ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ- 92-10141	89110000205	3/22/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI

334118

The Procter & Gamble Company
NA Regulatory & Technical Relations
One Procter & Gamble Plaza (C-6)
Cincinnati, OH 45202
www.pg.com

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U.S. EPA
Office of Pollution Prevention and Toxics
Document Control Office (7407M)
1200 Pennsylvania Ave., NW
Washington, DC 20460
Attn: TSCA Declassification Coordinator

Re: Declassification Activity-Health and Safety Filing 8EHQ-0892-10141 (EPA DCN 88920008442)

Dear Sir/Madam:

The Procter & Gamble Company (P&G) provides this submission to amend the Public Display Version of our submission pursuant to the TSCA Section 8(e) Compliance Audit Program (CAP) under terms of CAP Agreement # 8ECAP-0003.

This amended submission is composed of the following:

(a) new information provided in this cover letter and its attachment(s); and
(b) the unaltered original submission which directly follows.

Any CBI substantiation which appears in the original submission is no longer applicable as the information which was originally claimed CBI is disclosed in this revised submission.

Should you have any questions concerning this amended submission, please contact me at (513) 983-2531 or froelicher.jm@pg.com.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Julie Froelicher
NA Regulatory & Technical Relations Manager
The Procter & Gamble Company
One Procter & Gamble Plaza
Cincinnati, OH 45202
(513) 983-2531
froelicher.jm@pg.com

8 9 1 1 0 0 0 0 2 0 5

Attachment 1

Public Display Version

Chemical Identity	CAS RN
Benzenesulfonic acid, C10-16-alkyl derivatives	68584-22-5
Potassium hydroxide	
Potassium pyrophosphate	
Isopropanol	
Pine oil	
Cyclohexene, 1-methyl-4-(1-methylethenyl)-, (R)-	5989-27-5
Cyclohexene, 1-methyl-4-(1-methylethylidene)-	586-62-9
Cyclohexene, 1-methyl-4-(1-methylethenyl)-	138-86-3
1-Naphthalenesulfonic acid, 3-[(2,4-dimethyl-5-sulfophenyl)azo]-4-hydroxy-, disodium salt	4548-53-2
Benzenesulfonic acid, 2,5-dichloro-4-[4,5-dihydro-3-methyl-5-oxo-4-[(4-sulfophenyl)azo]-1H-pyrazol-1-yl]-, disodium salt	6359-98-4
Water	

Procter&Gamble

8EHQ-0892-10141s

COMPANY SANITIZED

92 AUG 31 PM 1:18

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August 20, 1992

8EHQ-92-10141s INIT
88920008442

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M St. S.W.
Washington, D.C. 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

This submission is being made pursuant to the TSCA Section 8(e) Compliance Audit Program and the terms of CAP Agreement # 8ECAP-0003. This report discharges our Company obligation to report the attached data under TSCA Section 8(e). The filing of these studies does not indicate that we agree that "substantial risk" exists. We are following the agency's guidance and the terms of the CAP agreement, but we expressly disclaim that the filings reflect a decision that these materials pose any significant human or environmental safety risks.

The material identified in the attached report as B0429-01 is a confidential mixture. The composition of the mixture is appended as Attachment 1. The report is titled "Acute Oral Toxicity (LD_{50} Value in Rats)". Any correspondence relating to this submission should reference study # 1105-26478.

The attached study report indicates oral administration of the test material resulted in pharmacotoxic signs including ataxia, high carriage, hypoactivity, and piloerection following oral administration of 5000, 5750, 6613, 7604, and 8745 mg/kg of the test material. Tremors were observed in the 7604 and 8745 mg/kg groups, and impaired righting reflex was observed in the 8745 mg/kg group. The acute oral LD_{50} is calculated to be 7.0 g/kg.

We do not believe findings in this report reasonably support a conclusion of substantial risk to human health or the environment. Nevertheless, we are submitting this report to discharge any potential liability under TSCA Section 8(e).

To our knowledge, this report has not been the subject of a prior submission to EPA under the provisions of TSCA.

The specific chemical constituents and percentage composition of this mixture is claimed as confidential business information. A sanitized version of this submission containing generic chemical names has been included as part of this submission. Answers to the seven questions required to substantiate this claim of confidentiality are provided below:

1. Confidentiality of the chemical constituents and their percentages should be maintained indefinitely. There are no plans for this information to be otherwise disclosed, and this technology has significant commercial value.

2. To our knowledge, there have been no government confidentiality determinations made for this mixture.

3. The specific chemical identity and exact proportions of the constituents of this mixture have not been disclosed outside the Company. There are no plans to disclose publicly the exact composition of this mixture at any time in the future.

4. Measures for protection of the compositional information include "need to know" internal restriction within the Company. An internal code is used to protect the identity of the material. Information is maintained in locked files. Employees leaving the Company are contractually bound not to disclose Company secrets.

5. The exact composition of this mixture has not appeared in advertising or promotional literature, MSD sheets, any publications or any other media available to the general public or competitors.

6. Disclosure of the information claimed as CBI would result in substantial harm to the Company's competitive position. This formula provides an important commercial opportunity for a competitor. Knowledge of the exact composition of this mixture could enable a competitor to duplicate the formula without R&D cost, thus providing an unfair competitive disadvantage to the Procter & Gamble Company. Development of this formula required many technically trained personnel, hundreds of hours of research and development, and significant capital investment valued in aggregate at . Any competitor would normally be required to make a similar investment to duplicate the formula. Disclosure of this information would allow a competitor to duplicate the formula without incurring significant R&D costs, thus doing substantial harm to our competitive position.

7. The information we have identified as confidential is not health or safety data.

Any questions concerning this submission, may be directed to me at (513) 627-5551.

