ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ- 92-6343	89110000196	3/22/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI

334109

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
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1200 Pennsylvania Ave., NW
Washington, DC 20460
Attn: TSCA Declassification Coordinator

Re: Declassification Activity-Health and Safety Filing
8EHQ-0892-6343 (EPA DCN 88920004989)

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Any CBI substantiation which appears in the original submission is no longer applicable as the information which was originally claimed CBI is disclosed in this revised submission.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

8911000019 6

Attachment 1

Public Display Version

Chemical Identity	CAS RN
Poly(oxy-1,2-ethanediyl), alpha.-sulfo-.omega.-hydroxy-, C10-16-alkyl ethers, sodium salts	68585-34-2
Amines, C10-16-alkyldimethyl, N-oxides	70592-80-2
9-Octadecenoic acid	112-80-1
Ethanol, 2-amino-	141-43-5
Benzenesulfonic acid, methyl-, sodium salt	12068-03-0
Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis-[5-[[4-[(2-hydroxyethyl)methylamino] -6-(phenyl-amino)-1,3,5-triazin-2-yl]amino]-, disodium salt	13863-31-5
1,2-Ethanediamine, N-(2-aminoethyl)-N'-[3-(tri-methoxysilyl)propyl]-	35141-30-1
Benzenesulfonic acid, 2,2'-[(9,10-dihydro-9,10-dioxo-1,4-anthracenediyl)diimino]bis[5-methyl-, disodium salt	4403-90-1
1H-Pyrazole-3-carboxylic acid, 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-4-[(4-sulfophenyl)azo]-, trisodium salt	1934-21-0
Sodium nitrilotriacetate	
Sodium Sulfite	
Fragrance Mixture	
Water	

COMPANY SANITIZED

Procter & Gamble

92 AUG 17 PM 1:52

The Procter & Gamble Company
Ivorydale Technical Center
5299 Spring Grove Avenue, Cincinnati, Ohio 45217-1087

8EHQ-0892-6343 S Init **Public Display Copy**

August 5, 1992

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

88920000489 S

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 P1105 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 # 1096-26295.

The attached study report indicates oral administration of the test material resulted in pharmacotoxic signs including ataxia, body tremors, prostration, decreased limb tone, and hypoactivity following oral administration of 9500, 10925, 12564, and 14449 mg/kg of the test material. Decreased righting reflex was observed in the 12564 and 14449 mg/kg groups and convulsions were observed in the 9500, 10925, and 14449 mg/kg groups. The acute oral LD_{50} is calculated to be 10.4 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.

0 0 0 3

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

Public Display Copy

Sodium alkyl ethoxy sulfate

Alkylamine oxide

Fatty acid

Substituted amine

Sodium nitrilotriacetate

Substituted benzene

Substituted stilbene

Sodium Sulfite

Silicone

Fragrance Mixture

Colorant

Water

1096-26295

International Research
and Development Corporation
MATTAWAN, MICHIGAN U.S.A. 49071 TELEPHONE (616) 668-1336

SPONSOR: The Procter and Gamble Company

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

DRD NO.: BTS 2738

TSIN: P1105

REPORT NO.: 191-693

DATE OF SUBMISSION: February 5, 1982

RECEIVED BY
FEB 11 1982
OPERATIONS SECTION

191-693

"credence through research"

International Research & Development Corporation

STUDY SUMMARY

Study No: 191-693
Sponsor Ref: BTS 2738

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:
November 18, 1981 to December 2, 1981
According to the attached protocol
(P & G No. C1)
Issue Date: September 1, 1981

Test Substance (TSIN)	Color	Physical Form	Storage Condition
P1105	green	liquid	room temperature

Sponsor's Divisional Toxicologist: John Yam

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: 9500 mg/kg--8.3 ml/kg; 10925 mg/kg--9.6 ml/kg; 12564 mg/kg--11.0 ml/kg and 14449 mg/kg--12.7 ml/kg.

