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TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ- 92-10109	89110000203	3/22/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI

334116

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

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Attn: TSCA Declassification Coordinator

8EHQ-0311-10109C

DCN: 89110000203

Re: Declassification Activity-Health and Safety Filing
8EHQ-0892-10109 (EPA DCN 88920008410)

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Any CBI substantiation which appears in the original submission is no longer applicable as the information which was originally claimed CBI is disclosed in this revised submission.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

89110000203

Attachment 1

Public Display Version

Chemical Identity	CAS RN
Benzenesulfonic acid, mono-C10-14-alkyl derivatives, sodium salts	69669-44-9
Benzenesulfonic acid, 4-methyl-, potassium salt	16106-44-8
Fatty acids, C8-18 and C18-unsatd.	67701-05-7
Ethanol, 2-butoxy-	111-76-2
Potassium pyrophosphate	
Sodium carbonate	
Sodium bicarbonate	
Water	

8EHQ-0892-10109

Procter & Gamble PANY SANITIZED

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

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August 24, 1992

8EHQ-92-10109 INIT
88920008410

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 K0216.01 is a confidential mixture. The composition of the mixture is appended as Attachment 1. The report is titled "Acute Oral Toxicity Study in Albino Rats with K0216.01". Any correspondence relating to this submission should reference study # 1079-25736.

The attached study report indicates a necropsy finding of kidney nephrosis following oral administration of 2.6, 3.6, 5.0, 7.0, and 9.8 g/kg of the test material. Nephrosis occurred in a dose-related manner, with greater incidence in higher dose groups. The acute oral LD_{50} was determined to be 6.114 g/kg. Nephrosis is an expected effect following high dose oral administration of phosphates.

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.

Procter&Gamble

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

Sodium alkyl benzene sulfonate

Substituted benzene

Potassium pyrophosphate

Sodium carbonate

Sodium bicarbonate

Fatty acid

Substituted alcohol

Water

1079-25736

WIL RESEARCH LABORATORIES, INC.

Project No.: WIL-81236
Client: The Procter & Gamble Company
Client Doc. Req. No.: CASTR 97

Acute Oral Toxicity Study in Albino Rats with KO215.01

RECEIVED BY
JUL 21 1981
OPERATIONS SECTION

3154 EXON AVENUE • CINCINNATI, OHIO 45241 • (513) 563-8060

Acute Oral Toxicity Study in Albino Rats with KO216.01

Introduction:

A sample identified as KO216.01 received from The Procter and Gamble Company, Cincinnati, Ohio for the purpose of conducting acute toxicity studies. A plastic bottle containing a clear liquid was received on May 11, 1981. The test material and container weighed 366.4 grams and was stored at room temperature in a locked test compound cabinet. A test material stability statement was not provided by the sponsor.

Objective:

The objective of this study was to determine the LD_{50} of the test material following a single dose to albino rats. Study authorization was received from The Procter and Gamble Company, on May 11, 1981. This study was conducted at the Cincinnati facilities of WIL Research Laboratories, Inc. This report presents the results of that investigation from the initiation date, May 12, 1981, to the termination date May 27, 1981.

Procedure:

Experimental Animals:

Young adult albino rats of the Sprague Dawley CD strain were employed as test animals. On May 8, 1981, the rats were received from Harlan Industries and inspected for general health and suitability as test animals. The animals were randomly placed in numbered cages (males first) using a computer generated list of random numbers. Each rat was sexed, weighed and ear tagged according to individual animal number and each cage bore that number. The rats were individually housed in wire-bottomed cages suspended above the droppings. Purina Certified Rodent Chow, 5002 and water were offered ad libitum, except during the 24 hour period immediately prior to oral intubation when food was withheld. Approximately 1 hour after dosing, food was offered.

The rats were quarantined and acclimated to laboratory conditions for 4 days prior to initiation of the study. Animals were observed twice daily during the quarantine period. On the last day of the quarantine period (i.e. the day prior to initiation of exposure to the test material) six groups consisting of ten rats (5 males and 5 females) was selected from the animal shipment and used for the study. Animals received in this shipment were observed to have intermittent loose feces, the resident veterinarian was contacted and stated the animals were suitable test subjects. Records kept during the quarantine period substantiate this. Body weights were measured and they ranged from 200 to 248 grams.

