Report Title: 14-Day Range-Finding Study in Rats

Test Type: Reproduction Toxicity

Conducting Laboratory and Location: International Research and Development Corporation

Test Substance(s): #G0539.03 – Octopirox in PEG/methylcellulose vehicle

Species: Rat

# of Animals: 5 male rats per group

Test Conditions: 0, 50, 100 and 250 mg/kg/day of test material administered by gavage as a single daily dose (2 ml/kg) for 14 consecutive days. 5 male rats per group. Blood samples taken prior to study and on Day 14.

Results: Study was conducted to set dose levels for a segment I fertility study. There were no treatment related clinical signs of toxicity. The doses used in this study were selected for the fertility study.

Study #: IRDC-191-1394
Report Date: 07/21/88
Accession #: 34619

BIOLOGICAL SAFETY TEST SUMMARY REVIEW

Test Substance: Octopirox™

Test Substance Identification Number: 60539.03

Contract Laboratory: IR&DC — Report #: 191-1394

Type of Study: 14-Day Range-Finding in Rats — DRD #: BY07645

Toxicologist: G. S. Allgood — Division: SYC

Date Report Written: 7-21-88 — Date Rec'd by Operations Section: 7-25-88

This report has been reviewed and found in agreement with the Protocol and there appear to be no inaccuracies in the numerical data or written portions with the following exceptions: None

SO Operations Section Monitor: S. A. Nixon — Date: 7/28/88
S. A. Nixon

This report has been reviewed for scientific quality and is summarized, with comments (if any) as follows:

See attached sheet

Divisional Toxicologist: G. S. Allgood — Date: 8/26/88
G. S. Allgood

This report is approved for entry into the Safety Data System and microfilming.

Corporate HSD Liaison: H. L. Alden — Date: 8/27/88
H. L. Alden

Return to Marilyn Brown, Room 2N211, MVL

Entered into Safety Data System by M. L. Brown — Date: 9-7-88

Microfilming Completed by _____ Date: _____

STUDY SUMMARY FOR 14-DAY RANGE-FINDING IN RATS DRD#BY07645

This study was conducted to set dose levels for a Segment I fertility study. Dosage levels of 0, 50, 100, and 250 mg/kg/day Octopirox in a PEG/methylcellulose vehicle were administered orally by gavage. Dosing was as a single daily dose (2.5 ml/kg) for 14 consecutive days to five young male rats/group (37 days old at start of study). Blood samples were taken prior to test article administration and on day 14 for analysis.

Hematological analysis revealed a change from baseline (pre- to post-treatment) in peripheral lymphocytes that was significantly decreased in the 250 mg/kg/day group compared to controls. However, the number of lymphocytes in this high dose group was not statistically different from the control group at day 14. Hematological analysis revealed no other meaningful differences between the control group and any of the treated groups. There were no treatment-related clinical signs of toxicity. Based on these findings, dosage levels of 0, 10, 100, and 250 mg/kg/day were selected for the fertility study.

International Research
and Development Corporation
MATTAWAN, MICHIGAN U.S.A. 49071 TELEPHONE (616) 668-1136

SPONSOR: The Procter and Gamble Company

TEST ARTICLE: (TSIN) G0539.03

SUBJECT: 14-Day Range-Finding Study in Rats

DAD NO.: BY07648

DATE OF STUDY COMPLETION: July 21, 1988

191-1394

RECEIVED BY
JUL 25 1988
OPERATIONS SECTION

"credence through research"

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I. QUALITY ASSURANCE STATEMENT

Study Title: 14-Day Range-Finding Study in Rats

Test Article: (TSIN) G0539.03

The conduct of this study has been subjected to periodic inspections. The dates of inspection and the dates that findings were reported to management and the Study Director are listed in Appendix A.

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 Good Laboratory Practice Regulations of June 20, 1979 and as modified by the final rule effective October 5, 1987.

Approved By: Margery J. Wirth, B.S. 7/21/88
Margery J. Wirth, B.S.
Director of Quality Assurance
Date

191-1394

II. SYNOPSIS

Twenty-five male Charles River COBS® CD® rats, randomly assigned to one control and four treatment groups of five animals each, were used in this range-finding study to determine dosage levels of G0539.03 for a fertility study. Dosage levels of 10, 50, 100 and 250 mg/kg/day were administered orally by gavage as a single daily dose for 14 consecutive days at a constant volume of 2.5 ml/kg. The control group received the vehicle only, a combination of 1.0% methylcellulose and polyethylene glycol (PEG) 400, on a comparable regimen. Blood samples were taken prior to test material administration and on the fourteenth day of treatment for analysis. The animals were sacrificed and discarded after the second blood samples were collected.

The ~~number of~~ peripheral lymphocytes was significantly decreased in the 250 mg/kg/day group at day 14 compared to controls. Additional moderate deviations from control values were also observed for other hematological parameters at this dosage level; however, these values were within historical control ranges and any association of these deviations with test article treatment is unclear. There were no other meaningful differences in hematological values between the control group and any of the treated groups. There were no treatment-related clinical signs of toxicity noted in any of the study groups, and body weight and food consumption values for all treated groups were comparable to those of the control group.

change from baseline

Based on these findings, dosage levels of 10, 100 and 250 mg/kg/day were selected for a fertility study with Charles River COBS® CD® rats.

the total number of peripheral lymphocytes was

III. INTRODUCTION

A. OBJECTIVE

The objective of this study was to establish appropriate dosage levels to be used in a subsequent study to determine the effect of the test substance on the fertility of rats.

B. TEST ARTICLE IDENTIFICATION

The test article was received from The Procter and Gamble Company, Cincinnati, Ohio, on February 12, 1988, as indicated below:

Label	Description
TEST SUBST. (TSIN) G0539.03	white powder
DIV. REQUEST DOC. (DRD) BY0764S	(1 container)
DATE REC'D. (OPER. SECTION) 2/10/88	
TYPE OF TEST 14-DAY RANGE FINDING STUDY	
GROSS WT. (INC. LID, CONT., LABEL) 751.26	
*TARE WT. 471.62 NET WT. 269.64 g	
STORAGE CONDITIONS AMBIENT	
EXPIRATION DATE 2/89	
HAZARD ~~NON-HAZARDOUS~~ Corrosive CWC ~~2/8/88~~	
D.O.T. HAZARD Non-Hazardous	
RETURN TO DIVISIONAL TOXICOLOGIST WHEN TEST IS COMPLETED	

*CONTAINER, LID, LABEL

CAUTION: THE TOXICITY OF THIS MATERIAL HAS NOT BEEN COMPLETELY EVALUATED.

C. VEHICLE CONTROL ARTICLE IDENTIFICATION

The vehicle control article used on this study was a combination of 1.0% methylcellulose (4000 cps) in deionized distilled water and polyethylene glycol (PEG) 400. Specific receipt, label and descriptive information is available upon Sponsor request.

IV. METHODS AND PROCEDURES

This study was conducted in accordance with the protocol as approved by the Sponsor and in compliance with the Standard Operating Procedures of International Research and Development Corporation (IRDC). Procedures pertinent to this study are described herein.

A. EXPERIMENTAL DESIGN

1. Animal Receipt and Maintenance

Thirty-eight 28-day old male Sprague-Dawley derived Charles River COBS® CD® rats were received from Charles River Laboratories, Inc., Portage, Michigan, on February 24, 1988. Upon receipt, the animals were assigned temporary animal numbers and housed individually in suspended wire-mesh cages. During the nine-day acclimation period, the animals were carefully observed for changes in appearance and behavior. Five days after receipt of the animals, blood samples were taken and baseline hematological values were determined. From acquisition until sacrifice, each animal was provided with basal laboratory diet of Purina® Certified Rodent Chow® #5001 and tap water available ad libitum.

The basal laboratory diet was analyzed by the manufacturer for the presence of pesticides, heavy metals and aflatoxins; the diet-lot used was recorded. The drinking water at IRDC is analyzed quarterly for the presence of pesticides, heavy metals and coliforms. The results of these analyses are stored in the IRDC Archives in Mattawan, Michigan, and are available upon request. The Study Director was not aware of any potential contaminants of either diet or drinking water that might have interfered with the results of this study.

Throughout the study, all animals were housed in an environmentally controlled room. Temperature ranged between 72°F and 74°F, with a mean temperature ± standard deviation of 73 ± 0.9°F; humidity ranged between 46% and 50%, with a mean humidity ± standard deviation of 48 ± 2.1%. Fluorescent lighting provided illumination 12 hours per day. The

rats were housed individually in suspended wire-mesh cages from receipt until sacrifice. Each animal was identified by cage, by group and individually by a Monel® metal ear tag bearing its animal number. The individual animal number plus the IRDC study number comprised a unique identification number for each animal. The animals were 37 days old on the first day of dosing and weighed between 160 and 178 g on the day prior to initiation of dosing.

The study was initiated with Study Director approval of the protocol on February 15, 1988. Test article administration began on March 4, 1988, and the study terminated on March 17, 1988.

2. Rationale for Selection of Species and Strain

The rat is one rodent commonly used for the evaluation of teratogenicity and is acceptable in the guidelines of the FDA, EPA and OECD.

3. Organization of Test Groups

At the end of the acclimation period, all animals were weighed and subjected to a detailed physical evaluation. Any rat with abnormal baseline hematological values was discarded. Animals considered suitable for study were randomly assigned to one control group and four treatment groups of five rats each by the following computer-generated system. Animal numbers and corresponding body weights were entered onto magnetic tape that was used as the data source for the randomization procedure. The mean body weight and standard deviation were calculated and a computer-generated edit developed a listing of those animals whose body weights were within $\pm$ 1.5 standard deviations of the mean. From the qualifying animals, the randomization procedure selected and assigned the required number of animals. Bartlett's test for homogeneity of variance was applied to the groups; the groups were judged to be homogeneous.

