; this effect was attributed to the use of Elizabethan collars.

Urinalysis

Urinalysis results are summarized on pages 35 - 36. Individual animal data are presented in Appendix A.

No treatment-related changes were detected in urinalysis. When the urine was tested for the presence of blood, a moderate amount was present for one control and two low-dose male rats, a small amount was present for one mid-dose male rat, and a trace amount of non-hemolyzed blood was detected for one mid-dose female rat. The results of microscopic examination of urine sediment for the treated groups were comparable with those of the control groups.

Hematology

Mean hematology values and analysis of blood cell morphology are presented in summary tables on pages 37 - 39. Individual animal data are presented in Appendix A.

All hematologic parameters for male and female rats from all treated groups were comparable with the control groups. A number of abnormalities, primarily of minimal severity, were observed in red blood morphology of the peripheral blood smears from animals at all dose levels, including the controls. There appeared to be a slight increase in abnormal cells types for the high-dose male and high- and mid-dose female groups; however, there was no consistent effect in any particular cell type.

Clinical Chemistry

Serum clinical chemistry data are presented as means and standard deviations are presented on pages 40 - 41. Individual animal data are presented in Appendix A.

The mean serum phosphorus level was lower ($p \leq 0.05$) for the high-dose male group, and the mean serum triglyceride level was higher ($p \leq 0.05$) for the high-dose female group when compared with the control group. In addition, trace to moderate levels of red blood cell hemolysis were observed in the serum. For male groups, slight hemolysis was observed for 1/5 mid-dose and 1/5 control rats. For female groups, moderate, slight, and trace levels of hemolysis were each observed for 1/5 high-dose rats, trace levels of hemolysis were observed for 1/5 mid-dose rats, and slight hemolysis was observed for 1/5 low-dose rats. All other clinical chemistry parameters for treated groups were comparable with the control groups.

Organ Weights

Means and standard deviations of selected organ weights and organ-to-body weight ratios are presented on page 42. Individual animal data are listed in Appendix A.

Mean relative (to body weight) liver weights were elevated ($p \leq 0.05$) for the high-dose female group when compared with the control group. The mean terminal body weights and all other absolute and relative (to body weight) organ weights for male and female rats were comparable among the groups.

Gross Pathology

Treatment-related lesions observed at the time of necropsy were limited to the skin at the application site. For the high-dose group, lesions consisted of erythema (2/5 female rats) and desquamation (2/5 male and 5/5 female rats). For the mid-dose group, lesions consisted of desquamation (2/5 female rats). For the low-dose group, lesions consisted of desquamation (4/5 female rats). All other lesions were considered incidental to exposure to the test substance.

Histopathology

No treatment-related microscopic changes were observed. A slight increase in the severity of hepatocellular cytoplasmic vacuolation for the high-dose female rats when compared with the control rats (mild versus minimal) was not considered biologically significant or indicative of hepatocyte toxicity by the pathologist. See the pathologist's report beginning on page 43 for details of the gross and histopathology examinations.

DISCUSSION

Animals were topically treated with 2000, 500, 100, or 0 mg/kg of the neat test substance for six hours/day on thirteen consecutive weekdays. No mortality or test substance-related changes in body weight or feed consumption were observed during the study. In addition, examination of the urine for blood and microscopic examination of urine sediment revealed no test substance-related changes.

Test substance-related clinical abnormalities were restricted to erythema, desquamation, and crust/scale formation at the sites of test substance application, and gross lesions observed at necropsy were restricted to erythema and desquamation at the sites of test substance application.

An increased incidence in frequency of abnormalities observed in red blood cell morphology was not considered biologically significant because the abnormalities were primarily of minimal severity and were not associated with any particular cell type. Red blood cell hemolysis observed in the serum for animals from all groups was considered an artifact of the bleeding procedure because a treatment-related effect was not observed during urinalysis for blood, and there was no adverse effect on hematologic parameters (red blood cell count, hemoglobin concentration, or hematocrit), or the spleen (weight change or histopathology). The mean serum phosphorus level was lower for the high-dose male group, and the mean serum triglyceride level was higher for the high-dose female group when compared with the control group. These slight serum chemistry changes, which were observed in only one sex, were not considered toxicologically significant.

A slight elevation in mean relative, but not absolute, liver weight and a slight increase in the severity of hepatocellular cytoplasmic vacuolation (mild versus minimal) were observed for the high-dose female group when compared with the control group. The slight elevation in relative liver weight was primarily due to a slightly, but not significantly, lower mean body weight for the high-dose group. Since the liver weight change and cytoplasmic vacuolation were slight, and serum analytes associated with liver function were comparable among the groups, these changes were not considered toxicologically significant.

CONCLUSION

Based on the dermal irritation observed at all treatment levels, a no-observed-effect level (NOEL) was not determined. However, based on the absence of significant histopathologic and serum clinical chemistry changes, 2000 mg/kg was considered to be the no-observed-adverse-effect level (NOAEL) for systemic toxicity.

REFERENCES

National Research Council (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press. Washington, D.C.

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	2	10.	1.	451,453
NOSE				
DRIED PORPHYRIN DISCHARGE	5	5.	0.	451-455
EYES				
DRIED PORPHYRIN DISCHARGE	3	5.	0.	451-453
NECK				
ENLARGED,NOS	1	12.	0.	455
GROUP 2 - 100 MG/KG				
* NORMAL	1			458
ELIZABETHAN COLLAR FOUND OFF	2	1.	0.	457,460
NOSE				
DRIED PORPHYRIN DISCHARGE	3	5.	0.	456,459-460
EYES				
DRIED PORPHYRIN DISCHARGE	2	5.	0.	456-457
NECK				
ENLARGED,NOS	1	12.	0.	460
GROUP 3 - 500 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	4	7.	6.	461-464
NOSE				
DRIED PORPHYRIN DISCHARGE	5	6.	3.	461-465
EYES				
DRIED PORPHYRIN DISCHARGE	2	5.	0.	462,465
SKIN OF BACK				
ERYTHEMA	2	11.	8.	462,464
DESQUAMATION	1	12.	0.	463

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 4 - 2000 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	2	16.	1.	467-468
NOSE				
DRIED PORPHYRIN DISCHARGE	4	5.	0.	466-467,469-470
EYES				
DRIED PORPHYRIN DISCHARGE	3	5.	0.	466-467,469
SKIN OF BACK				
CRUST/SCALE ON SKIN	2	5.	0.	467,470
ERYTHEMA	5	11.	6.	466-470
DESQUAMATION	4	12.	0.	466-468,470
SKIN OF FLANK				
ERYTHEMA	1	17.	0.	468
DESQUAMATION	1	17.	0.	468

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0 MG/KG				
* NORMAL	2			452,455
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	451-455
EYES				
DRIED PORPHYRIN DISCHARGE	3	1.	0.	451,453-454
SKIN OF NECK				
ENLARGED,NOS	1	2.	0.	454
NOSE				
DRIED PORPHYRIN DISCHARGE	1	4.	0.	454
GROUP 2 - 100 MG/KG				
* NORMAL	1			460
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	456-460
EYES				
DRIED PORPHYRIN DISCHARGE	2	2.	1.	456,458
SKIN OF BACK				
ERYTHEMA	3	10.	6.	457-459
GROUP 3 - 500 MG/KG				
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	461-465
EYES				
DRIED PORPHYRIN DISCHARGE	4	2.	2.	461-462,464-465
SKIN OF BACK				
ERYTHEMA	5	7.	3.	461-465
DESQUAMATION	2	9.	0.	461,463
NOSE				
DRIED PORPHYRIN DISCHARGE	1	15.	0.	462
GROUP 4 - 2000 MG/KG				
DEHYDRATION	1	11.	0.	466
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	466-470
EYES				
DRIED PORPHYRIN DISCHARGE	1	1.	0.	470
SKIN OF BACK				
ERYTHEMA	5	5.	3.	466-470
CRUST/SCALE ON SKIN	2	4.	0.	467,470
DESQUAMATION	3	10.	1.	467-468,470

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	1	1.	0.	472
NOSE				
DRIED PORPHYRIN DISCHARGE	3	5.	0.	471-472,474
HEAD				
ENLARGED,NOS	1	5.	0.	473
NECK				
ENLARGED,NOS	2	5.	0.	473,475
EYES				
DRIED PORPHYRIN DISCHARGE	1	5.	0.	474
GROUP 2 - 100 MG/KG				
NOSE				
DRIED PORPHYRIN DISCHARGE	4	7.	4.	476,478-480
EYES				
DRIED PORPHYRIN DISCHARGE	2	5.	0.	476,479
SKIN OF BACK				
ERYTHEMA	2	11.	8.	477,480
DESQUAMATION	5	14.	3.	476-480
CRUST/SCALE ON SKIN	1	12.	0.	478
GROUP 3 - 500 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	3	1.	0.	481-482,485
SKIN OF BACK				
ERYTHEMA	3	5.	0.	481-482,485
DESQUAMATION	3	12.	0.	482,484-485
NOSE				
DRIED PORPHYRIN DISCHARGE	4	5.	0.	482-485
EYES				
DRIED PORPHYRIN DISCHARGE	3	5.	0.	483-485
HAIR OF INGUINAL REGION				
HAIRCOAT, DRY URINE STAIN	2	5.	0.	483,485
HEAD				
ENLARGED,NOS	1	5.	0.	485
NECK				
ENLARGED,NOS	1	5.	0.	485

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 4 - 2000 MG/KG				
ELIZABETHAN COLLAR FOUND OFF	3	2.	1.	486-487,490
DEHYDRATION	1	5.	0.	486
URINE				
DISCOLORATION,GREEN	1	2.	0.	488
HEMATURIA	1	2.	0.	488
NOSE				
DRIED PORPHYRIN DISCHARGE	4	5.	0.	486-487,489-490
EYES				
DRIED PORPHYRIN DISCHARGE	4	5.	0.	486-487,489-490
HAIR OF INGUINAL REGION				
HAIRCOAT, DRY URINE STAIN	1	5.	0.	489
SKIN OF BACK				
CRUST/SCALE ON SKIN	3	7.	4.	488-490
DESQUAMATION	5	12.	0.	486-490
ERYTHEMA	4	13.	3.	487-490
SKIN OF FLANK				
ERYTHEMA	1	17.	0.	486
DESQUAMATION	2	17.	0.	486,488

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0 MG/KG				
* NORMAL	2			473-474
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	471-475
EYES				
DRIED PORPHYRIN DISCHARGE	2	1.	0.	471,475
SKIN OF NECK				
ENLARGED,NOS	1	3.	0.	472
HAIR OF INGUINAL REGION				
HAIRCOAT, WET BY URINE	2	3.	0.	472,475
GROUP 2 - 100 MG/KG				
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	476-480
EYES				
DRIED PORPHYRIN DISCHARGE	3	1.	1.	476,479-480
SKIN OF BACK				
ERYTHEMA	3	10.	6.	476-477,480
CRUST/SCALE ON SKIN	2	11.	5.	477,479
DESQUAMATION	5	10.	1.	476-480
GROUP 3 - 500 MG/KG				
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	481-485
NOSE				
DRIED PORPHYRIN DISCHARGE	1	1.	0.	483
SKIN OF BACK				
ERYTHEMA	5	3.	1.	481-485
CRUST/SCALE ON SKIN	2	4.	1.	481,485
DESQUAMATION	5	9.	1.	481-485
EYES				
DRIED PORPHYRIN DISCHARGE	2	6.	4.	483,485
HAIR OF INGUINAL REGION				
HAIRCOAT, WET BY URINE	1	3.	0.	485

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

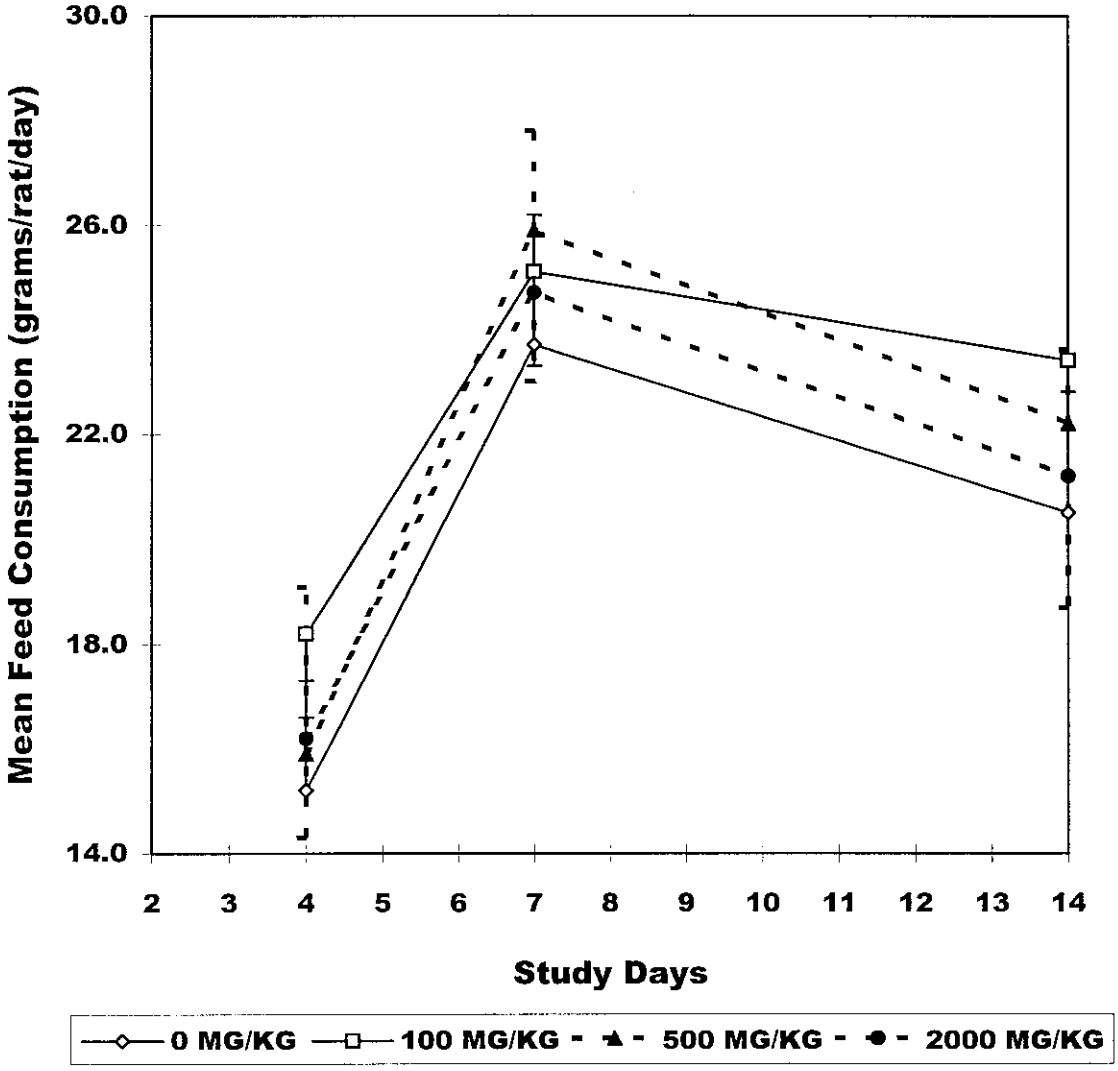
GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 4 - 2000 MG/KG				
DEHYDRATION	2	3.	0.	486,488
INDUCED DEATH, CARBON DIOXIDE	5	17.	0.	486-490
EYES				
DRIED PORPHYRIN DISCHARGE	3	1.	1.	486-488
SKIN OF BACK				
ERYTHEMA	5	4.	3.	486-490
CRUST/SCALE ON SKIN	5	4.	2.	486-490
WOUND	1	4.	0.	489
DESQUAMATION	5	8.	1.	486-490
HAIR OF INGUINAL REGION				
HAIRCOAT, WET BY URINE	4	3.	1.	486-489
NOSE				
DRIED PORPHYRIN DISCHARGE	1	11.	0.	486
SKIN OF FLANK				
DESQUAMATION	2	15.	1.	486,488
ERYTHEMA	2	15.	1.	486,488