Experimental Design:

This study utilized five dose levels and a treated control with ten rats (5 males and 5 females) per level. The treated control group animals were dosed with distilled water.

Group Number	Actual Dose Amount ml/kg	Dose Level g/kg
1 (Treated Control)*	5.00	0.0
2	2.30	2.6
3	3.19	3.6
4	4.42	5.0
5	6.19	7.0
6	8.62	9.8

1 ml of test material weighed approximately 1.13 g.
*Distilled water, W-2, Lot 710781, Fisher Scientific Company, Fairlawn, New Jersey

Test Material Administration:

Individual dose amounts were calculated by using fasted body weights (Day 0, Mean: Males = 209.73, Females = 200.93) taken prior to dosing. The undiluted test material was measured in a plastic disposable syringe and administered directly into the rat's stomach using a rubber catheter and tubing adapter.

Body Weights:

All animals selected for the study were weighed on days -1, 0, 6 and 14 and final body weights were taken on those animals found dead.

Observations and Mortality:

All animals were observed closely for gross signs of systemic toxicity and mortality at frequent intervals during the day of dosing and at least twice daily thereafter for a total of 15 days. Room conditions, as well as availability of adequate food and water, were checked and any noteworthy conditions recorded.

Necropsy:

All animals were sacrificed by carbon dioxide inhalation and a gross necropsy was performed on the visceral and thoracic cavities. A histopathologic examination was conducted on the liver and kidney of the surviving animals.

Calculation LD_{50}

The WIL computer program based on the techniques of Litchfield and Wilcoxon[a] were used to calculate the LD_{50}.

[a]Litchfield, J. J. and F. Wilcoxon, "A Simplified Method of Evaluation of Dose-Effect Experiments", J. Pharm. and Exp. Ther., 99-113 (1949).

Results:

Body Weight Change Data

Individual body weights and means are presented in Table 1. Mean body weight changes of the test groups appeared not to be statistically significant when compared to the treated control group.

Observations and Mortality:

9.8 g/kg Reactions were first observed 1/2 hour after dosing and consisted of inactivity, loose feces with fecal stains and salivation. From 1 hour on reactions consisted of tremors, inactivity, lethargy, prostration, cool to touch, blue extremities, and rapid and/or irregular respiration with lacrimation (females only) and blood in urine (females only). Three males were found dead 3-6 hours after dosing and the remaining survivors were found dead on day 1.

7.0 g/kg Reactions were first observed 1/2 hour after dosing and consisted of salivation and ataxia (1/10). From 2 hours on, reactions consisted of tremors (5 hours), inactivity, lethargy, ataxia, prostration, cool to touch, rapid and/or irregular respiration, congestion and blood in urine. One female was found dead 6 hours after dosing and three females on day 1 and one male on day 2. All survivors appeared normal by day 3 with the exception of three males with intermittent loose feces. Signs observed on days 1-2 for the survivors consisted of lethargy, ataxia, inactivity, dehydration, cool to touch, loose feces with fecal stains, blood in urine and decreased defecation.

5.0 g/kg Reactions were first observed 1/2 hour after dosing and consisted of salivation and inactivity (1/10) and lethargy (1/10). Additional reactions were observed 4-5 hours after dosing and consisted of inactivity, lethargy, labored respiration (1/10) and blood around vaginal area. Deaths occurred in 4 animals during days 1-5. All survivors appeared normal by day 5 with the exception of intermittent loose feces in three animals. Signs observed on days 1-4 for the survivors consisted of loose feces with fecal stains and decreased defecation.

3.6 g/kg Reactions were first observed 1/2 hour after dosing and consisted of salivation. An additional reaction was observed 5 hours after dosing and consisted of blood around vaginal area. No deaths occurred at this dose level. All animals appeared normal by day 3 with the exception of intermittent loose feces in 6 animals. Signs observed on days 1-2 consisted of loose feces with fecal stains, decreased defecation and severe bloody feces (1F).

2.6 g/kg Reactions were first observed 1/2 hour after dosing and consisted of salivation (1/10). An additional reaction was observed 5 hours after dosing and consisted of blood around vaginal area. No deaths occurred at this dose level. All animals appeared normal by day 3 with the exception of intermittent loose feces in 5 animals. Signs observed on days 1-2 consisted of loose feces with fecal stains, congestion (1M), decreased defecation and blood in urine (1F). One female (260) had a litter of pups on day 13, as parturition time is approximately 21 days the animal became pregnant before it was received at WIL Research facilities.