Sincerely,

THE PROCTER AND GAMBLE COMPANY

Richard H. Hall, Ph.D.
Manager
Regulatory & Government Affairs
The Procter & Gamble Company

Procter&Gamble

Attachment I

Public Display Copy

Alkyl benzene sulfonic acid

Potassium hydroxide

Potassium pyrophosphate

Isopropanol

Pine oil

Mixed terpenes

Colorant

Water

1105-26478

International Research
and Development Corporation
MATTAWAN, MICHIGAN U.S.A. 49071 TELEPHONE (616) 668-3336

SPONSOR: The Procter and Gamble Company

SUBJECT: Acute Oral Toxicity (LD_{50} Value in Rats)

DRD NO.: BSBTS 734S

TSIN: B0429-01

REPORT NO.: 191-722

DATE OF SUBMISSION: March 16, 1982

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MAR 22 1982
OPERATIONS SECTION

"credence through research"

STUDY SUMMARY

Study No: 191-722
Sponsor Ref: BSBTS 734S

Acute Oral Toxicity (LD_{50} Value in Rats)
Report of a biological test performed at:

International Research and Development Corporation
Mattawan, Michigan

Deviation from
Protocol: None

During the period:
December 29, 1981 to January 19, 1982
According to the attached protocol
(P & G No. C1)
Issue Date: September 1, 1981

Test Substance (TSIN)	Color	Physical Form	Storage Condition
B0429-01	amber	liquid	room temperature

Sponsor's Divisional Toxicologist: James H. Benedict

Source and Strain of Animals Used: Charles River Laboratories, Inc., Portage, MI
Sprague-Dawley rats

Concentration and Amount of
Test Substance Dosed: Administered undiluted as received at the following dosage levels and respective volumes: 5000 mg/kg--4.6 ml/kg; 5750 mg/kg--5.3 ml/kg; 6613 mg/kg-- 6.1 ml/kg; 7604 mg/kg--7.1 ml/kg; 8745 mg/kg--8.1 ml/kg.

RESULTS

Dose - Mortality Data:

Dosage Level mg/kg	Number of Deaths: Hrs 0-4		Days 1		2		3		4		5		6		7 - 14		Total Mortalities: Male	Female	Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F			
5000																	0/5	0/5	0/10
5750				2		2											0/5	4/5	4/10
6613				2		1											0/5	3/5	3/10
7604			1	2				1								1	1/5	4/5	5/10
8745			4	4		1											4/5	5/5	9/10

LD_{50} (95% Confidence Limits) Combined Male and Female[1]: 7.0 (6.4 - 7.7) g/kg

REFERENCE

1. Bliss, C. I., "The Determination of the Dosage Mortality Curve from Small Numbers", Quarterly Journal Pharm. Pharmacol, 11: p. 192-216, 1938.

Results (Cont.)

Pharmacotoxic Signs (Appendix A):

The major pharmacotoxic signs observed in all dosage levels were: ataxia, high carriage, hypoactivity, piloerection and possible respiratory congestion.

Body Weights (Appendix B):

No remarkable changes or differences were observed in the body weights during the study period.

Pathology (Appendix C):

Treatment related changes were seen at 6613 mg/kg and higher dose levels, in the gastrointestinal tract of animals that died during the study. The changes consisted of mucosal hyperemia of gastrointestinal tract with or without a reddish mucoid fluid content. No macroscopic changes were evident in survivors that were sacrificed at the termination of the study period.

Prepared By: Daniel Rajasekaran, D.V.M., M.V.Sc. (Path), F.R.V.C.S. (Path) Sweden
Staff Pathologist — Date 3/15/82

Reviewed By: Ward R. Richter, D.V.M., A.C.V.P.
Director, Pathology Division — Date 3-16-82

191-722

Technical Supervisory Staff,

Acute Toxicology and Special Studies:

Paul Moxon, B.S.
Unit Supervisor

Adalsteinn Olafsson, B.S.
Group Supervisor

Prepared By: _____ 3-4-82
Julie L. Schmidt, B.S. Date
Unit Supervisor,
Acute Toxicology
and Special Studies

Reviewed By: _____ 3/12/82
Dale E. Johnson, Pharm.D., Ph.D. Date
Associate Director,
Toxicology Division

STUDY DIRECTOR STATEMENT

The methods used in IRDC Study Number 191-722 followed the experimental criteria specified in the protocol.

To the best of my knowledge, there were no significant deviations from the Good Laboratory Practice Regulations which affected the quality or integrity of this study. This study was conducted in conformance with the Good Laboratory Practice Regulations. This report accurately reflects the raw data obtained during the performance of this study.

All data including the final study report are stored in the International Research and Development Corporation Archives.

_____ 3/12/82.
James R. Myer, B.S. Date
Study Director

191-722

APPENDIX A

Individual Pharmacotoxic Signs

80429-01

Individual Pharmacotoxic Signs
5000 mg/kg

Sex	Male										Female										Male	Female
Animal Number	99626		99631		99633		99636		99643		99657		99666		99671		99672		99675		Total Incidence	
Pharmacotoxic Sign	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance		
Clear wet stain around mouth	a	d			a	c			a	d											1	0
Ataxia	a	d							a	d	b	c			a	1	b	1	a	d	2	4
High carriage	a	c[a]							b	c							d	1	a	1	2	2
Piloerection	b	6							b	1											2	0
Hypersensitive to touch	b	c													a	d					1	1
Dry reddish brown stain around mouth and nose	d	3																			1	0
Abdomen distended	1	2																			1	0
Soft stool	2	3																			1	0
Possible respiratory congestion	2	5																			1	0
Wet yellow stained anogenital area							d	1	d	5							d	1			3	1
Dry yellow stained anogenital area					d	1			d	1					a	1	a	1	c	1	2	3
Mucoid diarrhea					1	4			1	3					1	7	1	4	1	3	2	3
Hypoactivity											d	1									0	1
															d	1					0	1
Day of Death																					0	0

