

ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ- 92-6351	89110000198	3/22/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI



334111
The Procter & Gamble Company
 NA Regulatory & Technical Relations
 One Procter & Gamble Plaza (C-6)
 Cincinnati, OH 45202
 www.pg.com

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

11 MAR 22 AM 9:03
 RECEIVED
 9891 0216

**Re: Declassification Activity-Health and Safety Filing
 8EHQ-0892-6351 (EPA DCN 88920004997)**

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Any CBI substantiation which appears in the original submission is no longer applicable as the information which was originally claimed CBI is disclosed in this revised submission.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



Attachment 1

Public Display Version

Chemical Identity

CAS RN

Benzenesulfonic acid, mono-C10-16-alkyl derivatives,
sodium salts 68081-81-2

Sulfuric acid, mono-C10-16-alkyl esters, sodium salts 68585-47-7

1-Dodecanaminium, N,N,N-trimethyl-, chloride 112-00-5

Alcohols, C9-11, ethoxylated 68439-46-3

Alcohols, tallow, ethoxylated 61791-28-4

Siloxanes and Silicones, di-Me 63148-62-9

Triphosphoric acid, pentasodium salt 7758-29-4

Sodium nitrilotriacetate

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

Subtilisin 9014-01-1

Silica 7631-86-9

Sodium silicate

Sodium carbonate

Sodium sulfate

Fragrance

Water

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

92 AUG 17 PM 1:47

8EHO-0892-6351 $\frac{1}{2}$ 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

8892000497S

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 P1165 is a confidential mixture. The composition of the mixture is appended as Attachment 1. The report is titled "Acute Oral Toxicity (LD₅₀ Value in Rats)". Any correspondence relating to this submission should reference study # 1144-27274.

The attached study report indicates oral administration of the test material resulted in pharmacotoxic signs including ataxia, diarrhea, and high carriage following oral administration of 1500, 1875, 2344, and 2930 mg/kg of the test material. Hypoactivity was observed in the 1875, 2344, and 2930 mg/kg groups and decreased limb tone was observed in the 2930 mg/kg group. The acute oral LD₅₀ is calculated to be 2.5 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:

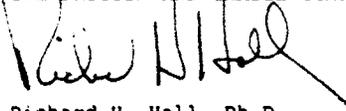
1. Confidentiality of the chemical constituents and their percentages should be maintained indefinitely. There are no plans for this information to be otherwise disclosed, and this technology has significant commercial value.
2. To our knowledge, there have been no government confidentiality determinations 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.

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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

0 0 0 4

Procter & Gamble

Attachment I

Public Display Copy

Sodium alkyl benzene sulfonate

Sodium alkyl sulfate

Substituted amine

Alkyl Ethoxylate

Silicone

Sodium silicate

Complex sodium phosphate

Sodium nitrilotriacetate

Substituted stilbene

Sodium carbonate

Sodium sulfate

Enzyme

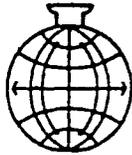
Sodium aluminosilicate

Fragrance

Water

0 0 0 5

1144 272.74



International Research
and Development Corporation

MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3334

RECEIVED BY

JUN 25 1982

OPERATIONS SECTION

SPONSOR: The Procter and Gamble Company

SUBJECT: Acute Oral Toxicity (LD₅₀ Value in Rats)

DED NO.: BTS 2771

TSIN: P1165

REPORT NO.: 191-778

DATE OF SUBMISSION: June 17, 1982

191-778

"credence through research"

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STUDY SUMMARY

Study No: 191-778
 Sponsor Ref: BTS 2771

Acute Oral Toxicity (LD₅₀ Value in Rats)
 Report of a biological test performed at:
 International Research and Development Corporation
 Mattawan, Michigan

Deviation from
 Protocol: None

During the period:
 April 2, 1982 to April 21, 1982
 According to the attached protocol
 (P & G No. C1)
 Issue Date: September 1, 1981

<u>Test Substance (TSIN)</u>	<u>Color</u>	<u>Physical Form</u>	<u>Storage Condition</u>
P1165	white	granular	room temperature

Sponsor's Divisional Toxicologist: J. H. Saylor

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

Concentration and Amount of

Test Substance Dosed (Appendix A): Administered as a 40% w/v suspension in deionized water
 at the following dosage levels and respective volumes:
 1500 mg/kg--3.8 ml/kg, 1875 mg/kg--4.7 ml/kg, 2344
 mg/kg--5.9 ml/kg and 2930 mg/kg--7.3 ml/kg.