0.0 g/kg Loose feces were observed in animals at this dose level intermittently throughout the 14 day observation period. One female (255) had a litter of pups on day 13, as parturition time is approximately 21 days, the animal became pregnant before it ~~received~~ was received at WIL Research facilities.

Mortality is presented in Table 2.

Necropsy:

Examination of the thoracic and visceral cavities of the test animals at necropsy by the pathologist revealed the following findings. The gross and histopathologic findings for the liver and kidney are presented in Appendix A.

0.0 g/kg Right kidney slightly pitted (238M).
No significant gross pathologic findings (all others).

2.6 g/kg Dark red-brown material in hindstomach, red material in intestines (259F).
No significant gross pathologic findings (all others).

3.6 g/kg No significant gross pathologic findings (all).

5.0 g/kg Gastrointestinal hemorrhage, renal congestion with blood in the urinary bladder (278F).
Urinary bladder contained blood, diffuse gastrointestinal hemorrhage (277F).
Postmortem autolysis (229M and 279F).
No significant gross pathologic findings (all others).

7.0 g/kg Diffuse gastrointestinal hemorrhage; marked renal congestion and bladder markedly contracted and filled with a bloody fluid (271F, 272F and 273F).
Hemorrhage of the hind and forestomach and intestinal tract (242M).
Dark red-brown foci in the hindstomach, forestomach appeared thickened (233M and 253M).
Gastrointestinal hemorrhage (269F).
No significant gross pathologic findings (all others).

9.8 g/kg Hindstomach dark red, stomach distended with red-orange fluid, intestines reddened and congested and contained mucoid material (281M, 282M and 283M).

Stomach dark red, intestines reddened and congested, blood vessels distended with red-gold water fluid, urinary bladder contained dark red-brown fluid (280M, 284M and all females).

Calculation of LD_{50}:

From the data presented the LD_{50} of KO216.01 is 7.137 g/kg of body weight (95% confidence limits 5.193 - 9.809) and a slope of 1.29. (95% confidence limits 1.06 - 1.57 for males and 5.237 g/kg, (95% confidence limits 3.888 - 7.054) and a slope of 1.27, (95% confidence limits 1.07 - 1.51) for females and 6.114 g/kg, (95% confidence limits 5.122 - 7.297) and a slope of 1.33, (95% confidence limits 1.18 - 1.50) for both sexes.

Summary:

When KO216.01 was administered orally at five dose levels each containing 10 rats (5 males and 5 females) signs of systemic toxicity were observed at all dose levels, increasing in incidence and severity with dose amount. Reactions ranged from inactivity, lethargy, salivation to ataxia, prostration, labored and/or irregular respiration, body cool to touch, tremors and blood in urine. No systemic reactions were observed in the control animals. Mean body weight changes of the test groups appeared not to be statistically significant compared to the treated control group.

Deaths occurred at the 5.0 (4/10), 7.0 (5/10) and 9.8 (10/10) g/kg dose levels. Gross pathologic examination revealed diffuse gastrointestinal hemorrhage with urinary bladder filled with a bloody fluid. Histopathologic examination revealed nephrosis in kidneys of the surviving test animals.

From the data presented in the report the LD_{50} of KO216.01 is 6.114 g/kg for both sexes.

Yvette L Johnson Yvette Johnson, Technician	7-14-81 Date
Marty Criswell, Technician	Date
Arlene F Kingery Arlene P. Kingery, B. S., Section Head	7-14-81 Date
Dale A Mayhew Dale A. Mayhew, Ph. D., Study Director	7/14/81 Date

Marty Criswell is no longer employed at WIL Research Laboratories.

