FINAL REPORT

CRUDE MCHM

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

ACUTE ORAL TOXICITY STUDY IN THE RAT

GUIDELINE

OECD: 401
EEC: Annex V., Test B.1

AUTHOR

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TESTING FACILITY

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LABORATORY PROJECT ID

97-0216A0

STUDY SPONSOR

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

STUDY COMPLETION DATE

February 24, 1998

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
ACCESSION NUMBER: 972790 12/17/97

STUDY TYPE: ACUTE ORAL TOXICITY

Jonnie M. Bisbee, Jr. 12/20/97
(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
08/05/97	PROTOCOL APPENDIX/AMENDMENT SUBMISSION	
08/28/97	CLINICAL SIGNS AT 48 HRS.	08/28/97
11/25/97	GROSS PATHOLOGY HISTOPATHOLOGY PATHOLOGY REPORT	11/25/97
12/17/97	FINAL REPORT REVIEW	12/17/97

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted according to:

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

Lisa G. Bernard, M.S.
Study Director

2-24-98
Month/Day/Year

SIGNATURE PAGE

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ABSTRACT

CRUDE MCHM

HAEL No.: 97-0216 EAN: 972790
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ACUTE ORAL TOXICITY STUDY IN THE RAT

An acute oral toxicity study was conducted in which three groups of five male and five female rats were administered 2000, 1000, or 500 mg/kg of the neat test substance by gavage. All animals assigned to the 2000 mg/kg dose groups and three male and four female rats assigned to the 1000 mg/kg dose group died within 24 hours of dosing. In addition, one 500 mg/kg female rat was euthanatized *in extremis* on Day 2. Clinical signs observed during the 14-day observation period included slight to severe weakness, prostration, stumbling, a reduced amount or lack of feces, inguinal haircoat wet with urine, red urine, dehydration, gasping, and red staining of the hair of face, hair of forearms, and skin of front paws. Severe weakness and prostration were noted only in animals assigned to the 1000 or 2000 mg/kg dose groups which subsequently died. Transient slight weakness was observed for all 500 mg/kg animals and transient moderate weakness was observed for the surviving 1000 mg/kg animals on the day of dosing (Day 0). Stumbling, which was observed for animals from all dose groups on the day of dosing (Day 0), was either transient or observed prior to death. All surviving male rats appeared clinically normal by Day 2 and all surviving female rats appeared clinically normal by Day 4. Since red urine was noted for some animals, urine was tested for the presence of blood using a semi-quantitative dipstick (N-Multistix) The urine from all rats with red discolored urine, produced a positive response with the N-Multistix. The urine from approximately half of the rats which did not have red urine produced a positive response with the N-Multistix. A positive N-Multistix response in the absence of red discolored urine was considered indicative of levels of blood in the urine too low to produce visible color changes. All animals which survived to scheduled necropsy gained weight during both weeks of the study. The test substance was a gastric irritant as evidenced by edema of the glandular gastric mucosa for one 1000 mg/kg rat which died on Day 1. In addition, red discoloration of the urine in the urinary bladder observed for four 1000 mg/kg rats which died on Day 1 was considered treatment-related, although the source of discoloration was not determined. No other treatment-related changes were detected for the other 1000 mg/kg rats or for any 500 or 2000 mg/kg rats during the necropsy examinations and no treatment-related changes were observed during the histopathology examinations.

The acute oral LD_{50} for this test substance was calculated to be 933 mg/kg for male rats and 707 mg/kg for female rats. Based on the oral LD_{50} calculated by combining male and female mortality data (825 mg/kg), the test substance was classified as slightly toxic according to the criteria set forth by Hodge and Sterner (1949) and harmful if swallowed as defined in the 18th Adaptation of the EC Classification, Packaging and Labelling of Dangerous Substances Directive.

STUDY AND TEST SUBSTANCE INFORMATION

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
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Project Participants

Study Director:	Lisa G. Bernard, M.S.
Principal Investigator:	John W. Mosher, B.S.
Veterinarian:	Milan S. Vlaovic, D.V.M., Ph.D.

Sponsor

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

Sponsor's 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:	97-0216A0

Study Dates

Study Initiation Date:	August 5, 1997
Experimental Start Date:	August 5, 1997
Experimental Completion Date:	November 26, 1997

PURPOSE

The purpose of the study was to determine the estimated oral LD_{50} of the test substance in male and female rats and the clinical signs of toxicity associated with a single oral dose.

MATERIALS AND METHODS

Test System

Male and female Sprague-Dawley rats [SAS:VAF(SD)] obtained from SASCO, Inc., Stone Ridge (Kingston), NY were randomly assigned to each dose group. For the range-finding study, one male and one female rat were randomly assigned to each dose group. At the start of the range-finding study, the male rats were 11 to 12 weeks of age and weighed 267 to 313 grams and the female rats were 12 weeks of age and weighed 196 to 221 grams. For the oral toxicity study, five male and five female rats were randomly assigned to each dose group. At the start of the oral toxicity study, the male rats were 8 weeks of age and weighed 207 to 241 grams and the female rats were 8 to 9 weeks of age and weighed 152 to 181 grams. Rats were chosen for this study because they are a common representative species for toxicity studies. The rat is the preferred rodent species recommended for use in the Organisation for Economic Cooperation and Development (OECD) and European Economic Community (EEC) 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, wire mesh cages. Cages and racks were washed once a week. Absorbent paper, used to collect excreta, was changed at least three times a week.