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

Mean Feed Consumption - Male Rats



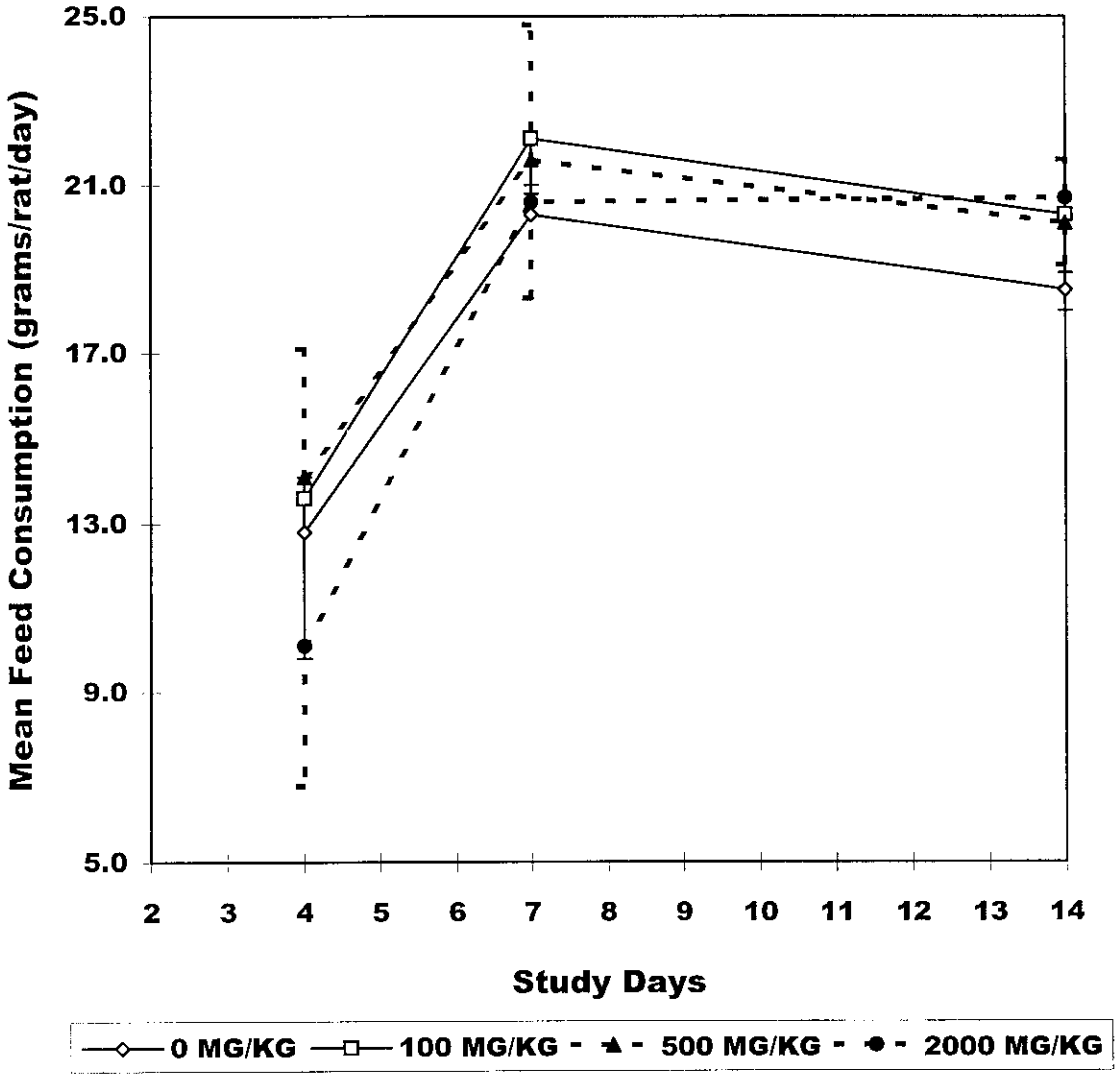
MEAN FOR FEED CONSUMPTION (GRAMS/ANIMAL/DAY) - MALE RATS

		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WEEK #	1				
DAY	4	15.2	18.2	15.9	16.2
		2.1	1.6	3.2	1.9
		5	5	5	5
DAY	7	23.7	25.1	25.9	24.7
		2.5	1.8	1.9	1.7
		5	5	5	5
WEEK #	2				
DAY	14	20.5	23.4	22.2	21.2
		2.3	2.2	1.4	2.5
		5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

Mean Feed Consumption - Female Rats



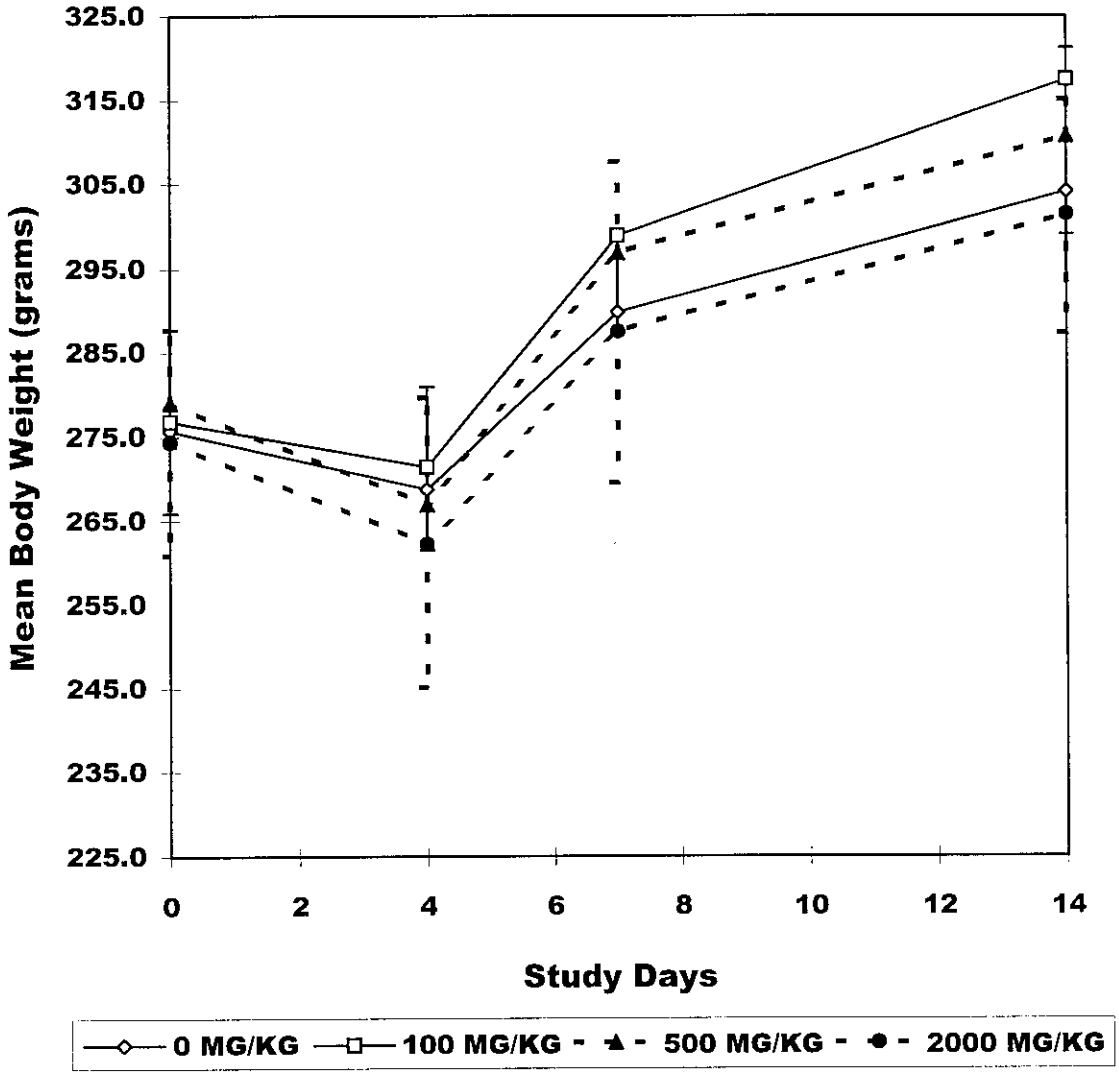
MEAN FOR FEED CONSUMPTION (GRAMS/ANIMAL/DAY) - FEMALE RATS

		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WEEK #	1				
DAY	4	12.8	13.6	14.1	10.1
		1.3	3.8	3.0	3.3
		5	5	5	5
DAY	7	20.3	22.1	21.6	20.6
		0.7	1.3	3.2	2.3
		5	5	5	5
WEEK #	2				
DAY	14	18.5	20.3	20.1	20.7
		0.4	2.3	1.5	1.6
		5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

Mean Body Weight - Male Rats



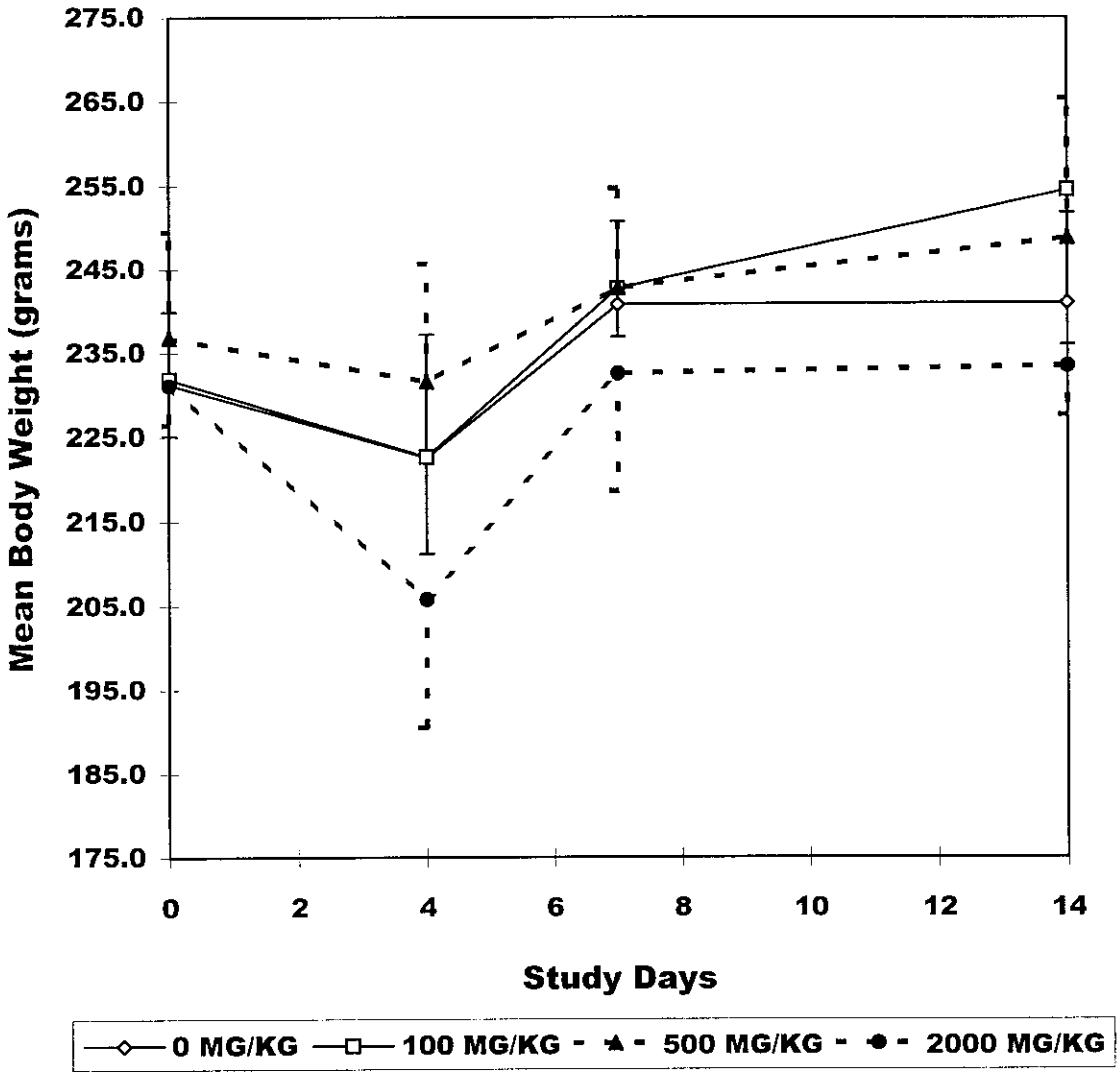
MEAN FOR BODY WEIGHT (GRAMS) - MALE RATS

		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WEEK #	1				
DAY	0	275.7	276.8	279.0	274.4
		12.0	10.9	8.7	13.5
		5	5	5	5
DAY	4	268.7	271.4	266.9	262.2
		12.2	9.9	12.7	17.1
		5	5	5	5
DAY	7	289.8	298.9	296.9	287.5
		9.6	11.6	10.7	18.0
		5	5	5	5
WEEK #	2				
DAY	14	304.1	317.4	310.7	301.4
		17.1	18.4	4.3	14.1
		5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

Mean Body Weight - Female Rats



MEAN FOR BODY WEIGHT (GRAMS) - FEMALE RATS

		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WEEK #	1				
DAY	0	231.3	231.9	236.8	231.2
		8.6	6.8	12.7	4.8
		5	5	5	5
DAY	4	222.5	222.6	231.6	205.8
		14.7	11.4	14.0	15.3
		5	5	5	5
DAY	7	240.8	242.7	242.8	232.6
		10.0	5.8	11.9	14.0
		5	5	5	5
WEEK #	2				
DAY	14	241.0	254.5	248.8	233.5
		10.8	18.5	16.5	5.9
		5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

SUMMARY URINE MICROSCOPIC EXAMINATION

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

MALE RATS

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
RBC/HPF	0 to 5	0 to 15	0 to 2	0 to 1
WBC/HPF	0 to 3	0 to 4	0 to 4	0 to 4
EPITHELIAL CELLS/HPF	0	0 to 2	0	0 to 2
BACTERIA/HPF	2+ to 3+	1+ to 3+	2+ to 3+	1+ to 3+
Triple Phosphate CRYSTALS/HPF	1+ to 3+	1+ to 3+	1+ to 3+	1+ to 3+
AMORPHOUS SEDIMENT/HPF	Not seen to 1+	Not seen to 1+	Not seen to 2+	Not seen to 2+
SPERM/HPF	1+ to 2+	0+ to 1+	0+ to 2+	1+ to 3+
YEAST/HPF	Not seen to 0+	Not seen to 0+	Not seen to 1+	Not seen to 1+

FEMALE RATS

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
RBC/HPF	0 to 1	0 to 1	0 to 1	0 to 1
WBC/HPF	0 to 5	0 to 4	0 to 2	0 to 5
EPITHELIAL CELLS/HPF	0 to 2	0 to 2	0 to 1	0 to 3
BACTERIA/HPF	2+ to 4+	2+ to 4+	1+ to 3+	1+ to 3+
Triple Phosphate CRYSTALS/HPF	Not seen to 1+	0+ to 2+	0+ to 1+	0+ to 1+
AMORPHOUS SEDIMENT/HPF	Not seen to 2+	0+ to 2+	0+ to 2+	Not seen to 3+
SPERM/HPF	Not seen	Not seen	Not seen	Not seen
YEAST/HPF	Not seen to 1+	Not seen to 1+	Not seen to 1+	Not seen to 1+

SUMMARY URINE DIPSTICK EXAMINATION

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

MALE RATS

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BLOOD	5	5	5	5
Negative	4	3	4	5
Small			1	
Moderate	1	2		

FEMALE RATS

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BLOOD	5	5	5	5
Negative	5	5	4	5
Non-Hemolyzed Trace			1	

SUMMARY HEMATOLOGY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: BLOOD

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WBC/MM3 X3	13.5	13.4	12.0	10.1
	3.2	2.3	1.6	1.6
	5	5	5	5
RBC/MM3 X6	8.6	8.3	8.3	8.3
	0.6	0.3	0.4	0.4
	5	5	5	5
HB CONC , G/DL	16.1	15.7	15.8	15.5
	0.7	0.8	0.9	0.4
	5	5	5	5
HCT , %	49.4	48.6	48.3	47.8
	2.2	2.1	2.5	1.1
	5	5	5	5
MCV , U3	57.8	58.7	58.1	57.7
	2.0	2.2	0.9	2.1
	5	5	5	5
MCH , UUG	18.8	19.0	19.0	18.8
	0.6	0.7	0.3	0.6
	5	5	5	5
MCHC , %	32.6	32.4	32.7	32.5
	0.3	0.4	0.6	0.1
	5	5	5	5
PLATELETS/MM3 X3	909.2	1011.8	914.4	1055.2
	74.1	227.6	94.2	119.1
	5	5	5	5
POLYS , %	11.2	15.2	8.6	9.0
	7.5	5.4	3.0	5.1
	5	5	5	5
BANDS , %	0.4	0.2	0.2	0.0
	0.5	0.4	0.4	0.0
	5	5	5	5
LYMPHOCYTES,%	82.6	76.6	84.8	82.6
	8.0	5.7	4.5	6.3
	5	5	5	5
MONOCYTES,%	4.4	5.0	4.2	4.8
	0.9	1.4	2.9	2.8
	5	5	5	5
EOSINOPHIL,%	1.0	2.2	1.4	2.6
	1.4	1.1	0.9	1.7
	5	5	5	5
BASOPHIL,%	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES ATYPICAL, %	0.4	0.8	0.8	1.0
	0.5	0.8	0.8	0.7
	5	5	5	5
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
PROTHROMBIN TIME,SEC	16.3	15.6	15.9	15.6
	0.6	0.8	0.4	0.2
	5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

