

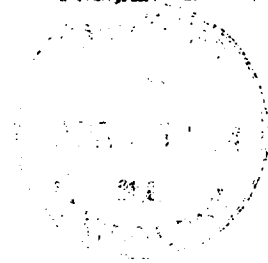


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FINAL REPORT



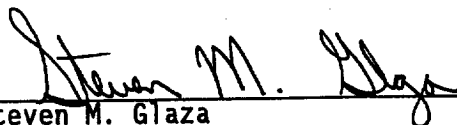
Roger G. Perkins, PhD
3M
Toxicology Services
Building 220-2E-02
St. Paul, MN 55144-1000

HWI Number: 40200468

Study Title:

**Acute Oral Toxicity Study of T-5898 in Rats
(OECD Guidelines)**

Signed:


Steven M. Glaza
Study Director
Acute Toxicology

Date

4-22-94

Sample: T-5898

KEY PERSONNEL

Acute Toxicology

Steven M. Glaza
Study Director
Manager

Steven R. Sorenson
Study Coordinator

Patricia Padgham
In-life Supervisor

Rose M. Bridge
Report Supervisor

Laboratory Animal Medicine

Cindy J. Cary, DVM
Diplomate, ACLAM
Supervisor

Anatomical Pathology

Thomas E. Palmer, PhD
Anatomical Pathologist

Deborah L. Pirkel/
Jack Serfort
Supervisors
Necropsy

Anne Mosher
Supervisor
Pathology Data

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Sample: T-5898

OBJECTIVE

The objective of this study was to assess the acute oral toxicity produced when the test material is administered by the oral route (gavage) to rats.¹

TEST MATERIAL

Identification

The test material was identified as T-5898 and described as a clear, light-yellow liquid.

Purity and Stability

The Sponsor assumes responsibility for purity and stability determinations (including under test conditions).

Storage and Retention

The test material was stored at room temperature. Any unused test material will be returned to the Sponsor after issuance of the final report according to Hazleton Wisconsin (HWI) Standard Operating Procedure (SOP).

Safety Precautions

The test material handling procedures were according to HWI SOPs and policies.

TEST SYSTEM

Test Animal

Adult albino rats of the CrI:CD®(SD)BR strain were procured from Charles River Laboratories, Inc. and maintained at the Hazleton Wisconsin facility at 3802 Packers Avenue, Madison, Wisconsin. Animal husbandry and housing at HWI comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals".² The animals were separated by sex, housed in temperature- and humidity-controlled quarters, provided continuous access to Laboratory Rodent Diet® #5001, PMI Feeds, Inc., and water, and held for an acclimation period of at least 7 days. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water that would have interfered with or affected the results of the study.

Sample: T-5898

Ten male and 10 female acclimated rats, weighing from 225 to 280 g, were assigned to two treatment groups of 500 and 5,000 mg/kg of body weight. Each dose level consisted of five male and five female rats. Animals were group housed by sex and identified by animal number and corresponding ear tag throughout the study. Food and water were available *ad libitum*, except for an overnight period before test material administration when food, but not water, was withheld. If variations from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

Justification for Species Selection

Historically, rats have been used as a representative of a rodent species and are preferred by various regulatory agencies.

PROCEDURES

Preparation and Administration of Test Material

The undiluted test material was administered by gavage using a bulk density determination of 1.13 g/mL to determine the dose volume for each dose level. An individual dose was calculated for each animal based on its fasted body weight.

Reason for Route of Administration

Historically, the oral route has been the route of choice for administering a known amount of test material.

Observations

Clinical observations and mortality checks were conducted at approximately 1, 2.5, and 4 hours after test material administration. Additional clinical observations and twice a day mortality checks (morning and afternoon) were conducted daily thereafter for 14 days.

Body weights were determined before test material administration (Day 0). Additional body weights were determined at Day 7, at termination of the experimental phase (Day 14), or at death when survival exceeded 1 day.

Sample: T-5898

Pathology

At termination of the experimental phase, surviving animals were euthanized. All animals, whether found dead during the study or euthanized, were subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animals were discarded and no tissues were saved.

Statistical Analyses

No statistical analyses were required by the protocol.

Location of Raw Data, Records, and Final Report

The raw data, records, and a copy of the final report will be retained in the archives of HWI in accordance with HWI SOP.

