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1201 Constitution Avenue NW
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ATTN: 8(d) Health & Safety Reporting Rule (Notification/Reporting)

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Re: TSCA Section 8(d) Submission (71 FR 47310, August 16, 2006)
[EPA-HQ-OPPT-2005-0055; FRL-7764-7]

Dear Sir or Madam:

This submission is being made by The Procter & Gamble Company (P&G) in accordance with TSCA Section 8(d) health and safety data reporting requirements.

We are submitting health and safety studies for substances listed in the TSCA 8(d) final rule originally published in the Federal Register on August 16, 2006 (71 FR 47310) and subsequently modified via two Federal Register Notices published September 15, 2006 (71 FR 54434) and September 29, 2006 (71 FR 57439). Please note that some of the studies being submitted are for substances that are used by P&G solely in FDA-regulated applications. While TSCA reporting obligations do not apply for these materials, we have included these safety data as information we believe is of interest to the Agency.

We have attached an index that lists the applicable chemical names and CAS Numbers listed in the final rule and the corresponding study titles/descriptions. We have also attached a summary to each study to facilitate the review of information being submitted.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,
THE PROCTER & GAMBLE COMPANY

R. J. Hackman

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Index of Health & Safety Studies submitted by Procter & Gamble

Chemical Name	CAS #	Lab Study #	Title	Company Acc #
1,3-Hexanediol, 2-ethyl-	94-96-2	85-029	Semi-Continuous Activated Sludge (SCAS) Removability Test on B0859.01	31559
1,3-Hexanediol, 2-ethyl-	94-96-2	BW-86-1-1928	Acute Toxicity of B0859.01 to Bluegill (*Lepomis macrochirus*)	32348
1,3-Hexanediol, 2-ethyl-	94-96-2	165-09-1100-1	Toxicity of B0859.01 to *Microcystis aeruginosa*.	32358
1,3-Hexanediol, 2-ethyl-	94-96-2	85-030	CO_2 Production Test on B0859.01	32091
1,3-Hexanediol, 2-ethyl-	94-96-2	BW-85-11-1884	Acute Toxicity of B0859.01 to *Daphnia magna*.	32066
1,3-Hexanediol, 2-ethyl-	94-96-2	MVS1482	Testing 2-ethyl-1,3-hexanediol in the mouse *in vivo* skin micronucleus model	MVS1482
1,3-Hexanediol, 2-ethyl-	94-96-2	191-1215	Rabbit Eye Irritation (Low Volume Procedure)	31928
1,3-Hexanediol, 2-ethyl-	94-96-2	T4636.380	Test for Chemical Induction of Unscheduled DNA Synthesis in Primary Cultures of Rat Hepatocytes (by Autoradiography)	33081
1,3-Hexanediol, 2-ethyl-	94-96-2	851013	Repeated Insult Patch Test	44564
1,3-Hexanediol, 2-ethyl-	94-96-2	LSR 69	Human Repeat Insult Patch Test LSR 69 ECM BTS 1083, E2751.01	35365
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	4708-126/69	Delayed Contact Hypersensitivity Study in the Guinea Pig, (Buehler Test) Test Article RO 163	42321
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	2-5-253-85	Guinea Pig Sensitization Testing modified by Ritz and Buehler on R 0163	42322
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	78-368-21	Delayed Contact Hypersensitivity Study in Guinea Pigs of R0060-01	21114
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	WIL-1179-78	Delayed Hypersensitivity Study in Guinea Pigs of R0060-02.	20749
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	78-086-21	Delayed Contact Hypersensitivity Study in Guinea Pigs of R0060	19932
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	L08321-SNO9	Performance of the Murine Local Lymph Node Assay	36754
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	930/040	Magnusson & Kligman Maximisation Study in the Guinea Pig.	100345
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	V 92.392/352063	Sensitization study with xxx in guinea pigs (maximization test).	103104
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	TES810036	Guinea Pig Sensitization Study – Magnusson-Kligman Maximization Method – Positive Control	44906
Benzene, 1-chloro-2,4,-dinitro-	97-00-7	50931	Delayed Contact Hypersensitivity Study in Guinea Pigs (Buehler Sensitization Test) of xxx	103074

Index of Health & Safety Studies submitted by Procter & Gamble

Chemical Name	CAS #	Lab Study #	Title	Company Acc #
Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-	131-57-7	130	Drosophila Melanogaster Somatic Mutation and Recombination Test Assay of MV#2820-019	36113
Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-	131-57-7	003-347-595-7	Test for Chemical Induction of Mutation in Mammalian Cells in Culture the L5178Y TK+/- Mouse Lymphoma Assay	25950
Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-	131-57-7	T8880.105	Cytogenicity Study Rat Bone Marrow In-Vivo of MV# 2820-019, P89-018	36648
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	7L647	Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells	43693
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	7L646	Bacterial Reverse Mutation Study of RE1122.03	43692
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	7L747	Primary Dermal Irritation Study of RE1122.03 in Rabbits.	43696
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	7L748	Primary Eye Irritation Study of RE1122.03 in Rabbits (Low Dose Procedure).	43694
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	3029-2073	A Low Volume Eye Irritation Study in Rabbits with RE1122.01	40235
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	916-014	Oral (gavage) Chernoff-Kavlock Developmental Toxicity Assay of RE-0981.05, RE-1122.01, RE-1123.01, and RE-1125.01 in Rats	43658
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	L08607 SN15	Murine Local Lymph Node Assay	40229
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	L08607 SN23	Murine Local Lymph Node Assay	43675
Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)	25646-71-3	7L749	Dermal Single-Dose Toxicity Study of RE1122.03 in Rats	43695
Tannins	1401-55-4	B86-0168	Rabbit Skin Irritation (Modified Closed Patch Test)	32487

Acc# 43693

7L647

Submitted to:

Procter & Gamble Far East, Inc.

Final Report

Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells

(Study Number : 7L647)

(P&G DRD# : HBE BTS0707/01-06) b

January 6, 2000

Mitsubishi Chemical Safety Institute Ltd.

Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Procter & Gamble Far East, Inc.

Title: Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells

Study Number: 7L647

The study in this report was conducted in compliance with the following Good Laboratory Practice Standards.

Japanese GLP Standards for Nonclinical Safety Studies on Drugs (Ministry of Health and Welfare Ordinance No. 21, 1997)

Management: Katsuhisa Kohyama sealed Date: January 6, 2000

Quality Assurance Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Procter & Gamble Far East, Inc.

Title: Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells

Study Number: 7L647

By the inspections and audits listed below, I hereby certify that this study was carried out in accordance with its protocol and with our Standard Operating Procedures, and that this report faithfully describes the methods and procedures employed, and that the reported results accurately reflect the raw data of the study.

Inspection or audit	Quality assurance personnel	Date of inspection or audit	Date of reporting to the study director	Date of reporting to the management
Study protocol	Kunihiko Ofuchi	November 11, 1997	November 11, 1997	November 11, 1997
Protocol amendment No. 1	Hidetsugu Watabe	June 3, 1999	June 3, 1999	June 3, 1999
Study procedure				
Measurement of surviving cells	Hidetsugu Watabe	December 3, 1997	December 3, 1997	December 8, 1997
Treatment with the test substance	Hidetsugu Watabe	December 8, 1997	December 8, 1997	December 8, 1997
Staining of specimens	Hidetsugu Watabe	December 10, 1997	December 10, 1997	December 11, 1997
Raw data, Draft report	Akiko Esaki	January 30, 1998 - February 2, 1998	February 2, 1998	February 5, 1998
Final report	Hidetsugu Watabe	January 6, 2000	January 6, 2000	January 6, 2000

Date : January 6, 2000

Quality Assurance Manager : Tamotsu Nishitomi sealed

Outline of the Study

1. Title : Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells
(Study Number: 7L647)
(P&G DRD# : HBE BTS0707/01-06)

2. Purpose : To assess the clastogenicity of the test substance by the chromosomal aberration test in cultured mammalian cells

3. Guideline : Japanese Guidelines for Toxicity Studies of Drugs (1989)

4. GLP : Japanese GLP on Drugs (1997)

5. Sponsor : Procter & Gamble Far East, Inc.
1-17, Koyo-cho, Naka, Higashinada-ku, Kobe, Hyogo, 658-0032 Japan
Responsible person Akihiro Kurishita, Ph. D

6. Organization in contract : Mitsubishi Chemical Safety Institute Ltd.
1-30, Shiba 2-chome, Minato-ku, Tokyo, 105-0014 Japan

7. Testing facility : Kashima Laboratory Mitsubishi Chemical Safety Institute Ltd.
14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-0255 Japan

8. Study contributors :

Study director : Munehiro Nakagawa sealed January 6, 2000

Other contributors : Erina Ohta, Yuko Ishige, Yumiko Anazawa,
Megumi Tamagawa, Akemi Shinohara

9. Study schedule : (Initiation of the study) November 11, 1997
(Initiation of the tests) November 22, 1997
(Completion of the tests) January 20, 1998
(Completion of the study) January 6, 2000

10. Unforeseeable circumstances that may have affected the quality or integrity of the study and deviation from the protocol : None

11. Retention :

All data and documents as follows will be retained in the archive of Kashima Laboratory. The sponsor and the testing facility, however, will discuss regarding further retention of data 5 years after submission of the final report.

Protocol and all amendments

Test material

Record of the test material

Record of inspection

Record of the experiments

- A guarantee of S9 quality
- Record of cell culture
- Record of the solvent selection test
- Work sheet

Final report

All other data

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Summary

An *in vitro* chromosomal aberration study of RE1122.03 was conducted using the established cell line (CHL/IU) from the lungs of a female Chinese hamster.

Concentrations selected for the cell growth inhibition test were 50, 40, 30, 20, 10, 5, 2.5 and 1.25 μg/ml for the 24 h and 48 h continuous treatment and the pulse treatment without S9 mix, and 500, 400, 300, 200, 100, 50, 25 and 12.5 μg/ml for the pulse treatment with S9 mix. The 50 % cell growth inhibition concentrations were 6.6 μg/ml in the 24 h continuous treatment, 8.0 μg/ml in the 48 h continuous treatment, 7.9 μg/ml in the pulse treatment without S9 mix, and 87 μg/ml in the pulse treatment with S9 mix.

From these results, concentrations selected for the chromosomal aberration test were 10, 5, 2.5 and 1.25 μg/ml for the 24 h and 48 h continuous treatment and the pulse treatment without S9 mix, and 100, 50, 25 and 12.5 μg/ml for the pulse treatment with S9 mix. The incidences of cells with structurally aberrant chromosomes were 10.0 and 13.5 % at 10 μg/ml in the 24 h continuous treatment and in the pulse treatment without S9 mix, respectively, and the judgement was positive. The incidences of cells with numerically aberrant chromosomes were less than 5% in each treatment.

RE1122.03 was concluded to have clastogenic potential in this CHL/IU cell line system.

Materials and Methods

1. Test materials

1.1 Test substance

Name	: RE1122.03
General chemical name	: Paraphenylendiamine derivative
Lot #	: 75161
Solubility in water	: 380 g/l at 25 ℃
Solubility in DMSO	: More than 50 mg/ml
Solubility in acetone	: N/A
Storage condition	: Room temperature
Stability	: The stability data was verified by the sponsor.
Appearance	: Off-white free flowing crystalline powder
Odor	: None
Melting point	: 300 ℃
Boiling point	: N/A
Activity (%)	: 99.6 %

1.2 Control substance

1) Negative control substance

Japanese Pharmacopoeia saline (saline, Otsuka Pharmaceutical Factory, Inc., lot no. K6K83)

2) Positive control substance

(1) For the continuous treatment

Mitomycin C (MMC; Kyowa Hakko Kogyo Co., Ltd., lot no. 139AFK, purity 104 %)

(2) For the pulse treatment

Benzo[a]pyrene (BP; Tokyo Kasei Kogyo Co., Ltd., lot no. AX01, purity 99.5 %)

2. Cell line

The CHL/IU cell line which was originally derived from the lungs of a female Chinese hamster was used. It was purchased from Dainippon Pharmaceutical Co., Ltd. on November

6, 1996. The cell suspension was mixed with one tenth volume of dimethylsulfoxide (DMSO, Kanto Chemical Co. Inc., lot no. 810S1814), then it was frozen in 1 ml and stored in liquid nitrogen. After thawing and cultivation within 5 passages, the cells were used in this study. The cells were cultured in plastic dishes (Becton Dickinson and Company ; diameter : 6 cm or 10 cm) in an automated CO_2 incubator (NAPCO model 7300 ; CO_2 5 %, temperature 37 ℃, humid condition).

3. Culture media

3.1 Eagle's minimum essential medium

Eagle's minimum essential medium (MEM; Eagle's MEM " Nissui"① ; Nissui Pharmaceutical Co., Ltd.) was prepared under the manufacturer's direction and was autoclaved at 121 ℃ for 15 min. One liter of this solution was supplemented with 10 ml of sterilized 2.92 % L-glutamine solution and 12.7 ml of sterilized 10 % sodium bicarbonate solution.

3.2 Growth medium

Nine hundred milliliters of the above MEM solution was supplemented with 100 ml of heat-inactivated (56 ℃, 30 min) calf serum (GIBCO BRL, lot no. 39K0464).

4. S9 mix

4.1 S9

S9, which was prepared from the liver of male Sprague-Dawley rats treated with phenobarbital (PB ; 30, 60, 60, 60 mg/kg on every 24 h, respectively, i.p.) and 5,6-benzoflavone (80 mg/kg i.p. at the third PB injection), was purchased from Kikkoman Corporation (lot no. RAA-368; prepared on August 29, 1997). The S9 was stored below -80 ℃ until use.

4.2 S9 mix

The following table shows the composition of 10 ml of S9 mix. The S9 mix was freshly prepared for each test and kept on ice until use.

D-glucose-6-phosphate	14.1 mg
β -NADP$^+$	33.5 mg
(These were weighed just before use.)	
20 mM HEPES (pH 7.2)	2 ml
50 mM $MgCl_2(6H_2O)$	1 ml
330 mM KCl	1 ml
sterilized purified water	3 ml
(These were prepared in advance.)	
S9	3 ml

5. Preparation of test material solutions

5.1 Test substance solutions

In a preliminary test for solvent selection, the test substance was soluble in saline at 50 mg/ml. Therefore, saline was used as the solvent for the test substance.

The test substance was dissolved in saline just before use and was sterilized with a membrane filter. Then this solution was diluted with saline to each concentration.

5.2 Positive control solutions

MMC was dissolved in saline (Otsuka Pharmaceutical Factory, Inc., lot no. K6K83) at 3 μg/ml just before use. BP was dissolved in DMSO (Kanto Chemical Co., Inc., lot no. 810S1814) at 4 mg/ml and was frozen in advance. This solution was thawed at room temperature just before use.

6. Cell growth inhibition test

A cell growth inhibition test was conducted for finding appropriate concentrations in the chromosomal aberration test.

6.1 Test substance concentration

Before the cell growth inhibition test, a preliminary test was performed at three concentrations of 5000, 500 and 50 μg/ml in 24 and 48 h continuous treatment and the pulse treatment with S9 mix. In this test, one plate was used for each concentration and cells were observed with a phase contrast microscope.

The cell growth rates to that of the negative control were 0 % at all concentrations in the continuous treatments. These were 0 % at 5000 and 500 μg/ml, and 70 % at 50 μg/ml in the pulse treatment.

From this result, concentrations for the cell growth inhibition test were selected as follows.

the 24 h continuous treatment : 50, 40, 30, 20, 10, 5, 2.5, 1.25 μg/ml

the 48 h continuous treatment : 50, 40, 30, 20, 10, 5, 2.5, 1.25 μg/ml

the pulse treatment without S9 mix : 50, 40, 30, 20, 10, 5, 2.5, 1.25 μg/ml

the pulse treatment with S9 mix : 500, 400, 300, 200, 100, 50, 25, 12.5 μg/ml

6.2 Treatment of cells

In a 6 cm plastic plate, 5 ml of cell suspension (4×10^3 cells/ml) were incubated for 3 days.

After the culture medium was removed from each plate, the cells were treated for 24 or 48 h with a mixture of 0.5 ml of one of the test substance solutions and 4.5 ml of the growth medium in the continuous treatment.

In the pulse treatment without S9 mix, cells were treated for 6 h with a mixture of 0.3 ml of one of the test substance solutions and 2.7 ml of the growth medium. In the pulse treatment with S9 mix, the cells were treated for 6 h with a mixture of 0.3 ml of one of the test substance solutions, 0.5 ml of S9 mix and 2.2 ml of the growth medium. After treatment, the cells were washed three times with MEM, and then were incubated in 5 ml of fresh growth medium for further 18 h.

In the negative control groups, the cells were similarly treated with the vehicle (saline).

The test was performed using two plates for each concentration.

At the beginning of the treatment and at the end of the treatment (at the end of the 6 h treatment in the pulse treatment), a small quantity of the medium of each treatment was collected and was measured pH with a pH meter (twin pH B-212, Horiba Ltd.). The pH of the test substance solutions were measured in the same way.

6.3 Measurement of surviving cells

Cells were washed with Ca^{2+}, Mg^{2+} free Dulbecco's phosphate buffer saline (PBS(-); Dulbecco's PBS "Nissui", Nissui Pharmaceutical Co., Ltd.), were fixed with methanol for 10 min, were stained with 3 % Giemsa's solution (diluted with 1/150 M phosphate buffer solution, pH 6.8) for 10 min, were washed with water and were dried. Cell density was measured with a cell density counter (Monocellator, Olympus Co., Ltd.).

6.4 Measurement of 50 % inhibition concentration of cell growth

For each treatment, the ratio of surviving cells to that in the corresponding negative control was calculated, and a survival curve was drawn and 50 % inhibition concentration of cell growth (IC_{50}) was calculated.

7. Chromosomal aberration test

7.1 Test substance concentration

In the cell growth inhibition test, IC_{50}s were as follows.

the 24 h continuous treatment : 6.6 μg/ml

the 48 h continuous treatment : 8.0 μg/ml

the pulse treatment without S9 mix : 7.9 μg/ml

the pulse treatment with S9 mix : 87 μg/ml

From this result, concentrations for the chromosomal aberration test were selected as follows.

the 24 h continuous treatment : 10, 5, 2.5, 1.25 μg/ml

the 48 h continuous treatment : 10, 5, 2.5, 1.25 μg/ml

the pulse treatment without S9 mix : 10, 5, 2.5, 1.25 μg/ml

the pulse treatment with S9 mix : 100, 50, 25, 12.5 μg/ml

In the positive controls, the final concentrations of MMC and BP were set at 0.03 and 20 μg/ml, respectively, which are the concentrations to induce chromosomal aberration.

7.2 Treatment of cells

The cultured cells were treated with the test substance in the same procedure as described in section 6.2.

For the positive controls, the cells were treated with a mixture of 50 μl of the MMC solution and 5 ml of the growth medium in the continuous treatment. In the pulse treatment, the cells were treated with a mixture of 3 ml of the growth medium and 15μl of the BP solution (without S9 mix), or with a mixture of 2.5 ml of the growth medium, 0.5 ml of S9 mix and 15 μl of the BP solution (with S9 mix). For the positive controls, the measurement of pH was not conducted.

7.3 Preparation of specimens

Two hours before the end of the cell treatment, colcemid was added to the medium in each plate at the final concentration of 0.1 μg/ml to accumulate cells in metaphase. After cell treatment, the cells were washed with PBS(-), were dissociated with 0.25 % trypsin solution (solvent : PBS(-)), and were centrifuged at 1000 rpm for 5 min to collect the cells. After the supernatant was removed, 4 ml of 0.075 M potassium chloride solution was added for hypotonic treatment (37 ℃, 15 min). The cells were then fixed in 4 ml of cold methanol/acetic acid mixture (3:1 v/v). After centrifugation, the supernatant was removed and 4 ml of the fresh fixative was added. This fixation procedure was repeated 3 or 4 times. Thereafter, the cells were suspended in a small amount of the fixative, and a drop of the cell suspension was placed at two points on a slide glass on a wet towel, and then was dried. The cells were stained for 20 min in 3 % Giemsa's solution. The slide was washed with water, dried, and was coated with a mounting medium. Two slides were prepared for each plate.

7.4 Observation

1) Preliminary observation

Each specimen was preliminarily observed to confirm that it has an adequate numbers of mitotic cells.

For positive and negative controls, the incidence of structural aberrations was confirmed to be appropriate.

2) Structural and numerical aberrations

Structural and numerical aberrations were observed in a blind method.

(1) Structural aberration

One hundred metaphase cells per plate (i.e. 200 cells for each concentration) were observed.

Metaphase cells having well-spread chromosomes were selected and were observed for structural aberrations. A cell without aberration but not having 25 ± 2 chromosomes was omitted from the survey. Structural aberrations are classified as follows [1].

- gaps (gap, including chromatid and chromosome type lesions)
- chromatid breaks (ctb)
- chromatid exchanges (cte)
- chromosome breaks (csb)
- chromosome exchanges (cse: dicentric, ring, etc.)
- fragmentation (frg)

A "gap" is distinguished from a "break" as follows. The "gap" is an achromatic region in a single chromatid which is equal to or slightly larger than the width of the chromatid and whose shape is clearly defined.

(2) Numerical aberration

One hundred metaphase cells per plate (i.e. 200 cells for each concentration) were observed and polyploid cells including endoreduplicated cells were scored.

7.5 Judgement

A cell having at least one structural chromosomal aberration was classified as an aberrant cell. Aberrant cells were counted up in two ways, that is, including (+ gap) and excluding (− gap) cells having only gaps.

The test was acceptable when the following requirements are filled.

(1) Both of the incidences of cells with chromosomal structural aberration and those with numerical aberration are less than 5% in all negative control groups.

(2) In the continuous treatment and in the pulse treatment with S9 mix, the incidences of cells with chromosomal structural aberration are 10% or more in the positive control groups.

(3) In the pulse treatment without S9 mix, the incidences of cells with chromosomal structural aberration are less than 5% in the positive control group.

The test substance was judged to have a potential to induce chromosomal aberration as follows. When both of incidence of +gap aberrant cells and that of numerical aberrations are less than 5%, the test substance is negative (−). When either of the incidences is 5% or more and less than 10%, the test substance is inconclusive (±). When either of the incidences is 10% or more, the test substance is positive (+).

7.6 Expression of the result

The incidences of the structural and numerical aberration were showed in table.

For positive results, the results of the tests were illustrated in figures, and photographs of representative aberrant chromosomes were attached to the final report.

Results and Conclusion

Figures 1 – 3 show the results of the cell growth inhibition test, and Table 3 shows the results of the measurement of pH.

IC_{50}s were as follows.

the 24 h continuous treatment : 6.6 μg/ml
the 48 h continuous treatment : 8.0 μg/ml
the pulse treatment without S9 mix : 7.9 μg/ml
the pulse treatment with S9 mix : 87 μg/ml

From this result, selected concentrations for the chromosomal aberration test were 10, 5, 2.5 and 1.25 μg/ml for the 24 h and 48 h continuous treatment and the pulse treatment without S9 mix, and 100, 50, 25 and 12.5 μg/ml for the pulse treatment with S9 mix.

Tables 1 and 2 and Figures 4 – 9 show the results of the chromosomal aberration test, and Table 4 shows the results of the measurement of pH.

In the preliminary observation, there were 50 or more mitotic cells in all specimen. So all specimens were used for the survey.

The incidences of cells with structurally aberrant chromosomes were 10.0 and 13.5 % at 10 μg/ml in the 24 h continuous treatment and in the pulse treatment without S9 mix, respectively, and the judgement was positive. The incidences of cells with numerically aberrant chromosomes were less than 5% in each treatment.

The incidences of structural aberrations in the positive control groups were higher than these in the negative control groups and this taught that procedures in this study were technically appropriate.

RE1122.03 was suggested to have clastogenic potential in this CHL/IU cell line system.

Reference

1: Mammalian Mutagenicity Study Group of Japan Environmental Mutagen Society: Atlas of chromosomal aberrations induced by chemicals, Asakura Press, Tokyo, 1988.

Table 1 Results of the chromosomal aberration study of RE1122.03 (continuous treatment)

Test substance : RE1122.03

Treatment group	Exposure Time (h)	Concentration (μg/ml)	No. of cells analysed	Polyploids		No. of cells with chromosomal structural aberration 1) (%)								
						Gaps	Chromatid type		Chromosomal type		frg	Total		Judgement2)
				(%)	Judgement2)	gap	ctb	cte	csb	cse		-gap	+gap	
Negative control [Saline]	24	0	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	1	0	0	1	1	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
	48	0	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	0	0	0	0	0	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Test substance	24	1.25	100	0		0	0	0	1	0	0	1	1	
			100	1	−	0	0	0	0	0	0	0	0	−
			200	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		2.5	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	1	0	0	0	1	1	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		5	100	0		0	0	0	0	0	0	0	0	
			100	1	−	0	0	1	0	0	0	1	1	−
			200	1 (0.5)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		10	100	0		0	4	3	2	0	0	8	8	
			100	1	−	0	4	7	3	0	1	12	12	+
			200	1 (0.5)		0 (0.0)	8 (4.0)	10 (5.0)	5 (2.5)	0 (0.0)	1 (0.5)	20 (10.0)	20 (10.0)	
	48	1.25	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	0	0	0	0	0	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		2.5	100	0		0	0	0	1	0	0	1	1	
			100	0	−	0	0	0	2	0	0	2	2	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)	3 (1.5)	3 (1.5)	
		5	100	1		0	0	0	0	0	0	0	0	
			100	2	−	0	0	0	1	0	0	1	1	−
			200	3 (1.5)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		10	100	1		0	0	0	1	0	0	1	1	
			100	1	−	0	0	3	3	0	0	5	5	−
			200	2 (1.0)		0 (0.0)	0 (0.0)	3 (1.5)	4 (2.0)	0 (0.0)	0 (0.0)	6 (3.0)	6 (3.0)	
Positive control [MMC]	24	0.03	100	0		2	6	14	0	0	0	20	22	
			100	0	−	1	2	14	0	0	0	15	16	+
			200	0 (0.0)		3 (1.5)	8 (4.0)	28 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)	35 (17.5)	38 (19.0)	
	48	0.03	100	0		0	7	21	4	0	0	30	30	
			100	1	−	0	11	19	2	1	0	29	29	+
			200	1 (0.5)		0 (0.0)	18 (9.0)	40 (20.0)	6 (3.0)	1 (0.5)	0 (0.0)	59 (29.5)	59 (29.5)	

1) gap : chromomatid and chromosome type lestions, ctb : chromatid breaks, cte : chromatid exchanges, csb : chromosome breaks, cse : chromosome exchanges, frg : fragments
2) Judgement (polyploids or +gap) less than 5% : negative (−), from 5% to less than 10% : inconclusive (±), 10% or more : positive(+)
MMC : Mitomycin C Saline : JP saline

Table 2 Results of the chromosomal aberration study of RE1122.03 (pulse treatment)

Test substance : RE1122.03

Treatment group	With or without S9 mix	Concentration (μg/ml)	No. of cells analysed	Polyploids (%)	Judgement2)	No. of cells with chromosomal structural aberration 1) (%) Gaps: gap	Chromatid type: ctb	Chromatid type: cte	Chromosomal type: csb	Chromosomal type: cse	frg	Total: -gap	Total: +gap	Judgement2)
Negative control [Saline]	−	0	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	1	0	0	1	1	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
	+	0	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	1	0	0	0	1	1	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
Test substance	−	1.25	100	2		0	0	0	0	0	0	0	0	
			100	0	−	0	0	1	0	0	0	1	1	−
			200	2 (1.0)		0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
		2.5	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	0	0	0	0	0	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		5	100	0		0	0	1	2	1	0	4	4	
			100	1	−	0	0	0	0	0	0	0	0	−
			200	1 (0.5)		0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)	1 (0.5)	0 (0.0)	4 (2.0)	4 (2.0)	
		10	100	0		0	9	12	1	0	0	17	17	
			100	0	−	0	4	6	1	0	0	10	10	+
			200	0 (0.0)		0 (0.0)	13 (6.5)	18 (9.0)	2 (1.0)	0 (0.0)	0 (0.0)	27 (13.5)	27 (13.5)	
	+	12.5	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	1	1	0	0	0	2	2	−
			200	0 (0.0)		0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.0)	
		25	100	0		0	0	0	0	0	0	0	0	
			100	0	−	0	0	0	0	0	0	0	0	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
		50	100	0		0	0	1	1	1	0	3	3	
			100	0	−	0	1	0	0	0	0	1	1	−
			200	0 (0.0)		0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	4 (2.0)	4 (2.0)	
		100	100	0		0	0	1	1	0	0	2	2	
			100	0	−	0	0	2	2	0	0	4	4	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	3 (1.5)	3 (1.5)	0 (0.0)	0 (0.0)	6 (3.0)	6 (3.0)	
Positive control [BP]	−	20	100	0		0	0	0	1	0	0	1	1	
			100	0	−	0	0	0	0	0	0	0	0	−
			200	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
	+	20	100	0		0	13	94	2	0	1	96	96	
			100	0	−	0	6	94	1	1	0	94	94	+
			200	0 (0.0)		0 (0.0)	19 (9.5)	188 (94.0)	3 (1.5)	1 (0.5)	1 (0.5)	190 (95.0)	190 (95.0)	

1) gap : chromomatid and chromosome type lestions, ctb : chromatid breaks, cte : chromatid exchanges, csb : chromosome breaks, cse : chromosome exchanges, frg : fragments
2) Judgement (polyploids or +gap) less than 5% : negative (−), from 5% to less than 10% : inconclusive (±), 10% or more : positive(+)
Cell were treated with S9 (5% of final conc.) or with out S9 for 6 hours and recovered 18 hours.
BP : Benzo[a]pyrene Saline : JP saline

7L647

Table 3 Results of the measurement of pH [the cell.growth inhibition test]

1. Test substance solution

(1) The 24 h continuous treatment and the pulse treatment without S9 mix

Concentration (μg/ml)	saline	1.25	2.5	5	10	20	30	40	50
pH	7.1	7.0	6.8	6.2	5.0	3.7	3.2	3.1	2.7

(2) The 48 h continuous treatment

Concentration (μg/ml)	saline	1.25	2.5	5	10	20	30	40	50
pH	8.4	7.3	7.1	6.4	5.2	3.5	3.0	2.9	2.9

(3) The pulse treatment with S9 mix

Concentration (μg/ml)	saline	12.5	25	50	100	200	300	400	500
pH	7.1	4.2	3.4	2.7	2.5	2.2	2.0	1.9	1.8

2. Culture medium

(1) The 24 h continuous treatment

Concentration (μg/ml)	saline	1.25	2.5	5	10	20	30	40	50
*	7.9	8.0	7.9	7.9	8.0	7.9	8.0	8.0	7.9
**	7.4	7.5	7.4	7.4	7.4	7.5	7.4	7.4	7.5

(2) The 48 h continuous treatment

Concentration (μg/ml)	saline	1.25	2.5	5	10	20	30	40	50
*	8.0	8.0	8.0	8.0	8.0	7.9	8.0	8.0	7.9
**	7.1	7.2	7.2	7.3	7.2	7.2	7.2	7.2	7.2

(3) The pulse treatment without S9 mix

Concentration (μg/ml)	saline	1.25	2.5	5	10	20	30	40	50
*	8.1	8.0	8.1	8.1	8.1	8.2	8.2	8.1	8.2
**	7.5	7.8	7.8	7.8	7.8	7.6	7.7	7.7	7.7

(4) The pulse treatment with S9 mix

Concentration (μg/ml)	saline	12.5	25	50	100	200	300	400	500
*	7.9	8.0	7.9	7.9	7.8	7.7	7.6	7.6	7.4
**	7.3	7.3	7.4	7.3	7.4	7.4	7.4	7.5	7.4

* : pH (at the beginning of the treatment)

** : pH (at the end of the treatment)

Table 4 Results of the measurement of pH [the chromosomal aberration test]

1. Test substance solution

Concentration (μg/ml)	saline	1.25	2.5	5	10	12.5	25	50	100
pH	6.7	5.3	4.6	4.2	4.2	4.5	3.6	3.0	2.6

2. Culture medium

(1) The continuous treatment

Concentration (μg/ml)		saline	1.25	2.5	5	10
pH	*	7.8	7.7	7.7	7.6	7.6
	* * (24 h)	7.4	7.3	7.2	7.3	7.3
	* * (48 h)	7.2	7.3	7.3	7.3	7.4

(2) The pulse treatment without S9 mix

Concentration (μg/ml)		saline	1.25	2.5	5	10
pH	*	8.0	8.0	8.0	8.1	8.0
	* *	7.2	7.3	7.3	7.3	7.3

(3) The pulse treatment with S9 mix

Concentration (μg/ml)		saline	12.5	25	50	100
pH	*	7.7	7.6	7.5	7.6	7.5
	* *	7.1	7.2	7.2	7.2	7.2

* : At the beginning of the treatment

* * : At the end of the treatment

Figure 1 Cell growth index of RE1122.03
(continuous treatment)

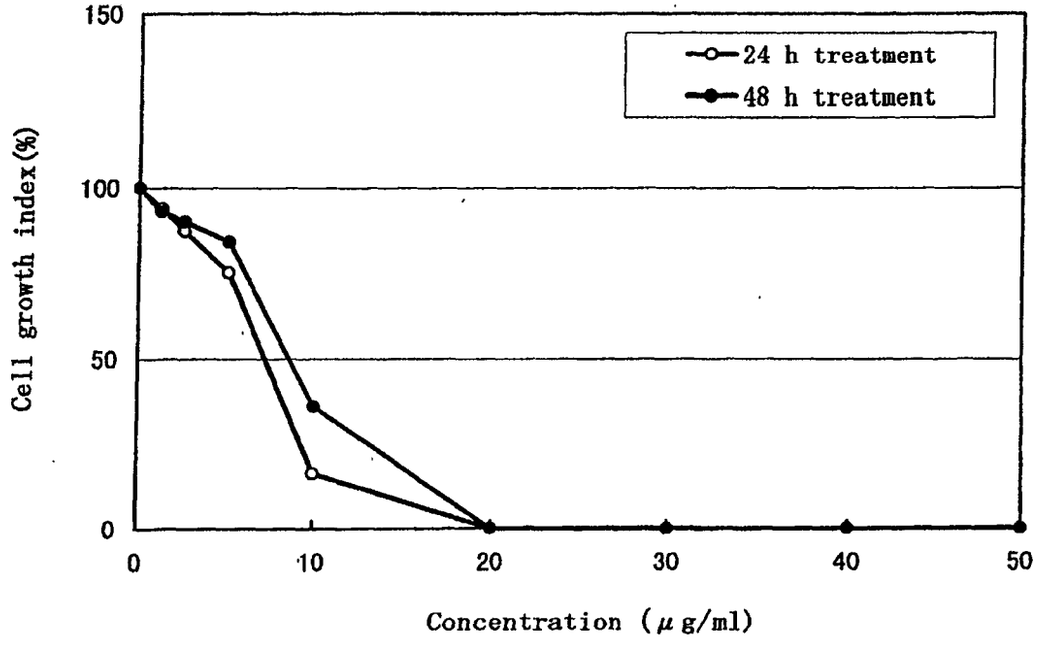


Figure 2 Cell growth index of RE1122.03
(pulse treatment with S9 mix)
(6 h treatment and 18 h recovery)

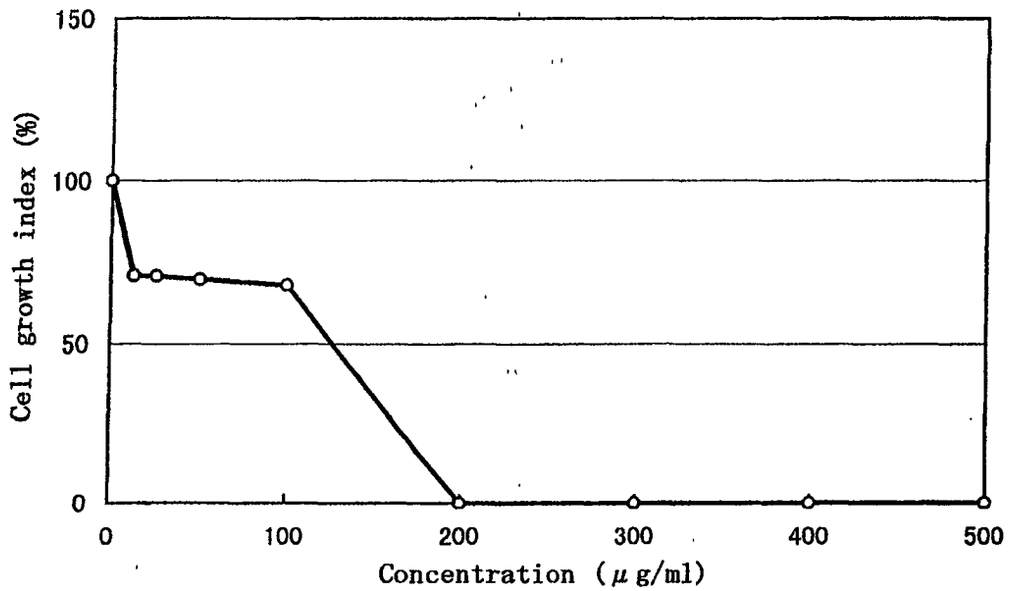


Figure 3 Cell growth index of RE1122.03
(pulse treatment without S9 mix)
(6 h treatment and 18 h recovery)

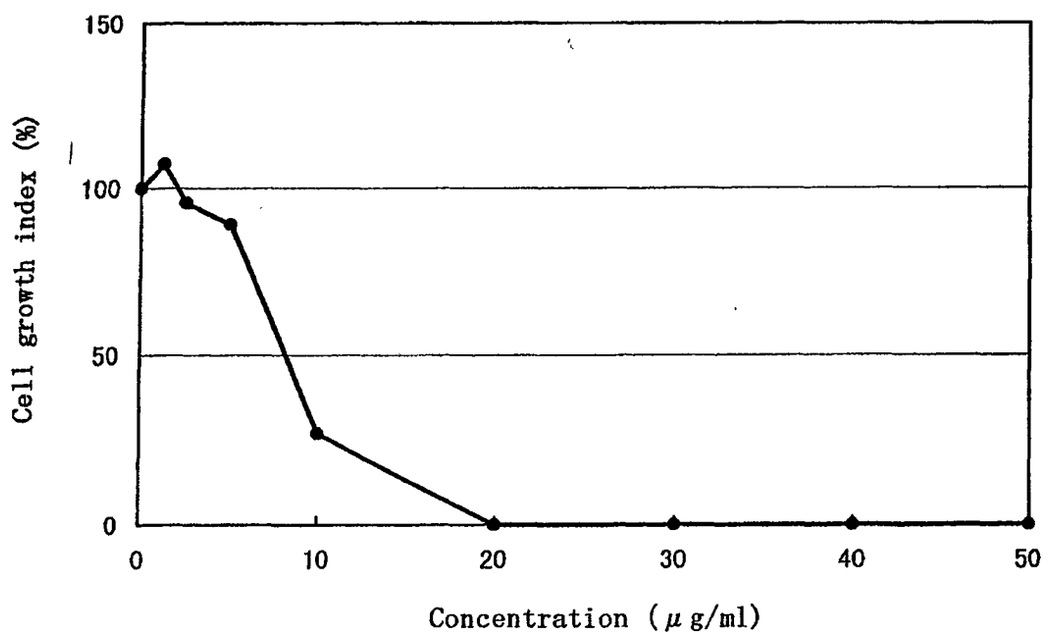


Figure 4 Incidence of aberrant cell treated with RE1122.03 (continuous treatment)

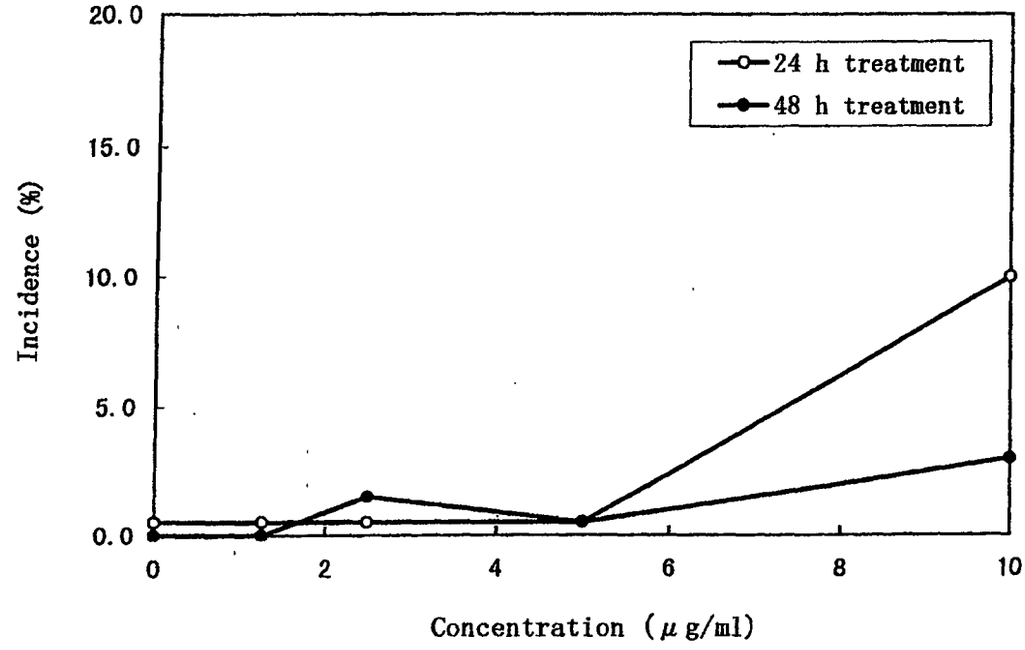


Figure 5 Incidence of aberrant cell treated with RE1122.03 (pulse treatment with S9 mix)

