8CHQ-95-13311

MILES

(A)

Miles Inc.
Mobay Road
Pittsburgh, PA 15205-9741
Phone: 412 777-2000

January 13, 1995

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

COMPANY SANITIZED

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Dear Sir:

Miles Inc. is submitting a recently completed acute oral tox study on

substituted heterocycle an experimental herbicide of interest to Miles.

In this study, young adult male and female Sprague-Dawley rats (5/sex/dose) were administered the test substance once by gavage at doses ranging from 0 - 5210 mg/kg. Compound-related clinical signs of toxicity included decreased activity, salivation, and convulsions. These clinical signs began soon after dosing and some lasted up to 7 days, although the majority had disappeared within two days post-dosing. The resultant LD50 values were: Males - 1300 mg/kg, and Females - 1015 mg/kg.

Even though the majority of the clinical signs were fairly transient and not indicative of a frank neurotoxic effect, a few were of the type in the EPA Reporting Guidance Document to indicate neurotoxicity. This, in conjunction with the fact that such clinical signs occurred in non-moribund animals for durations exceeding two days, triggers the potential that these results are reportable under TSCA 8(e).

Presently this experimental herbicide has very limited distribution and exposure potential, however we will provide this information in our regular worker hazard communications literature and training programs. Further studies are planned to evaluate the toxicological profile of this potential product.

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The information submitted in this study is considered "Confidential Business Information". A sanitized as well as a confidential version are being submitted.

Please contact me if you have any questions.

Sincerely,

Donald W Lamb

Donald W. Lamb, Ph.D
Vice President
Product Safety & Regulatory Affairs
412-777-7431

95-2-2.doc:vmk
Attachment
Certified Mail: P 921 654 843

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Study Title

Acute Oral Toxicity Study
with Technical Grad[redacted]in Rats

Data Requirement

40 CFR Part 158
US-EPA-FIFRA, Section 158.340, Guideline 81-1

Author

M. A. Zorbas

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Study Completion Date

December 12, 1994

Test Facility

Miles Inc.
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, Kansas 66085-9104

Study Number

94-012-ZH

STATEMENT OF DATA CONFIDENTIALITY

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

Company: Miles Inc.

Company Agent: J. H. Thyssen Date: 12-9-94

Vice President, Toxicology J. H. Thyssen
Signature

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with the FIFRA Good Laboratory Practice Standards of 40 CFR Part 160, TSCA Good Laboratory Practice Standards of 40 CFR Part 792 and the OECD Principles of Good Laboratory Practice, C(81)30 (Final) Annex 2 (Paris, May 1981).

SUBMITTER

MILES INC.

J. H. Thyssen: _____
Vice President, Toxicology

Date: 12-9-94

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SPONSOR

AGRICULTURE DIVISION

J. H. Thyssen: _____
Vice President, Toxicology

Date: 12-9-94

STUDY DIRECTOR

D. L. Warren: _____

Date: 12/12/94.

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SPONSOR

MILES INC.
Agriculture Division
Box 4913, Hawthorn Road
Kansas City, Missouri 64120-0013

TEST FACILITY

MILES INC.
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, Kansas 66085-9104

DATES

Experimental Start Date: May 3, 1994
Terminal Sacrifice Date: May 24, 1994

PERSONNEL AND RESPONSIBILITIES

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Toxicology and Sponsor Representative:	J. H. Thyssen	
Toxicology Laboratory:	G. K. Sangha	
Experimental Toxicology:	R. N. Shiotsuka	
Study Direction:	D. L. Warren	
Study Conduct:	D. R. Smith	
Pathology Services:	B. P. Stuart	
Gross Necropsy:	H. E. Hoss	
Animal Care:	R. E. Mueller	
Analytical Chemistry:	K. D. Moore	
Quality Assurance:	C. A. Halder	

QUALITY ASSURANCE STATEMENT

Audit reports have been submitted to the study director and laboratory management documenting the status of compliance with applicable departmental standard operating procedures, the study protocol, and Good Laboratory Practice regulations.