a - 1/2 hour after dosing, Day 0
b - 1 hour after dosing, Day 0
c - 2 1/2 hours after dosing, Day 0
d - 4 hours after dosing, Day 0

e - Sign reappeared at 4 hours and cleared on Day 2

80429-01

Individual Pharmacotoxic Signs
5750 mg/kg

Sex	Male										Female										Male	Female
Animal Number	99627		99634		99641		99646		99647		99663		99667		99668		99670		99678		Total Incidence	
Pharmacotoxic Sign	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance		
Clear wet stain around mouth	a	1	a	1			a	d	a	d	a	d	a	d			a	1	a	d	4	4
Ataxia	a	d	b	4			a	d	a	d	a	g	a	c[i]	a	g	a	g	a	7	4	5
Mucoid diarrhea	d	1															c	1			1	1
High carriage			a	2			a	c[f]	a	2	a	g	a	c[h]	a	g	a	1	a	4	3	5
Piloerection			b	1			2	7					1	g			1	g			2	2
Possible respiratory congestion			d	5			1	4							d	g			d	4	2	2
Wet yellow stained anogenital area			d	1					1	2	d	g	1	g	b	g	d	g	a	3	2	5
Dry yellow stained anogenital area			1	10					2	3									4	11	2	1
Hairloss anogenital region			7	13															4	1	1	1
Hypersensitive to touch							a	d			a	c					a	d			1	2
Dry reddish brown stain around nose, mouth, ventral surface							d	4													1	0
Hypoactivity											d	g	1	g	d	g	1	g	d	3	0	5
Dry reddish-brown stain around mouth													1	g					1	6	0	2
Wet yellow stain around mouth															a	d					0	1
Wet reddish brown stain - ventral surface																			1	3	0	1
Dry reddish-brown stain - ventral surface																			3	10	0	1
Hairloss abdomen																			12	1	0	1
Day of Death											1		2		1		2				0	4

a - 1/2 hour after dosing, Day 0
b - 1 hour after dosing, Day 0
c - 2 1/2 hours after dosing, Day 0
d - 4 hours after dosing, Day 0
f - Sign reappeared on Day 1 and cleared on Day 2

g - Sign did not clear prior to death
h - Sign reappeared at 4 hours and did not clear prior to death
i - Sign reappeared on Day 1 and did not clear prior to death
j - Sign did not clear prior to study termination

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Individual Pharmacotoxic Signs
6613 mg/kg

Sex	Male										Female										Male	Female
Animal Number	99624		99632		99635		99637		99642		99655		99658		99665		99673		99676		Total Incidence	
Pharmacotoxic Sign	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance		
Hypersensitive to touch	a	d							a	c											2	0
High carriage	d	1	d	2	b	c[e]	d	1	a	b	b	4	c	g	a	h[h]			a	4	5	4
Wet yellow stained anogenital area	d	2	d	3	d	2	d	3			d	1	d	g	d	g			d	7	4	4
Piloerection	1	7									2	12	1	g			c	d			1	3
Possible respiratory congestion	1	2									d	4[l]	d	g			d	g	d	4	1	4
Ataxia			a	c[k]	a	2	a	3	a	1	b	11	a	g	a	g	a	g	a	7	4	5
Wet clear stain around mouth			a	c							a	d	a	c			a	d	a	d	1	4
Hypoactivity			1	3			d	1	d	1	d	4	1	g	d	g	d	g	d	6	3	5
Dry yellow stained anogenital region			3	12															7	10	1	1
Distended abdomen									1	2											1	0
Dry reddish-brown stain around mouth and nose											1	9							d	8	0	2
Dry yellow stained ventral surface											1	7									0	1
Mucoid diarrhea											3	4									0	1
Hairloss anogenital area											4	13							7	13	0	2
Hairloss on face											10	j									0	1
Decreased limb tone													a	c	d	g	d	g			0	3
Clear wet stain under mouth															a	b					0	1
Clear dry stain under mouth															b	c					0	1
Bradypnea																	d	g			0	1
Wet reddish-brown stain around nose and mouth																	d	g			0	1
Day of Death													2		1		1				0	3

a - 1/2 hour after dosing, Day 0
b - 1 hour after dosing, Day 0
c - 2 1/2 hours after dosing, Day 0
d - 4 hours after dosing, Day 0
e - Sign reappeared at 4 hours and cleared on Day 2
h - Sign reappeared at 4 hours and did not clear prior to death
g - Sign did not clear prior to death
j - Sign did not clear prior to study termination
k - Sign reappeared at 4 hours and cleared on Day 3
l - Sign reappeared on Day 7 and cleared on Day 11