Environmental Conditions

The study room was maintained at 19-22°C and 48-62% relative humidity. A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained.

Acclimation Period

The animals were isolated upon arrival and allowed to acclimate for a period of 5 days. Animals were judged to be healthy prior to testing.

Husbandry, continued

Feed

Certified Rodent Diet (PMI #5002, pelleted) 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 contained the study-specific animal number and the ear tag number.

Experimental Design

Test Procedures

This study was conducted according to the Organisation for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals: Guideline 401, Acute Oral Toxicity; and European Economic Community (EEC): Annex V., Test B.1, Acute Toxicity (Oral).

Randomization

The procedure for including animals in the study was to randomly select and assign animals from the same shipment to the study. Randomization was done by computer-generated lists. After assignment of animals to the study, the body weights were determined to ensure that individual body weights were within 20% of the mean weight for each sex.

Experimental Design, continued

Determination of Dose Levels

Initially, a limit dose of 2000 mg/kg of the test substance/kg body weight was selected as the dose level for the oral toxicity study. Based on results of a subsequent range-finding test, dose levels of 500, and 1000 mg/kg of the test substance were also selected for the oral toxicity study.

Test Substance Exposure

A single dose of the test substance was administered by gavage to animals that had been fasted overnight.

Preparation of Test Substance in the Vehicle

The test substance was administered as received.

Distribution of Animals

TABLE 1

Dose Level	Number Of Animals	Animal Numbers	
		Males	Females
Range-Finding Test			
1000 mg/kg	1 Male & 1 Female	513	516
500 mg/kg	1 Male & 1 Female	512	515
250 mg/kg	1 Male & 1 Female	511	514
Oral Toxicity Study			
2000 mg/kg	5 Males & 5 Females	501 - 505	506 - 510
1000 mg/kg	5 Males & 5 Females	526 - 530	536 - 540
500 mg/kg	5 Males & 5 Females	521 - 525	531 - 535

Body Weights

Body weights were collected on Days 0 (prior to treatment), 7, and 14. For animals which died or were euthanatized more than 24 hours after dosing, terminal body weights were collected at the time of necropsy.

Experimental Design, continued

Clinical Observations

Animals were observed three times on the day of dosing (Day 0), and once each day thereafter for the duration of the experiment. 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.

Necropsy

Any animal that died during the study was necropsied as soon as possible. All surviving animals were euthanatized and necropsied at the completion of the 14-day observation period.

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.

Data Analysis

No statistical procedures were required during the study. No dose/mortality curve was constructed since graphs become statistically useful only with the use of large numbers of animals and dose groups. The LD_{50} values and 95% confidence intervals were determined separately for male and female rats and for male and female rats combined according to the method of Weil (Weil, C.S., 1952).

Protocol and Standard Operating Procedure Deviations

There were no SOP or protocol deviations during the study.

RESULTS

RANGE-FINDING TEST

In a range-finding test, single male and female rats were administered single oral doses of 1000, 500, or 250 mg/kg of the test substance. The male and female rats administered 1000 mg/kg of the test substance were found dead on Day 1 (the day following administration). No other deaths occurred in the range-finding test during a 7-day observation period. Initially, a limit dose of 2000 mg/kg of the test substance/kg body weight was selected as the dose level for the oral toxicity study. Based on results of this range-finding test, dose levels of 1000 and 500 mg/kg of the test substance were also selected for the oral toxicity study.

ORAL TOXICITY STUDY

Mortality

Mortality was 100% for both sexes of rats at a dose level of 2000 mg/kg, and 60% for male rats and 80% for female rats at a dose level of 1000 mg/kg. Mortality was 0% for male and female rats at a dose level of 500 mg/kg, however, one 500 mg/kg female rat was euthanatized *in extremis*. The dose level, the number of animals dosed, the number of deaths, and the day of death are listed in Table 2.

TABLE 2

Mortality Table

Dose (mg/kg)	Number Of Rats Exposed (Male, Female)	Number Of Deaths (Male, Female)	Time Of Death
2000	5, 5	5, 5	Day 0-1
1000	5, 5	3, 4	Day 1
500	5, 5	0, 1[α]	Day 2

[α] One female rat was euthanatized *in extremis* on Day 2.

LD_{50} for male rats[β]: 933 mg/kg (95% C.I. = 664 - 1310)
LD_{50} for female rats[β]: 707 mg/kg (95% C.I. = 433 - 1154)
LD_{50} for the combined sexes[β]: 825 mg/kg (95% C.I. = 633 - 1074)

[β] Calculated according to the method of Weil (Weil, C.S., 1952).

Clinical Signs

Abnormal clinical signs observed during the 14-day observation period included slight to severe weakness, prostration, stumbling, dehydration, gasping, a reduced amount or lack of feces, inguinal haircoat wet with urine, red urine, and red staining of the hair of face, hair of forearms, and skin of front paws. The time of each observation and the number of animals involved at

each dose level are listed in Table 3. Due to the observation of red urine, urine was tested for the presence of blood using a semi-quantitative dipstick product (N-Multistix, Miles Inc., Diagnostic Division, Elkhart, IN.) on Days 1 and 3. The results of the N-Multistix tests are presented in Table 4.