B. TEST ARTICLE ADMINISTRATION

The selected route of administration was oral in order to maximize systemic exposure. The anticipated route of exposure in humans is dermal.

For the control group, the required amounts of polyethylene glycol (PEG) 400 and 1.0% methylcellulose (at a ratio of 1:19) were weighed into a beaker and mixed using magnetic stir bars and a stir plate. The resulting suspension was sonicated for approximately 90 seconds. For the treated groups, the appropriate amount of the test article, G0539.03, was weighed and dissolved in a beaker with the required amount of PEG 400 using magnetic stir bars and a stir plate. The PEG 400 was warmed to approximately 37°C to facilitate dissolution of the test article. The required amount of 1.0% methylcellulose was weighed into a separate beaker and then slowly added to the PEG/test article solution at a ratio of 19:1. The resulting suspension was stirred using magnetic stir bars and a stir plate and then sonicated for approximately 90 seconds. The pH of the vehicle control and test article suspensions were adjusted to 7.0 using 1M citric acid and/or 1N sodium hydroxide as necessary. The suspensions were then dispensed into amber capped containers and stored refrigerated prior to dispensation. The suspensions were stirred using magnetic stir bars and a stir plate during administration.

The test article was prepared weekly at concentrations to permit the administration of dose levels of 10, 50, 100 and 250 mg/kg/day at a dosage volume of 2.5 ml/kg. Samples from the top, middle and bottom of the mixing container from the first weekly dosing preparations were sent to the Sponsor for homogeneity determination. Samples from the second weekly dosing preparations were sent to the Sponsor for concentration and/or stability analysis.

The test article was administered as a single daily dose for 14 consecutive days. Test article administration was accomplished by intragastric intubation using 1 cc disposable plastic syringes and 16 gauge, 7.6-cm long, straight stainless steel dosing needles. The control group received the vehicle only on a comparable regimen at a volume of 2.5 ml/kg. The control and test article solutions were warmed to room temperature and sonicated prior to each daily dosing. Individual dosages

were determined from the most recently recorded body weights. Dosing began approximately 5 to 7 1/2 hours after initiation of the illuminated phase of the photoperiod. The protocol specified that dosing was to occur at least six hours after initiation of illumination of the housing area; however, the animals were inadvertently dosed five hours after initiation of illumination on four occasions. In the opinion of the Study Director, these deviations did not affect the quality or integrity of the study.

C. OBSERVATIONS

1. Survival, Appearance and Behavior

The animals were observed twice daily for mortality and clinical signs of toxicity during the treatment period.

2. Body Weights

Individual body weights were recorded on the day prior to initiation of dosing and on treatment days 4, 7, 10 and 14.

3. Food Consumption

Food consumption was recorded weekly during the treatment period.

D. CLINICAL PATHOLOGY

Hematological evaluations were conducted on all animals once prior to study initiation and on day 14. Blood samples were obtained from the orbital sinus. The parameters listed below were determined using the instrument listed in accordance with the reference cited.

Summary of Clinical Pathology Determinations

Parameter	Sample Type	Instrument Used	Reference
Leukocyte Count	WB	Ortho ELT-8®	1
Erythrocyte Count	WB	Ortho ELT-8®	1
Hemoglobin	WB	Ortho ELT-8®	1
Hematocrit	WB	Ortho ELT-8®	1
MCV, MCH, MCHC	WB	Ortho ELT-8®	1
Platelets	WB	Ortho ELT-8®	1
Differential Leukocyte Count	WB	Light Microscope	2

WB = Whole Blood
MCV = Mean corpuscular volume
MCH = Mean corpuscular hemoglobin
MCHC = Mean corpuscular hemoglobin concentration

6. DATA RETENTION

All raw data, a sample of the test article and copies of the final report are retained in the Archives of International Research and Development Corporation, 500 N. Main, Mattawan, Michigan 49071.

F. STATISTICAL ANALYSIS

Hematological values (changes from baseline), body weight changes and final body weights were analyzed using analysis of variance (one-way classification) and Bartlett's test for homogeneity of variance. Treatment groups were compared to the control group using the appropriate t-statistic (for equal or unequal variance) as described by Steel and Torrie[3] and Ostle.[4] Dunnett's[5] multiple comparison tables were used to determine the significance of differences.

Rama K. Kalra, M.B.A.
Director of Statistics and
Data Processing

Date 7/14/88

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V. RESULTS

A. OBSERVATIONS (Appendix B)

1. Survival, Appearance and Behavior (Table 1)

All animals on study survived to scheduled sacrifice. Clinical signs were noted for only two animals on study, both in the 250 mg/kg/day group. One animal had an eye abnormality and another had black material around an eye; these findings were considered to be incidental.

2. Body Weights (Table 2)

Values of group mean body weights and body weight changes for all treated groups were comparable to those of the control group.

3. Food Consumption (Table 3)

Food consumption values (g/animal/day and g/kg/day) for all treated groups were comparable to those of the control group.

B. CLINICAL PATHOLOGY

Hematology Values (Table 4, Appendix C)

A significant decrease ($p<0.01$) in the number of peripheral lymphocytes was observed in the 250 mg/kg/day group at day 14. Additional moderate deviations from control values were also observed for other hematological values at this dosage level. However, these differences were within expected ranges for this species in this laboratory and thus any association of these deviations with test article treatment is unclear.

which ones?

Prepared By: _____ _____
Kit A. Keller, Ph.D. Date
Assistant Director, Reproductive
and Developmental Toxicology Division

Reviewed By: _____ 7/18/88
Robert G. Geil, D.V.M., A.C.V.P. Diplomate Date
Scientific Director of Pathology Division

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VI. SIGNATURES

Prepared By: _____ 7/14/88
Susan J. Hubert, M.A.
Report Writer
Department of Report Writing
Date

Reviewed By: _____ 7/14/88
Kit A. Keller, Ph.D.
Assistant Director, Reproductive and
Developmental Toxicology Division
Date

Reviewed By: _____ 7/17/88
James L. Schardein, M.S., D.A.T.S.
Scientific Director, Reproductive and
Developmental Toxicology Division
Date

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changed from baseline compared to controls but not in total number compared to controls.

VII. DISCUSSION AND CONCLUSION

There were no treatment-related clinical signs of toxicity noted in any of the study groups, and body weight and food consumption values for all treated groups were comparable to those of the control group.

The number of peripheral lymphocytes was decreased in the 250 mg/kg/day group at day 14. Additional moderate deviations from control values were also observed for other hematological parameters at this dosage level; however, these values were within historical control ranges and any association of these deviations with test article treatment is unclear.

which one?

Based on these considerations, dosage levels of 10, 100 and 250 mg/kg/day were selected for a fertility study with Charles River COBS® CD® rats.

To the best of my knowledge, there were no significant deviations from the Good Laboratory Practice Regulations that affected the quality or integrity of the 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 the study.

Kit A. Keller — 7/5/88

Kit A. Keller, Ph.D.
Assistant Director, Reproductive and Developmental Toxicology Division
Study Director

Date

191-1394

VIII. REFERENCES

1. Ortho ELT-8 Operator Reference Manual. Ortho Diagnostic Systems, Westwood, MA. 1979.

2. Miale, J. B. (1977). Laboratory Medicine Hematology. The C. V. Mosby Company, St. Louis, MO.

3. Steel, R. G. D. and Torrie, J. H., (1960). Principles and Procedures of Statistics, McGraw-Hill Book Company, Inc., New York, N.Y.

4. Ostle, B., (1954). Statistics in Research, Iowa State College Press, Ames, IA.

5. Dunnett, C. W., (1964). New tables for multiple comparisons with a control. Biometrics, 20; 482-491.

TABLE 1. Summary of Antemortem Observations

	00539-08 (mg/kg/day)									
	0 (Control)		10		50		100		250	
	No.	%	No.	%	No.	%	No.	%	No.	%
Number of animals observed:	5	-	5	-	5	-	5	-	5	-
Antemortem Observations										
No overt signs of toxicity[a]:	5	100	5	100	5	100	5	100	5	100.0
Incidental Findings										
Eye abnormality:									1	20.0
Material around eye, black:									1	20.0

[a]Includes animals noted to have no overt signs of toxicity throughout the observation period, but may exhibit incidental findings

No. - Number

- - Not applicable

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TABLE 2. Summary of Body Weights and Body Weight Changes

Day of Study	Group Mean Body Weights (grams)									
	00539.08 (mg/kg/day)									
	0 (Control)		10		50		100		250	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0[b]	169	3.1	166	5.9	172	6.3	170	6.9	168	4.2
4	200	3.4	200	8.9	207	7.1	205	9.4	204	7.2
7	226	4.5	227	12.4	234	10.0	231	8.9	231	9.9
0	246	6.9	249	14.6	258	11.2	255	10.2	250	9.3
14	279	8.5	284	21.3	293	16.2	284	9.4	286	14.7

Day of Study	Group Mean Body Weight Changes (grams)[a]									
0[b] to 4	32	3.4	34	3.4	35	1.8	35	2.9	35	3.6
4 to 7	26	2.2	27	4.1	27	5.6	26	0.7	27	2.9
7 to 10	20	2.9	22	2.3	24	1.6	21	1.6	19	4.7
10 to 13	33	2.0	36	6.7	35	5.5	31	4.2	35	5.7
0[b] to 14	110	9.2	118	16.5	121	10.0	113	4.0	117	12.1