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80429-01

Individual Pharmacotoxic Signs

7604 mg/kg

Sex	Male										Female										Male	Female
Animal Number	99625		99638		99639		99640		99644		99658		99660		99661		99662		99669		Total Incidence	
Pharmacotoxic Sign	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance		
Clear wet stain around mouth	a	d							a	d	a	d			a	d	a	d			2	3
High carriage	b	4	d	4	b	c[m]	d	g	d	4	c	g	a	b[o,n]	c	g	b	4	a	1	5	5
Ataxia	b	7	a	6	a	6	a	g	b	4	a	g	a	g	a	g	a	c[p]	a	g	5	5
Possible respiratory congestion	d	4							1	4	d	g					1	7			2	2
Hypoactivity	1	3	d	4	c	4	d	g	1	3	d	g	d	g	d	g			d	g	3	4
Dry yellow stained anogenital area	1	1	1	9	1	3			3	12			2	3[o]			1	10			4	2
Piloerection	1	3	1	10	1	7							1	g	b	g			d	g	3	3
Hypersensitive to touch			b	c																	1	0
Wet yellow stained anogenital area			d	1			c	g	d	3	c	g	1	2	c	g			1	g	3	4
Clear wet stain under mouth					a	d	a	d											a	d	2	1
Mucoid diarrhea							d	g													1	0
Body tremors													1	2							0	1
Abdomen distended													7	g							0	1
Dry reddish-brown stain around nose and mouth															d	g					0	1
Dry reddish-brown stain around mouth																	d	8			0	1
Ptosis																			2	g	0	1
Body hypothermic to touch																			2	g	0	1
Day of Death							1				1		9		1				3		1	4

a - 1/2 hour after dosing, Day 0
b - 1 hour after dosing, Day 0
c - 2 1/2 hours after dosing, Day 0
d - 4 hours after dosing, Day 0
e - Sign reappeared at 4 hours and cleared on Day 2
g - Sign did not clear prior to death
j - Sign did not clear prior to study termination.
m - Sign reappeared at 4 hours and cleared on Day 4
n - Sign reappeared on Day 7 and cleared on Day 8
o - Sign reappeared on Day 4 and did not clear prior to death
p - Sign reappeared on Day 2 and cleared on Day 8

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80429-01

Individual Pharmacotoxic Signs
8745 mg/kg

Sex	Male										Female										Male	Female
Animal Number	99688		99703		99705		99706		99714		99761		99765		99774		99778		99782		Total Incidence	
Pharmacotoxic Sign	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance	Day First Appeared	Day of Clearance		
Ataxia	a	j	a	g	a	g	b	g	a	g	a	g	a	g	a	g	a	g	a	g	5	5
Piloerection	b	j	d	g			b	g	c	g	d	g	b	g	d	g					4	3
Hypoactivity	b	49	d	g	c	g	c	g	c	g	b	g	a	g	d	g	a	g			5	4
Possible respiratory congestion	d	1			a	g	d	g													3	0
Wet yellow stained anogenital area	1	3					c	g					b	g	1	g			d	g	2	3
Ptosis	2	9r																			1	0
Dry yellow stained anogenital region	3	j																			1	0
Protrusion of penis	5	6																			1	0
Red crusty material around eyes	6	14																			1	0
High carriage					b	g	b	g	a	g					d	1	b	g	a	c	3	3
Wet clear stain around mouth					a	g									a	d	a	g			1	2
Decreased limb tone											a	g	b	g			d	g	b	g	0	4
Bradypnea													d	g					d	g	0	2
Clear discharge - both eyes															1	g					0	1
Body tremors															1	g					0	1
Impaired righting reflex																			c	g	0	1
Body hypothermic to touch																			d	g	0	1
Day of Death			1		1		1		1		1		1		2		1		1		4	5

a - 1/2 hour after dosing, Day 0
b - 1 hour after dosing, Day 0
c - 2 1/2 hours after dosing, Day 0
d - 4 hours after dosing, Day 0

g - Sign did not clear prior to death
j - Sign did not clear prior to study termination
q - Sign reappeared on Day 6 and cleared on Day 10
r - Sign reappeared on Day 10 and did not clear prior to study termination

191-722

APPENDIX B

Body Weights

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND B0429-01 STUDY NO. 191-722

IRDC NO. 7500

DOSE VOLUME ml/kg: Refer to dose volume calculation sheet SPECIES Rat SEX F

ROUTE OF ADMINISTRATION Oral DATE ANIMALS RECEIVED 12/14/91 SOURCE Charles River

TIME OF FASTING[a] ① FASTING TECHNICIAN ① DATE ①

TIME OF DOSING ① DOSING TECHNICIAN ① DATE ①

							TECHNICIAN	DATE
7 ml/kg DOSAGE	ANIMAL NUMBER	99638	99640	99641	99642	99644		
	PREFASTED WEIGHT (g)	235	238	216	235	235	*	
	INITIAL BODY WEIGHT (g)	214	216	201	212	218	*	
	ACTUAL DOSE (ml)	1.5	1.5	1.4	1.5	1.5	ML	12/14
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	●	①
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	231	[illegible]	[illegible]	1/12
	DAY BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]		[illegible]		
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg DOSAGE	ANIMAL NUMBER						Dose Chemical Hours 12/14/91	
	PREFASTED WEIGHT (g)						Dose Chemical Hours 12/14/91	
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg DOSAGE	ANIMAL NUMBER							
	PREFASTED BODY WEIGHT (g)							
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							

NA - Not Applicable a - food removed ✓ - Dose indicated was administered

PREFASTED BODY WEIGHTS BALANCE NO. 4 DAY 14 BODY WEIGHT BALANCE NO. [illegible] DAY BODY WEIGHT BALANCE NO. [illegible]

INITIAL BODY WEIGHTS BALANCE NO. 4 DAY BODY WEIGHT BALANCE NO. [illegible] DAY BODY WEIGHT BALANCE NO. [illegible]

IR36-61-4 * Refer to fasted/prefasted Bodyweight sheet [illegible]

① Refer to first LD_{50} sheet [illegible]

Supervisory review [illegible]

Supervisory review [illegible]

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND BO 429-01 STUDY NO. 191-722

IRDC NO. 7500

DOSE VOLUME ml/kg: Refer to dose volume calculation sheet. SPECIES Rat SEX F

ROUTE OF ADMINISTRATION Oral. DATE ANIMALS RECEIVED 12/14/81 SOURCE Charles River