TABLE 3

Table Of Clinical Observations

Dose (mg/kg)	Time	Clinical Signs	Number Of Animals Affected	
2000	Immediately after dosing	Appeared Clinically Normal Stumbling	4/5 Males 1/5 Males	5/5 Females - - - - -
2000	30 minutes after dosing	Severe Weakness Prostration Stumbling	5/5 Males - - - - - - - - - -	1/5 Females 1/5 Females 4/5 Females
2000	1 hour after dosing	Severe Weakness Prostration	5/5 Males 5/5 Males	5/5 Females 5/5 Females
2000	1-4 hours after dosing	Found Dead	1/5 Males	1/5 Females
2000	4 hours after dosing	Severe Weakness Prostration	4/4 Males 4/4 Males	4/4 Females 4/4 Females
2000	>4 hours after dosing	Found Dead	- - - - -	1/4 Females
2000	Day 1	Found Dead	4/4 Males	3/3 Females
1000	Immediately after dosing	Appeared Clinically Normal	5/5 Males	5/5 Females
1000	25 minutes after dosing	Appeared Clinically Normal Slight Weakness Moderate Weakness Stumbling	3/5 Males 1/5 Males 1/5 Males 2/5 Males	1/5 Females 4/5 Females - - - - - 4/5 Females
1000	1 hour after dosing	Slight Weakness Moderate Weakness Severe Weakness Stumbling	- - - - - 5/5 Males - - - - - 5/5 Males	2/5 Females - - - - - 3/5 Females 2/5 Females
1000	4 hour after dosing	Slight Weakness Moderate Weakness Severe Weakness Prostration Stumbling	- - - - - 3/5 Males 2/5 Males 2/5 Males 3/5 Males	- - - - - 2/5 Females 3/5 Females 3/5 Females 2/5 Females

Continued on the next page

TABLE 3, continued

Table Of Clinical Observations

Dose (mg/kg)	Time	Clinical Signs	Number Of Animals Affected	
1000	Day 1	Found Dead	1/5 Males	3/5 Females
		Severe Weakness	2/4 Males	1/2 Females
		Prostration	2/4 Males	1/2 Females
		Reduced Feces Amount	4/4 Males	- - - - -
		Red Urine	2/4 Males	2/2 Females
	Later that morning	Found Dead	2/4 Males	1/2 Females
1000	Day 2	Appeared Clinically Normal	2/2 Males	- - - - -
		Lack of Feces	- - - - -	1/1 Females
		Red Urine	- - - - -	1/1 Females
		Inguinal Haircoat Wet With Urine	- - - - -	1/1 Females
1000	Day 3	Appeared Clinically Normal	2/2 Males	- - - - -
		Reduced Feces Amount	- - - - -	1/1 Females
		Red Urine	- - - - -	1/1 Females
		Inguinal Haircoat Wet With Urine	- - - - -	1/1 Females
1000	Day 4	Appeared Clinically Normal	2/2 Males	- - - - -
		Inguinal Haircoat Wet With Urine	- - - - -	1/1 Females
1000	Days 5-14	Appeared Clinically Normal	2/2 Males	1/1 Females
500	Immediately after dosing	Appeared Clinically Normal	5/5 Males	5/5 Females
500	25 minutes after dosing	Appeared Clinically Normal	4/5 Males	5/5 Females
		Slight Weakness	1/5 Males	- - - - -
		Stumbling	1/5 Males	- - - - -
500	1 hour after dosing	Appeared Clinically Normal	3/5 Males	4/5 Females
		Slight Weakness	2/5 Males	1/5 Females
		Stumbling	2/5 Males	1/5 Females
500	4 hour after dosing	Slight Weakness	5/5 Males	5/5 Females
		Stumbling	3/5 Males	3/5 Females
500	Day 1	Appeared Clinically Normal	5/5 Males	- - - - -
		Reduced Feces Amount	- - - - -	5/5 Females
		Red Urine	- - - - -	2/5 Females
500	Day 2	Appeared Clinically Normal	5/5 Males	4/5 Females
		Inguinal Haircoat Wet With Urine; Gasping; Dehydration; Hair of Face, Hair of Forearms, and Skin of Front Paws Stained Red; Reduced Feces Amount; Euthanatized *In Extremis*	- - - - -	1/5 Females
500	Day 3	Appeared Clinically Normal	5/5 Males	4/4 Females
500	Days 4-14	Appeared Clinically Normal	5/5 Males	4/4 Females

TABLE 4

N-Multistix Results For Animals With Red Urine

Dose (mg/kg)	Time	Clinical Signs	Number Of Animals Affected	
1000	Day 1	Large (+++) Amount	- - - - -	1/1 Females
1000	Day 3	Large (+++) Amount	- - - - -	1/1 Females
500	Day 1	Small (+) Amount Large (+++) Amount	- - - - - - - - - -	1/2 Females 1/2 Females

N-Multistix Results For Animals Which Did Not Have Red Urine

Dose (mg/kg)	Time	Clinical Signs	Number Of Animals Affected	
1000	Day 1	Small (+) Amount Trace Amount (Non-hemolyzed)	1/2 Males 1/2 Males	- - - - - - - - - -
1000	Day 3	Moderate (++) Amount	2/2 Males	- - - - -
500	Day 1	Negative Small (+) Amount Large (+++) Amount	3/5 Males 1/5 Males 1/5 Males	2/3 Females - - - - - 1/3 Females
500	Day 3	Negative Small (+) Amount Moderate (++) Amount Large (+++) Amount	1/5 Males 1/5 Males 2/5 Males 1/5 Males	3/4 Females - - - - - 1/4 Females - - - - -

Body Weights

All animals which survived to termination of the 14-day observation period gained weight during both weeks of the study. The individual body weights are listed in Table 5.