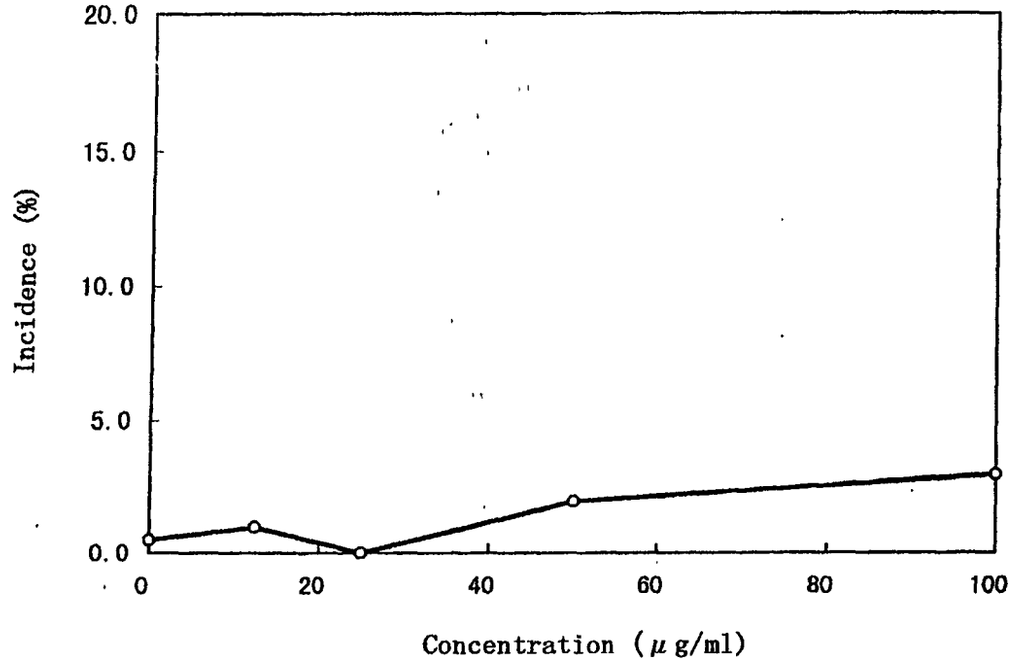


Figure 6 Incidence of aberrant cell treated with RE1122.03 (pulse treatment without S9 mix)

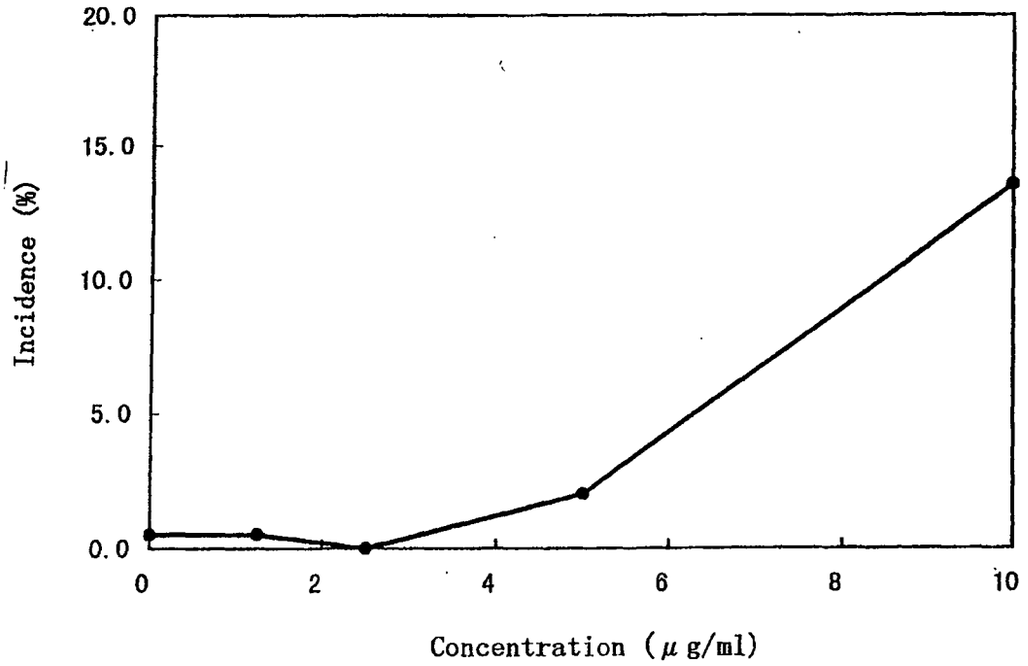


Figure 7 Incidence of polyploid cell treated with RE1122.03 (continuous treatment)

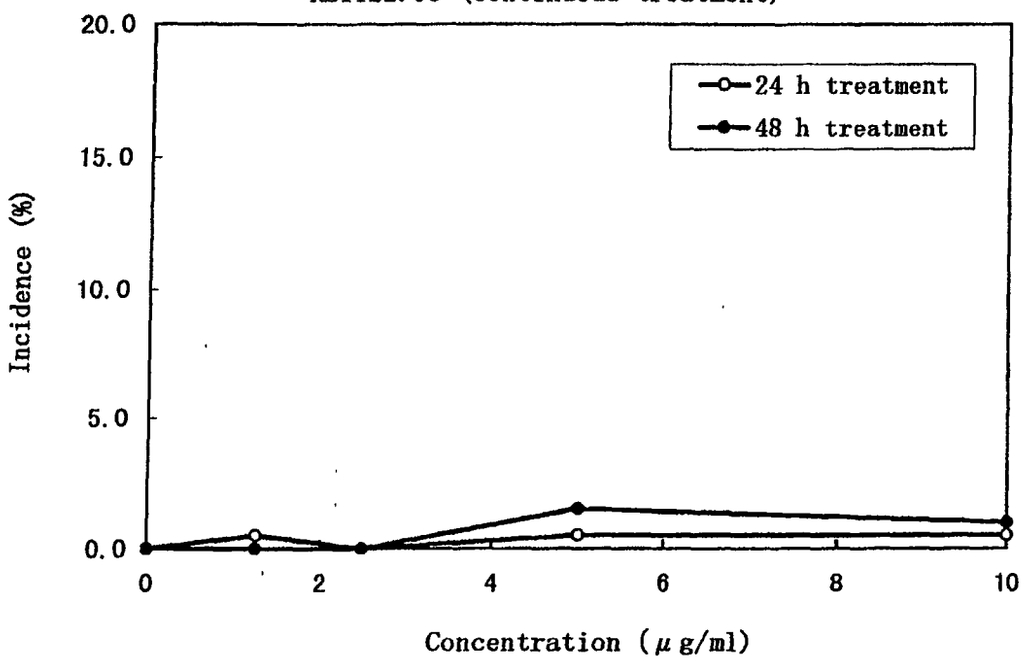


Figure 8 Incidence of polyploid cell treated with RE1122.03 (pulse treatment with S9 mix)

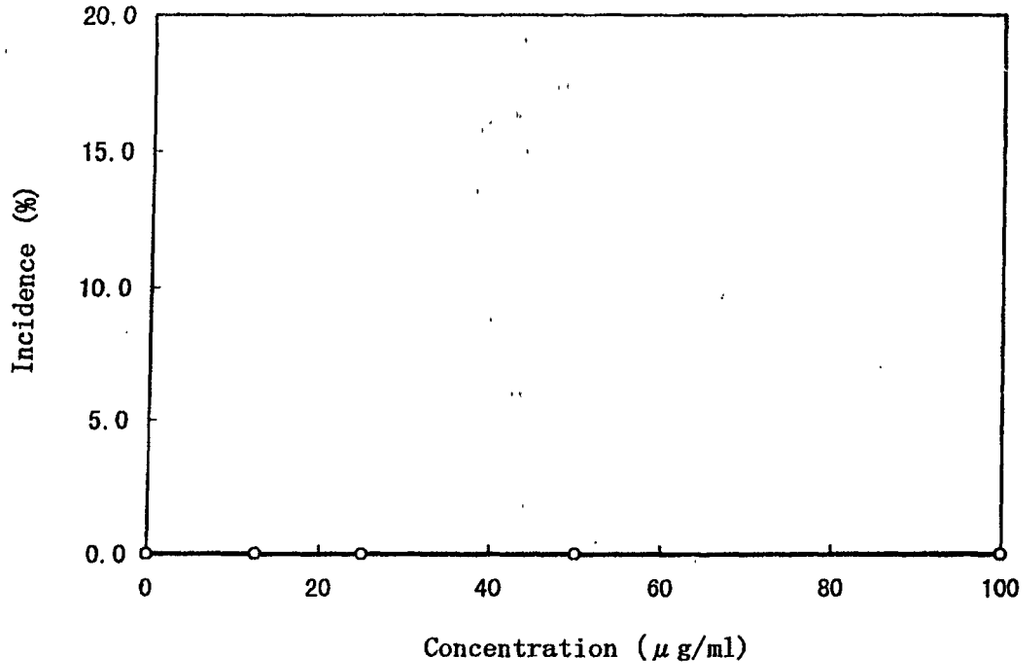
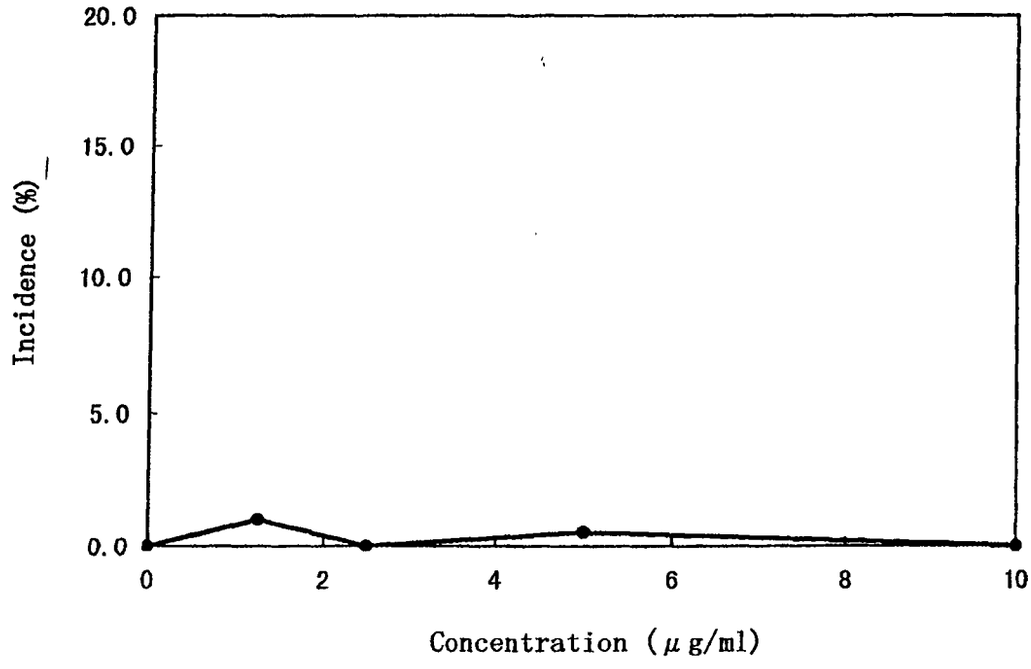
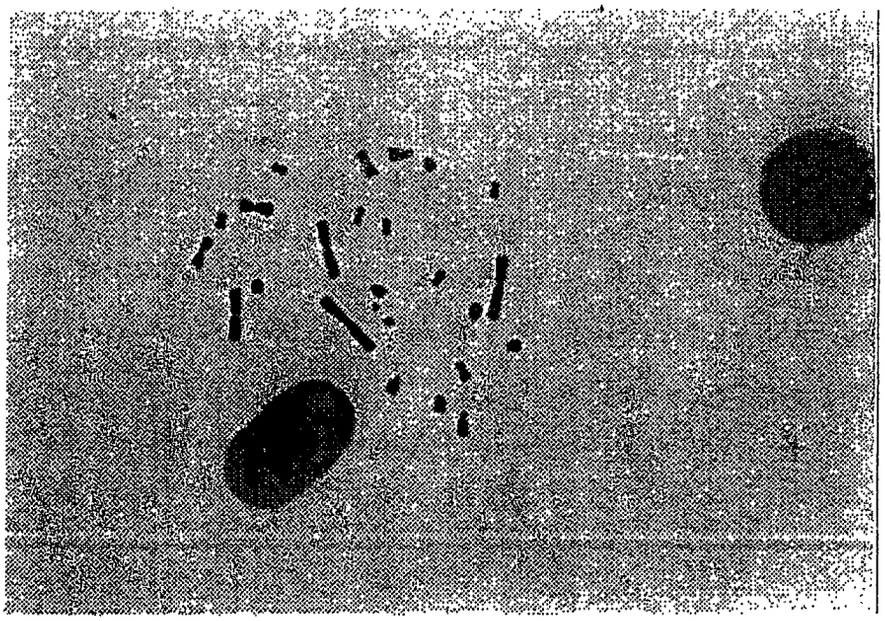
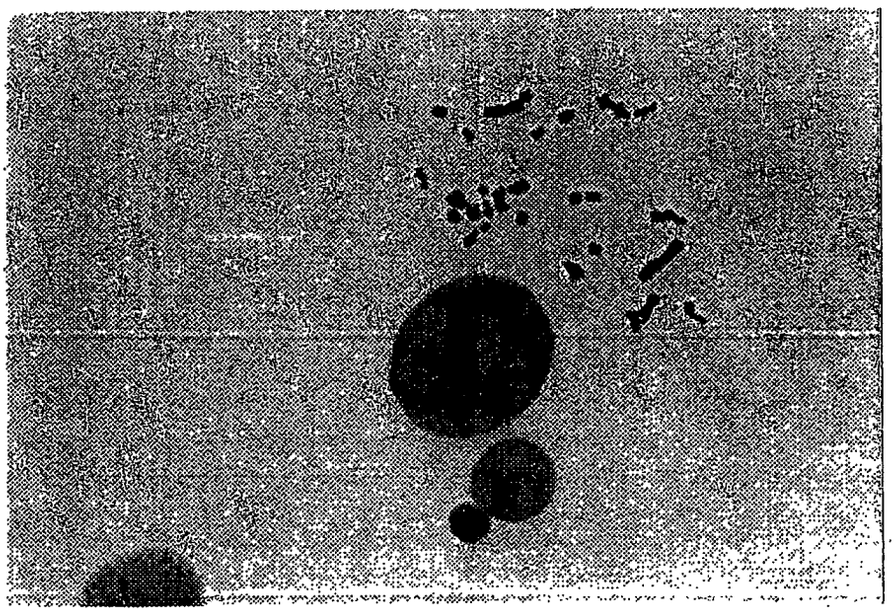


Figure 9 Incidence of polyploid cell treated with RE1122.03 (pulse treatment without S9 mix)





Photograph 1 Normal cell in the negative control group
(the pulse treatment without S9 mix)



Photograph 2 Chromosomal aberration cell in the test substance treated group
(the pulse treatment without S9 mix, 10 μg/ml, ctb, cte)

Translation Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Procter & Gamble Far East, Inc.

Title: Chromosomal Aberration Study of RE1122.03 in Cultured Mammalian Cells

Study Number: 7L647

This study was conducted in Kashima Laboratory of Mitsubishi Chemical Safety Institute Ltd. The original report was written in Japanese. I hereby declare that this report faithfully reflects the original report as accurately as possible to my knowledge.

Translator : Munehiro Nakagawa Date: March 21, 2000

Munehiro Nakagawa

Genetic Toxicology Group of Kashima Laboratory

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.03
Divisional Request Document(s) HBE BTS 0707/01 - 06

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman LOT # 75161 TM 25-9-97
Brand Notebook Reference_N01511/30 M217/19922 leg M217/19923
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NK at: NK %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions:_Store at Room temperature Viscosity:_NA
Expiration Date (Day/Month/Year):_01 Sep 98 Ingredient Stability: NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: G.GENAIN (Name) G.Genain (Signature) 24-9-97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for thesfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: pp V. Hoyle (Name) P M Mclaren (Signature) 24/09/97. (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	ARP 2581	I.R	conforms to spec	N1486/113

Description: Tan powder free from any visible contamination

22/9/97

Compositional Information Provided by:

DOMINIC PRATT 17/09/97

(ORIGINATOR NAME/SIGNATURE/DATE)

Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:

P.O. Gracie 26/9/97.

(ANALYTICAL MGR NAME/SIGNATURE/DATE)

Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required ✓

Material approved [ ]

JASON WILLIAMS

(NAME/SIGNATURE/DATE)

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

Test Substance Description

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine
Purity:	99.6%
Remarks:	Also described as para-phenylendiamine derivative and Test Substance Number RE-1122.03

Method

GLP:	Yes (Japanese)
Report Year:	2000
Test Type:	Bacterial reverse mutation assay
System:	*Salmonella typhimurium* TA98, TA100, TA1535, and TA1537; *Escherichia coli* WP2 *uvrA*
Test Concentration:	0.610-5000 µg/plate
Metabolic Activation:	with and without
Remarks:	Bacterial suspension (0.1 ml) added in 0.5 ml phosphate buffer (0.1 M, pH 7.4) containing test substance. Controls: negative control (water), positive controls (2-(2-furyl)-3-(5-Nitro-2-furyl) acrylamide, sodium azide, N-ethyl-N′-nitro-N-nitrosoguanidine, 9-aminoacridine, and 2-aminoanthracene)

Results

Result:	The number of revertant colonies was not smaller than twice that of the corresponding negative control in TA100 in absence of S9 mix, and TA100 and WP2*uvrA* in the presence of S9 mix. The number of revertant colonies was smaller than twice that of the corresponding negative control in TA1535, TA98, and TA1537 regardless of the presence or absence of S9 mix.
Conclusion:	The results suggest that RE-1122.03 is mutagenic under the conditions of the study.
Remarks:	The number of revertant colonies induced by the positive controls was more than twice those of the negative controls in each of the tester strains regardless of presence/absence of metabolic activation. Negative and positive control values were within the proper ranges of the historical data in the laboratory.

Data Quality

Reliability (Klimisch):	1

Reference

Report/Study Number:	7L646
Reference:	Procter & Gamble, Inc., 2000. Bacterial Reverse Mutation Study of RE1122.03. Accession #43692.

7L646

ACC# 43692

Submitted to:

Procter & Gamble Far East, Inc.

FINAL REPORT

Bacterial Reverse Mutation Study of RE1122.03

(Study No. : 7L646)

(P&G DRD# : HBE BTS0707/01-06) a

January 6, 2000

Mitsubishi Chemical Safety Institute Ltd.

Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor : Procter & Gamble Far East, Inc.

Title : Bacterial Reverse Mutation Study of RE1122.03

Study No. : 7L646

The study in this report was conducted in compliance with the following Good Laboratory Practice Standards.

Japanese GLP Standards for Nonclinical Safety Studies on Drugs (Ministry of Health and Welfare Ordinance No.21, 1997)

Date : January 6, 2000

Study Director : Katsuhisa Kohyama sealed

Quality Assurance Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor : Procter & Gamble Far East, Inc.

Title : Bacterial Reverse Mutation Study of RE1122.03

Study No. : 7L646

By the inspections and audits listed below, we hereby certify that this study was carried out in accordance with its protocol and with our Standard Operating Procedures, and that this report faithfully describes the methods and procedures employed, and that the reported results accurately reflect the raw data of the study.

Inspection or audit	Quality assurance personnel	Date of inspection or audit	Date of reporting to the study director	Date of reporting to the management
Study protocol	Kunihiko Ofuchi	November 11, 1997	November 11, 1997	November 11, 1997
Protocol Amendment No. 1	Hidetsugu Watabe	June 7, 1999	June 7, 1999	June 7, 1999
Study procedure				
Treatment of the test substance	Hidetsugu Watabe	November 18, 1997	November 18, 1997	November 19, 1997
Observation	Hidetsugu Watabe	November 27, 1997	November 27, 1997	November 28, 1997
Raw data, Draft report	Hidetsugu Watabe	January 23, 1998 ~ January 26, 1998	January 26, 1998	January 26, 1998
Final report	Hidetsugu Watabe	January 6, 2000	January 6, 2000	January 6, 2000

Date : January 6, 2000

Quality Assurance Manager : Tamotsu Nishitomi sealed

Study Outline

1. Title : Bacterial Reverse Mutation Study of RE1122.03
(Study No. 7L646)
(P&G DRD# : HBE BTS0707/01-06)

2. Purpose : To assess the mutagenicity of the test substance in the reverse mutation assays in *Salmonella typhimurium* and *Escherichia coli.*

3. Guideline : Japanese Guidelines for Toxicity Studies of Drugs (1989)

4. GLP : Japanese GLP on Drugs (1997)

5. Sponsor : Procter & Gamble Far East, Inc.
1-17, Koyo-cho, Naka, Higashinada-ku, Kobe, 658-0032, Japan
Responsible Person Akihiro Kurishita, Ph.D.

6. Organization under Contract :
Mitsubishi Chemical Safety Institute Ltd.
2-1-30, Shiba, Minato-ku, Tokyo, 105-0014, Japan

7. Testing Facility :
Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd.
14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-0255, Japan

8. Study Contributors :
Study Director : Makoto Miyagawa sealed January 6, 2000

Other Contributors : Yoshiaki Enomoto, Yuko Shimizu, Tomoko Okubo

9. Study Schedule :

(Initiation of the Study)	November 11, 1997
(Dose-Finding Test)	November 17 - November 20, 1997
(Main Test)	November 24 - November 27, 1997
(Completion of the Study)	January 6, 2000

10. Unexpected study circumstances that may affect the reliability of the study and deviation from the protocol : none

11. Retention :

All data and documents as follows will be retained in the archive of the Kashima Laboratory. The sponsor and the testing facility, however, will discuss regarding further retention of data 5 years after submission of the final report.

- Protocol and all amendments
- Test material
- Record of the test material
- Record of inspection
- Record of the experiments
  - A guarantee of S9 quality
  - Conversion sheet of turbidity to number of cells
  - Input data sheet for figures and specific activity
  - Record of the solvent selection test
  - Work sheet
- Final report
- All other data

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Summary

Mutagenicity of the test substance, RE1122.03, was assessed in bacterial assays using *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP2*uvrA*.

A dose-finding test was conducted at seven concentrations of 5000, 1250, 313, 78.1, 19.5, 4.88, and 1.22 μg/plate, and it showed the number of revertant colonies was not smaller than twice that of the corresponding negative (solvent) control in TA100 and WP2*uvrA* either in the absence or presence of S9 mix. Microbial toxicity was observed at 1250 μg/plate or more for all tester strains in the absence of S9 mix, and at 5000 μg/plate in TA100, TA1535, TA98, and TA1537 in the presence of S9 mix. Then, the main test was conducted at six concentrations from 1250 to 39.1 μg/plate at a common ratio of 2 in TA100, TA1535, and TA1537, and at seven concentrations from 2500 to 39.1 μg/plate at a common ratio of 2 in TA98 and WP2*uvrA* in the absence of S9 mix, and six concentrations from 19.5 to 0.610 μg/plate at a common ratio of 2 in TA100, and at six concentrations from 5000 to 156 μg/plate at a common ratio of 2 in TA1535, WP2*uvrA*, TA98, and TA1537 in the presence of S9 mix.

In the main test, the number of revertant colonies was not smaller than twice that of the corresponding negative (solvent) control in TA100 in the absence of S9 mix, and TA100 and WP2*uvrA* in the presence of S9 mix. The number of revertant colonies was smaller than twice that of the corresponding negative (solvent) control in TA1535, TA98, and TA1537 regardless of the presence or absence of S9 mix.

These results suggest that RE1122.03 is mutagenic under the conditions of this study.

Materials and Methods

1. Test materials

1.1 Test substance

Name : RE1122.03

General chemical name : Paraphenylendiamine derivative

Lot # : 75161

Solubility in water : 380 g / *l* at 25℃

Solubility in DMSO : More than 50 mg/ml

Solubility in acetone : N/A

Storage condition : Room temperature

Stability : The stability data was verified by the sponsor.

Appearance : Off-white free flowing crystalline powder

Odor : None

Melting point : 300℃

Boiling point : N/A

Activity (%): 99.6%

1.2 Control substances

Negative (solvent) and positive control substances were as follows.

Negative control	Abbrev.	Supplier	Lot no.	Purity (%)
water for injection	DW	Otsuka Pharmaceutical Factory, Inc.	K7B87	—

Positive control	Abbrev.	Supplier	Lot no.	Purity (%)
2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide	AF-2	Wako Pure Chemical Industries, Ltd.	PTQ1296	98.8
sodium azide	NaN_3	Wako Pure Chemical Industries, Ltd.	KWE6685	96.5
N-ethyl-*N*'-nitro-*N*-nitrosoguanidine	ENNG	Sigma Chemical Company	56F-3651	99.0
9-aminoacridine	9-AA	Sigma Chemical Company	80F-0186	99
2-aminoanthracene	2-AA	Wako Pure Chemical Industries, Ltd.	TWH2355	98.0

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was dissolved in one liter of purified water. The medium was autoclaved for 15 min at 121℃.

3.2 Minimal glucose agar plate

CLIMEDIA AM-N MEDIUM (Oriental Yeast Co., Ltd., lot no. AN420HM) was purchased and used.

3.3 Top agar

Bacto-agar (Difco Laboratories, lot no. 58007AJA) of 0.6 g and 0.5 g of sodium chloride was dissolved in 100 ml of purified water, and this solution was autoclaved. Amino acid solution containing 0.5 mM D-biotin and 0.5 mM L-histidine for *Salmonella typhimurium* or 0.5 mM L-tryptophan for *Escherichia coli* was added to this agar solution at a ratio of 1 to 10. The top agar was kept at about 45℃ until use.

4. S9 mix

4.1 S9

S9 (lot no. RAA-368) was prepared by Kikkoman Corporation on August 29, 1997 from the liver of male Sprague-Dawley rats which were intraperitoneally injected with phenobarbital (PB) at 30, 60, 60 and 60 mg/kg every 24h, and 5,6-benzoflavone at 80 mg/kg at the third PB injection. The S9 was stored below -80℃ until use.

4.2 S9 mix

The following table shows the composition of the S9 mix. The S9 mix was freshly prepared for each test and was kept on ice until use.

Component	Amount in 1 ml
S9	0.1 ml
$MgCl_2 \cdot 6H_2O$	8 μmol
KCl	33 μmol
D-glucose-6-phosphate	5 μmol
β-NADPH	4 μmol
β-NADH	4 μmol
sodium phosphate buffer (pH 7.4)	100 μmol
sterilized purified water	remainder

5. Test method [3)]

5.1 Preparation of test substance solutions and positive control solutions

A solvent selection test indicated that the test substance was soluble in water at 50 mg/ml. Then, water for injection (DW) was selected as the solvent.

The test substance was dissolved in DW at 50 mg/ml, and was sterilized with a membrane filter, and this solution was serially diluted with the same solvent into each test substance concentration.

Sodium azide was dissolved in DW (Otsuka Pharmaceutical Factory, Inc., lot no. K6C75) and the other positive control substances were dissolved in DMSO (Kanto Chemical Co., Inc., lot no. 810S1814).

5.2 Test substance concentration

A dose-finding test was conducted at seven concentrations of 5000, 1250, 313, 78.1, 19.5, 4.88, and 1.22 μg/plate, and it showed the number of revertant colonies was not smaller than twice that of the corresponding negative (solvent) control in TA100 and WP2*uvrA* either in the absence or presence of S9 mix. Microbial toxicity was observed at 1250 μg/plate or more for all tester strains in the absence of S9 mix, and at 5000 μg/plate in TA100, TA1535, TA98, and TA1537 in the presence of S9 mix. Then, the main test was conducted at six concentrations of 1250, 625, 313, 156, 78.1, and 39.1 μg/plate in TA100, TA1535 and TA1537, and at seven concentrations of 2500, 1250, 625, 313, 156, 78.1, and 39.1 μg/plate in TA98 and WP2*uvrA* in the absence of S9 mix, and six concentrations of 19.5, 9.77, 4.88, 2.44, 1.22, and 0.610 μg/plate in TA100, and at six concentrations of 5000, 2500, 1250, 625, 313, and 156 μg/plate in TA1535, WP2*uvrA*, TA98 and TA1537 in the presence of S9 mix.

5.3 Reverse mutation test

The test was conducted by the pre-incubation method. For one concentration, 0.1 ml of one of the test substance solutions, 0.5 ml of either 0.1 M sodium phosphate buffer (pH 7.4) for assays without metabolic activation or S9 mix for assays with metabolic activation, and 0.1 ml of each bacterial suspension were mixed in a sterilized test tube. The mixture was incubated under gentle shaking at 37℃ for 20 min. After pre-incubation, 2 ml of the molten top agar was added to this mixture and then poured onto a minimal glucose agar

plate. After the agar overlay solidified, the plates were incubated at 37℃ for 48 h.

The level of microbial toxicity was checked by background lawn with a stereoscopic microscop, The agar plates were checked for precipitates by eye. Revertant colonies in each plate were counted with an automatic colony counter or by eye. Two plates were used for each concentration and the test was performed twice, that is the dose-finding test and the main test.

Negative (solvent) control and positive controls listed in the following table were assayed by the same method.

Strain	Without S9 mix	(μg/plate)	With S9 mix	(μg/plate)	Negative control
TA98	AF-2	0.1	2-AA	0.5	DMSO
TA100	AF-2	0.01	2-AA	1	DMSO
TA1535	NaN_3	0.5	2-AA	2	DMSO
TA1537	9-AA	80	2-AA	2	DMSO
WP2*uvrA*	ENNG	2	2-AA	10	DMSO

5.4 Checking for bacterial contamination

The mixture of the highest concentration or S9 mix and the top agar on the agar plate was similarly incubated to check for bacterial contamination.

5.5 Judgement

The test substance was judged to be mutagenic (or positive) when the mean number of revertant colonies at any concentration increased two or more times that of the corresponding negative control for at least one tester strain either in the presence or absence of S9 mix, and when the number increased dose-dependently and reproducibly. The data were not analyzed statistically.

Results and Conclusion

Table 1 and 2 show the results of the dose-finding and main test.

A dose-finding test was conducted at seven concentrations of 5000, 1250, 313, 78.1, 19.5, 4.88 and 1.22 μg/plate, and it showed the number of revertant colonies was not smaller than twice that of the corresponding negative (solvent) control in TA100 and WP2*uvrA* either in the absence or presence of S9 mix. Microbial toxicity was observed at 1250 μg/plate or more for all tester strains in the absence of S9 mix, and at 5000 μg/plate in TA100, TA1535, TA98 and TA1537 in the presence of S9 mix. Then, the main test was conducted at six concentrations from 1250 to 39.1 μg/plate at a common ratio of 2 in TA100, TA1535 and TA1537, and at seven concentrations from 2500 to 39.1 μg/plate at a common ratio of 2 in TA98 and WP2*uvrA* in the absence of S9 mix, and six concentrations from 19.5 to 0.610 μg/plate at a common ratio of 2 in TA100, and at six concentrations from 5000 to 156 μg/plate at a common ratio of 2 in TA1535, WP2*uvrA*, TA98 and TA1537 in the presence of S9 mix.

In the main test, the number of revertant colonies was not smaller than twice that of the corresponding negative (solvent) control in TA100 in the absence of S9 mix, and TA100 and WP2*uvrA* in the presence of S9 mix. The number of revertant colonies was smaller than twice that of the corresponding negative (solvent) control in TA1535, TA98 and TA1537 regardless of the presence or absence of S9 mix.

At 5000 μg/plate in the presence of S9 mix, precipitates were observed on the agar plates.

The numbers of revertant colonies induced by the positive controls were more than twice those of the negative controls in all the tester strains regardless of the presence or absence of S9 mix. Negative (solvent) control values and positive control values were within the proper ranges of the historical data in our laboratory. Bacterial or fungous contamination which would have affected the test system was not observed in the checking for bacterial contamination.

These results suggest that RE1122.03 is mutagenic under the conditions of this study.

References

1) Maron, D. M. and Ames, B. N. (1983) : Revised methods for the *Salmonella* mutagenicity test, *Mutat. Res.*, **113**, 173-215.

2) Green, M. H. L. and Muriel, W. J. (1976) : Mutagen testing using Trp^+ reversion in *Escherichia coli*, *Mutat. Res.*, **38**, 3-32.

3) Mutagenicity test in Industrial Safety and Health Law (1991) : Edited by the Chemical Substance Investigation Division of the Industrial Safety and Health Department of the Ministry of Labor of Japan, Japan Industrial Safety and Health Association, Tokyo.

Table 1

Results of Dose-Finding Test

Test substance : RE1122.03 (No. 7L646)

with(+) or without(-) S9 mix	Test substance concentration (μg/plate)	Number of revertants (number of colonies / plate)				
		Base-pair change type			Frameshift type	
		TA100	TA1535	WP2uvrA	TA98	TA1537
S9 mix (−)	Solvent control	125 148 (137)	17 15 (16)	15 19 (17)	23 19 (21)	12 11 (12)
	1.22	148 147 (148)	9 11 (10)	16 20 (18)	19 22 (21)	10 8 (9)
	4.88	120 131 (126)	11 12 (12)	13 20 (17)	16 21 (19)	6 11 (9)
	19.5	175 163 (169)	17 18 (18)	17 22 (20)	20 22 (21)	9 11 (10)
	78.1	145 181 (163)	10 20 (15)	28 26 (27)	30 16 (23)	10 9 (10)
	313	255 302 (279)	19 18 (19)	27 31 (29)	25 18 (22)	10 9 (10)
	1250	0* 0* (0)	0* 0* (0)	38* 40* (39)	17* 13* (15)	0* 0* (0)
	5000	0* 0* (0)	0* 0* (0)	0* 0* (0)	0* 0* (0)	0* 0* (0)
S9 mix (+)	Solvent control	169 168 (169)	14 20 (17)	24 25 (25)	27 26 (27)	10 13 (12)
	1.22	232 221 (227)	19 18 (19)	24 28 (26)	24 26 (25)	16 9 (13)
	4.88	377 357 (367)	18 19 (19)	22 18 (20)	37 32 (35)	10 10 (10)
	19.5	489 441 (465)	19 25 (22)	23 25 (24)	41 40 (41)	12 11 (12)
	78.1	495 496 (496)	27 22 (25)	25 17 (21)	35 49 (42)	16 13 (15)
	313	383 262 (323)	14 15 (15)	24 22 (23)	41 34 (38)	12 20 (16)
	1250	309 321 (315)	23 20 (22)	44 38 (41)	34 31 (33)	8 9 (9)
	5000	0*C 0*C(0)	0*C 0*C(0)	95 C 85 C(90)	0*C 0*C(0)	0*C 0*C(0)
Positive control S9mix(−)	Name	AF-2	NaN3	ENNG	AF-2	9-AA
	Concentration (μg/plate)	0.01	0.5	2	0.1	80
	Number of revertants	731 682 (707)	460 431 (446)	487 478 (483)	480 430 (455)	238 244 (241)
Positive control S9mix(+)	Name	2-AA	2-AA	2-AA	2-AA	2-AA
	Concentration (μg/plate)	1	2	10	0.5	2
	Number of revertants	1045 1035 (1040)	341 290 (316)	1228 1290 (1259)	320 393 (357)	111 130 (121)

(Note) * : Microbial toxicity was observed in a background lawn. (Mean)

C : Precipitates were observed.

AF-2 : 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, NaN_3 : sodium azide

ENNG : *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine, 9-AA : 9-aminoacridine

2-AA : 2-aminoanthracene

Table 2

Results of Reverse Mutation Test (Main Test)

Test substance : RE1122.03 (No. 7L646)

with(+) or without(-) S9 mix	Test substance concentration (μg/plate)	Number of revertants (number of colonies / plate)				
		Base-pair change type			Frameshift type	
		TA100	TA1535	WP2uvrA	TA98	TA1537
S9 mix (−)	Solvent control	148 140 (144)	9 12 (11)	27 19 (23)	15 12 (14)	12 15 (14)
	39.1	160 148 (154)	5 10 (8)	24 28 (26)	24 23 (24)	11 16 (14)
	78.1	194 172 (183)	8 12 (10)	28 34 (31)	21 17 (19)	13 10 (12)
	156	182 186 (184)	10 10 (10)	26 19 (23)	22 26 (24)	11 6 (9)
	313	369 357 (363)	12 16 (14)	30 28 (29)	17 20 (19)	12 23 (18)
	625	151* 356* (254)	8* 8* (8)	40 36 (38)	34 20 (27)	9* 10* (10)
	1250	0* 0* (0)	0* 0* (0)	23* 32* (28)	15* 9* (12)	0* 0* (0)
	2500	( )	( )	0* 0* (0)	0* 0* (0)	( )
S9 mix (+)	Solvent control	165 166 (166)	9 11 (10)	16 23 (20)	29 20 (25)	19 14 (17)
	0.610	187 151 (169)	( )	( )	( )	( )
	1.22	185 178 (182)	( )	( )	( )	( )
	2.44	291 243 (267)	( )	( )	( )	( )
	4.88	407 312 (360)	( )	( )	( )	( )
	9.77	418 425 (422)	( )	( )	( )	( )
	19.5	462 489 (476)	( )	( )	( )	( )
	156	( )	11 9 (10)	23 32 (28)	41 43 (42)	19 12 (16)
	313	( )	15 9 (12)	27 19 (23)	29 28 (29)	17 23 (20)
	625	( )	12 8 (10)	44 47 (46)	23 29 (26)	12 16 (14)
	1250	( )	15 12 (14)	59 37 (48)	42 36 (39)	15 9 (12)
	2500	( )	16 19 (18)	41 52 (47)	35 28 (32)	18 14 (16)
	5000	( )	0*C 0*C(0)	83 C 104 C(94)	0*C 0*C(0)	0*C 0*C(0)
Positive control S9mix(-)	Name	AF-2	NaN3	ENNG	AF-2	9-AA
	Concentration (μg/plate)	0.01	0.5	2	0.1	80
	Number of revertants	646 579 (613)	383 414 (399)	400 356 (378)	405 373 (389)	199 179 (189)
Positive control S9mix(+)	Name	2-AA	2-AA	2-AA	2-AA	2-AA
	Concentration (μg/plate)	1	2	10	0.5	2
	Number of revertants	910 871 (891)	237 302 (270)	1095 1231 (1163)	338 382 (360)	101 115 (108)

(Note) * : Microbial toxicity was observed in a background lawn. (Mean)

C : Precipitates were observed.

AF-2 : 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, NaN_3 : sodium azide

ENNG : *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine, 9-AA : 9-aminoacridine

2-AA : 2-aminoanthracene

Table 3 Specific Activity of Reverse Mutation Test

Test substance : RE1122.03 No.7L646

	Bacterial tester strains	−S9 mix		+S9 mix	
		Specific activity [1]	Concentration [2] (μg / plate)	Specific activity [1]	Concentration [2] (μg / plate)
Dose finding test	TA100	4.54×10^{2}	313	4.06×10^{4}	4.88
	TA1535	—	—	—	—
	WP2*uvrA*	1.76×10	1250	1.30×10	5000
	TA98	—	—	—	—
	TA1537	—	—	—	—
Main test	TA100	7.00×10^{2}	313	3.98×10^{4}	4.88
	TA1535	—	—	—	—
	WP2*uvrA*	—	—	4.16×10	625
	TA98	—	—	—	—
	TA1537	—	—	—	—

1) Number of revertant colonies per 1 mg test substance

2) The concentration of the maximum specific activity was entered.

Submitted to:

Procter&Gamble Far East Inc.

[Protocol]

Bacterial Reverse Mutation Study of Substance B

(Study No. : 7L***)

******** **, 1997

Mitsubishi Chemical Safety Institute Ltd.

Outline of the Study

1. Title : Bacterial Reverse Mutation Study of Substance B (Study No. : 7L***)

2. Purpose : To assess mutagenicity of the test substance in the reverse mutation assays in *Salmonella typhimurium* and *Escherichia coli*.

3. Guideline : Japanese Guidelines for Toxicity Studies of Drugs (1989)

4. GLP : Japanese GLP on Drugs (1997)

5. Sponsor : Procter&Gamble Far East Inc.
   ****** (Address) ******
   Responsible person ****** ******

6. Organization under contract :
   Mitsubishi Chemical Safety Institute Ltd.
   1-30, Shiba 2-chome, Minato-ku, Tokyo, 105, Japan

7. Testing facility :
   Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd.
   14 Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-02, Japan

8. Management : Osamu Fujii

9. Study director : Makoto Miyagawa

10. Quality assurance manager :
    Kunihiko Ofuchi

11. Study schedule :

Initiation of the study	****** **, 1997
Dose-finding test	****** **, 1997
Main test	****** **, 1997
Issue of draft report	****** **, 1997

12. Amendments :

If it becomes necessary to change the approved study protocol, the change and the justfication will be documented and approved by the sponsor.

13. Retention :

The protocol, raw data, a sample of the test substance, documents and the final report will be retained in the archive of Kashima Laboratory. Row data, however, will be retained for the period of ** years after submission of the final report, after which time the sponsor will be contacted to determine the disposition of these materials.

Materials and Methods

1. Test materials

1.1 Test substance

Name : Substance B

Storage condition : **********

Stability : The stability data will be obtained from the sponsor.

Safety precautions : Wear protective glasses, a mask and rubber gloves.