TIME OF FASTING[a] 0 FASTING TECHNICIAN 0 DATE 0

TIME OF DOSING 0 DOSING TECHNICIAN 0 DATE 0

							TECHNICIAN	DATE
DOSAGE 5000 mg/kg	ANIMAL NUMBER	99657	99666	99671	99672	99675	ML	12/29
	PREFASTED WEIGHT (g)	218	241	227	208	226	*	
	INITIAL BODY WEIGHT (g)	202	225	205	190	215	*	
	ACTUAL DOSE (ml)	0.93	1.0	0.94	0.87	0.99	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	●	ML	12/29
	DAY 14 BODY WEIGHT (g)	237	261	238	218	271	DN	1/12
	DAY ~~BODY WEIGHT (g)~~							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE 5750 mg/kg	ANIMAL NUMBER	99663	99667	99668	99670	99678	ML	12/29
	PREFASTED WEIGHT (g)	226	228	206	236	211	*	
	INITIAL BODY WEIGHT (g)	208	210	188	217	199	*	
	ACTUAL DOSE (ml)	1.1	1.1	1.0	1.2	1.1	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/29
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	230	DN	1/12
	DAY ~~BODY WEIGHT (g)~~	[illegible]	[illegible]	[illegible]	[illegible]			
	DAY BODY WEIGHT (g)				[illegible]			
	DAY BODY WEIGHT (g)							
DOSAGE 6613 mg/kg	ANIMAL NUMBER	99655	99659	99665	99673	99676	ML	12/29
	PREFASTED BODY WEIGHT (g)	209	202	221	235	210	*	
	INITIAL BODY WEIGHT (g)	191	188	205	214	193	*	
	ACTUAL DOSE (ml)	1.2	1.1	1.3	1.3	1.2	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/29
	DAY 14 BODY WEIGHT (g)	211	[illegible]	[illegible]	[illegible]	223	DN	1/12
	DAY ~~BODY WEIGHT (g)~~		[illegible]	[illegible]	[illegible]			
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							

NA - Not Applicable a - food removed ✓ - Dose indicated was administered

PREFASTED BODY WEIGHTS BALANCE NO. * DAY 14 BODY WEIGHT BALANCE NO. 10400 DN 1/12/82 DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. * DAY BODY WEIGHT BALANCE NO. NA DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4

* Refer to fasted/prefasted body weight sheet ML 12/29/81
0 Refer to first LD_{50} record sheet ML 12/29/81
* Inadvertently not recorded at time of dosing [illegible]

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND EO-251-01 STUDY NO. 141-722

IRDC NO. 7500

DOSE VOLUME ml/kg: Refer to dose volume calculation sheet SPECIES Rat SEX M

ROUTE OF ADMINISTRATION oral DATE ANIMALS RECEIVED 12/14/91 SOURCE Charles River

TIME OF FASTING[a] 0 FASTING TECHNICIAN 0 DATE 0

TIME OF DOSING 0 DOSING TECHNICIAN 0 DATE 0

							TECHNICIAN	DATE
7500 mg/kg DOSAGE	ANIMAL NUMBER	99625	99635	99639	99640	99644		
	PREFASTED WEIGHT (g)	267	261	263	265	271	*	
	INITIAL BODY WEIGHT (g)	245	254	238	243	250	*	
	ACTUAL DOSE (ml)	1.7	1.8	1.7	1.7	1.8	ML	12/24
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/24
	DAY 14 BODY WEIGHT (g)	321	323	292	[illegible]	330	[illegible]	1/2
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg DOSAGE	ANIMAL NUMBER							
	PREFASTED WEIGHT (g)							
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg DOSAGE	ANIMAL NUMBER							
	PREFASTED BODY WEIGHT (g)							
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							

NA - Not Applicable a - food removed ✓ - Dose indicated was administered

PREFASTED BODY WEIGHTS BALANCE NO. *

DAY 14 BODY WEIGHT BALANCE NO. 0-4 10 12/12/92

DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. *

DAY BODY WEIGHT BALANCE NO. NA

DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4

* Refer to fasted/prefasted body weight sheet ML 12/24/91

0 Refer to first day dosed sheet ML 12/24/91

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND B0429-01 STUDY NO. 191-722

IRDC NO. 7500

DOSE VOLUME ml/kg: Refer to dose volume calculation sheet. SPECIES Rat SEX M

ROUTE OF ADMINISTRATION Oral DATE ANIMALS RECEIVED 11/14/81 SOURCE Charles River

TIME OF FASTING* 1610 FASTING TECHNICIAN ML DATE 12/28/81

TIME OF DOSING 1045 DOSING TECHNICIAN ML DATE 12/29/81

							TECHNICIAN	DATE
5000 mg/kg DOSAGE	ANIMAL NUMBER	99626	99634	99633	99636	99643	ML	12/29
	PREFASTED WEIGHT (g)	271	283	274	265	252	•	
	INITIAL BODY WEIGHT (g)	247	258	248	242	226	•	
	ACTUAL DOSE (ml)	1.1	1.2	1.1	1.1	1.0	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/29
	DAY 14 BODY WEIGHT (g)	299	362	321	313	308	GN	1/12
	DAY ~~BODY WEIGHT (g)~~							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
5250 mg/kg DOSAGE	ANIMAL NUMBER	99627	99634	~~99633~~	99646	99647	ML	12/29
	PREFASTED WEIGHT (g)	299	258	266	281	255	•	
	INITIAL BODY WEIGHT (g)	271	244	245	260	229	•	
	ACTUAL DOSE (ml)	1.4	1.3	1.3	1.4	1.2	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/29
	DAY 14 BODY WEIGHT (g)	371	293	321	330	258	GN	1/12
	DAY ~~BODY WEIGHT (g)~~							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
5613 mg/kg DOSAGE	ANIMAL NUMBER	99624	99632	99635	99637	99642	ML	12/29
	PREFASTED BODY WEIGHT (g)	270	268	286	278	273	•	
	INITIAL BODY WEIGHT (g)	243	244	257	254	254	•	
	ACTUAL DOSE (ml)	1.5	1.5	1.6	1.5	1.5	ML	12/29
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	ML	12/29
	DAY 14 BODY WEIGHT (g)	321	302	341	332	331	GN	1/12
	DAY ~~BODY WEIGHT (g)~~							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							