RESULTS

Dose — Mortality Data:

Dosage Level mg/kg	Number of Deaths: Hrs 0-4 M	Hrs 0-4 F	Days 1 M	Days 1 F	Days 2 M	Days 2 F	Days 3 M	Days 3 F	Days 4 M	Days 4 F	Days 5 M	Days 5 F	Days 6 M	Days 6 F	Days 7 - 14 M	Days 7 - 14 F	Total Mortalities Male	Total Mortalities Female	Total Mortalities Total
9500		2				1											0/5	3/5	3/10
10925	2	5															2/5	5/5	7/10
12564	2	4		1													2/5	5/5	7/10
14449	3	5															3/5	5/5	8/10

LD_{50} (95% Confidence Limits) Combined Male and Female[1]: 10.4 (8.8 - 12.3) g/kg

REFERENCE

1. Bliss, C. I., "The Determination of the Dosage Mortality Curve from Small Numbers", Quarterly Journal Pharm. Pharmacol, 11: p. 192-226, 1938.

Results (Cont.)

Major Pharmacotoxic Signs:

The major pharmacotoxic signs observed in all dosage levels were: ataxia, hypoactivity, ptosis - both eyes, decreased limb tone and body tremors.

Body Weights: No remarkable changes or differences in body weight were observed during the study period.

Pathology: There were no test article-related macroscopic changes observed during post-mortem examination of animals dying on study or sacrificed at the termination of the study. All changes observed were considered to be agonal or non-specific in nature.

Prepared By: Linda C. Urath, D.V.M., M.S.
Staff Pathologist
Date

Ward R. Richter, D.V.M., A.C.V.P.
Director, Pathology Division
Date 2-1-82

191-693

Technical Supervisory Staff,

Acute Toxicology and Special Studies:

Paul Moxon, B.S.
Unit Supervisor

Adalsteinn Olafsson, B.S.
Group Supervisor

Prepared By: _____ 1-27-82
Julie K. Schmidt, B.S. — Date
Unit Supervisor,
Acute Toxicology
and Special Studies

Reviewed By: _____ 1/27/82
Dale E. Johnson, Pharm.D., Ph.D. — Date
Associate Director,
Toxicology Division

STUDY DIRECTOR STATEMENT

The methods used in IRDC Study Number 191-693 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.

_____ 2/3/82
James R. Myer, B.S. — Date
Study Director

191-693

APPENDIX A

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND D1105 STUDY NO. 191-653 ~~191-653~~ ②

IRDC NO. 7460 (container #1)

DOSE VOLUME ml/kg: See dose volume calculation sheet SPECIES RAT SEX m

ROUTE OF ADMINISTRATION ORAL DATE ANIMALS RECEIVED 11/9/81 SOURCE Charles River

TIME OF FASTING[a] 1615 FASTING TECHNICIAN JP ME DATE 11/17/81

TIME OF DOSING 1150 DOSING TECHNICIAN ⑤ DATE ⑤

DOSAGE								
mg/kg	ANIMAL NUMBER	97364	97365	97367	97373	97382	TECHNICIAN KS	DATE 11/18
	PREFASTED WEIGHT (g)	233	252	224	252	230	*	
	INITIAL BODY WEIGHT (g)	212	222	204	224	204	*	
	ACTUAL DOSE (ml)	1.8	1.8	1.7	1.9	1.7	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	NA	NA	NA	NA	NA	NA	
	DAY 14 BODY WEIGHT (g)	306	312	275	332	275	[illegible]	[illegible]
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg	ANIMAL NUMBER	97370	97371	97374	97375	97378	KS	[illegible]
	PREFASTED WEIGHT (g)	236	250	232	225	243	*	
	INITIAL BODY WEIGHT (g)	214	223	206	[illegible]	220	*	
	ACTUAL DOSE (ml)	2.1	2.1	2.0	[illegible]	2.1	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	NA	NA	NA	[illegible]	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	[illegible]	322	305	[illegible]	[illegible]	[illegible]	[illegible]
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg	ANIMAL NUMBER	97363	97364	97372	97376	97380	KS	11/18
	PREFASTED BODY WEIGHT (g)	228	253	262	248	245	*	
	INITIAL BODY WEIGHT (g)	205	226	236	221	217	*	
	ACTUAL DOSE (ml)	2.3	2.5	2.6	2.4	2.4	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	NA	NA	[illegible]	[illegible]	NA	NA	
	DAY 14 BODY WEIGHT (g)	284	326	[illegible]	[illegible]	3[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 7 BODY WEIGHT BALANCE NO. NA DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. * DAY 14 BODY WEIGHT BALANCE NO. [illegible] DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4 * Refer to Body weight Record KS 11/18/81