SUMMARY HEMATOLOGY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: BLOOD

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
WBC/MM3 X3	9.6	9.6	10.3	10.8
	2.3	3.3	2.7	3.4
	5	4	5	5
RBC/MM3 X6	8.2	8.0	8.0	8.0
	0.7	0.5	0.5	0.8
	5	4	5	5
HB CONC , G/DL	15.6	15.2	15.2	15.4
	1.2	1.1	0.9	1.2
	5	4	5	5
HCT , %	46.8	45.7	45.7	46.9
	3.4	3.2	2.7	3.4
	5	4	5	5
MCV , U3	57.3	56.9	57.4	58.9
	2.5	1.2	1.4	1.9
	5	4	5	5
MCH , UUG	19.1	18.9	19.1	19.3
	0.6	0.2	0.3	0.5
	5	4	5	5
MCHC , %	33.3	33.2	33.2	32.8
	0.7	0.5	0.3	0.2
	5	4	5	5
PLATELETS/MM3 X3	1044.4	1101.3	1031.2	1054.8
	61.1	58.3	140.8	150.7
	5	4	5	5
POLYS , %	16.8	14.0	13.8	11.8
	11.7	6.0	6.7	8.8
	5	5	5	5
BANDS , %	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES,%	77.4	79.8	79.0	79.2
	12.0	8.3	8.1	9.1
	5	5	5	5
MONOCYTES,%	3.6	4.8	3.8	6.0
	1.9	1.9	2.2	2.0
	5	5	5	5
EOSINOPHIL,%	0.6	0.8	1.4	1.4
	0.9	0.8	1.1	1.5
	5	5	5	5
BASOPHIL,%	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES ATYPICAL, %	1.6	0.6	2.0	1.6
	1.5	0.5	1.2	1.8
	5	5	5	5
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
PROTHROMBIN TIME,SEC	15.1	15.2	15.6	15.4
	0.3	0.9	0.6	0.9
	5	4	4	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

STUDY SUMMARY OF CELL MORPHOLOGY

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

MALE RATS

GROUP	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BLOOD ERYTHROCYTES	5	5	5	5
POIKILOCYTOSIS	2	1		2
ANISOCYTOSIS		1	1	
MICROCYTOSIS				1
SPHEROCYTOSIS				1
HYPOCHROMASIA				1
BLOOD LEUKOCYTES	5	5	5	5
BLOOD PLATELETS	5	5	5	5

FEMALE RATS

GROUP	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BLOOD ERYTHROCYTES	5	5	5	5
ANISOCYTOSIS	2	1	1	2
MICROCYTOSIS	1		1	1
POIKILOCYTOSIS	2	3	4	1
MACROCYTOSIS			1	3
POLYCHROMASIA, INCREASED				1
HYPOCHROMASIA				2
BLOOD LEUKOCYTES	5	5	5	5
BLOOD PLATELETS	5	5	5	5

NUMBERS REPRESENT NUMBER OF ANIMALS EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF ANIMALS WITH EACH ABNORMALITY

SUMMARY CLINICAL CHEMISTRY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: SERUM

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
ALT (GPT) , U/L	34.63	30.71	35.39	30.46
	6.24	4.91	7.83	5.84
	5	5	5	5
UREA NITROGEN,MG/DL	14.36	14.12	14.60	12.63
	2.32	1.07	0.88	1.69
	5	5	5	5
GLUCOSE,MG/DL	96.87	106.50	103.00	111.21
	10.12	15.74	10.59	20.77
	5	5	5	5
CREATININE,MG/DL	0.68	0.68	0.63	0.65
	0.04	0.06	0.04	0.04
	5	5	5	5
SDH , U/L	6.49	6.54	10.94	5.76
	1.54	2.46	8.80	1.02
	5	5	5	5
BILIRUBIN TOTAL,MG/DL	0.01	0.03	0.04	0.04
	0.01	0.02	0.05	0.05
	5	5	5	5
TOTAL PROTEIN,G/DL	5.60	5.52	5.50	5.81
	0.47	0.17	0.24	0.14
	5	5	5	5
A/G RATIO	1.09	1.20	1.18	1.22
	0.02	0.07	0.12	0.18
	5	5	5	5
ALBUMIN,G/DL	2.92	3.01	2.96	3.18
	0.22	0.12	0.12	0.19
	5	5	5	5
CHOLESTEROL,MG/DL	52.77	51.91	53.20	51.96
	12.53	11.39	10.92	4.77
	5	5	5	5
TRIGLYCERIDES,MG/DL	28.71	31.76	28.53	28.27
	10.19	13.82	9.88	8.72
	5	5	5	5
CALCIUM , MG/DL	11.38	11.90	11.77	11.41
	0.38	0.93	0.89	0.60
	5	5	5	5
PHOSPHORUS , MG/DL	11.98	11.38	11.27	10.26 *
	0.26	0.66	0.43	0.65
	5	5	5	5
SODIUM , MEQ/L	148.00	148.80	148.00	149.40
	1.58	1.48	1.22	2.61
	5	5	5	5
POTASSIUM , MEQ/L	8.17	7.02	7.23	7.57
	1.34	0.35	0.65	1.53
	5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* -STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

SUMMARY CLINICAL CHEMISTRY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: SERUM

	0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG	
ALT (GPT) , U/L	31.40	26.70	30.00	32.28	
	2.72	2.86	4.12	3.35	
	5	5	5	5	
UREA NITROGEN,MG/DL	17.38	19.06	18.03	14.68	
	2.33	2.68	4.22	1.79	
	5	5	5	5	
GLUCOSE,MG/DL	91.89	97.96	107.24	89.76	
	5.14	7.25	12.29	17.26	
	5	5	5	5	
CREATININE,MG/DL	0.77	0.79	0.78	0.79	
	0.10	0.11	0.09	0.05	
	5	5	5	5	
SDH , U/L	6.71	6.27	7.10	6.46	
	1.38	0.71	1.44	1.36	
	5	5	5	5	
BILIRUBIN TOTAL,MG/DL	0.04	0.06	0.01	0.03	
	0.04	0.05	0.02	0.02	
	5	5	5	5	
TOTAL PROTEIN,G/DL	6.67	6.38	6.31	6.18	
	0.38	0.31	0.46	0.44	
	5	5	5	5	
A/G RATIO	1.27	1.21	1.19	1.15	
	0.12	0.21	0.07	0.10	
	5	5	5	5	
ALBUMIN,G/DL	3.72	3.47	3.42	3.30	
	0.22	0.32	0.23	0.29	
	5	5	5	5	
CHOLESTEROL,MG/DL	58.25	58.70	60.01	65.87	
	11.87	13.03	3.14	20.57	
	5	5	5	5	
TRIGLYCERIDES,MG/DL	28.41	32.82	33.77	56.55	*
	6.14	15.90	11.32	12.73	
	5	5	5	5	
CALCIUM , MG/DL	11.87	11.82	11.57	11.41	
	0.57	1.17	0.68	1.27	
	5	5	5	5	
PHOSPHORUS , MG/DL	9.88	9.97	10.34	9.99	
	0.89	0.63	0.79	0.66	
	5	5	5	5	
SODIUM , MEQ/L	146.00	145.20	145.80	145.80	
	2.65	1.30	1.10	1.30	
	5	5	5	5	
POTASSIUM , MEQ/L	7.55	7.69	7.24	7.43	
	0.83	1.62	0.60	1.01	
	5	5	5	5	

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* -STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

MEAN TERMINAL ORGAN WEIGHTS AND BODY WEIGHTS

TERMINATION DAY - 17

MALE RATS

GROUP		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BODY WEIGHT	(G)	260.7	275.3	271.6	262.8
		13.6	21.8	2.0	12.5
		5	5	5	5
LIVER	(G)	7.6990	8.5715	8.3936	8.6764
		0.6710	0.8845	0.7601	0.6019
		5	5	5	5
	%	2.9528	3.1103	3.0898	3.2999
		0.1841	0.1317	0.2641	0.1377
		5	5	5	5
KIDNEYS	(G)	2.3564	2.4515	2.4493	2.4616
		0.1715	0.1850	0.1101	0.1927
		5	5	5	5
	%	0.9043	0.8921	0.9020	0.9362
		0.0544	0.0569	0.0426	0.0522
		5	5	5	5
SPLEEN	(G)	0.5697	0.6211	0.6054	0.5147
		0.0461	0.0844	0.0947	0.0651
		5	5	5	5
	%	0.2187	0.2254	0.2228	0.1956
		0.0164	0.0237	0.0331	0.0198
		5	5	5	5

FEMALE RATS

GROUP		0 MG/KG	100 MG/KG	500 MG/KG	2000 MG/KG
BODY WEIGHT	(G)	214.2	213.5	211.7	197.3
		7.4	13.7	11.7	4.6
		5	5	5	5
LIVER	(G)	6.8157	6.5717	6.5416	6.8515
		0.5368	0.6119	0.3520	0.3149
		5	5	5	5
	%	3.1842	3.0742	3.0927	3.4740 *
		0.2742	0.0964	0.1216	0.1654
		5	5	5	5
KIDNEYS	(G)	1.8421	1.7352	1.7878	1.6921
		0.1099	0.2166	0.3174	0.0541
		5	5	5	5
	%	0.8595	0.8106	0.8430	0.8577
		0.0330	0.0568	0.1291	0.0159
		5	5	5	5
SPLEEN	(G)	0.4985	0.4976	0.5104	0.4685
		0.0485	0.0837	0.0508	0.0189
		5	5	5	5
	%	0.2330	0.2323	0.2413	0.2375
		0.0252	0.0276	0.0225	0.0075
		5	5	5	5

KEY: FOR EACH GROUP, VALUES ARE REPORTED AS - MEAN, +/- STANDARD DEVIATION AND NUMBER PER GROUP

* - STATISTICALLY DIFFERENT FROM CONTROLS (P</=0.05), ONE WAY ANOVA

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CRUDE MCHM

HAEL NO.: 97-0216 EAN: 972790
PM No. 18717-00

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

970216G1

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

Sponsor's Representative:
Karen R. Miller, Ph.D.

(22 Pages)

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Those portions of this study which were performed at the laboratory of Consultants in Veterinary Pathology were conducted in compliance with the appropriate sections of the following Good Laboratory Practice Standards: United States Environmental Protection Agency, Toxic Substances Control Act, 40 CFR Part 792 and Annex 2, Organisation for Economic Cooperation and Development, Guidelines for Testing of Chemicals [C(81)30 (Final)].

Robert H. Garman 12-12-98

Robert H. Garman, DVM Date
Diplomate, ACVP
Consultant Pathologist

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

TABLE OF CONTENTS

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY

Microscopic evaluations were performed on a limited selection of tissues from male and female Sprague-Dawley (CRL:CD(SD)BR/VAF Plus) rats which had received topical applications of the test chemical on the skin of the back or left flank. These dermal exposures were made by application of a fiber pad and a semi-occlusive wrap which were left in position for six hours per day for 13 consecutive week days. Five rats/sex were present in each of the following four dosage groups: 0, 100, 500, and 2000 mg/kg. Microscopic examinations were performed on sections of the liver, spleen, bone marrow (sternal) and kidneys from all of the male and female rats in the high dose and control groups. Tissues with gross lesions (excepting for the skin) were also examined for the rats in the high dose and control groups, as well as for the rats in the middle and low dose groups.

Treatment-related gross lesions were limited to the treated area of skin, with at least some female rats in each test chemical-treated group having minimal to moderate degrees of desquamation, with the severity of desquamation being greatest in the high dose group. For the male rats, desquamation was also seen in two high dose group rats but not in the middle and low dose group. Desquamation was not seen in the control group rats.

No treatment-related microscopic lesions were found on this study, but the severity of hepatocellular cytoplasmic vacuolation was slightly increased in the high dose female rat group in comparison to the female control group. Four of the control group female rats were graded as minimal for hepatocellular vacuolation, while all five female rats in the high dose group were graded as mild. This difference may be of little biologic significance and may merely indicate increased mobilization of fat to the livers of the high dose group females or decreased caloric intake by these rats. This difference in degree of hepatocellular vacuolation was not seen for male rats.

INTRODUCTION

This report details the materials and methods followed for the histopathology portion of this study and includes the results of the microscopic evaluations performed on selected tissues from male and female Sprague-Dawley (CRL:CD(SD)BR/VAF Plus) rats which had received topical dermal applications of the test chemical for six hours/day for 13 consecutive week days. Five rats/sex were present in each of four dosage groups (0, 100, 500, and 2000 mg/kg).

MATERIALS AND METHODS

Study Overview and Group Assignments:

There were five male and five female Sprague-Dawley (CRL:CD(SD)BR/VAF Plus) rats in each of four dosage groups - *i.e.* 0, 100, 500, and 2000 mg/kg. Microscopic examinations were performed on sections of the liver, spleen, bone marrow (sternal) and kidneys from all of the male and female rats in the high dose and control groups. Tissues with gross lesions (excepting for the skin) were also examined for the rats in the high dose and control groups, as well as for the rats in the middle and low dose groups.

Necropsy Procedures:

The necropsy examinations on these rats had been conducted at the Performing Laboratory which also conducted the in-life phase of this study. As part of the necropsy procedure, the following tissues were collected in 10% buffered formalin: liver, sternum (with bone marrow), kidneys, spleen, and tissues with gross lesions.

Histotechnology Procedures:

The collected tissues were received in formalin from the Performing Laboratory. After checking each bottle label against the animal numbers on the individual animal Necropsy Report forms, the tissues were trimmed according to standard procedures and processed for embedding in paraffin. As the tissues were trimmed, the abbreviated gross findings listed on the individual animal Necropsy Report forms were also checked and, if additional gross observations were made, these were recorded on the Histology Processing Sheets. All tissues with grossly visible lesions were trimmed for microscopic evaluation with the exception of the skin.

The block list for the tissues evaluated from the high dose and control group male and female rats is as follows:

Block 1: Liver, Spleen
Block 2: Kidneys
Block 3: Sternum (with Bone Marrow)
Block 4: Tissues with gross lesions

When target tissues or tissues with gross alterations were processed from the rats in middle and low concentration groups, the same respective tissue block numbers (from the above list) were used.

The tissue blocks were sectioned with a rotary microtome set at a section thickness of four micrometers. The resulting sections were stained with hematoxylin and eosin.

Microscopic Evaluations:

Gross and microscopic findings were recorded and tabulated using a PC-based computer program (GLPATH; Great Laboratory ProgramS®), and gross/microscopic correlates were made whenever possible. If any additional gross observations had been recorded on the Histology Processing Sheets during the trimming of the tissues, these additional findings would also have been entered into the computer data base. All microscopic lesions were assigned one of five severity grades (*viz.* minimal, mild, moderate, marked, and severe). The distribution pattern of each lesion (focal, multifocal, or diffuse) was also assigned. These distributions will be found with the individual animal data (Tables 5 and 6) rather than in the microscopic lesion summary tables (Tables 3 and 4). Correlates were made, whenever possible, between the gross observations and the appropriate microscopic changes.

RESULTS AND DISCUSSION

Gross necropsy observations for the male rats necropsied at the conclusion of the study are presented in Table 1, while graded microscopic summary findings for these male rats are presented in Table 3. For the female rats necropsied at the end of the study, the gross observations are presented in Table 2, and the summary microscopic findings are presented in Table 4. The individual animal microscopic findings for these rats are presented in Table 5 for the male rats and in Table 6 for the female rats.

For both the male and female rats, the only treatment-related gross finding was that of desquamation in the area of the treated skin. The females were more prone to develop this alteration than were the males. Only two of

the high dose group male rats had evidence of desquamation, and this was recorded as having been minor in degree for both of these males. For the female groups, on the other hand, the numbers of rats with desquamation were 0, 4, 2, and 5 for the 0, 100, 500, and 2000 mg/kg dose groups, respectively. There was evidence of a dose-related increase in severity of desquamation, with three of the four females in the 100 mg/kg group being graded as minimal and two of the five females in the 2000 mg/kg being graded as moderate. Two females in the high dose group also had evidence of minimal degrees of skin erythema within the treatment area. Desquamation of the skin (*i.e.* flaking or dander formation) may develop as a result of nonspecific surface irritation leading to hyperkeratosis or may reflect altered hydration of the stratum corneum. Desquamation is a common finding in dermal application studies, particularly when dehydrating agents are used or when test materials are applied under occlusive dressings.

No treatment-related microscopic lesions were found on this study, but the severity of hepatocellular cytoplasmic vacuolation was slightly increased in the high dose female rat group in comparison to the female control group. Four of the control group female rats were graded as minimal for hepatocellular vacuolation, while all five female rats in the high dose group were graded as mild. The degree of vacuolaton of the cytoplasm of hepatocytes is most frequently a reflection of the amount of fat present within these cells and will be altered by fasting and by levels of caloric intake. Although such vacuolation was not recorded for the male rats, very minimal degrees of vacuolation were found in the male rat livers as well (as is to be expected when animals are fasted overnight prior to a necropsy). However, no differences in the degrees of hepatocyte vacuolation were noted between the control and high dose group male rats, and the degrees of vacuolation in the male rat livers were considered to be insufficient to merit documentation.