TABLE 5

Table Of Individual Body Weights (grams)

Dose (mg/kg)	Animal Number	Day 0	Day 7	Day 14
MALE RATS				
2000	501	207	Found Dead on Day 1	x
2000	502	211	Found Dead on Day 0	x
2000	503	212	Found Dead on Day 1	x
2000	504	225	Found Dead on Day 1	x
2000	505	241	Found Dead on Day 1	x

Continued on the next page

TABLE 5, continued

Table Of Individual Body Weights (grams)

Dose (mg/kg)	Animal Number	Day 0	Day 7	Day 14
MALE RATS, continued				
1000	526	212	Found Dead on Day 1	x
1000	527	227	Found Dead on Day 1	x
1000	528	240	299	344
1000	529	216	260	290
1000	530	198	Found Dead on Day 1	x
500	521	215	275	306
500	522	219	269	306
500	523	211	256	292
500	524	213	268	288
500	525	227	305	345
FEMALE RATS				
2000	506	178	Found Dead on Day 1	x
2000	507	168	Found Dead on Day 1	x
2000	508	162	Found Dead on Day 0	x
2000	509	181	Found Dead on Day 1	x
2000	510	164	Found Dead on Day 0	x
1000	536	152	Found Dead on Day 1	x
1000	537	165	194	215
1000	538	171	Found Dead on Day 1	x
1000	539	167	Found Dead on Day 1	x
1000	540	176	Found Dead on Day 1	x
500	531	160	187	195
500	532	166	192	210
500	533	174	209	237
500	534	172	Euthanatized on Day 2	(142 Day 2)
500	535	167	190	211

x A terminal body weight was not recorded for any animal which died within 24 hours of dosing.

Gross Pathology and Histopathology

Treatment-related gross pathological changes were only observed for three of seven 1000 mg/kg animals which died on Day 1. These changes consisted of edema of the glandular gastric mucosa (1/5 male rats), and red discoloration of the urine in the urinary bladder (2/5 male and 1/5 female rats). No other treatment-related changes were detected for the 1000 mg/kg rats or for any 2000 or 500 mg/kg rats. Incidental gross findings were observed in the lungs, thymus, stomach, liver, pancreas, spleen, and small intestine.

Selected gross lesions were processed for microscopic evaluation. No treatment-related changes were observed during the histopathology examinations. Incidental microscopic findings were observed in the liver, lungs, thymus, and spleen.

For a detailed record of the incidence and severity of gross and histopathology lesions, see the pathologist's report and computer-generated tables which are included in the Appendix.

DISCUSSION

An acute oral toxicity study was conducted in which rats were administered 2000, 1000, or 500 mg/kg of the neat test substance by gavage. Mortality was 100% for both sexes of rats at a dose level of 2000 mg/kg, and 60% for male rats and 80% for female rats at a dose level of 1000 mg/kg. Mortality was 0% for male and female rats at a dose level of 500 mg/kg, however, one 500 mg/kg female rat was euthanatized *in extremis* on Day 2. For the purpose of evaluating the data, this death was treated as a treatment-related death. Most animals which died exhibited severe weakness and/or prostration prior to death. The oral LD_{50} for this test substance was calculated to be 933 mg/kg for male rats and 707 mg/kg for female rats.

Clinical signs observed during the 14-day observation period included slight to severe weakness, prostration, stumbling, a reduced amount or lack of feces, inguinal haircoat wet with urine, red urine, dehydration, gasping, and red staining of the hair of face, hair of forearms, and skin of front paws. Severe weakness and prostration were noted only in animals assigned to the 1000 or 2000 mg/kg dose groups which subsequently died. Moderate weakness was observed for the surviving 1000 mg/kg animals and slight weakness was observed for all 500 mg/kg animals on the day of dosing (Day 0). Stumbling was observed for animals from all dose groups on the day of dosing (Day 0). All surviving male rats appeared clinically normal by Day 2 and all surviving female rats appeared clinically normal by Day 4. Since red urine was noted for a number of animals, urine was tested for the presence of blood using N-Multistix dipsticks on Days 1 and 3. For rats which had red urine and survived until the time of testing, the N-Multistix results ranged from +1 to +3. For the ten rats which did not have red urine on Day 1, the urine from five rats produced trace non-hemolyzed to +3 N-Multistix results. For the 11 rats which did not have red urine on Day 3, the urine from seven rats produced +1 to +3 N-Multistix results. A positive response for animals which did not have red discolored urine was considered indicative of levels of blood in the urine too low to produce visible color changes. All animals which survived to scheduled necropsy gained weight during both weeks of the study.

Treatment-related gross pathology changes observed for 1000 mg/kg rats which died on Day 1 consisted of edema of the glandular gastric mucosa (1/5 male rats), and red discoloration of the urine in the urinary bladder (2/5 male and 1/5 female rats). No other treatment-related changes were detected for the 1000 mg/kg rats or for any 2000 or 500 mg/kg rats during the necropsy examinations and no treatment-related changes were observed during the histopathology examinations.

CONCLUSION

The test substance was a gastric irritant as evidenced by edema of the glandular gastric mucosa. In addition, red discoloration of the urine in the urinary bladder of four 1000 mg/kg rats was considered treatment-related, although the source of discoloration was not determined. Based on the oral LD_{50} calculated by combining male and female mortality data (825 mg/kg), the test substance was classified as slightly toxic according to the criteria set forth by Hodge and Sterner (1949) and harmful if swallowed as defined in the 18th Adaptation of the EC Classification, Packaging and Labelling of Dangerous Substances Directive.