TABLE 1

PROJECT NO.: MIL-81236 — *** INDIVIDUAL BODY WEIGHTS (G), MEANS AND STATISTICS *** — 29-JUN-81 PAGE 1

CLIENT: PROCTER & GAMBLE COMPANY — ACUTE ORAL TOXICITY IN RATS WITH K0216.01 — DAY -1

CLIENT STUDY NO.:

MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
237=244.0	230=231.0	241=241.0	229=226.0	251=235.0	280=208.0		265=223.0	259=222.0	258=219.0	275=212.0	269=222.0	291=204.0
239=225.0	231=241.0	243=222.0	245=223.0	253=227.0	281=223.0		255=211.0	260=218.0	252=226.0	276=222.0	270=232.0	292=206.0
240=222.0	234=227.0	244=223.0	246=237.0	233=229.0	282=209.0		256=227.0	261=229.0	266=224.0	277=236.0	271=215.0	293=222.0
254=225.0	235=236.0	249=226.0	247=215.0	242=234.0	283=233.0		257=234.0	262=228.0	267=219.0	278=223.0	272=213.0	294=207.0
238=248.0	236=248.0	250=245.0	248=228.0	232=242.0	284=215.0		264=217.0	263=213.0	268=219.0	279=226.0	273=212.0	295=206.0
232.800	236.600	231.400	225.800	233.400	217.600	MEAN	222.400	222.000	221.400	223.800	218.800	207.800
12.194	8.264	10.784	7.981	5.857	10.478	S.D.	8.877	6.745	3.362	8.614	8.349	8.378
5.453	3.696	4.823	3.569	2.619	4.684	S.E.	3.970	3.017	1.503	3.852	3.734	3.747
5	5	5	5	5	5	(N)	5	5	5	5	5	5

F = 2.61, DF= 5/ 24, P=0.0487 — ANOVA — F= 2.99, DF= 5/ 24, P=0.0298

GROUP	DIFFERENCE	.05	.01
2	3.8	16.6	20.7
3	-1.4	16.6	20.7
4	-7.0	16.6	20.7
5	0.6	16.6	20.7
6	-15.2	16.6	20.7

DUNNETT'S

GROUP	DIFFERENCE	.05	.01
2	-0.4	13.3	16.7
3	-1.0	13.3	16.7
4	1.4	13.3	16.7
5	-3.6	13.3	16.7
6	-14.6	13.3	16.7

TABLE 1

PROJECT NO.: WIL-81236 *** INDIVIDUAL BODY WEIGHTS (G), MEANS AND STATISTICS *** 13-JUL-81 PAGE 1

CLIENT: PROCTER & GAMBLE COMPANY ACUTE ORAL TOXICITY IN RATS WITH K0216.01 DAY 0

CLIENT STUDY NO.:

MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
237-220.0	230-210.0	241-216.0	229-213.0	251-214.0	280-195.0		265-204.0	259-200.0	258-197.0	276-200.0	269-206.0	291-188.0
239-203.0	231-216.0	243-204.0	245-199.0	253-210.0	281-206.0		255-194.0	260-201.0	252-211.0	275-206.0	270-212.0	292-185.0
240-202.0	234-210.0	244-207.0	246-217.0	233-211.0	282-190.0		256-205.0	261-211.0	266-202.0	277-212.0	271-200.0	293-203.0
234-203.0	235-215.0	249-208.0	247-198.0	242-215.0	283-215.0		257-211.0	262-207.0	267-204.0	278-202.0	272-194.0	294-187.0
238-230.0	236-219.0	250-224.0	248-264.0	232-222.0	284-198.0		264-201.0	263-195.0	269-198.0	279-205.0	273-194.0	295-195.0
211.600	214.000	211.800	206.200	214.400	205.400	MEAN	203.000	202.800	202.400	205.000	201.200	191.200
12.740	3.937	8.136	8.488	4.722	10.015	S.D.	6.205	6.261	5.595	4.583	7.823	7.225
5.697	1.761	3.639	3.797	2.112	4.479	S.E.	2.775	2.800	2.502	2.049	3.499	3.231
5	5	5	5	5	5	(N)	5	5	5	5	5	5

F = 2.02, DF= 5/ 24, P=0.1079 | ANOVA | F= 2.99, DF= 5/ 24, P=0.0297

GROUP	DIFFERENCE	.05	.01
2	2.4	14.9	18.6
3	0.2	14.9	18.6
4	-5.4	14.9	18.6
5	2.8	14.9	18.6
6	-11.2	14.9	18.6

DUNNETT'S

GROUP	DIFFERENCE	.05	.01
2	-0.2	11.1	13.9
3	-0.6	11.1	13.9
4	2.0	11.1	13.9
5	-1.8	11.1	13.9
6	-11.8*	11.1	13.9

TABLE 1

PROJECT NO.: WIL-81236 *** INDIVIDUAL BODY WEIGHTS (G), MEANS AND STATISTICS *** 29-JUN-81 PAGE 1

CLIENT: PROCTER & GAMBLE COMPANY ACUTE ORAL TOXICITY IN RATS WITH K0216.01 DAY 6

CLIENT STUDY NO.:

MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
237=269.0	230=237.0	241=246.0	245=241.0	251=251.0			265=236.0	259=239.0	258=232.0	275=214.0	270=216.0	
239=255.0	231=260.0	243=258.0	246=270.0	253=245.0			255=253.0	260=213.0	252=237.0	276=225.0		
240=259.0	234=249.0	244=245.0	247=228.0	233=229.0			256=241.0	261=242.0	266=234.0			
254=237.0	235=252.0	249=249.0	248=247.0	232=254.0			257=242.0	262=234.0	267=195.0			
238=291.0	236=260.0	250=253.0					264=226.0	263=206.0	268=234.0			
262.200	251.600	250.200	246.500	244.750	0.0001	MEAN	239.600	226.800	226.400	219.500	216.000	0.000
19.829	9.503	5.357	17.559	11.147	0.0001	S.D.	9.813	16.239	17.644	7.778	0.000	0.000
8.868	4.250	2.396	8.780	5.573	0.0001	S.E.	4.389	7.262	7.891	5.500	0.000	0.000
5	5	5	4	4	01	(N)	5	5	5	2	1	0
F = 1.16, DF= 4/ 18, P=0.3461						ANOVA	F= 1.15, DF= 4/ 13, P=0.3626					

GROUP	DIFFERENCE	.05	.01	DUNNETT'S	GROUP	DIFFERENCE	.05	.01
2	-10.6	24.5	30.9		2	-12.8	27.2	35.0
3	-12.0	24.5	30.9		3	-13.2	27.2	35.0
4	-15.7	26.0	32.7		4	-20.1	36.0	46.3
5	-17.5	26.0	32.7		5	-23.6	36.0	46.3

TABLE I

PROJECT NO.: WIL-81236 *** INDIVIDUAL BODY WEIGHTS (G), MEANS AND STATISTICS *** 29-JUN-81 PAGE 1

CLIENT: PROCTER & GAMBLE COMPANY ACUTE ORAL TOXICITY IN RATS WITH K02(6.0) DAY 14

CLIENT STUDY NO.:

MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
237=305.0	230=248.0	241=269.0	245=259.0	251=282.0			265=240.0	259=234.0	258=234.0	275=231.0	270=236.0	
239=278.0	231=296.0	243=289.0	246=324.0	253=281.0			255=232.0	260=225.0	252=249.0	276=236.0		
240=291.0	234=276.0	244=272.0	247=261.0	233=263.0			256=242.0	261=252.0	266=229.0			
254=257.0	235=287.0	249=277.0	248=284.0	232=283.0			257=232.0	262=243.0	267=235.0			
238=324.0	236=300.0	250=285.0					264=226.0	263=218.0	268=246.0			
291.000	281.400	278.400	282.000	277.250	0.000	MEAN	234.400	234.400	238.600	233.500	236.000	0.000
25.544	20.828	8.474	30.210	9.535	0.000	S.D.	6.542	13.613	8.503	3.536	0.000	0.000
11.424	9.315	3.790	15.105	4.768	0.000	S.E.	2.926	6.088	3.803	2.500	0.000	0.000
5	5	5	4	4	0	(N)	5	5	5	2	1	0
F = 0.33, DF= 4/ 18, P=0.8193						ANOVA	F= 0.18, DF= 4/ 13, P=0.9046					

GROUP	DIFFERENCE	.05	.01
2	-9.6	37.0	46.7
3	-12.6	37.0	46.7
4	-9.0	39.3	49.5
5	-13.0	39.3	49.5

DUNNETT'S	GROUP	DIFFERENCE	.05	.01
	2	0.0	18.1	23.3
	3	4.2	18.1	23.3
	4	-0.9	23.9	30.8
	5	1.6	23.9	30.8

TABLE 1 (FOUND DEAD)