1.2 Control substances (KSOP/MUT/104)

Negative control	Abbrev.	Supplier	Purity (%)
******	****	********	** *

Positive control	Abbrev.	Supplier	Purity (%)
2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide	AF-2	Wako Pure Chemical Industries, Ltd.	98.8
sodium azide	NaN_3	Wako Pure Chemical Industries, Ltd.	96.5
N-ethyl-*N'*-nitro-*N* -nitrosoguanidine	ENNG	Sigma Chemical Company	99.0
9-aminoacridine	9-AA	Sigma Chemical Company	99
2-aminoanthracene	2-AA	Wako Pure Chemical Industries, Ltd.	98.0

2. Bacterial tester strains

2.1 Tester strains (KSOP/MUT/140)

The tester strains used in this study are *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 received from Prof. Bruce N. Ames of the University of California at Berkeley, on May 27, 1983 and *Escherichia coli* WP2*uvrA* received from Prof. T. Matsushima of the Institute of Medical Science, University of Tokyo, on October 14, 1985.

Their genetic properties are as follows.

Strain	Gene affected	Additional mutations			Mutation type
		Repair	LPS	R-factor	
TA98	*hisD*	*uvrB*	*rfa*	pKM 101	frameshift
TA100	*hisG*	*uvrB*	*rfa*	pKM 101	base pair change
TA1535	*hisG*	*uvrB*	*rfa*	—	base pair change
TA1537	*hisC*	*uvrB*	*rfa*	—	frameshift
WP2*uvrA*	*trpE*	*uvrA*	+	—	base pair change

2.2 Checking on genetic properties (KSOP/MUT/143)

The genetic properties of the tester strains were already checked with regard to amino acid dependency, UV sensitivity, membrane mutation and drug resistance.

2.3 Storage (KSOP/MUT/142)

The stock suspensions of the tester strains were prepared by mixing 4.0 ml of the fresh bacterial suspension (cultured under shaking for 8 h at 37℃ in the liquid growth medium) and 0.35 ml of dimethylsulfoxide (DMSO). These mixtures were then quickly frozen in a dry ice-acetone mixture and stored at below -80℃.

2.4 Bacterial suspension (KSOP/MUT/141)

A frozen stock culture (20 μl) of each tester strain will be inoculated into 10 ml of the liquid growth medium and grown under shaking at 37℃ for 8 h. The bacterial density of the suspension will be measured with a turbidometer.

3. Media

3.1 Liquid growth medium (KSOP/MUT/109)

This medium contains 25 g of nutrient broth (Oxoid Nutrient Broth No. 2, Unipath Ltd.) per liter of purified water. The medium will be autoclaved for 15 min at 121℃ and used for bacterial cultures.

3.2 Minimal glucose agar plate

CLIMEDIA AM-N MEDIUM (Oriental Yeast Co., Ltd.) will be used.

3.3 Top agar (KSOP/MUT/111,112)

Bacto-agar (Difco Laboratories) of 0.6 g and sodium chloride of 0.5 g will be dissolved per 100 ml of purified water, and this solution will be autoclaved. Amino acid solution containing 0.5 mM D-biotin and 0.5 mM L-histidine (*Salmonella typhimurium*) or 0.5 mM

L-tryptophan (*Escherichia coli*) will be added to this agar solution at a ratio of 1 to 10. The top agar will be kept at about 45℃ until use.

4. S9 mix

4.1 S9

S9 prepared by Kikkoman Corporation is a liver fraction from male Sprague-Dawley rats which were intraperitoneally injected with phenobarbital (PB) at 30, 60, 60, 60 mg/kg every 24 h, respectively and 5,6-benzoflavone at 80 mg/kg at the third PB injection. The S9 will be stored below -80℃ until use.

4.2 S9 mix (KSOP/MUT/113,114)

The following table shows the composition of the S9 mix. The S9 mix will be freshly prepared for each test and kept on ice until use.

Component	Amount in 1 ml
S9	0.1 ml
$MgCl_2 \cdot 6H_2O$	8 μmol
KCl	33 μmol
D-glucose 6-phosphate	5 μmol
β-NADPH	4 μmol
β-NADH	4 μmol
sodium phosphate buffer (pH 7.4)	100 μmol
sterilized purified water	remainder

5. Test methods

5.1 Preparation of test substance solutions/suspensions and positive control solutions

A solvent selection test indicated that the test substance was soluble/insoluble in water/DMSO at 50 mg/ml. Then, water for injection (DW) /DMSO will be selected for the solvent. The test substance will be solved/suspended in DW/DMSO, (and will be sterized with a membrane filter,) and this solution/suspension will be serially diluted with the same solvent into each test substance concentration. Adjustments will be made , if necessary, to compensate for purity.

Positive controls will be solved in DMSO except for sodium azide which will be solved in water for injection (Otsuka Pharmacentical Factory Inc.,).

5.2 Test substance concentration (KSOP/MUT/102)

A dose-finding test will be conducted under conditions similar to those of the main test at six or more concentrations at a common ratio of 4 to know the toxicity of the test substance to the tester strains. The highest dose will be 5000 μg/plate. In the main test, the highest dose will be 5000 μg/plate in case of no microbial toxicity, or at a concentration with definite microbial toxicity. Five or more concentrations at a common ratio of 2 will be assayed. When the dose-finding test suggests apparent increasing revertant colonies, the main test will be carried out at concentrations likely to reveal dose-dependency.

5.3 Reverse mutation test (KSOP/MUT/101,104,106,121,122,190,191)

The test will be conducted by the pre-incubation method.

For one concentration, 0.1 ml of one of the test substance solutions/suspensions, 0.5 ml of either 0.1 M sodium phosphate buffer (pH 7.4) for assays without metabolic activation or S9 mix for assays with metabolic activation, and 0.1 ml of each bacterial suspension will be mixed in a sterilized test tube, and the mixture will be incubated under gentle shaking at 37℃ for 20 min. After pre-incubation, 2 ml of molten top agar will be added to this mixture and then poured onto a minimal glucose agar plate. When the overlay solidifies, the plate will be incubated at 37℃ for 48 h.

A background lawn will be examined with a stereoscopic microscope and microbial toxicity will be checked. The number of revertant colonies in each plate will be counted with an automatic colony counter or eyes. Two plates will be used for each concentration and the test will be performed at least twice, including the dose-finding test.

The negative and positive controls in the following table will also be assayed in the same manner.

Strain	Without S9 mix	(μg/plate)	With S9 mix	(μg/plate)
TA98	AF-2	0.1	2-AA	0.5
TA100	AF-2	0.01	2-AA	1
TA1535	NaN_3	0.5	2-AA	2
TA1537	9-AA	80	2-AA	2
WP2*uvrA*	ENNG	2	2-AA	10

5.4 Checking for bacterial contamination (KSOP/MUT/133)

The mixture of the highest concentration or S9 mix and the top agar on the agar plate will be similarly incubated to check for bacterial contamination.

5.5 Judgement (KSOP/MUT/192)

The test substance will be judged to be mutagenic (or positive) when the number of revertant colonies at any concentration increased two or more times that of the corresponding negative control for at least one tester strain either in the presence or absence of S9 mix, and when the number increase dose-dependently and reproducibly. The data will not be analyzed statistically.

Approval

Sponsor : Procter&Gamble Far East Inc.

Title : Bacterial Reverse Mutation Study of Substance B

Study No. : *L***

Organization under contract :

Study Director	Makoto Miyagawa	sealed	******* **, 1997
Quality Assurance Manager	Kunihiko Ofuchi	sealed	******* **, 1997
Management	Osamu Fujii	sealed	******* **, 1997

Sponsor :

Sponsor Representive	***** *******	sealed	******* **, 1997

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.03
Divisional Request Document(s) HBE BTS 0707/01 - 06

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman Lot # 75161 TM 25-9-97
Brand Notebook Reference N01511/30 M217/19922 leg M217/19923
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NK at: NK %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions: Store at Room temperature Viscosity: NA
Expiration Date (Day/Month/Year): 01 Sep 98 Ingredient Stability: NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: G·GENAIN (Name) Cg.Genain (Signature) 24-9-97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for thesfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: pp V. Hoyle (Name) PMMclaren (Signature) 24/09/97. (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	ARP 2581	I.R	conforms to spec	N1486/113

Description: Tan powder free from any visible contamination

22/9/97

Compositional Information Provided by:

Dominic PRATT 17/09/97

(ORIGINATOR NAME/SIGNATURE/DATE)

Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:

P.O. Graham 24/9/97.

(ANALYTICAL MGR NAME/SIGNATURE/DATE)

Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

JASON WILLIAMS

(NAME/SIGNATURE/DATE)

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulponylaminoethyl)-2-methylphenylenediamine
Purity:	99.6%
Remarks:	Test substance coded as RE-1122.03.

Method

Method/Guideline Followed:	Primary Eye Irritation Rabbit – Low Volume Method
GLP:	Yes (Japanese)
Report Year:	1999
Species:	Rabbit (Japanese White)
Gender:	Male
Number of Animals:	3
Vehicle:	Water
Concentration:	12.5% aqueous
Remarks:	10 µL (12.5% test substance in water) was placed directly on the cornea of one eye on each animal. The contralateral eye of each animal was untreated and served as the control. There was no rinse.

Results

	Minimally irritating.
Classification:	Non irritant.
Remarks:	Slight corneal opacity and conjunctivae redness were observed within 24 hours of the application and resolved by 48 hours. RE-1122.03 has reversible and minimal irritation potential to the eyes of rabbits under the conditions of this study.

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	7L748
Reference:	Procter & Gamble, 1999. Primary Eye Irritation Study of RE1122.03 in Rabbits (Low Dose Procedure). Accession #43694

ACC# 43694

Submitted to:

Proctor & Gamble Far East, Inc.

FINAL REPORT

Primary Eye Irritation Study of RE1122.03 in Rabbits

(Low-Dose-Procedure)

(Study No. 7L748)

DRD: HBE BTS 0707/01-06 C

December 24, 1999

Mitsubishi Chemical Safety Institute Ltd.

Statement

Kashima Laboratory
Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Eye Irritation Study of RE1122.03 in Rabbits (Low-Dose-Procedure)

Study number: 7L748

This study was conducted in compliance with the following Good Laboratory Practice standards.

Japanese GLP Standards for Nonclinical Safety Studies on Drugs (Ministry of Health and Welfare Ordinance No. 21, 1997)

Date: December 24, 1999

Management: Katsuhisa Kohyama (sealed)

Quality Assurance Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Eye Irritation Study of RE1122.03 in Rabbits (Low-Dose-Procedure)

Study number: 7L748

By the inspections and audits listed below, I hereby certify that this study was carried out in accordance with its protocol and with our Standard Operating Procedures, and that this report faithfully describes the methods and procedures employed, and that the reported results reflect accurately the raw data of the study.

Inspection or audit	Inspector	Date of inspection or audit	Date of reporting to	
			the study director	the management
Study protocol	Hidetsugu Watabe	November 21, 1997	November 21, 1997	November 21, 1997
Protocol amendment				
Amendment No.(1)	Hidetsugu Watabe	November 28, 1997	November 28, 1997	November 28, 1997
Amendment No.(2)	Hidetsugu Watabe	August 21, 1998	August 21, 1998	August 21, 1998
Amendment No.(3)	Hidetsugu Watabe	June 8, 1999	June 8, 1999	June 8, 1999
Study procedure				
Administration	Hidetsugu Watabe	December 1, 1997	December 1, 1997	December 2, 1997
Observation	Hidetsugu Watabe	December 2, 1997	December 2, 1997	December 3, 1997
Raw data / draft report	Hidetsugu Watabe	March 10, 1998	March 10, 1998	March 11, 1998
Final report	Hidetsugu Watabe	December 24, 1999	December 24, 1999	December 24, 1999

December 24, 1999

Quality Assurance Manager: Tamotsu Nishitomi (sealed)

Study Outline

1. Title: Primary Eye Irritation Study of RE1122.03 in Rabbits (Low-Dose-Procedure) (Study No. 7L748)

2. Purpose: To assess the primary eye irritation effects of RE1122.03 in rabbits.

3. Study methods: Low volume eye irritation test method (ASTM, 1985)[1]

4. GLP: Japanese GLP on Drugs (1997)

5. Sponsor: Proctor & Gamble Far East, Inc.
   1-17, Koyo-cho Naka Higashinada-ku, Kobe 658-0032, Japan
   Responsible person: Akihiro Kurishita, Ph. D.

6. Organization under contract:
   Mitsubishi Chemical Safety Institute Ltd.
   1-30, Shiba 2-chome, Minato-ku, Tokyo 105-0014, Japan

7. Testing facility:
   Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd.
   14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki 314-0255, Japan

8. Study contributors:
   Study director: Seiji Otake, D.V.M. (sealed) Date: December 24, 1999

   Other contributor: Hiroyuki Aoki

9. Study schedule:

Initiation of the study	November 21, 1997
Receipt of animals	November 26, 1997
Administration	December 1, 1997
Final observation	December 4, 1997
Completion of the study	December 24, 1999

10. Unforeseeable circumstances that may have adverse effects on the reliability of the study and deviation from the protocol: none

11. Retention: The records and documents listed below are retained in the archives of the Kashima Laboratory. Raw data is retained for five years after submission of the final report and further retention will be discussed with the sponsor.

Protocol and all amendments
Test substance
Test substance data and records
Animal care data and facility maintenance data
Quarantine and acclimatization records
Dosing records
Clinical signs observation records
Body weight measurement records
Eye irritation reactions observation records
Photographs of eye observation
Records of inspection by Quality Assurance Unit
Final report
Others

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Summary

Primary eye irritation potential of RE1122.03 was assessed in three male Japanese White rabbits (Kbl:JW, SPF) in accordance with the low volume eye irritation test method (ASTM, 1985).

The test substance (12.5% test substance in water) was directly placed on the cornea on one eye of each animal at a dose volume of 10 μL.

Slight corneal opacity and conjunctivae redness were observed within 24 hour of the application, but these eye lesions disappeared by 48 hours after the application.

The median number of days to recovery was 1 day (within 24 hours). In addition, the maximum average score (MAS) of the weighted score by the Draize's was 2.3, and the test substance was classified as "minimally irritating" for convenience' sake based on MAS.

Based on the results in this study, it was concluded that RE1122.03 has reversible and minimally irritation potential to the eyes of the rabbits under the conditions of this study.

Materials and Methods

1. Test substance

RE1122.03 (lot no. 75161) was supplied by Proctor & Gamble Far East, Inc. The test substance is a white crystal powder with a melting point of 300℃. The sponsor warranted the stability of the test substance during the study period.

Water for injection (Otsuka Pharmaceutical Factory, Inc., lot no. K7B86, J.P.) was used as a vehicle for the test substance.

2. Experimental animals

Three male Japanese White rabbits (Kbl:JW, SPF) purchased from Kitayama LABES Co., Ltd. on November 26, 1997 were used in this study. The animals were confirmed to be in good health by the quarantine and acclimatization period of five days. About 4 hours before application, their eyes were examined and animals without abnormalities in their eyes were selected for this study. The animals were 11 weeks old and weighed 2.0 kg on the day of application.

Each animal was identified by a number marked on the earlobe with oil-base ink. Each cage was identified with a label bearing the study number, name of the test substance, name of animal group, animal number, gender, the date of administration, species, and strain.

3. Animal management

Throughout the study including the quarantine-acclimatization period, the rabbit room was maintained at a temperature of 22±2℃ (target value) and a relative humidity of 55± 15% (target value). It was ventilated by 12 flesh air change per hour and was lit for 12 hours per day (7:00-19:00). The animals were individually housed in aluminum cages (32W×48D×33H cm, Tokiwa Kagaku Kikai Co., Ltd.) furnished with a metal mesh flooring. The cages were mounted on an automatic maintenance device (Tokiwa Kagaku Kikai Co., Ltd.) and excrement was washed out automatically with water. Diet was supplied from a stainless feeder (Tokiwa Kagaku Kikai Co., Ltd.) and water from an automatic watering system (Tokiwa Kagaku Kikai Co., Ltd.). Cages and feeders were disinfected with steam and were changed weekly.

A pellet diet for experimental animals (LRC4, Oriental Yeast Co., Ltd.) and tap water

filtered through a 5 μm filter and irradiated with UV were given to the animals *ad libitum*. A fresh diet was added daily, the remainder was discarded once a week, and a new diet was provided. An analytical report on hazardous contaminants such as pesticide residues in the diet showed that the diet met our laboratory's specifications. The tap water was analyzed periodically in accordance with the Waterworks Law of Japan, and met the required specifications.

4. Preparation of test sample

The test substance was dissolved in water for injection to prepare the test substance at 12.5 w/v%.

5. Number of animals

Three animals (eye-unwashed group)

6. Administration

6.1 Dose level and frequency of administration

10 μL, once

6.2 Treatment

The eyelids of one eye of each animal were gently held open, and then the test substance measured in microsyringe was placed directly on the cornea. The eyelids were released immediately after application without forcible closing or movement. The treated eyes remained untreated for 24 hours following application. The other eye of each animal remaining untreated to serve as the control

A plastic Elizabethan collar was fitted around the neck of the animals to protect the eyes from shortly before administration until 24 or 48 hours after the application.

6.3 Reason for the choice of dose level, frequency of administration and methods

This study was performed according to the low volume eye irritation test method (ASTM, 1985)[1].

7. Observation

Eyes were examined 1, 24, 48 and 72 hours after the application. Clinical signs were observed everyday.

The cornea, iris and conjunctivae were examined for abnormalities with a portable slit lamp (SL-5: Kowa Co., Ltd.). At 24 hour after application and thereafter, 1% sodium fluorescein (Wako Pure Chemical Ind. Ltd.) aqueous solution was instilled in the treated eye and was rinsed out with purified water. then the cornea was fully examined for any lesions under UV lighting (UVM-57, Funakoshi Co., Ltd.).

8. Criteria for scoring, calculation of median recovery time, calculation of the maximal average score and classification of eye irritation for convenience' sake

8.1 Criteria for scoring

Opacity of the cornea and area of opacity, injuries of iris, and redness, swelling and discharge of the conjunctivae were scored according to Draize's method[2] shown in Annex 1.

8.2 Calculation of median recovery time

Number of days to disappearance of all eye lesions was determined individually to calculate the median number of days to recovery.

8.3 Calculation of the maximal average score

The sum of the weighted scores for cornea, iris and conjunctivae was calculated for each animal according to the formula shown in Annex 1, then the mean score was calculated for each observation time. The maximal average score (MAS) was determined by selecting the highest mean score within 96 hours (four days) of application. In this study, the mean score at 96 hours was accounted as 0 because eyes of all animals recovered within 72 hours.

8.4 Classification of eye irritation for convenience' sake

Eye irritation property was classified for convenience' sake based on the MAS in conformity with criteira[3] shown in Annex 2.

9. Body weight measurement

Individual body weights of all animals were measured with an electric balance (EB-16KS, Shimadzu Corp.) shortly before administration and at the final observation.

10. Fate of animals

The animals used in this study were sacrificed by an overdose (approx. two times higher than the optimal dose) of barbiturates (RAVONAL: Tanabe Seiyaku Co., Ltd.).

Results and Conclusion

1. Ocular reactions (Table 1)

   Corneal opacity of score 1 (area: 1) was observed in one animal and conjunctival redness of score 1 was observed in all animals within 24 hour of the application. These eye lesions disappeared by 48 hours after the application.

2. Median recovery time and the maximal average score (Table 2)

   The number of days to disappearance of all eye lesions was 1 day (within 24 hours) for two animals and 2 days (within 48 hours) for one animal, and the median number of days to recovery was 1 day (within 24 hours). The MAS was 2.3 at 24 hour after the application.

3. Classification of eye irritation for convenience' sake

   The test substance was classified as "minimally irritating" for convenience' sake based on the MAS of the weighted score by the Draize's method.

4. Clinical signs

   No abnormal clinical signs were observed in any animal during the observation period.

5. Body weights (Table 3)

   No abnormalities in body weight change that could be ascribed to the test substance were observed in any animal.

6. Conclusion

   RE1122.03 has reversible and minimally irritation potential to the eyes of the rabbits under the conditions of this study.

References

1. American Society for Testing and Materials (1985): Standard method for evaluation of eye irritation in albino rabbits, E1055-85. In Annual Book of ASTM Standards, Philadelphia.

2. Draize, J. H., Woodard, G., Calvery, H. O. (1944): Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes, J. Pharmacol. Exp. Therap., 82, 377-390.

3. Kay, J. H. & Calandra, J. C. (1962): Interpretation of eye irritation test, J. Soc. Cosm. Chem., *13*, 281-289.

Annex I Scale of weighted score for grading the severity of ocular lesions

I . Cornea

A. Opacity - degree of density (area most dense taken for reading)

No opacity	0
Scattered or diffuse area, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4

B. Area of cornea involved

One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half less than three quarters	3
Greater than three quarters up to whole area	4

Score equals A × B × 5 Total maximum = 80

II . Iris

A. Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any one or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage; gross destruction (any one or all of these)	2

Score equals A × 5 Total maximum = 10

III. Conjunctivae

A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

B. Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of the lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

C. Discharge

No discharge	0
Any amount different from normal (does not include small amount observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to the lids	2
Discharge with moistening of the lids and considerable area around the eye	3

Score (A + B + C) × 2 Total maximum = 20

The maximum total score is the sum of all scores obtained for the cornea, iris and conjunctivae.

Annex 2 Classification of compounds based on eye irritation properties

(Steps 1 and 2)

Step 1

Find the maximum, mean total score for all three tissues occurring within the first 96 hr. following instillation for which the incidence of this score plus or minus 5 points is at least 40 per cent.

Step 2

Choose an initial or tentative rating on the basis of the score found in step 1 as follows:

Score from step 1				Tentative eye irritation rating
0.0	to	0.5	points	Nonirritating (N)
0.5	to	2.5	points	Practically nonirritating (PN)
2.5	to	15	points	Minimally irritating (M_1)
15	to	25	points	Mildly irritating (M_2)
25	to	50	points	Moderately irritating (M_3)
50	to	80	points	Severely irritating (S)
80	to	100	points	Extremely irritating (E)
100	to	110	points	Maximally irritating (Mx)

For borderline scores choose the higher rating

(Step 3)

Tentative rating	Requirement for maintenance
N	$MTS_{24} = 0$; for $MTS_{24} > 0$, raise one level
PN	As for N
M_1	$MTS_{48} = 0$; for $MTS_{48} > 0$, raise one level
M_2	$MTS_{96} = 0$; for $MTS_{96} > 0$, raise one level
M_3	(1) $MTS_f \leqq 20$; for $MTS_f > 20$, raise one level
	(2) $ITS_f \leqq 10$ (60%); if not true then no rabbit may show $ITS_f > 30$; otherwise raise one level
S	(1) As for M_3 except use $MTS_f \leqq 40$
	(2) As for M_3 except use $ITS_f \leqq 30$ (60%) and 60 for high
E	(1) As for M_3 except use $MTS_f \leqq 80$
	(2) As for M_3 except use $ITS_f \leqq 60$ (60%) and 100 for high
Mx	(1) $MTS_f > 80$; for $MTS_f \leqq 80$, lower one level
	(2) $ITS_f > 60$ (60%); otherwise lower one level

Symbols: MTS = Mean total score. ITS = Individual rabbit total score.
Subscripts denote scoring interval: 24, 48 or 96 hr. f = final score (7 days)

Test material:12.5%RE1122.03 (unwashed eye)

Animal No.	Observation Time		Score for ocular reaction: Cornea Opacity	Cornea Area	Iris	Conjunctivae Redness	Conjunctivae Chemosis	Conjunctivae Discharge	Other findings
1	1	Hours	0	0	0	1	0	0	-
	24		1 *	1 *	0	1	0	0	-
	48		0 *	0 *	0	0	0	0	-
	72		0	0	0	0	0	0	-
2	1	Hours	0	0	0	1	0	0	-
	24		0 *	0 *	0	0	0	0	-
	48		0	0	0	0	0	0	-
	72		0	0	0	0	0	0	-
3	1	Hours	0	0	0	1	0	0	-
	24		0 *	0 *	0	0	0	0	-
	48		0	0	0	0	0	0	-
	72		0	0	0	0	0	0	-

*: Examined with fluorescein

-: No findings

Table 2 Weighted scores and the median of days for eyes to clear all effects

Test material:12.5%RE1122.03 (unwashed eye)

Animal No.	Score* Observation time 0 [1 hours]	1 24 hours	2 48 hours	3 72 hours	4 days	Days for eyes to clear
1	2	7	0	0	—	2
2	2	0	0	0	—	1
3	2	0	0	0	—	1
Mean score	2.0	2.3 **	0	0	0	Median 1

*: The maximum score:110

**: MAS

Table 3 Individual body weights

(kg)

Animal No.	Before application	72 hours after application
1	2.0	2.1
2	2.0	2.0
3	2.0	2.0

Submitted to: Procter and Gamble Far East Inc.
****

+IBE BTS 707 105

[PROTOCOL]

Primary Eye Irritation Study of

********** in Rabbits

(Low-Volume-Procedure)

(Study No. *L***)

RE1122.03

******* **, 199*

Mitsubishi Chemical Safety Institute Ltd.

97-10-24:18:18 ;P&G P&RS/R&CD :078 845 6949 # 2/ 61

Outline of the Study

1. Title: Primary Eye Irritation Study of ********* in Rabbits (CRE1122.03)
(Low-Volume-Procedure) (Study No. *L***)

2. Purpose: To assess the primary eye irritation effect of *********
in rabbits

3. Study method: Low volume eye irritation test method (ASTM. 1985)

4. GLP: Japanese GLP on Drugs (1982, 1988)

5. Sponsor: **(Company Name)********** Procter & Gamble Far East, Inc.
(Address)********#-17, Koyo-cho Naka
Responsible Person: ****** ***** Higashinada-ku, Kobe 658 Japan
Akihiro Kurishita, Ph. D.

6. Organization under contract:
Mitsubishi Chemical Safety Institute Ltd.
1-30, Shiba 2-chome, Minato-ku, Tokyo 105, Japan

7. Testing facility:
Kashima Laboratory
14 Sunayama, Hasaki-machi, Kashima-gun, Ibaraki 314-02, Japan

8. Management: ***** *****

9. Study director: ***** ******

10. Quality assurance manager:
Kunihiko Ofuchi

97-10-24;18:18 ;P&G P&RS/R&CD ;078 845 6949 # 3/ 61

11. Study schedule:

initiation of the study	***** **, 1996
arrival of animals	***** **, 1996
administration	***** **, 1996
submission of the draft report	***** **, 199*

12. Amendment: If necessary, the amendment and its reasoning shall be documented and they shall be approved by the sponsor.

---

13. Retention: The records and specimens listed below will be retained in the safekeeping facility of Kashima Laboratory for 5 years after submission of the final report. Further retention of the specimens and raw data will be discussed with the sponsor at 5 years after submission of the final report.

Protocol and all amendments
Test substance
Test substance data and records
Animal care data and facility maintenance data
Quarantine and acclimatization records
Dosing records
Clinical signs observation records
Body weight measurement records
~~Dermal~~ irritation reactions observation records
Photographs of ~~dermal~~ observations (if necessary)
Records of inspection by Quality Assurance Unit
Final report
Others (if necessary)

eye

Eye

97-10-24;18:18 ;PBG PBRS/RBCD :078 845 6949 # 4/ 61

Physicochemical properties: Appearance : Off-white free flowing crystalline powder
Order : NONE
Melting point : 300°C

Materials and Methods

1. Test substance

Name: RE 1122.03
Lot number : 75161
Storage condition: ********* Room temperature
Stability: The sponsor will confirm the stability of the test substance, ~~by analyzing the lot used before and after the study.~~

Safety precautions: Wear glasses, a mask and rubber gloves,

2. Experimental animals

2.1 Species: Rabbit

2.2 Strain: Japanese White variety (Kbl:JW)

2.3 Reasons for choice of strain:
This strain has been commonly used in primary eye irritation studies and is easy to be obtained, and much historical data are available.

2.4 Microbial level: SPF

2.5 Supplier: Kitayama LABES Co., Ltd.

2.6 Number of animals: *** male (or female) animals (for two studies: *L*** and *L***)

2.7 Quarantine and acclimatization:
According to daily clinical observation during 5-day acclimatization, healthy animals will be selected.

2.8 Age at administration: 9~11 weeks old

2.9 Body weight at administration: 2.0~2.8 kg

2.10 Selection of animals:
About four hours before administration, the eyes of the animals will be examined using a portable slit lamp, and UV lamp (Funakoshi Co.) with instilation of 1% sodium fluorescein water solution. Only healthy animals without abnormality in eyes will be used.

97-10-24;18:18 ;P&G P&RS/R&CO ;078 845 6949 # 5/ 61

2.11 Identification: Animals will be identified by a number marked on the earlobe. Cages will be identified by a label listing the study number, name of the test substance, group name, animal number, the sex, the day of administration, the name of species and strain.

3. Animal husbandry

3.1 Environmental control

1) Room temperature: 22± 2℃

2) Relative humidity: 55±15%

3) Ventilation: About 12 changes per hour with fresh filtered air

4) Lighting period: 12 hours per day (7:00-19:00)

3.2 Animal accommodation

1) Cage: Aluminum cage (32W×48D×33H cm, Tokiwa Kagaku Kikai Co., Ltd.); this will be disinfected by steam and renewed once a week.

2) Feeder: Stainless steel feeder (Tokiwa Kagaku Kikai Co., Ltd.); this will be disinfected by steam and renewed once a week.

3) Watering: Automatic watering system (Tokiwa Kagaku Kikai Co., Ltd.)

4) Rack: Automatic cascade type maintenance device (Tokiwa Kagaku Kikai Co., Ltd.)

3.3 Diet

1) Name: Pellet diet for experimental animals (LRC4: Oriental Yeast Co., Ltd.)

2) Feeding: *ad libitum*; the diet will be renewed once a week.

3) Analysis: An analytical report on hazardous contaminants will show that the diet met our laboratory's specifications.

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3.4 Water supply

1) Description: Tap water filtered with a 5μm filter and UV irradiated

2) Watering: *ad libitum*

3) Analysis: Tap water has been analyzed periodically according to the Waterworks Law of Japan and meets the specifications.

3.5 Housing: one animal per cage

4. Preparation of the test materials

~~Liquids will be used undiluted as supplied. Solids may be ground to a fine powder, if necessary.~~ The test substance will be diluted ~~as~~ at 10% (w/v) with distilled water the injection (JP, Otsuka ...) for administration.

5. Number of animals

Initially three animals will be treated as eye-unwashed group. If necessary, three additional animals as eye-washed group will be treated.

6. Application

6.1 Dose volume: 10μl

If the test substance is a powder, a convenient volume of the test substance is measured in a small graduate cylinder or syringe (at least 2 ml), as follows:

1) Tapping gently, the weight in grams and the volume in mililiters are recoreded. The bulk density (d) of the test substane is calculated to the nearest 0.1 g/ml using the following calculations:

$$\frac{\text{Weight of test substance (g)}}{\text{Volume of test substance (ml)}} = \text{density (d)}$$

2) The weight of test substance which occupies a 10μl volume is calculated, as follows:

Density (d) × 10 = X mg of test substance to be used in the eye

The quantity of test substance equivalent to a 10μl volume is weighed to the nearest 0.1 mg using a suitable analytical balance.

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6.2 Dosing frequency: Once

6.3 Treatment

The eyelids of one eye will be held open gently and 10μl. or the weight equivalent. of the test substance will be placed directly on the cornea of one eye of each rabbit. The eyelids will be then released immediately without any forced blinking or manipulation. The other eye remains untreated to serve as a control. The treated eye will be left unwashed for 24 hours in the eye-unwashed group. After 24 hours. a rinse may be applied if it is considered to be appropriate. For eye-washed group. immediately after application the eye will be rinsed for about four seconds by spraying 20 ml of tepid purified water from a syringe fitted a 16- or 18-gauge plastic needle.

A plastic Elizabethan collar is then fitted to each animal for more than 24 hours after application to protect the treated eye.

6.4 Justification of dose. method and frequency

These are widely used for ocular-mucous irritation studies using the low-volume-procedure (American Society for Testing and Materials. 1985).

7. Observations. materials used in the examination. criteria. classification and calculation of median day

7.1 Observations (KSOP/ANH/456)

The eyes will be examined at 1. 24. 48 and 72 hours after application to assess ocular reactions. If there is no ocular irritation at 72 hours. the study will be complete. If irritation reactions persistent. additional observation will be made on day 4. 7. 10. 14. 18. and 21 as necessary to assess the progression of the lesions and their reversibility. If all the eyes ~~will~~ are not cleared by 21 days after application. the laboratory should contact the sponsor regarding an extension of the observation period. In addition. any other eye abnormalities and clinical signs will be recorded.

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7.2 Materials used in the examination

1) Hand slit lamp to be used if necessary.

2) UV lamp (UVL-56 or UVM-57, Funakoshi Co.):

To be used for the examination with 1% sodium fluorescein water solution at one hour and later following application in the eye-washed group, and at 24 hours and later following application in the eye-unwashed group.

7.3 Criteria and scoring of ocular reactions (KSOP/ANH/281)

Opacity of the cornea and its area, congestion and swelling of the iris, and redness, swelling, discharge of the conjunctivae should be scored after Draize shown in Table 1.

7.4 Median day to clear

If an ocular reaction occurs at treated site, the median number of days for eyes to clear of all effects will be determined for eye-unwashed group and eye-washed group by arranging the days for each animal to clear in increasing numerical sequence.

7.5 Maximum average score

According to formula shown in Table 1, the Primary Irritation Score at each observation period for eye-unwashed group and eye-washed group of animals will be calculated by totaling all of the cornea, iris, and conjunctivae scores and dividing by the original number of animals in the group.

The Maximum Average Score (MAS) will be determined for eye-unwashed group and eye-washed group. The MAS is the highest Primary Irritation Score recorded for any given observation period.

8. Body weights

Individual body weights of all animals will be measured shortly before application and at the final observation. When observation is extended beyond one week, subsequent body weights will be measured weekly.

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9. Fate of animals

The animals used in this sudy will be sacrificed by overdosing barbiturates (about twice of optimal dose) after the termination of observation.

10. Final Report:

The Draft Final Report including tables will be presented by April 25, 1997. The sponsor shall review the Report and indicate as soon as possible whether it is acceptable as the Final Report. With the sponsor's approval, the Final Report will be delivered to the sponsor by May 25, 1997. If more time is needed to discuss the Report, the date of presentation of the Final Report will be postponed. The Report will consist of the following sections:

Summary
Materials and methods
Results
1) ~~Dermal~~ Eye reactions
2) Body weight
3) Clinical signs
Conclusion
Tables
1) ~~Dermal~~ reactions
2) Body weight
3) Clinical signs (if necessary)
Photographs (if necessary)

97-10-24;18:18 ;P&G P&RS/R&CD
;078 845 6949 # 10/ 61

Table 1
Scale of weighted scores for grading the severity of ocular lesions

I. Cornea
A. Opacity - degree of density (area most dense taken for reading)
No opacity 0
Scattered or diffuse area, details of iris clearly visible 1
Easily discernible translucent areas, details of iris slightly obscured 2
Opalescent areas, no details of iris visible, size of pupil barely discernible 3
Opaque, iris invisible 4

B. Area of Cornea Involved
One quarter (or less) but not zero 1
Greater than one quarter, but less than half 2
Greater than half less than three quarters 3
Greater than three quarters up to whole area 4

Score equals A×B×5 Total maximum = 80

II. Iris
A. Values
Normal 0
Folds above normal, congestion, swelling, circumcorneal injection (any one or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive) 1
No reaction to light, hemorrhage ; gross destruction (any one or all of these) 2

Score equals A×5 Total maximum = 10

III. Conjunctivae
A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)
Vessels normal 0
Vessels definitely injected above normal 1
More diffuse, deeper crimson red, individual vessels not easily discernible 2
Diffuse beefy red 3

B. Chemosis
No swelling 0
Any swelling above normal (includes nictitating membrane) 1
Obvious swelling with partial eversion of the lids 2
Swelling with lids about half closed 3
Swelling with lids about half closed to completely closed 4

C. Discharge
No discharge 0
Any amount different from normal (does not include small amount observed in inner canthus of normal animals) 1
Discharge with moistening of the lids and hairs just adjacent to the lids 2
Discharge with moistening of the lids and considerable area around the eye 3

Score (A+B+C) ×2 Total maximum = 20

The maximum total score is the sum of all scores obtained for the cornea, iris and conjunctivae.

97-10-24;18:18 ;P&G P&RS/R&CD :078 845 6949 # 11/ 61

Approval

Sponsor : **********

Title : Primary Eye Irritation Study of ********** in Rabbit
(Low-Volume-Procedure)

Study No. : *L***

Study Director

***** ****** sealed ****** **, 1996

Quality Assurance Manager

Kunihiko Ofuchi sealed ****** **, 1996

Management

***** ***** sealed ****** **, 1996

Responsible Person of the Sponsor

******** ******* sealed ****** **, 1996

97-10-24:18:18 :P&G P&RS/R&CD :078 845 6949 # 12/ 61

05

プロクター・アンド・ギャンブル・ファー・イースト・インク　殿

試験報告書

試験報告書（7L748）の英訳

2000年6月15日

株式会社三菱化学安全科学研究所

Translation Statement

Kashima Laboratory
Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Eye Irritation Study of RE1122.03 in Rabbits (Low-Dose-Procedure)

Study number: 7L748

This study was conducted in the Kashima Laboratory of Mitsubishi Chemical Safety Institute Ltd. The original study report was written in Japanese. I hereby declare that this report faithfully reflects the original study report.

Translator: Seiji Otake Date: June 15, 2000

Seiji Otake, D.V.M.

Research Scientist, Toxicology Division of Kashima Laboratory

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.03
Divisional Request Document(s) HBE BTS 0707/01 - 06

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman LOT # 75161 TM 25-9-97
Brand Notebook Reference_N01511/30 M217/19922 leg M217/19923
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NK at: NK %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions:_Store at Room temperature Viscosity:_NA
Expiration Date (Day/Month/Year):_01 Sep 98 Ingredient Stability:NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: G·GENAIN (Name) G. Genain (Signature) 24-9-97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for thesfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: pp V. Hoyle (Name) P M Mclaren (Signature) 24/09/97. (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	ARP 2581	I.R	conforms to spec	N1486/113

Description: Tan powder free from any visible contamination
22/9/97 [signature]

Compositional Information Provided by:
[signature] Dominic PRATT 17/09/97
(ORIGINATOR NAME/SIGNATURE/DATE)
Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:
[signature] 24/9/97.
(ANALYTICAL MGR NAME/SIGNATURE/DATE)
Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

JASON WILLIAMS
(NAME/SIGNATURE/DATE)
[signature]

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.
COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.
NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.
ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

ssu\tscr.doc
Issue Date: August 22, 1996
Supersedes: July 25, 1996

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulponylaminoethyl)-2-methylphenylenediamine
Purity:	99.6%
Remarks:	Test substance was coded as RE-1122.03.

Method

GLP:	Yes (Japanese)
Report Year:	1999
Method/Guideline Followed:	Primary Dermal Irritation
Species:	Rabbit (Japanese White)
Gender:	Male
Number of Animals:	3
Vehicle:	Water
Concentration:	2.5 or 12.5% aqueous
Remarks:	No abnormal clinical signs were observed in any animal during the observation period. No abnormalities in body weight change that could be ascribed to the test substance were observed in any animal.

Results

Result:	The test substance at 2.5% and 12.5% was considered "mildly irritating".
Classification:	Non irritant.
Remarks:	A single occluded application of the 2.5% and 12.5% RE1122.03 caused slight to mild erythema and slight edema on both intact and abraded skin. It was concluded that the test substance has reversible and mild irritation potential to the skin of rabbits under the conditions of this study.

2.5% Intact skin PII= 1.3
2.5% Abraded skin PII = 1.5

12.5% Intact skin PII = 1.3
12.5% Abraded skin PII= 1.7

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	7L747
Reference:	Procter & Gamble, 1999. Primary Dermal Irritation Study of RE1122.03 in Rabbits. Accession #43696

Acc# 43696

Submitted to:

Proctor & Gamble Far East, Inc.

FINAL REPORT

Primary Dermal Irritation Study of

RE1122.03 in Rabbits

(Study No. 7L747)

DRD: HBE BTS 0707/01-06 e

December 24, 1999

Mitsubishi Chemical Safety Institute Ltd.

Statement

Kashima Laboratory
Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Dermal Irritation Study of RE1122.03 in Rabbits

Study number: 7L747

This study was conducted in compliance with the following Good Laboratory Practice standards.

Japanese GLP Standards for Nonclinical Safety Studies on Drugs (Ministry of Health and Welfare Ordinance No. 21, 1997)

Date: December 24, 1999

Management: Katsuhisa Kohyama (sealed)

Quality Assurance Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Dermal Irritation Study of RE1122.03 in Rabbits

Study number: 7L747

By the inspections and audits listed below, I hereby certify that this study was carried out in accordance with its protocol and with our Standard Operating Procedures, and that this report faithfully describes the methods and procedures employed, and that the reported results reflect accurately the raw data of the study.

Inspection or audit	Inspector	Date of inspection or audit	Date of reporting to	
			the study director	the management
Study protocol	Hidetsugu Watabe	November 21, 1997	November 21, 1997	November 21, 1997
Protocol amendment				
Amendment No.(1)	Hidetsugu Watabe	November 28, 1997	November 28, 1997	November 28, 1997
Amendment No.(2)	Hidetsugu Watabe	August 21, 1998	August 21, 1998	August 21, 1998
Amendment No.(3)	Hidetsugu Watabe	June 8, 1999	June 8, 1999	June 8, 1999
Study procedure				
Administration	Hidetsugu Watabe	December 2, 1997	December 2, 1997	December 3,1997
Observation	Hidetsugu Watabe	December 3, 1997	December 3, 1997	December 3, 1997
Raw data / draft report	Hidetsugu Watabe	March 9, 1998	March 9, 1998	March 11, 1998
Final report	Hidetsugu Watabe	December 24, 1999	December 24, 1999	December 24, 1999

December 24, 1999

Quality Assurance Manager: Tamotsu Nishitomi (sealed)

Study Outline

1. Title: Primary Dermal Irritation Study of RE1122.03 in Rabbits
   (Study No. 7L747)

2. Purpose: To assess the primary dermal irritation effects of RE1122.03 in rabbits.

3. Study method: Draize method[1]

4. GLP: Japanese GLP on Drugs (1997)

5. Sponsor: Proctor & Gamble Far East, Inc.
   1-17, Koyo-cho Naka Higashinada-ku, Kobe 658-0032, Japan
   Responsible person: Akihiro Kurishita, Ph. D.