RESULTS

Dose - Mortality Data:

Dosage Level mg/kg	Number of Deaths														Total Mortalities			
	Hrs		Days												Male	Female	Total	
	0-4	1	2	3	4	5	6	7-14	M	F	M	F	M	F				
1500																0/5	0/5	0/10
1875							1									0/5	1/5	1/10
2344			3		1											6/5	4/5	4/10
2930		1	5	1												2/5	5/5	7/10

LD₅₀ (95% Confidence Limits) Combined Male and Female^{1,2}: 2.5 (2.3-2.9) g/kg

REFERENCES

- Bliss, C. I., "The Determinations of the Dosage Mortality Curve from Small Numbers", Quarterly Journal Pharm. Pharmacol., 11: p. 192-216, 1938.
- Litchfield, J. T. and Wilcoxon, F., "A Simplified Method of Evaluating Dose - Effect Experiments", The Journal of Pharmacology and Experimental Therapeutics, 96: p. 99-113, 1949.

International Research and Development Corporation

RESULTS (Continued)

Major Pharmacotoxic Signs (Appendix B):

The major pharmacotoxic signs observed in all dosage levels were: diarrhea, wet/dry yellow staining of the anogenital area and high carriage. Other pharmacotoxic signs observed were: ataxia and wet/dry brown staining of the anogenital area.

Body Weights (Appendix C): No remarkable changes or differences in body weights were observed during the study period.

Pathology (Appendix D): In animals that died during the study, test-article-related lesions, characterized as mild to moderate hyperemia of gastric mucosa or red liquid stomach contents, were observed in males of the 2930 mg/kg dose group and in females of the 2344 and 2930 mg/kg dose groups. No macroscopic lesions were evident in animals sacrificed at the termination of study. Dark foci or congestion in thymus, seen in two females that died (2344 mg/kg), were considered to be non-specific changes. The nodule seen in the kidney of rat #5886 (2344 mg/kg) was considered to be a spontaneous lesion unrelated to the test article.

Prepared By:

Daniel Rajsekaran

Daniel Rajsekaran, D.V.M., M.V.Sc. (Path),
F.R.V.C.S. (Path) Sweden
Staff Pathologist

6/14/82

Date

Reviewed By:

Ward R. Richter

Ward R. Richter, D.V.M., A.C.V.P.
Director, Pathology Division

6-14-82

Date

International Research and Development Corporation

Technical Supervisory Staff,
Acute Toxicology and Special Studies:

Paul Moxon, B.S.
Unit Supervisor

Adalsteinn Olafsson, B.S.
Group Supervisor

Prepared By:

Julie L. Schmidt
Julie L. Schmidt, B.S.
Unit Supervisor,
Acute Toxicology
and Special Studies

6-14-82
Date

Reviewed By:

Walter E. Johnson
Dale E. Johnson, Pharm.D., Ph.D.
Associate Director,
Toxicology Division

6/14/82
Date

STUDY DIRECTOR STATEMENT

The methods used in IRDC Study Number 191-778 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.

James R. Myer
James R. Myer, B.S.
Study Director

6/16/82
Date

191-778

"credence through research"

APPENDIX A
Dose-Volume Calculations

191-778

Dose Volume Calculations

The dose volume for RDs has been calculated by using the following general formula:

$$\frac{\text{Dose Level (g/Kg)}}{\% \text{ Concentration (g/ml)}} = \text{Dose Volume (ml/Kg)}$$

$$1506 \text{ mg/Kg} - \frac{1506 \text{ g/Kg}}{0.4 \text{ g/ml}} = 3.8 \text{ ml/Kg}$$

$$1875 \text{ mg/Kg} - \frac{1875 \text{ g/Kg}}{0.4 \text{ g/ml}} = 4.7 \text{ ml/Kg}$$

$$2344 \text{ mg/Kg} - \frac{2344 \text{ g/Kg}}{0.4 \text{ g/ml}} = 5.9 \text{ ml/Kg}$$