REFERENCES

Hodge, H.C. and Sterner, J.H. (1949). Tabulation of toxicity classes. *Am. Indust. Hyg. Quart.*, **10**, 93-96.

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

Weil, C.S. (1952). Table for Convenient Calculation of Median Effective Dose (LD50 or ED50) and Instructions in Their Use. *Biometrics.*, **8**, 249-263.

APPENDIX

HAEL No. 97-0216
EAN 972790

PATHOLOGY REPORT

Test Substance: Crude MCHM

Male and female rats given 2000, 1000, or 500 mg/kg of the test substance by gavage, as part of an acute oral toxicity study, were necropsied. Necropsy lesions are listed in computer-generated tables.

RESULTS

GROSS PATHOLOGY:

Male Rats - 2000 mg/kg dose group: No treatment-related changes were observed in a single rat that died on the day of dosing and the remaining four rats died on Day 1.

Incidental findings were observed in the lungs, thymus, stomach, and small intestines.

The lungs did not collapse completely when the thoracic cavity was opened during necropsy (4/5), thymus showed minor hemorrhage (4/5), non-glandular gastric mucosa was discolored red (1/5), and the gastric and small intestinal contents were watery (1/5). The carcasses of four rats showed minor autolysis.

Male Rats - 1000 mg/kg dose group: Treatment-related changes included a minor edema in the glandular gastric mucosa (1/5), and red discoloration of the urine in the urinary bladder (2/5).

Three rats died on Day 1 and the remaining two rats survived the observation period.

Incidental findings included incomplete collapse of the lungs when the thoracic cavity was opened during necropsy (1/5), minor thymus hemorrhage (2/5), dark livers (2/5), granular appearance of the hepatic capsule (2/5), minimal red discoloration (2/5) and firmness of the pancreas (2/5), and fluid contents in the stomach and small intestines of Rat 526.

Male Rats - 500 mg/kg dose group: No treatment-related changes were observed. All rats survived the observation period.

Incidental findings included a dark liver (1/5), granular appearance of the hepatic capsule (3/5), and minimal red discoloration (5/5) and firmness of the pancreas (5/5).

Female Rats - 2000 mg/kg dose group: No treatment-related changes were observed.

Two rats died on the day of dosing and the remaining three rats died on Day 1.

Incidental findings included incomplete collapse of the lungs when the thoracic cavity was opened during necropsy (5/5), minimal or minor thymus hemorrhage (3/5), minor fluid contents in the stomach (2/5) and small intestines (2/5), and minor red discoloration of the non-glandular gastric mucosa (2/5).

The carcasses of three rats showed minor autolysis .

Female Rats - 1000 mg/kg dose group: Treatment-related changes consisted of minor red discoloration of the urine in the urinary bladder (1/5).

Four rats died on Day 1 and the remaining rat survived the observation period.

Incidental findings included incomplete collapse of the lungs when the thoracic cavity was opened during necropsy (2/5), minimal or minor thymus hemorrhage (4/5), and minimal red discoloration (1/5) and firmness of the pancreas (1/5).

The carcasses of three rats showed minor or moderate autolysis.

Female Rats - 500 mg/kg dose group: No treatment-related changes were observed. One rat was euthanatized on Day 2 and the remaining four rats survived the observation period.

Incidental findings included incomplete collapse of the lungs when the thoracic cavity was opened during necropsy (1/5), moderate red discoloration of the lungs (1/5), minimal thymus hemorrhage (1/5), minor distention of the jejunum (1/5) and ileum with gas (1/5), a dark liver (1/5), minimal red discoloration (3/5) and firmness of the pancreas (3/5), small (1/5) and pale (1/5) spleen, minor red discoloration of the skin of the forepaws (1/5), minor wetness of the inguinal hair by urine (1/5), and minor red discoloration of the hair of the face (1/5).

HISTOPATHOLOGY:

Selected gross lesions were processed for microscopic evaluation.

Male Rats - 1000 mg/kg dose group: No treatment-related changes were observed.

Incidental findings included minor or moderate congestion of the liver (2/2), and minor cytoplasmic vacuolization of the hepatocytes (2/2).

Male Rats - 500 mg/kg dose group: No treatment-related changes were observed.

Incidental findings included minimal chronic focal inflammation of the liver (1/3), and minor cytoplasmic vacuolization of the hepatocytes (3/3).

Female Rats - 1000 mg/kg dose group: No treatment-related or incidental findings were observed.

Female Rats - 500 mg/kg dose group: No treatment-related changes were observed.

Incidental findings were observed in Rat 534 which included moderate lung congestion, minimal thymus hemorrhage, minor atrophy of the thymic cortex, moderate congestion of the liver, and a minor atrophy of the splenic red pulp.

COMMENTS:

No concurrent control group was available for observation. Therefore, the conclusions in this study were based on the experience of the pathologist with control animals from other studies.

Gross lesions that were associated with the treatment included minor edema in the glandular gastric mucosa of Rat 526 (1000 mg/kg), and minor distention of the urinary bladder with red discolored urine in Rats 527, 530, and 540 (1000 mg/kg).

There were no microscopic lesions that were associated with the treatment.

Incidental microscopic findings were observed in the liver, lungs, thymus, and spleen.

