

Report Title: Emetic Study in Beagle Dogs

Test Type: Supplemental Toxicity

Conducting Laboratory and Location: P&G Miami Valley Laboratories, Biological Testing Facility, Cincinnati, OH

Test Substance(s): E2501.01 – 0.3% Octopirox in hair conditioner

Species: Beagle Dogs

Test Conditions: Purebred beagle dog dosed by gastric intubation with a single dose of the undiluted test material. The first dosage tested was 16.0 ml/kg.

Results: ED50 for emesis was greater than 16.0 ml/kg. Could not go higher as volume limit would be exceeded. This test indicated that the conditioner with 0.3% OP is essentially non-emetic.

Study #: B85-6007

Report Date: 3/18/85

QA statement and GLP compliance: Yes

Accession #: 30487

SUMMARY REVIEW FOR P&G BTF NONCLINICAL SAFETY STUDIES

Test Substance: Head & Shoulders BC-3b DRD BYCR 0372
Type of Study: Emetic TSIN G0506.01
Sponsor's Div. Toxicologist C.W. Gardin Study # BB5-6007
Study Director D.K. Hysell Path Ref. N/A
Final Report Date: March 18, 1985 Notebook # YE-816

This report packet has been examined and is ready for Summary Review.

Study Director [Signature] Date 19 Mar 1985
Line Manager [Signature] Date 3/21/85
R&ES Pathobiology Section N/A Date _____

This report has been reviewed for scientific quality and is summarized as follows:

The ED₅₀ of G0506.01 was greater than 16.0 ml/kg. No emesis occurred at this dose level. G0506.01 is a very poor or essentially non-emetic as indicated by this test.

Div. Toxicologist [Signature] Date 4-17-85
James E. Weaver

When applicable, the retention limits for archived specimens are as follows:

Net Tissues _____ Teratology _____ Blood Mounts _____
Blocks _____ Mutagenicity _____
Slides _____ (Month/Year)

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

H&ES Divisional Liaison [Signature] Date 5/7/85
Study Director [Signature] Date 13 May 1985
D.K. Hysell

NOTE: Report should be returned to Line Manager only if major questions have been raised, or for information if revision has been made.

Return to QAU MVL [Signature] Date 5/14/85
Entered into SDRS [Signature] Date 5-17-85
Microfilming Completed _____ Date _____

Hard Copy to be Returned to: Sponsor's Divisional Toxicologist

All specimens (when applicable), raw data and final reports will be handled and stored at Procter & Gamble according to the procedures described in the Biological Safety Testing Standards.

6/1/83 Supersedes: Issue Dated 2/1/83
erb:HQAD

THE PROCTER & GAMBLE COMPANY
Miami Valley Laboratories
P.O. Box 39175
Cincinnati, Ohio 45247

EMETIC DOSE STUDY

885-6007

BYCR 0372

G0506.01

March 18, 1985

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THE PROCTER & GAMBLE COMPANY

MIAMI VALLEY LABORATORIES

P. O. BOX 19175
CINCINNATI, OHIO 45241

The following study was reviewed by the Quality Assurance Unit:

LABORATORY: The Procter & Gamble Company
BIF - Miami Valley Laboratories
P.O. Box 39175
Cincinnati, Ohio 45247

STUDY NUMBER: B85-6007

DIVISIONAL REQUEST DOCUMENT: BYCR 0372

TSIN: G0506.01

TYPE OF STUDY: Emetic

PORTION(S) OF STUDY REVIEWED:	REVIEWED BY:	DATE(S) OF REVIEW:	DATE(S) FINDINGS REPORTED TO STUDY DIRECTOR:
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Test Substance Handling	L.K. Klahm	2/21/85	2/21/85
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The protocol was reviewed for compliance to the GLP regulations.

Significant audit findings (if any) were reported to the Study Director and Facility Management immediately. All audit findings are reported to Management on a periodic basis.

The final study report was reviewed for inaccuracies and procedural compliance. The results reflect the raw data of the study.