The Quality Assurance Unit monitors at least one phase of each study, and at least annually, all phases of this study type including the functions of all support areas for this study type. The following are the audit dates, phases inspected, auditors, and report dates of Quality Assurance inspections of this study and, if applicable, of this study type as well as relevant support areas:

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AUDITS			
Date	Phases	Auditor	REPORT TO STUDY DIRECTOR/ MANAGEMENT
	Phase of Study		
05/04/94	Clinical Observations	D. Wallace	05/05/94
11/07-08/94	Final Report Review	J. Ranjbar	11/08/94
	Phase of Study Type		
01/18-19/94	Dose Preparation and Test Substance Inventory, Analytical Sample Submission, Tail Marking, Fasting, Body Weights, Dosing, Test Animal Inventory	J. Ranjbar	01/20/94
02/02/94	Euthanasia and Gross Necropsy	J. Ranjbar	02/03/94
	Analytical Chemistry Support Area Functions		
05/11/94	Verification of Dose Concentration	S. Bailey	05/12/94
	Animal Care Support Area Functions		
01/25/94	Animal Receiving, Shipment Examination, Randomization, Animal Inventory, Animal Identification (Cage Cards), Quarantine	C. A. Cox	01/25/94
01/25/94	AM/PM Observations	C. A. Cox	01/25/94

QUALITY ASSURANCE STATEMENT (Continued)

AUDITS			REPORT TO STUDY DIRECTOR/
Date	Phases	Auditor	MANAGEMENT
	Animal Care Support Area Functions (Continued)		
01/25/94	Cleaning of Racks, Cages, Trays, and Feeders	C. A. Cox	01/25/94
01/26/94	Filter Inspection/Change	C. A. Cox	01/31/94
01/27/94	Room Disinfection	C. A. Cox	02/01/94
01/28/94	Bedding Change, Room Maintenance, Rack Change	C. A. Cox	01/31/94
01/28/94	Feeding	C. A. Cox	01/31/94
01/31/94	Release of Animal Shipment	C. A. Cox	01/31/94
02/02/94	Rack Preparation	C. A. Cox	02/02/94

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In compliance with the Good Laboratory Practice regulations, this final report for study number 94-012-ZH has been reviewed by the Quality Assurance Unit. The results presented in this report accurately describe the methods and standard operating procedures and reflect the raw data collected during the conduct of the study.

C. A. Halder, Quality Assurance

November 28, 1994
Date

ABSTRACT

Young-adult male and female Sprague-Dawley rats (5/sex/dose) were used to determine the acute oral toxicity of technical grade [redacted]. The test substance was administered by gavage in 0.5% carboxymethylcellulose (w/v) and 0.4% Tween 80 (v/v) (20 mL/kg) at analytically-confirmed doses of 0, 98.4, 252, 816, 978, 1334, 1710, 3388 and 5210 mg/kg for males and 0, 98.4, 252, 816, 1218, 1710, 3388 and 5210 mg/kg for females. Animals were observed for 14 days after dosing for mortality and clinical signs. Body weights were recorded just prior to treatment (day 0), when found dead and on days 7 and 14. A gross necropsy was performed as soon as possible after death on any animal found dead or at the end of the study for surviving animals.

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Compound-related signs of toxicity in males included decreased activity, salivation, convulsions, various stains and secretions about the head and ventrum and the observation that the animal jumps when touched. Compound-related signs of toxicity in females included decreased activity, salivation, convulsions, various stains and secretions about the head and ventrum and the observation that the animal jumps when touched. Compound-related signs were apparent on day 0 and resolved in surviving animals by day 7.

Body weight gain decreased between days 0 and 7 in a dose-related manner in surviving males administered a dose of 978 mg/kg or higher. Recovery from this body weight gain decrement was evident by day 14. Body weight gain was not affected by treatment with the test substance in surviving females.

Evidence of salivation, ventrum stains, reddened lungs and blackened zones in the stomach glandular mucosa were considered compound-related gross lesions in all animals found dead. Evidence of lacrimation was an additional compound-related gross lesion found in males. There were no compound-related gross lesions observed at necropsy in animals which survived to day 14.