② correction KS 11/18/81

⑤ [illegible]

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND P1105 STUDY NO. 191-693

IRDC NO. 7460 (container #1)

DOSE VOLUME ml/kg: see dose volume calculation sheet SPECIES RAT SEX M

ROUTE OF ADMINISTRATION ORAL DATE ANIMALS RECEIVED 11/9/81 SOURCE Charles River

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

TIME OF DOSING ① DOSING TECHNICIAN ① DATE ①

							TECHNICIAN KS	DATE 11/18
DOSAGE mg/kg	ANIMAL NUMBER	97366	97369	97377	97378	97331		
	PREFASTED WEIGHT (g)	240	229	233	254	220	*	
	INITIAL BODY WEIGHT (g)	216	205	209	233	202	*	
	ACTUAL DOSE (ml)	2.7	2.6	2.7	3.0	2.6	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	[illegible]	[illegible]	NA	NA	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	254	287	[illegible]	P-	12/2
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE mg/kg	ANIMAL NUMBER	97	97	97	97	97	[illegible]	
	PREFASTED WEIGHT (g)						[illegible]	
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY 7 BODY WEIGHT (g)							
	DAY 14 BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE mg/kg	ANIMAL NUMBER	97	97	97	97	97		
	PREFASTED BODY WEIGHT (g)							
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
	DAY 7 BODY WEIGHT (g)							
	DAY 14 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 7 BODY WEIGHT BALANCE NO. NA DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. * DAY 14 BODY WEIGHT BALANCE NO. 00644 F- 10/1/81 DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4 ① see first sheet KS 11/18/81

* Refer to body weight Record KS 11/18/81

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND P1105

IRDC NO. 7460 (container #1) STUDY NO. 191-693

DOSE VOLUME ml/kg: see dose volume calculation sheet SPECIES RAT SEX F

ROUTE OF ADMINISTRATION ORAL DATE ANIMALS RECEIVED 11/9/81 SOURCE Charles River

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

TIME OF DOSING ① DOSING TECHNICIAN ① DATE ①

DOSAGE 5500 mg/kg	ANIMAL NUMBER	97459	97460	97461	97465	97466	TECHNICIAN KS	11/18 DATE 1981
	PREFASTED WEIGHT (g)	232	213	235	234	239	*	
	INITIAL BODY WEIGHT (g)	203	197	218	213	215	*	
	ACTUAL DOSE (ml)	1.7	1.6	1.8	1.8	1.8	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	NA	[illegible]	NA	[illegible]	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	264	[illegible]	268	[illegible]	[illegible]	[illegible]	12/2
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE 10525 mg/kg	ANIMAL NUMBER	97454	97463	97464	97467	97472	KS	11/18
	PREFASTED WEIGHT (g)	240	232	223	249	232	*	
	INITIAL BODY WEIGHT (g)	210	209	204	224	211	*	
	ACTUAL DOSE (ml)	2.0	2.0	2.0	2.2	2.0	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
DOSAGE 12564 mg/kg	ANIMAL NUMBER	97468	97469	97471	97473	97474	KS	11/18
	PREFASTED BODY WEIGHT (g)	224	229	255	233	225	*	
	INITIAL BODY WEIGHT (g)	202	213	227	213	210	*	
	ACTUAL DOSE (ml)	2.2	2.3	2.5	2.3	2.3	KS	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KS	11/18
	DAY 7 BODY WEIGHT (g)	[illegible]	[illegible]	Found [illegible]	[illegible]	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	Day 1 [illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)			[illegible]				
	DAY BODY WEIGHT (g)							

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

PREFASTED BODY WEIGHTS BALANCE NO. * DAY 7 BODY WEIGHT BALANCE NO. NA DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. * DAY 14 BODY WEIGHT BALANCE NO. 00624 [illegible] DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4 ① see first sheet KS 11/18/81

* Refer to body weight record KS 11/18/81

ACUTE TOXICITY (LD_{50}) RECORD

TEST COMPOUND P1105 STUDY NO. 191-693

IRDC NO. 7460 (container #1)