KD 4/2/82

D - 4/2/82

Dose Volume Calculations

19-772

The dose volumes for IRDC 7502 were calculated by using the following general formula.

$$\frac{\text{Dose Level (g/Kg)}}{\% \text{ concentration (g/ml)}} = \text{Dose Volume (ml/Kg)}$$

$$2930 \text{ mg/Kg} - \frac{2930 \text{ g/Kg}}{0.4 \text{ g/ml}} = 7.3 \text{ ml/Kg}$$

KD 4/7/82

AO 4/7/82

Test Article Preparation

The test article IRDC 7502 was prepared for dosing in an identical manner as conducted on 4/2/82. Refer to Test Article Preparation of 4/2/82 for specific details.

KD 4/7/82

AO 4/7/82

Dosing Procedure

The test article IRDC 7502 was ~~dosed~~^{OP-1112} dosed in an identical manner as conducted on 4/2/82. Refer to Dosing Procedure of 4/2/82 for specific details.

KD 4/7/82

OP-4/7/82

APPENDIX B
Individual Pharmacotoxic Signs

191-778

P1165

Individual Pharmacotoxic Signs
1500 mg/kg

Sex	Animal Number	Male				Female				Total Incidence			
		5797	5801	5804	5806	5871	5872	5875	5876		5877		
Pharmacotoxic Sign		Day First Appeared	Day of Clearance										
Ataxia		d	1	d	1							2	0
Piloerection			d	1								1	0
High carriage					a	1						1	0
Diarrhea						a	1	d	1	d	1	0	3
Soft stool						1	2					0	1
Dry yellow stained anogenital area						1	3	2	3			0	2
Wet yellow stained anogenital area								1	2			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

191-778

P1165

Individual Pharmacotoxic Signs
1875 mg/kg

Sex	Male						Female						Total Incidence
	3795	3799	3800	3803	3807	3874	3880	3883	3887	3886	3887	3886	
Animal Number	Day First Appeared	Day of Clearance											
Pharmacotoxic Sign													
Ataxia		b 2		d 3					b 1	b 1	b 3		
Hypocoativity				d 3					c 1				
Hypersensitive to touch				2 3									
High carriage													
Diarrhea													
Prostris													
Wet yellow stained anogenital area													
Prostration													
Bradypnea													
Clear discharge, both eyes													
Dry yellow stained anogenital area													
Clear wet stain around mouth													
Dry yellow-stained abdomen													
Piloerection													
Day of Death						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 did not clear prior to death

APPENDIX C
Individual Body Weights

191-778

ACUTE TOXICITY (LD₅₀) RECORD

TEST COMPOUND 2115 STUDY NO. 752
 IPDC NO. 752
 DOSE VOLUME ml/kg: 200 SPECIES Dog SEX ♂
 ROUTE OF ADMINISTRATION Oral DATE ANIMALS RECEIVED 3/23/52 SOURCE ...
 TIME OF FASTING^a Ⓢ FASTING TECHNICIAN Ⓢ DATE 3
 TIME OF DOSING Ⓢ DOSING TECHNICIAN Ⓢ DATE 3