PROJECT NO.: WIL-81236 *** INDIVIDUAL BODY WEIGHTS (G), MEANS AND STATISTICS *** 29-JUN-81 PAGE 1

CLIENT: PROCTER & GAMBLE COMPANY ACUTE ORAL TOXICITY IN RATS WITH K0216.01

CLIENT STUDY NO.:

MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.		FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
			229*	242=189.0	280=191.0						277=197.0	269=193.0	291=182.0
					281=205.0						278=192.0	271=194.0	292=181.0
					282=184.0						279*	272=189.0	293=198.0
					283=212.0							273=193.0	294=183.0
					284=189.0								295=182.0
0.000	0.000	0.000	0.000	189.000	196.200	MEAN		0.000	0.000	0.000	194.500	192.250	185.200
0.000	0.000	0.000	0.000	0.000	11.777	S.D.		0.000	0.000	0.000	3.536	2.217	7.190
0.000	0.000	0.000	0.000	0.000	5.267	S.E.		0.000	0.000	0.000	2.500	1.109	3.216
0	0	0	0	1	5	(N)		0	0	0	2	4	5
F = 0.00, DF= 0/ 0, P=0.0000						ANOVA		F= 0.00, DF= 0/ 0, P=0.0000					
GROUP DIFFERENCE		.05	.01			DUNNETT'S		GROUP DIFFERENCE		.05	.01		
								4	0.0	0.0	0.0		
5	0.0	0.0	0.0					5	0.0	0.0	0.0		
6	0.0	0.0	0.0					6	0.0	0.0	0.0		

*Terminal Body Weight Not Recorded.

TABLE 1

PROJECT NO.: MIL-81236
CLIENT: PROCTER & GAMBLE COMPANY
CLIENT STUDY NO.:

*** BODY WEIGHT (G) - SUMMARY OF MEANS ***
ACUTE ORAL TOXICITY IN RATS WITH K0216.01

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MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	MALE 6	SEX / DOSE GRP.	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5	FEMALE 6
232.8	236.6	231.4	225.8	233.4	217.6	DAY -1	222.4	222.0	221.4	223.8	218.8	207.8*
211.6	214.0	211.8	206.2	214.4	200.4	DAY 0	203.0	202.8	202.4	205.0	201.2	191.2*
262.2	251.6	250.2	246.5	244.8	0.0	DAY 6	239.6	226.8	226.4	219.5	216.0	0.0
291.0	281.4	278.4	282.0	277.3	0.0	DAY 14	234.4	234.4	238.6	233.5	236.0	0.0
0.0	0.0	0.0	0.0	189.0	196.2	DAY 15	0.0	0.0	0.0	194.5	192.3	185.2

* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP AT .05 LEVEL USING DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP AT .01 LEVEL USING DUNNETT'S TEST

Acute Oral Toxicity Study in Albino Rats with KO216.01

Table 2 - Mortality

Dose Group g/kg	Sex	Time of Death (Hours) 0	3	6	12	24	48	96	120	Total Died/Tested
0.0	Male	0	0	0	0	0	0	0	0	0/5
	Female	0	0	0	0	0	0	0	0	0/5
2.5	Male	0	0	0	0	0	0	0	0	0/5
	Female	0	0	0	0	0	0	0	0	0/5
3.8	Male	0	0	0	0	0	0	0	0	0/5
	Female	0	0	0	1	0	0	0	0	0/5
5.0	Male	0	0	0	0	0	0	0	1	1/5
	Female	0	0	0	0	1	1	1	0	3/5
7.0	Male	0	0	0	0	0	1	0	0	1/5
	Female	0	0	1	0	3	0	0	0	4/5
9.8	Male	0	2	1	0	2	0	0	0	5/5
	Female	0	0	0	0	5	0	0	0	5/5

Acute Oral Toxicity Study in Albino Rats with KO216.01

Quality Assurance Unit Statement

Dates of Inspection(s)	Date(s) Findings Reported to Management and Study Director
May 12, 1981	May 14, 1981
May 26, 1981	June 11, 1981
July 9, 1981	July 13, 1981
July 13, 1981	July 13, 1981

All phases of the above study were inspected in accordance with the Good Laboratory Practice regulations, the Standard Operating Procedures of WIL Research Laboratories, Inc. and the sponsor's protocol. To the best of the signator's knowledge there were no significant deviations from the Good Laboratory Practice regulations which affected the quality or integrity of the study. Quality Assurance findings, derived from the inspection(s) during the conduct of the study and from the inspection of the final report, are documented and have been made available to the study director and to the test facility management.