Because the degree of hepatocyte vacuolation ("fatty metamorphosis") will be affected by the length of fasting, one must be cognizant of the order in which the animals are necropsied (unless the necropsy order is randomized). In this particular study, the difference in the degrees of hepatocyte vacuolation between the female control and high dose group is rather mild and probably not of biologic significance or indicative of a hepatocyte toxicity.

CONCLUSION

Treatment-related gross findings were limited to the area of the treated skin and were not considered to be of a sufficient degree to indicate anything other than possible mild irritation. No treatment-related microscopic findings were present other than for a slight enhancement in the degree of hepatocellular cytoplasmic vacuolation ("fatty metamorphosis") for the female rats. There is, therefore, no evidence within the limited tissue sample evaluated of toxicity even at the highest dose of the test material (2000 mg/kg) when applied to the skin of rats under the conditions of this study.

Robert H. Garman 12-17-98

Robert H. Garman, DVM
Diplomate, ACVP
Consultant Pathologist

Date

A|TX98129.DOC; 12/11/98

TABLE 1

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY GROSS NECROPSY OBSERVATIONS FOR MALE RATS

GROUP:		1	2	3	4
Number of animals included		5	5	5	5
TREATED SKIN					
DESQUAMATION		0	0	0	2
	minor	-	-	-	2
SPLEEN					
DARKER THAN NORMAL		0	1	0	0
	minimal	-	1	-	-

Group Legend: 1 is 0 mg/kg, 2 is 100 mg/kg, 3 is 500 mg/kg,
4 is 2000 mg/kg

TABLE 2

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY GROSS NECROPSY OBSERVATIONS FOR FEMALE RATS

		GROUP:	1	2	3	4
Number of animals included			5	5	5	5
TREATED SKIN						
DESQUAMATION			0	4	2	5
	minimal		-	3	1	-
	minor		-	1	1	3
	moderate		-	-	-	2
ERYTHEMA			0	0	0	2
	minimal		-	-	-	2
STOMACH						
HEMORRHAGE, GLANDULAR PORTION			1	0	0	1
	minimal		1	-	-	-
	minor		-	-	-	1
UTERUS						
HYDROMETRA			0	0	0	1
	minor		-	-	-	1

Group Legend: 1 is 0 mg/kg, 2 is 100 mg/kg, 3 is 500 mg/kg,
4 is 2000 mg/kg

TABLE 3

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY OF MICROSCOPIC DIAGNOSES FOR MALE RATS

GROUP:		1	2	3	4
Number of animals included		5	1	0	5
LIVER					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		1	-	-	2
No. With Microscopic Diagnoses		4	-	-	3
MONONUCLEAR CELL INFILTRATE(S)		4	-	-	3
	minimal	4	-	-	3
SPLEEN					
Number of Tissues Examined		5	1	0	5
Microscopically Normal		5	1	-	5
BONE MARROW					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5
BONE, STERNUM					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5
KIDNEYS					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5

Group Legend: 1 is 0 mg/kg, 2 is 100 mg/kg, 3 is 500 mg/kg,
4 is 2000 mg/kg
Statistics performed using Fisher's exact (1-tail)
None significantly different from GROUP 1

TABLE 4

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY OF MICROSCOPIC DIAGNOSES FOR FEMALE RATS

GROUP:		1	2	3	4
Number of animals included		5	4	2	5
STOMACH					
Number of Tissues Examined		1	0	0	1
No. With Microscopic Diagnoses		1	-	-	1
ULCER		1	-	-	1
	mild	1	-	-	1
LIVER					
Number of Tissues Examined		5	0	0	5
No. With Microscopic Diagnoses		5	-	-	5
HEPATOCELLULAR CYTOPLASMIC VACUOLATION		5	-	-	5
	minimal	4	-	-	-
	mild	1	-	-	5
MONONUCLEAR CELL INFILTRATE(S)		3	-	-	2
	minimal	3	-	-	2
SPLEEN					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5
BONE MARROW					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5
BONE, STERNUM					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		5	-	-	5

Group Legend: 1 is 0 mg/kg, 2 is 100 mg/kg, 3 is 500 mg/kg,
4 is 2000 mg/kg
Statistics performed using Fisher's exact (1-tail)
None significantly different from GROUP 1

TABLE 4

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

SUMMARY OF MICROSCOPIC DIAGNOSES FOR FEMALE RATS

GROUP:		1	2	3	4
Number of animals included		5	4	2	5
KIDNEYS					
Number of Tissues Examined		5	0	0	5
Microscopically Normal		4	-	-	5
No. With Microscopic Diagnoses		1	-	-	0
MINERALIZATION		1	-	-	0
	minimal	1	-	-	-
UTERUS					
Number of Tissues Examined		0	0	0	1
No. With Microscopic Diagnoses		-	-	-	1
LUMINAL ECTASIA		-	-	-	1
	moderate	-	-	-	1

Group Legend: 1 is 0 mg/kg, 2 is 100 mg/kg, 3 is 500 mg/kg,
4 is 2000 mg/kg
Statistics performed using Fisher's exact (1-tail)
None significantly different from GROUP 1

TABLE 5

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR MALE RATS

Group: 0 mg/kg

ANIMAL ID: 451 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

ANIMAL ID: 452 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

ANIMAL ID: 453 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE

The following tissues/anatomic sites are microscopically normal:

LIVER	SPLEEN	BONE MARROW
BONE, STERNUM	KIDNEYS	

TABLE 5

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR MALE RATS

Group: 0 mg/kg

ANIMAL ID: 454 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

ANIMAL ID: 455 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

Group: 100 mg/kg

ANIMAL ID: 460 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SPLEEN (gross)	DARKER THAN NORMAL Comment: Minimal.	

The following tissues/anatomic sites are microscopically normal:
SPLEEN

TABLE 5

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR MALE RATS

Group: 2000 mg/kg

ANIMAL ID: 466 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE

The following tissues/anatomic sites are microscopically normal:

LIVER	SPLEEN	BONE MARROW
BONE, STERNUM	KIDNEYS	

ANIMAL ID: 467 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), focal, minimal	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

ANIMAL ID: 468 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	
SKIN, TREATED (gross)	DESQUAMATION Comment: Minor; skin of back.	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

TABLE 5

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR MALE RATS

Group: 2000 mg/kg

ANIMAL ID: 469 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

ANIMAL ID: 470 DATE OF DEATH:30-APR-98 MALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	

The following tissues/anatomic sites are microscopically normal:

LIVER	SPLEEN	BONE MARROW
BONE, STERNUM	KIDNEYS	

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 0 mg/kg

ANIMAL ID: 471 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

ANIMAL ID: 472 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	MONONUCLEAR CELL INFILTRATE(S), focal, minimal	
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

ANIMAL ID: 473 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 0 mg/kg

ANIMAL ID: 474 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, minimal	
	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	
KIDNEYS (microscopic)		
	MINERALIZATION, focal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM

ANIMAL ID: 475 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
STOMACH (gross)		
	HEMORRHAGE, GLANDULAR PORTION	G-01
	Comment: Minimal.	
STOMACH (microscopic)		
	ULCER, multifocal, mild	M-01
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, minimal	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

The two digit number correlates one or more microscopic findings (M-) with one or more gross findings (G-)

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 100 mg/kg

ANIMAL ID: 477 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minimal; skin of back.	

ANIMAL ID: 478 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minimal; skin of back.	

ANIMAL ID: 479 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minimal; skin of back.	

ANIMAL ID: 480 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 500 mg/kg

ANIMAL ID: 482 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	

ANIMAL ID: 484 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minimal; skin of back.	

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 2000 mg/kg

ANIMAL ID: 486 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Moderate; skin of back.	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

ANIMAL ID: 487 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	
	ERYTHEMA	
	Comment: Minimal; skin of back.	

The following tissues/anatomic sites are microscopically normal:
SPLEEN BONE MARROW BONE, STERNUM
KIDNEYS

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 2000 mg/kg

ANIMAL ID: 488 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Moderate; skin of back.	
UTERUS (gross)		
	HYDROMETRA	
	Comment: Minor.	
UTERUS (microscopic)		
	LUMINAL ECTASIA, diffuse, moderate	
	Comment: Probably related to the estrous cycle, but the ovaries are not available for microscopic evaluation.	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

ANIMAL ID: 489 DATE OF DEATH:30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
STOMACH (gross)		
	HEMORRHAGE, GLANDULAR PORTION	G-01
	Comment: Minor.	
STOMACH (microscopic)		
	ULCER, multifocal, mild	M-01
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	
	ERYTHEMA	
	Comment: Minimal; skin of back.	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

The two digit number correlates one or more microscopic findings (M-) with one or more gross findings (G-)

TABLE 6

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

INDIVIDUAL ANIMAL GROSS AND/OR MICROSCOPIC DIAGNOSES FOR FEMALE RATS

Group: 2000 mg/kg

ANIMAL ID: 490 DATE OF DEATH: 30-APR-98 FEMALE SCHEDULED SACRIFICE

TISSUE/ANATOMIC SITE	DIAGNOSES	GROSS/MICRO CORRELATE
LIVER (microscopic)		
	HEPATOCELLULAR CYTOPLASMIC VACUOLATION, multifocal, mild	
	MONONUCLEAR CELL INFILTRATE(S), multifocal, minimal	
SKIN, TREATED (gross)		
	DESQUAMATION	
	Comment: Minor; skin of back.	

The following tissues/anatomic sites are microscopically normal:

SPLEEN	BONE MARROW	BONE, STERNUM
KIDNEYS		

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

QUALITY ASSURANCE STATEMENT

Consultant Pathologist: R. H. Garman, DVM

The following internal inspections were conducted to assure procedural quality and accuracy of data handling and reporting of results:

Inspection	Dates Performed
1. Accuracy of microslide labelling.	6/17/98
2. Quality of microslide preparations.	6/17/98
3. Comparison of microslides and corresponding blocks.	6/17/98

In addition, the following inspections were conducted by an independent Quality Assurance Monitor, and the results of these inspections were reported to the Pathologist and to the Sponsor's Representative:

Inspections Performed	Date Performed and Reported to Pathologist	Date Reported To Sponsor's Representative
1. Records of the above internal inspections.	6/22/98	
2. Raw data, final report.	6/22/98	7/12/98
3. Revised final report.	11/11/98	11/13/98

Denise L. Fait 12/12/98

Denise L. Fait, B.S. Date
Quality Assurance Consultant

APPENDIX A

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	0 MG/KG				
ANIMAL #	451	452	453	454	455
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
NOSE					
DRIED PORPHYRIN DISCHARGE	1	2	2	2	2
EYES					
DRIED PORPHYRIN DISCHARGE	1	2	2		
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
NOSE					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
ELIZABETHAN COLLAR FOUND OFF	P				
MORIBUNDITY/MORTALITY CHECK, NORMAL		N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF			P		
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	0 MG/KG				
ANIMAL #	451	452	453	454	455
DAY # 12					
CLINICAL EXAMINATION, NORMAL		N	N		
NOSE					
DRIED PORPHYRIN DISCHARGE	1			1	
NECK					
ENLARGED,NOS					1
DAY # 13					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	100 MG/KG				
ANIMAL #	456	457	458	459	460
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			P
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
CLINICAL EXAMINATION, NORMAL			N		
NOSE					
DRIED PORPHYRIN DISCHARGE	2			1	1
EYES					
DRIED PORPHYRIN DISCHARGE	1	2			
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 12					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
ELIZABETHAN COLLAR FOUND OFF		P			
NECK					
ENLARGED,NOS					1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	100 MG/KG				
ANIMAL #	456	457	458	459	460
DAY # 13					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	500 MG/KG				
ANIMAL #	461	462	463	464	465
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF			P		
DAY # 5					
CLINICAL EXAMINATION, NORMAL			N		
ELIZABETHAN COLLAR FOUND OFF			P		
NOSE					
DRIED PORPHYRIN DISCHARGE	3	2		2	1
EYES					
DRIED PORPHYRIN DISCHARGE		1			1
SKIN OF BACK					
ERYTHEMA				1	
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF				P	
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	500 MG/KG				
ANIMAL #	461	462	463	464	465
DAY # 12					
CLINICAL EXAMINATION, NORMAL		N		N	N
NOSE					
DRIED PORPHYRIN DISCHARGE	2		1		
SKIN OF BACK					
DESQUAMATION			1		
DAY # 13					
SKIN OF BACK					
DESQUAMATION			1		
CLINICAL EXAMINATION, NORMAL	N	N		N	N
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF	P				
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	2000 MG/KG				
ANIMAL #	466	467	468	469	470
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
CLINICAL EXAMINATION, NORMAL			N		
NOSE					
DRIED PORPHYRIN DISCHARGE	1	1		2	2
EYES					
DRIED PORPHYRIN DISCHARGE	1	1		2	
SKIN OF BACK					
CRUST/SCALE ON SKIN		1			1
ERYTHEMA		1			1
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF BACK					
CRUST/SCALE ON SKIN		1			1
ERYTHEMA		1			1
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - A.M.	2000 MG/KG				
ANIMAL #	466	467	468	469	470
DAY # 12					
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
DESQUAMATION	1	1	1		1
ERYTHEMA			1		
DAY # 13					
CLINICAL EXAMINATION, NORMAL		N		N	
SKIN OF BACK					
DESQUAMATION	1		1		1
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF			P		
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 17					
CLINICAL EXAMINATION, NORMAL		N			
SKIN OF BACK					
ERYTHEMA	1			1	
DESQUAMATION					2
SKIN OF FLANK					
ERYTHEMA			1		
DESQUAMATION			2		

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	0 MG/KG				
ANIMAL #	451	452	453	454	455
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N			N
EYES					
DRIED PORPHYRIN DISCHARGE	2		2	2	
DAY # 2					
CLINICAL EXAMINATION, NORMAL		N	N		N
EYES					
DRIED PORPHYRIN DISCHARGE	2			2	
SKIN OF NECK					
ENLARGED,NOS				2	
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
EYES					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
NOSE					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 8					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 9					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 10					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 11					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 15					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 16					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	0 MG/KG				
ANIMAL #	451	452	453	454	455
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	100 MG/KG				
ANIMAL #	456	457	458	459	460
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N	N	N	N
EYES					
DRIED PORPHYRIN DISCHARGE	1				
DAY # 2					
CLINICAL EXAMINATION, NORMAL	N	N		N	N
EYES					
DRIED PORPHYRIN DISCHARGE			1		
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 8					
CLINICAL EXAMINATION, NORMAL	N	N		N	N
EYES					
DRIED PORPHYRIN DISCHARGE			2		
DAY # 9					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			
DAY # 10					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			
DAY # 11					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
SKIN OF BACK					
ERYTHEMA				1	
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 15					
CLINICAL EXAMINATION, NORMAL	N	N			N
SKIN OF BACK					
ERYTHEMA			1	1	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	100 MG/KG				
ANIMAL #	456	457	458	459	460
DAY # 16					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
SKIN OF BACK					
ERYTHEMA				1	
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	500 MG/KG				
ANIMAL #	461	462	463	464	465
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N	N		
EYES					
DRIED PORPHYRIN DISCHARGE	2			3	1
DAY # 2					
CLINICAL EXAMINATION, NORMAL		N	N		N
EYES					
DRIED PORPHYRIN DISCHARGE	1			2	
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
SKIN OF BACK					
ERYTHEMA					1
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N		N		N
EYES					
DRIED PORPHYRIN DISCHARGE		1			
SKIN OF BACK					
ERYTHEMA				1	
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 8					
CLINICAL EXAMINATION, NORMAL	N	N		N	
SKIN OF BACK					
ERYTHEMA			1		1
DAY # 9					
CLINICAL EXAMINATION, NORMAL		N		N	N
SKIN OF BACK					
DESQUAMATION	1		1		
ERYTHEMA	1				
DAY # 10					
CLINICAL EXAMINATION, NORMAL	N				N
SKIN OF BACK					
ERYTHEMA		1	2	1	
DAY # 11					
SKIN OF BACK					
DESQUAMATION			1		
ERYTHEMA				1	
CLINICAL EXAMINATION, NORMAL	N	N			N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	500 MG/KG				
ANIMAL #	461	462	463	464	465
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			
DAY # 15					
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
ERYTHEMA	1	2	1		2
NOSE					
DRIED PORPHYRIN DISCHARGE		1			
DAY # 16					
CLINICAL EXAMINATION, NORMAL					N
SKIN OF BACK					
ERYTHEMA	1	1	1	1	
DESQUAMATION	1				
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	2000 MG/KG				
ANIMAL #	466	467	468	469	470
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
EYES					
DRIED PORPHYRIN DISCHARGE					2
DAY # 2					
CLINICAL EXAMINATION, NORMAL	N	N		N	
SKIN OF BACK					
ERYTHEMA			1		2
EYES					
DRIED PORPHYRIN DISCHARGE					2
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
SKIN OF BACK					
ERYTHEMA					1
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF BACK					
CRUST/SCALE ON SKIN		2			1
ERYTHEMA		1			1
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF BACK					
ERYTHEMA		1			1
CRUST/SCALE ON SKIN					1
DAY # 8					
CLINICAL EXAMINATION, NORMAL		N	N	N	
SKIN OF BACK					
ERYTHEMA	1				1
DAY # 9					
SKIN OF BACK					
ERYTHEMA	1	1	2	1	
DESQUAMATION					1
CRUST/SCALE ON SKIN		1			
DAY # 10					
SKIN OF BACK					
ERYTHEMA	1	1	2	1	2
DESQUAMATION		1	1		1
DAY # 11					
* DEHYDRATION	3				
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
DESQUAMATION		2	1		1
ERYTHEMA			1		1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - MALE RATS