DOSEAGE	mg/kg	ANIMAL NUMBER					TECHNICIAN	DATE
		5271	5272	5275	5276	5277		
		PREFASTED WEIGHT (g)	223	226	210	234	223	Ⓢ
		INITIAL BODY WEIGHT (g)	205	207	200	209	205	Ⓢ
		ACTUAL DOSE (ml)	0.78	0.79	0.76	0.79	0.78	RD
		DOSE ADMINISTRATION	✓	✓	✓	✓	✓	RD
		DAY 14 BODY WEIGHT (g)	221	210	227	227	230	NL
		DAY BODY WEIGHT (g)						
		DAY BODY WEIGHT (g)						
		DAY BODY WEIGHT (g)						
DOSEAGE	mg/kg	ANIMAL NUMBER					TECHNICIAN	DATE
		5274	5278	5273	5277	5278		
		PREFASTED WEIGHT (g)	224	230	220	229	230	Ⓢ
		INITIAL BODY WEIGHT (g)	204	218	201	210	215	Ⓢ
		ACTUAL DOSE (ml)	0.96	1.0	0.94	0.99	1.0	RD
		DOSE ADMINISTRATION	✓	✓	✓	✓	✓	RD
		DAY 14 BODY WEIGHT (g)	225	250	235	251	260	NL
		DAY BODY WEIGHT (g)	223	241				
		DAY BODY WEIGHT (g)	215					
		DAY BODY WEIGHT (g)						
DOSEAGE	mg/kg	ANIMAL NUMBER					TECHNICIAN	DATE
		5273	5279	5282	5284	5286		
		PREFASTED BODY WEIGHT (g)	219	227	235	224	230	Ⓢ
		INITIAL BODY WEIGHT (g)	197	210	215	192	209	Ⓢ
		ACTUAL DOSE (ml)	1.2	1.2	1.3	1.2	1.2	RD
		DOSE ADMINISTRATION	✓	✓	✓	✓	✓	RD
		DAY 14 BODY WEIGHT (g)	212	243	241	241	241	NL
		DAY BODY WEIGHT (g)	212		212	212	212	
		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. 27 20 mg DAY 14 BODY WEIGHT BALANCE NO. 16
 INITIAL BODY WEIGHTS BALANCE NO. Ⓢ DAY 14 BODY WEIGHT BALANCE NO. 16 DAY 14 BODY WEIGHT BALANCE NO. 16

ACUTE TOXICITY (LD₅₀) RECORD

TEST COMPOUND P125 STUDY NO. 100-111
 EPDC NO. 7489
 DOSE VOLUME ml/kg: 420% Dose Limitation SPECIES Rat SEX M
 ROUTE OF ADMINISTRATION Oral DATE ANIMALS RECEIVED 3/22/82 SOURCE 100-111
 TIME OF FASTING^a 1615 FASTING TECHNICIAN AO DATE 4-6-82
 TIME OF DOSING 1200 DOSING TECHNICIAN KD DATE 4/7/82

ANIMAL NUMBER	5265	5266	5267	5268	5270	TECHNICIAN	KD	DATE	4/7
PREFASTED WEIGHT (g)	276	274	221	265	225		⊖		
INITIAL BODY WEIGHT (g)	254	249	254	239	257		⊖		
ACTUAL DOSE (ml)	1.9	1.8	1.9	1.7	1.9		KD		4/7
DOSE ADMINISTRATION	✓	✓	✓	✓	✓		KD		4/7
DAY 14 BODY WEIGHT (g)	328	329	Food Depr	Food Depr	327		OK		4/6/1
DAY BODY WEIGHT (g)			Day 14	Day 14					
DAY BODY WEIGHT (g)			KD	KD					
DAY BODY WEIGHT (g)			4/6/82	4/6/82					
ANIMAL NUMBER	5941	5942	5943	5944	5946		KD		4/7
PREFASTED WEIGHT (g)	240	227	250	236	255		⊖		
INITIAL BODY WEIGHT (g)	222	211	231	217	232		⊖		
ACTUAL DOSE (ml)	1.6	1.5	1.7	1.6	1.7		KD		4/7
DOSE ADMINISTRATION	✓	✓	✓	✓	✓		KD		4/7
DAY 14 BODY WEIGHT (g)	Food Depr	Food Depr	Food Depr	Food Depr	Food Depr				
DAY BODY WEIGHT (g)	Day 14								
DAY BODY WEIGHT (g)	KD	KD	KD	KD	KD				
DAY BODY WEIGHT (g)	4/6/82	4/6/82	4/6/82	4/6/82	4/6/82				
ANIMAL NUMBER									excluded from study by 4/7/82
PREFASTED BODY WEIGHT (g)									dehydrated administration
INITIAL BODY WEIGHT (g)									see file 8/4/7/82
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 J - Dose indicated was administered

PREFASTED BODY WEIGHTS DAY 14 BODY WEIGHT DAY 14 BODY WEIGHT
 BALANCE NO. ⊖ BALANCE NO. ⊖ BALANCE NO. NA
 INITIAL BODY WEIGHTS DAY NA BODY WEIGHT DAY NA BODY WEIGHT
 BALANCE NO. ⊖ BALANCE NO. NA BALANCE NO. NA