The incidence of mortality increased with dose for both males and females, with all deaths occurring between days 0 and 2 post-dosing. For males, the acute oral LD50 (with 95% confidence intervals) was 1300 mg/kg (1085-1639 mg/kg). For females, the acute oral LD50 (with 95% confidence intervals) was 1015 mg/kg (653-1395 mg/kg). The No-Observed-Effect Level (NOEL) for technical grade [redacted] was 98.4 mg/kg for males and females.

MATERIALS

I. The test substance was supplied by the sponsor with the following information:

Test Substance:

Identification:	Technical Grad[redacted]
Physical Appearance:	beige powder
Batch Number:	17004/93
Purity:	97.8% (analysis on 12/14/93) 98.2% (analysis on 6/17/94)
Stability At Storage Conditions:	At least six months (based on % purity)

Active Ingredient: Confidential Information Has Been Sanitized

Common Name:	None Assigned
Chemical Name:	[redacted]
Structural Formula:	[redacted]
CAS Registry Number:	[redacted]

II. The test substance was stored at freezer conditions. Doses were prepared on the day prior to administration.

PURPOSE

The purpose of this study type was to provide information on the health hazards likely to arise from short-term exposure by the oral route.

TEST GUIDELINES

This study was conducted in accordance with:

1) US-EPA-FIFRA, Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Guideline 81-1, November 1984.

2) US-EPA-TSCA, Health Effects Testing Guidelines, 40 CFR Section 798.1175.

3) OECD Guidelines for Testing of Chemicals, Section 4, Guideline 401, February 1987.

4) Japan, Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985.

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METHODS

Animal Information

Source, Number and Age

Young-adult male and female Sprague-Dawley rats (Sas:CD(SD)BR), (Sasco, Inc., St. Louis, Missouri) were used in this study. 35 male rats were approximately eight weeks of age (57 days of age) on the day of treatment. An additional 10 male rats dosed one week later were approximately nine weeks of age (64 days of age) on the day of treatment. 35 female rats were approximately nine weeks of age (64 days of age) on the day of treatment. An additional five female rats dosed one week later were approximately 10 weeks of age (71 days of age) on the day of treatment. Females were nulliparous and non-pregnant.

Examination and Acclimation

Animals were held for six days. During this period each animal was examined daily for changes in general appearance, behavior and gross external abnormalities. On the sixth day, each animal was examined by a veterinarian and released for use prior to assignment to the study. Animals with abnormalities were not used.

Care and Housing

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Animals were housed individually in stainless steel cages suspended over Deotized Animal Cage Board bedding material. Bedding was changed at least three times weekly and animals were transferred to clean cages at least every three weeks. The room was disinfected with a quaternary ammonium compound at least once every three weeks. The environmental conditions were set for a room temperature of 18 to 26°C, a relative humidity of 40 to 70% and a 12 hour photoperiod. Environmental conditions were monitored continuously. Unlimited municipal water and food (Purina Rodent Lab Chow 5001-4) were available for consumption.

Identification

Each animal was identified by cage card and tail marking.

Randomization

Animals were randomly assigned to cages using a software program [1]. Animals, which satisfied study requirements, were assigned to dose groups from consecutively-numbered cages.

Analytical Chemistry

Dosing suspensions were analyzed for technical grade [redacted] by high-performance liquid chromatographic analysis [2]. The homogeneity and concentration of the active ingredient in the vehicle were determined by analysis of three samples of each of the nominal 5 and 250 mg/mL (100 and 5000 mg/kg body weight) dosing suspensions. The concentration of the active ingredient was also verified for the nominal 0, 100, 250, 800, 1000, 1200, 1300, 1600, 3200 and 5000 mg/kg body weight dosing suspensions. Overnight stability of the test substance in the vehicle at room temperature was also verified since doses were prepared on the day prior to administration.

Experimental Design

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Route, Dose and Number of Animals

All animals were fasted overnight prior to dosing. Doses were prepared as suspensions in 0.5% (w/v) carboxymethylcellulose and 0.4% (v/v) Tween 80 in deionized water and were administered by gavage at a volume of 20 mL/kg. Groups of five males each received a single dose of 0, 100, 250, 800, 1000, 1300, 1600, 3200 or 5000 mg/kg. Groups of five females each received a single dose of 0, 100, 250, 800, 1200, 1600, 3200 or 5000 mg/kg.