OBSERVATION PERIOD - P.M.	2000 MG/KG				
ANIMAL #	466	467	468	469	470
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N	N		N	
SKIN OF BACK					
ERYTHEMA			1		1
DESQUAMATION			1		1
DAY # 15					
CLINICAL EXAMINATION, NORMAL	N			N	
SKIN OF BACK					
ERYTHEMA		1	1		1
DAY # 16					
CLINICAL EXAMINATION, NORMAL		N		N	
SKIN OF BACK					
ERYTHEMA	1		1		1
DESQUAMATION			2		2
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	0 MG/KG				
ANIMAL #	471	472	473	474	475
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
NOSE					
DRIED PORPHYRIN DISCHARGE	1	1		1	
HEAD					
ENLARGED,NOS			2		
NECK					
ENLARGED,NOS			2		1
EYES					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N	N		N	N
NECK					
ENLARGED,NOS			1		
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 12					
CLINICAL EXAMINATION, NORMAL	N	N	N		N
NOSE					
DRIED PORPHYRIN DISCHARGE				1	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	0 MG/KG				
ANIMAL #	471	472	473	474	475
DAY # 13					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	100 MG/KG				
ANIMAL #	476	477	478	479	480
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
CLINICAL EXAMINATION, NORMAL					N
NOSE					
DRIED PORPHYRIN DISCHARGE	1		1	1	
EYES					
DRIED PORPHYRIN DISCHARGE	1			1	
SKIN OF BACK					
ERYTHEMA		1			
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
ERYTHEMA		1			
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 12					
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
DESQUAMATION	1	1			1
CRUST/SCALE ON SKIN			1		
NOSE					
DRIED PORPHYRIN DISCHARGE					1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	100 MG/KG				
ANIMAL #	476	477	478	479	480
DAY # 13					
CLINICAL EXAMINATION, NORMAL			N	N	
SKIN OF BACK					
DESQUAMATION	1	1			1
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N				
SKIN OF BACK					
DESQUAMATION		1	1	1	2
ERYTHEMA					1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	500 MG/KG				
ANIMAL #	481	482	483	484	485
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF	P	P			P
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			P
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
SKIN OF BACK					
ERYTHEMA	1	1			1
NOSE					
DRIED PORPHYRIN DISCHARGE		1	2	1	2
EYES					
DRIED PORPHYRIN DISCHARGE			1	1	2
HAIR OF INGUINAL REGION					
HAIRCOAT, DRY URINE STAIN			1		1
HEAD					
ENLARGED,NOS					1
NECK					
ENLARGED,NOS					1
DAY # 6					
CLINICAL EXAMINATION, NORMAL			N	N	
SKIN OF BACK					
ERYTHEMA	1	1			1
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	500 MG/KG				
ANIMAL #	481	482	483	484	485
DAY # 12					
CLINICAL EXAMINATION, NORMAL	N		N		
SKIN OF BACK					
DESQUAMATION		1		1	1
DAY # 13					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF BACK					
DESQUAMATION		1			1
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
CLINICAL EXAMINATION, NORMAL	N		N		
SKIN OF BACK					
ERYTHEMA		2			
DESQUAMATION		2		1	2

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	2000 MG/KG				
ANIMAL #	486	487	488	489	490
DAY # 0					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 1					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF		P			
DAY # 2					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N		N	N
ELIZABETHAN COLLAR FOUND OFF					P
URINE					
DISCOLORATION,GREEN			1		
* HEMATURIA			4		
DAY # 3					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
ELIZABETHAN COLLAR FOUND OFF	P				P
DAY # 4					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 5					
DEHYDRATION	3				
CLINICAL EXAMINATION, NORMAL			N		
NOSE					
DRIED PORPHYRIN DISCHARGE	1	1		2	1
EYES					
DRIED PORPHYRIN DISCHARGE	1	1		1	1
HAIR OF INGUINAL REGION					
HAIRCOAT, DRY URINE STAIN				3	
SKIN OF BACK					
CRUST/SCALE ON SKIN				3	1
DAY # 6					
CLINICAL EXAMINATION, NORMAL	N	N	N		
SKIN OF BACK					
CRUST/SCALE ON SKIN				3	1
DAY # 7					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 8					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 9					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 10					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - A.M.	2000 MG/KG				
ANIMAL #	486	487	488	489	490
DAY # 11					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 12					
NOSE					
DRIED PORPHYRIN DISCHARGE	1			1	
SKIN OF BACK					
DESQUAMATION	2	1	2	2	1
ERYTHEMA		1	1	1	
CRUST/SCALE ON SKIN			2	2	
DAY # 13					
CLINICAL EXAMINATION, NORMAL					N
SKIN OF BACK					
DESQUAMATION	1	1	2	1	
CRUST/SCALE ON SKIN			2	1	
DAY # 14					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 15					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 16					
MORIBUNDITY/MORTALITY CHECK, NORMAL	N	N	N	N	N
DAY # 17					
SKIN OF FLANK					
ERYTHEMA	2				
DESQUAMATION	3		3		
SKIN OF BACK					
ERYTHEMA		1		1	2
DESQUAMATION		2		2	2

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	0 MG/KG				
ANIMAL #	471	472	473	474	475
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N	N	N	
EYES					
DRIED PORPHYRIN DISCHARGE	2				2
DAY # 2					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
EYES					
DRIED PORPHYRIN DISCHARGE					1
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF NECK					
ENLARGED,NOS		2			
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE		2			2
EYES					
DRIED PORPHYRIN DISCHARGE					1
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 8					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	
EYES					
DRIED PORPHYRIN DISCHARGE					1
DAY # 9					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 10					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 11					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 15					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 16					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	0 MG/KG				
ANIMAL #	471	472	473	474	475
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	100 MG/KG				
ANIMAL #	476	477	478	479	480
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N	N		N
EYES					
DRIED PORPHYRIN DISCHARGE	1			1	
DAY # 2					
CLINICAL EXAMINATION, NORMAL	N	N	N		
EYES					
DRIED PORPHYRIN DISCHARGE				2	1
DAY # 3					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 4					
CLINICAL EXAMINATION, NORMAL	N		N		N
SKIN OF BACK					
ERYTHEMA		1			
EYES					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N		N	N	N
SKIN OF BACK					
CRUST/SCALE ON SKIN		1			
DAY # 8					
CLINICAL EXAMINATION, NORMAL		N	N		N
EYES					
DRIED PORPHYRIN DISCHARGE	1			2	
DAY # 9					
CLINICAL EXAMINATION, NORMAL	N		N		
SKIN OF BACK					
DESQUAMATION		1			1
ERYTHEMA		1			
EYES					
DRIED PORPHYRIN DISCHARGE				1	
DAY # 10					
CLINICAL EXAMINATION, NORMAL			N		
SKIN OF BACK					
ERYTHEMA	1	1			
DESQUAMATION				1	1
DAY # 11					
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
DESQUAMATION	1	1	1		1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	100 MG/KG				
ANIMAL #	476	477	478	479	480
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N		N		N
SKIN OF BACK					
ERYTHEMA		1			
CRUST/SCALE ON SKIN				1	
DAY # 15					
CLINICAL EXAMINATION, NORMAL		N	N		
SKIN OF BACK					
ERYTHEMA	1				2
DESQUAMATION	1			1	
DAY # 16					
CLINICAL EXAMINATION, NORMAL			N		
SKIN OF BACK					
ERYTHEMA	1	1			2
DESQUAMATION	1			1	2
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	500 MG/KG				
ANIMAL #	481	482	483	484	485
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL	N	N		N	N
NOSE					
DRIED PORPHYRIN DISCHARGE			1		
DAY # 2					
CLINICAL EXAMINATION, NORMAL		N	N	N	
SKIN OF BACK					
ERYTHEMA	2				1
DAY # 3					
CLINICAL EXAMINATION, NORMAL		N			
SKIN OF BACK					
ERYTHEMA	1		1	1	2
CRUST/SCALE ON SKIN	2				
EYES					
DRIED PORPHYRIN DISCHARGE			2		
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE					4
DAY # 4					
CLINICAL EXAMINATION, NORMAL			N	N	
SKIN OF BACK					
ERYTHEMA	1	2			
CRUST/SCALE ON SKIN					2
DAY # 7					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 8					
CLINICAL EXAMINATION, NORMAL		N		N	
EYES					
DRIED PORPHYRIN DISCHARGE					2
SKIN OF BACK					
ERYTHEMA	1		1		
DAY # 9					
CLINICAL EXAMINATION, NORMAL			N	N	
SKIN OF BACK					
DESQUAMATION	1	2			2
ERYTHEMA	1				1
DAY # 10					
SKIN OF BACK					
DESQUAMATION	1	1	1	1	1
SKIN OF BACK					
ERYTHEMA			1	1	1

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	500 MG/KG				
ANIMAL #	481	482	483	484	485
DAY # 11					
CLINICAL EXAMINATION, NORMAL	N		N		
SKIN OF BACK					
ERYTHEMA		1		1	1
DESQUAMATION		1		1	1
DAY # 14					
CLINICAL EXAMINATION, NORMAL	N		N	N	
SKIN OF BACK					
ERYTHEMA		1			1
DESQUAMATION		1			1
DAY # 15					
CLINICAL EXAMINATION, NORMAL				N	
SKIN OF BACK					
ERYTHEMA	1	1	1		1
DESQUAMATION		1			1
DAY # 16					
CLINICAL EXAMINATION, NORMAL			N		
SKIN OF BACK					
ERYTHEMA	1	2		2	1
DESQUAMATION		2			1
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	2000 MG/KG				
ANIMAL #	486	487	488	489	490
DAY # 0					
CLINICAL EXAMINATION, NORMAL	N	N	N	N	N
DAY # 1					
CLINICAL EXAMINATION, NORMAL		N		N	N
EYES					
DRIED PORPHYRIN DISCHARGE	1		2		
DAY # 2					
CLINICAL EXAMINATION, NORMAL	N				N
SKIN OF BACK					
ERYTHEMA		1			
EYES					
DRIED PORPHYRIN DISCHARGE		1	1		
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE			4	3	
DAY # 3					
DEHYDRATION	4		2		
SKIN OF BACK					
ERYTHEMA		1	2	2	2
CRUST/SCALE ON SKIN				2	
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE	3	2		3	
DAY # 4					
DEHYDRATION	4				
SKIN OF BACK					
CRUST/SCALE ON SKIN		2	2	3	1
* WOUND				2	
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE				3	
DAY # 7					
CLINICAL EXAMINATION, NORMAL			N		
SKIN OF BACK					
CRUST/SCALE ON SKIN	1	2		3	1
ERYTHEMA				1	
DAY # 8					
CLINICAL EXAMINATION, NORMAL	N				
SKIN OF BACK					
DESQUAMATION		2	1		1
ERYTHEMA				2	1
CRUST/SCALE ON SKIN				3	
DAY # 9					
SKIN OF BACK					
DESQUAMATION	2	2	3	1	2
ERYTHEMA	2	1	2	1	
CRUST/SCALE ON SKIN				2	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

INDIVIDUAL ANIMAL CLINICAL SIGNS - FEMALE RATS

OBSERVATION PERIOD - P.M.	2000 MG/KG				
ANIMAL #	486	487	488	489	490
DAY # 10					
SKIN OF BACK					
CRUST/SCALE ON SKIN				2	1
DESQUAMATION	2	2	2	2	
ERYTHEMA	2	2	2	2	
DAY # 11					
SKIN OF BACK					
DESQUAMATION	2	1	2	2	1
ERYTHEMA	2	2	3	2	1
CRUST/SCALE ON SKIN			2	2	
NOSE					
DRIED PORPHYRIN DISCHARGE	2				
DAY # 14					
SKIN OF FLANK					
* DESQUAMATION	1				
* ERYTHEMA	1				
SKIN OF BACK					
ERYTHEMA		2	1	2	1
DESQUAMATION		1	2		1
DAY # 15					
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE	4				
EYES					
DRIED PORPHYRIN DISCHARGE	1				
SKIN OF FLANK					
DESQUAMATION	2				
ERYTHEMA	1				
SKIN OF BACK					
ERYTHEMA		2	3	2	2
DESQUAMATION		2	3	2	2
DAY # 16					
SKIN OF FLANK					
ERYTHEMA	3		2		
DESQUAMATION	3		3		
SKIN OF BACK					
ERYTHEMA		2		1	1
DESQUAMATION		3			3
DAY # 17					
INDUCED DEATH, CARBON DIOXIDE	P	P	P	P	P

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE
P - PRESENT, A - ABSENT, * - SEE COMMENT REPORT

CLINICAL COMMENT REPORT

DAY	DOSE LEVEL	ANIMAL	PERIOD	COMMENT
2	2000 MG/KG	488	A.M.	URINE TESTED W/ N-MULTISTIX - LARGE AMOUNTS OF BLOOD (+3)
4	2000 MG/KG	489	P.M.	WOUND CAUSED BY TAPE REMOVAL
11	2000 MG/KG	466	P.M.	WATER NIPPLE NOT WORKING
14	2000 MG/KG	486	P.M.	LEFT FLANK USED

INDIVIDUAL ANIMAL FEED CONSUMPTION (GRAMS) - MALE RATS

0 MG/KG

ANIMAL #	451	452	453	454	455
DAY 4	14.8	18.2	13.4	13.3	16.5
DAY 7	22.0	25.4	20.0	25.5	25.4
DAY 14	18.4	24.3	19.1	20.7	20.3

100 MG/KG

ANIMAL #	456	457	458	459	460
DAY 4	16.8	20.1	18.0	19.3	16.6
DAY 7	23.9	28.0	23.4	24.8	25.6
DAY 14	22.9	25.5	19.9	24.9	24.0

500 MG/KG

ANIMAL #	461	462	463	464	465
DAY 4	12.2	13.2	16.3	19.9	18.2
DAY 7	27.6	24.2	27.8	26.2	23.7
DAY 14	20.0	22.2	23.5	23.5	22.1

2000 MG/KG

ANIMAL #	466	467	468	469	470
DAY 4	17.4	16.8	13.3	18.1	15.3
DAY 7	27.3	25.4	22.9	23.7	24.0
DAY 14	16.8	22.5	22.1	22.2	22.7

INDIVIDUAL ANIMAL FEED CONSUMPTION (GRAMS) - FEMALE RATS

0 MG/KG

ANIMAL #	471	472	473	474	475
DAY 4	13.6	14.3	12.1	12.9	11.1
DAY 7	19.9	21.0	19.7	21.2	19.7
DAY 14	18.0	18.5	19.0	18.6	18.6

100 MG/KG

ANIMAL #	476	477	478	479	480
DAY 4	12.6	16.9	16.7	14.1	7.6
DAY 7	21.8	24.1	22.1	20.5	22.2
DAY 14	18.9	20.1	19.2	18.7	24.3

500 MG/KG

ANIMAL #	481	482	483	484	485
DAY 4	15.6	18.2	10.3	13.8	12.3
DAY 7	16.6	24.3	24.4	21.3	21.4
DAY 14	19.1	19.9	21.6	21.5	18.2

2000 MG/KG

ANIMAL #	486	487	488	489	490
DAY 4	4.1	11.3	11.9	11.7	11.4
DAY 7	19.1	18.2	23.6	22.2	19.7
DAY 14	22.8	18.7	21.5	20.9	19.8

INDIVIDUAL ANIMAL BODY WEIGHTS (GRAMS) - MALE RATS

0 MG/KG

ANIMAL #	451	452	453	454	455
DAY 0	257.9	275.2	291.6	276.1	277.6
DAY 4	247.6	276.2	276.8	273.8	269.3
DAY 7	274.5	299.9	288.1	292.1	294.5
DAY 14	282.9	330.3	300.5	306.6	300.2

100 MG/KG

ANIMAL #	456	457	458	459	460
DAY 0	264.1	283.8	266.2	281.9	288.2
DAY 4	264.4	273.9	258.2	282.3	278.3
DAY 7	290.8	307.0	282.4	307.3	307.1
DAY 14	320.3	320.1	286.0	332.1	328.7

500 MG/KG

ANIMAL #	461	462	463	464	465
DAY 0	288.8	276.0	287.5	273.0	269.6
DAY 4	267.8	247.0	275.1	280.1	264.6
DAY 7	308.0	280.1	301.9	300.9	293.8
DAY 14	313.1	305.3	312.1	307.2	315.6

2000 MG/KG

ANIMAL #	466	467	468	469	470
DAY 0	289.9	252.8	278.1	276.8	274.3
DAY 4	284.8	244.5	259.4	274.0	248.2
DAY 7	308.6	261.4	288.1	298.5	280.6
DAY 14	305.4	278.2	307.9	315.3	300.2