DOSE VOLUME ml/kg: see dose volume calculation sheet SPECIES RAT SEX F

ROUTE OF ADMINISTRATION ORAL DATE ANIMALS RECEIVED 11/9/81 SOURCE Charles River

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

TIME OF DOSING ① DOSING TECHNICIAN ① DATE ①

mg/kg	ANIMAL NUMBER	97456	97457	97458	97462	97470	TECHNICIAN	DATE
	PREFASTED WEIGHT (g)	233	237	246	244	245	*	
	INITIAL BODY WEIGHT (g)	214	217	221	222	225	*	
	ACTUAL DOSE (ml)	2.7	2.8	2.9	2.9	2.9	KJ	11/18
	DOSE ADMINISTRATION	✓	✓	✓	✓	✓	KJ	11/18
DOSAGE	DAY 7 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	NA	
	DAY 14 BODY WEIGHT (g)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg	ANIMAL NUMBER	97	97	97	97	97	[illegible]	
	PREFASTED WEIGHT (g)						[illegible]	
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
DOSAGE	DAY 7 BODY WEIGHT (g)							
	DAY 14 BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
	DAY BODY WEIGHT (g)							
mg/kg	ANIMAL NUMBER	97	97	97	97	97		
	PREFASTED BODY WEIGHT (g)							
	INITIAL BODY WEIGHT (g)							
	ACTUAL DOSE (ml)							
	DOSE ADMINISTRATION							
DOSAGE	DAY 7 BODY WEIGHT (g)							
	DAY 14 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 7 BODY WEIGHT BALANCE NO. _____ DAY BODY WEIGHT BALANCE NO. NA

INITIAL BODY WEIGHTS BALANCE NO. * DAY 14 BODY WEIGHT BALANCE NO. _____ DAY BODY WEIGHT BALANCE NO. NA

IR36-61-4 ① see first sheet KS 11/18/81

* Refer to Day weight record. KS 11/19/81

Test Article Preparation

161-613

Specific Gravity Determination

Refer to specific gravity determination in dose range of this study, conducted on 11/4/81

Specific gravity = 1.142 g/ml

Dose Volume Calculation

The dose volume for each dose level was calculated as follows.

$$\text{Dosage level}\left(\frac{mg}{kg}\right) : \frac{\text{dosage level}\,(g/kg)}{\text{specific gravity}\,(g/ml)} = \text{Dose volume}\,(ml/kg)$$

9.500 mg/kg : $\frac{9.500}{1.142}$ = 8.3 ml/kg

10.925 mg/kg : $\frac{10.925}{1.142}$ = 9.6 ml/kg

12.564 mg/kg : $\frac{12.564}{1.142}$ = 11.0 ml/kg

14.449 mg/kg : $\frac{14.449}{1.142}$ = 12.7 ml/kg

[illegible] 11/12/81

[illegible] 11/12/81

APPENDIX B

P1105

Individual Pharmacotoxic Signs
9500 mg/kg

Sex	Male										Female										Male	Female
Animal Number	97364		97365		97367		97373		97382		97459		97460		97461		97465		97466		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	b	2			b	2	1	2	a	6			a	f			a	f	1	f	4	3
Wet brown stain anogenital region	1	2																			1	0
Hypoactivity			1	2	b	2			a	6			a	f	1	4			1	f	3	3
Wet yellow stain anogenital region					1	5	1	3	1	5									1	f	3	1
Clear stain around mouth									a	2											1	0
Red stain on nose									c	4											1	0
Piloerection									1	5									1	f	1	1
Possible respiratory congestion									1	2*											1	0
Dry red material around nose and mouth											1	4									0	1
Wet yellow stain ventral surface											1	4									0	1
Ptosis - both eyes													a	f			a	f			0	2
Body tremors													a	c							0	1
Decreased limb tone													b	f							0	1
Clonic convulsions													b	c			b	f			0	2
Bradypnea													b	f							0	1
Prostration													c	f							0	1
Hypersensitive to touch															b	3			b	f	0	2
Yellow stained anogenital region															1	4					0	1
High carriage																			d	f	0	1
Diarrhea																			1	f	0	1
Clear discharge - both eyes																			1	f	0	1
Day of Death													d				c		2		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 on Day 3 and cleared on Day 8
f - Sign did not clear prior to death