Minor or moderate liver congestion was observed in Rats 534 (500 mg/kg) and Rats 528 and 529 (1000 mg/kg). This was considered to be either an agonal phenomenon not related to the treatment, or a consequence of an incomplete bleeding prior to necropsy. Minimal chronic focal inflammation of the liver was observed in Rat 523 (500 mg/kg). The foci of chronic inflammation were routinely distributed throughout the liver and were characterized by small accumulations of predominantly mononuclear cells. Minor cytoplasmic vacuolization of hepatocytes was present in Rats 521, 522, 523 (500 mg/kg) and in Rats 528 and 529 (1000 mg/kg). On gross observation, cytoplasmic vacuolization in hepatocytes was characterized as granularly appearing liver capsule. Cytoplasmic vacuolization of hepatocytes was characterized by the presence of small membrane-bound vacuoles. These vacuoles may have contained either glycogen or lipids: however, the unambiguous determination of vacuolar content depends on avoiding embedment procedures that extract glycogen and lipid, and on the use of special stains.

Moderate lung congestion in Rat 534 (500 mg/kg) was considered an agonal phenomenon not related to the treatment.

Thymic hemorrhage was an incidental finding observed in Rat 534 (500 mg/kg). Thymic hemorrhage was considered an agonal lesion, although it may have also occurred as a result of dissection of the thymus during necropsy. Minor atrophy of the thymic cortex that was observed in Rat 534 (500 mg/kg) was considered to be secondary to stress. Minor atrophy of the splenic red pulp in Rat 534 (500 mg/kg) was considered to be secondary to stress.

CONCLUSIONS

The test substance was a gastric irritant as evidenced by edema of the glandular gastric mucosa. Red discoloration of the urine in the urinary bladder of two male and one female rats from the 1000 mg/kg dose group was considered treatment-related, although the source of discoloration was not determined.

11/26/97

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11/26/97

Reviewed by
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MSV:jnt
11/25/97

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
TRACHEA	5	5	5
LUNGS	5	5	5
COLLAPSE INCOMPLETE ON THORACOTOMY	0	1	4
THYMUS	5	5	5
HEMORRHAGE	0	2	4
HEART	5	5	5
ESOPHAGUS	5	5	5
STOMACH	5	5	5
STOMACH, GLANDULAR			
EDEMA	0	1	0
GASTRIC CONTENTS			
INCREASED	0	1	1
STOMACH, NON-GLANDULAR			
DISCOLORATION,RED	0	0	1
DUODENUM	5	5	5
INTESTINAL CONTENTS			
INCREASED	0	1	1
JEJUNUM	5	5	5
INTESTINAL CONTENTS			
INCREASED	0	1	1
ILEUM	5	5	5
INTESTINAL CONTENTS			
INCREASED	0	1	1
CECUM	5	5	5
COLON	5	5	5
RECTUM	5	5	5
LIVER	5	5	5
COLOR-DARKER THAN NORMAL	1	2	0
HEPATIC CAPSULE			
GRANULAR APPEARANCE	3	2	0
KIDNEYS	5	5	5
URINARY BLADDER	5	5	5
DISTENTION	0	2	0
PITUITARY GLAND	5	5	5
ADRENALS	5	5	5
PANCREAS, NOS	5	5	5
DISCOLORATION,RED	5	2	0
THYROID GLANDS	5	5	5
PARATHYROID GLANDS	5	5	5
SPLEEN	5	5	5
MESENTERIC LYMPH NODES	5	5	5
BONE MARROW	5	5	5
BRAIN	5	5	5
EYES	5	5	5
SALIVARY GLANDS	5	5	5
ADIPOSE TISSUE	5	5	5
SKIN, NOS	5	5	5
SALIVARY GLANDS	5	5	5
ADIPOSE TISSUE	5	5	5

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

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
SKIN, NOS	5	5	5
HAIR	5	5	5
ACCESSORY SEX ORGANS (MALE)	5	5	5
EPIDIDYMIDES	5	5	5
TESTES	5	5	5
BODY AS A WHOLE, NOS	0	0	4
AUTOLYSIS	0	0	4

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

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
TRACHEA	5	5	5
LUNGS	5	5	5
COLLAPSE INCOMPLETE ON THORACOTOMY	1	2	5
DISCOLORATION,RED	1	0	0
THYMUS	5	5	5
HEMORRHAGE	1	4	3
HEART	5	5	5
ESOPHAGUS	5	5	5
STOMACH	5	5	5
STOMACH, NON-GLANDULAR			
DISCOLORATION,RED	0	0	2
GASTRIC CONTENTS			
INCREASED	0	0	2
DUODENUM	5	5	5
INTESTINAL CONTENTS			
INCREASED	0	0	2
JEJUNUM	5	5	5
DISTENTION	1	0	0
INTESTINAL CONTENTS			
INCREASED	0	0	2
ILEUM	5	5	5
DISTENTION	1	0	0
INTESTINAL CONTENTS			
INCREASED	0	0	1
CECUM	5	5	5
COLON	5	5	5
RECTUM	5	5	5
LIVER	5	5	5
COLOR-DARKER THAN NORMAL	1	0	0
KIDNEYS	5	5	5
URINARY BLADDER	5	5	5
DISTENTION	0	1	0
PITUITARY GLAND	5	5	5
ADRENALS	5	5	5
PANCREAS, NOS	5	5	5
DISCOLORATION,RED	3	1	0
THYROID GLANDS	5	5	5
PARATHYROID GLANDS	5	5	5
SPLEEN	5	5	5
SMALL	1	0	0
PALLOR	1	0	0
MESENTERIC LYMPH NODES	5	5	5
BONE MARROW	5	5	5
BRAIN	5	5	5
EYES	5	5	5
SALIVARY GLANDS	5	5	5
ADIPOSE TISSUE	5	5	5
SKIN, NOS	5	5	5
SKIN OF FOOT AND TOE			
DISCOLORATION,RED	1	0	0