Clinical Signs and Body Weight Measurements

Animals were observed for mortality and signs of toxicity twice daily on weekdays and once daily on weekends for 14 days following treatment. Animals were weighed just prior to treatment and on days 7 and 14 after treatment. Terminal body weights were obtained on all animals that died during the study.

Gross Pathology

All animals were subjected to gross pathologic examinations as soon as possible after death. Survivors were sacrificed by CO_2 asphyxiation on day 14 after treatment and then subjected to gross pathologic examinations.

Statistical Methods

LD50 values and 95% confidence intervals were calculated by probit analysis [1]. Analysis of body weight changes were performed using an analysis of variance (ANOVA) [1]. For the ANOVA, a p-value less than or equal to 0.05 was considered to be significant.

Archival Procedures

The protocol, raw data, a sample of the test substance, and the final report are archived at locations specified by Miles Inc., Agriculture Division, Toxicology, 17745 South Metcalf, Stilwell, Kansas 66085-9104.

RESULTS AND DISCUSSION

The analytical chemistry results are summarized in Table 1. The stability of technical grade [redacted] in the dosing suspension was established with no significant change in the concentration of the technical grade of the active ingredient following approximately 25 hours of storage at room temperature. Homogeneity of the active ingredient in the dosing suspension was also established, with a coefficient of variation of less than or equal to 6% for the nominal 5 and 250 mg/mL dosing suspensions. Nominal doses of 0, 100, 250, 800, 1000, 1200, 1300, 1600, 3200 and 5000 mg/kg were determined to be 97.9% to 107% of the nominal dose level. Based on these results, the analytically-confirmed doses were 0, 98.4, 252, 816, 978, 1218, 1334, 1710, 3388 and 5210 mg/kg.

The relationship between the dose administered and incidence/duration of clinical signs, body weight changes and mortality for males and females are summarized in Table 2.

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The range of incidence and time of occurrence for clinical signs and their relationship to the dose administered for males and females are summarized in Table 3. Compound-related signs of toxicity in males were decreased activity, oral stains, red nasal stains, salivation, urine stains, convulsions, red nasal discharge, clear lacrimation, red lacrimal stains and the observation that the animal jumps when touched. Protruding penis, loose stool, red tinged fur nose to chest and perianal stain were observed in males but considered not to be compound-related signs due to their minor incidence or late onset of appearance. Compound-related signs of toxicity in females were decreased activity, oral stains, red and clear nasal stains, salivation, urine stains, convulsions, red nasal discharge, red and clear lacrimation, clear lacrimal stains and the observation that the animal jumps when touched. Red tinged fur nose to chest, red tinged fur on the head, chest and forearms and perianal stains were observed but considered not to be compound-related signs due to their minor incidence. Compound-related signs were apparent on day 0 and resolved in surviving animals by day 7.

Body weight information is summarized in Table 2, with individual weights shown in Appendix I. The body weight ranges on the day animals were treated were 164 to 236 g for males and 174 to 202 g for females. The weight range for all female and most male animals was within 20% of the mean body weights for each sex. One male weighed 1 gram less than the lower limit of the range for 20% of the mean body weight and was within 20.4% of the mean body weight for males. For surviving males administered a dose of 978 mg/kg or higher, body weight gain decreased in a dose-related manner between days 0 and 7, with recovery evident by day 14. Body weight gain was not affected in surviving females.

Table 4 summarizes the gross lesions observed at necropsy at each dose level. Evidence of salivation, ventrum stains, reddened lungs and blackened zones in the glandular stomach mucosa were considered compound-related gross lesions in all animals found dead. Evidence of lacrimation was an additional compound-related gross lesion only found in males found dead. There were no compound-related gross lesions observed at necropsy in animals which survived to day 14.