The raw data and a copy of the final report will be kept in the archives at WIL Research Laboratories, Inc.

Ralph Anderson
Ralph Anderson, B.S.
Manager-Quality Assurance Unit

7/14/81
Date

APPENDIX A

TO: Dr. D. A. Mayhew, Study Director

FROM: F. W. Sigler, D.V.M., Pathologist

DATE: June 24, 1981

SUBJECT: Pathology* Report for Study No. WIL 81236

I. Methodology:

The necropsy and tissue processing were conducted according to WIL SOP's

II. Results: (Liver and Kidneys only)

Animal No. & Sex	Dose Level (g/kg)	Pathological Findings
237 M	0.0	Liver Throughout, the centrolobular hepatocytes either have oval, clear cytoplasmic vacuoles or acidophilic, homogenous material of varying size. This intra-cytoplasmic material displaces the normal cytoplasmic RNA material to the periphery of the cell.
238 M	0.0	NSCO(1)
239 M	0.0	Liver - Same as 237 M
240 M	0.0	Liver - Same as 237 M
254 M	0.0	Liver - Similar to 237 M
255 F	0.0	Liver Mild, hepatocytic, cytoplasmic microvacuoles
256 F	0.0	NSCO
257 F	0.0	NSCO
264 F	0.0	NSCO
265 F	0.0	NSCO

*Represents Gross and Histopathology
(1) No significant changes observed

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Animal No. & Sex	Dose Level (g/kg)	Pathological Findings
259 F	2.6	NSCO
230 M	2.6	Liver Similar to 237 M
231 M	2.6	Liver Similar to 237 M
234 M	2.6	Liver Similar to 237 M
235 M	2.6	Liver Similar to 237 M
236 M	2.6	Liver Similar to 237 M
260 F	2.6	Kidney Throughout the cortex of both kidneys, the proximal convoluted tubules are lined by hyperchromatic, basophilic epithelium. These tubules contain intraluminal casts, which are either cellular, (composed of necrotic debris) acellular dull, golden hemoglobin, neutrophils or blood. The intersitium in these areas are infiltrated by lymphocytes and there are a few hemosiderin-laden macrophages present. These changes are consistent with an endogenous nephrosis.
261 F	2.6	NSCO
262 F	2.6	NSCO
263 F	2.6	NSCO
241 M	3.6	Liver Similar to 237 M
243 M	3.6	Liver Similar to 237 M
244 M	3.6	Liver Similar to 237 M
249 M	3.6	Liver Similar to 237 M

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Animal No. & Sex	Dose Level (g/kg)	Pathological Findings
250 M	3.6	Liver Similar to 237 M Kidneys Focal cortical tubules are dilated, containing acellular, eosinophilic hyalinized casts, indicative of an early glomerulonephrosis.
252 F	3.6	Kidney - Same as 260 M
258 F	3.6	NSCO
266 F	3.6	Kidney - Similar to 260 M
267 F	3.6	Kidney - Similar to 260 M
268 F	3.6	NSCO
245 M	5.0	Liver - Similar to 237 M
246 M	5.0	Liver - Similar to 237 M
247 M	5.0	Liver - Similar to 237 M Kidney - Similar to 260 M ✓
248 M	5.0	Liver - Similar to 237 M
275 F	5.0	Kidney - Similar to 260 M ✓
276 F	5.0	Kidney - Similar to 260 M ✓
232 M	7.0	Liver - Similar to 237 M
233 M	7.0	Kidney - Similar to 260 M ✓
251 M	7.0	NSCO
253 M	7.0	NSCO
270 F	7.0	Kidney - Same as 260 M ✓

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Dr. Dale A. Mayhew

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III. Discussion:

An unusual hepatic alteration was found in the males of all dose groups including the controls, the incidence was as follow:

Dose Group (g/kg	No. and Sex	Incidence/Sex
0.0	5 M, 5 F	4/5 M's, 1/5 F's
2.6	5 M, 5 F	5/5 M's, 0/5 F's
3.6	5 M, 5 F	5/5 M's, 0/5 F's
5.0	4 M, 2 F	4/4 M's, 0/2 F's
7.0	4 M, 1 F	1/4 M's, 0/1 F's

This hepatic alteration consisted of mild to marked, centrolobular cytoplasmic vacuolization or acidophilic degeneration. Zimmerman, H[1] (Hepatotoxicity. Applanton-Century-Crofts, N.Y. 1978. pp-59-64) considers cytoplasmic vacuolization as steatosis, while Bruni, C[2] (Lab. Invest. Vol 9, 1960. pp-209-215) considers acidophilic degeneration as hyalin degeneration.