191-693

P1105

Individual Pharmacotoxic Signs

10925 mg/kg

Sex	Male										Female										Male	Female
Animal Number	97370		97371		97374		97375		97379		97454		97463		97464		97467		97472		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 stain around mouth	a	1																			1	0
Dry red material around nose and mouth	1	5	1	4																	2	0
Hypoactivity	1	2			a	3	a	f	a	f	a	f	b	f			a	f			4	3
Ataxia	1	2	b	4	a	4	a	f	a	f	a	f	a	f			a	f			5	3
Wet yellow stained anogenital region	1	4	1	3																	2	0
Piloerection					1	4															1	0
Body tremors							a	f	a	f	b	f	b	f			a	f	a	f	2	4
Decreased limb tone							b	f	b	f											2	0
Ptosis - both eyes									a	f			c	f							1	1
High carriage													b	c							0	1
Prostration													c	f	a	f			a	f	0	3
Bradypnea															a	f					0	1
Hypopnea															b	f					0	1
Clonic convulsions																			a	f	0	1
Day of Death							c		c		c		d		c		b		b		2	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
f - Sign did not clear prior to death

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Individual Pharmacotoxic Signs
12564 mg/kg

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Sex	Male										Female										Male	Female
Animal Number	97363		97368		97372		97376		97380+		97468		97469		97471		97473		97474		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	2							a	d											2	0
Diarrhea	b	1	b	3																	2	0
Ataxia	c	2	a	4	a	f	a	f	c	3	a	f	a	f	a	f					5	3
No stool on papers	1	2																			1	0
Hypoactivity	1	3	b	4	a	f	a	f	1	3	a	f	a	f	a	f					5	3
Wet yellow stain anogenital region	1	3																			1	0
Piloerection	1	5	c	5																	2	0
Ptosis - both eyes					a	f	a	f					a	f	a	f	a	f	a	f	2	4
Decreased limb tone					a	f	b	f			a	f	b	f							2	2
Prostration					b	f									c	f			a	f	1	2
Bradypnea					b	f													a	f	1	1
Body tremors							b	f			a	f	a	f	b	c	a	f			1	4
Hypopnea															d	f					0	1
Body and tail rigid upon touch															b	c					0	1
Decreased righting reflex																	a	f			0	1
Yellow stained anogenital region			d	3																	1	0
Day of Death						c		c				b		c		1		c		b	2	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
f - Sign did not clear prior to death
e - Signs were inadvertently not recorded on Day 11

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Individual Pharmacotoxic Signs

14449 mg/kg

Sex	Male										Female										Male	Female
Animal Number	97366		97369		97377		97378		97381		97456		97457		97458		97462		97470		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	c			a	6															2	0
Ptosis - both eyes	b	c	a	f					a	f					a	f	a	f			3	2
High carriage	b	c			b	1[g]															2	0
Prostration	c	f									a	f	b	f					b	f	1	3
Bradypnea	c	f									a	f									1	1
Hypopnea	c	f																			1	0
Decreased righting reflex			a	f											b	f			a	f	1	2
Hypoactivity			a	f	1	3	c	3	a	f							a	f			4	1
Clear stain around mouth					a	1	a	1													2	0
Ataxia					b	3	b	3	a	f							a	f			3	1
Dry red material around nose and mouth					1	3	1	5													2	0
Wet yellow stained anogenital region					1	3	1	5													2	0
Dry yellow stained anogenital region					4	7	5	h													2	0
Body tremors									a	f	a	f	a	f	a	f			a	f	1	4
Decreased limb tone									b	f			a	f	a	f					1	2
Clonic convulsions											a	f									0	1
Day of Death	d		c						c		b		c		c		b		c		3	5

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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 did not clear prior to death
g - Sign reappeared on Day 2 and cleared on Day 3
h - Sign did not clear prior to study termination

APPENDIX C

P1105

Individual Macroscopic Observations
Died on Study, MALES

SITE - OBSERVATION	10925 mg/kg	12564 mg/kg	14449 mg/kg
ANIMALS EXAMINED	97375, 97379	97372, 97376	97366, 97369, 97381
BRAIN			
- Subdural vessels, hyperemic, moderate	97375		
INTESTINAL TRACT			
- Hyperemic, diffuse, mild/moderate			97366, 97381
INTESTINE			
- Filled with clear liquid/pink/red/tan, mucoid material	97375	97372, 97376	
- Mucosa, hyperemic, moderate	97375, 97379	97372, 97376	
LIVER			
- Color, dark	97375		
LUNG			
- Congestion, focal, bilateral, moderate			97369
STOMACH			
- Liquid filled, red/clear/mixed with ingesta	97375	97372, 97376	
- Glandular mucosa, foci, dark red/hyperemic/hemorrhage, NOS/moderate/severe	97375, 97379	97372, 97376	97366, 97369, 97381
THYMUS			
- congested, slight	97375	97376	