NE. Gilman 3/18/85
Quality Assurance Unit Coordinator

The Procter & Gamble Company, Research and Development
Department Memorandum, H&EE Division

EMETIC DOSE STUDY (Dogs)

Report of a biological test performed
at MVL Laboratories
during the period 01-31-85
through 01-31-85 according to
the attached protocol

Divisional Safety Test

Request Number: BYCR 0372
Study Number: B85-6007
Test Substance
Identification Number: G0506.01
Sponsor's Divisional Toxicologist
C. W. Cardin

Raw Data Notebook: YE-816

Analysis Results

Breed and source of animals: Beagle, MVL Colony

Sample Preparation and Dosing Technique: Sample as received, by gavage.

Test Results and Summary

ED₅₀

An ED₅₀ value for test substance G0506.01 has not been determined. The next indicated dose level, 32 ml/kg, will cause a Volume effect in emesis.

D. E. Stitzel
D.E. Stitzel-Technician

D. K. Hybell
D.K. Hybell-Study Director

STUDY DATA SHEET

EMETIC DOSE STUDY (DOGS)

Divisional Safety Test

Request Number: PYCR 0372

"UP*DOWN" PROCEDURE

Test Substance

Identification Number: G0506.01

Study Number: B85-6007

Dog #	Wt. (kg)	Dose Level ml/kg	Dose Vol. ml	Response X or O	Onset (Min.)
2985	13.2	16.0	211.2	0	

X = Response

O = No Response

Sequence

ED₅₀ Calculation

$$\text{Log Final Test Dose} + k(\text{log of Spacing of Doses}) = \text{Log of ED}_{50}$$

An ED₅₀ value for test substance G0506.01 has not been determined. The next indicated dose level, 32 ml/kg, will cause a volume effect in emesis.

INTERDEPARTMENTAL CORRESPONDENCE

FROM: Operations Section

DATE: January 24, 1985

TO: D. K. Hysell

SUBJECT: STUDY PLACEMENT AUTHORIZATION

This is to authorize you to carry out the following study according to the attached protocol.

Notice: This study is expected to be submitted to the following regulatory agency: FDA. The stipulations of the protocol are to be implemented in complete conformance with Good Laboratory Practices Regulations (21 CFR, Part 58) for nonclinical laboratory studies.

Test: Emetic (ED₅₀) in the Dog (Dixon "Up and Down" Method)
Protocol No.: C5 Issue Date: July 1, 1983
Test Substance No.: G0506.01 Doc. Req. No.: BYCR 0372
Physical Form: viscous liquid

885-6007

Matters involving the scientific aspects of the work can be handled directly with the Divisional Toxicologist. All unused samples are to be returned to the Divisional Toxicologist at the following address:

Ms. C. W. Gardin
SWTC - Room No. 2D23
Telephone No. 8-55-2302

Complete both copies of the attached protocol by adding your study number and proposed start and completion dates. The Study Director should define the start and completion dates on the protocol and sign and date both copies. Retain one and return one copy to the BTF's Quality Assurance Unit.

J. W. Williamson for HAD

H. A. Derner
Human & Environmental Safety Division

Attachments

cc: Quality Assurance Unit
C. W. Gardin

TO Operations Section - NYL

RETENTION LIMIT

SUBJECT NONCLINICAL STUDY - REGULATORY
STATUS

ATTENTION

Notifications pertaining to:

IND # ByuR0372
TEIN 60518-01

1. Studies requested on the above document:

- are expected to be submitted to the following regulatory agencies as a GLP regulated study: FOA

- are expected to be submitted to the following regulatory agencies but is not a GLP regulated study: _____

Metabolism, Pharmacological Screen, Other: _____

- are not expected to be submitted to a regulatory agency. (Boxes #3 and #4 below need not be checked).

2. - The test substance has been characterized and results are shown on the test substance characterization report which accompanies the IND.

3. - The method of synthesis fabrication or derivation of the test related substances has been documented. (Required for regulated studies).

4. - Stability testing has been done or will be done on the test substance. (Required for regulated studies).