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

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
HAIR	5	5	5
HAIR OF INGUINAL REGION			
HAIRCOAT, WET BY URINE	1	0	0
HAIR OF FACE			
DISCOLORATION,RED	1	0	0
FALLOPIAN TUBES	5	5	5
VAGINA	5	5	5
UTERUS	5	5	5
OVARIES	5	5	5
CERVIX UTERI	5	5	5
BODY AS A WHOLE, NOS	0	3	3
AUTOLYSIS	0	3	3

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

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS
500.000 MG/KG

ANIMAL #	521	522	523	524	525
DAYS ON TEST	14	14	14	14	14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X	X	X
THYMUS	X	X	X	X	X
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER				X	X
COLOR-DARKER THAN NORMAL		2			
HEPATIC CAPSULE					
GRANULAR APPEARANCE	1	1	1		
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
*PANCREAS, NOS					
DISCOLORATION,RED	1	1	1	1	1
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

1000.000 MG/KG

ANIMAL #	526	527	528	529	530
DAYS ON TEST	1	1	14	14	1
TRACHEA	X	X	X	X	X
LUNGS		X	X	X	X
COLLAPSE INCOMPLETE ON THORACOTOMY	P				
THYMUS			X	X	X
HEMORRHAGE	2	2			
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
*STOMACH		X	X	X	X
STOMACH, GLANDULAR					
EDEMA	2				
GASTRIC CONTENTS					
INCREASED	2				
*DUODENUM		X	X	X	X
INTESTINAL CONTENTS					
INCREASED	2				
*JEJUNUM		X	X	X	X
INTESTINAL CONTENTS					
INCREASED	2				
*ILEUM		X	X	X	X
INTESTINAL CONTENTS					
INCREASED	2				
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X			X
COLOR-DARKER THAN NORMAL			2	2	
HEPATIC CAPSULE					
GRANULAR APPEARANCE			1	1	
KIDNEYS	X	X	X	X	X
*URINARY BLADDER	X		X	X	
DISTENTION		2			2
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
*PANCREAS, NOS	X	X			X
DISCOLORATION,RED			1	1	
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

1000.000 MG/KG

ANIMAL #	526	527	528	529	530
DAYS ON TEST	1	1	14	14	1
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - MALE RATS

2000.000 MG/KG

ANIMAL #	501	502	503	504	505
DAYS ON TEST	1	0	1	1	1
TRACHEA	X	X	X	X	X
LUNGS				X	
COLLAPSE INCOMPLETE ON THORACOTOMY	P	P	P		P
THYMUS		X			
HEMORRHAGE	2		2	2	2
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
*STOMACH	X		X	X	X
GASTRIC CONTENTS					
INCREASED		2			
STOMACH, NON-GLANDULAR					
DISCOLORATION,RED		3			
*DUODENUM	X		X	X	X
INTESTINAL CONTENTS					
INCREASED		2			
*JEJUNUM	X		X	X	X
INTESTINAL CONTENTS					
INCREASED		2			
*ILEUM	X		X	X	X
INTESTINAL CONTENTS					
INCREASED		2			
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X
BODY AS A WHOLE, NOS					
AUTOLYSIS	2		2	2	2

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

500.000 MG/KG

ANIMAL #	531	532	533	534	535
DAYS ON TEST	14	14	14	2	14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X		X
COLLAPSE INCOMPLETE ON THORACOTOMY				P	
DISCOLORATION,RED				3	
THYMUS	X	X	X		X
HEMORRHAGE				1	
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
*JEJUNUM	X	X	X		X
DISTENTION				2	
*ILEUM	X	X	X		X
DISTENTION				2	
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X		X
COLOR-DARKER THAN NORMAL				3	
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
*PANCREAS, NOS			X	X	
DISCOLORATION,RED	1	1			1
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X		X
SMALL				3	
PALLOR				3	
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
*SKIN, NOS	X	X	X		X
SKIN OF FOOT AND TOE					
DISCOLORATION,RED				2	
HAIR	X	X	X		X
HAIR OF INGUINAL REGION					
HAIRCOAT, WET BY URINE				2	
HAIR OF FACE					
DISCOLORATION,RED				2	
FALLOPIAN TUBES	X	X	X	X	X
VAGINA	X	X	X	X	X
UTERUS	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

500.000 MG/KG

ANIMAL #	531	532	533	534	535
DAYS ON TEST	14	14	14	2	14
OVARIES	X	X	X	X	X
CERVIX UTERI	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

1000.000 MG/KG

ANIMAL #	536	537	538	539	540
DAYS ON TEST	1	14	1	1	1
TRACHEA	X	X	X	X	X
LUNGS	X	X	X		
COLLAPSE INCOMPLETE ON THORACOTOMY				P	P
THYMUS		X			
HEMORRHAGE	2		2	1	2
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
*URINARY BLADDER	X	X	X	X	
DISTENTION					2
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
*PANCREAS, NOS	X		X	X	X
DISCOLORATION,RED		1			
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X
VAGINA	X	X	X	X	X
UTERUS	X	X	X	X	X
OVARIES	X	X	X	X	X
CERVIX UTERI	X	X	X	X	X
BODY AS A WHOLE, NOS					
AUTOLYSIS	3		3	2	