Sample: T-5898

SUMMARY OF RESULTS

Test Animal: Albino Rats - Cr1:CD®(SD)BR

Source: Charles River Laboratories, Inc., Portage, MI

Date Animals Received: 01/14, 01/28, 2/04, and 02/25/94

Experimental Start Date: 02/22/94 Experimental Termination Date: 03/23/94

Estimated Oral LD₅₀: Male - Between 500 and 5,000 mg/kg of Body Weight
 Female - Between 500 and 5,000 mg/kg of Body Weight

Individual Body Weights (g)

Animal Number	Day 0	Day 7		Day 14	
	Weight	Weight	Gain*	Weight	Gain*
<u>Males (500 mg/kg)</u>					
C29181	267	224	-43	319	52
C29232	274	302	28	382	108
C29184	253	284	31	354	101
C29234	280	312	32	390	110
C29190	257	289	32	353	96
Mean	266	282	16	360	93
<u>Females (500 mg/kg)</u>					
C27615	241	228	-13	261	20
C28047	230	225	-5	255	25
C28043	225	180	-45	(131) ⁸	-
C28070	232	207	-25	239	7
C28050	238	225	-13	250	12
Mean	233	213	-20	251	13

* Gain from the Day 0 body weight.

() Value in parentheses is the body weight at the time the animal was found dead. Superscript number indicates day of death. This number was not considered when calculating the mean.

- Not applicable.

Sample: T-5898

Individual Body Weights (g)

<u>Animal Number</u>	<u>Day 0 Weight</u>	<u>Day 7</u>		<u>Day 14</u>	
		<u>Weight</u>	<u>Gain*</u>	<u>Weight</u>	<u>Gain*</u>
<u>Males (5,000 mg/kg)</u>					
C28621	269	(203) ⁷	-	-	-
C28613	271	(228) ³	-	-	-
C28598	266	†	-	-	-
C28619	267	(215) ⁵	-	-	-
C28625	271	(234) ²	-	-	-
Mean	269	-	-	-	-
<u>Females (5,000 mg/kg)</u>					
C28099	246	(209) ⁵	-	-	-
C28117	250	(235) ²	-	-	-
C28118	267	(238) ³	-	-	-
C28104	267	(235) ²	-	-	-
C28120	255	(225) ²	-	-	-
Mean	257	-	-	-	-

* Gain from the Day 0 body weight.

† Animal was found dead on the day of dosing. No body weight required.

() Value in parentheses is the body weight at the time the animal was found dead. Superscript number indicates day of death. This number was not considered when calculating the mean.

- Not applicable.

Sample: T-5898

Individual Clinical Signs

Animal Number	Observation	Hour			Day													
		1.0	2.5	4.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
<u>Males (500 mg/kg)</u>																		
C29181	Appeared normal	/	/	/	/	/	/	/	/	-	-	-	-	-	-	/	/	/
	Thin appearance	-	-	-	-	-	-	-	-	/	/	/	/	/	/	-	-	-
C29232	Appeared normal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C29184	Appeared normal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C29234	Appeared normal	/	/	-	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	Soft stool	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C29190	Appeared normal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
<u>Females (500 mg/kg)</u>																		
C27615	Appeared normal	/	/	/	-	-	/	/	-	-	-	-	-	-	-	-	-	-
	Red-stained face	-	-	-	/	/	-	-	-	-	-	-	-	-	-	-	-	-
	Thin appearance	-	-	-	-	-	-	-	/	/	/	/	/	/	/	/	/	/
	Alopecia - rear quarters	-	-	-	-	-	-	-	/	/	/	/	/	/	/	/	/	/
C28047	Appeared normal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C28043	Appeared normal	/	/	/	-	-	/	/	/	/	-	-	-	-	-	-	-	-
	Red-stained face	-	-	-	/	/	-	-	-	-	/	-	-	-	-	-	-	-
	Hypoactivity	-	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-
	Thin appearance	-	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-
	Hunched posture	-	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-
	Aggressive behavior	-	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-
	Found dead	-	-	-	-	-	-	-	-	-	/	-	-	-	-	-	-	-
C28070	Appeared normal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C28050	Appeared normal	/	/	/	/	-	/	/	/	/	/	/	/	/	/	/	/	/
	Red-stained face	-	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-

/ Condition existed.

- Condition not evident.