Sponsor's Divisional Toxicologist: Cassie Bardin

Date: 1/16/85

By: NIQA2

PROTOCOL NO. 65

EMETIC (ED₅₀) IN THE DOG (DIXON "UP-AND-DOWN" METHOD)

Issue Date: July 1, 1983
Supersedes Issued Dated: August 16, 1982

Test Substance Identification Number (TSIN) BYK0372

Divisional Request Document Number (DRD) G0306-01

Sponsor : The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility : The Procter & Gamble Company Study # 385-6007
Ecological Testing Facility (to be completed
Miami Valley Laboratories by Test Facility)
P. O. Box 39175
Cincinnati, Ohio 45247

Purpose : To determine the emetic potential of a test substance
in the dog.

Justification for
Selection of Test
System :

The Beagle dog is the animal of choice because
experience has shown that this species is a good model
in predicting the emetic activity of a substance.

Route of Administration
of Test Substance :

Administer substance by stomach tube.

Reason for Choice :

This provides an accurate method of delivering the
desired dose to the animals' stomach.

Diet Analyses
Required :

None (no known contaminants expected which would
interfere with this study).

Water Analysis
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 the protocol.

PROTOCOL NO. C5

ENETIC (ED₅₀) IN THE DOG (DIXON "UP-AND-DOWN" METHOD)

Issue Date: July 1, 1983
Supersedes Issued Dated: August 18, 1982

Test Substance(s)

<u>TSIN #</u>	<u>DRD Number</u>	<u>Description</u>		<u>Expiration Date</u>
		<u>Color</u>	<u>Physical Form</u>	
G0226.01	BVCC0372	Aqua-blue	viscous liquid	1/9/86

Storage Conditions: (check one)

Test Substance:

[] Room temp. [] Refrigerator [] Freezer [] Other (specify):

Test Substance/Carrier Mixture:

[] Room temp. [] Refrigerator [] Freezer [] Other (specify):

Hazards: (check one)

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

Special Instructions: (check one)

[] None.
[] As follows:

Dose Preparation: (check one)

[] Dose test substance as received
[] Dose test substance as ___% solution/suspension w/v
in _____.

Note:

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

If a concentration analysis is required:

[] Prepare a sufficient quantity of the test substance - vehicle mixture(s) so that a portion can be returned to the Sponsor's Divisional Toxicologist.

Shipping Instructions:

Send approximately _____ ml. Send [] frozen; [] under ambient conditions; [] other _____.

PROTOCOL NO. C5

EMETIC (ED₅₀) IN THE DOG (DIXON "UP-AND-DOWN" METHOD)

Issue Date: July 1, 1983

Supersedes Issued Dated: August 16, 1982

- Dosage Levels : Initial dose level should be:
LD50 ~ 16 ml/kg
___ ml/kg of test substance as received
___ ml/kg of the required solution/suspension
- Animals : Beagles, pure bred, 6 months to 5 years. Animals will be selected from the stock colony as needed. Total of animals to be used will vary from a minimum of 6 animals.
- Animal Care & Diet : 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.
- Procedure : Fast the dogs for a minimum of 19 hours and deprive them of water for approximately 3 hours before dosing. Prior to dosing each dog, record its collar number, run number, weight (kg) and gender. Calculate the volume of test substance to be dosed to the first dog and record it. The first dog is removed from its run and given the recorded amount of test substance using the appropriate method.
- After dosing the first animal, return it to its run. Observe the dog for one hour, recording whether or not emesis occurs, and the time of emesis onset (if any). At the end of the one hour observation period, allow the animal access to water ad libitum. The animal will be fed at the regular feeding time the next day. Subsequent doses will be determined as described in Appendix 1 and will be administered the same as the first dose.

PROTOCOL NO. C5

EMETIC (ED₅₀) IN THE DOG (DIXON "UP-AND-DOWN" METHOD)

Issue Date: July 1, 1983

Supersedes Issued Dated: August 16, 1982

At the termination of the study, the animals should be returned to the stock colony of the Facility.

Statistical Analysis:

The ED₅₀ is computed by using the method described in Appendix 1.

Protocol Changes:

If it becomes necessary to change the approved protocol, verbal agreement to make this change should be made between the Study Director or his designate 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.