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

	2000.000 MG/KG				
ANIMAL #	506	507	508	509	510
DAYS ON TEST	1	1	0	1	0
TRACHEA	X	X	X	X	X
LUNGS					
COLLAPSE INCOMPLETE ON THORACOTOMY	P	P	P	P	P
THYMUS			X		X
HEMORRHAGE	2	2		1	
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
*STOMACH	X	X		X	
STOMACH, NON-GLANDULAR					
DISCOLORATION,RED			2		2
GASTRIC CONTENTS					
INCREASED			2		2
*DUODENUM	X	X		X	
INTESTINAL CONTENTS					
INCREASED			2		2
*JEJUNUM	X	X		X	
INTESTINAL CONTENTS					
INCREASED			2		2
*ILEUM	X	X		X	X
INTESTINAL CONTENTS					
INCREASED			2		
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X
VAGINA	X	X	X	X	X
UTERUS	X	X	X	X	X
OVARIES	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE - FEMALE RATS

	2000.000 MG/KG				
ANIMAL #	506	507	508	509	510
DAYS ON TEST	1	1	0	1	0
CERVIX UTERI	X	X	X	X	X
BODY AS A WHOLE, NOS					
AUTOLYSIS	2	2		2	

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, X-NORMAL BUT NOT COLLECTED, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE, P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT

GROSS PATHOLOGY COMMENT REPORT

DAY	DOSE LEVEL	ANIMAL #	COMMENT
45	500.000 MG/KG	534	SKIN OF FOERPAWS WAS DISCOLORED RED.
45	500.000 MG/KG	534	ILEUM WAS DISTENDED WITH GAS.
45	500.000 MG/KG	534	JEJUNUM WAS DISTENDED WITH GAS.
45	2000.000 MG/KG	510	STOMACH HAD FLUID CONTENTS.
45	2000.000 MG/KG	510	DUODENUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	510	JEJUNUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	508	STOMACH HAD FLUID CONTENTS.
45	2000.000 MG/KG	508	DUODENUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	508	JEJUNUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	508	ILEUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	502	STOMACH HAD FLUID CONTENTS.
45	2000.000 MG/KG	502	DUODENUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	502	JEJUNUM HAD FLUID CONTENTS.
45	2000.000 MG/KG	502	ILEUM HAD FLUID CONTENTS.
45	1000.000 MG/KG	540	URINARY BLADDER WAS DISTENDED WITH RED URINE.
45	1000.000 MG/KG	530	URINARY BLADDER WAS DISTENDED WITH RED URINE.
45	1000.000 MG/KG	526	STOMACH HAD FLUID CONTENTS.
45	1000.000 MG/KG	526	DUODENUM CONTAINED FLUID.
45	1000.000 MG/KG	526	JEJUNUM CONTAINED FLUID.
45	1000.000 MG/KG	526	ILEUM CONTAINED FLUID.
45	1000.000 MG/KG	527	URINARY BLADDER WAS DISTENDED WITH RED URINE.
48	500.000 MG/KG	521	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	522	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	523	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	524	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	525	PANCREAS WAS FIRM (2).
48	1000.000 MG/KG	528	PANCREAS WAS FIRM (2).
48	1000.000 MG/KG	529	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	531	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	532	PANCREAS WAS FIRM (2).
48	500.000 MG/KG	535	PANCREAS WAS FIRM (2).
48	1000.000 MG/KG	537	PANCREAS WAS FIRM (2).

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - MALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
LIVER	3	2	0
INFLAMMATION, CHRONIC FOCAL	1	0	0
CONGESTION	0	2	0
HEPATOCYTE			
CYTOPLASMIC VACUOLIZATION	3	2	0
PANCREAS, NOS	5	2	0
LUNGS	0	0	0
THYMUS	0	0	0
SPLEEN	0	0	0

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

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

GROUP	500.000 MG/KG	1000.000 MG/KG	2000.000 MG/KG
PANCREAS, NOS	3	1	0
LUNGS	1	0	0
CONGESTION	1	0	0
THYMUS	1	0	0
HEMORRHAGE	1	0	0
THYMIC CORTEX ATROPHY	1	0	0
LIVER	1	0	0
CONGESTION	1	0	0
SPLEEN	1	0	0
SPLENIC RED PULP ATROPHY	1	0	0

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

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE - MALE RATS

	500.000 MG/KG				
ANIMAL #	521	522	523	524	525
DAYS ON TEST	14	14	14	14	14
LIVER					
INFLAMMATION, CHRONIC FOCAL			1		
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION	2	2	2		
PANCREAS, NOS	N	N	N	N	N
LUNGS					
THYMUS					
SPLEEN					

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

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

1000.000 MG/KG

ANIMAL #	526	527	528	529	530
DAYS ON TEST	1	1	14	14	1
LIVER					
CONGESTION			3	2	
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION			2	2	
PANCREAS, NOS			N	N	
LUNGS					
THYMUS					
SPLEEN					

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

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

500.000 MG/KG

ANIMAL #	531	532	533	534	535
DAYS ON TEST	14	14	14	2	14
PANCREAS, NOS	N	N			N
LUNGS					
CONGESTION				3	
THYMUS					
HEMORRHAGE				1	
THYMIC CORTEX					
ATROPHY				2	
LIVER					
CONGESTION				3	
SPLEEN					
SPLENIC RED PULP					
ATROPHY				2	

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

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE - FEMALE RATS

	1000.000 MG/KG				
ANIMAL #	536	537	538	539	540
DAYS ON TEST	1	14	1	1	1
PANCREAS, NOS		N			

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