The incidence of mortality increased with dose for males between 978 mg/kg and 1710 mg/kg and for females between 816 mg/kg and 1710 mg/kg. All deaths occurred on days 0, 1 or 2. For males, the acute oral LD50 (with 95% confidence limits) was 1300 mg/kg (1085-1639 mg/kg). Mortality data from the 5210 mg/kg dose group in males was not used for calculating LD50 values. This data was excluded from the LD50 calculations because the response (4/5 dead) was considered not to be biologically relevant (i.e., anomalous) since two lower doses showed complete mortality (5/5 dead). Furthermore, it was not feasible to confirm the relevance of the deaths at 5210 mg/kg by testing a higher dose since this is the oral limit dose (5000 mg/kg). For females, the acute oral LD50 (with 95% confidence limits) was 1015 mg/kg (653-1395 mg/kg). The No-Observed-Effect Level (NOEL) was 98.4 mg/kg for males and females.

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SUMMARY AND CONCLUSIONS

Young-adult Sprague-Dawley rats were used to determine the acute oral toxicity of technical grade [redacted] using analytically-confirmed doses of 0, 98.4, 252, 816, 978, 1334, 1710, 3388 and 5210 mg/kg for males and 0, 98.4, 252, 816, 1218, 1710, 3388 and 5210 mg/kg for females (5/sex/dose).

Compound-related signs of toxicity in males and females were decreased activity, salivation, convulsions, various stains and secretion about the head and ventrum and animals that jumped when touched. These signs were apparent on day 0 and resolved by day 7.

A compound-related decrease in body weight gain was apparent for surviving males at doses of 978 mg/kg or higher but no decrease in body weight gain was apparent for females.

Evidence of salivation, ventrum stains, reddened lungs and blackened zones in the stomach glandular mucosa were considered compound-related gross lesions in all animals found dead. Evidence of lacrimation was an additional compound-related gross lesion in males found dead. There were no compound-related gross lesions observed at necropsy in animals which survived to day 14.

The incidence of mortality increased with dose for both sexes, with all deaths occurring on days 0,1 or 2. For males, the acute oral LD50 (with 95% confidence limits) was 1300 mg/kg (1085-1639 mg/kg). For females, the acute oral LD50 (with 95% confidence limits) was 1015 mg/kg (653-1395 mg/kg). The No-Observed-Effect Level (NOEL) was 98.4 mg/kg for males and females.

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REFERENCES

1. SAS Institute Inc., Cary, North Carolina.

2. K. D. Moore and L. S[redacted]on. A liquid chromatographic method for the determination of [redacted]n dose mixtures. Miles Inc., Agriculture Division Rep[redacted]06372, 1994.

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Table 1

Chemical Analysis of Technical Grad[redacted] Concentrations in an Acute Oral Toxicity Study in Rats

Study N[redacted]2-ZH

Nominal Dose[a] (mg/kg)	Nominal Concentration (mg/mL)	Analytically-determined Concentration (mg/mL)	Analytically-determined Dose[b,c] (mg/kg)
		MALES	
0	0	0	0
100	5.0	4.92	98.4
250	12.5	12.6	252
800	40.0	40.8	816
1000	50.0	48.9	978
1300	65.0	66.7	1334
1600	80.0	85.5	1710
3200	160.0	169.4	3388
5000	250.0	260.5	5210
		FEMALES	
0	0	0	0
100	5.0	4.92	98.4
250	12.5	12.6	252
800	40.0	40.8	816
1200	60.0	60.9	1218
1600	80.0	85.5	1710
3200	160.0	169.4	3388
5000	250.0	260.5	5210

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[a] *The same nominal 0, 100, 250, 800, 1600, 3200 and 5000 mg/kg dosing suspension was administered to both males and females.*

[b] *Based on an administered volume of 20 mL/kg body weight.*

[c] *The control (vehicle) suspension (0 mg/mL) did not indicate the presence of test substance. Therefore, the control (vehicle) suspension administered to control animals was considered to have 0 mg/kg test substance.*