TR-6-81-6 ⊖ File to Pre-Initiation Body Weight Record KD 4/7/82

APPENDIX D
Individual Macroscopic Observations

191-778

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Died on Study, MALES

SITE	1500 mg/kg	1875 mg/kg	2344 mg/kg	2930 mg/kg
- OBSERVATION				
ANIMALS EXAMINED	None	None	None	5867, 5868

STOMACH

- Gas distention, mild
- Hyperemic, glandular/nonglandular mucosa, mild - moderate

5868

5868, 5867

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Died on Study, FEMALES

<u>SITE</u> - OBSERVATION	1500 mg/kg	1875 mg/kg	2344 mg/kg	2930 mg/kg
<u>ANIMALS EXAMINED</u>	None	5874	5873, 5882 5884, 5886	5941, 5942, 5943, 5944, 5946
<u>ANIMALS WITHIN NORMAL LIMITS</u>	-	5874	5884	
<u>KIDNEY</u> - Nodule, 2 mm x 2 mm, unilateral			5886	
<u>STOMACH</u> - Red liquid contents			5873, 5882 5886	5941, 5942, 5943, 5944, 5946
- Glandular mucosa, hyperemic, mild - moderate				
<u>THYMUS</u> - Foci, dark, small, few - Congestion, moderate			5873 5886	

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Terminal Sacrifice, MALS

<u>SITE</u> - OBSERVATION	1500 mg/kg	1875 mg/kg	2344 mg/kg	2930 mg/kg
ANIMALS EXAMINED	5797, 5801, 5804, 5805, 5806	5795, 5799, 5800, 5803, 5807	5796, 5798, 5802, 5808, 5809	5865, 5866, 5870
ANIMALS WITHIN NORMAL LIMITS	5797, 5801, 5804, 5805, 5806	5795, 5799, 5800, 5803, 5807	5796, 5798, 5802, 5808, 5809	5865, 5866, 5870

INDIVIDUAL MACROSCOPIC OBSERVATIONS
Terminal Sacrifice, FEMALES

SITE - OBSERVATION	1500 mg/kg	1875 mg/kg	2344 mg/kg
ANIMALS EXAMINED	5871, 5872, 5875, 5876, 5877	5880, 5883, 5887, 5888	5879
ANIMALS WITHIN NORMAL LIMITS	5871, 5872, 5875, 5876, 5877	5880, 5883, 5887, 5888	

International Research and Development Corporation

QUALITY ASSURANCE STATEMENT

Study Title: Acute Oral Toxicity (LD₅₀ Value in Rats)

Test Article: P1165

An inspection of the protocol for this study was conducted on March 25, 1982. A randomly sampled phase of the conduct of this study was inspected on April 2, 1982. Findings were reported to management and the Study Director on June 8, 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:


Harry W. Benson, B.S.
Director of Quality Assurance

6/15/82
Date

191-778

"credence through research"

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

Protocol Sheet No. 1 Study No. 191-778

TITLE: ACUTE ORAL TOXICITY (LD₅₀ VALUE IN RATS)

<u>ITEM</u>	<u>JUSTIFICATION</u>
1	Study initiation.
2	Clarification of IRDC Quality Assurance procedures.
3	Clarification of submission to regulatory agency.
4	Clarification of vehicle.

<u>ITEM</u>	<u>PROTOCOL REVISION OR CLARIFICATION</u>
1	Conduct study in accordance with the attached protocol.
2	This study is subject to IRDC Quality Assurance procedures.
3	This study is intended to support the registration of products regulated by the Environmental Protection Agency.
4	The Sponsor clarified that the vehicle will be deionized water.

Approved by:

W. D. Whitehouse 3/29/82
Sponsor's Representative Date

Study Director James R. Myer, B.S.

James R. Myer 3/17/82
Signature Date

A. J. W. Douglas

PROTOCOL NO. C1

Acute Oral Toxicity (LD₅₀ Value in Rats)

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

Test Substance Identification Number (TSIN) # P 1165

Divisional Request Document Number (DRD) # BTS 2711

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: International Research and Development Corporation
(To be filled in by Operations Section) Mattawan, Michigan 49071
Study # 191-778
(To be filled in by Testing Facility)

Purpose: To establish the acute oral toxicity and/or the LD₅₀ 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 (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Test Substance(s) ISIN #	DRD Number	Description		Expiration Date
		Color	Physical Form	
P1165	BTS 2771	White	Granular	6/83

Storage Conditions: (Check one)

Room temperature Refrigerator Freezer
 Other

Hazards: (Check one)

None known. Take ordinary precautions in handling.
 As follows:

Special Instructions: (Check one)

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 (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Estimated LD₅₀ value of the undiluted test substance: 3.0 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 LD₅₀ 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 LD₅₀ value would be >20 g/kg, report an estimated LD₅₀ value of >20 g/kg.