INDIVIDUAL ANIMAL BODY WEIGHTS (GRAMS) - FEMALE RATS

0 MG/KG

ANIMAL #	471	472	473	474	475
DAY 0	223.7	241.3	239.6	223.5	228.5
DAY 4	220.8	244.6	223.0	220.7	203.4
DAY 7	235.3	256.6	240.7	241.5	229.7
DAY 14	229.8	244.0	256.8	232.1	242.6

100 MG/KG

ANIMAL #	476	477	478	479	480
DAY 0	221.2	235.8	234.7	229.2	238.5
DAY 4	207.8	233.8	229.3	229.0	213.1
DAY 7	238.3	240.6	237.3	247.2	250.4
DAY 14	238.3	246.6	245.6	256.5	285.5

500 MG/KG

ANIMAL #	481	482	483	484	485
DAY 0	221.5	235.8	255.3	241.5	229.9
DAY 4	224.6	240.3	248.2	232.7	212.0
DAY 7	229.6	255.9	251.6	245.6	231.3
DAY 14	240.4	254.8	272.7	247.9	228.4

2000 MG/KG

ANIMAL #	486	487	488	489	490
DAY 0	234.6	231.7	223.3	235.6	231.0
DAY 4	179.9	219.6	214.1	208.7	206.9
DAY 7	216.9	233.5	252.7	237.7	222.4
DAY 14	231.4	236.5	239.3	224.1	236.0

INDIVIDUAL ANIMAL URINE MICROSCOPIC EXAMINATION - MALE RATS

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

	0 MG/KG				
ANIMAL #	451	452	453	454	455
RBC/HPF	0	0	3-5	0-1	0
WBC/HPF	0-1	0-3	1-3	0-2	0-1
EPITHELIAL CELLS/HPF	0	0	0	0	0
BACTERIA/HPF	3+	3+	3+	3+	2+
Triple Phosphate CRYSTALS/HPF	3+	2+	2+	1+	2+
AMORPHOUS SEDIMENT/HPF	0+	Not seen	0+	Not seen	1+
SPERM/HPF	1+	1+	2+	1+	1+
YEAST/HPF	Not seen	Not seen	Not seen	0+	Not seen

	100 MG/KG				
ANIMAL #	456	457	458	459	460
RBC/HPF	6-15	0	0-2	0-2	0-1
WBC/HPF	1-4	0-1	0-3	0-4	0-1
EPITHELIAL CELLS/HPF	0-2	0	0	0	0
BACTERIA/HPF	3+	1+	3+	2+	3+
Triple Phosphate CRYSTALS/HPF	3+	1+	2+	1+	3+
AMORPHOUS SEDIMENT/HPF	1+	0+	Not seen	Not seen	1+
SPERM/HPF	1+	1+	1+	0+	1+
YEAST/HPF	0+	Not seen	0+	0+	Not seen

	500 MG/KG				
ANIMAL #	461	462	463	464	465
RBC/HPF	0-1	0-1	1-2	0-1	0
WBC/HPF	0-4	1-2	1-2	0-4	0-1
EPITHELIAL CELLS/HPF	0	0	0	0	0
BACTERIA/HPF	3+	3+	3+	3+	2+
Triple Phosphate CRYSTALS/HPF	1+	3+	3+	3+	3+
AMORPHOUS SEDIMENT/HPF	1+	0+	1+	Not seen	2+
SPERM/HPF	1+	0+	2+	1+	1+
YEAST/HPF	1+	Not seen	Not seen	1+	Not seen

	2000 MG/KG				
ANIMAL #	466	467	468	469	470
RBC/HPF	0-1	0	0-1	0	0-1
WBC/HPF	1-3	1-4	3-4	0-3	0-1
EPITHELIAL CELLS/HPF	0-1	0	0-2	0-1	0
BACTERIA/HPF	1+	1+	2+	3+	1+
Triple Phosphate CRYSTALS/HPF	1+	3+	2+	2+	1+
AMORPHOUS SEDIMENT/HPF	2+	Not seen	1+	0+	Not seen
SPERM/HPF	1+	1+	3+	1+	2+
YEAST/HPF	Not seen	1+	0+	1+	Not seen

INDIVIDUAL ANIMAL URINE MICROSCOPIC EXAMINATION - FEMALE RATS

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

	0 MG/KG				
ANIMAL #	471	472	473	474	475
RBC/HPF	0-1	0	0	0-1	0
WBC/HPF	2-4	0-3	1-3	3-5	0-1
EPITHELIAL CELLS/HPF	1-2	0	0-2	0-1	0-2
BACTERIA/HPF	3+	2+	4+	3+	2+
Triple Phosphate CRYSTALS/HPF	1+	0+	1+	1+	Not seen
AMORPHOUS SEDIMENT/HPF	Not seen	Not seen	Not seen	2+	Not seen
SPERM/HPF	Not seen	Not seen	Not seen	Not seen	Not seen
YEAST/HPF	Not seen	Not seen	1+	Not seen	1+

	100 MG/KG				
ANIMAL #	476	477	478	479	480
RBC/HPF	0-1	0-1	0	0	0
WBC/HPF	0-3	1-3	2-3	0	1-4
EPITHELIAL CELLS/HPF	0-2	0	0	0	0-2
BACTERIA/HPF	4+	2+	2+	3+	2+
Triple Phosphate CRYSTALS/HPF	1+	2+	1+	0+	0+
AMORPHOUS SEDIMENT/HPF	1+	2+	2+	1+	0+
SPERM/HPF	Not seen	Not seen	Not seen	Not seen	Not seen
YEAST/HPF	1+	Not seen	1+	Not seen	1+

	500 MG/KG				
ANIMAL #	481	482	483	484	485
RBC/HPF	0-1	0	0-1	0	0-1
WBC/HPF	0-1	0-1	1-2	1-2	0-1
EPITHELIAL CELLS/HPF	0	0-1	0	0-1	0
BACTERIA/HPF	3+	3+	3+	1+	1+
Triple Phosphate CRYSTALS/HPF	0+	1+	1+	0+	0+
AMORPHOUS SEDIMENT/HPF	2+	0+	1+	0+	1+
SPERM/HPF	Not seen	Not seen	Not seen	Not seen	Not seen
YEAST/HPF	Not seen	1+	Not seen	1+	Not seen

	2000 MG/KG				
ANIMAL #	486	487	488	489	490
RBC/HPF	0-1	0	0	0	0-1
WBC/HPF	2-4	0	0-1	0	3-5
EPITHELIAL CELLS/HPF	0-3	0	0	0	0-1
BACTERIA/HPF	3+	3+	3+	1+	2+
Triple Phosphate CRYSTALS/HPF	1+	1+	0+	0+	0+
AMORPHOUS SEDIMENT/HPF	2+	1+	1+	Not seen	3+
SPERM/HPF	Not seen	Not seen	Not seen	Not seen	Not seen
YEAST/HPF	1+	Not seen	Not seen	Not seen	Not seen

INDIVIDUAL ANIMAL URINE DIPSTICK DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

			0 MG/KG			
	ANIMAL #	451	452	453	454	455
BLOOD		Negative	Negative	Moderate	Negative	Negative
			100 MG/KG			
	ANIMAL #	456	457	458	459	460
BLOOD		Moderate	Negative	Negative	Negative	Moderate
			500 MG/KG			
	ANIMAL #	461	462	463	464	465
BLOOD		Negative	Negative	Small	Negative	Negative
			2000 MG/KG			
	ANIMAL #	466	467	468	469	470
BLOOD		Negative	Negative	Negative	Negative	Negative

INDIVIDUAL ANIMAL URINE DIPSTICK DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: URINE
SAMPLE DAY # 14

			0 MG/KG			
	ANIMAL #	471	472	473	474	475
BLOOD		Negative	Negative	Negative	Negative	Negative
			100 MG/KG			
	ANIMAL #	476	477	478	479	480
BLOOD		Negative	Negative	Negative	Negative	Negative
			500 MG/KG			
	ANIMAL #	481	482	483	484	485
BLOOD		Negative	Negative	Non-Hemolyzed Trace	Negative	Negative
			2000 MG/KG			
	ANIMAL #	486	487	488	489	490
BLOOD		Negative	Negative	Negative	Negative	Negative

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: BLOOD

0 MG/KG

ANIMAL #	451	452	453	454	455
WBC/MM3 X3	10.6	17.5	15.9	13.1	10.1
RBC/MM3 X6	9.0	8.6	9.1	7.6	8.5
HB CONC , G/DL	16.8	16.3	16.4	15.0	15.9
HCT , %	51.6	50.5	50.4	46.2	48.1
MCV , U3	57.1	58.8	55.7	60.8	56.6
MCH , UUG	18.6	19.0	18.1	19.7	18.7
MCHC , %	32.5	32.3	32.6	32.5	33.0
PLATELETS/MM3 X3	822.0	964.0	997.0	849.0	914.0
POLYS , %	23.0	12.0	3.0	11.0	7.0
BANDS , %	1.0	0.0	0.0	1.0	0.0
LYMPHOCYTES,%	71.0	80.0	91.0	82.0	89.0
MONOCYTES,%	5.0	5.0	3.0	5.0	4.0
EOSINOPHIL,%	0.0	2.0	3.0	0.0	0.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	1.0	0.0	1.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.8	15.8	17.0	16.0	17.0

100 MG/KG

ANIMAL #	456	457	458	459	460
WBC/MM3 X3	13.8	13.0	10.0	13.7	16.4
RBC/MM3 X6	8.4	8.1	8.7	7.8	8.4
HB CONC , G/DL	15.1	15.3	17.1	15.5	15.7
HCT , %	46.4	48.1	52.1	47.9	48.5
MCV , U3	55.6	59.1	60.1	61.1	57.5
MCH , UUG	18.1	18.8	19.7	19.8	18.6
MCHC , %	32.5	31.7	32.8	32.4	32.4
PLATELETS/MM3 X3	1078.0	737.0	844.0	1319.0	1081.0
POLYS , %	16.0	12.0	18.0	8.0	22.0
BANDS , %	0.0	0.0	1.0	0.0	0.0
LYMPHOCYTES,%	77.0	76.0	76.0	85.0	69.0
MONOCYTES,%	5.0	7.0	3.0	5.0	5.0
EOSINOPHIL,%	2.0	4.0	1.0	2.0	2.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	1.0	1.0	0.0	2.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.4	14.5	15.9	15.5	16.8

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: BLOOD

	500 MG/KG				
ANIMAL #	461	462	463	464	465
WBC/MM3 X3	12.8	12.0	10.0	14.1	11.1
RBC/MM3 X6	7.7	8.6	8.7	8.4	8.1
HB CONC , G/DL	14.6	16.7	16.6	15.6	15.4
HCT , %	44.3	50.8	49.7	48.2	48.3
MCV , U3	57.7	58.8	57.0	57.6	59.3
MCH , UUG	19.1	19.4	19.1	18.7	18.9
MCHC , %	33.0	32.9	33.4	32.5	31.9
PLATELETS/MM3 X3	783.0	935.0	993.0	856.0	1005.0
POLYS , %	10.0	6.0	13.0	6.0	8.0
BANDS , %	0.0	1.0	0.0	0.0	0.0
LYMPHOCYTES,%	88.0	89.0	81.0	87.0	79.0
MONOCYTES,%	2.0	2.0	3.0	5.0	9.0
EOSINOPHIL,%	0.0	2.0	2.0	1.0	2.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	0.0	1.0	1.0	2.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.4	16.2	16.0	15.5	16.3

	2000 MG/KG				
ANIMAL #	466	467	468	469	470
WBC/MM3 X3	10.7	10.2	7.4	11.5	10.9
RBC/MM3 X6	7.9	8.6	8.0	8.2	8.8
HB CONC , G/DL	15.1	15.9	15.2	15.8	15.6
HCT , %	46.6	48.7	46.8	48.9	47.8
MCV , U3	59.1	56.7	58.7	59.6	54.5
MCH , UUG	19.2	18.4	19.1	19.3	17.8
MCHC , %	32.5	32.5	32.5	32.4	32.6
PLATELETS/MM3 X3	1239.0	923.0	1028.0	996.0	1090.0
POLYS , %	14.0	4.0	5.0	7.0	15.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	74.0	89.0	88.0	83.0	79.0
MONOCYTES,%	8.0	2.0	7.0	5.0	2.0
EOSINOPHIL,%	2.0	4.0	0.0	4.0	3.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	2.0	1.0	0.0	1.0	1.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.5	15.4	15.3	15.9	15.7

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: BLOOD

	0 MG/KG				
ANIMAL #	471	472	473	474	475
WBC/MM3 X3	5.8	10.9	11.6	9.4	10.7
RBC/MM3 X6	8.0	7.8	8.0	7.7	9.4
HB CONC , G/DL	15.6	15.1	15.7	14.2	17.4
HCT , %	45.6	46.2	48.2	42.5	51.7
MCV , U3	56.8	59.5	60.3	54.9	55.0
MCH , UUG	19.5	19.5	19.7	18.3	18.5
MCHC , %	34.3	32.7	32.7	33.4	33.6
PLATELETS/MM3 X3	998.0	1150.0	1009.0	1025.0	1040.0
POLYS , %	30.0	11.0	8.0	6.0	29.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	63.0	87.0	83.0	88.0	66.0
MONOCYTES,%	3.0	1.0	6.0	5.0	3.0
EOSINOPHIL,%	0.0	0.0	2.0	1.0	0.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	4.0	1.0	1.0	0.0	2.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	14.9	15.3	15.0	15.5	14.8

	100 MG/KG				
ANIMAL #	476	477	478	479	480
WBC/MM3 X3	c	7.2	12.4	6.4	12.5
RBC/MM3 X6		8.7	7.9	8.1	7.4
HB CONC , G/DL		16.6	14.6	15.2	14.2
HCT , %		50.4	44.2	44.9	43.2
MCV , U3		57.7	56.1	55.7	58.2
MCH , UUG		19.1	18.6	18.9	19.1
MCHC , %		33.0	33.1	33.9	32.8
PLATELETS/MM3 X3		1071.0	1164.0	1134.0	1036.0
POLYS , %	12.0	7.0	12.0	23.0	16.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	82.0	89.0	84.0	67.0	77.0
MONOCYTES,%	6.0	2.0	4.0	7.0	5.0
EOSINOPHIL,%	0.0	1.0	0.0	2.0	1.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	1.0	0.0	1.0	1.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	q	14.9	15.5	16.3	14.0

KEY: c - NO SAMPLE AVAILABLE FOR ANALYSIS, TUBE CLOTTED
q - QUANTITY INSUFFICIENT

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: BLOOD

			500 MG/KG		
ANIMAL #	481	482	483	484	485
WBC/MM3 X3	10.7	9.4	13.8	6.5	11.2
RBC/MM3 X6	7.5	8.0	7.4	8.3	8.5
HB CONC , G/DL	14.3	14.8	14.5	15.9	16.3
HCT , %	42.8	44.3	44.2	47.8	49.3
MCV , U3	57.0	55.4	59.4	57.5	57.8
MCH , UUG	19.0	18.6	19.5	19.2	19.1
MCHC , %	33.4	33.5	32.9	33.3	33.0
PLATELETS/MM3 X3	853.0	1022.0	1086.0	964.0	1231.0
POLYS , %	24.0	9.0	11.0	17.0	8.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	70.0	82.0	84.0	71.0	88.0
MONOCYTES,%	2.0	7.0	3.0	5.0	2.0
EOSINOPHIL,%	2.0	1.0	0.0	3.0	1.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	2.0	1.0	2.0	4.0	1.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	16.2	q	15.9	15.2	15.0

			2000 MG/KG		
ANIMAL #	486	487	488	489	490
WBC/MM3 X3	9.6	12.0	7.3	16.1	9.0
RBC/MM3 X6	6.9	8.4	7.5	8.2	8.9
HB CONC , G/DL	13.5	15.9	14.9	15.9	16.6
HCT , %	41.5	48.2	45.8	48.2	50.6
MCV , U3	60.6	57.3	61.2	58.5	57.0
MCH , UUG	19.7	18.9	20.0	19.3	18.8
MCHC , %	32.6	32.9	32.7	33.0	32.9
PLATELETS/MM3 X3	1154.0	1238.0	893.0	1078.0	911.0
POLYS , %	18.0	2.0	3.0	21.0	15.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	72.0	88.0	90.0	71.0	75.0
MONOCYTES,%	7.0	5.0	3.0	8.0	7.0
EOSINOPHIL,%	0.0	1.0	3.0	0.0	3.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	3.0	4.0	1.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	16.1	14.5	16.5	15.0	14.9

KEY: q - QUANTITY INSUFFICIENT

INDIVIDUAL ANIMAL CELL MORPHOLOGY - MALE RATS

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

				0 MG/KG	
ANIMAL #	451	452	453	454	455
BLOOD ERYTHROCYTES		N		N	N
POIKILOCYTOSIS	1		1		
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				100 MG/KG	
ANIMAL #	456	457	458	459	460
BLOOD ERYTHROCYTES		N		N	N
POIKILOCYTOSIS	1				
ANISOCYTOSIS			1		
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				500 MG/KG	
ANIMAL #	461	462	463	464	465
BLOOD ERYTHROCYTES		N	N	N	N
ANISOCYTOSIS	1				
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				2000 MG/KG	
ANIMAL #	466	467	468	469	470
BLOOD ERYTHROCYTES		N	N	N	
POIKILOCYTOSIS	2				1
MICROCYTOSIS					1
SPHEROCYTOSIS					1
HYPOCHROMASIA	1				
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