6. Organization under contract:
   Mitsubishi Chemical Safety Institute Ltd.
   1-30, Shiba 2-chome, Minato-ku, Tokyo 105-0014, Japan

7. Testing facility:
   Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd.
   14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki 314-0255, Japan

8. Study contributors:
   Study director: Seiji Otake, D.V.M. (sealed) Date: December 24, 1999

   Other contributor: Hiroyuki Aoki

9. Study schedule:

Initiation of the study	November 21, 1997
Receipt of animals	November 26, 1997
Administration	December 2, 1997
Final observation	December 9, 1997
Completion of the study	December 24, 1999

10. Unforeseeable circumstances that may have adverse effects on the reliability of the study and deviation from the protocol: none

11. Retention: The records and documents listed below are retained in the archives of the Kashima Laboratory. Raw data is retained for five years after submission of the final report and further retention will be discussed with the sponsor.

Protocol and all amendments
Test substance
Test substance data and records
Animal care data and facility maintenance data
Quarantine and acclimatization records
Dosing records
Clinical signs observation records
Body weight measurement records
Dermal irritation reactions observation records
Photographs of dermal observation
Records of inspection by Quality Assurance Unit
Final report
Others

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Summary

The primary dermal irritation test of RE1122.03 was conducted in three male Japanese White rabbits (Kbl:JW, SPF) in accordance with the Draize's method[1].

The test substance was dissolved in water for injection (J.P.), and three test samples, 2.5 w/v% and 12.5 w/v% test substances and water for injection (control substance), were applied separately to one application site on both intact and abrade skin.

After an occluded application for 24 hours, slight to mild erythema and slight edema were observed at the area applied with 2.5% and 12.5% test substances on both intact and abraded skin. These dermal reactions disappeared by seven days after the application. No dermal reactions were observed at the area applied with the control substance on the intact skin. Slight erythema was observed on abraded skin, but theses dermal reactions on abraded skin disappeared by 72 hours after application.

The primary irritation index (P.I.I.) for the 2.5% test substance applied area was 1.3 for intact skin and 1.5 for abraded skin, and the 12.5% test substance applied area was 1.3 for intact skin and 1.7 for abraded skin. Based on these indexes, 2.5% and 12.5% test substances were classified as "mildly irritant", and there is no obvious difference in irritation effect between the intact and abraded skins.

Based on the results in this study, it was concluded that RE1122.03 has reversible and mild irritation potential to rabbit skin under the conditions of this study.

Materials and Methods

1. Test substance

RE1122.03 (lot no. 75161) was supplied by Proctor & Gamble Far East, Inc. The test substance is a white crystal powder with a melting point of 300℃. The sponsor warranted the stability of the test substance during the study period.

Water for injection (Otsuka Pharmaceutical Factory, Inc., lot no. K7B86, J.P.) was used as the vehicle for the test substance.

2. Experimental animals

Three male Japanese White rabbits (Kbl:JW, SPF) purchased from Kitayama LABES Co., Ltd. on November 26, 1997 were used in this study. The animals were confirmed to be in good health by the quarantine and acclimatization period of six days. The hair on the dorsal area of the trunk was removed with electric clippers one day before the administration, and the animals with smooth skin were selected for this study. They were 11 weeks old and their body weight ranged form 2.0 to 2.1 kg on the day of the administration.

Each animal was identified by a number marked on the earlobe with oil-base ink. Each cage was identified with a label bearing the study number, name of the test substance, name of animal group, animal number, gender, the date of administration, species, and strain.

3. Animal management

Throughout the study including the quarantine-acclimatization period, the rabbit room was maintained at a temperature of 22±2℃ (target value), and at a relative humidity of 55±15% (target value). It was ventilated by 12 fresh air change per hour and was lit for 12 hours per day (7:00-19:00). The animals were individually housed in an aluminum cages (32W×48D×33H cm, Tokiwa Kagaku Kikai Co., Ltd.) furnished with a metal mesh flooring. The cages were mounted on an automatic maintenance device (Tokiwa Kagaku Kikai Co., Ltd.) and excrement was washed out automatically with water. Diet was supplied from a stainless feeder (Tokiwa Kagaku Kikai Co., Ltd.) and water from an automatic watering system (Tokiwa Kagaku Kikai Co., Ltd.). Cages and feeders were

disinfected with steam and were changed weekly.

A pellet diet for experimental animals (LRC4, Oriental Yeast Co., Ltd.) and tap water filtered through a 5 μm filter and irradiated with UV were given to the animals *ad libitum*. A fresh diet was added daily, the remainder was discarded once a week, and a new diet was provided. An analytical report on hazardous contaminants such as pesticide residues in the diet showed that the diet met our laboratory's specifications. The tap water was analyzed periodically in accordance with the Waterworks Law of Japan, and met the required specifications.

4. Preparation of test sample

The test substance was dissolved in water for injection to prepare the test substance at 2.5 w/v% and 12.5 w/v%.

5. Test group

Test group and number of animals are shown in the following table.

Group name	Test materials	Number of animals	Animal number
Test substance administration-1	1) water for injection 2) RE1122.03 (2.5%) 3) RE1122.03 (12.5%)	3	1~3

6. Administration

6.1 Dose level

0.5 mL/application site

6.2 Frequency of administration and exposure period

A single 24-hours, occluded application

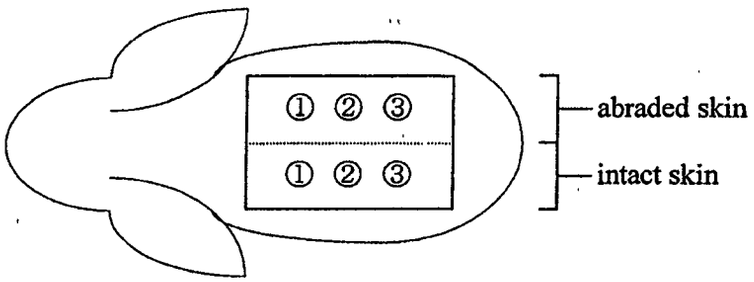
6.3 Treatment

Six application sites, three sites on one side of the midline, were assigned on the dorsal area of the rabbit trunk. Three of the six application sites were placed on the intact skin and other three sites were placed on the abraded skin that was stripped three times using an adhesive tape (Fig.1).

The test samples of each concentration were separately spread on gauze patch (about 2.5 ×2.5 cm, about 6 cm^2) and were applied to the skin; thus each test sample were applied on

one site on both intact and abraded skin as shown in Fig.1. The patches were fixed loosely with 1.2×7 cm adhesive tape in a crisscross-shape. The administration sites were covered with an impervious sheet and secured with a semi-occlusive elastic bandage around the trunk. Furthermore, the rabbit was dressed with fixing clothes (made here) to keep loose contact of patches to the skin. The site applied with the vehicle served as the control. The patches were removed 24 hours after the application, and residue of the test substance was washed out with tepid water. The application sites on each animal were rotated to confirm that the dermal reactions were not dependent on location.

A plastic Elizabethan collar was fitted around the neck of the animals to protect the application site immediately after application until 7 days after the application.



① : water for injection (vehicle)
② : RE1122.03 (0.5%)
③ : RE1122.03 (2.5%)

Fig.1 Administration sites (example)

6.4 Reason for the choice of dose level, frequency of administration and methods

Dose level, frequency of administration and methods in this study are widely used for primary dermal irritation studies.

7. Observation, criteria for scoring and classification of dermal irritation

7.1 Observation

The application sites were examined for dermal reactions at 24 (within 1 hour of the patch removal), 48, 72 hours, and 7 days after the application. Clinical signs were observed everyday.

7.2 Criteria for scoring

Dermal reactions were scored according to Draize's criteria[1] shown in Annex 1.

7.3 Classification of dermal irritation

All scores (erythema and edema) of all animals at 24 and 72 hours after the application

were summed up, and the Primary Irritation Index (P.I.I.) was calculated for each application site by dividing the sum of score by six (three animals times two observation). These indexes were used for classification of the dermal irritation potential according to the criteria shown in Annex 2.

8. Body weight measurement

Individual body weights of all animals were measured with an electric balance (EB-16KS, Shimadzu Corp.) shortly before application and at the final observation.

9. Fate of animals

The animals used in this study were sacrificed by an overdose (approx. two times higher than the optimal dose) of barbiturates (RAVONAL: Tanabe Seiyaku Co., Ltd.).

Results

1. Dermal reactions (Table 1)

1.1 Test substance applied area

RE1122.03 caused dermal reactions at 2.5% from 24 hours after the application. The dermal reactions observed at 2.5% RE1122.03 applied area on the intact skin were erythema of score 2 and edema of score 1 in two animals, and were erythema of score 1 or 2 in all animals and edema of score 1 in one animal on the abraded skin. These dermal reactions observed at the 2.5% RE1122.03 applied area gradually diminished and disappeared by seven days after the application. RE1122.03 at 12.5% also caused dermal reactions from 24 hours after the application. The dermal reactions observed at the 12.5% RE1122.03 applied area on the intact skin were erythema of score 2 and edema of score 1 in two animals, and that on the abraded skin were erythema of score 1 or 2 in all animals and edema of score 1 in two animal. These dermal reactions disappeared by seven days after the application in the same manner as on the 2.5% RE1122.03 applied area.

There were no obvious differences in the dermal reactions between intact and abraded skin.

1.2 Control area (applied with water for injection)

No dermal reactions were observed on intact skin. While erythema of score 1 was observed on abraded skin in one animal from 24 hours after the application, this dermal reaction disappeared by 72 hours after application.

2. Classification of dermal irritation

Primary irritation index (P.I.I.) for the 2.5% test substance applied area was 1.3 for intact skin and 1.5 for abraded skin, and the P.I.I. for the 12.5% test substance applied area was 1.3 for intact skin and 1.7 for abraded skin. Based on these indexes, 2.5% and 12.5% RE1122.03 were classified as "mildly irritant".

Water for injection was classified as "non-irritant" based on P.I.I. (0) for the intact skin and "mildly irritant" based on P.I.I. (0.2) for the abraded skin.

3. Clinical signs

No abnormal clinical signs were observed in any animal during the observation period.

4. Body weights (Table 2)

No abnormalities in body weight change that could be ascribed to the test substance were observed in any animal.

Discussion and Conclusion

A single occluded application of the 2.5 and 12.5% RE1122.03 caused slight to mild erythema and slight edema on both intact and abraded skin. In addition, application of the vehicle (control area) also caused slight erythema on the abraded skin. The dermal reactions at the control area could be ascribed to physical irritation by the stripping, because the dermal reactions at the control area disappeared by 72 hours after application. On the other hand, dermal reactions at the test substance applied area were considered to cause by the mild irritation of the test substance, because the dermal reactions at the test substance applied area persisted for 72 hours or more and the reactions were observed on intact skin which did not receive stripping.

In conclusion, the results indicated that RE1122.03 has reversible and mild irritation potential to the rabbit skin under the conditions of this study.

Reference

1. Draize, J. H., Woodard, G., Calvery, H. O. (1944) : Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes, J. Pharmacol. Exp. Therap., 82, 377-390.

Annex 1 Evaluation of skin reactions

A. Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Total possible erythema score	4

B. Edema Formation

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (area raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total possible edema score	4

Annex 2 Classification of primary irritation index

Primary irritation index (I)	Classification
$I = 0$	Non-irritant
$0 < I \leqq 2$	Mildly irritant
$2 < I \leqq 6$	Moderately irritant
$6 < I \leqq 8$	Severely irritant

Table 1-1 Individual dermal irritation reactions

Test material: 2.5%RE1122.03 (Intact skin)

Animal No.	Reactions	Score			
		Hours*			Days*
		24	48	72	7
1	Erythema**	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	2	1	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
3	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
P.I.I.		1.3			

Test material: 2.5%RE1122.03 (Abraded skin)

Animal No.	Reactions	Score			
		Hours			Days
		24	48	72	7
1	Erythema	1	1	1	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	2	2	1	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
3	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
P.I.I.		1.5			

*: Time after application

**: Erythema and/or eschar formation

-: No finding

Table 1-2 Individual dermal irritation reactions

Test material: 12.5%RE1122.03 (Intact skin)

Animal No.	Reactions	Score			
		Hours*			Days*
		24	48	72	7
1	Erythema**	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
3	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
P.I.I.		1.3			

Test material: 12.5%RE1122.03 (Abraded skin)

Animal No.	Reactions	Score			
		Hours			Days
		24	48	72	7
1	Erythema	1	1	1	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
3	Erythema	2	2	1	0
	Edema	1	0	0	0
	Other findings	-	-	-	-
P.I.I.		1.7			

*: Time after application

**: Erythema and/or eschar formation

-: No finding

Table 1-3 Individual dermal irritation reactions

Test material: Distilled water for the injection (Intact skin)

Animal No.	Reactions	Score			
		Hours*			Days*
		24	48	72	7
1	Erythema**	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
3	Erythema	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
P.I.I.			0		

Test material: Distilled water for the injection (Abraded skin)

Animal No.	Reactions	Score			
		Hours			Days
		24	48	72	7
1	Erythema	1	1	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
2	Erythema	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
3	Erythema	0	0	0	0
	Edema	0	0	0	0
	Other findings	-	-	-	-
P.I.I.			0.2		

*: Time after application

**: Erythema and/or eschar formation

-: No finding

Table 2 Individual body weights

(kg)

Animal No.	Before application	7 days after application
1	2.0	2.0
2	2.0	2.1
3	2.1	2.1

プロクター・アンド・ギャンブル・ファー・イースト・インク　殿

試 験 報 告 書

試験報告書（7L747）の英訳

2000年6月15日

株式会社三菱化学安全科学研究所

Translation Statement

Kashima Laboratory
Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Proctor & Gamble Far East, Inc.

Title: Primary Dermal Irritation Study of RE1122.03 in Rabbits

Study number: 7L747

This study was conducted in the Kashima Laboratory of Mitsubishi Chemical Safety Institute Ltd. The original study report was written in Japanese. I hereby declare that this report faithfully reflects the original study report.

Translator: Seiji Otake Date: June 16, 2000

Seiji Otake, D.V.M.
Research Scientist, Toxicology Division of Kashima Laboratory

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.03
Divisional Request Document(s) HBE BTS 0707/01 - 06

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman LOT #75161 TM 25-9-97
Brand Notebook Reference_N01511/30 M217/19922 leg M217/19923
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NK at: NK %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions:_Store at Room temperature Viscosity:_NA
Expiration Date (Day/Month/Year):_01 Sep 98 Ingredient Stability:NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: G.GENAIN (Name) G.Genain (Signature) 24-9-97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for thesfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: pp V.Hoyle (Name) P M Mclaren (Signature) 24/09/97 (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	ARP 2581	I.R	conforms to spec	N1486/113

Description: Tan powder free from any visible contamination.

22/9/97

Compositional Information Provided by:

Dominic PRATT 17/09/97

(ORIGINATOR NAME/SIGNATURE/DATE)

Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:

P.G. Smith 26/9/97.

(ANALYTICAL MGR NAME/SIGNATURE/DATE)

Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required ✓

Material approved [ ]

JASON WILLIAMS

(NAME/SIGNATURE/DATE)

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulponylaminoethyl)-2-methylphenylenediamine
Purity:	Not stated
Remarks:	Test substance coded as RE-1122.01

Method

Method/Guideline Followed:	Primary Eye Irritation Rabbit – Low Volume Method
GLP:	Yes
Report Year:	1997
Species:	Rabbit
Strain:	New Zealand White
Gender:	Male
Number of Animals:	3
Vehicle:	Water
Concentration:	5% aqueous
Remarks:	10 µL (5% test substance in water) was placed directly on the cornea of one eye on each animal. The contralateral eye of each animal was untreated and served as control. Test and control eyes were examined for signs of irritation for up to 72 hours following dosing. There was no rinse.

Results

Classification:	Non irritant.
Remarks:	Slight conjunctivae redness was observed within 24 hours of the application and resolved by 48 hours. RE-1122.01 has reversible and minimal irritation potential to the eyes of rabbits under the conditions of this study.

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	3029-2073
Reference:	Procter & Gamble, 1997. A Low Volume Eye Irritation Study in Rabbits with RE1122.01 Accession #40235

Acc # 40235

96C302

A LOW VOLUME EYE IRRITATION STUDY IN RABBITS WITH RE1122.01

FINAL REPORT

Author

Todd N. Merriman, B.S., LATG

Study Completed on

January 27, 1997

Performing Laboratory

Springborn Laboratories, Inc. (SLS)
Health and Environmental Sciences
640 N. Elizabeth Street
Spencerville, Ohio 45887

SLS Study No.

3029.2073

P & G DRD No.

HBEBTS0675/01

P & G Study File No.

96C302

Submitted to

Dr. Vivienne Hoyle
PROCTER & GAMBLE (Health & Beauty Care) Ltd.
Lovett House, Lovett Road
Staines, Middlesex TW18 3AZ, U.K.

RECEIVED BY
JAN
OPERATIONS STATION

Springborn

COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the OECD [Annex 2 C(81)30].

Todd N. Merriman Date 1/27/97

Todd N. Merriman, B.S., LATG
Study Director/Author
Springborn Laboratories, Inc.

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

Phase	Date
Animal Receipt	11/04/96
Dose Preparation	11/25/96
Data Audit	12/13/96
Final Report Review	01/27/97
Reports to Study Director and Management	11/13/96, 01/27/97

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the OECD [Annex 2 C(81)30].

Stephanie J. Schulte Date 1-27-97
Stephanie J. Schulte, B.S.
Quality Assurance Auditor I

Anita M. Bosau Date 1/27/97
Anita M. Bosau
Director of Compliance Assurance

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SUMMARY

The potential eye irritant effects of RE1122.01 were evaluated on New Zealand White rabbits. Each of three rabbits received a 10 µl dose of a 5% w/v concentration of the test article placed directly on the cornea of the right eye. The contralateral eye of each animal remained untreated and served as a control. Test and control eyes were examined for signs of irritation for up to 72 hours following dosing.

Exposure to the test article produced conjunctival redness in 1/3 test eyes by the 1 hour scoring interval and in 1/3 test eyes at the 24 hour scoring interval. The conjunctival irritation resolved completely in all animals by the 48 hour scoring interval.

Based on the data, the Maximum Average Score (MAS) of RE1122.01 was determined to be 0.67, which occurred at the 24 hour scoring interval. The median number of days for the eyes to clear of all effects was 1.0.

I. INTRODUCTION

This study was performed to assess the irritant effects of RE1122.01 in New Zealand White rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio. The protocol was signed by the Study Director on October 15, 1996 (GLP initiation date). The in-life phase of the study was initiated with test article administration on November 25, 1996 and concluded with final scoring on November 28, 1996.

II. MATERIALS AND METHODS

A. Experimental Protocol

The study protocol and amendment are presented in Appendix A.

B. Test Article

The test article was received from the Sponsor and identified as follows:

Sponsor's ID	Assigned SLS ID	Physical Description	Receipt Date	Expiration Date
RE1122.01 Lot No. 01	596.066 3029	Pink powder	November 19, 1996	December 1998

The test article was stored at room temperature. The Sponsor is responsible for any necessary evaluations related to the chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

C. Retention Sample

Where necessary, the Sponsor was responsible for maintaining a retention sample of the test article.

D. Test Article Disposition

The test article was returned to the Sponsor following completion of all studies with the test article.

E. Method of Test Article Preparation

The test article was mixed with distilled water to produce a 5% w/v concentration for dose administration. A sample of dose preparation solution was taken and returned to the Sponsor for possible analysis.

F. Animals and Animal Husbandry

1. Description, Identification and Housing

Adult, New Zealand White rabbits were received at SLS from Myrtle's Rabbitry, Thompson Station, TN. Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage. The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

2. Environment

The animal room temperature and relative humidity ranges were 67-70°F and 25-35%, respectively. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle and room ventilation was set to produce 10-15 air changes per hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

3. Food

PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there were no contaminants reasonably expected in the diet which

would interfere with the conduct of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLS.

4. Water

Municipal tap water following treatment by reverse osmosis was available to the animals ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants was conducted by SLS and the records are available for inspection. Levels of contaminants which may have been present were not expected to compromise the purpose of this study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR Part 141).

5. Acclimation

Upon receipt, the animals were removed from the shipping cartons and placed into individual cages. The animals were examined by qualified personnel, identified with plastic ear tags and then acclimated to the laboratory conditions for a minimum of five days. The animals were observed daily for overt physical or behavioral abnormalities, as well as for moribundity and mortality.

6. Animal Selection

The animals chosen for study use were randomly selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest examination prior to dosing. Only healthy animals were chosen for study use. Females were nulliparous and nonpregnant.

III. EXPERIMENTAL DESIGN AND PROCEDURES

A. Study Group Design

The experimental design [2] is described in Protocol Attachment I.

B. Preliminary Examination

On study day 0 (day of dose administration) prior to dosing, both eyes of each animal provisionally selected for test use were examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface was examined using fluorescein sodium dye. One drop of fluorescein/physiological saline mixture was

gently dropped onto the superior sclera of each eye. Following an approximate 15 second exposure, the eyes were rinsed with physiological saline. The corneal surface was then examined for dye retention under a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention were not used on study. All animals found to be acceptable for test use were returned to their cages until dosing.

C. Dosing

A minimum of one hour after the preliminary ocular examination, the test article was instilled as follows.

Group	Concentration (% w/v)	Amount Instilled	No. of Animals Males	Females
No Rinse	5	10 µl	1	2

The test article was placed directly on the cornea between the center of the cornea and the superior limbus of the right eye of each animal. Following instillation, the eyelids were released without forced blinking or manipulation and the animal was returned to its cage. The contralateral eye remained untreated to serve as a control.

D. Ocular Observations

The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Ocular Grading System presented in Protocol Appendix A which is based on Draize [3]. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure was repeated on all test and control eyes and any residual test article was gently rinsed from the eye at this time (if possible) with physiological saline. If any fluorescein findings were noted at 24 hours, a fluorescein exam was conducted on the affected eyes at each subsequent interval until a negative response was obtained.

E. Clinical Observations

Any unusual observations or mortality were recorded. Mortality checks were performed twice daily, in the morning and afternoon.

F. Body Weights

Individual body weights were obtained for each animal prior to dosing on study day 0.

G. Gross Necropsy

Each animal was euthanized by an intravenous injection of sodium pentobarbital following its final observation interval. Gross necropsy examinations were not required for these animals.

H. Protocol Deviations

The animal room relative humidity range during this study (25-35%) exceeded the preferred range (40-70%) but did not affect the study outcome. Test article was stored at room temperature as opposed to refrigerated as stated on Protocol Attachment I; however, test article was received at ambient temperature, and MSDS and label say to store only in a cool, dry place. A concentration sample of the test article dose preparation was taken, though not required by protocol. These occurrences had no adverse effect on the study outcome.

IV. ANALYSIS OF DATA

For each group, the ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) was multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score was then calculated for each scoring interval based on the number of animals initially dosed in each group. The group mean ocular irritation score for each interval was calculated and the Maximum Average Score (MAS), excluding the 1 hour scoring interval, was determined. The median number of days for the eyes to clear of all effects was also determined for each group by arranging the days for each rabbit to clear in increasing numerical sequence. For any group with an even number of animals remaining, the middle two animals in the series were averaged (rounded to the nearest 0.1 day); for any group with an odd number of animals remaining, the day for the middle animal was used.

V. MAINTENANCE OF RAW DATA AND RECORDS

All original paper data, the final report and magnetically encoded records were transferred to the SLS archives for a period of 20 years. The Sponsor will be contacted prior to final disposition of these items.

VI. RESULTS

Ocular Observations

Individual Data: Table 1

Exposure to the test article produced conjunctival redness in 1/3 test eyes by the 1 hour scoring interval and in 1/3 test eyes at the 24 hour scoring interval. The conjunctival irritation resolved completely in all animals by the 48 hour scoring interval.

No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

VII. CONCLUSION

Based on the data, the Maximum Average Score (MAS) of RE1122.01 was determined to be 0.67, which occurred at the 24 hour scoring interval. The median number of days for the eyes to clear of all effects was 1.0.

Todd N. Merriman, B.S., LATG
Study Director

Date 1/27/97

VIII. REPORT REVIEW

Deborah A. Douds, M.S.
Toxicologist

Date 1/27/97

Kimberly L. Bonnette, M.S., LATG
Manager of Acute Toxicology

Date 1/27/97

IX REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 96-03, 1996.

2. American Society for Testing and Materials, Standard Method for Evaluation of Eye Irritation in Albino Rabbits, E 1055-85, in Annual Book of ASTM Standards, Philadelphia, PA, 1985.

3. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

SLS STUDY NO.: 3029.2073
CLIENT: PROCTER & GAMBLE CO.

TABLE 1
A LOW VOLUME EYE IRRITATION STUDY IN RABBITS
INDIVIDUAL OCULAR IRRITATION SCORES

Animal No./Sex / Body Weight (kg)	Scoring Interval	Cornea			Iris		Conjunctivae				Total	Test Eye*		Control Eye*	
		O	A	OxAx5	I	IxS	R	S	D	(R+S+D)2		Fluorescein Examination	Secondary Ocular Findings	Fluorescein Examination	Secondary Ocular Findings
84003/F	1 Hour	0	0	0	0	0	0	0	0	0	0				
2.717	24 Hours	0	0	0	0	0	0	0	0	0	0	[-]		[-]	
	48 Hours	0	0	0	0	0	0	0	0	0	0				
	72 Hours	0	0	0	0	0	0	0	0	0	0				
54024/F	1 Hour	0	0	0	0	0	1	0	0	2	2				
2.805	24 Hours	0	0	0	0	0	0	0	0	0	0	[-]		[-]	
	48 Hours	0	0	0	0	0	0	0	0	0	0				
	72 Hours	0	0	0	0	0	0	0	0	0	0				
54001/M	1 Hour	0	0	0	0	0	0	0	0	0	0				
2.821	24 Hours	0	0	0	0	0	1	0	0	2	2	[-]		[-]	
	48 Hours	0	0	0	0	0	0	0	0	0	0				
	72 Hours	0	0	0	0	0	0	0	0	0	0				

*See Protocol Appendix A for definition of codes.

(14)

Mean Ocular Scores

1 Hour	-	0.67
24 Hours	-	0.67 (MAS)
48 Hours	-	0.00
72 Hours	-	0.00

APPENDIX A

Protocol and Amendment

(16)

A LOW VOLUME EYE IRRITATION STUDY IN RABBITS WITH RE1122.01

PROTOCOL

Springborn Study No. 3029.2073
P & G DRD No. HBEBTS0675/01
P & G Study File No. 96C302

Springborn Laboratories, Inc. (SLS)
Health and Environmental Sciences
640 North Elizabeth Street
Spencerville, Ohio 45887

Todd N. Merriman, B.S., LATG
Study Director

For

Dr. Vivienne Hoyle
PROCTER & GAMBLE (Health & Beauty Care) Ltd.
Lovett House, Lovett Road
Staines, Middlesex TW183AZ, U.K.

Springborn

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I PURPOSE

The objective of this study is to assess the irritant effects of a test article in rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

II. RESPONSIBILITIES

A. Sponsor

See Protocol Attachment I

B. Sponsor's Representative

See Protocol Attachment I

C. Testing Location

Springborn Laboratories, Inc.
Health and Environmental Sciences
553 North Broadway
Spencerville, Ohio 45887
Phone: (419) 647-4196
FAX: (419) 647-6560

D. Personnel Responsibilities

1. Todd N. Merriman, B.S., LATG
   Study Director/Toxicologist

2. Kimberly L. Bonnette, M.S., LATG
   Alternate Contact/Manager of Acute Toxicology

3. Deborah A. Douds, M.S.
   Toxicologist

4. Robert B. Foster
   President and Managing Director

5. Malcolm Blair, Ph.D.
   Vice President and Laboratory Director

6. Rusty E. Rush, M.S., LAT, DABT
   Associate Director of Toxicology

7. J. Dale Thurman, D.V.M., M.S., DACVP
   Director of Pathology

8. Elaine M. Daniel, Ph.D., DABT
   Associate Director of Toxicology

9. Anita M. Bosau
   Director of Compliance Assurance

III. PROPOSED STUDY SCHEDULE

A. Initiation of In-Life Phase: October 1996

B. Completion of In-Life Phase: October 1996

C. Audited Report Date. 4 weeks following Sponsor's approval for study termination

IV. TEST ARTICLE IDENTIFICATION

A. Test Article

1. Sponsor Identification

RE1122.01

2. SLS Test Article Identification Number

S96.066.3029

3. Characteristics

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

4. Handling Precautions

Safety data regarding the test article should be provided by the Sponsor [Material Safety Data Sheet (MSDS) or equivalent, if available]. Technical personnel are required to read this information prior to handling the test article. Any question concerning this information should be referred to the Study Director.

Additional safety and handling information may be provided by the Study Director and/or Sponsor. Minimum safety requirements include safety glasses, impervious gloves, and laboratory wear. MSDS sheets (or equivalent) shall also be available for any other chemical entities utilized in the conduct of this study.

B. Retention Sample

Where necessary, the Sponsor is responsible for maintaining a retention sample of the test article.

C. Test Article Disposition

The test article will be returned to the Sponsor following completion of all studies with the test article(s) unless otherwise instructed by the Sponsor.

D. Method of Test Article Preparation

1. Test Article

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are generally ground and sieved prior to dose administration.

The weight of the test article that occupies a volume of 10 µl will be determined prior to grinding by measuring a convenient volume (at least 2 mL) of the powder in a suitable volumetric container. The powder will be gently compacted by tapping the measuring container. The calculated amount of test article will then be ground in a mortar with a pestle and passed through a No. 40 mesh sieve. The test article (weight equivalent of 10 µl, not to exceed 10 mg) will then be dispensed for dosing. The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report.

2 Homogeneity Measurements of Test Article Dilutions/Solutions

Homogeneity measurements are not required for materials that are soluble in the vehicle. For suspensions, a sample of top, middle, and bottom will be taken and sent to the Sponsor for analysis. Samples will be stored and shipped per the Sponsor's instructions.

V TEST SYSTEM

A. Justification of the Test System

1. The rabbit is the preferred species for primary eye irritation testing by various U.S. and International regulatory agencies.

2. The New Zealand White rabbit has been shown to be sensitive to the irritant effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary eye irritation testing of drugs and chemicals for human safety assessment.

3. The New Zealand White rabbit has been used extensively for eye irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.

4. Historical information concerning New Zealand White rabbits is available at SLS and in the published literature.

5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.

6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

SLS has conducted literature searches through Medline, Toxline and Bioethics and there are no validated generally accepted alternatives to this test for regulatory classification purposes. In a 1989 position paper prepared by the Animals in Research Committee of The Society of Toxicology (SOT) and approved by the SOT Council, it was concluded that "none of the proposed models are yet validated or evaluated for a broad range of chemical moieties, and none can be relied upon to provide the scientific reliability or predictive accuracy which would be required for a new test for regulatory or legal acceptability" [1].

B. Justification of the Route of Exposure and Number of Animals

1. Ocular administration of the test substance was selected since this is a potential route of human exposure.

2. Since New Zealand White rabbits have no pigment and have an easily accessible ocular area, substances may be accurately instilled and any resulting effects easily observed.

3. The number of animals used on this study is the minimum number required to give scientifically meaningful results.

C. Description

1. Species

Rabbit

2. Strain

New Zealand White

3. Source

Myrtle's Rabbitry or another USDA approved supplier

4. Age and Body Weight Range

Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0). The body weights and approximate age will be documented in the study records.

5. *Number and Sex*

1 Rabbit Test: (1 male and/or female per test article)
3 Rabbit Test: (3 males and/or females per test article)
6 Rabbit Test: (6 males and/or females per test article)

D Method of Identification

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. Cage cards displaying at least the study number, animal number, and sex will be affixed to each cage.

E. Animal Husbandry

1. Housing

The animals will be housed individually in suspended stainless steel cages. All housing and care will be based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [2].

2. Environment

The environmental conditions for the animal room will be set to maintain room temperature and relative humidity ranges of 67 ± 6°F and 55 ± 15%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle and room ventilation will be set to produce 10-15 air changes per hour. The room temperature and relative humidity will be recorded a minimum of once daily.

3. Food

PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.) will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there are no contaminants reasonably expected in the diet which would interfere with the conduct of the study. Results of the

dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the testing laboratory. Feed that is outside the ranges set for the above mentioned criteria will not be utilized by the testing facility.

4. Water

Municipal tap water following treatment by reverse osmosis will be available ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted by the testing laboratory according to SLS Standard Operating Procedures and the records will be available for inspection. Levels of contaminants which may be present are not expected to compromise the purpose of the study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR Part 141).

F. Acclimation

Upon receipt, the animals will be removed from the shipping cartons and placed into individual cages. The animals will be examined by qualified personnel, identified with plastic ear tags, and then acclimated to the laboratory conditions for a minimum of 5 days. The animals will be observed daily for overt physical or behavioral abnormalities, as well as for morbundity and mortality.

G. Animal Selection

The animals chosen for study use will be randomly selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest observation prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

VI. EXPERIMENTAL DESIGN AND PROCEDURES

A. Study Group Design

The experimental design [3] is described in Protocol Attachment I.

B. Preliminary Examination

On study day 0 (day of dose administration) prior to dosing, both eyes of each animal provisionally selected for test use will be examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface will be examined using fluorescein sodium dye. One drop of fluorescein/physiological saline mixture will be gently dropped onto the superior sclera of each eye. Following an approximate 15 second exposure, the eyes will be rinsed with physiological saline. The corneal surface will then be examined for dye retention under a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention will not be used on study. All animals found to be acceptable for test use will be returned to their cages until dosing.

C. Dosing

A minimum of one hour after preliminary ocular examination, the test article will be placed directly on the cornea between the center of the cornea and the superior limbus of the right eye of each animal. Liquids, gels and pastes will be administered at a volume of 10 µl. A 100 µl Hamilton glass luer tip or equivalent brand syringe with a teflon tipped plunger will be loaded with a 10 µl volume of sample to dose one animal. This procedure will be repeated for the remaining animals. Solids and powders will be administered as a weight equivalent to 10 µl volume not to exceed 10 mg. Following instillation, the eyelids will be released without forced blinking or manipulation and the animal returned to its cage. The contralateral eye will remain untreated to serve as a control. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized.

D. Rinsing Procedure

If a rinse procedure is selected, the rinsing procedure will be as follows. Approximately 4 seconds following instillation of the test article, the test eyes will be rinsed with approximately 20 mL of tepid tap water using a 20 mL syringe with an 18 gauge blunted needle. The control eye of each animal will be rinsed in the same manner.

E. Body Weights

Individual body weights will be obtained for each animal prior to dosing on study day 0.

F. Clinical Observations

Any unusual observations and mortality will be recorded. Mortality checks will be performed twice daily (in the morning and afternoon).

G. Ocular Observations

The eyes will be macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Ocular Grading System presented in Protocol Appendix A which is based on Draize [4]. At the discretion of the Study Director, a biomicroscopic slit-lamp may be utilized to further examine and clarify ocular lesions. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure will be repeated on all test and control eyes and any residual test article should be gently rinsed from the eye at this time (if possible) with physiological saline. If any fluorescein findings are noted at 24 hours, a fluorescein exam will be conducted on the affected eyes at each subsequent interval until a negative response is obtained.

If there is no evidence of treatment related ocular irritation at the 72 hour scoring interval, the study will be terminated. If ocular irritation persists in any test eye, the observation period may be extended for the affected animals (scored on days 4, 7, 10, 14 and 21). Animals requiring an extended observation period will remain on test (up to and including 21 days postdose) until the irritation has resolved, permanent injury is evident or the Study Director and Sponsor determines that additional scoring intervals are unnecessary.

H. Unscheduled Deaths and Euthanasia

Any animals dying or euthanized for cause (sodium pentobarbital injection) during the study period will be necropsied. Body cavities (cranial, thoracic, abdominal and pelvic) will be opened and examined. Any abnormalities will be documented. No tissues will be retained.

I. Scheduled Euthanasia

Each surviving animal will be euthanized by an intravenous injection of sodium pentobarbital following its final observation interval. No necropsy examination will be performed.

VII PROTOCOL AMENDMENT

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific consent of the Sponsor's Representative. A protocol amendment will be prepared and signed by the Study Director, SLS Quality Assurance and Sponsor's Representative for any such changes.

VIII. DATA REPORTING

Two unbound copies of the draft report (if requested) will be submitted to the General Toxicology Organization and to the Divisional Toxicologist. Four unbound copies of the final report will be submitted to the Procter & Gamble Operations Section. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- SLS Personnel Responsibilities

IX. ANALYSIS OF DATA

For each group, the ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) will be multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score will then be calculated for each scoring interval based on the number of animals initially dosed in each group. If an animal dies during the study, the total animals in that group will be reduced (by the number of animals dead) for each subsequent scoring interval for the purpose of calculating the mean ocular irritation score for each interval. The group mean ocular irritation score for each interval will be calculated and Maximum Average Score (MAS), excluding the 1 hour scoring interval, will be determined. The median number of days for eyes to clear of all effects will also be determined for each group by arranging the days for each rabbit to clear in increasing numerical sequence. For any group with an even number of animals remaining, the middle two animals in the series will be averaged (round off to the nearest 0.1 day); for any group with an odd number of animals remaining, the day for the middle animal will be used.

X. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLS to facilitate auditing of the study during its progress and prior to acceptance of the final report. All original paper data, the final report and magnetically encoded records will be transferred to the SLS archives for a period of 20 years. The Sponsor will be contacted prior to the final disposition of these items. Any specimens obtained during this study will be forwarded to Pathology Associates, Inc., Cincinnati, Ohio.

XI. REGULATORY COMPLIANCE

This study may be submitted to and will be conducted in accordance with the GLP requirements of the regulatory agency(s) specified in Protocol Attachment I.

XII. QUALITY ASSURANCE

A minimum of one critical phase of this study will be inspected during the in-life phase by the Springborn Laboratories, Inc., Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLS's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

XIII. USDA ANIMAL WELFARE COMPLIANCE STATEMENT

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia [5]. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 9 animals per test article.

This study is being conducted to evaluate potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress post-dose or if delayed severe ocular or clinical changes subsequently develop. If severe reactions are noted, the Study Director will contact the Facility Veterinarian and/or Sponsor to consider an appropriate course of action. In the event that the Sponsor cannot be contacted, the Study Director and/or Facility Veterinarian may authorize treatment or euthanasia of the animals. In general, the ocular tissue will not be anesthetized prior to or following dosing since these substances have been shown to inhibit the blink and/or tear response which may alter the irritation response. Furthermore, anesthetic agents may interact with and/or dilute the test article and thereby alter the experimental results. However, if it is suspected that the test article may induce more than transient pain/distress based on existing information, preanesthesia will be considered. In such circumstances, the Study Director and/or Facility Veterinarian will consult with the Sponsor to devise an appropriate study plan.

XIV. DECLARATION OF INTENT

This study will be listed on the SLS Quality Assurance Master Schedule for the EPA.

XV. PROTOCOL APPROVAL

The Sponsor's signature on Protocol Attachment I documents for the Study Director that there are no acceptable non-animal alternatives for this study, the study does not unnecessarily duplicate previous studies and that the study is needed for regulatory purposes and/or human safety assessment.

Todd N. Merriman

Date: 10/15/96

Todd N. Merriman, B.S., LATG
Study Director (SLS)

Date: 10/15/96

Quality Assurance Unit (SLS)

XVI REFERENCES

1. SOT Position Paper, "Comments on the LD50 and Acute Eye and Skin Irritation Tests, Fundamental and Applied Toxicology, 13, 621-623, 1989.

2. Guide for the Care and Use of Laboratory Animals. DHHS Publication No. (NIH) 96-03, 1996.

3. American Society for Testing and Materials, Standard Method for Evaluation of Eye Irritation in Albino Rabbits, E 1055-85, *in* Annual Book of ASTM Standards, Philadelphia, Pa., 1985.

4. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

5. 1993 Report of the American Veterinary Medical Assoc. Panel on Euthanasia, JAVMA, Vol. 202, No. 2, pp. 229-249, January 15, 1993.

PROTOCOL APPENDIX A

OCULAR GRADING SYSTEM

(O) CORNEAL OPACITY–DEGREE OF DENSITY (AREA MOST DENSE TAKEN FOR READING)	
OBSERVATION	CODE
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	1
Easily discernible translucent area, details of iris slightly obscured	2
Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through opacity	4

(A) AREA OF CORNEA INVOLVED (TOTAL AREA EXHIBITING ANY OPACITY REGARDLESS OF DEGREE)*	
OBSERVATION	CODE
No ulceration or opacity	0
One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

*Area of highest density will also be noted.