Sample: T-5898

Individual Clinical Signs
(Continued)

Animal Number	Observation	Hour			Day													
		1.0	2.5	4.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males (5,000 mg/kg)																		
C28621	Appeared normal	/	/	/	-	-	-	-	-	-								
	Red-stained face	-	-	-	/	/	/	-	-	-								
	Hypoactivity	-	-	-	-	-	-	/	/	/								
	Found dead	-	-	-	-	-	-	-	-	-								/
C28613	Appeared normal	/	/	/	-	-	-											
	Red-stained face	-	-	-	/	/	/											
	Hunched posture	-	-	-	-	-	/											
	Red nasal discharge	-	-	-	-	-	/											
	Staggered gait	-	-	-	-	-	/											
	Hypoactivity	-	-	-	-	-	/											
	Dyspnea	-	-	-	-	-	/											
	Miosis	-	-	-	-	-	/											
	Found dead																	
	(after clinical observation)	-	-	-	-	-	/											
C28598	Appeared normal	/	-															
	Miosis	-	/															
	Hypoactive	-	/															
	Clear nasal discharge	-	/															
C28619	Found dead	-	-	/														
	Appeared normal	/	-	-	-	-	-	-										
	Red-stained face	-	/	/	/	/	/	/										
	Hypoactivity	-	-	-	-	-	-	/										
C28625	Found dead	-	-	-	-	-	-	-										/
	Appeared normal	/	-	-	-													
	Red-stained face	-	/	/	/													
	Dark-stained urogenital area	-	-	-	/													
C28625	Found dead	-	-	-	-	/												

/ Condition existed.

- Condition not evident.

Sample: T-5898

Individual Clinical Signs
(Continued)

Animal Number	Observation	Hour			Day													
		1.0	2.5	4.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Females (5,000 mg/kg)																		
C28099	Appeared normal	✓	✓	✓	✓	-	-	-										
	Red-stained face	-	-	-	-	✓	✓	✓										
	Miosis	-	-	-	-	✓	✓	-										
	Hypoactivity	-	-	-	-	-	-	✓										
	Found dead	-	-	-	-	-	-	-		✓								
C28117	Appeared normal	✓	-	✓	-													
	Soft stool	-	✓	-	-													
	Yellow-stained urogenital area	-	-	-	✓													
	Red-stained face	-	-	-	✓													
	Lacrimation	-	-	-	✓													
	Hypoactivity	-	-	-	✓													
	Found dead	-	-	-	-	✓												
C28118	Red-stained face	✓	✓	✓	✓	✓												
	Dark staining around eyes	-	-	-	-	✓												
	Hypoactivity	-	-	-	-	✓												
	Yellow-stained urogenital area	-	-	-	-	✓												
	Found dead	-	-	-	-	-	✓											
C28104	Appeared normal	✓	✓	-	-	-												
	Red-stained face	-	-	✓	✓	✓												
	Yellow-stained urogenital area	-	-	-	-	✓												
	Staggered gait	-	-	-	-	✓												
	Hunched posture	-	-	-	-	✓												
	Found dead																	
	(after clinical observations)	-	-	-	-	✓												
C28120	Appeared normal	✓	✓	✓	-	-												
	Red-stained face	-	-	-	✓	✓												
	Hunched posture	-	-	-	✓	✓												
	Hypoactivity	-	-	-	✓	✓												
	Miosis	-	-	-	-	✓												
	Found dead																	
(after clinical observations)	-	-	-	-	✓													

/ Condition existed.

- Condition not evident.

Sample: T-5898

Individual Pathology Comments

Dose Level: 500 mg/kg of Body Weight

<u>Animal Number</u>	<u>Sex</u>	<u>Test Day</u>		<u>Necropsy Observation</u>
		<u>Died</u>	<u>Sacrificed</u>	
C29181	M	-	14	No visible lesions.
C29232	M	-	14	No visible lesions.
C29184	M	-	14	No visible lesions.
C29234	M	-	14	No visible lesions.
C29190	M	-	14	No visible lesions.
C27615	F	-	14	There is alopecia on both hind limbs, 60 x 35 mm.
C28047	F	-	14	No visible lesions.
C28043	F	8	-	Due to the animal being cannibalized the spleen, pancreas, left kidney, duodenum, jejunum, ileum, cecum, colon were not found at necropsy.
C28070	F	-	14	No visible lesions.
C28050	F	-	14	Each horn of the uterus is filled with a clear fluid .

Sample: T-5898

Individual Pathology Comments

Dose Level: 5,000 mg/kg of Body Weight

<u>Animal Number</u>	<u>Sex</u>	<u>Test Day</u>		<u>Necropsy Observation</u>
		<u>Died</u>	<u>Sacrificed</u>	
C28621	M	7	-	No visible lesions.
C28613	M	3	-	No visible lesions.
C28598	M	0	-	There is red ocular discharge in both eyes.
C28619	M	5	-	There is a tan, moist abraded area on the dorsal cervical region, 15 x 10 mm.
C28625	M	2	-	The perianal region is stained yellow. There is red nasal discharge. The nonglandular mucosa of the stomach has multiple dark red areas, pinpoint and up to 1 mm in diameter.
C28099	F	5	-	No visible lesions.
C28117	F	2	-	The perianal region is stained yellow. There is red nasal discharge. The nonglandular mucosa of the stomach has multiple dark red areas, pinpoint and up to 1 mm in diameter.
C28118	F	3	-	No visible lesions.
C28104	F	2	-	The perianal region is stained yellow. There is red nasal discharge. The nonglandular mucosa of the stomach has multiple dark red areas, up to 3 x 1 mm. The thymus has multiple dark red areas, up to 1 mm in diameter.
C28120	F	2	-	The perianal region is stained yellow.