KEY: N-NORMAL, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT

INDIVIDUAL ANIMAL CELL MORPHOLOGY - FEMALE RATS

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

				0 MG/KG	
ANIMAL #	471	472	473	474	475
BLOOD ERYTHROCYTES		N		N	
ANISOCYTOSIS	1				1
MICROCYTOSIS	1				
POIKILOCYTOSIS			1		1
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				100 MG/KG	
ANIMAL #	476	477	478	479	480
BLOOD ERYTHROCYTES		N		N	
POIKILOCYTOSIS	1		1		1
ANISOCYTOSIS					1
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				500 MG/KG	
ANIMAL #	481	482	483	484	485
BLOOD ERYTHROCYTES				N	
POIKILOCYTOSIS	1	1	1		1
ANISOCYTOSIS					1
MACROCYTOSIS					1
MICROCYTOSIS		1			
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N
				2000 MG/KG	
ANIMAL #	486	487	488	489	490
BLOOD ERYTHROCYTES					
MACROCYTOSIS	1	1			1
POLYCHROMASIA, INCREASED		1			
HYPOCHROMASIA		1			1
ANISOCYTOSIS	2		1		
MICROCYTOSIS	1				
POIKILOCYTOSIS				1	
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

KEY: N-NORMAL, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: SERUM

	0 MG/KG				
ANIMAL #	451	452	453	454	455
ALT (GPT) , U/L	42.80	26.01	32.79	37.84	33.69
UREA NITROGEN,MG/DL	14.63	10.59	16.59	15.83	14.18
GLUCOSE,MG/DL	93.07	82.76	110.12	97.00	101.40
CREATININE,MG/DL	0.62	0.69	0.67	0.70	0.73
SDH , U/L	8.51	5.78	5.78	7.65	4.74
BILIRUBIN TOTAL,MG/DL	0.02	0.00	0.00	0.00	0.02
TOTAL PROTEIN,G/DL	5.81	5.91	6.07	5.02	5.18
A/G RATIO	1.10	1.06	1.08	1.11	1.12
ALBUMIN,G/DL	3.04	3.05	3.15	2.64	2.73
CHOLESTEROL,MG/DL	40.30	53.06	71.16	57.26	42.09
TRIGLYCERIDES,MG/DL	33.27	32.97	25.42	39.19	12.72
CALCIUM , MG/DL	11.40	11.90	11.55	10.94	11.09
PHOSPHORUS , MG/DL	12.18	11.76	11.96	11.70	12.30
SODIUM , MEQ/L	147.00	149.00	150.00	146.00	148.00
POTASSIUM , MEQ/L	10.42	7.77	8.11	7.72	6.85

	100 MG/KG				
ANIMAL #	456	457	458	459	460
ALT (GPT) , U/L	31.37	23.64	37.50	30.54	30.48
UREA NITROGEN,MG/DL	13.07	14.53	15.74	13.35	13.89
GLUCOSE,MG/DL	107.83	129.24	89.37	111.81	94.23
CREATININE,MG/DL	0.59	0.66	0.72	0.76	0.69
SDH , U/L	7.09	5.06	10.45	4.03	6.09
BILIRUBIN TOTAL,MG/DL	0.01	0.03	0.06	0.01	0.02
TOTAL PROTEIN,G/DL	5.35	5.65	5.73	5.46	5.39
A/G RATIO	1.30	1.25	1.17	1.17	1.12
ALBUMIN,G/DL	3.02	3.14	3.09	2.95	2.84
CHOLESTEROL,MG/DL	47.51	66.70	39.76	60.90	44.67
TRIGLYCERIDES,MG/DL	32.50	52.96	15.22	25.44	32.67
CALCIUM , MG/DL	10.80	12.31	10.99	12.55	12.83
PHOSPHORUS , MG/DL	10.75	12.32	11.61	11.46	10.75
SODIUM , MEQ/L	149.00	148.00	151.00	147.00	149.00
POTASSIUM , MEQ/L	7.46	6.89	7.14	7.11	6.50

	500 MG/KG				
ANIMAL #	461	462	463	464	465
		s			
ALT (GPT) , U/L	47.59	32.65	35.46	35.27	25.96
UREA NITROGEN,MG/DL	14.91	14.30	14.55	13.41	15.82
GLUCOSE,MG/DL	103.12	112.80	104.85	108.94	85.29
CREATININE,MG/DL	0.63	0.64	0.56	0.67	0.64
SDH , U/L	26.64	7.37	7.05	7.67	5.97
BILIRUBIN TOTAL,MG/DL	0.00	0.11	0.02	0.00	0.08
TOTAL PROTEIN,G/DL	5.34	5.65	5.84	5.40	5.28
A/G RATIO	1.21	1.29	0.98	1.19	1.21
ALBUMIN,G/DL	2.92	3.18	2.89	2.93	2.88
CHOLESTEROL,MG/DL	61.65	66.97	41.68	44.23	51.47
TRIGLYCERIDES,MG/DL	27.60	34.76	12.55	38.26	29.49
CALCIUM , MG/DL	11.00	11.29	12.79	12.67	11.08
PHOSPHORUS , MG/DL	11.59	11.25	11.80	10.82	10.89
SODIUM , MEQ/L	146.00	149.00	148.00	148.00	149.00
POTASSIUM , MEQ/L	8.12	7.52	7.20	6.36	6.96

KEY: s - SLIGHT HEMOLYSIS

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION - MALE RATS

ANALYTICAL MATERIAL: SERUM

	2000 MG/KG				
ANIMAL #	466	467	468	469	470
ALT (GPT) , U/L	29.05	34.75	26.40	38.07	24.02
UREA NITROGEN,MG/DL	11.09	13.94	10.51	13.97	13.62
GLUCOSE,MG/DL	99.16	114.96	100.55	95.48	145.92
CREATININE,MG/DL	0.64	0.69	0.67	0.65	0.59
SDH , U/L	5.59	5.63	5.13	7.50	4.95
BILIRUBIN TOTAL,MG/DL	0.01	0.01	0.00	0.11	0.06
TOTAL PROTEIN,G/DL	5.76	5.80	5.67	5.76	6.04
A/G RATIO	1.31	1.01	1.47	1.14	1.17
ALBUMIN,G/DL	3.27	2.91	3.38	3.07	3.26
CHOLESTEROL,MG/DL	52.50	45.39	56.60	49.09	56.20
TRIGLYCERIDES,MG/DL	35.12	22.11	39.69	24.99	19.44
CALCIUM , MG/DL	12.15	11.12	10.55	11.69	11.53
PHOSPHORUS , MG/DL	10.46	10.56	10.35	10.80	9.13
SODIUM , MEQ/L	151.00	147.00	149.00	147.00	153.00
POTASSIUM , MEQ/L	6.91	8.31	6.96	9.83	5.85

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: SERUM

			0 MG/KG		
ANIMAL #	471	472	473	474	475
ALT (GPT) , U/L	28.98	27.92	33.27	33.56	33.27
UREA NITROGEN,MG/DL	15.52	17.97	14.42	19.17	19.82
GLUCOSE,MG/DL	93.54	99.21	85.42	92.13	89.13
CREATININE,MG/DL	0.69	0.87	0.73	0.68	0.88
SDH , U/L	6.47	5.17	8.53	5.74	7.65
BILIRUBIN TOTAL,MG/DL	0.04	0.00	0.10	0.07	0.01
TOTAL PROTEIN,G/DL	6.58	6.79	6.52	6.21	7.23
A/G RATIO	1.17	1.32	1.16	1.44	1.25
ALBUMIN,G/DL	3.54	3.87	3.50	3.66	4.01
CHOLESTEROL,MG/DL	43.76	67.32	58.57	49.44	72.18
TRIGLYCERIDES,MG/DL	22.68	26.21	24.73	30.23	38.21
CALCIUM , MG/DL	11.20	11.99	11.74	11.67	12.74
PHOSPHORUS , MG/DL	9.19	9.27	10.96	9.23	10.75
SODIUM , MEQ/L	147.00	145.00	150.00	145.00	143.00
POTASSIUM , MEQ/L	6.95	6.90	7.98	7.12	8.82

			100 MG/KG		
ANIMAL #	476	477	478	479	480
	s				
ALT (GPT) , U/L	22.34	26.61	27.81	30.22	26.52
UREA NITROGEN,MG/DL	20.56	18.57	22.16	14.99	19.03
GLUCOSE,MG/DL	97.48	107.06	98.70	99.71	86.84
CREATININE,MG/DL	0.89	0.67	0.86	0.68	0.87
SDH , U/L	6.38	6.20	5.44	5.95	7.36
BILIRUBIN TOTAL,MG/DL	0.03	0.14	0.06	0.00	0.09
TOTAL PROTEIN,G/DL	6.35	6.78	6.55	6.23	5.97
A/G RATIO	1.16	1.22	1.10	1.56	1.00
ALBUMIN,G/DL	3.41	3.72	3.44	3.79	2.99
CHOLESTEROL,MG/DL	50.40	74.87	63.43	41.29	63.53
TRIGLYCERIDES,MG/DL	21.90	60.72	26.62	30.28	24.57
CALCIUM , MG/DL	10.90	13.76	10.97	12.03	11.45
PHOSPHORUS , MG/DL	10.32	10.48	9.10	10.43	9.50
SODIUM , MEQ/L	143.00	146.00	146.00	145.00	146.00
POTASSIUM , MEQ/L	9.88	8.63	6.75	7.50	5.71

			500 MG/KG		
ANIMAL #	481	482	483	484	485
		t			
ALT (GPT) , U/L	32.33	26.32	35.24	25.42	30.71
UREA NITROGEN,MG/DL	24.47	19.53	16.07	13.31	16.79
GLUCOSE,MG/DL	111.36	108.27	85.92	114.84	115.83
CREATININE,MG/DL	0.83	0.71	0.85	0.65	0.84
SDH , U/L	6.34	5.65	7.11	9.46	6.95
BILIRUBIN TOTAL,MG/DL	0.00	0.05	0.00	0.02	0.00
TOTAL PROTEIN,G/DL	5.93	5.81	6.34	6.52	6.95
A/G RATIO	1.23	1.24	1.07	1.22	1.17
ALBUMIN,G/DL	3.27	3.21	3.28	3.58	3.75
CHOLESTEROL,MG/DL	55.90	61.16	64.45	58.87	59.69
TRIGLYCERIDES,MG/DL	30.72	21.15	45.24	25.76	45.96
CALCIUM , MG/DL	11.34	10.61	11.51	11.98	12.42
PHOSPHORUS , MG/DL	10.86	9.45	10.07	11.43	9.91
SODIUM , MEQ/L	146.00	146.00	147.00	146.00	144.00
POTASSIUM , MEQ/L	7.10	6.47	6.97	8.00	7.67

KEY: s - SLIGHT HEMOLYSIS
t - TRACE HEMOLYSIS

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION - FEMALE RATS

ANALYTICAL MATERIAL: SERUM

	2000 MG/KG				
ANIMAL #	486	487	488	489	490
	m			t	s
ALT (GPT) , U/L	32.91	35.44	29.30	35.43	28.33
UREA NITROGEN,MG/DL	12.26	15.09	15.52	16.90	13.61
GLUCOSE,MG/DL	81.78	110.22	92.20	99.52	65.09
CREATININE,MG/DL	0.77	0.80	0.72	0.86	0.79
SDH , U/L	6.61	7.12	4.08	7.18	7.31
BILIRUBIN TOTAL,MG/DL	0.05	0.03	0.04	0.01	0.04
TOTAL PROTEIN,G/DL	5.71	6.24	5.79	6.74	6.44
A/G RATIO	1.03	1.23	1.15	1.06	1.27
ALBUMIN,G/DL	2.90	3.44	3.09	3.47	3.60
CHOLESTEROL,MG/DL	58.42	59.31	39.18	91.37	81.07
TRIGLYCERIDES,MG/DL	45.90	69.26	40.57	60.22	66.78
CALCIUM , MG/DL	11.00	11.30	9.97	13.45	11.31
PHOSPHORUS , MG/DL	11.02	9.76	9.32	10.23	9.63
SODIUM , MEQ/L	144.00	146.00	147.00	147.00	145.00
POTASSIUM , MEQ/L	8.92	7.98	6.41	6.84	7.02

KEY: s - SLIGHT HEMOLYSIS
t - TRACE HEMOLYSIS
m - MODERATE HEMOLYSIS

INDIVIDUAL ANIMAL ORGAN WEIGHTS AND TERMINAL BODY WEIGHT(GRAMS) - MALE RATS

0 MG/KG

ANIMAL #	451	452	453	454	455
BODY WEIGHT	242.7	279.4	254.0	263.2	264.1
LIVER	7.3818	8.7990	7.5621	7.7389	7.0133
	3.0415	3.1492	2.9772	2.9403	2.6555
KIDNEYS	2.1455	2.3340	2.2464	2.5574	2.4986
	0.8840	0.8354	0.8844	0.9717	0.9461
SPLEEN	0.5399	0.5633	0.5168	0.6342	0.5943
	0.2225	0.2016	0.2035	0.2410	0.2250

100 MG/KG

ANIMAL #	456	457	458	459	460
BODY WEIGHT	276.7	298.6	239.9	285.6	275.9
LIVER	8.5206	9.8262	7.4974	8.9485	8.0647
	3.0794	3.2908	3.1252	3.1332	2.9231
KIDNEYS	2.5950	2.4119	2.1563	2.4787	2.6155
	0.9378	0.8077	0.8988	0.8679	0.9480
SPLEEN	0.5808	0.6453	0.5078	0.6356	0.7362
	0.2099	0.2161	0.2117	0.2225	0.2668

500 MG/KG

ANIMAL #	461	462	463	464	465
BODY WEIGHT	274.9	269.4	270.5	271.5	271.6
LIVER	9.5714	8.5856	7.9671	7.5614	8.2824
	3.4824	3.1869	2.9453	2.7850	3.0495
KIDNEYS	2.3372	2.3367	2.5441	2.4602	2.5683
	0.8504	0.8674	0.9405	0.9062	0.9456
SPLEEN	0.7623	0.5133	0.6140	0.5670	0.5705
	0.2774	0.1905	0.2270	0.2088	0.2101

2000 MG/KG

ANIMAL #	466	467	468	469	470
BODY WEIGHT	265.9	248.2	269.8	278.3	252.0
LIVER	9.3965	8.0476	8.5811	9.1913	8.1655
	3.5338	3.2424	3.1805	3.3027	3.2403
KIDNEYS	2.7225	2.3223	2.4297	2.5840	2.2494
	1.0239	0.9357	0.9006	0.9285	0.8926
SPLEEN	0.5693	0.4906	0.4600	0.5978	0.4558
	0.2141	0.1977	0.1705	0.2148	0.1809

INDIVIDUAL ANIMAL ORGAN WEIGHTS AND TERMINAL BODY WEIGHT(GRAMS) - FEMALE RATS

0 MG/KG

ANIMAL #	471	472	473	474	475
BODY WEIGHT	213.1	224.9	215.9	212.9	204.4
LIVER	6.6584	7.4036	6.3284	6.3230	7.3653
	3.1245	3.2920	2.9312	2.9699	3.6034
KIDNEYS	1.8589	2.0271	1.7642	1.7807	1.7794
	0.8723	0.9013	0.8171	0.8364	0.8705
SPLEEN	0.5098	0.4841	0.4386	0.5718	0.4881
	0.2392	0.2153	0.2031	0.2686	0.2388

100 MG/KG

ANIMAL #	476	477	478	479	480
BODY WEIGHT	197.2	215.0	202.7	221.9	230.5
LIVER	5.7603	6.6788	6.1914	6.8964	7.3318
	2.9216	3.1064	3.0545	3.1079	3.1808
KIDNEYS	1.4274	1.8122	1.5978	1.9312	1.9073
	0.7240	0.8429	0.7883	0.8703	0.8275
SPLEEN	0.4706	0.4446	0.4139	0.5343	0.6247
	0.2387	0.2068	0.2042	0.2408	0.2710

500 MG/KG

ANIMAL #	481	482	483	484	485
BODY WEIGHT	195.6	219.2	219.2	221.6	202.7
LIVER	5.9987	6.5676	6.9860	6.5723	6.5836
	3.0668	2.9956	3.1870	2.9658	3.2480
KIDNEYS	1.4245	1.7019	1.6531	2.2734	1.8861
	0.7283	0.7763	0.7542	1.0259	0.9305
SPLEEN	0.4501	0.4676	0.5715	0.5202	0.5426
	0.2301	0.2133	0.2607	0.2347	0.2677

2000 MG/KG

ANIMAL #	486	487	488	489	490
BODY WEIGHT	189.3	198.3	201.1	199.4	198.3
LIVER	6.6908	7.3055	6.5920	7.0546	6.6145
	3.5345	3.6841	3.2780	3.5379	3.3356
KIDNEYS	1.6104	1.7370	1.7312	1.6639	1.7181
	0.8507	0.8759	0.8609	0.8345	0.8664
SPLEEN	0.4498	0.4687	0.4746	0.4968	0.4528
	0.2376	0.2364	0.2360	0.2491	0.2283

APPENDIX B

PROTOCOL

CRUDE MCHM

HAEL No.: 97-0216 **EAN: 972790**
PM No.: 18717-00

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

970216G1

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

Sponsor's Representative:
Karen R. Miller, Ph.D.