Table 2

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Summary

Acute Oral Toxicity Study with Technical Grad[redacted]in Rats

Study Number 94-012-ZH

MALES

Dose[a] (mg/kg)	No. of Animals With Signs/ Found Dead/ Treated	Signs Begin on (Day)	Signs End Within (Day)	Day Found Dead (Range)	Day 0 Body Weight Range (g)	Average Body Weights (g) (Day) 0[b]	7	0-7[c]	14	7-14[d]	No-Observed-Effect Level (mg/kg)	LD50 (mg/kg)
0	0/0/5	-[e]	-	-	184-211	200	261	61	289	28	98.4	1300
98.4	1[f]/0/5	7	7	-	185-217	202	262	60	292	30		
252	4/0/5	0	1	-	164-215	198	263	65	296	32		
816	3/0/5	0	1	-	198-210	203	255	52	280	24		
978	4/1/5	0	6	0	212-231	224	269	45*	301	32		
1334	4/2/5	0	2	0-1	217-236	228/230	273	43*	305	32		
1710	4/5/5	0	1	0-1	194-208	202	-	-	-	-		
3388	3/5/5	0	2	0-2	190-209	198	-	-	-	-		
5210	3/4/5	0	1	0-1	184-204	196/196	231	35*	282	51		

[a] *Analytically-determined.*
[b] *Fasted; for all rats/for rats surviving to day 7.*
[c] *Mean of the body weight change from day 0 to day 7.*
[d] *Mean of the body weight change from day 7 to day 14.*
[e] *Not applicable*
[f] *Including a sign considered to be incidental to treatment.*
* *Statistically significant decrement in body weight gain compared to control animals ($p \leq 0.05$).*

Table 2 (continued)

Summary

Acute Oral Toxicity Study with Technical Grad[redacted]n Rats

Confidential Information Has Been Sanitized

Study Number 94-012-ZH

FEMALES

Dose[a] (mg/kg)	No. of Animals With Signs/ Found Dead/ Treated	Signs Begin on (Day)	Signs End Within (Day)	Day Found Dead (Range)	Day 0 Body Weight Range (g)	Average Body Weights (g) (Day) 0[b]	7	0-7[c]	14	7-14[d]	No-Observed-Effect Level (mg/kg)	LD50 (mg/kg)
0	0/0/5	-[e]	-	-	181-202	191	217	25	222	5	98.4	1015
98.4	0/0/5	-	-	-	182-196	188	209	21	220	11		
252	2/0/5	0	1	-	182-199	190	216	26	226	10		
816	4/2/5	0	2	0-2	181-192	186/185	213	28	222	9		
1218	5/3/5	0	7	0-1	189-193	192/193	221	28	235	15		
1710	3/5/5	0	0	0	185-197	190	-	-	-	-		
3388	4/5/5	0	1	0-1	178-193	186	-	-	-	-		
5210	1/5/5	0	0	0	174-195	184	-	-	-	-		

[a] *Analytically-determined.*
[b] *Fasted; for all rats/for rats surviving to day 7.*
[c] *Mean of the body weight change from day 0 to day 7.*
[d] *Mean of the body weight change from day 7 to day 14.*
[e] *Not applicable*
[f] *Including a sign considered to be incidental to treatment.*

Table 3

Clinical Signs in an Acute Oral Toxicity Study
with Technical Grad[redacted]n Rats

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Study Number 94-012-ZH[redacted]

MALE

Signs	Dose[a] (mg/kg) 0	98.4	252	816	978	1334	1710	3388	5210
Within Normal Limits	5	4	1	2	-[b]	-	-	-	-
Decreased Activity	-	-	4/0-1[c]	3/0-1	4/0-2	4/0-2	4/0-1	3/0-2	3/0-1
Oral Stain	-	-	2/0-1	3/0-1	2/0-2	2/0-1	-	2/0-2	1/0-1
Nasal Stain									
Red	-	-	1/0-1	1/0-1	2/0-6	2/0-2	1/0-1	1/1-2	1/0-1
Salivation	-	-	-	1/0-0	2/0-1	3/0-1	4/0-1	3/0-1	2/0-1
Nasal Discharge									
Red	-	-	-	-	1/0-1	-	-	-	-
Lacrimation									
Clear	-	-	-	-	1/0-1	-	-	-	-
Urine Stain	-	-	-	-	2/0-2	2/0-2	3/0-1	2/0-2	2/0-1
Convulsions	-	-	-	-	1/0-0	2/0-1	4/0-1	3/0-1	2/0-1
Protruding Penis	-	-	-	-	1/1-2	-	2/0-1	-	-
Loose Stool	-	1[d]/7-7	-	-	-	-	-	-	-
Red Tinged Fur Nose to Chest	-	-	-	-	-	1/0-1	2/0-1	-	1/0-0
Jumps When Touched	-	-	-	-	-	1/0-1	-	-	-
Perianal Stain	-	-	-	-	-	-	2/0-1	1/1-2	-
Lacrimal Stain									
Red	-	-	-	-	-	-	-	1/1-2	-