Report:

Report dates of initiation and completion of the in-life portion of the study. Include a summary of analysis of raw data collected during the study and a transcription of the raw data. The report shall conform to all requirements outlined in Section 58.185, Subpart J, Good Laboratory Practices regulations.

Sponsor: Carroll Carlin
Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist: 1/10/85

Proposed Starting Date: 1-31-85
Defined as: first day of dosing

Proposed Completion Date: to be determined
Defined as: last day of dosing

Study Director: Dale E. Stibel
Date: 1-31-85

The up-and-down method of experimentation (Reference 1) is used in order to minimize the number of animals that must be dosed and to reduce the stress to animals due to over-dosing.

ANIMALS :

The number of animals tested will vary depending upon how close the initial dose (see Test Conduction & Observations below) is to the dose which will produce emetic episodes in 50% of the animals (ED_{50}). A minimum of six animals will be dosed; it should seldom be necessary to dose more than nine or ten animals.

Test Conduction & Observations :

To start the test, choose an initial dose, i , and a multiplier, m . The initial dose should be close to the estimated ED_{50} ; if this estimate is poor, it would be best to err on the low side. The multiplier, m , determines the spacing between doses; multipliers will typically lie between 1.5 and 3.

The first animal is dosed at i . If emesis is not observed within 1 hour, the dose for the next animal is raised to i times m ; if emesis is observed, then the dose for the next animal is lowered to i divided by m . Again, the second animal is observed and the dose for the next animal will be raised by the multiple m if emesis is not observed or lowered by the factor m if emesis is observed. This sequence is continued, each time dosing the next animal with a dose based upon the current animal's dose adjusted upwards or downward by the factor m depending upon whether emesis is not observed (next dose upward) or is observed (next dose downward).

The observations may begin with a series of animals who react similarly (either, all are free of emetic episodes or all have emetic episodes). This will be the case when the initial dose, i , is far from the ED_{50} . In deciding on when to terminate the study, only the last animal in such a sequence is counted; the study terminates when, including this animal, a minimum of six animals have been tested.

Report :

The ED_{50} is computed by following the procedure on pages 386-388 of Reference 1. Note that in applying the formula on page 387, X_r should be the logarithm of the final dose and d is the logarithm of m . The result of applying the formula is the logarithm of the ED_{50} . The antilogarithm of this result is the ED_{50} .

Reference:

1. Dixon, W. J. and Massey, F. J., Introduction to Statistical Analysis, 3rd Ed., McGraw-Hill, New York, 1969, pages 380-393.

Values of k for estimating LD_{50} from up and down sequence of trials if the table is entered from the Foot, the sign of k is to be reversed.

Second Part of Series	k for Test Series Whose First Part is				
	<u>0</u>	<u>00</u>	<u>000</u>	<u>0000</u>	
X0000	-.547	-.547	-.547	-.547	OXXXX
X000X	-1.250	-1.247	-1.246	-1.246	OXXXO
X00X0	.372	.380	.381	.381	OXXOX
X00XX	-.169	-.144	-.142	-.142	OXXOO
X0X00	.022	.039	.040	.040	OXXOX
X0X0X	-.500	-.458	-.453	-.453	OXXO0
X0XX0	1.169	1.237	1.247	1.248	OXXOX
X0XXX	.611	.732	.756	.758	OXXOO
XX000	-.296	-.266	-.263	-.263	OOXXX
XX00X	-.831	-.763	-.753	-.752	OOXXO
XX0X0	-.831	-.935	-.952	-.954	OOXXO
XX0XX	-.296	.463	.500	.504	OOXOO
XXX00	.500	.648	.678	.681	OOOXX
XXX0X	-.043	.187	.244	.252	OOOXX
XXXX0	1.603	1.917	2.000	2.014	OOOOX
XXXXX	.893	1.329	1.465	1.496	OOOOO
	X	XX	XXX	XXXX	Second Part of Series

-k for Series Whole First Part is

BEAUTY CARE DIVISION
TEST SUBSTANCE CHARACTERIZATION REPORT*
(TECH)