Cornea Score = O x A x 5 Total Maximum = 80

(I) IRITIS	
OBSERVATION	CODE
Normal	0
Markedly deepened rugae (folds above normal), congestion, swelling, moderate circumcorneal hyperemia or injection, any or all of these or combination of any thereof, iris is still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2

Iris Score = 1 x 5 Total Maximum = 10

PROTOCOL APPENDIX A--(Continued)

OCULAR GRADING SYSTEM

(R) CONJUNCTIVAL REDNESS (REFERS TO PALPEBRAL AND BULBAR CONJUNCTIVAE EXCLUDING CORNEA AND IRIS)	
OBSERVATION	CODE
Blood vessels normal	0
Some blood vessels definitely hyperemic (injected) above normal (slight erythema)	1
Diffuse, crimson color, individual vessels not easily discernible (moderate erythema)	2
Diffuse beefy red (marked erythema)	3

(S) CONJUNCTIVAL SWELLING (LIDS AND/OR NICTATING MEMBRANE)	
OBSERVATION	CODE
No swelling	0
Any swelling above normal (includes nictitating membrane, slightly swollen)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

(D) CONJUNCTIVAL DISCHARGE	
OBSERVATION	CODE
No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs and considerable area around the eye	3

Conjunctival Score = (R + S + D) x 2 Total Maximum = 20

PROTOCOL APPENDIX A–(Continued)

OCULAR GRADING SYSTEM

CORNEAL NEOVASCULARIZATION		
OBSERVATION	CODE	DEFINITION
Neovascularization - Very Slight	VAS-1	Total area of vascularized corneal tissue is < 10% of corneal surface
Neovascularization - Mild	VAS-2	Total area of vascularized corneal tissue is > 10% but < 25% of corneal surface
Neovascularization - Moderate	VAS-3	Total area of vascularized corneal tissue is > 25% but < 50% of corneal surface
Neovascularization - Severe	VAS-4	Total area of vascularized corneal tissue is > 50% of corneal surface

SECONDARY OCULAR FINDINGS		
OBSERVATION	CODE	DEFINITION
Sloughing of the corneal epithelium	SCE	Corneal epithelial tissue is observed to be peeling off the corneal surface.
Corneal bulging	CB	The entire corneal surface appears to be protruding outward further than normal.
Slight dulling of normal luster of the cornea	SDL	The normal shiny surface of the cornea has a slightly dulled appearance.
Raised area on the corneal surface	RAC	A defined area on the corneal surface that is raised above the rest of the cornea. This area is generally associated with neovascularization and has a off-white to yellow color.
Corneal edema	CE	The cornea has a swollen appearance.
Test article present in eye	TAE	Apparent residual test article is observed on the eye or in the conjunctival sac/inner canthus
Observation confirmed by slit lamp	OCS	A slit lamp examination was performed to confirm the initial observation.
Corneal mineralization	CM	Small white or off-white crystals that are observed in the corneal tissue.

PROTOCOL APPENDIX A–(Continued)

OCULAR GRADING SYSTEM

FLUORESCEIN EXAMINATION OF CORNEA	
OBSERVATION	CODE
Fluorescein retention associated with mechanical abrasion to the cornea	MI
Fluorescein retention associated with corneal stippling	ST
Fluorescein retention associated with corneal desquamation	DES
Fluorescein retention associated with the area of corneal opacity	FAO
Fluorescein retention is not associated with any other finding	FNF
No fluorescein retention is observed	(-)

POSTDOSE CLINICAL OBSERVATIONS	
OBSERVATION	CODE
Animal vocalized following dosing	VOC
Animal excessively pawed test eye following dosing	PAW
Animal exhibited excessive hyperactivity following dosing	HYP
Animal exhibited excessive head tilt following dosing	HT
Animal exhibited excessive squinting of test eye following dosing	SQ

Any additional findings will be noted in the raw data and in the final report.

(36)
PROTOCOL ATTACHMENT I

Low Volume Eye Irritation in Rabbits
Protocol Design Specifications and Sponsor Information and Approval

OCT 11 1995

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Testing Facility:
Springborn Laboratories, Inc.
Spencerville, Ohio

Sponsor's Representative:
Vivienne R. Hoyle, PhD
P&G Mark Europe
Lovett House, Lovett Rd
Staines, Middlesex, TW18 3AZ
Phone: 44-1784-495125
Fax: 44-1784-495043

Alternate Contact:
P. M. McNamee, PhD
same address
Phone: 44-1784-495125
Fax: 44-1784-495043

P & G DRD No.: ABE BTS 0475/01

Study design to meet the regulatory requirements of the following authorities:
[✓] FDA [ ] EPA-TSCA [ ] EPA-FIFRA [ ] CPSC [ ] DOT [✓] OECD [✓] EC
[✓] JMHW [ ] MAFF [ ] MITI [ ] Other (please specify) _____

Experimental Design:
[ ] Dose 1 animal per test article (additional animals possible with sponsor's approval).
[✓] Dose 3 animals per test article.
[ ] Dose 6 animals per test article.
[ ] Other: _____

Test Article Preparation
[ ] Dose test article undiluted.
[ ] Dose test article at a 5 % w/w, (w/v) v/v concentration. (circle appropriate units)
[ ] Other: _____

Test Article Vehicles:
[✓] Distilled water
[ ] 0.9% Sodium Chloride for Injection, USP
[ ] Other: _____

Test Substance (s):

TSIN	Color	Physical Form	Expiration Date
RE-1121.01	off white/pink	crystalline	30 Dec. 96

10-OCT-1995 10:45 FROM P&G TOXICOLOGY TO NIXON G P.06

Low Volume Eye Irritation in Rabbits

page 2 of 2

Test Substance Storage Condition: (Check one for each section as appropriate) OCT 1 1 1996

Bulk Material [ ] Room Temperature [✓] Refrigerated [ ] Frozen

Formulated Material [✓] Room Temperature [ ] Refrigerated [ ] Frozen

[ ] Other _____

Return Unused Samples To:
Mrs. A. Sanger
P&G HAFC Europe Ltd
Rusham Park, Whitehall Lane
Egham, Surrey
TW20 9NW, UK

Send Invoices To:
FAO: Ms. T. Merlin
P&G HAFC Europe Ltd
Lovett House, Lovett Rd
Staines, Middlesex, TW18 3AZ,
UK

Other Comments and Instructions:

Please inform Sponsor of score data, as it becomes available, by fax.

Relevant alternative test procedures were reviewed. No acceptable non-animal method was found to exist. Further, the relevant literature was reviewed and no data were found that would preclude the need to conduct this testing.

Divisional Toxicologist: VR Hoyle Date: 30-9-96

SLS No. P&G/EI-1-6/95

SLI Study No. 3029.2073 (38)
P & G DRD No. HBEBTS0675/01
P & G Study File No. 96C302

JAN 2 3 1997

A LOW VOLUME EYE IRRITATION STUDY IN RABBITS WITH RE1122.01

PROTOCOL AMENDMENT NO. 1

1) PART TO BE CHANGED/REVISED:

XIV. DECLARATION OF INTENT

CHANGE/REVISION:

Change sentence to read as follows:

This study will be listed on the SLS Quality Assurance Management Schedule for the OECD.

REASON FOR CHANGE/REVISION:

To correct a typographical error.

Todd N. Merriman, B.S., LATG
Study Director (SLI)

Date 1/6/97

Quality Assurance Unit (SLI)

Date 1-7-97

Dr. Vivienne Hoyle
Sponsor's Representative

Date 6 Jan 97

APPENDIX B

SLS Personnel Responsibilities

SLS PERSONNEL RESPONSIBILITIES

Todd N. Merriman, B.S., LATG	Study Director/Toxicologist
Kimberly L. Bonnette, M.S., LATG	Alternate Contact/Manager of Acute Toxicology
Robert Foster	President and Managing Director
Malcolm Blair, Ph.D.	Vice President and Laboratory Director
Rusty E. Rush, M.S., LAT, DABT	Associate Director of Toxicology
Deborah A. Douds, M.S.	Toxicologist
Pamela S. Smith, ALAT	Unit Leader
Kara E. Woeller, B.A.	Primary Technician/Senior Acute Technician
Jan K. Sevart, B.S., ALAT	Supervisor of Acute Report Preparation
Delores P. Knippen	Supervisor of Pharmacy
Anita M Bosau	Director of Compliance Assurance
Paul J. Grothaus, B.A.	Manager of Quality Assurance
Christopher W. Wilson, B.S.	Supervisor of Acute Quality Assurance
J. Dale Thurman, D.V.M., M.S., DACVP	Director of Pathology

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE-1122.01

Divisional Request Document(s) HBE STS 0676/01, 0676/01, 679/01

Section II: Test Substance General Characteristics
(To be completed by Originator, helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or Ingredient (or code designation): 4-(N-ethyl-N-2-methanesulphonylaminoethyl)-2-methylphenylenediamine sesquisulphate monohydrate. Also called Eastman Color Developing Agent CD-3

Supplier's Name: Eastman

Brand Notebook Reference M217 / 17197 / 17198, 17199, 17200 LA# 65171
(test substance source, production code if available and date ingredient received or date product made)

Physical Form: Crystals Color: Al. white/pink pH: ____ at ____ %

Density/Sp.Gravity: NA Ingredient Mol. Wt.: 436.52 Ingredient Solubility: 380g/L @ 25°C

Storage Conditions: Keep closed, 2 mg, Cool Viscosity: NA

Expiration Date (Day/Month/Year): 30/12/96 Ingredient Stability: Stable

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows: Harmful irritant sensitizer

Originator's Section Head: J C Dunbar (Name) J Dunbar (Signature) 27/9/96 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for the safety testing indicated by the Divisional Request Document (s).

Divisional Toxicologist: V R Hoyle (Name) V R HOYLE (Signature) 27-9-96 (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS #	EINECS #	CAS #	Nominal Level % by Wt.	Acceptable Range	LMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (SM no.)
Cas # 025646-71-3						ROI# 31860 FOR reference spectra collected for sample. N1016/47 [signature] 25Sep96			

Compositional Information Provided by:

(ORIGINATOR NAME/SIGNATURE/DATE)
Signature verifies integrity of all data provided (including Section II)

Analytical Verification by: [signature] 25/9/96.

(ANALYTICAL MOR NAME/SIGNATURE/DATE)
Signature verifies only Analyzed Value & References.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

DMA #_____

No testing required [ ] ✓

Material approved [ ]

(SIGNATURE/DATE) [signature] 25/9/96

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for filters or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TECR is signed must be made on the original only and must be initiated and dated, and a reason for the change stated (GLP requirement).

10-OCT-1996 10:43 FROM PRG TOXICOLOGY TO NIXON G P.03

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine
Purity:	99%
Comments:	Test substance coded as RE-1122.01. The three other test material were not releated to the 8(d) rule.

Method

Method / Guideline:	Chernoff-Kavlock Developmental Toxicity
Test Type:	Teratology
Report Year:	1997
GLP Compliant:	Yes
Species:	Rat – Sprague-Dawley strain
Number of Animals:	415 (female)
Route of Administration:	gavage
Frequency of Treatment:	Daily on days 7 through 11 of presumed gestation
Doses:	Doses ranging from 25 to 200 mg/kg bw/day for Part 1 and from 0 or 200 mg/kg bw/day for Part II
Study Design:	Part 1 of this study was to determine the minimally toxic dose (MTD) for dose selection in Part 2 (Developmental Toxicity Assay) of the study. Part 1 - 200 female rats were assigned to 20 dosage groups (Groups I – XX), 10 rats per dosage group. These non-mated female rats were given one of the test substances once daily for five days. Part II - 180 presumed pregnant female rats were assigned to six dosage groups (Groups I – VI), 30 rats per dosage group. These mated females were given the test substance in vehicle. Dosages were administered once daily on day 7 and continued through to presumed gestational day 11. Observations – Rats were observed for viability at least twice daily and for clinical observations of the effects of the test substances before and approximately one hour after dosage. Signs of toxicity were recorded when observed. Body weights were recorded. Pups present in each litter were counted each day. Physical signs including gross external physical anomalies were recorded for the pups once each day of the 4-day post-partum period. Pup body weights, sexes and observed nursing behaviors were recorded on DLs 2 and 4. At sacrifice, a gross necropsy of the thoracic, abdominal and pervic viscera was performed. Tissues with gross lesions were retaned in neutral buffered 10% formalin.

Results

Results:	200 mg/kg bw/day of RE-1122.01 produced evidence of maternal toxicity but did not induce toxic effects in the conceptus after administration of the test substances to the dams during gestation.

Part 1 - Toxicity Test

Substance Tested	Dosage Group	Dose (mg/kg/day)	No. Animals	Unscheduled Deaths	Clinical Signs of Toxicity Observed	Body Weight Gain
RE-1122.01	VI	25	10	0	No	+18.4 ± 5.7
	VII	50	10	0	No	+14.9 ± 6.7
	VII	100	10	0	No	+9.9 ± 6.8
	IX	200	10	1	Yes	-4.2 ± 13.9 *
	X	300	10	9	Yes	-32.0 ± 0.0 *

* Excludes values for rats found dead

Part 2 - Definitive Test	
Material Tested:	RE-1122.01
Dosage Group	IV
Dose (mg/kg/day):	200
Number Treated:	30
Unscheduled Deaths	11**
Body Wt. Gain (g)	
Gestation Days7-12	-27.6 ± 18.2 ** [b]
Gestation Days 12-20	+125.2 ± 17.1 ** [b]
Gestation Days 7-20	+99.8 ± 22.5 ** [b]
Gestation Days 0-20	+139.5 ± 25.6 ** [b]
Lactation Days 1-4	+9.2 ± 9.8
Number Pregnant	27
Delivered Litters	16 [b]
Dams with Stillborn Pups	2
Dams with no Liveborn pups	0
Gestation Index (%)	100
Pup Viability Index	98.1
Average Litter Weight at Day 2	7.4 ± 0.6
Average Litter Weight at Day 4	8.9 ± 0.9
Average Litter Size at Day 4	15.9 ± 2.8

** = Significantly different from the vehicle control group

[b] = Excludes values for rats found dead

Data Quality

Reliability (Klimisch): 1

Reference

Laboratory Report Number: 916-014

Reference: Procter & Gamble, 1997. Oral (gavage) Chernoff-Kavlock Developmental Toxicity Assay of RE-0981.05, RE-1122.01, RE-1123.01, and RE-1125.01 in Rats. Accession #43658

96C283

ARGUS 916-014
HBE BTS 0679/01 R

Study Title

ORAL (GAVAGE) CHERNOFF-KAVLOCK DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

Data Requirement

U.S. Environmental Protection Agency
Pesticide Assessment Guidelines
Subdivision F, 83-3

U.S. Environmental Protection Agency
Toxic Substances Control Act Test Guidelines
Health Effects Testing Guidelines - 798.4900

RECEIVED BY WTDS
Accession #:
43658

Author

Raymond G. York, Ph.D., DABT

Study Completed On

November 7, 1997
(Final Report)

Performing Laboratory

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297, USA

RECEIVED BY
NOV 10 1997
OPERATIONS SECTION

Laboratory Project ID

Argus Research Laboratories, Inc., Protocol Number: 916-014

Confidentiality Page
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GOOD LABORATORY PRACTICE STATEMENT

This study was conducted according to U.S. Environmental Protection Agency (EPA FIFRA/TSCA) "Good Laboratory Practice Standards; Final Rule" (40 CFR Part 160/792). Any areas of noncompliance are documented in the study record. No deviations existed that significantly affected the validity of the study.

Submitter:

Study Director:

07-NOV-97

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
Argus Research Laboratories, Inc.

Sponsor: Proctor and Gamble HABC Europe Ltd.

VR Hoyle 14 Nov 97

Vivienne R. Hoyle, Ph.D. Date

Flagging Page
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

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TITLE: ORAL (GAVAGE) CHERNOFF-KAVLOCK DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

ARGUS RESEARCH LABORATORIES, INC.
PROTOCOL NUMBER: 916-014
SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

I. SUMMARY AND CONCLUSION

A. Methods[a]

The purpose of Part I of this study was to determine the minimally toxic dose (MTD) for the selection of dosages used in Part II of this study. The purpose of Part II (Chernoff-Kavlock[1] developmental toxicity assay) was designed to assess the potential of the test substances to induce toxic effects in the conceptus after administration to the dam during gestation.

In Part I of the study, two hundred Crl:CD®BR VAF/Plus® (Sprague-Dawley) female rats were assigned to each of twenty dosage groups (Groups I through XX), ten rats per dosage group. These nonmated female rats were given one of the test substances, RE-0981.05, RE-1122.01, RE-1123.01 or RE-1125.01, once daily for five days (Groups XI and XII were extended to eight days to attempt to elicit a toxic response).

In Part II of the study, one hundred and eighty presumed pregnant Crl:CD®BR VAF/Plus® (Sprague-Dawley) female rats were assigned to each of six dosage groups (Groups I through VI), thirty rats per group. These mated female rats were given one of the test substances or one of two vehicles, reverse osmosis membrane processed deionized water (R.O. deionized water) for RE-0981.05 and RE-1122.01, or aqueous 0.5% carboxymethlycellulose (prepared in R.O. deionized water) for RE-1123.01 and RE-1125.01. Dosages were administered once daily on days 7 through 11 of presumed gestation (DGs 7 through 11).

---

a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in APPENDIX D (PROTOCOL AND AMENDMENTS).

Dosages ranging from 25 to 2000 mg/kg/day were administered to the rats in Part I. Dosages of 0, 0, 250, 200, 1000 and 1000 mg/kg/day of the vehicles, RE-0981.05, RE-1122.01, RE-1123.01 and RE-1125.01, respectively, were administered to rats in Part II. All dosages were administered orally, via gavage, at a dosage volume of 10 mL/kg and were given at approximately the same time each day.

The female rats were observed for viability at least twice each day of the study. The rats were also examined for clinical observations of effects of the test substances before and approximately one hour after dosage. Signs of toxicity were recorded when observed. Cage-side observations included, but were not limited to changes in skin and fur, eye and mucous membranes, as well as respiratory autonomic and central nervous systems, somatomotor activity and behavioral patterns. Postdosage observations were recorded on the day of sacrifice (Part I), and daily on DG 12 through day 4 of lactation (DL 4) (Part II).

Body weights were recorded daily during the dosage period (Parts I and II) and postdosage period (Part II) and at sacrifice (Parts I and II).

The pups present in each litter were counted once each day. Physical signs (including gross external physical anomalies) were recorded for the pups once each day of the 4-day postpartum period. Pup body weights, sexes and observed nursing behaviors were recorded on DLs 2 and 4.

All rats in Parts I and II were sacrificed by carbon dioxide asphyxiation and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Tissues with gross lesions were retained in neutral buffered 10% formalin.

All surviving rats assigned to Part I of the study were sacrificed on the day following the last test substance administration.

All surviving rats assigned to Part II that delivered litters were sacrificed by carbon dioxide asphyxiation on DL 4. The number and distribution of implantation sites were recorded. Rats that did not deliver a litter were sacrificed on DG 23. The number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions.

On DL 4, all F1 generation pups were sacrificed by carbon dioxide asphyxiation, examined for gross lesions and the brain was examined for apparent hydrocephaly.

B. Results

In Part I, dosages of 250 mg/kg/day RE-0981.05, 200 mg/kg/day RE-1122.01, 1000 mg/kg/day RE-1123.01 and 1000 mg/kg/day RE-1125.01 were selected for the definitive study (Part II) based on the available maternally toxic endpoint data.

Part II - RE-0981.05

A dosage of 250 mg/kg/day of RE-0981.05 resulted in the death of 11 of 30 of the rats. Deaths occurred following one to five daily dosage administrations. Three rats were found dead on gestation day (DG) 7, three on DG 8, one on DG 9, two on DG 10, one on DG 11 and one on DG 12. Clinical observations during gestation considered related to the test substance included tachypnea, clonic convulsions, twitches, excess salivation, lacrimation, piloerection, loss of righting reflex, decreased motor activity and vocalization. There were no necropsy observations that were considered treatment-related. Average body weight gains during gestation were significantly reduced over DGs 8 to 9, 9 to 10, and 10 to 11 and over the entire treatment interval. Average body weight gains during the post-treatment period and lactation period were comparable to control group. Average body weights during gestation were reduced but not statistically different. A total of 29 females were pregnant and 19 of these survived and delivered litters. The duration of gestation and the gestation index were comparable to the control group. Average litter size, pup survival, and pup weights were comparable to the control group. A total of five pups were stillborn and two were found dead compared to 12 and nine, respectively, for the 0 (Vehicle) dosage group. There were no adverse F1 generation clinical observations or necropsy findings.

Part II - RE-1122.01

A dosage of 200 mg/kg/day of RE-1122.01 resulted in the death of 11 of 30 of the rats and adverse clinical observations (the death of one of the rats may have been due to an intubation error). Deaths occurred following two to five dosages. One rat was found dead on DG 8, two on DG 9, five on DG 10, two on DG 11 and one on DG 13. Clinical observations considered related to the test substance included decreased motor activity, urine-stained abdominal fur, chromodacryorrhea, emaciation, chromorhinorrhea, twitches, excess salivation, vocalization, red substance on abdomen, tachypnea, clonic convulsion, hyperactivity and perivaginal brown substance. There were no necropsy observations that were considered treatment-related. Average body weight gains during gestation were significantly reduced for DGs 7 to 8, 8 to 9, 9 to 10, 10 to 11 and 11 to 12, for the entire treatment interval and for the entire

gestational period. Average body weight gains during the post-treatment period were significantly increased, comparable to the control group. Average body weights during gestation were significantly reduced DGs 7 through 20. During the four days of lactation, average body weight gains were similar and body weights were reduced, compared to the control group. A total of 27 females were pregnant and 16 of these survived and delivered litters. The duration of gestation and the gestation index were comparable to the control group. Average litter size, pup survival, sex ratio and pup weights were comparable to the control group. A total of two pups were stillborn and one was found dead compared to 12 and nine, respectively, for the 0 (Vehicle) dosage group. There were no adverse F1 generation clinical observations or necropsy findings.

Part II - RE-1123.01

A dosage of 1000 mg/kg/day of RE-1123.01 did not result in any mortality or adverse clinical observations. There were two females with dark red and/or large spleens that were considered treatment-related. The average body weight gain was significantly reduced for DGs 8 to 9, 9 to 10, 10 to 11 and 11 to 12 and for the entire treatment interval. Average weight gains during the postdosage period and lactation period were comparable to the control group. Average body weights during gestation were significantly reduced DGs 7 through 20. A total of 28 females were pregnant and all delivered litters. The duration of gestation and the gestation index were comparable to the control group. The total number of liveborn pups was significantly reduced. Average litter size, pup survival, sex ratio and pup weights were comparable to control group. A total of 12 pups were stillborn and six were found dead compared to five and 12, respectively, for the 0 (Vehicle) dosage group. There were no adverse F1 generation clinical observations or necropsy findings.

Part II - RE-1125.01

A dosage of 1000 mg/kg/day of RE-1125.01 resulted in the death of 2 of 30 of the rats following four dosages and adverse clinical observations. Clinical observations considered related to the test substance included decreased motor activity, lacrimation, chromorhinorrhea and urine-stained abdominal fur. There were no necropsy observations that were considered treatment-related. Average body weight gains were significantly reduced for DGs 7 to 8 and 10 to 11, for the overall treatment interval and for the gestational period. Average body weight gains were comparable to the control group for post-treatment period and the lactation period. No parameter evaluated during the lactation period was significantly affected by administration during gestation. A total of 27 females were pregnant and 26 of the surviving pregnant rats delivered litters. The duration of gestation and the gestation index were comparable to the control

group. Average litter size, sex ratio and pup weights were comparable to the control group. Pup survival was significantly increased, compared to the control group. A total of two pups were stillborn and three were found dead compared to five and 12, respectively, for the 0 (Vehicle) dosage group. There were no adverse F1 generation clinical observations or necropsy findings.

C. Conclusion

Dosages of 250 mg/kg/day RE-0981.05 in reverse osmosis membrane processed deionized water produced evidence of maternal toxicity (death, clinical observations, decreased body weights and body weight gains) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 200 mg/kg/day RE-1122.01 in reverse osmosis membrane processed deionized water produced evidence of maternal toxicity (death, clinical observations, decreased body weights and body weight gains) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 1000 mg/kg/day RE-1123.01 in aqueous 0.5% carboxy-methlycellulose produced evidence of maternal toxicity (decreased body weights, enlarged spleens) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 1000 mg/kg/day RE-1125.01 in aqueous 0.5% carboxy-methlycellulose produced evidence of maternal toxicity (deaths, decreased body weight gain) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Mildred S. Christian, Ph.D., ATS Date
Executive Director of Research

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

II. DESCRIPTION OF TEST PROCEDURES

A. Conduct of Study:

A.1. Sponsor:

Procter & Gamble HABC Europe Ltd., Lovett House, Lovett Road, Staines, Middlesex TW18 3AZ, UK

A.2. Testing Facility:

Argus Research Laboratories, Inc., 905 Sheehy Drive, Building A, Horsham, Pennsylvania 19044-1297, USA

A.3. Study Number:

916-014

A.4. Sponsor's Study Number:

HBE BTS 0679/01

A.5. Purpose of the Study:

The purpose of Part I of this study was to determine the minimally toxic dose (MTD) for the selection of dosages that were used in Part II of this study. The purpose of Part II (developmental toxicity assay) was designed to assess the potential of the test substances to induce toxic effects in the conceptus after administration to the dam during gestation.

A.6. Regulatory Compliance:

The requirements of the U.S. Environmental Protection Agency (EPA FIFRA/TSCA)[2-4] were used as the basis for study design and compliance with Good Laboratory Practices (GLPs). There were no significant deviations from the GLP regulations that affected the quality or integrity of the study. Quality Assurance Unit findings derived from the inspections during the conduct of this study are documented and have been provided to the Study Director and the Testing Facility Management.

A.7. Ownership of the Study:

The Sponsor owns the study. All raw data, analyses, reports and specimens are the property of the Sponsor.

A.8. Study Monitor:

Vivienne R. Hoyle, Ph.D.

A.9. Study Director:

Raymond G. York, Ph.D., DABT (Associate Director of Research)

A.10. Technical Performance:

John F. Barnett, B.S. (Director of Laboratory Operations)
Samantha Porter-Wivell, B.S. (Research Associate)
E'len Garney, B.S. (Laboratory Technician)

A.11. Report Preparation:

Raymond G. York, Ph.D., DABT (Associate Director of Research)
Terry J. Clemson, B.S. (Data Management Specialist)
Cheryl L. Van, B.A. (Senior Methods Coordinator)
Georgia Y. Burnett, A.A.S. (Administrative Assistant)

A.12. Report Review:

Alan M. Hoberman, Ph.D, DABT (Director of Research)
Mildred S. Christian, Ph.D., ATS (Executive Director of Research)

A.13. Date Protocol Signed:

27 SEP 96

A.14. Dates of Technical Performance:

Part I

Arrival Date	08 OCT 96
Dosage Period[a]	13 OCT 96 - 20 OCT 96
Scheduled Sacrifice	18 OCT 96 and 21 OCT 96

---

a. The first day of dosage is defined as study day 1 (DS 1).

Part II

Arrival Date	08 OCT 96
Cohabitation Period	28 OCT 96 PM - 05 NOV 96 AM
DG[a] 0	29 OCT 96 - 05 NOV 96
Dosage Period (DGs 7 through 11)	05 NOV 96 - 16 NOV 96
Natural Delivery Period (DL[b] 1)	19 NOV 96 - 27 NOV 96
DG 23 Sacrifice	21 NOV 96 - 28 NOV 96
DL 4 Sacrifice	22 NOV 96 - 29 NOV 96

A.15. Records Maintained:

The original report, raw data and reserve samples of the test substances and vehicles are retained in the archives of Argus Research Laboratories, Inc. Any specimens are retained in the archives of the Testing Facility for twenty years after the mailing of the draft final report, until the Sponsor decides their final disposition. All unused test substance solutions/suspensions were discarded at the Testing Facility. Unused bulk test substance will remain at the Testing Facility until its disposition is decided by the Sponsor.

B. Test Substance Information:

B.1. Descriptions and Lot Numbers:

RE-0981.05 (lot number 05) - a beige powder
RE-1122.01 (lot number 01) - a pink powder
RE-1123.01 (lot number 01) - a white crystalline powder
RE-1125.01 (lot number 01) - a pale yellow powder

B.2. Date Received and Storage Conditions:

The test substances were received on 09 OCT 96 and 08 NOV 96, and stored refrigerated, in airtight containers.

B.3. Special Handling Instructions:

Standard safety precautions (use of protective clothing, gloves, dust-mist respirator, safety goggles or safety glasses and a face-shield) were taken when handling the bulk test substances and prepared solutions/suspensions.

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a. DG is an abbreviation for day of (presumed) gestation.
b. DL is an abbreviation for day of lactation.

B.4. Analysis of Activity:

Information regarding the purity, identity, strength, composition and stability of each test substance and a copy of the characterization report is on file with the Sponsor.

C. Vehicle Information:

C.1. Descriptions:

Vehicle 1 (for RE-0981.05 and RE-1122.01) - Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water)

Vehicle 2 (for RE-1123.01 and RE-1125.01) - Aqueous 0.5% carboxymethlycellulose (prepared in R.O. deionized water)

C.2. Lot Number:

The lot number for the powdered carboxymethlycellulose was 32H0921.

C.3. Date Received and Storage Conditions:

R.O. deionized water is available from a continuous source at the Testing Facility and is maintained at room temperature at the Testing Facility.

The powdered carboxymethlycellulose was obtained from Sigma Chemical Co., on 03 FEB 93, and stored at room temperature.

C.4. Special Handling Instructions:

Standard safety precautions (use of protective clothing, gloves, dust-mist respirator, safety goggles or safety glasses and a face-shield) were taken when handling the vehicles.

C.5. Analysis of Purity:

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to be present in either vehicle that would interfere with the results of this study.

D. Test Substance Preparation:

Solutions/suspensions of each test substance were prepared daily at the Testing Facility. Dosage calculations were adjusted for the purity of each test substance. Daily preparations were stored in the study room before dosage administration.

D.1. Sample Information:

Sample Type	Size	Date Retained	Storage Conditions	Shipped To	Date Shipped
Test Substance Reserves	500 mg	13 OCT 96[a]	Refrigerated	Testing Facility Archives	16 OCT 96
Bulk Vehicle Reserve (CMC)	1 g	12 OCT 96	Room temperature	Testing Facility Archives	16 OCT 96

a = First day of dosage

A 1 g bulk sample was retained from each test substance on 15 NOV 96 or 16 NOV 96. These samples are retained (refrigerated) at the Testing Facility. Triplicate samples (2 mL each) were taken from the top, middle and bottom of the prepared formulations on the first and last days prepared. These samples are stored refrigerated at the Testing Facility for possible future homogeneity and concentration analyses.

E. Test System:

E.1. Species:

Rat

E.2. Strain:

Crl:CD®BR VAF/Plus® (Sprague-Dawley)

E.3. Supplier (Source):

Charles River Laboratories, Inc., Kingston, New York

E.4. Sex:

Female (Note: Male rats were used only for the purposes of breeding and are not considered part of the Test System.)

E.5. Rationale for Test System:

The Crl:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins and has been widely used throughout industry for reproductive and developmental toxicity evaluations; 2) historical data and experience exist at the Testing Facility; and 3) this is one of the preferred species for this assay.

E.6. Test System Data:

Number of Rats	415
Approximate Date of Birth	05 AUG 96
Approximate Age at Arrival	65 days
Weight (g) on the Day After Arrival	175 to 232
Weight (g) at Study Assignment	204 to 237 (Part I) 223 to 329 (Part II)

E.7. Breeder Male Rat Data:

Number of Rats	220
Approximate Date of Birth	18 JUL 96
Approximate Age at Arrival	98 days
Weight (g) on the Day After Arrival	341 to 472
Weight (g) at Cohabitation	338 to 528

E.8. Method of Randomization:

Upon arrival, rats were assigned to individual housing on the basis of computer-generated random units. Female rats in Part I of the study were assigned to one of twenty dosage groups (Groups I through XX), ten rats per dosage group, using a computer-generated (weight-ordered) randomization procedure based on body weights recorded during acclimation. Female rats in Part II of the study were assigned to one of six dosage groups (Groups I through VI), thirty rats per group using a computer-generated (weight-ordered) randomization based on DG 0 body weights.

E.9. System of Identification:

Cage tags were marked with the study number, permanent rat number, sex, test substance identification and dosage level. Each rat was individually identified with a Monel® self-piercing ear tag (Gey Band and Tag Co., Inc., No. MSPT 20101) inscribed with the rat's designated unique permanent number.

F. Husbandry:

F.1. Research Facility Registration:

USDA Registration No. 23-R-099 under the Animal Welfare Act, 7 U.S.C. 2131 *et seq.*

F.2. Study Rooms:

The study rooms were maintained under conditions of positive airflow relative to a hallway and independently supplied with a minimum of ten changes per hour of 100% fresh air that had been passed through 99.97% HEPA filters (Airo Clean® rooms). Room temperature and humidity were recorded constantly throughout the study. Room temperature was targeted at 70°F to 78°F (±2%); relative humidity was targeted at 40% to 70% (±3%) [see DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY (APPENDIX E), item 1].

F.3. Housing:

Rats in Part I were housed in common nesting boxes (two rats per nesting box).

Rats in Part II were individually housed except during the cohabitation period. During cohabitation, each pair of male and female rats was housed in the male rat's cage. Beginning no later than DG 20, Fo generation female rats were individually housed in nesting boxes until they either naturally delivered litters or were sacrificed (DG 23). Each dam and delivered litter was housed in a common nesting box during the 4-day postpartum period. All cage sizes and housing conditions were in compliance with the *Guide for the Care and Use of Laboratory Animals*, NIH Publication No. 86-23[5].

F.4. Lighting:

An automatically-controlled fluorescent light cycle was maintained at 12-hours light:12-hours dark, with each dark period beginning at 1900 hours EST.

F.5. Sanitization:

Cage pan liners were changed approximately three times each week. Cages were changed approximately every other week.

F.6. Feed:

Rats were given *ad libitum* access to Certified Rodent Diet® #5002 (Purina Mills, Inc.) in individual feeders.

F.7. Feed Analysis:

Analyses were routinely performed by the feed supplier. No contaminants in the feed or deviations from expected nutritional requirements were detected by these analyses. Copies of the results of the feed analyses are available in the raw data.

No agent present in the feed was known to interfere with the results of this study.

F.8. Water:

Local water that had been processed by passage through a reverse osmosis membrane (R.O. water) was available to the rats *ad libitum* from an automatic watering system and/or individual water bottles. Chlorine was added to the processed water as a bacteriostat (see APPENDIX E, item 1).

F.9. Water Analysis:

The processed water is analyzed twice annually for possible chemical contamination (Lancaster Laboratories, Inc., Lancaster, Pennsylvania USA) and monthly for possible bacterial contamination (Analytical Laboratories, Inc., Chalfont, Pennsylvania USA). Copies of the results of the water analyses are available in the raw data.

No agent present in the water was known to interfere with the results of this study.

G. Methods:

G.1. Dosage Administration:

Part I

Group	Number of Female Rats	Descriptor	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)
I	10	RE-0981.05	25	2.5	10
II	10	RE-0981.05	50	5.0	10
III	10	RE-0981.05	100	10.0	10
IV	10	RE-0981.05	200	20.0	10
V	10	RE-0981.05	300	30.0	10
VI	10	RE-1122.01	25	2.5	10
VII	10	RE-1122.01	50	5.0	10
VIII	10	RE-1122.01	100	10.0	10
IX	10	RE-1122.01	200	20.0	10
X	10	RE-1122.01	300	30.0	10
XI	10	RE-1123.01	1500[b]	5.0	10
XII	10	RE-1123.01	2000[c]	15.0	10
XIII	10	RE-1123.01	300	30.0	10
XIV	10	RE-1123.01	550	55.0	10
XV	10	RE-1123.01	800	80.0	10
XVI	10	RE-1125.01	250	25.0	10
XVII	10	RE-1125.01	750	75.0	10
XVIII	10	RE-1125.01	1000	100.0	10
XIX	10	RE-1125.01	1500	150.0	10
XX	10	RE-1125.01	2000	200.0	10

a. Dosage calculations were adjusted for the purity of the test substances.
b. On DS 3, dosages for Group XI were increased from 50 to 1000 mg/kg/day; on DS 5, dosages were increased from 1000 to 1500 mg/kg/day, for three additional days of treatment (a total of eight days).
c. On DS 3, dosages for Group XII were increased from 150 to 1200 mg/kg/day; on DS 5 dosages were increased from 1200 to 2000 mg/kg/day, for three additional days of treatment (a total of eight days).

Part II

Group	Number of Female Rats	Descriptor	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)
I	30	Vehicle 1	0	0	10
II	30	Vehicle 2	0	0	10
III[b]	30	RE-0981.05	250	25.0	10
IV	30	RE-1122.01	200	20.0	10
V	30	RE-1123.01	1000	100.0	10
VI	30	RE-1125.01	1000	100.0	10

a. Dosage calculations were adjusted for the purity of the test substances.
b. See APPENDIX E, item 2.

G.2. Rationale for Dosage Selection:

Part I:

Dosages were selected by the Sponsor to cover a broad range of dosages up to and including the limit test dosage.

Part II:

Dosages were selected on the basis of the minimally toxic dose (MTD) determined in Part I of the study. The dosage level was expected to be high enough to cause overt maternal toxicity as evidenced by significant death, weight loss, or other adverse clinical manifestations, or 1 g/kg, if lower dosage levels failed to induce maternal toxicity.

G.3. Route of Administration:

Oral (gavage)

G.4. Rationale for Route of Administration:

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it allows the systemic toxic potential of the test substances to be fully characterized.

G.5. Frequency of Administration:

Dosages were adjusted daily for body weight changes and were given at approximately the same time each day. Formulations were stirred continuously (magnetic stir plate with stir bar) during dosage administration.

Part I

Nonmated female rats were given one of the test substances once daily for five days, except for Groups XI and XII, which were extended to eight days to attempt to elicit a toxic response.

Part II

Mated female rats were given one of the test substances once daily beginning on DG 7 and continued through DG 11. F1 generation pups were not directly given the test substances but may have possibly exposed to the test substances during maternal gestation (*in utero* exposure) or via maternal milk during lactation.

G.6. Length of Study:

Approximately 7 weeks

G.7. Method of Study Performance:

After acclimation, 200 healthy virgin female rats, designated for Part II of the study, were placed into cohabitation with 200 breeder male rats (one male rat per female rat in the male rat's cage). Female rats with spermatozoa observed in a smear of the vaginal contents or a copulatory plug *in situ* were considered to be at DG 0 and returned to individual housing.

The female rats were observed for viability at least twice each day of the study and for general appearance weekly during acclimation and on DG 0 (Part II only). The rats were also examined for clinical observations of effects of the test substances before and approximately one hour after dosage (see APPENDIX E, item 3). Signs of toxicity were recorded when observed. Cage-side observations included, but were not limited to: changes in skin and fur, eye and mucous membranes, as well as respiratory autonomic and central nervous systems, somatomotor activity and behavioral pattern. Postdosage observations were recorded on the day of sacrifice (Part I), and daily on DG 12 through DL 4 (Part II).

Body weights were recorded weekly during acclimation and predosage, on DG 0 (Part II), daily during the dosage period (Parts I and II) and postdosage period (Part II) and at sacrifice (Parts I and II) (see APPENDIX E, item 3).

The female rats assigned to natural delivery were evaluated for duration of gestation (DG 0 to the day the first pup was delivered), litter sizes (live and dead pups and live pups only) and pup viability (see APPENDIX E, item 4). Maternal behavior of the dams was evaluated daily when the pups were examined during the 4-day postpartum period. Observed maternal behavior was recorded on DLs 2 and 4. Variations from expected maternal behavior were recorded, if and when present, on all other days of the postpartum period.

F1 Generation Litters

Pups that either appeared stillborn or that died before initial examination of the litters for viability were examined for vital status at birth, unless precluded by autolysis or cannibalization by the dam. The lungs were removed and immersed in water. Pups with lungs that sank were considered stillborn; pups with lungs that floated were considered liveborn and to have died shortly after birth.

The pups present in each litter were counted once each day. Physical signs (including gross external physical anomalies) were recorded for the pups once each day of the 4-day postpartum period. Pup body weights, sexes and observed nursing behaviors were recorded on DLs 2 and 4.

G.8. Gross Necropsy:

All rats in Parts I and II were sacrificed by carbon dioxide asphyxiation and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed (see APPENDIX E, item 5). Tissues with gross lesions were retained in neutral buffered 10% formalin; photographs of gross lesions are available in the raw data (see APPENDIX E, item 5).

All surviving rats assigned to Part I of the study were sacrificed on the day following the last test substance administration. Rats in Part I that were found dead before the completion of the study were necropsied and evaluated following the same procedures used for rats that survived to scheduled sacrifice.

All surviving rats assigned to Part II that delivered litters were sacrificed by carbon dioxide asphyxiation on DL 4, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed (see APPENDIX E, item 5). The number and distribution of implantation sites were recorded. Group II (Vehicle 2, Part II) litter 9337 did not survive to DL 4. Dam 9337 was sacrificed, after the last pup was found dead, following the procedures described previously.

Rats that did not deliver a litter were sacrificed on DG 23. The number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. Uteri of rats that appeared nonpregnant were stained with 10% ammonium sulfide, to confirm the absence of implantation sites[6]. Uteri and ovaries from nonpregnant rats were retained in neutral buffered 10% formalin. Group VI (1125.01, 1000 mg/kg/day, Part II) rat 9480 was sacrificed on DG 23 and was determined to be pregnant. Each fetus was removed from the uterus, placed in an individual container and identified with a tag noting the study number, litter number, uterine distribution and fixative. Each fetus was subsequently weighed and examined for sex and gross external alterations (see APPENDIX E, item 5). Live fetuses were sacrificed according to the Standard Operating Procedures of the Testing Facility. Approximately one-half of the fetuses in this litter were retained in Bouin's solution; the remaining fetuses were retained in alcohol for possible future evaluation.