[a] *Analytically-determined.*
[b] *Sign not observed.*
[c] *Incidence/time range of occurrence (in days).*
[d] *Sign is considered to be incidental to treatment.*

Table 3 (continued)

Clinical Signs in an Acute Oral Toxicity Study
with Technical Grade [redacted] in Rats

Confidential Information Has Been Sanitized

Study Number 94-012-ZH

FEMALE

Signs	Dose[a] (mg/kg) 0	98.4	252	816	1218	1710	3388	5210
Within Normal Limits	5	5	3	-[b]	-	-	-	-
Decreased Activity	-	-	2/0-1[c]	3/0-2	5/0-3	3/0-0	4/0-1	1/0-0
Oral Stain	-	-	1/0-1	4/0-2	2/0-6	-	-	-
Nasal Stain								
Red	-	-	1/0-1	2/0-2	2/1-6	-	-	-
Clear	-	-	-	1/0-2	1/0-1	-	-	-
Salivation	-	-	-	4/0-1	4/0-1	3/0-0	4/0-1	1/0-0
Nasal Discharge								
Red	-	-	-	-	1/0-0	-	-	-
Lacrimation								
Clear	-	-	-	1/1-2	1/0-1	-	-	-
Red	-	-	-	-	1/1-1	-	-	-
Urine Stain	-	-	-	2/1-2	3/0-7	-	1/0-1	-
Convulsions	-	-	-	1/0-0	4/0-1	3/0-0	4/0-1	1/0-0
Red Tinged Fur Nose to Chest	-	-	-	-	-	1/0-0	1/0-0	-
Red Tinged Fur Head, Chest, Forearms	-	-	-	-	1/1-3	-	-	-
Jumps When Touched	-	-	-	2/1-2	2/0-3	-	-	-
Perianal Stain	-	-	-	-	1/2-6	-	-	-
Lacrimal Stain								
Clear	-	-	-	-	-	-	1/0-1	-

[a] *Analytically-determined.*
[b] *Sign not observed.*
[c] *Incidence/time range of occurrence (in days).*

Table 4

Gross Lesions Observed in an Acute Oral Toxicity Study
with Technical Grade [redacted] Rats

Confidential Information Has Been Sanitized

Study Number 94-012-ZH

MALE

Dose Level (mg/kg)[a]	Control	98.4	252	816	978		1334		1710	3388	5210	
Fate	5/5 SAC	5/5 SAC	5/5 SAC	5/5 SAC	4/5 SAC	1/5 FD	3/5 SAC	2/5 FD	5/5 FD	5/5 FD	1/5 SAC	4/5 FD
No Gross Lesions	5	5	5	4	4		3				1	
Salivation						1		2	5	5		4
Urine Stain								1	3	2		1
Lungs Reddened						1		1	2	1		
Lacrimation									2			
Black Zones, Stomach Glandular Mucosa								1				
Reduced Testicles				1								

FEMALE

Dose Level (mg/kg)	Control	98.4	252	816		1218		1710	3388	5210
Fate	5/5 SAC	5/5 SAC	5/5 SAC	3/5 SAC	2/5 FD	2/5 SAC	3/5 FD	5/5 FD	5/5 FD	5/5 FD
No Gross Lesions	5	5	5	2		2				
Salivation					2		3	5	5	5
Urine Stain					1		3			
Lungs Reddened							2			
Serosal Masses (On Uterus)				1						
Black Zones, Stomach Glandular Mucosa					1		1			