NA - Not Applicable a - food removed ✓ - Dose indicated was administered

PREFASTED BODY WEIGHTS BALANCE NO. •

DAY 14 BODY WEIGHT BALANCE NO. CHICO 1/12

DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. •

DAY BODY WEIGHT BALANCE NO. NA

DAY BODY WEIGHT BALANCE NO. NA

IR36-61-2 * Refer to fasted/indicated bodyweight sheet ML 12/29/81

Special Issue.

⊕ Fasted weight not recorded at time of dosing ML 12/29/81

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND B0429-01 STUDY NO. 191-722

IRDC NO. 7500

DOSE VOLUME ml/kg: See dose volume calculations SPECIES Rat SEX m/z

ROUTE OF ADMINISTRATION Oral DATE ANIMALS RECEIVED 12/17/81 SOURCE Charles River

TIME OF FASTING[a] 1600 FASTING TECHNICIAN JP DATE 1/4/82

TIME OF DOSING 1030 DOSING TECHNICIAN KD DATE 1/5/82

DOSAGE M 8745 mg/kg	ANIMAL NUMBER	99688	99703	99705	99706	99714	TECHNICIAN KD	DATE 1/5
	PREFASTED WEIGHT (g)	293	284	283	297	282	(W)	
	INITIAL BODY WEIGHT (g)	266	259	256	273	258	(W)	
	ACTUAL DOSE (ml)	2.2	2.1	2.1	2.2	2.1	KD	1/5
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KD	1/5
	DAY 14 BODY WEIGHT (g)	304	[illegible]	[illegible]	[illegible]	[illegible]	RW	1/19
	DAY BODY WEIGHT (g)		[illegible]	[illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE F 8745 mg/kg	ANIMAL NUMBER	99763	99765	99774	99775	99782	KD	1/5
	PREFASTED WEIGHT (g)	244	242	236	239	232	(W)	
	INITIAL BODY WEIGHT (g)	223	229	216	216	213	(W)	
	ACTUAL DOSE (ml)	1.8	1.9	1.7	1.7	1.7	KD	1/5
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KD	1/5
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE mg/kg	ANIMAL NUMBER						Dose Calculations Verified P-1/5/82	
	PREFASTED BODY WEIGHT (g)						Dose Administration Verified P-1/5/82	
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							

NA - Not Applicable a - food removed ✓ - Dose indicated was administered

PREFASTED BODY WEIGHTS BALANCE NO. (W) DAY 14 BODY WEIGHT BALANCE NO. [illegible] 1/4/82 DAY NA BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. (W) DAY NA BODY WEIGHT BALANCE NO. NA DAY NA BODY WEIGHT BALANCE NO. NA

IR36-61-4 (W) Refer to Body Weight Record 1/5/82

Dose Volume Calculation 191-722

The dose volumes for IRX 7500 were calculated using the following general formula:

$$\frac{\text{dose level g/kg}}{\text{specific gravity g/ml}} = \text{dose volume ml/kg}$$

5000 mg/kg $\frac{5.0 \text{ g/kg}}{1.078 \text{ g/ml}} = 4.6$ ml/kg

5750 mg/kg $\frac{5.750 \text{ g/kg}}{1.078 \text{ g/ml}} = 5.3$ ml/kg

6613 mg/kg $\frac{6.613 \text{ g/kg}}{1.078 \text{ g/ml}} = 6.1$ ml/kg

7604 mg/kg $\frac{7.604 \text{ g/kg}}{1.078 \text{ g/ml}} = 7.1$ ml/kg

ME 12/24/81
S 12/27/81

Dose Volume Calculation

191-722

The dose volume for IRDC 7500 will be calculated by using the following formula:

$$\text{Dose Volume} = \frac{\text{Dose level g/kg}}{\text{Specific gravity g/ml}} = \text{ml/kg}$$

The specific gravity will be used from the determination of 12/18/81.

Specific gravity of IRDC 7500 is 1.078 g/ml at 24°C.

$$5745 \text{ mg/kg} \quad \frac{8.745 \text{ g/kg}}{1.078 \text{ g/ml}} = 8.1 \text{ ml/kg}$$

KD 1/5/82
P– 1/5/82

Test Article Preparation

The test article IRDC 7500 was prepared for dosing in an identical manner as on 12/29/81. Refer to Test Article Preparation of 12/29/81 for specific details.

KD 1/5/82
P– 1/5/82

Dosing Procedure

The test article IRDC 7500 was dosed in an identical manner as on 12/29/81. Refer to Dosing Procedure of 12/29/81 for specific details.