[a]Values represent the mean of the individual changes in body weight for these intervals
[b]Day prior to initiation of dosing
S.D. - Standard deviation
Values of the treated groups were not significantly different from those of the control group; p>0.05

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TABLE 3. Summary of Food Consumption Values

Week of Study	G0539.03 (mg/kg/day)																			
	0 (Control)				10				50				100				250			
	g/rat/day		g/kg/day		g/rat/day		g/kg/day		g/rat/day		g/kg/day		g/rat/day		g/kg/day		g/rat/day		g/kg/day	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1	21.8	0.57	96.5	2.06	21.9	1.52	96.5	3.78	21.8	2.70	93.1	8.84	22.0	1.09	95.2	1.64	22.2	1.50	96.3	4.31
2	24.2	0.94	86.6	1.85	25.2	2.38	88.8	5.26	26.3	1.51	89.7	3.16	25.3	1.07	89.1	1.82	25.8	2.46	90.2	5.80

S.D. - Standard deviation

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TABLE 4. Summary of Hematological Values

Parameters Measured	DAY OF STUDY	GD539.03 (mg/kg/day) 0 (Control) MEAN	S.D.	N	10 MEAN	S.D.	N	50 MEAN	S.D.	N
Leukocytes	Pretest	11.8	1.73	5	10.5	1.53	5	9.7	1.22	5
$\times 10^3$/cmm	14	15.8	2.83	5	14.2	2.92	5	12.1	2.06	5
Erythrocytes	Pretest	4.99	0.149	5	5.02	0.244	5	5.06	0.276	5
$\times 10^6$/cmm	14	6.02	0.239	5	6.03	0.417	5	6.02	0.321	5
Hemoglobin	Pretest	12.4	0.54	5	12.2	0.51	5	12.6	0.75	5
g/dl	14	14.7	0.61	5	14.6	0.63	5	14.6	0.65	5
Hematocrit	Pretest	37.3	0.98	5	37.2	1.62	5	37.8	1.73	5
%	14	44.7	1.66	5	44.6	2.37	5	44.8	1.96	5
MCV	Pretest	75	1.1	5	74	0.8	5	75	1.1	5
microns	14	74	0.8	5	74	1.2	5	74	1.1	5
MCH	Pretest	24.9	0.95	5	24.4	0.39	5	24.9	0.57	5
pg	14	24.5	0.53	5	24.2	0.68	5	24.2	0.54	5
MCHC	Pretest	33.3	0.78	5	32.9	0.26	5	33.3	0.62	5
g/dl	14	32.9	0.56	5	32.6	0.46	5	32.5	0.43	5
Platelets	Pretest	606	125.6	5	540	50.1	5	559	23.5	5
$\times 10^3$/cmm	14	554	92.6	5	515	18.8	5	544	26.3	5

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S.D. - Standard Deviation
N Number of Animals

TABLE 4. Cont.

Summary of Hematological Values

Parameters Measured	DAY OF STUDY	G0539.03 (mg/kg/day) 100 MEAN	S.D.	N	250 MEAN	S.D.	N
Leukocytes	Pretest	11.3	1.43	5	10.9	3.05	5
$\times 10^3$/cmm	14	14.5	1.94	5	12.6	2.25	5
Erythrocytes	Pretest	4.87	0.063	5	4.82	0.229	5
$\times 10^6$/cmm	14	5.97	0.307	5	5.56	0.191	5
Hemoglobin	Pretest	12.3	0.37	5	12.1	0.33	5
g/dl	14	14.5	0.47	5	13.1	1.34	5
Hematocrit	Pretest	36.9	0.63	5	36.4	1.22	5
%	14	44.5	1.77	5	40.9	2.72	5
MCV	Pretest	76	1.1	5	75	1.7	5
microns[1]	14	74	1.1	5	74	2.6	5
MCH	Pretest	25.2	0.80	5	25.1	1.05	5
pg	14	24.3	0.58	5	23.6	1.74	5
MCHC	Pretest	33.2	0.77	5	33.2	0.75	5
g/dl	14	32.6	0.36	5	32.0	1.24	5
Platelets	Pretest	491	84.3	5	598	111.5	5
$\times 10^3$/cmm	14	488	62.2	5	610	94.3	5

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S.D. - Standard Deviation
N - Number of Animals

TABLE 4. Cont.

Summary of Hematological Values

Parameters Measured	DAY OF STUDY	0 (Control) MEAN	0 (Control) S.D.	0 (Control) N	G0539.03 (mg/kg/day) 1D MEAN	1D S.D.	1D N	5D MEAN	5D S.D.	5D N
Segmented Neutrophils $\times 10^3$/cmm	Pretest	2.4	0.85	5	2.0	0.58	5	2.2	0.62	5
	14	2.0	0.65	5	2.6	2.15	5	2.0	0.75	5
Lymphocytes $\times 10^3$/cmm	Pretest	8.7	1.05	5	7.9	1.61	5	7.0	1.19	5
	14	13.7	2.51	5	11.3	1.39	5	9.9	2.24	5

191-1394

S.D. Standard Deviation
N Number of Animals

TABLE 4. Cont.

Summary of Hematological Values

Parameters Measured	DAY OF STUDY	G0539.03 (mg/kg/day) 100 MEAN	100 S.D.	100 N	250 MEAN	250 S.D.	250 N
Segmented Neutrophils $x10^3$/cmm	Pretest	2.0	0.70	5	1.8	0.83	5
	14	1.9	0.49	5	3.6	1.78	5
Lymphocytes $x10^3$/cmm	Pretest	8.8	1.03	5	8.5	3.40	5
	14	12.4	1.86	5	9.1	2.07	5

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S.D. - Standard Deviation
N - Number of Animals

TABLE 4. Cont.

Summary of Hematological Values
Change from Baseline Day 0 vs Day 14

Parameters Measured	0 (Control) MEAN	0 (Control) S.D.	0 (Control) N	CO539.03 (mg/kg/day) 10 MEAN	10 S.D.	10 N	50 MEAN	50 S.D.	50 N
Leukocyte $\times 10^3$/cmm	4.0	1.22	5	3.6	2.68	5	2.4	0.90	5
Erythrocytes $\times 10^6$/cmm	1.03	0.169	5	1.01	0.233	5	0.96	0.227	5
Hemoglobin g/dl	2.3	0.66	5	2.3	0.35	5	2.0	0.70	5
Hematocrit %	7.4	1.61	5	7.5	1.30	5	7.0	1.60	5
MCV microns^3	0	0.9	5	0	1.3	5	0	0.5	5
MCH pg	-0.4	0.64	5	-0.1	0.60	5	-0.7	0.59	5
MCHC g/dl	-0.3	0.47	5	-0.2	0.53	5	-0.8	0.66	5
Platelets $\times 10^3$/cmm	-52	52.1	5	-25	41.8	5	-16	32.7	5

191.1994

S.D. - Standard Deviation
N - Number of Animals

Values of the treated groups were not significantly different from those of the control group; p>0.05

TABLE 6. Cont.

Summary of Hematological Values
Change from Baseline Day 0 vs Day 14

Parameters Measured	GD539.03 (mg/kg/day) 100 MEAN	100 S.D.	100 N	250 MEAN	250 S.D.	250 N
Leukocytes $\times 10^3$/cmm	3.2	1.88	5	1.7	2.77	5
Erythrocytes $\times 10^6$/cmm	1.10	0.317	5	0.73	0.353	5
Hemoglobin g/dl	2.2	0.67	5	1.0	1.39	5
Hematocrit %	7.6	2.20	5	4.5	3.51	5
MCV microns^3	-1	1.3	5	2	2.2	5
MCH pg	-0.9	0.90	5	-1.6	1.28	5
MCHC g/dl	-0.6	0.87	5	1.3	0.84	5
Platelets $\times 10^3$/cmm	-3	97.4	5	12	86.7	5

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S.D. Standard Deviation
N Number of Animals

Values of the treated groups were not significantly different from those of the control group; p>0.05

TABLE 4. Cont.

Summary of Hematological Values
Change from Baseline Day 0 vs Day 14
G0539.03 (mg/kg/day)

Parameters Measured	0 (Control) MEAN	0 (Control) S.D.	0 (Control) N	10 MEAN	10 S.D.	10 N	50 MEAN	50 S.D.	50 N
Segmented Neutrophils $\times 10^3$/cmm	-0.4	1.00	5	0.6	2.05	5	-0.1	1.12	5
Lymphocytes $\times 10^3$/cmm	5.0	1.82	5	3.3	0.83	5	2.4	1.26	5

[91-1304

S.D. - Standard Deviation
N - Number of Animals

Values of the treated groups were not significantly different from those of the control group; p>0.05

TABLE 4. Cont.