Sample: T-5898

DISCUSSION

The acute oral toxicity of T-5898 was evaluated in male and female rats when administered as a single gavage dose at levels of 500 and 5,000 mg/kg of body weight. Based on the observed mortality, the estimated oral LD₅₀ for male and female rats was determined to be between 500 and 5,000 mg/kg. Clinical signs of toxicity included thin appearance, hunched posture, hypoactivity, aggressive behavior, staggered gait, red-stained face, clear or red nasal discharge, miosis, lacrimation, dark staining around eyes, dyspnea, soft stool, yellow- or dark-stained urogenital area, alopecia (rear quarters), and death. All mortality occurred within 8 days of test material administration. Six of the 10 animals treated at 500 mg/kg exhibited body weight losses of 5 to 45 g during the first week of the study. Page 14 contains a pathology report by the study pathologist.

REFERENCES

1. "Acute Oral Toxicity," *Organisation for Economic Cooperation and Development's Guidelines for Testing of Chemicals*, Section 401 (adopted May 12, 1981).
2. NIH Publication No. 86-23 (revised 1985).

Sample: T-5898

PATHOLOGY REPORT

There were 10 rats (five males and five females) each from dose levels of 500 and 5,000 mg/kg, necropsied. All animals given 5,000 mg/kg and one female from the group given 500 mg/kg died on test (DOT). The remaining surviving animals were euthanized and necropsied at the termination of the study. The dose level, day of death, and gross observations recorded for each animal are in the Individual Pathology Comments that precede this report.

At necropsy, most of the changes observed were in the animals that died on test. Brown stains in the perianal region and red nasal discharge were indicative of acute death. All other changes in these animals were attributed to post mortem autolysis. The alopecia and fluid filled uterine horns observed in two of the females surviving to study termination were considered incidental findings and unrelated to the test material. There were no visible lesions in any of the remaining animals in either group.


Thomas E. Palmer, PhD
Pathologist

4-22-94
Date

(40200468.1hm)
041194

HWI Number: 40200468

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Sample: T-5898

APPENDIX

Raw Data

HWI: 40200468PERSONNEL SIGNATURE SHEET
ACUTE TOXICOLOGY

<u>Name</u>	<u>Job Title</u>	<u>Signature</u>	<u>Initials</u>
Rose M. Bridge	Report Supervisor	<u>Rose M. Bridge</u>	<u>RB</u>
Anthony Cass	Lab Animal Technician	<u>Anthony Cass</u>	<u>AC</u>
Cindy J. Cary, DVM	Lab Animal Veterinarian	<u>Cindy J. Cary</u>	<u>YC</u>
Donna J. Clemons, DVM, MS	Lab Animal Veterinarian	<u>Donna J. Clemons</u>	<u>DC</u>
John A. Disch	Lab Animal Caretaker	<u>John A. Disch</u>	<u>JD</u>
Charles W. Fritz	Lab Animal Technician	<u>Charles W. Fritz</u>	<u>CF</u>
Kari Garfoot	Lab Animal Technician	<u>Kari Garfoot</u>	<u>KG</u>
Steven M. Glaza	Manager	<u>Steven M. Glaza</u>	<u>SG</u>
Kevin Grossman	Lab Animal Caretaker	<u>Kevin Grossman</u>	<u>KG</u>
Jeff Hicks	Lab Animal Technician	<u>Jeff Hicks</u>	<u>JH</u>
Sharen L. Howery	Research Assistant	<u>Sharen L. Howery</u>	<u>SH</u>
Wayne A. Madison	Supervisor	<u>Wayne A. Madison</u>	<u>wam</u>
Doug McConnell	Lab Animal Technician	<u>Doug McConnell</u>	<u>DM</u>
Eileen McConnell	Staff Assistant	<u>Eileen McConnell</u>	<u>em</u>
Bud McDonald	Study Coordinator	<u>Bud McDonald</u>	<u>BMS</u>
Albert Oleson	Lab Animal Caretaker	<u>Albert Oleson</u>	<u>AO</u>
Patricia Padgham	In-life Supervisor	<u>Patricia Padgham</u>	<u>PP</u>
Steven R. Sorenson	Study Coordinator	<u>Steven R. Sorenson</u>	<u>SRS</u>
Annette R. Turner	Staff Assistant	<u>Annette R. Turner</u>	<u>AT</u>
Tamra L. Walker	Staff Assistant	<u>Tamra L. Walker</u>	<u>TW</u>
Lana M. Weeden	Staff Assistant	<u>Lana M. Weeden</u>	<u>LW</u>
Heather M. Weber	Lab Animal Caretaker	<u>Heather M. Weber</u>	<u>HW</u>
Janice Griffiths	Lab Animal Caretaker	<u>Janice Griffiths</u>	<u>JB</u>