Concurrently, according to Bannasch, P.[3] (Rat Hepatic Neoplasia, Newberne, P. and Butler, W. editors. MIT Press. Cambridge, Mass., 1978. p-67) steatosis and cytoplasmic acidophilia (acidophilic degeneration) are cytotoxic alterations which Zimmerman[1] states' are the result of a number of drugs and other chemicals.

Thus since these hepatic alterations were found in the control animals, (they may well represent evidence of prior treatment by the animal supplier), they are not considered induced by this test material.

However, an endogenous nephrosis was found in all treatment groups, but not the controls. According to Casey, H. et.el. (The Urinary System, In. Pathology of Laboratory Animals. Benirschke, K., Garner, F. & Jones, T. Editors. Springer-Verlag. N.Y. 1978. pp-145-149) this represents changes from toxic substances. Thus this is most probably test material related.

IV. Conclusion:

The acute oral administration of either 2.6, 3.6, 5.0 and 7.0 g/kg produces a nephrosis in those animals surviving the 14 day post treatment period.

Fred W. Sigler 7/14/81
Fred W. Sigler, D.V.M.
Pathologist

FWS:pf

THE PROCTER & GAMBLE COMPANY

PROTOCOL NO. G1

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

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

Test Substance Identification Number (TSIN) # KG216.01

Divisional Request Document Number (DRD) # CA-STR-97

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: (To be filled in by Operations Section)
WIL Research Laboratories, Inc.
3154 Exon Avenue
Cincinnati, Ohio 45241

Study # 81336 (To be filled in by Testing Facility)

Purpose: To establish 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.

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

Issue Date: September 15, 1980

Test Substance(s)

TSIN #	DRD Number	Description: Color	Description: Physical Form	Expiration Date
KD216.01	CA-STR-97	Clear, water white	Liquid	5/1/82

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: Forty (40) rats, Sprague-Dawley (cesarean-dervied), 20 males and 20 females, 190-300 grams prefasted weight. Additional animals will be required if more than four groups are requested. (See pp. 3 and 4.) Fewer animals will be required if only a single group is requested. (See p. 3.)

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 15, 1980

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 Acute Oral Toxicity/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 or Sponsor's estimate indicates an LD_{50} value of less than 20 g/kg, choose four (4) dosage levels, based upon the estimated LD_{50} value and/or 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.

Dose Preparation:

Test Group(s): (Check appropriate box)

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

Control Group

A control group should be [X]; should not be [ ] included in this study. If included, the control substance distilled water should be tested concurrently with the test substance at a dosage level of 5 ml/kg.

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.

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.*

More than four dosage levels may be required to establish a death-to-dose response that will allow the LD_{50} value to be calculated. (Note: If the data generated from four dosage levels do not lend themselves to statistical analysis by the Test Facility's Standard Operating Procedures, the Sponsor should be contacted prior to further experimental work.)

*Determine specific gravity values, 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 15, 1980

Dosing Instructions (Cont'd):

The test substance, at the concentration specified under "Dose Preparation", will be gavaged into the stomach of the animal 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 weigh and 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.

Conduct histopathologic examination of liver and kidney (one time sample per surviving animal, including controls). Results to be reported verbally within 14 days of sacrifice.

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.

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

Issue Date: September 15, 1980

Report: Report dates of study initiation and termination. Report all data regarding dose preparation, individual dose level, 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: J. Iavicoli
Divisional Toxicologist J. Iavicoli

Date Approved by Sponsor's Divisional Toxicologist 5/11/81

Proposed Starting Date: 5-12-81
Proposed Completion Date: 7-10-81
(Final Report Available)
Study Director: [illegible]
Date: 5/11/81
Study Cost: $300.00 / dose level + $6.00/tissue

(To be completed by the Test Facility)

*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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