Summary of Hematological Values
Change from Baseline Day 0 vs Day 14
G0539.01 (mg/kg/day)

Parameters Measured	100 MEAN	100 S.D.	100 N	250 MEAN	250 S.D.	250 N
Segmented Neutrophils $x10^3$/cmm	-0.1	1.08	5	1.2	1.91	5
Lymphocytes $x10^3$/cmm	3.7	1.91	5	0.9**	2.72	5

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S.D. - Standard Deviation
N - Number of Animals

**Significantly different from the Control group; p<0.01

APPENDIX A

Quality Assurance Inspections

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Quality Assurance Inspections

Dates of Inspections	Dates of Reports to Management	Dates of Reports to Study Director
2-29-88	3-03-88	3-03-88
3-03-88	3-07-88	3-07-88
3-04-88	3-21-88	3-21-88
3-07-88	6-01-88	6-01-88
3-14-88		
3-17-88		
3-21-88		
5-18-88		
6-01-88		

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APPENDIX B

Individual Experimental Data

Individual Antemortem Observations

Test Article, Dosage Level, Animal Number	Study Day Predose	Study Day Postdose	Antemortem Observations	Day of Sacrifice
0 mg/kg/day (Control):				
43976	1-14	1-14	No overt signs of toxicity	14
43977	1-14	1-14	No overt signs of toxicity	14
43978	1-14	1-14	No overt signs of toxicity	14
43979	1-14	1-14	No overt signs of toxicity	14
43980	1-14	1-14	No overt signs of toxicity	14
G0539.01 10 mg/kg/day:				
43981	1-14	1-14	No overt signs of toxicity	14
43982	1-14	1-14	No overt signs of toxicity	14
43983	1-14	1-14	No overt signs of toxicity	14
43984	1-14	1-14	No overt signs of toxicity	14
43985	1-14	1-14	No overt signs of toxicity	14

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Individual Antemortem Observations

Test Article, Dosage Level, Animal Number	Study Day Predose	Study Day Postdose	Antemortem Observations	Day of Sacrifice
G0539.03 50 mg/kg/day:				
43986	1-14	1-14	No overt signs of toxicity	14
43987	1-14	1-14	No overt signs of toxicity	14
43988	1-14	1-14	No overt signs of toxicity	14
43989	1-14	1-14	No overt signs of toxicity	14
43990	1-14	1-14	No overt signs of toxicity	14
G0539.03 100 mg/kg/day:				
43991	1-14	1-14	No overt signs of toxicity	14
43992	1-14	1-14	No overt signs of toxicity	14
43993	1-14	1-14	No overt signs of toxicity	14
43994	1-14	1-14	No overt signs of toxicity	14
43995	1-14	1-14	No overt signs of toxicity	14

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Individual Antemortem Observations

Test Article, Dosage Level, Animal Number	Study Day: Predose	Study Day: Postdose	Antemortem Observations	Day of Sacrifice
G0539.03				
250 mg/kg/day:				
43996	1-14	1-14	No overt signs of toxicity	14
43997	1-14	1-14	No overt signs of toxicity	14
	2-14	2-14	Eye abnormality, right eye	
43998	1-14	1-14	No overt signs of toxicity	14
43999	1-14	1-14	No overt signs of toxicity	14
44000	1-14	1-14	No overt signs of toxicity	14
	10-13	10-13	Material around left eye, black	

Individual Body Weights (grams)

Test Article, Dosage Level, Animal Number	Study Day 0[a]	4	7	10	14
0 mg/kg/day (Control):					
43976	171	206	234	258	293
43977	166	199	226	244	273
43978	174	200	223	240	272
43979	168	200	224	243	274
43980	165	197	224	246	281
G0539.03 10 mg/kg/day:					
43981	172	206	234	256	295
43982	160	189	209	227	253
43983	169	204	232	255	291
43984	160	192	220	241	274
43985	171	209	240	264	308
G0539.03 50 mg/kg/day:					
43986	171	208	234	257	287
43987	178	212	245	270	312
43988	167	200	225	250	280
43989	178	215	243	269	308
43990	164	199	223	245	277
G0539.03 100 mg/kg/day:					
43991	176	213	238	261	296
43992	173	209	235	255	287
43993	160	193	220	240	272
43994	176	214	240	263	287
43995	167	198	224	244	277
G0539.03 250 mg/kg/day:					
43996	172	211	242	261	305
43997	161	192	216	240	270
43998	169	206	233	245	279
43999	170	202	227	246	277
44000	169	207	236	259	297

[a]Day prior to initiation of dosing

Individual Food Consumption (grams)

Test Article, Dosage Level, Animal Number	Week of Study 1	Week of Study 2
0 mg/kg/day (Control):		
43976	157	177
43977	152	163
43978	149	162
43979	157	170
43980	149	174
G0539.03 10 mg/kg/day:		
43981	156	180
43982	137	150
43983	151	173
43984	157	187
43985	166	193
G0539.03 50 mg/kg/day:		
43986	156	172
43987	165	194
43988	153	175
43989	169	195
43990	121	183
G0539.03 100 mg/kg/day:		
43991	162	187
43992	159	174
43993	145	167
43994	158	181
43995	147	176
G0539.03 250 mg/kg/day:		
43996	161	192
43997	146	173
43998	153	159
43999	147	175
44000	171	203

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Individual Daily Total Volume of Test Material Administered

Test Article, Dosage Level, Animal Number	Volume of Test Material Administered (ml) Study Day 1-3	4-6	7-9	10-14
0 mg/kg/day (Control):				
43976	0.43	0.52	0.59	0.65
43977	0.42	0.50	0.57	0.61
43978	0.44	0.50	0.56	0.60
43979	0.42	0.50	0.56	0.61
43980	0.41	0.49	0.56	0.62
G0539.03 10 mg/kg/day:				
43981	0.43	0.52	0.59	0.64
43982	0.40	0.47	0.52	0.57
43983	0.42	0.51	0.58	0.64
43984	0.40	0.48	0.55	0.60
43985	0.43	0.52	0.60	0.66
G0539.03 50 mg/kg/day:				
43986	0.43	0.52	0.59	0.64
43987	0.45	0.53	0.61	0.68
43988	0.42	0.50	0.56	0.63
43989	0.45	0.54	0.61	0.67
43990	0.41	0.50	0.56	0.61
G0539.03 100 mg/kg/day:				
43991	0.44	0.53	0.60	0.65
43992	0.43	0.52	0.59	0.64
43993	0.40	0.48	0.55	0.60
43994	0.44	0.54	0.60	0.66
43995	0.42	0.50	0.56	0.61
G0539.03 250 mg/kg/day:				
43996	0.43	0.53	0.61	0.65
43997	0.40	0.48	0.54	0.60
43998	0.42	0.52	0.58	0.61
43999	0.43	0.51	0.57	0.62
44000	0.42	0.52	0.59	0.65

191-1394

APPENDIX C

Individual Hematological Values

191-1394

Codes for Individual Hematological Values

A - Erythrocyte Appearance Grades:

0 - Within normal limits
1 - 5 - 25% cells affected
2 - 26 - 50% cells affected
3 - 51 - 75% cells affected
4 - 76 - 100% cells affected

Other Notations

WBC - White blood cell = Leukocyte
NRBC - Nucleated red blood cell
NS - None seen in 100 cell differential
NA - Not applicable

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Individual Hematological Values - Pretest

Group, Animal Number	Sex	Leucocytes $\times 10^3$ /cmm	Erythrocytes $\times 10^6$ /cmm	Hemoglobin g/dl	Hematocrit %	MCV microns^3	MCH pg	MCHC g/dl	Platelets $\times 10^3$ /cmm
0 MG/KG/DAY (VEHICLE CONTROL)									
43976	M	13.9	4.60	11.7	35.8	75	24.4	32.7	788
43977	M	13.4	5.07	12.4	37.7	74	24.5	32.9	510
43978	M	10.9	5.18	12.5	38.1	73	24.1	32.8	667
43979	M	10.8	4.91	12.3	36.9	75	25.1	33.3	586
43980	M	10.0	4.98	13.2	38.1	76	26.5	34.6	477
10 MG/KG/DAY									
43981	M	10.3	4.84	11.9	36.3	75	24.6	32.8	504
43982	M	10.3	5.26	12.6	38.8	74	24.0	32.5	571
43983	M	13.1	5.19	12.4	37.8	73	23.9	32.8	563
43984	M	9.0	5.12	12.7	38.2	75	24.8	33.2	471
43985	M	10.0	4.69	11.5	34.8	74	24.5	33.0	590
50 MG/KG/DAY									
43986	M	10.1	5.39	13.3	38.7	73	24.7	33.5	551
43987	M	9.0	4.72	11.6	35.7	76	24.6	32.5	537
43988	M	12.5	5.05	13.1	38.3	76	25.9	34.2	572
43989	M	8.1	4.88	12.0	36.2	74	24.6	33.1	536
43990	M	8.8	5.28	13.0	38.9	74	24.6	33.4	561
100 MG/KG/DAY									
43991	M	12.4	4.84	12.4	36.8	76	25.6	33.7	531
43992	M	9.5	4.47	11.5	33.2	74	23.8	32.0	363
43993	M	13.1	4.80	12.4	36.0	77	25.8	33.6	556
43994	M	10.9	4.86	12.4	36.6	75	25.5	33.9	544
43995	M	10.7	4.97	12.5	37.8	76	25.2	33.0	469
250 MG/KG/DAY									
43996	M	13.9	4.84	11.6	34.9	75	23.9	33.2	445
43997	M	8.3	5.05	12.4	37.5	74	24.6	33.1	658
43998	M	14.5	4.86	12.4	37.1	76	25.5	33.4	715
43999	M	8.8	5.03	12.0	37.3	74	23.9	32.2	651
44000	M	8.9	4.54	12.1	35.1	78	26.7	34.3	519