[a] *Analytically Determined*
SAC = Sacrificed
FD = Found dead

Appendix I

Individual Body Weights (g) in an Acute Oral Toxicity Study with Technical Grad[redacted] in Rats

Study Number 94-012-ZH

Confidential Information Has Been Sanitized

MALE

Dose[a] (mg/kg)	Animal Number	Day 0	Day 7	Day 14	Found Dead
0	265	203	272	303	-[b]
	266	211	265	289	-
	267	204	273	307	-
	268	200	253	272	-
	269	184	243	273	-
98.4	270	185	244	275	-
	271	203	259	283	-
	273	198	260	299	-
	274	217	288	318	-
	300	205	258	286	-
252	275	208	262	287	-
	276	164	230	279	-
	277	196	265	300	-
	278	209	273	304	-
	279	215	286	308	-
816	281	198	238	249	-
	282	210	265	296	-
	283	203	258	287	-
	284	199	255	282	-
	301	206	260	284	-
978	305	212	253	276	-
	303	223	264	288	-
	304	231	271	319	-
	317	224	-	-	225
	307	231	288	322	-

[a] *Analytically-determined.*
[b] *Not Applicable*

Appendix I (continued)

Individual Body Weights (g) in an Acute Oral Toxicity Study
with Technical Grad[redacted]n Rats

Study Number 94-012-ZH

Confidential Information Has Been Sanitized

MALE

Dose[a] (mg/kg)	Animal Number	Day 0	Day 7	Day 14	Found Dead
1334	310	217	254	280	-
	312	236	277	318	-
	318	236	287	317	-
	322	223	-	-	210
	320	230	-	-	232
1710	285	194	-	-	182
	286	208	-	-	198
	287	204	-	-	204
	288	196	-	-	186
	289	208	-	-	190
3388	290	199	-	-	196
	291	198	-	-	173
	292	190	-	-	191
	293	209	-	-	207
	294	192	-	-	179
5210	295	184	-	-	174
	296	194	-	-	194
	297	203	-	-	201
	298	196	231	282	-
	299	204	-	-	194

[a] *Analytically-determined.*
[b] *Not Applicable*

Appendix I (continued)

Individual Body Weights (g) in an Acute Oral Toxicity Study
with Technical Grade [redacted] in Rats

Study Number 94-012-ZH

FEMALE

Confidential Information Has Been Sanitized

Dose (mg/kg)	Animal Number	Day 0	Day 7	Day 14	Found Dead
0	330	202	222	229	-[b]
	331	193	224	234	-
	332	187	206	207	-
	333	181	215	217	-
	334	194	217	223	-
98.4	335	182	201	209	-
	336	187	214	227	-
	337	184	208	221	-
	338	196	213	226	-
	339	191	210	219	-
252	340	182	209	211	-
	341	185	211	218	-
	342	189	217	229	-
	343	199	228	238	-
	344	195	217	235	-
816	345	192	225	247	-
	346	183	210	210	-
	347	188	-	-	167
	348	188	-	-	188
	349	181	205	209	-
1218	365	193	229	246	-
	366	193	-	-	190
	367	189	-	-	177
	368	193	212	224	-
	369	193	-	-	189

[a] *Analytically-determined*
[b] *Not Applicable*

Appendix I (continued)

Individual Body Weights (g) in an Acute Oral Toxicity Study with Technical Grad[redacted] in Rats

Study Number 94-012-ZH

Confidential Information Has Been Sanitized

FEMALE

Dose[a] (mg/kg)	Animal Number	Day 0	Day 7	Day 14	Found Dead
1710	350	187	-	-	188
	351	195	-	-	193
	352	197	-	-	197
	353	185	-	-	182
	354	188	-	-	186
3388	355	185	-	-	182
	356	193	-	-	190
	357	178	-	-	175
	358	186	-	-	178
	359	189	-	-	186
5210	360	176	-	-	176
	361	187	-	-	185
	362	195	-	-	195
	363	186	-	-	186
	364	174	-	-	173

[a] *Analytically-determined*
[b] *Not Applicable*