If the range finding experiment indicates an LD₅₀ 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 LD₅₀ 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)

- Dose test substance undiluted
 Dose as a freshly prepared _____ % (w/v) solution/suspension of test substance in _____
 Dose as a freshly prepared 40 % (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 included in this study. If included, the control substance _____ should be tested concurrently with the test substance at a dosage level of _____.

PROTOCOL NO. C1 (Cont'd)

Acute Oral Toxicity (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Dose Preparation
(Cont'd):

Test Group(s) (Cont'd)

Note

A concentration analysis of the test substance - vehicle mixture(s) will ; will not 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 10 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 LD₅₀ 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 (LD₅₀ 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 [] 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 [] 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 [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 (LD₅₀ 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 LD₅₀ 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: J. H. Saylor
Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist T. G. S.

Proposed Starting Date: 4/2/82

Defined as day of dosing

Proposed Completion Date: 4/16/82

Defined as day of last observation)To be completed
by the Test
Facility

Study Director: James R. Myer
James R. Myer, B.S.

Date: March 17, 1982

Study Cost: \$1,200.00

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

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

PROTOCOL NO. C1

Acute Oral Toxicity (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Supersedes Issue Dated: September 15, 1980

Test Substance Identification Number (TSIN) # B0447-01

Divisional Request Document Number (DRD) # BSBTS 743

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 # 191-731
(To be filled in by
Testing Facility)

Purpose:

To establish the acute oral toxicity and/or the LD₅₀ 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 (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Test Substance(s)		Description		Expiration
ISIN #	DRD Number	Color	Physical Form	Date
B0447-01	BSBTS 743	amber	liquid	N/K

Storage Conditions: (Check one)

Room temperature Refrigerator Freezer
 Other

Hazards: (Check one)

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

Special Instructions: (Check one)

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 (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Estimated LD₅₀ 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 LD₅₀ 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 LD₅₀ value would be >20 g/kg, report an estimated LD₅₀ value of >20 g/kg.

If the range finding experiment indicates an LD₅₀ 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 LD₅₀ 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)

- Dose test substance undiluted
 Dose as a freshly prepared _____% (w/v) 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 included in this study. If included, the control substance _____ should be tested concurrently with the test substance at a dosage level of _____.

PROTOCOL NO. C1 (Cont'd)

Acute Oral Toxicity (LD₅₀ Value in Rats)

Issue Date: September 1, 1981

Dose Preparation
(Cont'd):

Test Group(s) (Cont'd)

Note

A concentration analysis of the test substance - vehicle mixture(s) will ; will not 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 LD₅₀ 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 (LD₅₀ Value in Rats)

Issue Date: September 1, 1961

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
LD₅₀ 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
LD₅₀
+ 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
LD₅₀
+ 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 (LD₅₀ 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 LD₅₀ 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 58.165, Subpart J, Good Laboratory Practices Regulations.

Sponsor: J. H. Benedict


 Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist

11/19/81

Proposed Starting Date: 1/21/82

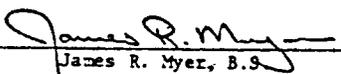
Defined as _____ day of dosing

Proposed Completion Date: 2/4/82

Defined as _____ day of last observation

) To be completed
) by the Test
) Facility

Study Director:

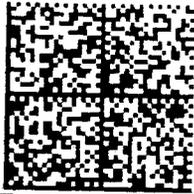

 James R. Myer, B.S.

Date: January 6, 1982

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.



neopost

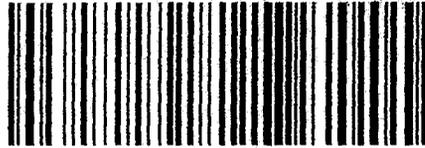
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