191-1394

Individual Hematological Values - Pretest

Group, Animal Number	Sex	Segmented Neutrophils $\times 10^3$ /cmm	Band Neutrophils $\times 10^3$ /cmm	Lymphocytes $\times 10^3$ /cmm	Eosinophils $\times 10^3$ /cmm	Monocytes $\times 10^3$ /cmm	Basophils $\times 10^3$ /cmm	Other Cells $\times 10^3$ /cmm
0 MG/KG/Day (VEHICLE CONTROL):								
43976	M	3.3	NS	9.7	0.1	0.7	NS	NS
43977	M	3.1	NS	9.0	0.1	0.4	NS	NS
43978	M	1.2	NS	8.5	0.2	1.0	NS	NS
43979	M	2.2	NS	8.0	0.1	0.5	NS	NS
43980	M	2.1	NS	7.4	NS	0.5	NS	NS
10 MG/KG/DAY:								
43981	M	1.1	NS	6.8	0.1	0.3	NS	NS
43982	M	2.3	NS	7.5	NS	0.5	NS	NS
43983	M	2.1	NS	10.2	NS	0.8	NS	NS
43984	M	1.7	NS	8.1	0.5	0.7	NS	NS
43985	M	2.6	NS	7.0	NS	0.4	NS	NS
50 MG/KG/DAY:								
43986	M	2.5	NS	7.1	0.2	0.3	NS	NS
43987	M	2.7	NS	6.1	NS	0.2	NS	NS
43988	M	2.6	NS	9.0	0.1	0.8	NS	NS
43989	M	1.3	NS	6.1	0.3	0.4	NS	NS
43990	M	1.7	NS	8.9	NS	0.3	NS	NS
100 MG/KG/DAY								
43991	M	2.0	NS	9.8	0.1	0.5	NS	NS
43992	M	1.3	NS	7.7	NS	0.5	NS	NS
43993	M	2.6	NS	9.7	0.1	0.5	NS	NS
43994	M	1.3	NS	9.0	0.1	0.4	NS	NS
43995	M	2.6	NS	7.7	NS	0.4	NS	NS
250 MG/KG/DAY:								
43996	M	1.6	NS	11.7	0.1	0.6	NS	NS
43997	M	1.2	NS	6.6	0.1	0.4	NS	NS
43998	M	1.0	NS	12.8	0.1	0.7	NS	NS
43999	M	2.0	NS	5.8	0.2	0.4	NS	NS
44000	M	2.9	NS	5.6	NS	0.4	NS	NS

191-1584

Individual Hematological Values - Protest

Test Article, Dosage Level, Animal Number	NRBC /100 WBC	Polychromasia[A]	Hypochromasia[A]	Poikilocytosis[A]	Anisocytosis[A]
0 MG/KG/DAY (CONTROL):					
43976	0	1	0	0	0
43977	0	1	0	0	0
43978	0	1	0	0	0
43979	0	1	0	0	0
43980	0	1	0	0	0
G0539.03 10 MG/KG/DAY:					
43981	0	1	0	0	0
43982	0	1	0	0	0
43983	0	1	0	0	0
43984	0	1	0	0	0
43985	0	1	0	0	0
G0539.03 20 MG/KG/DAY:					
43986	0	1	0	0	0
43987	0	1	0	0	0
43988	0	1	0	0	0
43989	0	1	0	0	0
43990	0	1	0	0	0
G0539.03 100 MG/KG/DAY:					
43991	0	0	0	0	0
43992	0	1	0	0	0
43993	0	1	0	0	0
43994	0	1	0	0	0
43995	0	1	0	0	0
G0539.03 250 MG/KG/DAY:					
43996	0	1	0	1	1
43997	0	1	0	0	0
43998	0	1	0	0	0
43999	0	1	0	0	0
44000	0	1	0	0	0

191-1394

Individual Hematological Values 14 Day

Group, Animal Number	Sex	Leukocytes $\times 10^3$ /cmm	Erythrocytes $\times 10^6$ /cmm	Hemoglobin g/dl	Hematocrit %	MCV microns^3	MCH pg	MCHC g/dl	Platelets $\times 10^3$ /cmm
0 MG/KG/DAY (VEHICLE CONTROL):									
43976	M	19.1	6.72	13.8	42.7	75	24.1	32.3	703
43977	M	18.7	6.22	14.9	40.0	74	24.0	37.4	513
43978	M	13.3	6.21	16.0	45.4	73	24.2	33.0	584
43979	M	14.6	6.14	15.4	46.3	75	25.1	33.3	488
43980	M	19.8	5.80	14.5	43.2	74	25.0	33.6	484
10 MG/KG/DAY:									
43981	M	13.8	5.58	14.0	41.9	75	25.1	33.4	485
43982	M	18.4	6.64	15.4	47.0	72	23.2	32.2	508
43983	M	15.6	6.14	14.9	45.5	74	24.3	32.7	514
43984	M	12.1	6.07	14.6	45.1	74	24.1	32.4	512
43985	M	11.0	5.70	13.9	42.8	75	24.4	32.5	546
50 MG/KG/DAY:									
43986	M	12.5	6.36	15.6	47.3	74	24.5	33.0	563
43987	M	10.8	6.86	14.4	44.7	75	24.2	32.2	575
43988	M	15.4	5.68	14.0	42.9	76	24.6	32.6	522
43989	M	11.7	5.78	14.1	42.8	74	24.5	32.9	513
43990	M	10.1	6.35	14.4	46.2	73	23.4	32.0	545
100 MG/KG/DAY									
43991	M	13.1	6.05	14.4	44.6	74	23.8	32.3	520
43992	M	14.7	5.99	14.5	44.8	75	24.7	32.4	516
43993	M	17.5	5.83	14.2	42.9	76	25.2	33.1	519
43994	M	14.8	6.43	15.3	47.2	73	23.8	32.4	508
43995	M	12.5	5.76	14.1	42.9	74	24.5	32.9	377
250 MG/KG/DAY:									
43996	M	15.1	5.75	14.2	43.2	75	24.7	32.9	546
43997	M	10.0	5.70	13.7	42.4	74	24.0	32.3	545
43998	M	12.9	5.48	13.9	41.0	75	24.1	32.4	689
43999	M	14.4	4.27	10.8	36.3	85	20.5	29.8	734
44000	M	10.9	5.58	13.6	41.8	75	24.4	32.5	535

191-1394

Individual Hematological Values - 14 Day

Group, Animal Number	Sex	Segmented Neutrophils $\times 10^3$ /cmm	Band Neutrophils $\times 10^3$ /cmm	Lymphocytes $\times 10^3$ /cmm	Eosinophils $\times 10^3$ /cmm	Monocytes $\times 10^3$ /cmm	Basophils $\times 10^3$ /cmm	Other Cells $\times 10^3$ /cmm
0 MG/KG/DAY (VEHICLE CONTROL):								
43976	M	2.1	NS	16.6	NS	0.4	NS	NS
43977	M	2.8	NS	15.9	NS	0.2	NS	NS
43978	M	2.5	NS	10.6	0.1	NS	NS	NS
43979	M	1.5	NS	12.8	0.1	0.1	NS	NS
43980	M	1.1	NS	12.5	NS	NS	NS	NS
10 MG/KG/DAY:								
43981	M	1.7	NS	11.9	0.3	NS	NS	NS
43982	M	6.4	NS	11.8	NS	0.4	NS	NS
43983	M	2.2	NS	13.0	0.4	0.2	NS	NS
43984	M	1.3	NS	10.4	0.1	0.2	NS	NS
43985	M	1.4	NS	8.4	0.1	0.1	NS	NS
50 MG/KG/DAY:								
43986	M	3.0	NS	9.4	0.1	NS	NS	NS
43987	M	1.5	NS	9.0	0.1	0.2	NS	NS
43988	M	1.4	NS	13.9	0.2	NS	NS	NS
43989	M	2.7	NS	8.0	NS	NS	NS	NS
43990	M	1.6	NS	8.4	0.1	NS	NS	NS
100 MG/KG/DAY:								
43991	M	2.4	NS	10.9	NS	0.3	NS	NS
43992	M	2.1	NS	12.6	NS	NS	NS	NS
43993	M	1.8	NS	15.4	0.2	0.2	NS	NS
43994	M	2.1	NS	12.4	NS	0.3	NS	NS
43995	M	1.1	NS	11.3	NS	0.1	NS	NS
200 MG/KG/DAY:								
43996	M	2.1	NS	12.4	0.5	0.3	NS	NS
43997	M	3.3	NS	6.7	NS	NS	NS	NS
43998	M	2.6	NS	9.5	0.7	NS	NS	NS
43999	M	6.8	NS	8.5	NS	NS	NS	NS
44000	M	1.2	NS	9.6	0.1	NS	NS	NS

191-1194

Individual Hematological Values - 14 Day

Test Article, Dosage Level, Animal Number	NRBC /100 WBC	Polychromasia[A]	Hypochromasia[A]	Poikilocytosis[A]	Anisocytosis[A]
0 MG/KG/DAY (CONTROL):					
43976	0	1	0	0	1
43977	0	1	0	0	1
43978	0	1	0	0	1
43979	0	1	0	0	1
43980	0	1	0	0	1
G0539.01 10 MG/KG/DAY:					
43981	0	1	0	0	1
43982	0	1	0	0	1
43983	0	1	0	0	1
43984	0	1	0	0	1
43985	0	1	0	0	1
G0539.03 50 MG/KG/DAY:					
43986	0	1	0	0	1
43987	0	1	0	0	1
43988	0	1	0	0	1
43989	0	1	0	0	1
43990	0	1	0	0	1
G0539.03 100 MG/KG/DAY:					
43991	0	1	0	0	1
43992	0	1	0	0	1
43993	0	1	0	0	1
43994	0	1	0	0	1
43995	0	1	0	0	1
G0539.03 250 MG/KG/DAY:					
43996	0	1	0	0	1
43997	0	1	0	0	1
43998	0	1	0	0	1
43999	0	1	0	0	1
44000	0	1	0	0	1