DOSE ADMINISTRATION/BODY WEIGHT/MORTALITY RECORD

HWI No.: 40200468Study Type: Acute Oral ToxicityRoute of Administration: Oral GavageTest Material: T-5898Vehicle: NAInitiated in Room No.: 102Dose Level: 500 (mg/kg) Species/Source Strain: Rat/CrI:CD[®]BR Date Received: 1-14-25-94 Fasted Date/Time/Tech: 3-8-94/14:40/C7Dose Volume: 0.44 (mL/kg) Syringe used/Size: disposable 1 cc Gavage Method used/Size: Ball-tipped stainless steel gavage needle / 3 in. x 16 gauge

Sex: <u>Male</u> /Female	Dose Time/Tech: <u>From 10:00 To 10:04/C7</u>					Technician	Date	Scale Used: <u>A4D</u>
Animal Number <u>C2-</u>	<u>9181</u>	<u>9232</u>	<u>9184</u>	<u>9234</u>	<u>9190</u>	<u>C7</u>	<u>3-9</u>	<u>NA</u>
Prefasted Body Weight (g)	<u>NA</u>							
Fasted Body Weight (g)	<u>267</u>	<u>274</u>	<u>253</u>	<u>280</u>	<u>257</u>	<u>C7</u>	<u>3-9</u>	<u>C022/330</u>
Actual Dose (mL)	<u>0.12</u>	<u>0.12</u>	<u>0.11</u>	<u>0.12</u>	<u>0.11</u>	<u>C7</u>	<u>3-9</u>	<u>Verified by</u>
Day 7 Body Weight (g)	<u>224^{C7}</u>	<u>302</u>	<u>284</u>	<u>312</u>	<u>289</u>	<u>C7</u>	<u>3-16</u>	<u>C022/330</u>
Day 14 Body Weight (g)	<u>319</u>	<u>382</u>	<u>354</u>	<u>390</u>	<u>353</u>	<u>C7</u>	<u>3-23</u>	<u>C022/330</u>
Dead Body Weight (g)						<u>NA</u>	<u>NA</u>	<u>NA</u>
Sex: <u>Male</u> / <u>Female</u>	Dose Time/Tech: <u>From 10:05 To 10:10/C7</u>							
Animal Number <u>C2-</u>	<u>7615</u>	<u>8047</u>	<u>8043</u>	<u>8070</u>	<u>8050</u>	<u>C7</u>	<u>3-9</u>	<u>NA</u>
Prefasted Body Weight (g)	<u>NA</u>							
Fasted Body Weight (g)	<u>241</u>	<u>230</u>	<u>225</u>	<u>232</u>	<u>238</u>	<u>C7</u>	<u>3-9</u>	<u>C022/330</u>
Actual Dose (mL)	<u>0.11</u>	<u>0.10</u>	<u>0.10</u>	<u>0.10</u>	<u>0.10</u>	<u>C7</u>	<u>3-9</u>	<u>Verified by</u>
Day 7 Body Weight (g)	<u>228^{C7}</u>	<u>225^{C7}</u>	<u>180^{C7}</u>	<u>207^{C7}</u>	<u>225^{C7}</u>	<u>C7</u>	<u>3-16</u>	<u>C022/330</u>
Day 14 Body Weight (g)	<u>261</u>	<u>255</u>	<u>FOUND DEAD</u>	<u>239</u>	<u>250</u>	<u>C7</u>	<u>3-23</u>	<u>C022/330</u>
Dead Body Weight (g)			<u>131</u>			<u>NA</u>	<u>NA</u>	<u>NA</u>

MORTALITY (NUMBER DIED/NUMBER DOSED)