P3105

Individual Macroscopic Observations
Died on Study, FEMALES

SITE - OBSERVATION	9500 mg/kg	10925 mg/kg	12564 mg/kg	14449 mg/kg
ANIMALS EXAMINED	97460, 97465, 97466	97454, 97463, 97464, 97467, 97472	97468, 97469, 97471, 97473, 97474	97456, 97457, 97458, 97462, 97470
ANIMALS WITHIN NORMAL LIMITS	97466			
BRAIN				
- Vessels injected, mild			97471	
INTESTINAL TRACT				
- Hyperemic, diffuse/multifocal, mild/moderate			97473	
INTESTINE				
- Material filled, tan mucoid				97456, 97458 97470
- Mucosa, hyperemic, slight/moderate/severe	97465 97465			
LIVER		97454, 97463	97469, 97473	
- Congestion, focal, mild				
LUNG				97456
- Congestion, diffuse, bilateral, slight				
STOMACH			97474	
- Liquid filled, clear	97465			
- Glandular mucosa, hyperemic/hemorrhage/dark red foci, mild/moderate/severe			97468, 97474	
	97460, 97465	97454, 97463, 97464, 97467, 97472	97468, 97469, 97471, 97473, 97474	97456, 97457, 97458, 97462, 97470
THYMUS				
- Congestion, slight/mild			97468, 97474, 97471	
- Foci, dark, small, few			97474	

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Individual Macroscopic Observations
Terminal Sacrifice, MALES

SITE - OBSERVATION	9500 mg/kg	10925 mg/kg	12564 mg/kg	14649 mg/kg
ANIMALS EXAMINED	97364, 97365, 97367, 97373, 97382	97370, 97371, 97374	97363, 97368, 97380	97377, 97378,
ANIMALS WITHIN NORMAL LIMITS	97364, 97365, 97367, 97373, 97382	97370, 97371, 97374	97363, 97368, 97380	97377, 97378

P1105

Individual Macroscopic Observations
Terminal Sacrifice, FEMALES

SITE - OBSERVATION	9500 mg/kg
ANIMALS EXAMINED	97459, 97461
ANIMALS WITHIN NORMAL LIMITS	97459, 97461

QUALITY ASSURANCE STATEMENT

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

Test Article: P1105

An inspection of the protocol for this study was conducted on November 17, 1981. A randomly sampled phase of the conduct of this study was inspected on November 20, 1981. Findings were reported to management and the Study Director on January 15, 1982.

This report has been reviewed by the International Research and Development Corporation Quality Assurance Department in accordance with the United States Food and Drug Administration's Good Laboratory Practice Regulations of June 20, 1979.

Approved And Submitted By: _____ 2/5/82
Barry W. Benson, B.S. Date
Director of Quality Assurance

191-693

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

Protocol Sheet No. 1 Study No. 191-693

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 procedures
3	This study will not be submitted to a regulatory agency

Approved by:

W. S. Hutchens

Sponsor's Representative Date

Study Director James R. Myer, B.S.

James R. Myer 11/2/81

Signature Date

IR90-49-5

THE PROCTER & GAMBLE COMPANY

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) # P1105

Divisional Request Document Number (DRD) # BTS 2738

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 # 191-693 (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
P1105	BTS-738	Green	Liquid	4/1/82

Storage Conditions: (Check one)

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

Hazards: (Check one)

[X] None known. Take ordinary precautions in handling.
[ ] As follows:

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.

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

Issue Date: September 1, 1981

Estimated LD_{50} value of the undiluted test substance: unknown 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.

PROTOCOL NO. C1 (Cont'd)

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

Issue Date: September 1, 1981

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.

THE PROCTER & GAMBLE COMPANY

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: [signature]
Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist 10/14/81

Proposed Starting Date: 11/18/81

Defined as day of dosing

Proposed Completion Date: 12/2/81

Defined as day of last observation

(To be completed by the Test Facility)

Study Director: [signature]
James R. Myer, B.S.

Date: November 2, 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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