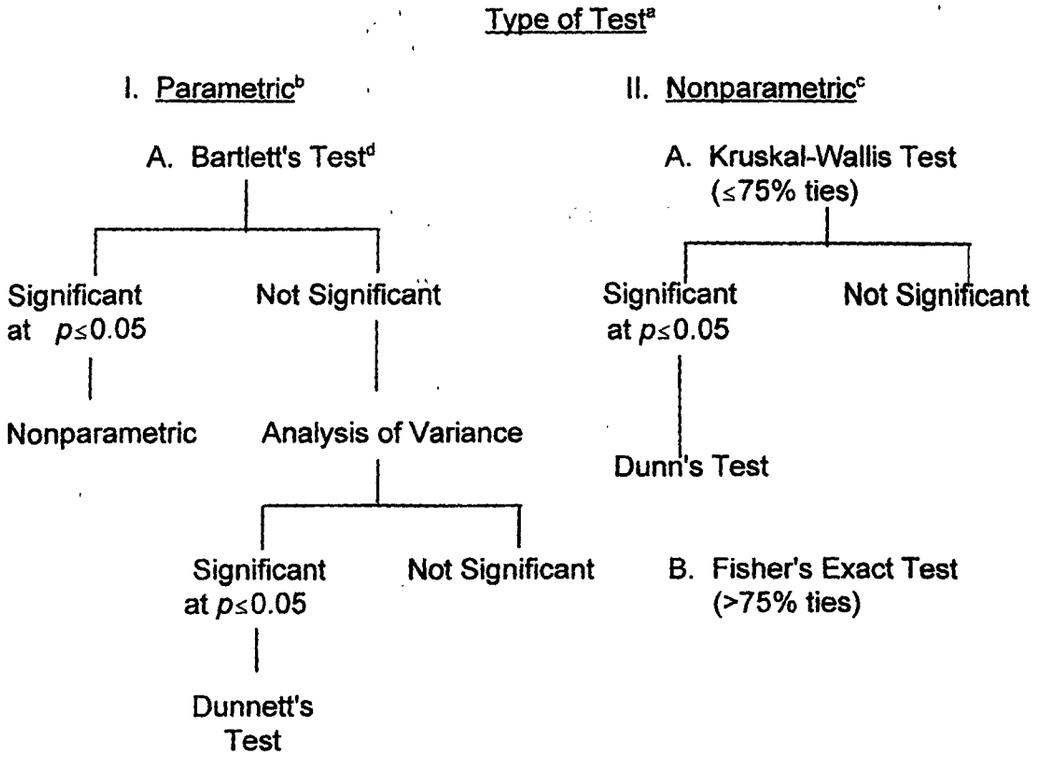
Rats that were found dead were necropsied and evaluated for pregnancy status, following the procedures described previously.

F1 Generation.

On DL 4, all F1 generation pups were sacrificed by carbon dioxide asphyxiation and examined for gross lesions. Necropsy included a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly. Tissues with gross lesions were retained in neutral buffered 10% formalin. Pups that were found dead were examined for gross lesions; pups with gross lesions were retained in Bouin's solution.

G.9. Statistical Analysis:

The following schematic represents the statistical analyses of the data:



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a. All tests evaluated at $p \leq 0.05$ to $p \leq 0.01$.
b. Used only to analyze data with homogeneity of variance.
c. Proportion data are not included in this category.
d. Test for homogeneity of variance.

Only Part II data were statistically analyzed; Groups III and IV were compared to Group I and Groups V and VI were compared to Group II.

Clinical observation and other proportion data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution[7].

Continuous data (e.g., maternal body weights, body weight changes) were analyzed using Bartlett's Test of Homogeneity of Variances[8] and the Analysis of Variance[9], when appropriate [i.e., Bartlett's Test was not significant ($p>0.05$)]. If the Analysis of Variance was significant ($p\leq0.05$), Dunnett's Test[10] was used to identify the statistical significance of the individual groups. If the Analysis of Variance was not appropriate [i.e., Bartlett's Test was significant ($p\leq0.05$)], the Kruskal-Wallis Test[11] was used, when less than or equal to 75% ties were present. In cases where the Kruskal-Wallis Test was statistically significant ($p\leq0.05$), Dunn's Method of Multiple Comparisons[12] was used to identify the statistical significance of the individual groups. If there were greater than 75% ties, Fisher's Exact Test[13] was used to analyze the data.

Natural delivery data involving discrete data were evaluated using the Kruskal-Wallis Test[11] procedures previously described.

III. RESULTS - PART I

RE-0981.05

A. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B4; Individual Data - Tables B5 and B7)

Adverse clinical observations were recorded at the 200 mg/kg/day dosage and higher and mortality at the 300 mg/kg/day dosage.

A.1 Mortality

There was one death, a high dosage group (300 mg/kg/day) female (8150) died on study day 5 (DS 5)[a]. Clinical observations of excess salivation and tachypnea were recorded DS 3 to 5 and loss of righting reflex, clonic convulsion, twitches and lacrimation on DS 5. Necropsy revealed no perforation of the trachea, esophagus and lungs and all tissues appeared normal.

A.2 Clinical Observations

Tachypnea (3/10) and excessive salivation (1/10) were observed at the 200 mg/kg/day dosage and decreased motor activity (1/10), clonic convulsion (2/10), twitches (1/10), lacrimation (3/10), excessive salivation (5/10) and tachypnea (8/10) were observed at the 300 mg/kg/day dosage.

All other clinical observations were considered unrelated to the test substance because: 1) the incidence was not dosage-dependent; and/or 2) the observation occurred in only one rat. This observation was lacrimation at the 50 mg/kg/day dosage.

A.3 Necropsy Observations

Scheduled necropsies for the remaining 49 rats revealed all tissues appeared to be normal.

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a. The first day of dosage is defined as study day 1 (DS 1).

B. Body Weights and Body Weight Changes (Summaries - Tables B2 and B3; Individual Data - Table B6)

Body weights and body weight changes were generally comparable across the five dosage groups for the five consecutive days of treatment.

RE-1122.01

A. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B4; Individual Data - Tables B5 and B7)

Adverse clinical observations, including mortality, were recorded at the 200 and 300 mg/kg/day dosages.

A.1. Mortality

There was one death (8185) at the 200 mg/kg/day dosage and nine deaths (8191, 8192, 8194, 8195, 8196, 8197, 8198, 8199, 8200) at the 300 mg/kg/day dosage. There were no adverse clinical observations for the 200 mg/kg/day dosage rat prior to being found dead on DS 3. Eight out of nine of the deaths at the 300 mg/kg/day dosage had the adverse clinical finding of decreased motor activity prior to death. All of these deaths were considered treatment-related, except for female 8194, because they were dosage-dependent. Necropsy of rat 8194 revealed the thoracic cavity contained approximately 3.0 mL of a clear yellow fluid with all other tissues normal; there was no perforation of the trachea, lungs or esophagus. There were no necropsy findings, including evidence of an intubation error, for the other rats found dead and all tissues appeared normal for the degree of autolysis at this dosage.

A.2. Clinical Observations

Clinical observations of decreased motor activity (7/10), red and dark red eye (1/10), lacrimation (2/10) and dry, red perioral substance (1/10) occurred at the 200 mg/kg/day dosage and decreased motor activity (9/10), impaired righting reflex (2/10), ataxia (1/10), tremors (2/10), hyperactivity (1/10), chromodacryorrhea (1/10), lacrimation (1/10), ptosis (1/10), pale in appearance (2/10), cold to touch (1/10), clonic convulsion (1/10), dry red perioral substance (1/10), urine stained abdominal fur (1/10), excessive salivation (2/10), and labored breathing (1/10) occurred at the 300 mg/kg/day dosage.

All other clinical observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one rat. These observations were a lesion on the

mouth for a 25 mg/kg/day dosage group rat (8157) and red and/or dark eyes and exophthalmos for the same rat (8188) at the 200 mg/kg/day dosage.

A.3. Necropsy Observations

Scheduled necropsies for the remaining 40 rats revealed all tissues appeared to be normal. The mouth lesion was confirmed on the 25 mg/kg/day dosage female but was not considered treatment-related because it was not dosage-dependent.

B. Body Weights and Body Weight Changes (Summaries - Tables B2 and B3; Individual Data - Table B6)

Body weights and body weight changes were depressed in a dose-dependent fashion, for the five consecutive days of treatment, at 50 mg/kg/day and higher dosages, when compared to the 25 mg/kg/day dosage. The females in the 200 and 300 mg/kg/day dosages had absolute body weight losses over the treatment period.

RE-1123.01

A. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B4; Individual Data - Tables B5 and B7)

There were no adverse clinical or necropsy observations nor deaths for dosages up to 2000 mg/kg/day of the test substance.

A.1. Mortality

There were no deaths at dosages up to 2000 mg/kg/day of the test substance.

A.2. Clinical Observations

There were no adverse clinical observations at dosages up to 800 mg/kg/day for the first two days of test substance administration. On the third day of study the lowest dosage group (Group XI) was increased from 50 to 1000 mg/kg/day and the second lowest dosage group (Group XII) was increased from 150 to 1200 mg/kg/day. Since no adverse clinical findings nor deaths occurred at these new dosages after an additional two days of treatment, Group XI was increased again from 1000 to 1500 mg/kg/day and Group XII was increased again from 1200 to 2000 mg/kg/day and dosed for three additional days (8 days total). There were no adverse clinical observations at dosages up to 2000 mg/kg/day.

A.3. Necropsy Observations

Scheduled necropsies for the 50 rats revealed all tissues to appear normal except for the spleen. This organ appeared dark red and enlarged for 8/10, 9/10, 10/10, 10/10 and 10/10 rats for the 300 (Group XIII), 550 (Group XIV), 800 (Group XV), 1500 (Group XI) and 2000 (Group XII) mg/kg/day dosage groups, respectively. The large dark red spleens of rats 8228 and 8236 also had a granular surface and a raised gray area (1.0 cm x 0.5 cm), respectively.

B. Body Weights and Body Weight Changes (Figure 1; Summaries - Tables B2 and B3; Individual Data - Table B6)

Groups XI and XII, which received the 1500 and 2000 mg/kg/day dosages, respectively, for the last three days of the extended treatment, experienced some reduction in body weight gains.

RE-1125.01

A. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B4; Individual Data - Tables B5 and B7)

Adverse clinical observations occurred at the 750 mg/kg/day dosage and higher and two deaths occurred at the 2000 mg/kg/day dosage. One death at the 750 mg/kg/day dosage was not treatment-related.

A.1. Mortality

Rat 8293 in the 2000 mg/kg/day dosage group died on DS 6. Clinical observations of chromodacryorrhea (DS 1), decreased motor activity (DS 1 to 2, 4 to 5), ataxia (DS 2) and lacrimation (DS 2 to 3, 5) were recorded prior to being found dead. Necropsy revealed no perforation of the trachea, esophagus and lungs and all tissues appeared normal.

Rat 8299 in the 2000 mg/kg/day dosage group died on DS 3. Clinical observations of decreased motor activity and lacrimation were recorded DSs 1 to 2. Necropsy revealed no perforation of the trachea, esophagus and lungs and all tissues appeared normal.

A single death (8261) occurred at the 750 mg/kg/day dosage. Decreased motor activity on DS 2 was recorded prior to being found dead on DS 3. This death was not considered treatment-related because there were no necropsy findings and the death was not dosage-dependent.

A.2. Clinical Observations

Decreased motor activity (2/10) was the only adverse clinical observation at the 750 mg/kg/day dosage in addition to the death previously cited. Decreased motor activity (10/10) and lacrimation (3/10) occurred at the 1000 mg/kg/day dosage and decreased motor activity (10/10) and lacrimation (10/10) also occurred at the 1500 mg/kg/day dosage. Clinical observations of death (2/10), decreased motor activity (10/10), ataxia (1/10), chromodacryorrhea (1/10) and lacrimation (10/10) occurred at the 2000 mg/kg/day dosage.

A.3 Necropsy Observations

Scheduled necropsies for the remaining 47 rats revealed all tissues to appear normal except for the spleen. This organ appeared dark red and/or enlarged for 0/10, 2/10, 6/10, 9/10 and 8/10 rats for the 250, 750, 1000, 1500 and 2000 mg/kg/day dosage groups, respectively. The spleens of rats 8253 (250 mg/kg/day dosage) and 8290 (1500 mg/kg/day dosage) also had multiple raised gray areas (0.3 cm x 0.4 cm and 0.2 cm x 0.5 cm, respectively).

B. Body Weights and Body Weight Changes (Summaries - Tables B2 and B3; Individual Data - Table B6)

Body weights and body weight gains were comparable across all treatment groups.

IV. CONCLUSION - Part I

A dosage of 250 mg/kg/day RE-0981.05, a dosage of 200 mg/kg/day RE-1122.01, a dosage of 1000 mg/kg/day RE-1123.01 and a dosage of 1000 mg/kg/day RE-1125.01 were recommended and agreed upon with the Sponsor for the definitive study (Part II) based on the available maternally toxic endpoint data.

V. RESULTS - PART II

RE-0981.05

A. Fo Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C11 and C12)

A dosage of 250 mg/kg/day of RE-0981.05 resulted in the death of 11 of 30 (37%) of the female rats and adverse clinical observations. Deaths occurred following one to five daily dosage administrations. Three rats were found dead

on gestation day (DG) 7, three on DG 8, one on DG 9, two on DG 10, one on DG 11 and one on DG 12.

A.1. Mortality

Rat 9363 had clinical observations of tachypnea and clonic convulsions recorded on the first day of test substance administration. A body weight loss (-12 g) and lacrimation, excessive salivation, loss of righting reflex, twitches, tachypnea and clonic convulsions were recorded prior to death on the second day of treatment. A necropsy revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal and the rat was not pregnant.

Dam 9366 died after the third test substance administration and had only a clinical observation of localized alopecia on the limbs and a modest body weight loss (-2 g) prior to being found dead. A necropsy revealed the perioral area wet and stained orange-brown and 15 normally developing implants. The stomach contained approximately 3 mL of clear yellow fluid. Perfusion of the lungs, trachea and esophagus revealed no perforations; all other tissues appeared normal.

Dam 9367 had a modest weight loss (-2 g) and appeared normal prior to death on the fifth day of test substance administration. Clinical observations on the day of death included twitches, vocalization, piloerection, dilated pupils, chromodacryorrhea, excessive salivation and clonic convulsions. At necropsy, perfusion of the lungs, trachea and esophagus revealed a perforation of the trachea, possibly damaged during the necropsy; all other tissues appeared normal with normally developing implants. The uterus contained 19 normally developing implants and one early resorption.

Dam 9368 lost body weight (-3 g) and had clinical observations that included twitches and clonic convulsions prior to death after the second test substance administration. A necropsy revealed the stomach distended with air/gas and containing 2 mL of clear fluid. Perfusion revealed no perforations of the esophagus, trachea or lungs; all other tissues appeared normal. The uterus contained 18 normally developing implants.

Dam 9369 had clinical observations that included tachypnea on the second and third day of dosage administration. Clinical observations were normal and there was a body weight gain (3 g) on the day of death, the fourth day of test substance administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 17 normally developing implants.

Dam 9371 had a modest body weight loss (-1 g) and clinical observations that included clonic convulsion, twitches, vocalization, excessive salivation, and piloerection prior to death on the fourth day of test substance administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 16 normally developing implants.

Dam 9377 had clinical observations that included excessive salivation, tachypnea, decreased motor activity, clonic convulsion, twitches, lacrimation and urine-stained abdominal fur prior to death on the day after the last test substance administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 12 normally developing implants

Dam 9381 appeared normal but had a body weight loss (-4 g) prior to being found dead after the second test substance administration. At necropsy, perfusion of the lungs, trachea and esophagus revealed no perforations; all tissues appeared normal with 14 normally developing implants.

Dam 9385 had clinical observations that included twitches, excessive salivation, clonic convulsions and death on the first day of administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 18 normally developing implants.

Dam 9387 gained weight (36 g) since DG 0 but had a clinical observation of clonic convulsion prior to death on the first day of administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 16 normally developing implants.

Dam 9388 gained weight (20 g) since DG 0 but had clinical observations that included clonic convulsion and twitches prior to death on the first day of test substance administration. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 17 normally developing implants.

A.2. Clinical Observations

Clinical observations during gestation considered related to the test substance included death (11/30; $p \leq 0.01$), tachypnea (15/30; $p \leq 0.01$), clonic convulsions (10/30; $p \leq 0.01$), twitches (9/30; $p \leq 0.01$), excess salivation (11/30), lacrimation (3/30), piloerection (2/30), loss of righting reflex (1/30), decreased motor activity (1/30) and vocalization (2/30). Tachypnea, clonic convulsions, twitches and excess salivation were observed for both dead and surviving rats.

All other clinical findings, including those observed during lactation, were considered unrelated to the test substance because: 1) the incidences were within the historical control of the Testing Facility[a]; and/or 2) the observation occurred in only one or two rats. These observations included chromodacryorrhea, dilated pupil, urine-stained abdominal fur and localized alopecia on the limbs or underside.

A.3. Necropsy Observations

There were no necropsy observations for surviving rats at study termination that were considered treatment-related.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables C3 through C6; Individual Data - Tables C13 and C14)

B.1. Gestation

Average body weight gains during gestation were significantly reduced ($p \leq 0.01$) over DGs 8 to 9, 9 to 10, and 10 to 11 and over the entire treatment interval (calculated as DGs 7 to 12), compared to the 0 (Vehicle) mg/kg/day dosage group. Average body weight gains during the post-treatment period (calculated as DGs 12 to 20) were comparable to the 0 (Vehicle) mg/kg/day dosage group .

Average body weights during gestation were reduced relative to the 0 (Vehicle) mg/kg/day dosage group, but not statistically different.

B.2. Lactation

During the four days of lactation, average body weight gains (3.9 g) and body weights (328.5 g) were reduced, compared to the 0 (Vehicle) mg/kg/day dosage group (8.7 g and 340.6 g, respectively), but not statistically different.

C. Natural Delivery Observations (Summary - Table C7; Individual Data - Table C15)

A total of 29 females were pregnant (96.7% pregnancy rate) and 19 (100%) of the surviving rats delivered litters. The duration of gestation (22.7 days) was the same as the 0 (Vehicle) mg/kg/day dosage group (22.9 days) and the gestational index was 100%.

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a. See APPENDIX F (HISTORICAL CONTROL DATA).

D. **Litter Observations (Summary -Table C8; Individual Data - Tables C16 through C18)**

Average litter size, pup survival, and pup weights were comparable to the 0 (Vehicle) dosage group and there were no statistically significant differences.

A total of 282 pups were liveborn (98.2%) and 5 (1.7%) were stillborn. Three (1.1%) pups died or were missing during lactation days 1 to 4 compared to 11 (2.6%) for the 0 (Vehicle) dosage group, for a viability index of 98.9% to 97.4%, respectively.

Litter size in live pups per litter on lactation days 2 (14.8) and 4 (14.7) and pup weight per litter on lactation days 2 (7.5 g) and 4 (9.4 g), were comparable to the 0 (Vehicle) dosage group (14.5 and 14.3; 7.4 g and 9.2 g, respectively).

E. **F1 Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C9 and C10; Individual Data - Table C19 and C20)**

A total of five pups were stillborn and two were found dead compared to 12 and nine, respectively, for the 0 (Vehicle) dosage group. There were no adverse clinical observations from birth to day 4 postpartum or necropsy findings for pups sacrificed on day 4 postpartum.

RE-1122.01

A. **Fo Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C11 and C12)**

A dosage of 200 mg/kg/day of RE-1122.01 resulted in the death of 11 of 30 (37%) of the rats and adverse clinical observations (the death of one of the rats may have been due to an intubation error). Deaths occurred following two to five dosages. One rat was found dead on DG 8, two on DG 9, five on DG 10, two on DG 11 and one on DG 13.

A.1. **Mortality**

Dam 9391 had a modest body weight loss (-2 g) after the first treatment and normal clinical observations until death occurred, after the third test substance administration. A necropsy revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 14 normally developing implants.

Dam 9392 lost body weight (-7 g) during treatment but had normal clinical observations until death after the fourth test substance administration. A necropsy revealed the stomach to contain approximately 3 mL of a clear yellow fluid. Perfusion revealed no perforations of the esophagus, trachea or lungs; all other tissues appeared normal with 16 normally developing implants.

Dam 9393 had clinical observations that included localized alopecia of the limbs, decreased motor activity, chromodacryorrhea, emaciation and urine-stained abdominal fur prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 14 normally developing implants.

Dam 9397 lost body weight (-45 g) during treatment and had clinical observations that included tachypnea, decreased motor activity, chromodacryorrhea, chromorhinorrhea and emaciation prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 19 normally developing implants.

Dam 9399 lost body weight (-23 g) during treatment but had only the clinical observation of chromorhinorrhea prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 20 normally developing implants.

Dam 9400 lost body weight (-13 g) during treatment and had clinical observations that included decreased motor activity, twitches, vocalization, clonic convulsion and excess salivation prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs but the lungs contained a white, frothy material; all other tissues appeared normal with 20 normally developing implants. This death may have been due to an intubation error.

Dam 9404 lost body weight (-5 g) but had only the clinical observation of localized alopecia on the limbs prior to being found dead after the second test substance administration. At necropsy, perfusion of the lungs, trachea and esophagus revealed no perforations; all tissues appeared normal with 19 normally developing implants.

Dam 9405 lost body weight (-20 g) during treatment but had normal clinical observations prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 16 normally developing implants.

Dam 9407 lost body weight (-27 g) during treatment and had clinical observations of localized alopecia on the limbs, decreased motor activity, excess salivation, incisors missing/broken and urine-stained abdominal fur prior to

death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 17 normally developing implants.

Dam 9413 lost body weight (-10 g) during treatment but had only a clinical observation of twitches prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 10 normally developing implants.

Dam 9420 lost body weight (-24 g) during treatment but had only a clinical observation of decreased motor activity prior to death. At necropsy, perfusion revealed no perforations of the esophagus, trachea or lungs; all tissues appeared normal with 15 normally developing implants.

A.2. Clinical Observations

Clinical observations considered related to the test substance included death (11/30; $p \leq 0.01$), decreased motor activity (12/30; $p \leq 0.01$), urine-stained abdominal fur (11/30; $p \leq 0.01$), chromodacryorrhea (3/30), emaciation (3/30), chromorhinorrhea (3/30), twitches (3/30), excess salivation (3/30), vocalization (2/30), red substance on abdomen (1/30), tachypnea (1/30), clonic convulsion (1/30), hyperactivity (1/30) and perivaginal brown substance (1/30). Decreased motor activity, urine-stained abdominal fur, chromodacryorrhea, emaciation, chromorhinorrhea and excess salivation were observed for both dead and surviving rats.

All other clinical findings, including those observed during lactation, were considered unrelated to the test substance because: 1) the incidences were within the historical control of the Testing Facility; and/or 2) the observation occurred in only one or two rats. These observations included localized alopecia on the limbs, head or underside and incisors missing/broken.

A.3. Necropsy Observations

There were no necropsy observations at termination that were considered treatment-related. One female (9403) had a large spleen (2.19 g) and all other tissues appeared normal.

B. Maternal Body Weights and Body Weight Changes (Figure 1; Summaries - Tables C3 through C6; Individual Data - Tables C13 and C14)

B.1. Gestation

Average body weight gains during gestation were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) for DGs 7 to 8, 8 to 9, 9 to 10, 10 to 11 and 11 to 12, for the entire treatment interval (calculated DGs 7 to 12) and for the entire gestational periods (calculated DGs 7 to 20 and 0 to 20), compared to the 0 (Vehicle) mg/kg/day dosage group. Average body weight gains during the post-treatment period (calculated as DGs 12 to 20) were significantly increased ($p \leq 0.01$), compared to the 0 (Vehicle) mg/kg/day dosage group. This is a common rebound effect seen with the cessation of treatment.

Average body weights during gestation were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$), relative to the 0 (Vehicle) mg/kg/day dosage group, on DGs 9 through 18.

B.2. Lactation

During the four days of lactation, average body weight gains (9.2 g) were similar and body weights (324.2 g) were reduced, compared to the 0 (Vehicle) mg/kg/day dosage group (8.7 g and 340.6 g, respectively).

C. Natural Delivery Observations (Summary - Table C7; Individual Data - Table C15)

A total of 27 females were pregnant (90.0%) and 16 (100%) of the surviving pregnant rats delivered litters. The duration of gestation (22.8 days) and the gestational index (100%) were comparable to the 0 (Vehicle) mg/kg/day dosage group (22.9 days and 100%, respectively).

D. Litter Observations (Summary-Table C8; Individual Data - Tables C16 through C18)

Average litter size, pup survival, sex ratio and pup weights were comparable to the 0 (Vehicle) dosage group. There were no statistically significant differences.

A total of 259 pups were liveborn (99.2%) and 2 (0.8%) were stillborn. Five pups (2.0%) died or were missing on lactation days 1 to 4 compared to 11 (2.6%) for the 0 (Vehicle) dosage group, for a viability index of 98.1% to 97.4%, respectively.

Litter size in live pups per litter on lactation days 2 (15.9) and 4 (15.9) was greater than and pup weight per litter on lactation days 2 (7.4 g) and 4 (8.9 g), was comparable to the 0 (Vehicle) dosage group (14.5 and 14.3; 7.4 g and 9.2 g, respectively).

E. F1 Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C9 and C10; Individual Data - Table C19 and C20)

A total of two pups were stillborn and one was found dead compared to 12 and nine, respectively, for the 0 (Vehicle) dosage group. There were no adverse clinical observations from birth to day 4 postpartum. A skull defect for one stillborn pup (litter 9402), no milk in the stomach for a found dead pup (litter 9398) and a liver with multiple tan areas for one pup (litter 9408) sacrificed on day 4 postpartum were the only necropsy findings.

RE-1123.01

A. Fo Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C11 and C12)

A dosage of 1000 mg/kg/day of RE-1123.01 did not result in any mortality or adverse clinical observations.

A.1. Mortality

There were no deaths.

A.2. Clinical Observations

There were no adverse clinical observations.

All clinical findings, including those observed during lactation, were considered unrelated to the test substance because: 1) the incidences were within the historical control of the Testing Facility; and/or 2) the observation occurred in only one or two rats. These observations included chromorhinorrhea, localized alopecia on the limbs, neck and/or underside, head lesion and chromodacryorrhea.

A.3. Necropsy Observations

There were two females (9437, 9441) with dark red and/or large spleens that were considered treatment-related. All other tissues appeared normal.

B. Maternal Body Weights and Body Weight Changes (Figure 2; Summaries - Tables C3 through C6; Individual Data - Tables C13 and C14)

B.1. Gestation

The average body weight gain was significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) for DGs 7 to 8, 8 to 9, 9 to 10, 10 to 11 and 11 to 12 and for the entire treatment interval (calculated as DGs 7 to 12), compared to the 0 (Vehicle) mg/kg/day dosage group. Average weight gain during the postdosage period (DGs 12 to 20) was comparable to the 0 (Vehicle) mg/kg/day dosage group.

Average body weights during gestation were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$), relative to the 0 (Vehicle) mg/kg/day dosage group, on DGs 9 through 15.

B.2. Lactation

During lactation, average body weight gains (11.8 g) were increased and body weights (331.5 g) were reduced, compared to the 0 (Vehicle) mg/kg/day dosage group (6.1 g and 334.2 g, respectively,) but not statistically different.

C. Natural Delivery Observations (Summary - Table C7; Individual Data - Tables C15)

There were no parameters evaluated during the lactation period that were affected by administration of RE-1123.01 during gestation.

A total of 28 females were pregnant (93.3%) and all 28 of the pregnant rats delivered litters (100%). The duration of gestation (22.9 days) was comparable to the 0 (Vehicle) mg/kg/day dosage group (22.7 days).

D. Litter Observations (Summary - Table C8; Individual Data - Tables C16 through C18)

The total number of liveborn pups was significantly reduced from the control group. Average litter size, pup survival, sex ratio and pup weights were comparable to the 0 (Vehicle) mg/kg/day dosage group; there were no statistically significant differences.

A total of 418 pups (97.0%; $p \leq 0.01$) were liveborn, 12 (2.8%) were stillborn and one pup was of unknown vital status. Eight (1.9%) pups died lactation days 1 to 4 compared to 16 (3.6%) for the 0 (Vehicle) mg/kg/day dosage group, for a

viability index of 98.0%, compared to 96.4% for the 0 (Vehicle) mg/kg/day dosage group.

Litter size in live pups per litter on lactation days 2 (15.3) and 4 (15.1) was slightly decreased and pup weight per litter on lactation days 2 (7.6 g) and 4 (9.4 g), was comparable to the 0 (Vehicle) mg/kg/day dosage group (16.0 and 15.8; 7.4 g and 9.0 g, respectively).

E. F1 Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C9 and C10; Individual Data - Table C19 and C20)

A total of 12 pups were stillborn and 6 were found dead compared to 5 and 12, respectively, for the 0 (Vehicle) mg/kg/day dosage group. There was one adverse clinical observation from birth to day 4 postpartum, one pup (litter 9440) had a purple muzzle. Three found dead pups (litters 9433, 9434, 9445) had no milk in the stomach, and were the only necropsy findings.

RE-1125.01

A. Fo Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C11 and C12)

A dosage of 1000 mg/kg/day of RE-1125.01 resulted in adverse clinical observations and the death of 2 of 30 (7%) of the rats following five dosages.

A.1. Mortality

Dam 9459 had gained body weight (7 g) during treatment but clinical observations of decreased motor activity were recorded on the first, third and fourth day of test substance administration and lacrimation and ptosis were recorded on the first and fifth day of test substance administration, respectively. This rat died on of the day after the last dosage administration. At necropsy, perfusion of the lungs, trachea and esophagus revealed no perforations; a red substance was present on the ventral abdomen and perioral surface. This rat was pregnant with 15 normally developing implants.

Rat 9461 gained body weight (8 g) during treatment but also died on of the day after the last administration. Decreased motor activity was observed on the first, second and fifth day of test substance administration. At necropsy, perfusion of the lungs, trachea and esophagus revealed no perforations; a red substance was present on the ventral abdomen, perioral surface and forepaws and the rat was not pregnant.

A.2. Clinical Observations

Clinical observations considered related to the test substance included decreased motor activity (28/30; $p \leq 0.01$), lacrimation (6/30; $p \leq 0.01$), chromorhinorrhea (3/30) and urine-stained abdominal fur (2/30). Decreased motor activity and lacrimation were observed for both dead and surviving rats.

All other clinical findings, including those observed during lactation, were considered unrelated to the test substance because: 1) the incidences were within the historical control of the Testing Facility; and/or 2) the observation occurred in only one or two rats. These observations included incisors missing/broken, ptosis, excess salivation and localized alopecia on the limbs.

A.3. Necropsy Observations

There were no necropsy observations that were considered treatment-related.

B. Maternal Body Weights and Body Weight Changes (Figure 2; Summaries - Tables C3 through C6; Individual Data - Tables C13 and C14)

B.1. Gestation

Average body weight gains were significantly reduced ($p \leq 0.01$) for DGs 7 to 8 and 10 to 11, for the overall treatment interval (calculated as DGs 7 to 12) and for the gestational period (calculated as DGs 7 to 20), compared to the 0 (Vehicle) mg/kg/day dosage group. Average body weight gains were comparable to the 0 (Vehicle) mg/kg/day dosage group for post-treatment period (calculated as DGs 12 to 20).

B.2. Lactation

During lactation, average body weight gains (11.4 g) were greater and body weights (329.8 g) were reduced, compared to the 0 (Vehicle) mg/kg/day dosage group (6.1 g and 334.2 g, respectively), but not statistically different.

C. Natural Delivery Observations (Summary - Table C7; Individual Data - Table C15)

No parameter evaluated during the lactation period was affected by administration of RE-1125.01 during gestation. There were no statistically significant differences.

A total of 27 females were pregnant (90.0%) and 26 of the surviving pregnant rats delivered litters (100%). The duration of gestation (22.8 days) and gestation index (100%) was comparable to the 0 (Vehicle) mg/kg/day dosage group (22.7 days and 100%, respectively).

D. Litter Observations (Summary -Table C8; Individual Data - Tables C16 through C18)

Average litter size, sex ratio and pup weights were comparable to the 0 (Vehicle) mg/kg/day dosage group.

A total of 429 pups were liveborn (99.5%) and 2 (0.5%) were stillborn. Seven pups died on lactation days 1 to 4 compared to 16 (3.6%) for the 0 (Vehicle) mg/kg/day dosage group, for a viability index of 98.4%, compared to 96.4% for the 0 (Vehicle) mg/kg/day dosage group.

Litter size in live pups per litter on lactation days 2 (16.2) and 4 (16.2) and pup weight per litter on lactation days 2 (7.3 g) and 4 (8.8 g), were comparable to the 0 (Vehicle) mg/kg/day dosage group (16.0 and 15.8; 7.4 g and 9.0 g, respectively).

E. F1 Generation Mortality, Clinical and Necropsy Observations (Summaries - Tables C9 and C10; Individual Data - Table C19 and C20)

A total of two pups were stillborn and three were found dead compared to five and 12, respectively, for the 0 (Vehicle) mg/kg/day dosage group. There was one adverse clinical observation from birth to day 4 postpartum, two pups (litter 9474) had a purple muzzle. Two found dead pups (litters 9462, 9474) had no milk in the stomach and one day 4 postpartum sacrificed pup (litter 9472) had moderate dilation of the left pelvis of the kidney, and were the only necropsy findings.

VI. CONCLUSION - Part II

Dosages of 250 mg/kg/day RE-0981.05 in reverse osmosis membrane processed deionized water (R.O. deionized water) produced evidence of maternal toxicity (death, clinical observations, decreased body weights and body weight gains) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 200 mg/kg/day RE-1122.01 in reverse osmosis membrane processed deionized water (R.O. deionized water) produced evidence of maternal toxicity (death, clinical observations, decreased body weights and body weight gains) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 1000 mg/kg/day RE-1123.01 in aqueous 0.5% carboxy-methlycellulose (prepared in R.O. deionized water) produced evidence of maternal toxicity (decreased body weights, enlarged spleens) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

Dosages of 1000 mg/kg/day RE-1125.01 in aqueous 0.5% carboxy-methlycellulose (prepared in R.O. deionized water) produced evidence of maternal toxicity (deaths, decreased body weight gain) but did not induce toxic effects in the conceptus after administration of the test substance to the dam during gestation.

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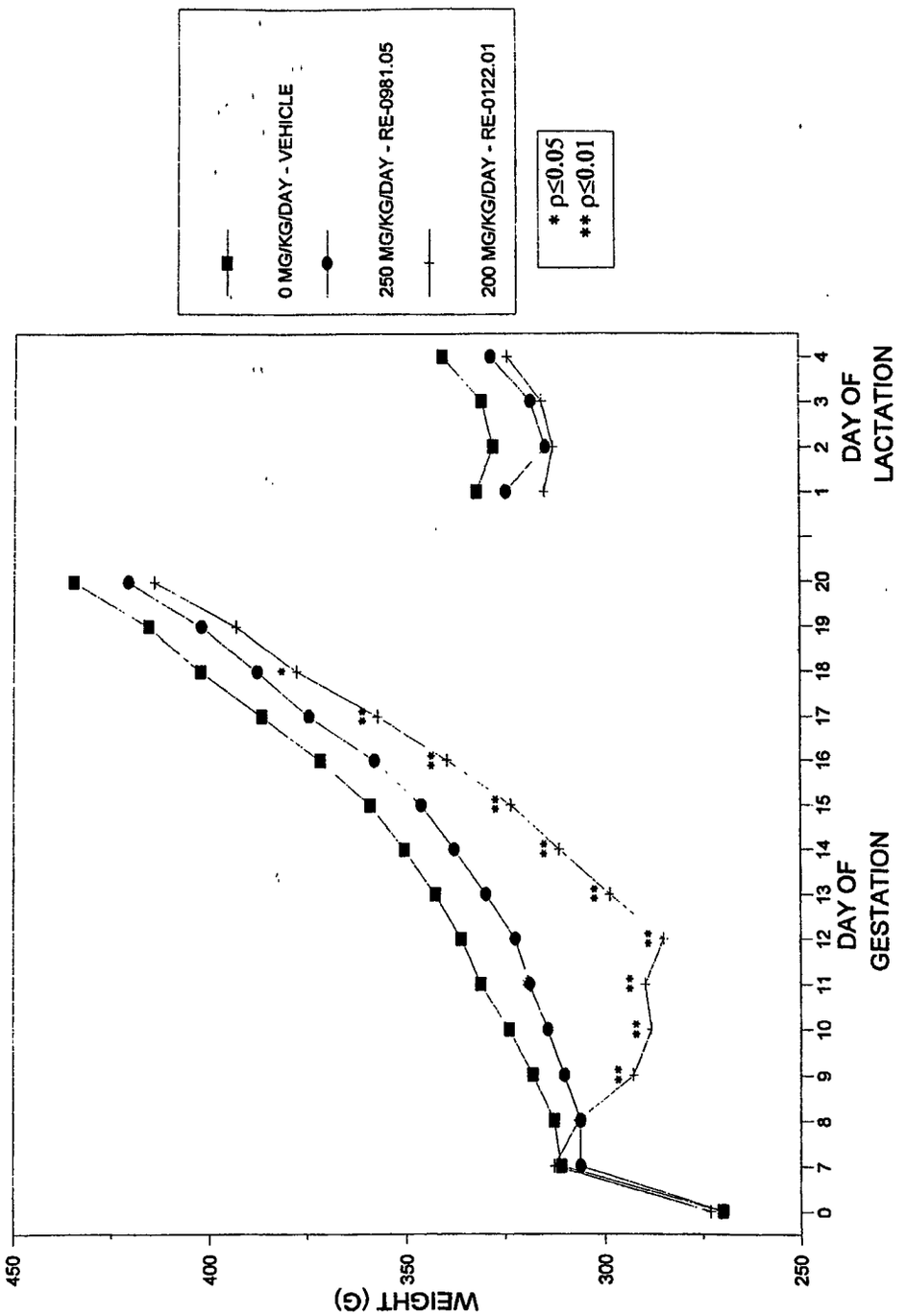
APPENDIX A

REPORT FIGURES

MATERNAL BODY WEIGHTS

Fo GENERATION FEMALE RATS - PART II

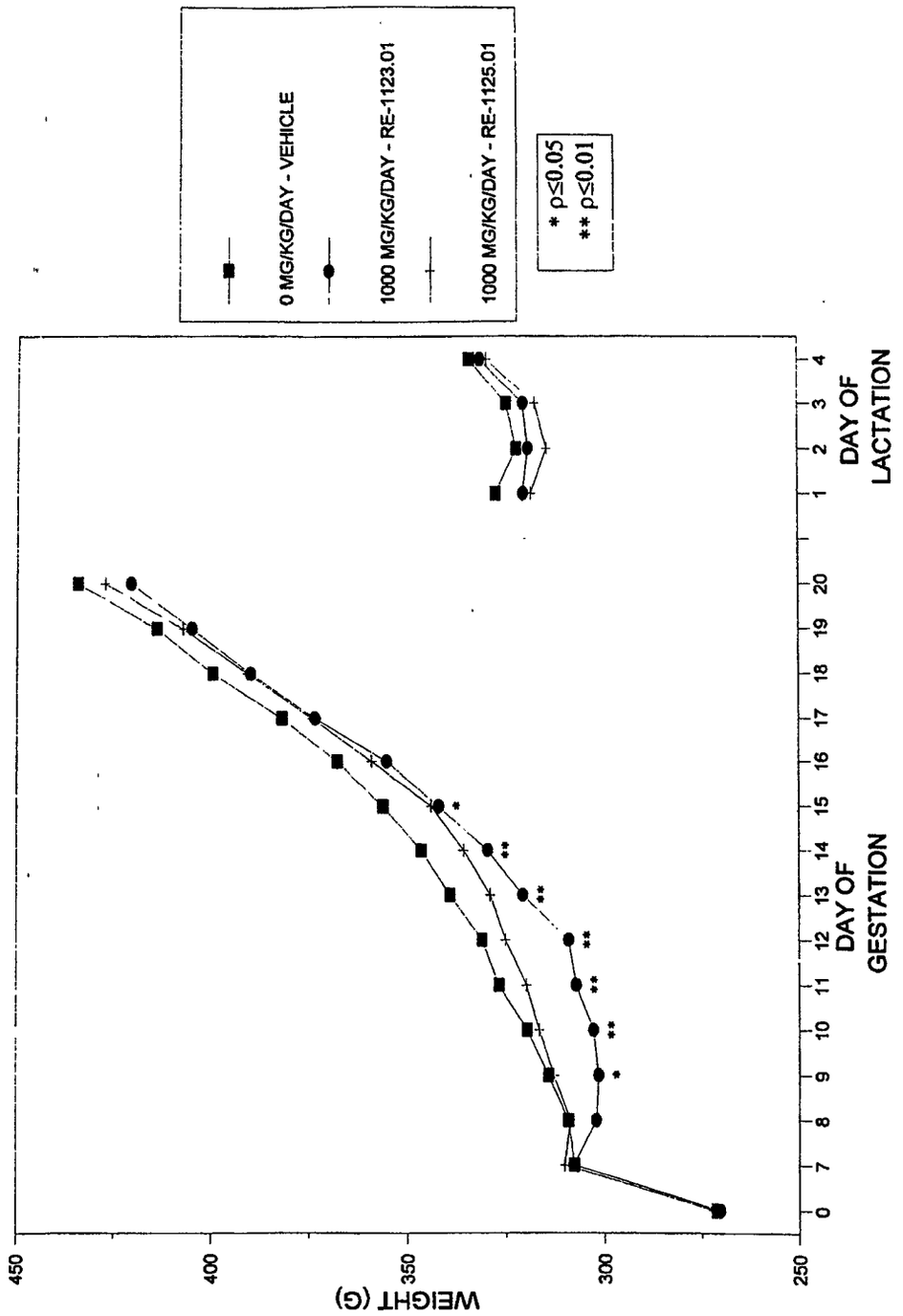
Figure 1



MATERNAL BODY WEIGHTS

Fo GENERATION FEMALE RATS - PART II

Figure 2



APPENDIX B

REPORT TABLES - PART I

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP	I	II	III	IV	V
DOSAGE (MG/KG/DAY)	25	50	100	200	300
DESCRIPTOR	RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05
MAXIMUM POSSIBLE INCIDENCE	60/ 10	60/ 10	60/ 10	60/ 10	59/ 10
FOUND DEAD a	0	0	0	0	1
TACHYPNEA	0/ 0	0/ 0	0/ 0	4/ 3	14/ 8
EXCESS SALIVATION	0/ 0	0/ 0	0/ 0	1/ 1	10/ 5
LACRIMATION	0/ 0	1/ 1	0/ 0	0/ 0	5/ 3
CONVULSION: CLONIC	0/ 0	0/ 0	0/ 0	0/ 0	2/ 2
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
LOST Rrighting REFLEX	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
TWITCHES	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Refer to the individual clinical observations table (Table B5) for rats that were found dead with adverse observations.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	VI 25 RE-1122.01	VII 50 RE-1122.01	VIII 100 RE-1122.01	IX 200 RE-1122.01	X 300 RE-1122.01
MAXIMUM POSSIBLE INCIDENCE	60/ 10	60/ 10	60/ 10	57/ 10	43/ 10
FOUND DEAD a	0	0	0	1	9
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	0/ 0	14/ 7	15/ 9
PALE IN APPEARANCE	0/ 0	0/ 0	0/ 0	0/ 0	3/ 2
EXCESS SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	2/ 2
IMPAIRED RIGHTING REFLEX	0/ 0	0/ 0	0/ 0	0/ 0	2/ 2
TREMORS	0/ 0	0/ 0	0/ 0	0/ 0	2/ 2
CHROMODACRYORRHEA	0/ 0	0/ 0	0/ 0	0/ 0	3/ 1
LACRIMATION	0/ 0	0/ 0	0/ 0	3/ 2	1/ 1
DRY RED PERIORAL SUBSTANCE	0/ 0	0/ 0	0/ 0	2/ 1	1/ 1
ATAXIA	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
HYPERACTIVITY	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
CONVULSION: CLONIC	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
PTOSIS	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
COLD TO TOUCH	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Refer to the individual clinical observations table (Table B5) for rats that were found dead with adverse observations.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	VI 25 RE-1122.01	VII 50 RE-1122.01	VIII 100 RE-1122.01	IX 200 RE-1122.01	X 300 RE-1122.01
MAXIMUM POSSIBLE INCIDENCE	60/ 10	60/ 10	60/ 10	57/ 10	43/ 10
FOUND DEAD a	0	0	0	1	9
URINE STAINED ABDOMINAL FUR	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
LABORED BREATHING	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
EYES: RED OR DARK RED	0/ 0	0/ 0	0/ 0	4/ 1	0/ 0
EXOPHTHALMOS	0/ 0	0/ 0	0/ 0	3/ 1	0/ 0
MOUTH: LESION	2/ 1	0/ 0	0/ 0	0/ 0	0/ 0

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Refer to the individual clinical observations table (Table B5) for rats that were found dead with adverse observations.