		MORTALITY (NUMBER DIED/NUMBER DOSED)																												
Sex	Hours 0 - 4	Study Day																												Total
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM		
Male	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	
Female	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	
Technician	C7	C7	C7	C7	C7	JH	JH	JH	JH	C7	C7	C7	C7	KG	C7	KG	C7	C7	C7	KG	KG	KG	KG	C7	C7	C7	C7	C7	C7	
Time	NA	7:06	15:26	7:58	14:40	6:41	12:25	6:50	12:40	7:13	14:47	7:03	15:03	7:15	14:25	7:41	14:35	8:55	16:56	6:41	12:23	6:45	12:12	8:36	15:17	6:55	14:03	6:56	NA	
Date 1994	3/9	3/10	3/10	3/11	3/11	3/12	3/12	3/13	3/13	3/14	3/14	3/15	3/15	3/16	3/16	3/17	3/17	3/18	3/18	3/19	3/19	3/20	3/20	3/21	3/21	3/22	3/22	3/23	3/23	

NA Not applicable.
(02/10-18-93)Final data review by/Date: OC 13-24-94

HWI No.: 40200468**INDIVIDUAL CLINICAL SIGNS**Dose level: 500 mg/kg Test material: T-5898

Animal Number	Male/Female	Observation	Pre-dose	Hours			Study Day													
				1	2.5	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C2- 9181		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Appears thin										✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 9232		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 9184		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 9234		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Soft stool			✓															
C2- 9190		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Time			NA	11:01	12:30	14:02	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Technician			C7	C7	C7	C7	C7	C7	JA	JA	C7	C7	K	K	C7	K	IG	C7	C7	C7
Date 1994			3/9	3/9	3/9	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23

Housing of animals:

NA Individual.☒ Group and separated by sex.Technician C7
Date 3-9-94

Surviving animals submitted for terminal necropsy.

Technician C7
Date 3-23-94

Surviving animals designated for sacrifice and discard.

Technician NA
Date NA

NA Not applicable.

☒ Condition exists.

- Condition not evident.

* Found dead, P.M. check.

HWI No.: 40200468**INDIVIDUAL CLINICAL SIGNS**Dose level: 500 mg/kg Test material: T-5898

Animal Number	Male/Female	Observation	Pre-dose	Hours			Study Day													
				1	2.5	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C2- 7615		Appeared normal	✓	✓	✓	✓	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-
		Red stained face					✓	✓	-	-	-	-	-	-	-	-	-	-	-	-
		Appears thin									✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Alopecia - rear quarters									✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 8047		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 8043		Appeared normal	✓	✓	✓	✓	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
		Red stained face					✓	✓	-	-	-	-	✓	-	-	-	-	-	-	-
		HYPOACTIVE											✓	-	-	-	-	-	-	-
		APPEARS THIN											✓	-	-	-	-	-	-	-
C2- 8070		HUNCHING POSTURE											✓	-	-	-	-	-	-	-
		AGGRESSIVE BEHAVIOR											✓	⓪	-	-	-	-	-	-
		Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C2- 8050		Appeared normal	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Red stained face						✓	-	-	-	-	-	-	-	-	-	-	-	-
Time			NA	11:04	12:34	14:05	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Technician			C7	C7	C7	C7	C7	C7	JH	JH	C7	C7	KG	KG	C7	KG	KG	C7	C7	C7
Date 1994			3/9	3/9	3/9	3/9	3/10	3/11	3/12	3/12	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23

DEAD ⓪
 ① ANIMAL FOUND DEAD AT
 7:41 ON 3-17-94.
 KG 3-17-94
 ② CORRECTION OF SPELLING
 ERROR. KG 3-28-94

Housing of animals:
~~NA~~ Individual.
 ✓ Group and separated
 by sex.
 Technician C7
 Date 3-9-94

Surviving animals
 submitted for terminal
 necropsy.
 Technician C7
 Date 3-23-94

Surviving animals
 designated for sacrifice
 and discard.
 Technician NA
 Date NA

NA Not applicable.
 ✓ Condition exists.
 - Condition not evident.
 * Found dead, P.M. check.