For Test Office
 Use Only:
 DRD # B/C20372
 TSN # Cc506.01

1. Test Article Name (should agree with DRD): H&S BC-3b Normal/Drv formula with 0.3% Octopirox
2. Making Notebook Ref. (with Plant Production Code if applicable): QC-0106-51A
3. Date Made: 1/9/85 Made by: S. K. McQueary Lab: 1B20
4. Physical Form: Viscous Liquid Color: Aqua-Blue Density: 0.99g/cc
5. Water Solubility: >50 % (wt/wt)
 For SENS test only - Ethanol Solubility: >50 % (wt/wt)
 Acetone Solubility: >50 % (wt/wt)
6. Sample Expiration Date: 1/9/86 Stability Testing is: Completed In Progress
7. Hazards: None Storage Conditions: Ambient (50-90°F)
8. D.O.T. Classification (see Regulatory Personnel): Not Hazardous
9. Microbial Susceptibility Classification Approval: Samuel Brown 1-15-85
 (Name) (Date) (Signature)
10. Making Data: List ingredients in descending order of predominance.
 (For drug products list active ingredient(s) first.)

#	RAW MATERIAL NAME	NOMINAL %	ACTUAL %	RMS # -LOT
1	OCTOPIROX	0.3000	0.3007	BX-288-1
2	DRD WATER	90.7270	90.7124	DX-158-2
3	STEDBAC	1.6000	1.6002	45595-5
4	CETAC	1.6000	1.6009	45570-6
5	CETYL ALCOHOL	1.3500	1.3505	48026-2
6	STEARYL ALCOHOL	1.3500	1.3505	48048-7
7	CETETH-2	0.8000	0.8001	45455-10
8	STEARETH-21	0.6000	0.6007	BX-076-2
9	CRTEIN Q	0.5000	0.5007	48040-8
10	GMS	0.5000	0.5004	45601-37
11	STEARETH-2	0.4000	0.4004	BX-241-2
12	FLORIEN PLUS PERFUME	0.1000	0.0997	XP-305-3
13	CITRIC ACID	0.0800	0.0900	45076-14
14	FD&C BLUE #1 SOL'N	0.0600	0.0600	56510-10
15	KATHON DS	0.0330	0.0327	45572-4
	TOTALS	100.0000	100.0000	

Comments on Making Data:

Packed in 16 oz. Cylinder Round Bottles (pc-008-9)
 Caps (pc-086-8)

Comments on Making Data: _____

*Submit typed original with DRD. Include copy of making records.

Issue Date 5/84

**TEST SUBSTANCE CHARACTERIZATION REPORT
(TSCR)**

For Tox Office
Use Only:
DSD # DN 2121A
TSCR # (0501-0)

11. Characterization, Microbial and Properties Information:

	Date Submitted	Submitter Code (if exists) or Lab Notebook #	Component or Property	(S)	Measured Value	Limits	Testing Lab or Data Source
1	1/9/85	JEM 101	WRT	✓	Pass 20/25K	Must Pass	
2	1/9/85	QC-0106-51A	7 Octopiros		32	0.25-0.35	1B21
3	1/10/85	B306-0366	Quar		43	0.37-0.43	Ann 1
4	1/9/85	QC-0106-51A	pH		4.66	4.6-4.8	1B21
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

12. Approvals:

The test substance as made and characterized is a representative example of the intended formulation. Making records for plant-made product should be obtained and evaluated by Products Research.

a. Process Development: ADM. ADM. J. J. J. J.W. Melanson 1/13/85
(Signature) (Name) (Date)

b. Products Research: J.W. Melanson T.J. Roussion 1/15/85
(Signature) (Name) (Date)

finished product samples will be retained by Quality Assurance.
7 samples

c. QAP-Quality Assur.: J.W. Melanson _____ 1/15/85
(Signature) (Name) (Date)

13. The characterization tests requested are appropriate and the test substance is acceptable for: acute animal test; subchronic animal test; chronic animal test; human safety test; in vitro test; environmental safety test.

Cassie Cardin CASSIE CARDIN 1/15/85
(Toxicologist's Signature) (Name) (Date)

TSCR Distribution: Original - Tox Office; Copies - Toxicologist, QAP/QA, Products Research and Process Dev.