KD 1/5/82
P– 1/5/82

APPENDIX C

Individual Macroscopic Observations

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Died on Study, Males

SITE - OBSERVATION	7604 mg/kg	8745 mg/kg
ANIMALS EXAMINED	99640	99703, 99705, 99706, 99714
ANIMALS WITHIN NORMAL LIMITS		99703, 99714
GASTROINTESTINAL TRACT		
- Mucosa, hyperemic, diffuse, mild		99705, 99706
STOMACH		
- Material, red mucoid contents	99640	
- Nonglandular mucosa, hyperemic, diffuse, mild	99640	

B0429-01

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Died on Study, Females

SITE - OBSERVATION	5750 mg/kg	6613 mg/kg	7604 mg/kg	8745 mg/kg
ANIMALS EXAMINED	99663, 99667, 99668, 99670	99659, 99665, 99673	99658, 99660, 99661, 99669	99763, 99765, 99774, 99778, 99782
ANIMALS WITHIN NORMAL LIMITS	99663, 99667, 99668, 99670	99659		
EXTERNAL				
- Stain, dry, yellow, anogenital area			99669	
GASTROINTESTINAL TRACT				
- Mucosa, hyperemic, diffuse, mild				99763
- Mucosa, hyperemic, multifocal, mild				99774
INTESTINE				
- Material filled, dark red mucoid			99669	
- Mucosa, hyperemia, moderate			99669	
SMALL INTESTINE				
- Hyperemic, multifocal, mild		99665, 99673	99658	
- Mucosa, hyperemic, diffuse, mild			99660	99778
STOMACH				
- Material, red mucoid contents			99661	
- Liquid filled, brown			99669	
- Mucosa, hyperemic, diffuse, mild				99778
- Mucosa, hyperemic, diffuse, moderate				99765
- Glandular mucosa, hyperemia, moderate			99669	
- Glandular mucosa, hyperemic, diffuse, mild			99658	
- Glandular mucosa, hyperemic, diffuse, moderate			99661	
- Nonglandular mucosa, hyperemic, diffuse, mild				99782

B0429-01

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Terminal Sacrifice, Males

SITE - OBSERVATION	5000 mg/kg	5750 mg/kg	6613 mg/kg	7604 mg/kg	8745 mg/kg
ANIMALS EXAMINED	99626, 99631, 99633, 99636, 99643	99627, 99634, 99641, 99646, 99647	99624, 99632, 99635, 99637, 99642	99625, 99638, 99639, 99644	99688
ANIMALS WITHIN NORMAL LIMITS	99626, 99631, 99633, 99636, 99643	99627, 99634, 99641, 99646, 99647	99624, 99632, 99635, 99637, 99642	99625, 99638 99639, 99644	99688

B0429-01

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Terminal Sacrifice, Females

SITE - OBSERVATION	5000 mg/kg	5750 mg/kg	6613 mg/kg	7604 mg/kg
ANIMALS EXAMINED	99657, 99666, 99671, 99672, 99675	99678	99655, 99676	99662
ANIMALS WITHIN NORMAL LIMITS	99657, 99666, 99671, 99672, 99675	99678	99655, 99676	99662

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

Protocol Sheet No. 1 Study No. 191-722

Title: ACUTE ORAL TOXICITY (LD_{50} VALUE IN RATS)

ITEM	JUSTIFICATION
1	Study initiation
2	Clarification of IRDC Quality Assurance procedures
3	Clarification of submission to regulatory agency

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	Conduct study in accordance with the attached protocol
2	This study is subject to IRDC Quality Assurance Department standard operating procedures, with the exception that the final report will not be reviewed by the IRDC Quality Assurance Department.
3	This study will not be submitted to a regulatory agency

Study Director James R. Myer, B.S.

James R. Myer 12/17/81

Signature Date

IR90-49-5

PROTOCOL NO. C1

Acute Oral Toxicity (LD_{50} Value in Rats)

Issue Date: September 1, 1981
Supersedes Issue Dated: September 15, 1980

Test Substance Identification Number (TSIN) # B0429-01

Divisional Request Document Number (DRD) # BSBTS 734S

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: (To be filled in by Operations Section) International Research and Development Corporation
Mattawan, Michigan 49071

Study # 191-722 (To be filled in by Testing Facility)

Purpose: To establish the acute oral toxicity and/or the LD_{50} value of a test substance in the rat so that it may be compared with more familiar substances.

Justification for Selection of Test System: The rat is the animal classically used due to its small size, ready availability, and the large amount of background data.

Route of Administration of Test Substance and Reason for Choice: By gavage. This is a method for administering a known quantity of test substance and has been the route of choice historically.

Diet and/or Water Analyses Required: None (no known contaminants expected which would interfere with this study)

Records to be Maintained: All records that would be required to reconstruct the study and demonstrate adherence to protocol.

PROTOCOL NO. C1 (Cont'd)

Acute Oral Toxicity (LD_{50} Value in Rats)

Issue Date: September 1, 1981

Test Substance(s)

TSIN #	DRD Number	Description: Color	Description: Physical Form	Expiration Date
B0429-01	BSBTS 734S	amber	liquid	N/K

Storage Conditions: (Check one)

[X] Room temperature [ ] Refrigerator [ ] Freezer
[ ] Other

Hazards: (Check one)

[ ] None known. Take ordinary precautions in handling.
[X] As follows: Ignitable liquid, flash point > 100°F. Avoid sparks and open flames.

Special Instructions: (Check one)

[X] None
[ ] As follows:

Animals: A sufficient number of rats, Sprague-Dawley (CD), 190-300 grams prefasted weight, so that each test group will contain five (5) males and five (5) females.

Animal Care: Follow the approved Standard Operating Procedures of the Test Facility.

Environmental Conditions: Follow the approved Standard Operating Procedures of the Test Facility.

Animal Identification: Follow the approved Standard Operating Procedures of the Test Facility.

PROTOCOL NO. C1 (Cont'd)

Acute Oral Toxicity (LD_{50} Value in Rats)

Issue Date: September 1, 1981

Estimated LD_{50} value of the undiluted test substance: 5 g/kg
(If unknown, conduct a range-finding experiment following the Standard Operating Procedures of the Test Facility.)

Group Assignment: Determine prefasted body weights and select animals weighing 190-300 grams for study.