TITLE **CRUDE MCHM: A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT**

Purpose

The purpose of this study is to evaluate the toxicity of a test substance when repeatedly applied to the skin of rats for approximately two weeks.

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, NY 14652-6272 USA

Sponsor

Eastman Chemical Company
P.O. Box 431
Kingsport, Tennessee 37662-5280

Authorized Representative: Karen R. Miller, Ph.D.

Study Dates: Definitions

Study Initiation: Date the protocol is signed by the Study Director.

Proposed Experiment Start: First date test system is exposed to the test substance.

Proposed Experiment Termination: Last date on which data are collected directly from the study.

Study Completion Date: Date the final report is signed by the Study Director.

Study Dates: Proposed Dates

Proposed Experiment Start: April 13, 1998

Proposed Experiment Termination: April 30, 1998

Proposed Study Completion Date: August 14, 1998

REGULATORY COMPLIANCE

Test Guidelines/ Regulations	There are no guidelines for an eleven-day toxicity study.
Test Standards	This study will be conducted according to: · United States Environmental Protection Agency, Toxic Substances Control Act, Good Laboratory Practice Standards, 40 CFR Part 792; and · Annex 2, Organisation for Economic Cooperation and Development, Guidelines for Testing of Chemicals [C(81)30(Final)]. with the following exceptions; · Test substance purity, stability, and structural identity will not be performed.

TEST ARTICLE CHARACTERIZATION

General Description	Test Substance Name:	Crude MCHM
	HAEL No.:	97-0216
	EAN:	972790
	PM No.:	18717-00
	SRID No.:	6-97
	Source of Test Substance:	Eastman Chemical Company, Kingsport, TN
	Experiment No.:	970216G1

Analyses

No analyses to characterize the test substance or test substance mixtures will be performed.

Storage

The bulk chemical (test substance) will be stored in a ventilated hood at ambient room temperature in a covered container unless conditions are otherwise required to maintain stability.

A reserve sample will be kept in the HAEL archive.

Safety

Precautions will be undertaken to avoid contact of the test substance with clothing, skin, or eyes.

Routine industrial hygiene practices will be employed in handling of this test substance.

TEST SYSTEM

Animals

Male and female, nulliparous and non-pregnant, Sprague-Dawley rats (CRL:CD(SD)BR/VAF Plus) will be purchased from Charles River Laboratories.

- Animals will be acclimated for at least five days prior to release from quarantine.
- At the start of the study, the rats will weigh 200 to 300 grams.

Rats were chosen for this study because they are a common representative species for toxicity studies. The OECD and EEC guidelines for a four-week study list the rat as an acceptable species for dermal toxicity studies.

Housing

Caging: Rats will be individually housed in stainless-steel, wire-mesh cages.

- The study will be conducted in the AAALAC-accredited vivarium area of Building 320.
- Housing cages will be washed weekly.
- Absorbent paper under the cages will be changed at least 3 times per week.

Room Conditions: The study room will be maintained at target levels of 22 ± 3°C and 30 - 70% relative humidity. A photoperiod of 12 hours from 6 a.m. to 6 p.m. will be maintained.

Feed

Certified Rodent Diet (PMI® #5002, meal) will be fed *ad libitum.*

- Feed containers will be cleaned and refilled at least once per week.
- Records of feed analyses are on file in Building 320.

TEST SYSTEM, continued

Water

Water will be supplied *ad libitum* via an automatic watering system.

The source of the water will be the local public water system. On a semiannual basis, the water is analyzed for metals, volatile organics, fluoride, pesticides, and PCBs. Additionally, a chemical analysis (AQMS No. 0148045) is performed. Records of water analyses are on file in Building 320.

There have been no contaminants identified in previous water analyses that would be expected to interfere with the conduct of the study.

Identification

Upon arrival, all rats will be identified by uniquely-numbered, metal ear tags. Ear tags which are lost during the course of the study will be replaced as soon as possible. Following the cull and randomization, each animal in the study will be assigned a study-specific animal number. This number and the ear tag number will be written on the cage-card, color-coded by group.

Randomization

For each sex, animals will be selected from the population based on body weight to yield a study population in which no animal's weight is more than 20% from the mean. These animals will be randomly placed into groups using computer-generated lists.

Following distribution into groups, an analysis of variance will be performed to determine if significant differences in body weight among the groups are present. The randomization will be accepted only if no significant differences are found.

STUDY DESIGN

Treatment Groups Animals will be distributed into groups as follows:

Group	Exposure Concentration	Number of Animals
1	Control / 0 mg/kg	5 Male and 5 Female Rats
2	Low / 100 mg/kg	5 Male and 5 Female Rats
5	Mid / 500 mg/kg	5 Male and 5 Female Rats
4	High / 2000 mg/kg	5 Male and 5 Female Rats

Dose levels were selected by the Sponsor.

Disposition of Groups The first day of exposure with the test substance will be designated as Day 0. Animals will be exposed 6 hours/day, for 13 consecutive week days (Monday to Friday of the first and second weeks and Monday to Wednesday of the third week). All animals will be necropsied on Day 17.

Test Substance Administration

- Route of Administration: Dermal
- Justification: Dermal contact is a potential route for human exposure and is an acceptable route of administration for toxicity studies as specified by regulatory agencies.
- Frequency/ Duration: 6 hours/day for 13 consecutive week days. (Monday to Friday of the first and second week and Monday to Wednesday of the third week).
- Application Site: The initial application site will be the back of each animal (intrascapular region). If erythema or edema of grade 3 or higher [graded as described in OECD Guideline 405 (Annex V., Test B.4) (Grading of Skin Reaction)], or induration are observed at the application site, the application site will be changed to the left flank and then to the right flank, as necessary.

STUDY DESIGN, continued

Test Substance Administration, continued	· Preparation Of Application Site:	On the day prior to the first application at a given application site, the hair will be removed using an electric clipper. An application site may be reclipped as necessary during the study.
	· Test Substance Preparation	The test substance will be administered as received.
	· Test Substance	Dose volumes will be calculated based on the most recent body weight. For test animals, single doses of the test substance will be placed in contact with the skin using a fiber pad (5 x 5 cm.) and a semi-occlusive wrap to hold the test substance in place for a period of six hours. After termination of exposure, the wrappings and patches will be removed. Residual test substance will be removed by gently wiping the application site using gauze pads soaked with physiological saline. The control animals will be treated in a like manner, except that they will receive a volume of distilled water equivalent to the volume of test substance administered to the test group.
	· Elizabethan Collars:	Immediately after each 6 hour exposure, Elizabethan collars will be placed around each animal's neck to restrict the ability to groom the area. The collars will be removed the following morning.
	· Test Concentrations:	2000, 500, 100, and 0 mg/kg. Exposure concentrations were selected by the Sponsor.

Body Weights

Body Weights: Body weights will be collected on Days 0 (the first day the animals are exposed to with the test substance), 4, 7, and 14.

Terminal Body Weights: Terminal body weights will be determined immediately prior to necropsy, but after exsanguination.

STUDY DESIGN, continued

Feed and Water Consumption

Feed Consumption: Feeders will be weighed on Days 0, 4, 7, and 14. Feeders will be weighed for animals that die spontaneously or are euthanatized *in extremis.*

Water Consumption: Water consumption will not be determined.

Clinical Observations

Clinical examinations (hands-on) will be performed immediately after each exposure and on weekend mornings. Each weekday morning, animals will be observed for moribundity and mortality.

Clinical examinations will include, but will not be limited to:

Hair coat	Level of motor activity	Eyes
Mucous membranes	Behavior patterns	Skin
Respiratory system	Circulatory system	Feces
Central nervous system	Autonomic nervous system	Urine

Urinalysis

On Day 13, all animals will be placed in metabolism cages for 24-hour urine collection. Water and feed will be available during the collection. Urinalysis for blood will be conducted using N-Multistix® Reagent Strips. Following centrifugation of the urine, microscopic examination of sediment will be conducted.

Blood Collection

Animals will be fasted overnight, anesthetized with carbon dioxide, and have blood collected from the posterior vena cava for hematology and clinical chemistry. Animals will be bled in a random order. Blood will not be collected from animals euthanatized *in extremis* prior to study termination.

STUDY DESIGN, continued

Hematology

Whole blood will be processed using a Technicon H•1 System hematology analyzer to determine the following:

Hemoglobin concentration	Hematocrit	Red blood cell count
Red blood cell indices	White blood cell count	Platelet count

and a BBL Fibrosystems will be used for measuring:

Prothrombin time

Blood smears will be examined for:

Cellular morphology — Differential white blood cell count
Reticulocyte cell count (These slides may be examined after review of the pathology report and consultation with the Sponsor)

Clinical Chemistry

Serum will be processed using a Roche Analytical Instruments Cobas Fara II serum chemistry analyzer to determine the following:

Alanine aminotransferase	Sorbitol dehydrogenase	Creatinine
Urea nitrogen	Glucose	Total protein
Total cholesterol	Triglycerides	Calcium
Phosphorus		

Total bilirubin (direct bilirubin may be measured at the discretion of the clinical biochemist if total bilirubin is elevated)

a Helena Laboratories Titan Gel Electrophoresis System will be used to determine the following:

Albumin — Albumin/Globulin ratios will be calculated from albumin and total protein values.

a Corning Flame 480 Photometer or a NOVA biomedical NOVA CRT5 electrolyte analyzer will be used for determining the following:

Sodium — Potassium

STUDY DESIGN, continued

Necropsy

1. Animals that die spontaneously or are euthanatized *in extremis* will be necropsied as soon as possible.
2. All surviving animals will be euthanatized and necropsied on Day 17.
3. The animals will be necropsied in a random pattern using a computer-generated list.
4. Animals will be fasted overnight prior to necropsy.
5. Animals will be anesthetized with carbon dioxide, and exsanguinated by severing the posterior vena cava after the collection of blood for analysis.
6. A gross necropsy will be conducted on each animal. Notation will be made of organs appearing grossly abnormal.

Organ Weights

Wet weights of the following organs will be collected from all animals at necropsy. Paired organs will be weighed together. Organ weights will not be collected from animals euthanatized *in extremis* prior to study termination.

Tissues to be weighed include:

Liver	Kidneys	Spleen

Organs to be Collected

The following tissues will be collected in 10% buffered formalin:

Liver	Kidneys	Spleen
Sternum (with Bone Marrow)	Gross Lesions	

The femurs from each animal will be removed for preparation of bone marrow slides.

STUDY DESIGN, continued

Bone Marrow Slide Preparation	The femurs from each animal will be removed. The adhering muscle and connective tissue will be removed, and the femurs placed in small, sealed plastic tubes containing 5 mL of fetal bovine serum (FBS). After opening both ends of the femur, the marrow will be flushed into a small (15mL) centrifuge tube using a syringe and needle filled with FBS. The marrow from both femurs of one animal will be collected into one tube. Following centrifugation at approximately 270 x g, the supernatant serum fraction will be poured off and portions of the resuspended bone marrow cell pellet prepared as blood films on four separate slides. The slides will then be air dried, and briefly fixed in methanol. The slides will be stained with May-Gruenwald-Giemsa, Wright-Giemsa, or other appropriate stain using standard staining procedures.
Bone Marrow Slide Examination	After review of the pathology report and consultation with the Sponsor, the bone marrow slides may be examined for: Differential bone marrow cell count Myeloid/Erythroid ratios will be calculated from the percentage of neutrophils and neutrophil precursors to the percentage of nucleated erythroid precursors.
Histopathology	All tissues listed above will be examined microscopically for animals from the control and high-dose groups. Tissues will be processed by routine techniques for paraffin embedment, hematoxylin-eosin staining, and light microscopic examination. Target organs and gross lesions will be examined microscopically for animals from the low- and mid-dose groups.

DATA EVALUATION

Means

Mean values will be calculated for:

- Body weight;
- Feed consumption;
- Hematology and clinical chemistry values; and
- Absolute and relative (to body weight) organ weights;

Continuous Data Analysis

Homogeneity of body weight, feed consumption, clinical pathology, and organ weight data will be evaluated using the following computer-generated statistical tests:

- Bartlett's test ($p \leq 0.01$);
- One-way analysis of variance (ANOVA) ($p \leq 0.05$); and
- Duncan's multiple range test ($p \leq 0.05$).

If the data are determined to be non-homogeneous, the data for that day will be evaluated using the following computer-generated statistical tests:

- Kruskal-Wallis H-test ($p \leq 0.05$) followed by
- Mann-Whitney U-test ($p \leq 0.05$) or
- Dunn's test ($p \leq 0.05$)

REPORTS

General Information

The final report will include the following general information:

- Name and address of the facility where the test was performed;
- Name and address of the Sponsor;
- A list of study participants;
- The inclusive dates of the test; and
- A summary of the data, including a statement of conclusions.

Materials Section

Materials section will include:

- HAEL No., EAN, and SRID No.;
- Results of any chemical analyses; and
- Identification of pertinent animal data collected including data on husbandry and caging conditions.

Methods Section

Methods section will include:

- A description of the experimental design and procedure; and
- Any deviations from standard operating procedures or the experimental design.

Results Section

Results section will include:

- Summary of mortality data;
- Description of clinical abnormalities and their subsequent course;
- Summary and individual animal clinical observations;
- Summary and individual animal weights and feed consumption;
- Summary and individual animal hematology, cell morphology, and clinical chemistry findings;
- Summary and individual animal urinalysis;
- Summary and individual absolute and relative (to body weight) organ weights;
- Summary and individual animal bone marrow counts; and
- Gross pathology and histopathology results.

Data Retention

The final report, tissues, paraffin blocks, slides, data sheets, all nonperishable raw data, and an aliquot of the test substance will be stored in the testing facility archive managed under GLP-mandated conditions.

ALTERATIONS TO THE PROTOCOL

Protocol Amendments

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, such change will be honored. However, it then becomes the responsibility of the Sponsor to follow such verbal change with a written verification. HAEL reserves the right to revise the protocol or deviate therefrom solely at the discretion of the Study Director if prior approval of the Sponsor cannot be obtained and the integrity of the study is considered to be in jeopardy. In this event, the Sponsor shall be notified of the alteration as soon as possible, and written verification of the change will be the responsibility of the Study Director. All protocol modifications will be signed by the Study Director and a representative of the Sponsor.

PERSONNEL

Project Participants

Study Director	Lisa G. Bernard, M.S.
Study Technician	Stephen D. Jessup, A.A.S.
Histopathologist	Robert H. Garman, D.V.M.

Other personnel may participate in the study on an as needed basis.

PROTOCOL

CRUDE MCHM

HAEL No.: 97-0216 **EAN: 972790**
PM No.: 18717-00

A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

Lisa Gayle Bernard
Study Director

April 2, 1998
Month/Day/Year

Mark C. Seaport
Unit Director, Mammalian Toxicology

3/30/98
Month/Day/Year

M. L. James
Quality Assurance Coordinator, HAEL

3/30/98
Month/Day/Year

John L. A. Hess
Director, Health and Environment Laboratories

4/1/98
Month/Day/Year

Karen R. Miller
Sponsor's Representative

4/7/98
Month/Day/Year

PROTOCOL AMENDMENT #1

TITLE: CRUDE MCHM: A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

Laboratory Project ID: 970216G1
EAN: 972790

The following changes are made to the protocol:

Location: Page 7, Test Substance Administration: Application Site
Change: "Guideline 405" to "Guideline 404".
Reason: The incorrect guideline number was entered into the protocol.

Lisa G. Bernard, M.S.
Study Director

4-13-98
Month/Day/Year

Karen R. Miller, Ph.D.
Sponsor's Representative

7/21/98
Month/Day/Year

PROTOCOL AMENDMENT #2

TITLE: CRUDE MCHM: A TWO-WEEK DERMAL TOXICITY STUDY IN THE RAT

Laboratory Project ID: 970216G1
EAN: 972790

The following changes are made to the protocol:

Location: Page 12, Bone Marrow Slide Preparation

Change: "2 mL of fetal bovine serum" to "5 mL of fetal bovine serum".

Change: "using a syringe and needle filled with FBS" to "using a syringe and needle or a syringe and amber latex rubber tubing filled with FBS."

Reason: Based upon pre-study certification of techniques, the procedures were modified.

Lisa Joyce Bernard — 4-30-98

Lisa G. Bernard, M.S.
Study Director

Month/Day/Year

Karen R. Miller — 5-7-98

Karen R. Miller, Ph.D.
Sponsor's Representative

Month/Day/Year