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TABLE B1 (PAGE 4): CLINICAL OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP	XI a	XII b	XIII	XIV	XV
DOSAGE (MG/KG/DAY)	50	150	300	550	800
DESCRIPTOR	RE-1123.01	RE-1123.01	RE-1123.01	RE-1123.01	RE-1123.01
MAXIMUM POSSIBLE INCIDENCE	90/ 10	90/ 10	60/ 10	60/ 10	60/ 10
MORTALITY	0	0	0	0	0
NO ADVERSE FINDINGS					

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.
b. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.

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TABLE B1 (PAGE 5): CLINICAL OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP	XVI	XVII	XVIII	XIX	XX
DOSAGE (MG/KG/DAY)	250	750	1000	1500	2000
DESCRIPTOR	RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01
MAXIMUM POSSIBLE INCIDENCE	60/ 10	57/ 10	60/ 10	60/ 10	57/ 10
FOUND DEAD a	0	1	0	0	2
DECREASED MOTOR ACTIVITY	0/ 0	4/ 2	26/ 10	36/ 10	40/ 10
LACRIMATION	0/ 0	0/ 0	3/ 3	21/ 10	21/ 10
ATAXIA	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
CHROMODACRYORRHEA	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Refer to the individual clinical observations table (Table B5) for rats that were found dead with adverse observations.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B2 (PAGE 1): BODY WEIGHTS - SUMMARY - PART I

DOSAGE GROUP			I	II	III	IV	V
DOSAGE (MG/KG/DAY)			25	50	100	200	300
DESCRIPTOR			RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05
RATS TESTED		N	10	10	10	10	10
BODY WEIGHT (G)							
DAY	1	MEAN±S.D	228.5 ± 9.7	224.8 ± 9.3	225.9 ± 7.3	226.6 ± 11.8	226.2 ± 11.6
DAY	2	MEAN±S.D	229.6 ± 8.1	229.5 ± 10.9	227.7 ± 10.2	229.4 ± 11.3	227.1 ± 9.9
DAY	3	MEAN±S.D	230.4 ± 10.6	228.8 ± 11.4	229.6 ± 13.1	233.7 ± 12.8	229.7 ± 9.5
DAY	4	MEAN±S.D	233.9 ± 11.0	230.9 ± 13.2	232.5 ± 9.4	237.6 ± 14.0	234.5 ± 10.0
DAY	5	MEAN±S.D	235.7 ± 10.1	234.4 ± 10.9	236.6 ± 11.4	239.4 ± 14.2	234.8 ± 11.8
DAY	6	MEAN±S.D	245.1 ± 9.6	243.9 ± 13.6	245.5 ± 12.5	248.5 ± 15.1	244.3 ± 16.5 [9]a

DAY = DAY OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes a value for a rat that was found dead.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B2 (PAGE 2): BODY WEIGHTS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR			VI 25 RE-1122.01	VII 50 RE-1122.01	VIII 100 RE-1122.01	IX 200 RE-1122.01	X 300 RE-1122.01
RATS TESTED		N	10	10	10	10	10
BODY WEIGHT (G)							
DAY	1	MEAN±S.D	225.6 ± 8.3	225.1 ± 9.9	225.1 ± 12.5	225.6 ± 6.8	225.6 ± 7.2
DAY	2	MEAN±S.D	228.2 ± 7.5	225.7 ± 9.4	224.8 ± 11.4	222.2 ± 8.6	217.3 ± 4.6
DAY	3	MEAN±S.D	230.4 ± 7.0	227.1 ± 10.9	226.9 ± 11.1	215.8 ± 10.8	206.8 ± 9.3 [8]a
DAY	4	MEAN±S.D	233.2 ± 5.4	232.1 ± 13.6	227.9 ± 11.1	219.6 ± 11.4 [9]a	200.7 ± 7.9 [6]a
DAY	5	MEAN±S.D	234.9 ± 7.3	233.3 ± 13.4	228.5 ± 12.5	220.1 ± 11.6 [9]a	202.5 ± 0.7 [2]a
DAY	6	MEAN±S.D	244.0 ± 6.5	240.0 ± 14.2	235.0 ± 12.2	222.2 ± 13.0 [9]a	194.0 ± 0.0 [1]a

DAY = DAY OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.

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TABLE B2 (PAGE 3): BODY WEIGHTS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR			XI a 50 RE-1123.01	XII b 150 RE-1123.01	XIII 300 RE-1123.01	XIV 550 RE-1123.01	XV 800 RE-1123.01
RATS TESTED		N	10	10	10	10	10
BODY WEIGHT (G)							
DAY	1	MEAN±S.D	225.9 ± 8.3	224.5 ± 9.8	228.5 ± 10.3	225.1 ± 7.4	223.4 ± 7.7
DAY	2	MEAN±S.D	227.5 ± 8.5	231.0 ± 7.5	227.0 ± 10.9	223.3 ± 8.7	222.0 ± 8.5
DAY	3	MEAN±S.D	228.8 ± 9.3	230.7 ± 5.7	226.6 ± 9.3	222.8 ± 9.5	220.4 ± 8.2
DAY	4	MEAN±S.D	228.5 ± 12.3	232.3 ± 7.9	232.6 ± 10.7	229.4 ± 9.7	224.8 ± 9.6
DAY	5	MEAN±S.D	227.2 ± 8.9	229.2 ± 8.3	234.5 ± 9.8	230.7 ± 10.1	225.6 ± 9.2
DAY	6	MEAN±S.D	235.1 ± 11.0	235.8 ± 7.8	242.0 ± 10.5	236.5 ± 11.1	233.3 ± 9.5
DAY	7	MEAN±S.D	229.8 ± 9.9	227.6 ± 8.3	c	c	c
DAY	8	MEAN±S.D	230.9 ± 9.6	227.4 ± 9.0			
DAY	9	MEAN±S.D	236.9 ± 10.5	236.9 ± 9.9			

DAY = DAY OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.
b. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.
c. Excludes values for rats that were sacrificed on day 6 of study.

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TABLE B2 (PAGE 4): BODY WEIGHTS - SUMMARY - PART I

DOSAGE GROUP			XVI	XVII	XVIII	XIX	XX
DOSAGE (MG/KG/DAY)			250	750	1000	1500	2000
DESCRIPTOR			RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01
RATS TESTED		N	10	10	10	10	10
BODY WEIGHT (G)							
DAY	1	MEAN±S.D	226.2 ± 8.2	224.8 ± 9.3	220.8 ± 10.2	212.0 ± 18.4	223.4 ± 7.6
DAY	2	MEAN±S.D	228.4 ± 8.7	223.0 ± 10.3	219.5 ± 10.4	215.4 ± 8.9	219.0 ± 6.2
DAY	3	MEAN±S.D	229.2 ± 8.1	228.4 ± 8.7 [9]a	224.0 ± 9.6	221.1 ± 8.3	222.9 ± 7.3 [9]a
DAY	4	MEAN±S.D	234.7 ± 10.0	232.7 ± 7.7 [9]a	226.4 ± 9.9	222.7 ± 8.2	227.2 ± 7.5 [9]a
DAY	5	MEAN±S.D	236.2 ± 10.6	231.0 ± 8.0 [9]a	225.8 ± 9.5	223.7 ± 8.5	224.8 ± 12.2 [9]a
DAY	6	MEAN±S.D	244.7 ± 12.0	237.3 ± 7.7 [9]a	234.0 ± 10.9	233.3 ± 8.0	238.9 ± 11.7 [8]a

DAY = DAY OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.

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TABLE B3 (PAGE 1): BODY WEIGHT CHANGES - SUMMARY - PART I

DOSAGE GROUP		I	II	III	IV	V
DOSAGE (MG/KG/DAY)		25	50	100	200	300
DESCRIPTOR		RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05	RE-0981.05
RATS TESTED	N	10	10	10	10	10
BODY WEIGHT CHANGE (G)						
DAYS 1 - 2	MEAN±S.D.	+1.1 ± 4.4	+4.7 ± 5.2	+1.8 ± 5.0	+2.8 ± 4.4	+0.9 ± 3.8
DAYS 2 - 3	MEAN±S.D.	+0.8 ± 5.6	-0.7 ± 5.0	+1.9 ± 4.7	+4.3 ± 3.1	+2.6 ± 3.9
DAYS 3 - 4	MEAN±S.D.	+3.5 ± 4.9	+2.1 ± 5.6	+2.9 ± 5.2	+3.9 ± 2.9	+4.8 ± 4.2
DAYS 4 - 5	MEAN±S.D.	+1.8 ± 6.0	+3.5 ± 5.7	+4.1 ± 4.6	+1.8 ± 2.7	+0.3 ± 3.6
DAYS 5 - 6	MEAN±S.D.	+9.4 ± 2.8	+9.5 ± 5.0	+8.9 ± 3.4	+9.1 ± 3.5	+10.3 ± 5.0 [9]a
DAYS 1 - 6	MEAN±S.D.	+16.6 ± 3.0	+19.1 ± 9.4	+19.6 ± 8.0	+21.9 ± 6.6	+19.6 ± 7.1 [9]a

DAYS = DAYS OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes a value for a rat that was found dead.

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TABLE B3 (PAGE 2): BODY WEIGHT CHANGES - SUMMARY - PART I

DOSAGE GROUP		VI	VII	VIII	IX	X
DOSAGE (MG/KG/DAY)		25	50	100	200	300
DESCRIPTOR		RE-1122.01	RE-1122.01	RE-1122.01	RE-1122.01	RE-1122.01
RATS TESTED	N	10	10	10	10	10
BODY WEIGHT CHANGE (G)						
DAYS 1 - 2	MEAN±S.D.	+2.6 ± 6.5	+0.6 ± 4.1	-0.3 ± 4.6	-3.4 ± 5.7	-8.3 ± 6.4
DAYS 2 - 3	MEAN±S.D.	+2.2 ± 4.7	+1.4 ± 4.0	+2.1 ± 3.6	-6.4 ± 8.4	-10.1 ± 9.0 [8]a
DAYS 3 - 4	MEAN±S.D.	+2.8 ± 5.4	+5.0 ± 3.7	+1.0 ± 3.7	+3.1 ± 3.6 [9]a	-9.7 ± 6.2 [6]a
DAYS 4 - 5	MEAN±S.D.	+1.7 ± 6.3	+1.2 ± 4.0	+0.6 ± 3.6	+0.6 ± 5.0 [9]a	-6.0 ± 8.5 [2]a
DAYS 5 - 6	MEAN±S.D.	+9.1 ± 3.6	+6.7 ± 4.2	+6.5 ± 3.8	+2.1 ± 5.6 [9]a	-8.0 ± 0.0 [1]a
DAYS 1 - 6	MEAN±S.D.	+18.4 ± 5.7	+14.9 ± 6.7	+9.9 ± 6.8	-4.2 ± 13.9 [9]a	-32.0 ± 0.0 [1]a

DAYS = DAYS OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.

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TABLE B3 (PAGE 3): BODY WEIGHT CHANGES - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR		XI a 50 RE-1123.01	XII b 150 RE-1123.01	XIII 300 RE-1123.01	XIV 550 RE-1123.01	XV 800 RE-1123.01
RATS TESTED	N	10	10	10	10	10
BODY WEIGHT CHANGE (G)						
DAYS 1 - 2	MEAN±S.D.	+1.6 ± 3.6	+6.5 ± 6.7	-1.5 ± 2.1	-1.8 ± 4.4	-1.4 ± 2.7
DAYS 2 - 3	MEAN±S.D.	+1.3 ± 3.8	-0.3 ± 4.0	-0.4 ± 4.9	-0.5 ± 2.5	-1.6 ± 3.4
DAYS 3 - 4	MEAN±S.D.	-0.3 ± 7.2	+1.6 ± 4.5	+6.0 ± 3.9	+6.6 ± 2.1	+4.4 ± 6.3
DAYS 4 - 5	MEAN±S.D.	-1.3 ± 5.1	-3.1 ± 10.7	+1.9 ± 3.0	+1.3 ± 2.9	+0.8 ± 5.2
DAYS 5 - 6	MEAN±S.D.	+7.9 ± 6.4	+6.6 ± 10.6	+7.5 ± 3.0	+5.8 ± 3.0	+7.7 ± 3.3
DAYS 1 - 6	MEAN±S.D.	+9.2 ± 6.8	+11.3 ± 7.2	+13.5 ± 3.2	+11.4 ± 7.0	+9.9 ± 6.0
DAYS 6 - 7	MEAN±S.D.	-5.3 ± 2.4	-8.2 ± 5.7	c	c	c
DAYS 7 - 8	MEAN±S.D.	+1.1 ± 3.1	-0.2 ± 6.5			
DAYS 8 - 9	MEAN±S.D.	+6.0 ± 3.7	+9.5 ± 6.0			
DAYS 1 - 9	MEAN±S.D.	+11.0 ± 6.2	+12.4 ± 9.7			

DAYS = DAYS OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.
b. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.
c. Excludes values for rats that were sacrificed on day 6 of study.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B3 (PAGE 4): BODY WEIGHT CHANGES - SUMMARY - PART I

DOSAGE GROUP		XVI	XVII	XVIII	XIX	XX
DOSAGE (MG/KG/DAY)		250	750	1000	1500	2000
DESCRIPTOR		RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01	RE-1125.01
RATS TESTED	N	10	10	10	10	10
BODY WEIGHT CHANGE (G)						
DAYS 1 - 2	MEAN±S.D.	+2.2 ± 4.2	-1.8 ± 6.3	-1.3 ± 3.0	+3.4 ± 13.1	-4.4 ± 4.1
DAYS 2 - 3	MEAN±S.D.	+0.8 ± 3.3	+4.3 ± 5.6 [9]a	+4.5 ± 4.1	+5.7 ± 4.2	+4.1 ± 4.6 [9]a
DAYS 3 - 4	MEAN±S.D.	+5.5 ± 2.5	+4.2 ± 3.2 [9]a	+2.4 ± 4.0	+1.6 ± 4.4	+4.3 ± 2.2 [9]a
DAYS 4 - 5	MEAN±S.D.	+1.5 ± 2.8	-1.7 ± 3.1 [9]a	-0.6 ± 3.3	+1.0 ± 3.4	-2.4 ± 7.0 [9]a
DAYS 5 - 6	MEAN±S.D.	+8.5 ± 3.1	+6.3 ± 6.2 [9]a	+8.2 ± 4.6	+9.6 ± 2.4	+11.9 ± 7.4 [8]a
DAYS 1 - 6	MEAN±S.D.	+18.5 ± 7.3	+11.3 ± 6.6 [9]a	+13.2 ± 5.8	+21.3 ± 15.5	+14.1 ± 10.5 [8]a

DAYS = DAYS OF STUDY
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.

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TABLE B4 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR		I 25 RE-0981.05	II 50 RE-0981.05	III 100 RE-0981.05	IV 200 RE-0981.05	V 300 RE-0981.05
RATS EXAMINED	N	10	10	10	10	10
FOUND DEAD a	N	0	0	0	0	1
APPEARED NORMAL	N	10	10	10	10	10

a. Refer to the individual necropsy observations table (Table B7) for rats that were found dead with adverse observations.

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TABLE B4 (PAGE 2): NECROPSY OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR		VI 25 RE-1122.01	VII 50 RE-1122.01	VIII 100 RE-1122.01	IX 200 RE-1122.01	X 300 RE-1122.01
RATS EXAMINED	N	10	10	10	10	10
FOUND DEAD a	N	0	0	0	1	9
APPEARED NORMAL	N	10	10	10	10	9
THORACIC CAVITY: CONTAINED CLEAR YELLOW FLUID	N	0	0	0	0	1

a. Refer to the individual necropsy observations table (Table B7) for rats that were found dead with adverse observations.

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TABLE B4 (PAGE 3): NECROPSY OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR		XI a 50 RE-1123.01	XII b 150 RE-1123.01	XIII 300 RE-1123.01	XIV 550 RE-1123.01	XV 800 RE-1123.01
RATS EXAMINED c	N	10	10	10	10	10
MORTALITY	N	0	0	0	0	0
APPEARED NORMAL	N	0	0	2	1	0
SPLEEN:						
LARGE AND/OR DARK RED	N	10	10	8	9	10
GRANULAR SURFACE	N	0	0	1	0	0
RAISED GRAY AREA(S)	N	0	0	0	1	0

a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.
b. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.
c. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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TABLE B4 (PAGE 4): NECROPSY OBSERVATIONS - SUMMARY - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR		XVI 250 RE-1125.01	XVII 750 RE-1125.01	XVIII 1000 RE-1125.01	XIX 1500 RE-1125.01	XX 2000 RE-1125.01
RATS EXAMINED	N	10	10	10	10	10
FOUND DEAD a	N	0	1	0	0	2
APPEARED NORMAL	N	9	8	4	1	2
SPLEEN:						
LARGE AND/OR DARK RED	N	0	2	6	9	8
RAISED GRAY AREA(S)	N	1	0	0	1	0

a. Refer to the individual necropsy observations table (Table B7) for rats that were found dead with adverse observations.

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP I	RE-0981.05	25 MG/KG/DAY
RAT #	DESCRIPTION	
8101	NO ADVERSE FINDINGS	
8102	NO ADVERSE FINDINGS	
8103	NO ADVERSE FINDINGS	
8104	NO ADVERSE FINDINGS	
8105	NO ADVERSE FINDINGS	
8106	NO ADVERSE FINDINGS	
8107	NO ADVERSE FINDINGS	
8108	NO ADVERSE FINDINGS	
8109	NO ADVERSE FINDINGS	
8110	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP II	RE-0981.05	50 MG/KG/DAY

RAT #		DESCRIPTION
8111	DS(5)	LACRIMATION
8112		NO ADVERSE FINDINGS
8113		NO ADVERSE FINDINGS
8114		NO ADVERSE FINDINGS
8115		NO ADVERSE FINDINGS
8116		NO ADVERSE FINDINGS
8117		NO ADVERSE FINDINGS
8118		NO ADVERSE FINDINGS
8119		NO ADVERSE FINDINGS
8120		NO ADVERSE FINDINGS

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP III	RE-0981.05	100 MG/KG/DAY
RAT #	DESCRIPTION	
8121	NO ADVERSE FINDINGS	
8122	NO ADVERSE FINDINGS	
8123	NO ADVERSE FINDINGS	
8124	NO ADVERSE FINDINGS	
8125	NO ADVERSE FINDINGS	
8126	NO ADVERSE FINDINGS	
8127	NO ADVERSE FINDINGS	
8128	NO ADVERSE FINDINGS	
8129	NO ADVERSE FINDINGS	
8130	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP IV RE-0981.05 200 MG/KG/DAY

RAT #		DESCRIPTION
8131		NO ADVERSE FINDINGS
8132	DS(3)	TACHYPNEA
8133		NO ADVERSE FINDINGS
8134		NO ADVERSE FINDINGS
8135		NO ADVERSE FINDINGS
8136		NO ADVERSE FINDINGS
8137	DS(5)	TACHYPNEA
8138		NO ADVERSE FINDINGS
8139	DS(3)	TACHYPNEA
	DS(5)	EXCESS SALIVATION
	DS(5)	TACHYPNEA
8140		NO ADVERSE FINDINGS

DS = DAY OF STUDY

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP V RE-0981.05 300 MG/KG/DAY

RAT #		DESCRIPTION
8141		NO ADVERSE FINDINGS
8142	DS(3)	TACHYPNEA
	DS(5)	TACHYPNEA
8143	DS(4)	EXCESS SALIVATION
	DS(4)	TACHYPNEA
8144	DS(5)	TACHYPNEA
8145	DS(3)	TACHYPNEA
8146	DS(3)	DECREASED MOTOR ACTIVITY
	DS(3)	CONVULSION: CLONIC
	DS(3)	LACRIMATION
	DS(3)	EXCESS SALIVATION
	DS(3)	TACHYPNEA
	DS(5)	TACHYPNEA
8147	DS(2)	EXCESS SALIVATION
	DS(2)	TACHYPNEA
	DS(3- 5)	LACRIMATION
	DS(4- 5)	EXCESS SALIVATION
	DS(4- 5)	TACHYPNEA
8148	DS(1)	EXCESS SALIVATION
	DS(5)	EXCESS SALIVATION
	DS(5)	TACHYPNEA
8149		NO ADVERSE FINDINGS
8150	DS(3- 5)	EXCESS SALIVATION
	DS(3- 5)	TACHYPNEA
	DS(5)	LOST RIGHTING REFLEX
	DS(5)	CONVULSION: CLONIC
	DS(5)	TWITCHES
	DS(5)	LACRIMATION
	DS(5)	FOUND DEAD

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 6): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP VI	RE-1122.01	25 MG/KG/DAY
RAT #		DESCRIPTION
8151		NO ADVERSE FINDINGS
8152		NO ADVERSE FINDINGS
8153		NO ADVERSE FINDINGS
8154		NO ADVERSE FINDINGS
8155		NO ADVERSE FINDINGS
8156		NO ADVERSE FINDINGS
8157	DS(5- 6)	MOUTH: LESION (0.1 CM IN DIAMETER)a
8158		NO ADVERSE FINDINGS
8159		NO ADVERSE FINDINGS
8160		NO ADVERSE FINDINGS

DS = DAY OF STUDY
a. Observation confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 7): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP VII	RE-1122.01	50 MG/KG/DAY
RAT #	DESCRIPTION	
8161	NO ADVERSE FINDINGS	
8162	NO ADVERSE FINDINGS	
8163	NO ADVERSE FINDINGS	
8164	NO ADVERSE FINDINGS	
8165	NO ADVERSE FINDINGS	
8166	NO ADVERSE FINDINGS	
8167	NO ADVERSE FINDINGS	
8168	NO ADVERSE FINDINGS	
8169	NO ADVERSE FINDINGS	
8170	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 8): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP VIII	RE-1122.01	100 MG/KG/DAY
RAT #	DESCRIPTION	
8171	NO ADVERSE FINDINGS	
8172	NO ADVERSE FINDINGS	
8173	NO ADVERSE FINDINGS	
8174	NO ADVERSE FINDINGS	
8175	NO ADVERSE FINDINGS	
8176	NO ADVERSE FINDINGS	
8177	NO ADVERSE FINDINGS	
8178	NO ADVERSE FINDINGS	
8179	NO ADVERSE FINDINGS	
8180	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 9): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP IX		RE-1122.01	200 MG/KG/DAY
RAT #			DESCRIPTION
8181	DS(4)		DECREASED MOTOR ACTIVITY
8182	DS(5)		DECREASED MOTOR ACTIVITY
8183			NO ADVERSE FINDINGS
8184			NO ADVERSE FINDINGS
8185			NO ADVERSE FINDINGS
	DS(3)		FOUND DEAD
8186	DS(4)		LACRIMATION
	DS(4- 5)		DECREASED MOTOR ACTIVITY
8187	DS(3- 4)		DRY RED PERIORAL SUBSTANCE
	DS(3- 5)		DECREASED MOTOR ACTIVITY
8188	DS(1)		EYES: RED
	DS(2- 4)		EXOPHTHALMOS
	DS(2- 4)		EYES: DARK RED
	DS(3- 6)		DECREASED MOTOR ACTIVITY
	DS(5- 6)		LACRIMATION
8189	DS(4- 5)		DECREASED MOTOR ACTIVITY
8190	DS(4)		DECREASED MOTOR ACTIVITY

DS = DAY OF STUDY

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 10): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP X RE-1122.01 300 MG/KG/DAY

RAT #		DESCRIPTION
8191	DS(3- 4)	DECREASED MOTOR ACTIVITY
	DS(4)	URINE STAINED ABDOMINAL FUR
	DS(5)	FOUND DEAD
8192	DS(3- 4)	DECREASED MOTOR ACTIVITY
	DS(5)	FOUND DEAD
8193	DS(4- 5)	DECREASED MOTOR ACTIVITY
8194	DS(2- 4)	DECREASED MOTOR ACTIVITY
	DS(3- 4)	PALE IN APPEARANCE
	DS(5)	FOUND DEAD
8195	DS(5)	DECREASED MOTOR ACTIVITY
	DS(6)	FOUND DEAD
8196	DS(2)	DECREASED MOTOR ACTIVITY
	DS(2)	IMPAIRED RIGHTING REFLEX
	DS(2)	ATAXIA
	DS(2)	TREMORS
	DS(2)	HYPERACTIVITY
	DS(2)	CONVULSION: CLONIC
	DS(2)	PALE IN APPEARANCE
	DS(2)	COLD TO TOUCH
	DS(2)	EXCESS SALIVATION
	DS(2)	FOUND DEAD
8197	DS(2)	DECREASED MOTOR ACTIVITY
	DS(2)	IMPAIRED RIGHTING REFLEX
	DS(2)	TREMORS
	DS(2)	LACRIMATION
	DS(2)	PTOSIS
	DS(2)	EXCESS SALIVATION
	DS(2)	LABORED BREATHING
	DS(3)	FOUND DEAD
8198	DS(3- 4)	DECREASED MOTOR ACTIVITY
	DS(4)	FOUND DEAD
8199	DS(3)	DECREASED MOTOR ACTIVITY
	DS(3)	DRY RED PERIORAL SUBSTANCE
	DS(4)	FOUND DEAD
8200	DS(1- 3)	CHROMODACRYORRHEA
	DS(3)	FOUND DEAD

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 11): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XI a	RE-1123.01	50 MG/KG/DAY
RAT #	DESCRIPTION	
8201	NO ADVERSE FINDINGS	
8202	NO ADVERSE FINDINGS	
8203	NO ADVERSE FINDINGS	
8204	NO ADVERSE FINDINGS	
8205	NO ADVERSE FINDINGS	
8206	NO ADVERSE FINDINGS	
8207	NO ADVERSE FINDINGS	
8208	NO ADVERSE FINDINGS	
8209	NO ADVERSE FINDINGS	
8210	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 study and 1500 mg/kg/day on day 5 of study.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 12): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XII a	RE-1123.01	150 MG/KG/DAY

RAT #	DESCRIPTION
8211	NO ADVERSE FINDINGS
8212	NO ADVERSE FINDINGS
8213	NO ADVERSE FINDINGS
8214	NO ADVERSE FINDINGS
8215	NO ADVERSE FINDINGS
8216	NO ADVERSE FINDINGS
8217	NO ADVERSE FINDINGS
8218	NO ADVERSE FINDINGS
8219	NO ADVERSE FINDINGS
8220	NO ADVERSE FINDINGS

DS = DAY OF STUDY

a. - Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 study and 2000 mg/kg/day on day 5 of study.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 13): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XIII	RE-1123.01	300 MG/KG/DAY
RAT #	DESCRIPTION	
8221	NO ADVERSE FINDINGS	
8222	NO ADVERSE FINDINGS	
8223	NO ADVERSE FINDINGS	
8224	NO ADVERSE FINDINGS	
8225	NO ADVERSE FINDINGS	
8226	NO ADVERSE FINDINGS	
8227	NO ADVERSE FINDINGS	
8228	NO ADVERSE FINDINGS	
8229	NO ADVERSE FINDINGS	
8230	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 14): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XIV RE-1123.01 550 MG/KG/DAY

RAT #	DESCRIPTION
8231	NO ADVERSE FINDINGS
8232	NO ADVERSE FINDINGS
8233	NO ADVERSE FINDINGS
8234	NO ADVERSE FINDINGS
8235	NO ADVERSE FINDINGS
8236	NO ADVERSE FINDINGS
8237	NO ADVERSE FINDINGS
8238	NO ADVERSE FINDINGS
8239	NO ADVERSE FINDINGS
8240	NO ADVERSE FINDINGS

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 15): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XV	RE-1123.01	800 MG/KG/DAY
RAT #	DESCRIPTION	
8241	NO ADVERSE FINDINGS	
8242	NO ADVERSE FINDINGS	
8243	NO ADVERSE FINDINGS	
8244	NO ADVERSE FINDINGS	
8245	NO ADVERSE FINDINGS	
8246	NO ADVERSE FINDINGS	
8247	NO ADVERSE FINDINGS	
8248	NO ADVERSE FINDINGS	
8249	NO ADVERSE FINDINGS	
8250	NO ADVERSE FINDINGS	

DS = DAY OF STUDY

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 16): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XVI	RE-1125.01	250 MG/KG/DAY

RAT #	DESCRIPTION
8251	NO ADVERSE FINDINGS
8252	NO ADVERSE FINDINGS
8253	NO ADVERSE FINDINGS
8254	NO ADVERSE FINDINGS
8255	NO ADVERSE FINDINGS
8256	NO ADVERSE FINDINGS
8257	NO ADVERSE FINDINGS
8258	NO ADVERSE FINDINGS
8259	NO ADVERSE FINDINGS
8260	NO ADVERSE FINDINGS

DS = DAY OF STUDY

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 17): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XVII	RE-1125.01	750 MG/KG/DAY

RAT #		DESCRIPTION
8261	DS(2)	DECREASED MOTOR ACTIVITY
	DS(3)	FOUND DEAD
8262	DS(2- 4)	DECREASED MOTOR ACTIVITY
8263		NO ADVERSE FINDINGS
8264		NO ADVERSE FINDINGS
8265		NO ADVERSE FINDINGS
8266		NO ADVERSE FINDINGS
8267		NO ADVERSE FINDINGS
8268		NO ADVERSE FINDINGS
8269		NO ADVERSE FINDINGS
8270		NO ADVERSE FINDINGS

DS = DAY OF STUDY

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 18): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XVIII RE-1125.01 1000 MG/KG/DAY

RAT #		DESCRIPTION
8271	DS(1)	LACRIMATION
	DS(1- 5)	DECREASED MOTOR ACTIVITY
8272	DS(1)	LACRIMATION
	DS(1- 5)	DECREASED MOTOR ACTIVITY
8273	DS(1)	LACRIMATION
	DS(1- 3)	DECREASED MOTOR ACTIVITY
	DS(5)	DECREASED MOTOR ACTIVITY
8274	DS(1)	DECREASED MOTOR ACTIVITY
	DS(3)	DECREASED MOTOR ACTIVITY
8275	DS(1- 2)	DECREASED MOTOR ACTIVITY
8276	DS(1- 2)	DECREASED MOTOR ACTIVITY
8277	DS(1)	DECREASED MOTOR ACTIVITY
	DS(4- 5)	DECREASED MOTOR ACTIVITY
8278	DS(1)	DECREASED MOTOR ACTIVITY
8279	DS(1)	DECREASED MOTOR ACTIVITY
8280	DS(1)	DECREASED MOTOR ACTIVITY

DS = DAY OF STUDY

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 19): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XIX RE-1125.01 1500 MG/KG/DAY

RAT #		DESCRIPTION
8281	DS(1)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
	DS(3- 5)	DECREASED MOTOR ACTIVITY
8282	DS(1- 5)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
8283	DS(1- 5)	DECREASED MOTOR ACTIVITY
	DS(2- 3)	LACRIMATION
8284	DS(1- 3)	DECREASED MOTOR ACTIVITY
	DS(1- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8285	DS(1)	DECREASED MOTOR ACTIVITY
	DS(1- 3)	LACRIMATION
	DS(3- 5)	DECREASED MOTOR ACTIVITY
8286	DS(1)	DECREASED MOTOR ACTIVITY
	DS(1- 3)	LACRIMATION
	DS(3)	DECREASED MOTOR ACTIVITY
	DS(5)	DECREASED MOTOR ACTIVITY
8287	DS(1)	DECREASED MOTOR ACTIVITY
	DS(2- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8288	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(2- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8289	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(2- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8290	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(2- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B5 (PAGE 20): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP XX RE-1125.01 2000 MG/KG/DAY

RAT #		DESCRIPTION
8291	DS(1- 2)	LACRIMATION
	DS(1- 5)	DECREASED MOTOR ACTIVITY
8292	DS(1- 2)	LACRIMATION
	DS(1- 5)	DECREASED MOTOR ACTIVITY
8293	DS(1)	CHROMODACRYORRHEA
	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(2)	ATAXIA
	DS(2- 3)	LACRIMATION
	DS(4- 5)	DECREASED MOTOR ACTIVITY
	DS(5)	LACRIMATION
	DS(6)	FOUND DEAD
8294	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
	DS(4- 5)	DECREASED MOTOR ACTIVITY
	DS(5)	LACRIMATION
8295	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
	DS(4- 5)	DECREASED MOTOR ACTIVITY
8296	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
	DS(4- 5)	DECREASED MOTOR ACTIVITY
8297	DS(1- 3)	DECREASED MOTOR ACTIVITY
	DS(1- 3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8298	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(3)	LACRIMATION
	DS(5)	DECREASED MOTOR ACTIVITY
8299	DS(1- 2)	DECREASED MOTOR ACTIVITY
	DS(1- 2)	LACRIMATION
	DS(3)	FOUND DEAD
8300	DS(1- 5)	DECREASED MOTOR ACTIVITY
	DS(2- 5)	LACRIMATION

DS = DAY OF STUDY

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B6 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP I		RE-0981.05		25 MG/KG/DAY	
8101	218.	224.	219.	214.	225.	233.
8102	228.	234.	243.	242.	236.	248.
8103	216.	219.	215.	223.	222.	231.
8104	234.	235.	231.	238.	241.	248.
8105	214.	219.	224.	224.	220.	234.
8106	240.	237.	235.	242.	245.	253.
8107	229.	221.	224.	234.	236.	242.
8108	241.	240.	250.	251.	245.	258.
8109	229.	230.	230.	231.	239.	249.
8110	236.	237.	233.	240.	248.	255.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 2): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP II			RE-0981.05		50 MG/KG/DAY
8111	214.	214.	210.	204.	216.	220.
8112	233.	248.	250.	246.	239.	255.
8113	216.	221.	225.	228.	226.	233.
8114	224.	227.	232.	230.	236.	246.
8115	229.	231.	226.	231.	231.	237.
8116	226.	237.	238.	238.	238.	258.
8117	215.	223.	228.	234.	239.	250.
8118	236.	234.	233.	239.	244.	252.
8119	216.	218.	214.	214.	222.	228.
8120	239.	242.	232.	245.	253.	260.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 3): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP III			RE-0981.05		100 MG/KG/DAY
8121	220.	213.	207.	217.	220.	227.
8122	238.	244.	249.	250.	257.	269.
8123	222.	224.	223.	226.	231.	239.
8124	221.	227.	234.	237.	233.	243.
8125	226.	219.	215.	227.	227.	232.
8126	237.	244.	243.	240.	252.	256.
8127	219.	222.	226.	227.	234.	246.
8128	230.	232.	238.	233.	241.	256.
8129	218.	221.	223.	228.	229.	238.
8130	228.	231.	238.	240.	242.	249.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 4): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP IV		RE-0981.05		200 MG/KG/DAY	
8131	205.	208.	210.	212.	215.	225.
8132	235.	243.	250.	252.	250.	267.
8133	234.	230.	230.	239.	240.	250.
8134	230.	225.	227.	231.	234.	239.
8135	221.	227.	232.	236.	240.	246.
8136	237.	240.	249.	254.	257.	264.
8137	230.	232.	238.	242.	247.	253.
8138	241.	243.	244.	252.	256.	267.
8139	210.	216.	219.	219.	219.	227.
8140	223.	230.	238.	239.	236.	247.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 5): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP V			RE-0981.05		300 MG/KG/DAY
8141	210.	212.	217.	222.	222.	228.
8142	234.	233.	241.	239.	241.	255.
8143	233.	232.	234.	241.	242.	255.
8144	218.	217.	225.	230.	230.	232.
8145	228.	227.	223.	230.	231.	242.
8146	244.	241.	242.	255.	259.	278.
8147	214.	215.	215.	220.	218.	225.
8148	228.	232.	234.	237.	235.	244.
8149	214.	224.	229.	235.	228.	240.
8150	239.	238.	237.	236.	242.	FOUND DEAD ON DAY 5 OF STUDY

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 6): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP VI		RE-1122.01		25 MG/KG/DAY	
8151	217.	217.	222.	226.	231.	240.
8152	240.	240.	246.	238.	248.	258.
8153	231.	231.	231.	243.	244.	250.
8154	222.	217.	226.	233.	232.	236.
8155	226.	225.	224.	229.	233.	244.
8156	233.	236.	235.	235.	241.	249.
8157	229.	227.	231.	233.	228.	239.
8158	225.	228.	235.	237.	231.	240.
8159	211.	227.	226.	232.	225.	242.
8160	222.	234.	228.	226.	236.	242.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 7): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP VII		RE-1122.01		50 MG/KG/DAY	
8161	209.	210.	205.	204.	208.	217.
8162	238.	237.	235.	242.	250.	254.
8163	224.	218.	225.	225.	226.	228.
8164	224.	230.	236.	241.	237.	250.
8165	223.	225.	223.	232.	237.	241.
8166	229.	226.	232.	238.	239.	239.
8167	220.	220.	221.	229.	228.	236.
8168	228.	226.	228.	231.	235.	244.
8169	214.	222.	221.	224.	220.	226.
8170	242.	243.	245.	255.	253.	265.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 8): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP VIII		RE-1122.01		100 MG/KG/DAY	
8171	200.	206.	208.	209.	206.	213.
8172	240.	238.	237.	236.	235.	239.
8173	228.	225.	224.	228.	228.	237.
8174	220.	216.	216.	219.	224.	234.
8175	221.	220.	222.	226.	225.	231.
8176	239.	240.	246.	246.	250.	258.
8177	212.	217.	224.	216.	213.	222.
8178	235.	230.	228.	233.	237.	243.
8179	224.	218.	226.	228.	233.	242.
8180	232.	238.	238.	238.	234.	231.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 9): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP IX			RE-1122.01		200 MG/KG/DAY
8181	223.	213.	199.	201.	203.	204.
8182	239.	235.	227.	229.	219.	218.
8183	230.	220.	222.	220.	229.	234.
8184	222.	229.	225.	229.	233.	232.
8185	218.	215.	210.	FOUND DEAD ON DAY 3 OF STUDY		
8186	232.	233.	226.	226.	226.	233.
8187	230.	227.	202.	205.	205.	210.
8188	221.	210.	210.	212.	211.	217.
8189	218.	217.	210.	220.	221.	211.
8190	223.	223.	227.	234.	234.	241.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 10): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP X		RE-1122.01		300 MG/KG/DAY	
8191	218.	212.	205.	193.	FOUND DEAD ON DAY 5 OF STUDY	
8192	230.	216.	207.	198.	FOUND DEAD ON DAY 5 OF STUDY	
8193	226.	217.	218.	214.	202.	194.
8194	225.	210.	206.	203.	FOUND DEAD ON DAY 5 OF STUDY	
8195	212.	219.	213.	203.	203.	FOUND DEAD ON DAY 6 OF STUDY
8196	232.	223.	FOUND DEAD ON DAY 2 OF STUDY			
8197	224.	215.	FOUND DEAD ON DAY 3 OF STUDY			
8198	228.	223.	213.	193.	FOUND DEAD ON DAY 4 OF STUDY	
8199	223.	215.	187.	FOUND DEAD ON DAY 4 OF STUDY		
8200	238.	223.	205.	FOUND DEAD ON DAY 3 OF STUDY		

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 11): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6	7	8	9
RAT #	DOSAGE GROUP XI a			RE-1123.01			50 MG/KG/DAY		
8201	221.	224.	228.	224.	222.	231.	225.	229.	230.
8202	240.	238.	244.	248.	244.	248.	243.	248.	253.
8203	224.	222.	215.	219.	218.	224.	220.	217.	223.
8204	214.	219.	222.	204.	216.	221.	220.	224.	235.
8205	221.	220.	223.	228.	223.	233.	227.	228.	232.
8206	237.	244.	242.	243.	238.	246.	243.	243.	250.
8207	220.	220.	223.	223.	222.	233.	227.	229.	231.
8208	221.	227.	230.	232.	226.	230.	224.	225.	228.
8209	230.	227.	225.	232.	231.	230.	224.	226.	237.
8210	231.	234.	236.	232.	232.	255.	245.	240.	250.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.