191-1394

Individual Hematological Values - Pretuse
Change from Baseline Day 0 vs Day 14

Group, Animal Number	Sex	Leucocytes $\times 10^3$ /cmm	Erythrocytes $\times 10^6$ /cmm	Hemoglobin g/dl	Hematocrit %	MCV microns^3	MCH pg	MCHC g/dl	Platelets $\times 10^3$ /cmm
0 MG/KG/DAY (VEHICLE CONTROL)									
43876	M	5.2	0.92	2.1	6.9	0	-0.1	-0.4	85
43877	M	5.9	1.15	2.5	8.3	0	-0.5	-0.5	3
43878	M	2.4	1.02	2.5	7.3	0	0.1	0.2	-83
43879	M	3.7	1.23	5.1	8.4	0	0.0	0.0	-100
43880	M	3.6	0.91	1.3	5.1	2	1.5	-1.0	1
10 MG/KG/DAY									
43981	M	3.6	0.74	2.1	5.6	3	0.5	0.6	9
43982	M	8.1	1.50	2.8	9.1	2	0.8	-0.3	-63
43983	M	2.4	0.95	2.5	7.7	1	0.4	-0.1	-49
43984	M	3.1	0.95	1.0	6.9	1	-0.7	-0.8	41
43985	M	1.0	1.01	2.4	8.0	1	-0.1	-0.5	44
50 MG/KG/DAY									
43986	M	2.4	0.97	2.3	7.6	0	-0.2	-0.5	-28
43987	M	1.8	1.24	2.6	9.0	1	-0.4	-0.3	58
43988	M	2.9	0.63	0.9	4.8	0	1.3	+1.6	-50
43989	M	3.8	0.88	2.1	6.7	0	-0.1	-0.2	-23
43990	M	1.3	1.07	1.8	7.3	-1	-1.3	-1.4	116
100 MG/KG/DAY									
43991	M	0.7	1.21	2.0	7.8	2	1.8	1.4	-11
43992	M	5.2	1.12	2.9	8.6	1	0.4	0.4	163
43993	M	4.4	0.83	1.8	8.0	-1	0.6	-0.5	-39
43994	M	3.9	1.57	2.9	10.6	-2	1.7	+1.5	-30
43995	M	1.0	0.79	1.6	5.0	-2	-0.7	-0.1	-92
250 MG/KG/DAY									
43996	M	1.4	1.11	2.6	8.3	0	1.3	-0.3	101
43997	M	1.7	0.85	1.3	4.9	0	-0.6	-0.8	113
43998	M	-2.2	0.62	0.9	3.9	1	-1.2	-1.0	-26
43999	M	6.6	0.24	-1.2	-1.0	-5	3.4	+7.4	81
44000	M	2.0	1.04	1.5	6.5	-3	-2.3	-1.8	16

191-1394

Individual Hematological Values Pretest
Change from baseline Day 0 vs Day 14

Group, Animal Number	Sex	Segmented Neutrophils $\times 10^3$ /cmm	Band Neutrophils $\times 10^3$ /cmm	Lymphocytes $\times 10^3$ /cmm	Eosinophils $\times 10^3$ /cmm	Monocytes $\times 10^3$ /cmm	Basophils $\times 10^3$ /cmm	Other Cells $\times 10^3$ /cmm
0 MG/KG/DAY (VEHICLE CONTROL).								
43976	M	-1.2	NA	6.9	NA	NA	NA	NA
43977	M	-0.6	NA	6.1	NA	NA	NA	NA
43978	M	1.3	NA	2.1	NA	NA	NA	NA
43979	M	-0.7	NA	4.8	NA	NA	NA	NA
43980	M	-1.0	NA	5.1	NA	NA	NA	NA
10 MG/KG/DAY.								
43981	M	0.8	NA	3.1	NA	NA	NA	NA
43982	M	4.1	NA	4.1	NA	NA	NA	NA
43983	M	0.1	NA	2.8	NA	NA	NA	NA
43984	M	-0.4	NA	4.9	NA	NA	NA	NA
43985	M	-1.2	NA	2.4	NA	NA	NA	NA
50 MG/KG/DAY:								
43986	M	0.5	NA	2.3	NA	NA	NA	NA
43987	M	-1.2	NA	2.9	NA	NA	NA	NA
43988	M	-1.2	NA	4.9	NA	NA	NA	NA
43989	M	1.4	NA	2.9	NA	NA	NA	NA
43990	M	0.1	NA	1.5	NA	NA	NA	NA
100 MG/KG/DAY.								
43991	M	0.4	NA	0.7	NA	NA	NA	NA
43992	M	0.8	NA	4.9	NA	NA	NA	NA
43993	M	-1.0	NA	5.7	NA	NA	NA	NA
43994	M	0.8	NA	3.4	NA	NA	NA	NA
43995	M	-1.5	NA	3.6	NA	NA	NA	NA
250 MG/KG/DAY.								
43996	M	0.6	NA	0.7	NA	NA	NA	NA
43997	M	2.1	NA	0.1	NA	NA	NA	NA
43998	M	1.6	NA	-3.1	NA	NA	NA	NA
43999	M	3.4	NA	2.7	NA	NA	NA	NA
44000	M	1.7	NA	-.0	NA	NA	NA	NA

191-1380

APPENDIX D

Historical Control Data

Individual studies have been subjected to Quality Assurance audit; the following historical compilation of data has not.

International Research & Development Corporation

CONTROL HEMATOLOGICAL VALUES

Rats (0-3 Months of Age

Test Name	Units	Male Mean	Male 2 S.D.	Male N	Female Mean	Female 2 S.D.	Female N
Leukocytes	$X10^3$ cmm	8.5	2.6-14.6	335	[illegible]	2.4-11.[illegible]	[illegible]
Erythrocytes	$X10^6$ cmm	6.06	3.06-8.4[illegible]	326	5.[illegible]	3.8[illegible]-6.29	[illegible]
Hemoglobin	g of [illegible]	13.8	8.5-19.1	342	13.9	9.0-19.7	352
Hematocrit	%	4[illegible].8	25.9-62.[illegible]	346	41.[illegible]	29.8-52.[illegible]	[illegible]
MCV	μ^3	68	56-80	345	68	[illegible]	[illegible]
MCH	$\mu\mu g$	23	19-27	346	23	19-27	[illegible]
MCHC	g/dl	34	27-40	345	34	27-40	351
Reticulocytes	/100 RBC	12.5	0.0-30.0	236	11.4	0.0-27.2	229
Platelet	$X10^3$/cmm	983	585-1381	346	1027	724-1331	351
Seg Neutrophils	/100 WBC	15	2-28	340	14	3-26	3[illegible]9
Band Neutrophils	/100 WBC	1	0-2	359	0	0-2	366
Lymphocyte	/100 WBC	81	68-95	335	82	70-94	34[illegible]
Eosinophils	/100 WBC	1	0-3	408	1	0-3	41[illegible]
Monocytes	/100 WBC	2	0-5	311	2	0-5	34[illegible]
Basophils	/100 WBC	0	0-0	35[illegible]	0	0-0	36[illegible]

191-1394

APPENDIX E

Protocol and Protocol Addenda

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

(TSIN# G0539.03)

Protocol Sheet No. 1 Study No. 191-1394 (IRDP BT0764S)

TITLE: 14-DAY RANGE-FINDING STUDY IN RATS

ITEM	JUSTIFICATION
1	Test article identification.
2	Addition of authorization letter to protocol.
3	Study initiation.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	The test article is identified as IRDC No. 9542.
2	Letter is appended to protocol as Appendix 3.
3	Conduct study in accordance with attached protocol.

Study Director Dr. Kit A. Keller

Signature 2/15/88
Date

IR90-49-5

Protocol

14-Day Range Finding Study in Rats

Test Substance Identification Number (TSIN) 6053903

Divisional Request Document (DRD) Number 8Y07645

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: International Research and Development Corporation
Kalamazoo, Michigan

Study Number: 191-1394

Purpose: To establish doses that will be used in a subsequent study to determine the effect of the test substance on the fertility of rats.

Study Duration: About 4 weeks

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

Test Substance:

TSIN:	DRD Number:	Description: Color	Physical Form	Expiration Date
60539.03	BY07645	White	Powder	Feb 1989

Purity (% Active):

nominally 100%

Storage Conditions: (Check One)

[ ] Room temperature [ ] Refrigerator [ ] Freezer

[X] Other Ambient (50°F-90°F)

Hazards: (Check One)

[ ] None known. Take ordinary precautions in handling.

[X] Other. Specify Irritant.

Special Instructions: (Check One)

[ ] None

[X] Avoid undue skin & eye contact. For skin contact, flush with water. For eye contact, flush properly and thoroughly with water.

Route of Administration of Test Substance and Reason for Choice: The oral route has been chosen to maximize systemic exposure. The anticipated route of exposure in humans is dermal.

Test System:	
Species	Rat
Strain	Sprague-Dawley, CDRS^{R} CD^{R}
Source	Charles River Breeding Laboratories, Portage, Michigan, or other source approved by Testing Facility and Sponsor.
Justification for Selection of Test System:	The rat is one rodent commonly used for the evaluation of teratogenicity and is acceptable in the guidelines of the FDA, EPA, and OECD.
Age and Weight:	Males 35-40 days old at start of study (dosing) weighing 130-170 g.
Housing:	Individually in suspended SS wire-mesh cages. Fluorescent lighting will provide illumination 12 hours per day. The lighting cycle will be maintained so that dosing occurs at least 6 hours after illumination of the housing area.
Quarantine:	Minimum of 5 days.
Identification:	Metal ear tags.
Animal Care:	Follow the approved Standard Operating Procedures of the Test Facility.
Diet:	A single lot of Purina Rodent Chow #5001, or other source approved by Sponsor and Study Director and water from a municipal water supply will be available *ad libitum*.
Diet and Water Analysis:	[X] None. There are no known contaminants expected which would interfere with the study. [ ] As follows: _____
Animal Groups and Dose Levels:	The study will consist of 4 test groups and 1 control group, each consisting of 5 males. Because of the possible elimination of animals after the initial blood exam and because of the body weight criteria, thirty rats will be ordered to begin the acclimation period. The control group will receive the vehicle on a comparable regimen. Individual dosages will be based on the most recent body weights. All animals, if treated by gavage, will be dosed at a constant volume, e.g. 2.5 ml/kg at weight, unless other specific instructions are supplied.