DOSE ADMINISTRATION/BODY WEIGHT/MORTALITY RECORD

HWI No.: 40200468Study Type: Acute Oral ToxicityRoute of Administration: Oral GavageTest Material: T-5898Vehicle: NAInitiated in Room No.: 102Dose Level: 5000 (mg/kg) Species/Source Strain: Rat/Crl:CD[®]BR Date Received: 1-28-94 Fasted Date/Time/Tech: 2-21-94/16:45/C7Dose Volume: 4.42 (mL/kg) Syringe used/Size: disposable 1.3 -cc Gavage Method used/Size: Ball-tipped stainless steel gavage needle / 3 in. x 16 gauge

Sex: <u>Male/Female</u>	Dose Time/Tech: From <u>11:49</u> To <u>11:53</u> <u>C7</u>					Technician	Date	Scale Used: <u>A&D</u>
Animal Number	<u>C2-8621</u>	<u>8613</u>	<u>8598</u>	<u>8619</u>	<u>8625</u>	<u>C7</u>	<u>2-22</u>	<u>NA</u>
Prefasted Body Weight (g)	<u>NA</u>							
Fasted Body Weight (g)	<u>269</u>	<u>271</u>	<u>266</u>	<u>267</u>	<u>271</u>	<u>C7</u>	<u>2-22</u>	<u>C022/330</u>
Actual Dose (mL)	<u>1.2</u>	<u>1.2</u>	<u>1.2</u>	<u>1.2</u>	<u>1.2</u>	<u>C7</u>	<u>2-22</u>	<u>Verified by</u>
Day 7 Body Weight (g)	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>			
Day 14 Body Weight (g)	<u>C7 2-1-94</u>	<u>C7 2-25-94</u>	<u>C7 2-22-94</u>	<u>JH 2-27-94</u>	<u>C7 2-24-94</u>			
Dead Body Weight (g)	<u>203</u>	<u>228</u>	<u>NA</u>	<u>215</u>	<u>234</u>	<u>NA</u>	<u>NA</u>	<u>NA</u>
Sex: <u>Male/Female</u>	Dose Time/Tech: From <u>11:54</u> To <u>11:58</u> <u>C7</u>							
Animal Number	<u>C2-8099</u>	<u>8117</u>	<u>8118</u>	<u>8104</u>	<u>8120</u>	<u>C7</u>	<u>2-22</u>	<u>NA</u>
Prefasted Body Weight (g)	<u>NA</u>							
Fasted Body Weight (g)	<u>246</u>	<u>250</u>	<u>267</u>	<u>267</u>	<u>255</u>	<u>C7</u>	<u>2-22</u>	<u>C022/330</u>
Actual Dose (mL)	<u>1.1</u>	<u>1.1</u>	<u>1.2</u>	<u>1.2</u>	<u>1.1</u>	<u>C7</u>	<u>2-22</u>	<u>Verified by</u>
Day 7 Body Weight (g)	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>	<u>Found Dead</u>			
Day 14 Body Weight (g)	<u>JH 2-27-94</u>	<u>C7 2-24-94</u>	<u>C7 2-25-94</u>	<u>C7 2-24-94</u>	<u>C7 2-24-94</u>			
Dead Body Weight (g)	<u>209</u>	<u>235</u>	<u>238</u>	<u>235</u>	<u>225</u>	<u>NA</u>	<u>NA</u>	<u>NA</u>

① Entry error, C7 2-24-94
 ② To clarify, time is 15:06, C7 2-25-94

		MORTALITY (NUMBER DIED/NUMBER DOSED)																											
		Study Day																											
Sex	Hours 0 - 4	1		2		3		4		5		6		7		8		9		10		11		12		13		14	Total
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
Male	1/5	0/5	0/5	0/5	0/5	0/5	1/5	0/5	0/5	1/5	0/5	0/5	0/5	1/5	NA														→ 5/5
Female	0/5	0/5	0/5	1/5	2/5	1/5	0/5	0/5	0/5	1/5	NA																		→ 5/5
Technician	C7	C7	C7	C7	C7	C7	C7	JH	JH	JH	JH	C7	C7	C7															C7
Time	NA	7:25	14:58	7:27	14:40	7:08	15:06	6:51	12:20	6:20	12:26	8:33	16:41	7:32															NA
Date 1994	2/22	2/23	2/23	2/24	2/24	2/25	2/25	2/26	2/26	2/27	2/27	2/28	2/28	3/1															3/1

NA Not applicable.
 (02/10-18-93)