If the range finding experiment or Sponsor's estimate indicates the LD_{50} value to be >20 g/kg of test substance, administer a single dose of 20 g/kg to ten (10) animals (5 males and 5 females). If the dose volume required to administer 20 g/kg exceeds 25 ml/kg, contact the Sponsor's Divisional Toxicologist for further instructions. If the mortality of these animals indicates that the LD_{50} value would be >20 g/kg, report an estimated LD_{50} value of >20 g/kg.

If the range finding experiment indicates an LD_{50} value of less than 20 g/kg, choose four (4) dosage levels, based upon the range finding experiment. When feasible, choose dosage levels following a geometric progression of 1.4. If high dose levels require dose volumes which exceed 25 ml/kg, contact Sponsor's Divisional Toxicologist for further instructions. Place ten (10) animals in each group, divided by sex (5 males, 5 females). Assign animals to groups following the Standard Operating Procedures of the Test Facility.

If Sponsor's estimate indicates an LD_{50} value of less than 20 g/kg, five (5) dosage levels may be used, if necessary (to better bracket the estimate), in lieu of running the range finding experiment.

Dose Preparation: Test Group(s): (Check appropriate box)

[X] Dose test substance undiluted
[ ] Dose as a freshly prepared _____% (w/w) solution/suspension of test substance in _____.
[ ] Dose as a freshly prepared _____% (w/v) solution/suspension of test substance in _____.
[ ] Dose per Special Instructions (see page 2)

Control Group

A control group should be [ ]; should not be [X] included in this study. If included, the control substance _____ should be tested concurrently with the test substance at a dosage level of _____.

Dose Preparation (Cont'd):

Test Group(s) (Cont'd)

Note

A concentration analysis of the test substance - vehicle mixture(s) will [ ]; will not [x] be required.

If a concentration analysis is required:

[ ] Prepare a sufficient quantity of the test substance - vehicle mixture(s) so that a portion can be returned to the Sponsor's Divisional Toxicologist. Store solution/mixture at [ ] room temperature; [ ] refrigerator; [ ] freezer; [ ] other _____

Shipping Instructions

Send approximately _____ml. Send [ ] frozen; [ ] under ambient conditions; [ ] other_____ _____

[ ] Analyze the test substance - vehicle mixture(s) for test substance concentration using the analytical method in Appendix _____.

Dosing Instructions: Deprive the animals of food for 18-20 hours before administering the test substance. Determine fasted body weights. Calculate the dose for each animal according to fasted body weight to give the specified quantities of test substance per unit of body weight.*

If additional dosage levels are required to establish a death-to-dose response that will allow the LD_{50} value to be calculated, the Sponsor should be contacted prior to further work.

*Determine density, if required, to calculate dose levels for all test substances dosed undiluted or solutions prepared for dosing on a weight to weight (w/w) basis.

Dosing Instructions (Cont'd):

The test substance, at the concentration specified under "Dose Preparation", will be gavaged following the Test Facility's Standard Operating Procedures. Record all information necessary to document animal weights and volume of test substance administered to each animal.

Immediately after dosing, return the animal to *ad libitum* feeding.

Observations:

Option A LD_{50} Only	[ ]	Observe all animals for mortality at frequent intervals during the first 4 hours after dosing (at least once during the first 30 minutes) and daily thereafter for the next 14 days. Record time of death. On day 14 discard survivors following the Test Facility's Standard Operating Procedures.
Option B LD_{50} + Symptoms	[ ]	Observe all animals for mortality and pharmacotoxic symptoms at frequent intervals during the first 4 hours after dosing (at least once during the first 30 minutes) and daily thereafter for the next 14 days. Record all pharmacotoxic symptoms and time of death. On day 14 weigh and discard survivors following the Test Facility's Standard Operating Procedures.
Option C LD_{50} + Symptoms + Necropsy	[X]	Observe all animals for mortality and pharmacotoxic symptoms at frequent intervals during the first 4 hours after dosing (at least once during the first 30 minutes) and daily thereafter for the next 14 days. Record all pharmacotoxic symptoms and time of death. Perform a gross necropsy on all animals that die following the Test Facility's Standard Operating Procedures. On day 14 weigh and perform a gross necropsy on the surviving animals. Record all findings. Discard animals following the Test Facility's Standard Operating Procedures.

Protocol Changes:

If it becomes necessary to change the approved protocol, verbal agreement to make this change should be made between the Study Director and the Sponsor. As soon as practical, this change and the reasons for it should be put in writing and signed by both the Study Director and the Sponsor's Divisional Toxicologist. This document is then attached to the protocol as an addendum.

PROTOCOL NO. C1 (Cont'd)

Acute Oral Toxicity (LD_{50} Value in Rats)

Issue Date: September 1, 1981

Report: Report dates of study initiation and termination. Report individual dose levels, body weights, mortality, pharmacotoxic signs, gross necropsy results, etc., where appropriate. Report the LD_{50} value and 95% confidence limits of the test substance preferably calculated by the Probit Method* by the use of the computer program BLISS17**. Other calculation methods may be used. The method used should be specified in the final report. This report shall conform to all requirements outlined in Section 58.185, Subpart J, Good Laboratory Practices Regulations.

Sponsor: James H. Benedict James H Benedict
Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist Nov. 4, 1981

Proposed Starting Date: 12/29/81
Defined as day of dosing

Proposed Completion Date: 1/12/82
Defined as day of last observation

(To be completed by the Test Facility)

Study Director: James R. Myer
James R. Myer, B.S.
Date: December 17, 1981

Study Cost:

*D. J. Finney, Probit Analysis, 3rd Ed., Cambridge Univ. Press 1971, pp. 50-90.

**Fortran version of BLISS17 program, written by D. J. Finney.

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