Dose Preparation:

Test Groups: (Check appropriate box)

[ ] Dose test substance undiluted

[ ] Dose as a _____% (w/v) solution/suspension of test substance in _____

[ ] Dose as a _____% (w/v) solution/suspension of test substance in _____

[X] Dose per special instructions in Appendix I and II.

Precise Requirements and Group Assignments:

Animal conditioning and Selection

Upon receipt, the animals will be inspected for disease and if accepted for the study will be housed individually and fed Purina Chow or feed described previously and water ad libitum during acclimation. The animals will be observed daily for any overt signs of disease and will be given a detailed physical examination just prior to study initiation. All animals with evidence of disease or other abnormalities will be discarded following the approved Standard Operating Procedures of the Test Facility.

Observations:

Prior to test substance administration, the rats will be observed daily for mortality and overt changes in appearance and behavior.

Hematology:

Five days after receipt of animals, blood samples will be collected into collection tubes containing EDTA anti-coagulant, following the approved Standard Operating Procedures of the Test Facility. The method used will be specified. Hemoglobin, hematocrit, white blood cell count, red blood cell count, mean corpuscular hemoglobin concentration, platelet count, and differential white blood cell count will be determined. Those animals judged to have an abnormal hemogram as defined by the Standard Operating Procedures of the Test Facility will be eliminated. Dosing will be started within seven (7) days of the baseline blood collections.

Test Substance Administration:

The test substance will be administered orally daily for 14 consecutive days. [X] Administer by gavage. [ ] Administer in the diet. [X] Other _____ Dose at least six hours after illumination of the housing area _____.

DOSE AT: 10, 50, 100, and 150 mg/kg/day.
See Instructions Appendix I and II.

Observations and Measurements:

Daily Observations	The animals will be observed twice daily for mortality and clinical signs of toxicity during the treatment period.
Body Weights	Body weights will be recorded at initiation, day 4, day 7, day 10, and day 14.
Hematology	On day 14 obtain and analyze blood samples as described in the pretreatment hematology screening (page 4).
Food Consumption	The food consumed will be measured once each week.
Deaths	Animals that die on the test will be discarded. All animals surviving at Day 14 will be sacrificed and discarded.
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 reason for it, should be documented in writing and signed by both the Study Director and the Sponsor's Divisional Toxicologist. This document is then to be attached to the protocol as an addendum.
Report	Report dates of study initiation and termination, deaths, body weights, gross abnormalities, clinical observations and hematological results. Statistically analyze the final body weights, body weight gains, and the changes from baseline for hemoglobin, hematocrit, total white blood cell count, red blood cell count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration values. Compare each test group to the control group. This report shall conform to all requirements outlined in Section 58.185, Subpart J, Good Laboratory Practices Regulations.

Sponsor: The Procter & Gamble Co., Cincinnati, Ohio

Date Approved by Sponsor's Divisional Toxicologist: G. S. Allgood, Ph.D. 2/4/88

Proposed Start Date: March 4, 1988
Defined as Beginning of Range-Finding Study - 1st Treatment Day

Proposed Completion Date: March 17, 1988
Defined as Last Day of Treatment and Sacrifice

Proposed Report Date: June 10, 1988
Defined as

Study Director: Kit A. Keller, Ph.D.
Date: Feb. 15, 1988

Protocol - Appendix I

Instructions for the Preparation and Handling of Test Substance - Vehicle Mixtures

1. Test substance - Vehicle mixture should be prepared:

   [ ] Daily [X] Weekly [X] See instructions below.

   Storage: [X] Room temperature [ ] Refrigerator [ ] Other

2. Mixtures that are not true solutions should be mixed with the use of a magnetic stirring bar during dosing procedures. Mixtures involving the diet, give special instructions below.

3. A homogeneity determination [X] will [ ] will not be required. If a homogeneity determination is required, sample the mixtures from the top, middle, and bottom of the mixing container, and return samples, appropriately labelled, to the Divisional Toxicologist. Amount of each sample 20 ml.

   A concentration and/or stability analysis of the mixture [X] will ~~not~~ be required. If required, amount of sample is 20 ml. Return parent material and dosing solutions to sponsor for analysis.

4. Shipping Instructions:

   Ship: [X] ambient temperature [ ] frozen [ ] other _____.

   Ship to: Sponsor

5. Special Instructions:

   Dosage Levels

Number	Dosage mg/kg/day	Dosing Suspension Conc. mg/ml	Dose Volume ml/kg
1	(vehicle control)	0	2.5
2	10	4.0	2.5
3	50	20.0	2.5
4	100	40.0	2.5
5	250	100.0	2.5

Protocol - Appendix II

Dosing Suspension Preparation Instructions

Note: These procedures provide instructions for the preparation of 100 grams of dosing suspensions. The procedures may be scaled up to produce larger quantities of dosing suspensions if necessary. Dosing suspension should be prepared weekly.

1. Prepare an appropriate volume of a solution of 1.0% (w/v) Methylcellulose (USP/FCC grade, 4000 cps) in deionized, distilled water.

2. Add the appropriate amount of the test substance (see below) in 5.0 grams of Polyethylene Glycol 400 (Carbowax PEG 400, NF). The PEG can be warmed to approximately 37 degrees Centigrade to improve the solubility of PEG.

3. Add the PEG solution slowly (under agitation) to the appropriate amount of the Methylcellulose solution (see below) to prepare 100 grams of the final dosing suspension.

Dosing Suspension Concentration (mg/ml)	Test Substance (grams) Added to PEG	PEG 400 (grams)	1% Methylcellulose Solution Needed to Make 100 Grams of Final Dosing Suspension
Placebo Vehicle	0	5.0	95.0
4 mg/ml	0.4	5.0	94.6
20 mg/ml	2.0	5.0	93.0
40 mg/ml	4.0	5.0	91.0
100 mg/ml	10.0	5.0	85.0

4. Sonicate the dosing suspension for approximately 90 seconds.

5. Adjust the pH of the dosing suspension to 7.0 using 1M citric acid.

6. Sonicate the dosing suspensions at the beginning of each day prior to commencement of dosing. Agitate the dosing suspension gently during the dosing procedures with a magnetic stir bar/stirrer.

Note: The components of the PEG:methylcellulose vehicle may be conveniently ordered through Fisher Scientific.

Methylcellulose (4000 centipoise)	Fisher Catalog #M-352-500
Carbowax PEG 400	Fisher Catalog #P-167-1

1/6/88
VAB/01/8

THE PROCTER & GAMBLE COMPANY
MIAMI VALLEY LABORATORIES
P.O. BOX [illegible], CINCINNATI, OHIO [illegible]

February 10, 1988

RECEIVED
TMC
FEB 12 1988
INTERNATIONAL RESEARCH and DEVELOPMENT CORPORATION

Mr. J. L. Schardein
International Research &
Development Corporation
500 North Main St.
Mattawan, Michigan 49071

Dear Mr. Schardein:

This is to authorize you to carry out the following study according to the attached protocol, and in conformance with the stipulations of our current Laboratory Services Agreement.

Notice: 1) This study is expected to be submitted to the following regulatory agency: Food and Drug Administration. The study should be listed on the Test Facility's master list of regulated studies. The stipulations of the protocol are to be implemented in complete conformance with the appropriate regulations [FDA Good Laboratory Practice Regulations (21 CFR, Part 58) or EPA GLP Regulations (40 CFR, Part 792)].

2) Quality Assurance Inspections:

All critical phases and the final report will be inspected. The critical phases may be defined by the QAU and Study Director.

3) Documentation of the derivation, characterization, and stability testing of the test substance will be the responsibility of the Sponsor.

4) The test substance is to be used for research and development purposes only.

Test: 14-Day Range Finding Study in Rats
Protocol No: Special Protocol dated 2/4/88
Test Substance No: 00539.03 Doc. Req. No.: BT07643
Physical Form: Powder

THE PROCTER & GAMBLE COMPANY

Mr. J. L. Schardein
International Research &
Development Corporation
February 10, 1989
Page 2

Matters involving the scientific aspects of the work can be handled direc.ly with the Sponsor's Divisional Toxicologist. All unused samples are to be returned to the Divisional Toxicologist at the following address (the cost of shipment should be included in the study cost). The cost of this study will be shared equally by two P&G Divisions. Please send separate invoices to:

Dr. Greg Allgood Tele. (513) 530-4098
The Procter & Gamble Company
11511 Reed Hartman Highway-Rm. HB2D39
Cincinnati, Ohio 45241

Dr. Gerald Haase
R&D Labs
Richardson-Vicks
Rusham Park
White Hall Lane
Egham, Surrey
TW20-9NQ, England

The Richardson-Vicks invoice should reference budget code 740-510-01D-8.

Complete both copies of the attached protocol by adding your study number, proposed start and completion dates, study cost and have the Study Director sign and date them. The Study Director should define the start and completion dates on the protocol. Retain one copy and return one copy to me, along with a letter stating that you agree to do the work specified in the attached protocol. Three copies of the draft report are needed as soon as possible, and are to be sent to my attention at the address shown on the letterhead. Also, complete the attached animal accounting form and return it with the final report.