Final data review by/Date: 16/13-5-94

INDIVIDUAL CLINICAL SIGNS

Dose level: 5000mg/kg Test material: T-5898

Animal Number	Male/Female	Observation	Pre-dose	Hours			Study Day													
				1	2.5	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C2- 8621		Appeared normal	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Red stained face					✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-
		HYPERACTIVE									✓	✓	✓	-	-	-	-	-	-	-
		Dead (7:32)											✓	-	-	-	-	-	-	-
C2- 8613		Appeared normal	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Red stained face					✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-
		Hunched posture							✓	-	-	-	-	-	-	-	-	-	-	-
		Red nasal discharge							✓	-	-	-	-	-	-	-	-	-	-	-
		Staggered gait							✓	-	-	-	-	-	-	-	-	-	-	-
C2- 8598		Appeared normal	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Miosis			✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Hypnactive			✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Clear nasal discharge			✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C2- 8619		Dead (15:51)				✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Appeared normal	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Red stained face			✓	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-
		HYPERACTIVE								✓	-	-	-	-	-	-	-	-	-	-
C2- 8625		Dead (2:20)																		
		Appeared normal	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Red stained face			✓	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-
		Dark stained urogenital area					✓	-	-	-	-	-	-	-	-	-	-	-	-	-
C2- 8625		Dead (7:27)						✓	-	-	-	-	-	-	-	-	-	-	-	-
		Time	NA	12:51	14:19	15:51	NA	NA	NA	NA	6:20	NA	NA	-	-	-	-	-	-	-
		Technician	C7	C7	C7	C7	C7	C7	C7	JH	JH	C7	C7	-	-	-	-	-	-	-
		Date 1994	2/22	2/22	2/22	2/22	2/23	2/24	2/25	2/26	2/27	2/28	3/1	-	-	-	-	-	-	-

Housing of animals:

NA Individual.

✓ Group and separated by sex.

Technician C7

Date 2-22-94

Surviving animals submitted for terminal necropsy.

Technician NA

Date NA

Surviving animals designated for sacrifice and discard.

Technician NA

Date NA

NA Not applicable.

✓ Condition exists.

- Condition not evident.

* Found dead, P.M. check.

INDIVIDUAL CLINICAL SIGNS

Dose level: 5000mg/kg Test material: T-5898

[illegible]

NA Not applicable.
✓ Condition exists.
- Condition not evident.
* Found dead, P.M. check.

INDIVIDUAL CLINICAL SIGNS

Dose level: 5000 mg/kg Test material: T-5898

Animal Number	Male/Female	Observation	Pre-dose	Hours			Study Day													
				1	2.5	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C2- 8099		Appeared normal	✓	✓	✓	✓	✓	-	-	-	-									
		Red stained face						✓	✓	✓	-									
		Miosis						✓	✓	-	-									
		HYPERACTIVE								✓	-									
		DEAD (6:00)									✓									
C2- 8117		Appeared normal	✓	✓	-	✓	-	-	-	-	-									
		Soft stool			✓	-	-	-	-	-	-									
		Yellow stained urogenital area						✓	-	-	-									
		Red stained face						✓	-	-	-									
		Lacrimation						✓	-	-	-									
C2- 8118		Appeared normal	✓	-	-	-	-	-	-	-	-									
		Red stained face		✓	✓	✓	✓	✓	-	-	-									
		Dark staining around eyes						✓	-	-	-									
		Hypactive						✓	-	-	-									
		Yellow stained urogenital area						✓	-	-	-									
C2- 8104		Dead (7:08)								✓	-									
		Appeared normal	✓	✓	✓	-	-	-	-	-	-									
		Red stained face				✓	✓	✓	-	-	-									
		Yellow stained urogenital area						✓	-	-	-									
		Staggered gait						✓	-	-	-									
C2- 8120		Hunched posture						✓	-	-	-									
		Dead (14:40)						*	-	-	-									
		Appeared normal	✓	✓	✓	✓	-	-	-	-	-									
		Red stained face					✓	✓	-	-	-									
		Hunched posture					✓	✓	-	-	-									
C2- 8120		Hypactive					✓	✓	-	-	-									
		Miosis						✓	-	-	-									
		Dead (14:40)						*	-	-	-									
		Time	NA	12:51	14:23	15:55	NA	NA	NA	NA	6:00									
		Technician	C7	C7	C7	C7	C7	C7	C7	JH	JH									
	Date/994	2/22	2/22	2/22	2/22	2/23	2/24	2/25	2/26	2/27										

Housing of animals:

NA Individual.

✓ Group and separated by sex.

Technician C7

Date 2-22-94

Surviving animals submitted for terminal necropsy.

Technician NA

Date NA

Surviving animals designated for sacrifice and discard.

Technician NA

Date NA

NA Not applicable.

✓ Condition exists.

- Condition not evident.

* Found dead, P.M. check.

INDIVIDUAL CLINICAL SIGNSDose level: 5000 mg/kg Test material: T-5898

Animal Number	Male/ <u>Female</u> Observation	Hours			Study Day													
		1	2.5	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C2- 8117	Dead (7:27)																	

Technician C7
Date 1994 2/24

NA Not applicable.
✓ Condition exists.
- Condition not evident.
* Found dead, P.M. check.