The invoice for this study should be sent to:

Mr. Jim Matthews
The Procter & Gamble Company
11511 Reed Hartman Highway - Room HB2D31
Cincinnati, Ohio 45241

Sincerely,

THE PROCTER & GAMBLE COMPANY
Research & Development Department

G. A. Nixon
Human & Environmental Safety Division

Approved: R. E. Winters
R. E. Winters, Ph.D.
Director, Human & Environmental Safety Div.

st
cc: Study File
MVL OAU
G. S. Allgood
J. L. Schardein
Dr. Kellen Mr. Warster

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

(TSIN# G0539.03)

Protocol Sheet No. 2 Study No. 191-1394 (DRD# BY07643)

TITLE: 14-DAY RANGE-FINDING STUDY IN RATS

ITEM	JUSTIFICATION
1	Inclusion of animal randomization procedure.
2	Correction of study duration.
3	Clarification of animal weight range at start of study.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	Animal numbers and corresponding body weights will be entered onto magnetic tape which will be used as the data source for the randomization procedure. The mean body weight and standard deviation will be calculated by sex and a computer-generated edit will develop a listing of those animals whose body weights are within ±1.5 standard deviations of the mean. From the qualifying animals, the randomization procedure will select and assign the required number of animals. Bartlett's test for homogeneity of variances will be applied to the groups. If the groups are judged to be nonhomogeneous, new randomizations will be generated until homogeneity is established.
2	Page 1 of 8 Study Duration: about 2 weeks.
3	Page 3 of 8 Age and weight: actual weight range as documented in study records is 158 - 183 grams.

Study Director Dr. Kit A. Keller

Signature 3/09/88
Date

IR90-49-5

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

(TSIN# G0539.03)

Protocol Sheet No. 3 Study No. 191-1394 (IRD# BY0764B)

TITLE: 14-DAY RANGE-FINDING STUDY IN RATS

ITEM	JUSTIFICATION
1	Provision for use of 1N NaOH in test article preparation as necessary.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	1. Appendix II: 5. Adjust the pH of the dosing suspension to 7.0 using 1M citric acid or 1N NaOH as necessary.

Study Director Dr. Kit A. Keller

Signature 3/23/88
Date

IRSO-49-5

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

(TSIW# G0539.03)

Protocol Sheet No. 4 Study No. 191-1394 (DXD# BY07645)

TITLE: 14-DAY RANGE-FINDING STUDY IN RATS

ITEM	JUSTIFICATION
1	Provision for use of 1N NaOH in test article preparation as necessary (repeat of Protocol Sheet No. 2, but with inclusion of Sponsor signature block).

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	1. Appendix II: 5. Adjust the pH of the dosing suspension to 7.0 using 1M citric acid or 1N NaOH as necessary.

Approved By:

Dr. Greg Allgood 11/5/88
Date

Study Director Dr. Kit A. Keller

9/28/88
Signature Date

IR90-49-5

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL REVISION OR CLARIFICATION

(TSIN# G0539.03)

Protocol Sheet No. 5 Study No. 191-1394 (DRD# BYD7645)

TITLE: 14-DAY RANGE-FINDING STUDY IN RATS

ITEM	JUSTIFICATION
1	Inclusion of actual animal weight range at randomization.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	Animal weight range: 158-183 grams

Approved By:

G. S. Allgood 4/18/88

Sponsor's Representative Date

Gregory S Allgood, PhD

Study Director Dr. Kit A. Keller

Kit A. Keller 4/08/88

Signature Date

IR90-49-5

INTERDEPARTMENTAL CORRESPONDENCE

FROM: G. A. Nixon DATE: April 20, 1988

TO: Study File R/L: NON-DISCRETIONARY

SUBJECT: MONITORING VISIT

The following study was reviewed for data quality:

LABORATORY: IRDC

STUDY NO.: 191-1394

TSIN: G0539.03 - 14-Day Fertility Range Finding

DATE OF REVIEW: 3/21/88

REVIEWED BY: G. A. Nixon
G.A. Nixon 4/20/88

st

cc: Divisional Toxicologist - G. S. Allgood
F. E. Freeberg

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)

DRD: BYO 764/5

TSIN: 60539.03

Test Article (Product/Ingredient): Octopirox®

Physical Form: Solid

Color: Off-White

Storage Conditions:

X Room Temperature

__ Other

Brand Notebook Ref: HC-0479-15

pH: 8-10 (1% solution in water)

Expiration Date: ~~5/8/88~~ 2/89

Hazards: corrosive

Stability Testing is:

X Completed

__ In Progress

D.O.T. Hazard Classification: Non-hazardous/Not combustible

These chemicals/test articles have been checked against the TSCA inventory list. X Yes __ No

Formulated Composition

Component[a]	(C.A.S.)[b] (Number)	Target Nominal Component Level	Target Actual Component Level	Measured Component Level	Stock Code No.	Lot Number
Octopirox®	-	100	100	99.5	BX288	2

(a) Use chemical or CTFA names which uniquely identifies each component. Common, non-chemical names such as (Tergitol 15-5-0 or yellow dye #10) should be indicated in parentheses following the chemical name. Non-definitive identification (e.g., BC-Base, Arquad) is not acceptable.

(b) CAS numbers should be included whenever available. They are especially important for main components of the formulation.

VA1/005
8/87

DRD: BY [illegible]

TSIN: G0509.03

ANALYSIS

Date Submitted	Submitter Code Or Lab Notebook	Analysis	(X) *	Measured Value	Limits	Laboratory Testing Or Data Source
5/8/87	85149005 and 88025018	MCT	X	Pass	Pass	SWTC Micr
	85149005 88025017	Active Assay Active Assay		99.5% 99.5%	98.0-101.5% " "	SWTC Analy " "
	85149005 and 98025017	IR		Pass	Must match standard spectrum	SWTC Analy
	85149005 and 87127003	Appearance		Pass	Pass	GMP

* Analysis required by toxicologist or microbiologist

Approvals: The test substance as made and characterized is a representative example of the intended formulation. Making records for plant-made product are being/have been obtained and evaluated by Products Research.

Process Development: [illegible] 2/4/88 1/15/88
(Signature) (Date)

Products Research: _____
(Signature) (Date)

Acceptable Microbial Susceptibility: [illegible] 2/4/88 2/26/88
(Signature) (Date)

GMP Quality Assurance: [illegible] 2/4/88 2/2/88
(Signature) (Date)

(Attach batch records for GMP review)

_____ finished products will be retained by Quality Assurance
(# samples)

This substance has been appropriately characterized and is acceptable for testing outlined in the attached DRD.

Division Toxicologist: [illegible] 2/4/88 2/2/88
(Signature) (Date)

VAI/005
8/87

SAFETY SAMPLE ANALYSIS
(submit to Toxicology Office with completed protocols)

DRD #BY 07645TSIN G 053903 TOXICOLOGIST G.S Allgood

COMPOUND/FORMULA/PRODUCT NAME[a] Octoprox

ANTICIPATED RECEIPT DATES: FIRST SAMPLE 3/15/88 LAST SAMPLE 9/1/88
(To be completed by JVM upon study placement, then copies to Analytical, Toxicologist, and DRD file.)

To verify the identity of returned safety samples, the following analysis(es) should be run on returned parent material(s) and/or dosing preparation(s) (please check items #1 and #2 as appropriate). These analyses are in addition to weights obtained on all returned samples. Toxicologists are encouraged to discuss this analytical program with Analytical personnel before initiation.

[X] 1. Please perform whichever analysis(es) Analytical Section considers feasible to confirm correct concentration of parent active and/or correct dilution of dosing preparation submitted for analysis[b].

[X] 2. The following specific analysis(es) in addition to, or instead of, #1 is/are needed.

Analytical Sample Code	Analysis	Material to be Tested (Estimated Concentration) Parent Material[c]	Dosing Solution #	Submitted to Analytical (Initials/Date)	Results (Initials/Date)
	IR	Octoprox	Octoprox #1 (2-wk study)		
	IR	Octoprox	#2 (3-wk study)		
	~~IR~~		~~#3 (wk. 1)~~	MAK 2/4/88	
	~~IR~~		~~#4 (mid study)~~	MAK 2/4/88	
	~~IR~~		~~#5 (last wk.)~~	MAK 2/4/88	
* Also two homogeneity determinations will be needed on returned samples					

[a] For further description of mate. I contact J. V. Matthews at extension 2561.
[b] The Toxicology Office will discuss this with Analytical personnel per agreement with ~~H. J. Weiser~~ D. P. Hesof
[c] The test substance before dilution.

Toxicologist (initials):
Date:
Received by Tox. Office (initials):
Date:

GJ/03ALK/sc2

INTERDEPARTMENTAL CORRESPONDENCE

FROM: DATE:

TO: Operations Section R/L:

SUBJECT: MONCLINICAL STUDY REGULATORY STATUS

Notification pertaining to: ORD # 07645

TSIN 60539.03

1. The study described in the above protocol is to be considered:

   [X] Safety
   [ ] Regulated Safety
   [ ] Investigational

2. [X] The data is expected to be submitted to the following regulatory agency:

   [X] FDA
   [ ] EPA
   [ ] Other _____

   [ ] The data is not expected to be submitted to a regulatory agency (Boxes #4 and #5 below need not be checked)

3. [X] The test substance has been characterized and results are shown on the test substance characterization report (TSCR).

4. [X] The method of synthesis, fabrication, or derivation of the test related substances has been documented (required for regulated studies).

5. [X] Stability testing has been done or will be done on the test substance (required for regulated studies).

Sponsor's Divisional Toxicologist M.S. Allgood

Date: 2/3/88

bg: REGSTAT
10/23/86