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TABLE B6 (PAGE 12): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6	7	8	9
RAT #	DOSAGE GROUP XII a			RE-1123.01			150 MG/KG/DAY		
8211	222.	223.	226.	227.	229.	236.	222.	230.	236.
8212	233.	240.	240.	238.	239.	246.	230.	223.	236.
8213	218.	227.	226.	223.	211.	228.	226.	215.	220.
8214	217.	223.	229.	226.	226.	226.	224.	217.	229.
8215	225.	225.	226.	227.	238.	227.	213.	220.	231.
8216	240.	242.	241.	246.	224.	247.	244.	242.	256.
8217	226.	227.	229.	235.	234.	233.	230.	230.	248.
8218	238.	241.	232.	243.	227.	243.	236.	240.	237.
8219	212.	229.	226.	226.	236.	232.	225.	230.	236.
8220	214.	233.	232.	232.	228.	240.	226.	227.	240.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.

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TABLE B6 (PAGE 13): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XIII		RE-1123.01		300 MG/KG/DAY	
8221	210.	208.	207.	212.	216.	221.
8222	248.	249.	240.	252.	252.	260.
8223	224.	225.	233.	236.	234.	242.
8224	231.	231.	232.	238.	235.	243.
8225	223.	221.	224.	223.	227.	241.
8226	236.	234.	230.	232.	239.	248.
8227	225.	222.	227.	233.	234.	237.
8228	233.	233.	232.	240.	244.	251.
8229	221.	219.	217.	226.	228.	233.
8230	234.	228.	224.	234.	236.	244.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 14): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XIV		RE-1123.01		550 MG/KG/DAY	
8231	213.	210.	208.	211.	211.	216.
8232	232.	237.	238.	245.	243.	246.
8233	236.	227.	226.	231.	238.	246.
8234	226.	225.	228.	234.	236.	242.
8235	213.	211.	214.	222.	224.	230.
8236	231.	233.	234.	240.	240.	252.
8237	226.	223.	220.	225.	228.	236.
8238	224.	219.	216.	225.	224.	229.
8239	226.	220.	216.	226.	224.	226.
8240	224.	228.	228.	235.	239.	242.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 15): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XV			RE-1123.01		800 MG/KG/DAY
8241	221.	217.	214.	215.	219.	227.
8242	227.	226.	224.	230.	224.	231.
8243	228.	226.	228.	228.	236.	242.
8244	234.	232.	223.	240.	241.	253.
8245	209.	210.	207.	214.	215.	220.
8246	223.	222.	220.	230.	233.	240.
8247	222.	225.	222.	220.	227.	232.
8248	231.	230.	230.	236.	228.	231.
8249	213.	206.	208.	212.	213.	225.
8250	226.	226.	228.	223.	220.	232.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 16): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XVI		RE-1125.01		250 MG/KG/DAY	
8251	215.	216.	214.	217.	219.	225.
8252	239.	245.	243.	254.	257.	266.
8253	235.	237.	232.	236.	242.	252.
8254	227.	231.	233.	240.	243.	252.
8255	220.	220.	226.	230.	232.	240.
8256	234.	228.	229.	237.	238.	249.
8257	215.	223.	227.	230.	227.	239.
8258	228.	228.	230.	234.	232.	234.
8259	222.	222.	221.	226.	230.	236.
8260	227.	234.	237.	243.	242.	254.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 17): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XVII		RE-1125.01		750 MG/KG/DAY	
8261	214.	213.	FOUND DEAD ON DAY 3 OF STUDY			
8262	244.	247.	244.	244.	241.	240.
8263	225.	226.	231.	234.	234.	233.
8264	222.	222.	231.	236.	232.	238.
8265	223.	217.	220.	230.	226.	238.
8266	232.	214.	230.	236.	230.	244.
8267	215.	219.	221.	228.	225.	226.
8268	234.	233.	237.	241.	245.	252.
8269	219.	218.	217.	220.	220.	235.
8270	220.	221.	225.	225.	226.	230.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 18): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XVIII		RE-1125.01		1000 MG/KG/DAY	
8271	205.	201.	207.	215.	214.	225.
8272	239.	233.	237.	245.	240.	252.
8273	223.	218.	226.	225.	227.	240.
8274	233.	233.	228.	233.	238.	244.
8275	212.	210.	218.	216.	216.	223.
8276	226.	230.	236.	235.	230.	232.
8277	217.	216.	218.	216.	216.	227.
8278	216.	216.	218.	222.	218.	222.
8279	214.	214.	219.	224.	226.	228.
8280	223.	224.	233.	233.	233.	247.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 19): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XIX			RE-1125.01		1500 MG/KG/DAY
8281	208.	204.	207.	215.	216.	228.
8282	232.	231.	238.	239.	239.	246.
8283	235.	224.	223.	229.	230.	238.
8284	211.	207.	214.	216.	220.	230.
8285	210.	218.	220.	219.	227.	232.
8286	218.	222.	225.	219.	222.	235.
8287	179.	205.	214.	212.	208.	217.
8288	184.	210.	224.	229.	229.	241.
8289	218.	217.	224.	222.	220.	230.
8290	225.	216.	222.	227.	226.	236.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B6 (PAGE 20): BODY WEIGHTS - INDIVIDUAL DATA - PART I

DAY	1	2	3	4	5	6
RAT #	DOSAGE GROUP XX		RE-1125.01		2000 MG/KG/DAY	
8291	218.	214.	214.	216.	208.	218.
8292	228.	225.	233.	236.	234.	242.
8293	211.	208.	215.	218.	207.	FOUND DEAD ON DAY 6 OF STUDY
8294	217.	220.	228.	230.	216.	244.
8295	227.	215.	220.	227.	228.	233.
8296	229.	223.	232.	235.	240.	254.
8297	215.	214.	215.	220.	223.	232.
8298	234.	229.	224.	231.	230.	236.
8299	225.	221.	FOUND DEAD ON DAY 3 OF STUDY			
8300	230.	221.	225.	232.	237.	252.

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE B7 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
I 25 RE-0981.05	8101	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8102	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8103	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8104	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8105	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8106	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8107	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8108	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8109	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8110	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
II 50 RE-0981.05	8111	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8112	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8113	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8114	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8115	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8116	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8117	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8118	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8119	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8120	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
III 100 RE-0981.05	8121	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8122	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8123	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8124	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8125	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8126	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8127	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8128	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8129	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8130	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
IV 200 RE-0981.05	8131	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8132	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8133	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8134	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8135	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8136	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8137	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8138	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8139	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8140	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 5): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
V 300 RE-0981.05	8141	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8142	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8143	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8144	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8145	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8146	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8147	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8148	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8149	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8150	DS 5	5	FOUND DEAD ON DAY 5 OF STUDY. ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 6): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
VI 25 RE-1122.01	8151	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8152	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8153	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8154	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8155	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8156	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8157	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8158	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8159	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8160	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 7): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
VII 50 RE-1122.01	8161	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8162	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8163	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8164	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8165	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8166	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8167	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8168	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8169	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8170	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY
a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 8): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
VIII 100 RE-1122.01	8171	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8172	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8173	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8174	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8175	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8176	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8177	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8178	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8179	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8180	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY
a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 9): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
IX 200 RE-1122.01	8181	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8182	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8183	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8184	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8185	DS 3	3	FOUND DEAD ON DAY 3 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8186	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8187	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8188	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8189	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8190	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 10): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
X 300 RE-1122.01	8191	DS 5	4	FOUND DEAD ON DAY 5 OF STUDY. ALL TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SLIGHT).
	8192	DS 5	4	FOUND DEAD ON DAY 5 OF STUDY. ALL TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SLIGHT).
	8193	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8194	DS 5	4	FOUND DEAD ON DAY 5 OF STUDY. THORACIC CAVITY: CONTAINED APPROXIMATELY 3.0 ML OF CLEAR YELLOW FLUID. ALL OTHER TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SLIGHT).
	8195	DS 6	5	FOUND DEAD ON DAY 6 OF STUDY. ALL TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SLIGHT).
	8196	DS 2	2	FOUND DEAD ON DAY 2 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8197	DS 3	2	FOUND DEAD ON DAY 3 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8198	DS 4	4	FOUND DEAD ON DAY 4 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8199	DS 4	3	FOUND DEAD ON DAY 4 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8200	DS 3	3	FOUND DEAD ON DAY 3 OF STUDY. ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 11): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XI b 50 RE-1123.01	8201	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8202	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8203	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8204	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8205	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8206	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8207	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8208	DS 9	8	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8209	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8210	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

b. Group XI dosage of 50 mg/kg/day was increased to 1000 mg/kg/day on day 3 of study and 1500 mg/kg/day on day 5 of study.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 12): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XII b 150 RE-1123.01	8211	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8212	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8213	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8214	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8215	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8216	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8217	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8218	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8219	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8220	DS 9	8	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY
a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.
b. Group XII dosage of 150 mg/kg/day was increased to 1200 mg/kg/day on day 3 of study and 2000 mg/kg/day on day 5 of study.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 13): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XIII 300 RE-1123.01	8221	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8222	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8223	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8224	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8225	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8226	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8227	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8228	DS 6	5	SPLEEN: LARGE, DARK RED AND GRANULAR SURFACE. ALL OTHER TISSUES APPEARED NORMAL.
	8229	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8230	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 14): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XIV 550 RE-1123.01	8231	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8232	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8233	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8234	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8235	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8236	DS 6	5	SPLEEN: LARGE AND DARK RED; RAISED GRAY AREA (1.0 CM X 0.5 CM). ALL OTHER TISSUES APPEARED NORMAL.
	8237	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8238	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8239	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8240	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 15): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XV 800 RE-1123.01	8241	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8242	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8243	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8244	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8245	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8246	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8247	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8248	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8249	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8250	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY
a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 16): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XVI 250 RE-1125.01	8251	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8252	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8253	DS 6	5	SPLEEN: MULTIPLE RAISED GRAY AREAS (TOO NUMEROUS TO COUNT, PINPOINT TO 0.3 CM X 0.4 CM). ALL OTHER TISSUES APPEARED NORMAL.
	8254	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8255	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8256	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8257	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8258	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8259	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8260	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 17): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XVII 750 RE-1125.01	8261	DS 3	2	FOUND DEAD ON DAY 3 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8262	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8263	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8264	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8265	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8266	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8267	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8268	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8269	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8270	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY
a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 18): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XVIII 1000 RE-1125.01	8271	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8272	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8273	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8274	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8275	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8276	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8277	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8278	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8279	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8280	DS 6	5	ALL TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 19): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XIX 1500 RE-1125.01	8281	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8282	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8283	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8284	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8285	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8286	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8287	DS 6	5	ALL TISSUES APPEARED NORMAL.
	8288	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8289	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8290	DS 6	5	SPLEEN: DARK RED; MULTIPLE RAISED GRAY AREAS (TOO NUMEROUS TO COUNT, 0.2 CM TO 0.5 CM IN DIAMETER). ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE B7 (PAGE 20): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART I

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	DOSAGES ADMINISTERED	OBSERVATIONS a
XX 2000 RE-1125.01	8291	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8292	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8293	DS 6	5	FOUND DEAD ON DAY 6 OF STUDY. ALL TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SEVERE).
	8294	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8295	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8296	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8297	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8298	DS 6	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	8299	DS 3	2	FOUND DEAD ON DAY 3 OF STUDY. ALL TISSUES APPEARED NORMAL.
	8300	DS 6	5	SPLEEN: LARGE AND DARK RED. ALL OTHER TISSUES APPEARED NORMAL.

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B5) for external observations confirmed at necropsy.

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APPENDIX C

REPORT TABLES - PART II

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP	I	III	IV
DOSAGE (MG/KG/DAY)a	0	250	200
DESCRIPTOR	VEHICLE	RE-0981.05	RE-1122.01
PRESUMED GESTATION:			
MAXIMUM POSSIBLE INCIDENCE	664/ 30	528/ 30	550/ 30
FOUND DEAD b	0	11**	11**
DECREASED MOTOR ACTIVITY	0/ 0	1/ 1	20/ 12**
URINE-STAINED ABDOMINAL FUR	0/ 0	1/ 1	47/ 11**
LOCALIZED ALOPECIA: TOTAL	52/ 5	7/ 3	28/ 6
LIMBS	52/ 5	6/ 2	21/ 4
HEAD	0/ 0	0/ 0	3/ 1
UNDERSIDE	0/ 0	1/ 1	4/ 1
CHROMODACRYORRHEA	0/ 0	1/ 1	7/ 3
EMACIATION	0/ 0	0/ 0	5/ 3
CHROMORHINORRHEA	0/ 0	0/ 0	5/ 3
TWITCHES	0/ 0	10/ 9**	3/ 3
EXCESS SALIVATION	0/ 0	16/ 11	3/ 3
VOCALIZATION	0/ 0	2/ 2	2/ 2
ABDOMEN: RED SUBSTANCE	0/ 0	0/ 0	3/ 1
RED PERIORAL SUBSTANCE	0/ 0	0/ 0	3/ 1
TACHYPNEA	0/ 0	29/ 15**	1/ 1
CONVULSION: CLONIC	0/ 0	11/ 10**	1/ 1

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 7 THROUGH 23 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 7 through 11 of presumed gestation.
b. Refer to the individual clinical observations table (Table C11) for rats that were found dead with adverse observations.
** Significantly different from the vehicle group value ($p \leq 0.01$).

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TABLE C1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP	I	III	IV
DOSAGE (MG/KG/DAY)a	0	250	200
DESCRIPTOR	VEHICLE	RE-0981.05	RE-1122.01
PRESUMED GESTATION: (cont.)			
MAXIMUM POSSIBLE INCIDENCE	664/ 30	528/ 30	550/ 30
LACRIMATION	0/ 0	3/ 3	1/ 1
HYPERACTIVITY	0/ 0	0/ 0	1/ 1
BROWN PERIVAGINAL SUBSTANCE	0/ 0	0/ 0	1/ 1
INCISORS: MISSING/BROKEN	0/ 0	0/ 0	1/ 1
PILOERRECTION	0/ 0	2/ 2	0/ 0
LOST RIGHTING REFLEX	0/ 0	1/ 1	0/ 0
DILATED PUPIL	0/ 0	1/ 1	0/ 0
MOUTH: LESION	5/ 1	0/ 0	0/ 0
SWOLLEN SNOUT	4/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 7 THROUGH 23 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 7 through 11 of presumed gestation.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		I 0 VEHICLE	III 250 RE-0981.05	IV 200 RE-1122.01
LACTATION:				
MAXIMUM POSSIBLE INCIDENCE		116/ 29	76/ 19	64/ 16
MORTALITY		0	0	0
MOUTH: LESION		3/ 1	0/ 0	0/ 0
LOCALIZED ALOPECIA:	TOTAL	17/ 5	1/ 1	7/ 2
	LIMBS	17/ 5	0/ 0	7/ 2
	UNDERSIDE	0/ 0	1/ 1	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 7 through 11 of presumed gestation.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C1 (PAGE 4): CLINICAL OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP	II	V	VI
DOSAGE (MG/KG/DAY)a	0	1000	1000
DESCRIPTOR	VEHICLE	RE-1123.01	RE-1125.01
PRESUMED GESTATION:			
MAXIMUM POSSIBLE INCIDENCE	659/ 30	672/ 30	649/ 30
FOUND DEAD b	0	0	2
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	57/ 28**
LACRIMATION	0/ 0	0/ 0	7/ 6**
CHROMORHINORRHEA	0/ 0	1/ 1	3/ 3
URINE-STAINED ABDOMINAL FUR	0/ 0	0/ 0	11/ 2
LOCALIZED ALOPECIA: TOTAL	54/ 4	51/ 6	8/ 1
LIMBS	39/ 3	32/ 3	8/ 1
NECK	15/ 1	13/ 1	0/ 0
UNDERSIDE	0/ 0	18/ 3	0/ 0
INCISORS: MISSING/BROKEN	7/ 1	0/ 0	7/ 1
PTOSIS	0/ 0	0/ 0	1/ 1
EXCESS SALIVATION	0/ 0	0/ 0	1/ 1
HEAD: LESION	0/ 0	8/ 1	0/ 0
CHROMODACRYORRHEA	0/ 0	1/ 1	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP ON DAYS 7 THROUGH 23 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 7 through 11 of presumed gestation.
b. Refer to the individual clinical observations table (Table C11) for rats that were found dead with adverse observations.
** Significantly different from the vehicle group value ($p \leq 0.01$).

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C1 (PAGE 5): CLINICAL OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		II	V	VI
DOSAGE (MG/KG/DAY)a		0	1000	1000
DESCRIPTOR		VEHICLE	RE-1123.01	RE-1125.01
LACTATION:				
MAXIMUM POSSIBLE INCIDENCE		112/ 29	109/ 28	104/ 26
MORTALITY		0	0	0
LOCALIZED ALOPECIA:	TOTAL	12/ 3	12/ 3	1/ 1
	LIMBS	8/ 2	10/ 3	1/ 1
	NECK	4/ 1	4/ 1	0/ 0
	UNDERSIDE	0/ 0	4/ 1	0/ 0
URINE-STAINED ABDOMINAL FUR		0/ 0	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.
a. Dosage occurred on days 7 through 11 of presumed gestation.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		I 0 VEHICLE	III 250 RE-0981.05	IV 200 RE-1122.01
RATS EXAMINED b	N	29c	30	29c
FOUND DEAD	N	0	11**	11**
APPEARED NORMAL	N	29	27	26
STOMACH:				
CONTAINED FLUID	N	0	2	1
DISTENDED WITH AIR	N	0	1	0
SPLEEN:				
LARGE	N	0	0	1
LUNGS:				
CONTAINED FLUID	N	0	0	1
TRACHEA:				
PERFORATION	N	0	1	0

a. Dosage occurred on days 7 through 11 of presumed gestation.
b. Refer to the individual necropsy observations table (Table C12) for rats that were found dead with adverse observations.
c. Excludes values for rats that did not have necropsy observations recorded.
** Significantly different from the vehicle group value ($p \leq 0.01$).

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C2 (PAGE 2): NECROPSY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		II 0 VEHICLE	V 1000 RE-1123.01	VI 1000 RE-1125.01
RATS EXAMINED b	N	30	30	30
FOUND DEAD	N	0	0	2
APPEARED NORMAL	N	30	28	28
SPLEEN:				
DARK RED	N	0	2	0
LARGE	N	0	1	0
EXTERNAL OBSERVATIONS:				
VENTRAL ABDOMEN AND PERIORAL SURFACE, RED SUBSTANCE	N	0	0	2
FOREPAWS, RED SUBSTANCE	N	0	0	1

a. Dosage occurred on days 7 through 11 of presumed gestation.
b. Refer to the individual necropsy observations table (Table C12) for rats that were found dead with adverse observations.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C3 (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	29	27
MATERNAL BODY WEIGHT (G)				
DAY 0	MEAN±S.D.	270.0 ± 21.3	269.9 ± 22.3	273.1 ± 20.1
DAY 7	MEAN±S.D.	311.0 ± 26.4	306.2 ± 26.2	312.7 ± 19.8
DAY 8	MEAN±S.D.	312.8 ± 25.5	306.2 ± 27.2 [26]b	306.8 ± 23.5
DAY 9	MEAN±S.D.	318.2 ± 27.4	310.2 ± 29.0 [24]b	292.8 ± 24.7** [25]b
DAY 10	MEAN±S.D.	324.0 ± 28.9	314.4 ± 29.4 [23]b	288.1 ± 26.1** [23]b
DAY 11	MEAN±S.D.	331.2 ± 29.7	318.9 ± 30.6 [21]b	289.8 ± 32.4** [17]b
DAY 12	MEAN±S.D.	336.0 ± 30.5	322.5 ± 30.5 [19]b	285.0 ± 30.3** [17]b
DAY 13	MEAN±S.D.	342.6 ± 31.3	329.9 ± 31.3 [19]b	298.6 ± 29.0** [16]b
DAY 14	MEAN±S.D.	350.3 ± 32.8	337.9 ± 32.1 [19]b	311.4 ± 28.2** [16]b
DAY 15	MEAN±S.D.	359.1 ± 34.1	346.1 ± 32.5 [19]b	323.5 ± 28.9** [16]b
DAY 16	MEAN±S.D.	371.7 ± 37.3	357.9 ± 31.6 [19]b	339.7 ± 30.7** [16]b

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
** Significantly different from the vehicle group value ($p \leq 0.01$).

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C3 (PAGE 2): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		I 0 VEHICLE	III 250 RE-0981.05	IV 200 RE-1122.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	29	27
INCLUDED IN ANALYSES	N	29	19b	16b
MATERNAL BODY WEIGHT (G)				
DAY 17	MEAN±S.D.	386.6 ± 38.3	374.5 ± 32.8	357.1 ± 28.9**
DAY 18	MEAN±S.D.	402.4 ± 42.3	388.0 ± 32.4	377.7 ± 32.6*
DAY 19	MEAN±S.D.	415.5 ± 45.6	402.2 ± 32.0	393.4 ± 35.0
DAY 20	MEAN±S.D.	434.9 ± 48.3	420.9 ± 34.3	414.1 ± 34.1

DAY = DAY OF GESTATION
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
* Significantly different from the vehicle group value ($p \leq 0.05$).
** Significantly different from the vehicle group value ($p \leq 0.01$).

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TABLE C3 (PAGE 3): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP			II	V	VI
DOSAGE (MG/KG/DAY)a			0	1000	1000
DESCRIPTOR			VEHICLE	RE-1123.01	RE-1125.01
RATS TESTED		N	30	30	30
PREGNANT		N	29	28	27
MATERNAL BODY WEIGHT (G)					
DAY	0	MEAN±S.D.	271.1 ± 20.8	270.3 ± 20.6	272.1 ± 19.9
DAY	7	MEAN±S.D.	307.6 ± 22.5	307.8 ± 22.8	310.1 ± 24.8
DAY	8	MEAN±S.D.	309.1 ± 21.0	302.0 ± 23.6	308.6 ± 26.1
DAY	9	MEAN±S.D.	314.2 ± 20.8	301.5 ± 24.2*	312.8 ± 27.0
DAY	10	MEAN±S.D.	319.6 ± 20.8	302.8 ± 24.0**	316.5 ± 26.6
DAY	11	MEAN±S.D.	326.7 ± 22.6	307.1 ± 22.7**	319.7 ± 27.7
DAY	12	MEAN±S.D.	331.1 ± 22.6	308.9 ± 23.5**	325.0 ± 29.5 [26]b
DAY	13	MEAN±S.D.	339.0 ± 23.8	320.6 ± 24.3**	328.9 ± 30.9 [26]b
DAY	14	MEAN±S.D.	346.4 ± 23.2	329.6 ± 27.1**	335.6 ± 31.3 [26]b
DAY	15	MEAN±S.D.	356.1 ± 24.1	341.9 ± 28.9*	343.8 ± 33.3 [26]b
DAY	16	MEAN±S.D.	367.7 ± 24.2	355.2 ± 30.5	359.0 ± 28.8 [26]b

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
* Significantly different from the vehicle group value ($p \leq 0.05$).
** Significantly different from the vehicle group value ($p \leq 0.01$).

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C3 (PAGE 4): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		II 0 VEHICLE	V 1000 RE-1123.01	VI 1000 RE-1125.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	28	27
INCLUDED IN ANALYSES	N	29	28	26b
MATERNAL BODY WEIGHT (G)				
DAY 17	MEAN±S.D.	381.7 ± 24.7	373.2 ± 32.2	374.0 ± 29.8
DAY 18	MEAN±S.D.	399.6 ± 26.5	389.8 ± 32.7	390.5 ± 33.5
DAY 19	MEAN±S.D.	413.9 ± 27.8	405.0 ± 34.9	407.2 ± 30.4
DAY 20	MEAN±S.D.	434.3 ± 27.1	420.6 ± 35.6 [27]b	427.2 ± 30.1

DAY = DAY OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C4 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	29	27
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 0 - 7	MEAN±S.D.	+41.0 ± 11.6	+36.4 ± 9.8	+39.6 ± 5.5
DAYS 7 - 8	MEAN±S.D.	+1.8 ± 3.5	+0.9 ± 3.1 [26]b	-5.9 ± 7.5**
DAYS 8 - 9	MEAN±S.D.	+5.4 ± 5.0	+2.5 ± 3.1** [24]b	-12.8 ± 10.4** [25]b
DAYS 9 - 10	MEAN±S.D.	+5.8 ± 3.5	+3.2 ± 3.3** [23]b	-5.2 ± 11.0** [23]b
DAYS 10 - 11	MEAN±S.D.	+7.2 ± 3.3	+4.7 ± 3.6** [21]b	+1.9 ± 10.0* [17]b
DAYS 11 - 12	MEAN±S.D.	+4.8 ± 4.0	+4.4 ± 3.5 [19]b	-4.7 ± 9.9** [17]b
DAYS 7 - 12	MEAN±S.D.	+25.0 ± 6.9	+16.5 ± 4.9** [19]b	-27.6 ± 18.2** [17]b
DAYS 12 - 20	MEAN±S.D.	+98.9 ± 21.8	+98.4 ± 9.4 [19]b	+125.2 ± 17.1** [16]b
DAYS 7 - 20	MEAN±S.D.	+123.9 ± 25.7	+114.8 ± 12.4 [19]b	+99.8 ± 22.5** [16]b
DAYS 0 - 20	MEAN±S.D.	+164.9 ± 33.2	+151.7 ± 19.0 [19]b	+139.5 ± 25.6** [16]b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
* Significantly different from the vehicle group value ($p \leq 0.05$).
** Significantly different from the vehicle group value ($p \leq 0.01$).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C4 (PAGE 2): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		II 0 VEHICLE	V 1000 RE-1123.01	VI 1000 RE-1125.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	28	27
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 0 - 7	MEAN±S.D.	+36.5 ± 7.6	+37.5 ± 10.5	+38.1 ± 10.2
DAYS 7 - 8	MEAN±S.D.	+1.5 ± 11.2	-5.8 ± 5.4**	-1.6 ± 5.8**
DAYS 8 - 9	MEAN±S.D.	+5.1 ± 3.8	-0.5 ± 4.3**	+4.2 ± 4.0
DAYS 9 - 10	MEAN±S.D.	+5.4 ± 3.3	+1.4 ± 3.8**	+3.7 ± 3.0
DAYS 10 - 11	MEAN±S.D.	+7.1 ± 4.2	+4.3 ± 5.0*	+3.2 ± 4.0**
DAYS 11 - 12	MEAN±S.D.	+4.4 ± 3.5	+1.8 ± 4.2**	+3.8 ± 5.5 [26]b
DAYS 7 - 12	MEAN±S.D.	+23.5 ± 9.1	+1.1 ± 7.8**	+13.5 ± 11.5** [26]b
DAYS 12 - 20	MEAN±S.D.	+103.2 ± 13.0	+113.1 ± 17.2** [27]b	+102.2 ± 12.1 [26]b
DAYS 7 - 20	MEAN±S.D.	+126.7 ± 16.0	+114.1 ± 16.8** [27]b	+115.7 ± 17.6** [26]b
DAYS 0 - 20	MEAN±S.D.	+163.2 ± 18.4	+151.8 ± 22.8* [27]b	+154.5 ± 20.2 [26]b

DAYS = DAYS OF GESTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
* Significantly different from the vehicle group value ($p \leq 0.05$).
** Significantly different from the vehicle group value ($p \leq 0.01$).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C5 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	29	27
DELIVERED LITTERS	N	29	19b	16b
MATERNAL BODY WEIGHT (G)				
DAY 1	MEAN±S.D.	332.0 ± 35.8	324.6 ± 31.9	314.9 ± 24.4
DAY 2	MEAN±S.D.	327.8 ± 34.9	314.6 ± 29.9	312.6 ± 27.1
DAY 3	MEAN±S.D.	330.8 ± 35.8	318.3 ± 31.6	315.6 ± 27.7
DAY 4	MEAN±S.D.	340.6 ± 35.0	328.5 ± 33.4	324.2 ± 27.0

DAY = DAY OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C5 (PAGE 2): MATERNAL BODY WEIGHTS - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP			II	V	VI
DOSAGE (MG/KG/DAY)a			0	1000	1000
DESCRIPTOR			VEHICLE	RE-1123.01	RE-1125.01
RATS TESTED		N	30	30	30
PREGNANT		N	29	28	27
DELIVERED LITTERS		N	29	28	26b
INCLUDED IN ANALYSES		N	29	27c	26b
MATERNAL BODY WEIGHT (G)					
DAY	1	MEAN±S.D.	327.3 ± 25.6	321.5 ± 27.9 [26]d	318.4 ± 27.6
DAY	2	MEAN±S.D.	322.0 ± 22.5 [28]e	319.0 ± 28.9	314.3 ± 25.2
DAY	3	MEAN±S.D.	323.6 ± 20.9 [28]e	321.7 ± 30.7	317.3 ± 25.2
DAY	4	MEAN±S.D.	334.2 ± 23.0 [27]e,f	331.5 ± 32.8 [26]f	329.8 ± 22.9

DAY = DAY OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
c. Excludes values for rat 9443, day 1 of lactation was incorrectly identified.
d. Excludes a value for rat 9440, which delivered one additional pup by day 2 of lactation.
e. Excludes values for rats that had no surviving pups.
f. Excludes values for rats that were sacrificed.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C6 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	29	27
DELIVERED LITTERS	N	29	19b	16b
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 1 - 2	MEAN±S.D.	-4.2 ± 8.2	-10.0 ± 27.9	-2.4 ± 8.1
DAYS 2 - 3	MEAN±S.D.	+3.0 ± 6.3	+3.7 ± 5.7	+3.0 ± 5.3
DAYS 3 - 4	MEAN±S.D.	+9.9 ± 12.6	+10.2 ± 10.5	+8.6 ± 9.7
DAYS 1 - 4	MEAN±S.D.	+8.7 ± 16.3	+3.9 ± 35.2	+9.2 ± 9.8

DAY = DAY OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C6 (PAGE 2): MATERNAL BODY WEIGHT CHANGES - LACTATION - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		II	V	VI
DOSAGE (MG/KG/DAY)a		0	1000	1000
DESCRIPTOR		VEHICLE	RE-1123.01	RE-1125.01
RATS TESTED	N	30	30	30
PREGNANT	N	29	28	27
DELIVERED LITTERS	N	29	28	26b
INCLUDED IN ANALYSES	N	28c	27d	26
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 1 - 2	MEAN±S.D.	-4.5 ± 8.0	-1.2 ± 9.8 [26]e	-4.1 ± 10.7
DAYS 2 - 3	MEAN±S.D.	+1.6 ± 11.5	+2.8 ± 5.0 [27]f	+3.0 ± 6.2
DAYS 3 - 4	MEAN±S.D.	+9.6 ± 10.3 [27]f	+11.2 ± 9.1 [26]f	+12.5 ± 7.7
DAYS 1 - 4	MEAN±S.D.	+6.1 ± 18.5 [27]f	+11.8 ± 13.6 [25]e,f	+11.4 ± 11.6

DAY = DAY OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
c. Excludes values for rats that had no surviving pups.
d. Excludes values for rat 9443, day 1 of lactation was incorrectly identified.
e. Excludes values for rat 9440, which delivered one additional pup by day 2 of lactation.
f. Excludes values for rats that were sacrificed.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C7 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		I 0 VEHICLE	III 250 RE-0981.05	IV 200 RE-1122.01
RATS ASSIGNED TO NATURAL DELIVERY	N	30	30	30
INCLUDED IN ANALYSES	N	30	19b	19b
PREGNANT	N(%)	29(96.7)	19(100.0)	16(84.2)
DELIVERED LITTERS	N(%)	29(100.0)	19(100.0)	16(100.0)
DURATION OF GESTATION c	MEAN±S.D.	22.9 ± 0.4	22.7 ± 0.6	22.8 ± 0.4
IMPLANTATION SITES	N	480	303	273
PER DELIVERED LITTER	MEAN±S.D.	16.6 ± 3.3	15.9 ± 2.9	17.1 ± 2.6
DAMS WITH STILLBORN PUPS	N(%)	6(20.7)	4(21.0)	2(12.5)
DAMS WITH NO LIVEBORN PUPS	N	0	0	0
GESTATION INDEX	% N/N	100.0 29/ 29	100.0 19/ 19	100.0 16/ 16
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N	0	0	0

GESTATION INDEX = (NUMBER OF DAMS WITH LIVEBORN PUPS/NUMBER OF PREGNANT RATS)*100.

a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
c. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as day 0) and the time (in days) the first pup was delivered.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C7 (PAGE 2): NATURAL DELIVERY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP		II	V	VI
DOSAGE (MG/KG/DAY)		0	1000	1000
DESCRIPTOR		VEHICLE	RE-1123.01	RE-1125.01
RATS ASSIGNED TO NATURAL DELIVERY	N	30	30	30
INCLUDED IN ANALYSES	N	30	30	28b
PREGNANT	N(%)	29(96.7)	28(93.3)	26(92.8)
DELIVERED LITTERS	N(%)	29(100.0)	27(100.0)c	26(100.0)
DURATION OF GESTATION d	MEAN±S.D.	22.7 ± 0.5	22.9 ± 0.5	22.8 ± 0.5
IMPLANTATION SITES	N	493	454	459
PER DELIVERED LITTER	MEAN±S.D.	17.0 ± 1.7	16.8 ± 2.2	17.6 ± 1.5
DAMS WITH STILLBORN PUPS	N(%)	4(13.8)	8(29.6)	2(7.7)
DAMS WITH NO LIVEBORN PUPS	N	0	0	0
GESTATION INDEX	%	100.0	100.0	100.0
	N/N	29/ 29	27/ 27	26/ 26
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N(%)	1(3.4)	0(0.0)	0(0.0)

GESTATION INDEX = (NUMBER OF DAMS WITH LIVEBORN PUPS/NUMBER OF PREGNANT RATS)*100.

a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for rats that were found dead.
c. Excludes values for rat 9443, day 1 of lactation was incorrectly identified.
d. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as day 0) and the time (in days) the first pup was delivered.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C8 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	29	19	16
PUPS DELIVERED (TOTAL)	N	440	287	261
	MEAN±S.D.	15.2 ± 3.8	15.1 ± 2.7	16.3 ± 2.7
LIVEBORN	MEAN±S.D.	14.7 ± 4.1	14.8 ± 2.8	16.2 ± 2.7
	N(%)	427(97.0)	282(98.2)	259(99.2)
STILLBORN	MEAN±S.D.	0.4 ± 1.2	0.3 ± 0.6	0.1 ± 0.3
	N(%)	12(2.7)	5(1.7)	2(0.8)
UNKNOWN VITAL STATUS	N	1	0	0
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED				
DAY 1	N/N(%)	5/427(1.2)	0/282(0.0)	1/259(0.4)
DAYS 2- 4	N/N(%)	6/422(1.4)	3/282(1.1)	4/258(1.6)
VIABILITY INDEX b	%	97.4	98.9	98.1
	N/N	416/427	279/282	254/259

DAY(S) = DAY(S) POSTPARTUM

a. Dosage occurred on days 7 through 11 of gestation.

b. Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C8 (PAGE 2): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS - PART II

DOSAGE GROUP		I	III	IV
DOSAGE (MG/KG/DAY)a		0	250	200
DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	29	19	16
SURVIVING PUPS/LITTER a				
DAY 2 b	MEAN±S.D.	14.5 ± 4.3	14.8 ± 2.8	15.9 ± 2.8
DAY 4	MEAN±S.D.	14.3 ± 4.3	14.7 ± 2.8	15.9 ± 2.8
PERCENT MALE PUPS PER NUMBER OF PUPS SEXED				
DAY 2 b	MEAN±S.D.	52.9 ± 18.2	51.7 ± 13.9	47.7 ± 13.2
DAY 4	MEAN±S.D.	52.8 ± 18.0	51.6 ± 14.3	47.7 ± 13.2
LIVE LITTER SIZE AT WEIGHING				
DAY 2	MEAN±S.D.	14.5 ± 4.3	14.8 ± 2.8	15.9 ± 2.8
DAY 4	MEAN±S.D.	14.3 ± 4.3	14.7 ± 2.8	15.9 ± 2.8
PUP WEIGHT/LITTER (GRAMS)				
DAY 2	MEAN±S.D.	7.4 ± 0.6	7.5 ± 0.9	7.4 ± 0.6
DAY 4	MEAN±S.D.	9.2 ± 1.1	9.4 ± 1.3	8.9 ± 0.9

DAY = DAY POSTPARTUM
a. Dosage occurred on days 7 through 11 of gestation.
b. Average number of live pups per litter, including litters with no surviving pups.
c. Includes pups born alive, found dead day 1 or 2 postpartum.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C3 (PAGE 3): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS - PART II

DOSAGE GROUP		II	V	VI
DOSAGE (MG/KG/DAY)a		0	1000	1000
DESCRIPTOR		VEHICLE	RE-1123.05	RE-1125.01
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	29	28	26
INCLUDED IN ANALYSES	N	29	27b	26
PUPS DELIVERED (TOTAL)	N	466	431	431
	MEAN±S.D.	16.1 ± 2.1	16.0 ± 2.2	16.6 ± 2.3
LIVEBORN	MEAN±S.D.	15.9 ± 2.2	15.5 ± 2.5	16.5 ± 2.2
	N(%)	461(98.9)	418(97.0)**	429(99.5)
STILLBORN	MEAN±S.D.	0.2 ± 0.5	0.4 ± 1.0	0.1 ± 0.3
	N(%)	5(1.1)	12(2.8)	2(0.5)
UNKNOWN VITAL STATUS	N	0	1	0
SACRIFICED	N	18	18	0
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED				
DAY 1	N/N(%)	11/461(2.4)	4/418(0.9)	0/429(0.0)**
DAYS 2- 4	N/N(%)	5/432(1.2)c	4/396(1.0)d	7/429(1.6)
VIABILITY INDEX e	%	96.4	98.0	98.4
	N/N	427/443c	392/400d	422/429

DAY(S) = DAY(S) POSTPARTUM
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for litter 9443, day 1 of lactation was incorrectly identified.
c. Excludes values for litter 9360, which was sacrificed on day 3 postpartum.
d. Excludes values for litter 9450, which was sacrificed on day 3 postpartum.
e. Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C3 (PAGE 4): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY)a DESCRIPTOR		II 0 VEHICLE	V 1000 RE-1123.01	VI 1000 RE-1125.01
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	29	28	26
INCLUDED IN ANALYSES	N	29	27b	26
SURVIVING PUPS/LITTER c				
DAY 2d	MEAN±S.D.	15.5 ± 3.4	15.3 ± 2.6	16.2 ± 2.2
DAY 4	MEAN±S.D.	15.2 ± 3.4 [28]e	15.1 ± 2.5 [26]e	16.2 ± 2.2
PERCENT MALE PUPS PER NUMBER OF PUPS SEXED				
DAY 2d	MEAN±S.D.	52.5 ± 14.9 [28]e	49.9 ± 14.1	50.6 ± 8.7
DAY 4	MEAN±S.D.	52.4 ± 15.0 [27]e,f	49.6 ± 14.4 [26]e	50.6 ± 8.7
LIVE LITTER SIZE AT WEIGHING				
DAY 2	MEAN±S.D.	16.0 ± 1.7 [28]e	15.2 ± 2.6	16.2 ± 2.2
DAY 4	MEAN±S.D.	15.8 ± 1.7 [27]e,f	15.1 ± 2.5 [26]e	16.2 ± 2.2
PUP WEIGHT/LITTER (GRAMS)				
DAY 2	MEAN±S.D.	7.4 ± 1.0 [28]e	7.6 ± 0.8	7.3 ± 0.8
DAY 4	MEAN±S.D.	9.0 ± 0.9 [27]e,f	9.4 ± 1.1 [26]e	8.8 ± 1.3

DAY = DAY POSTPARTUM
[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 11 of gestation.
b. Excludes values for litter 9443, day 1 of lactation was incorrectly identified.
c. Average number of live pups per litter, including litters with no surviving pups.
d. Includes pups born alive, found dead day 1 or 2 postpartum.
e. Excludes values for litters that were sacrificed.
f. Excludes values for litters that had no surviving pups.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C9 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 4 POSTPARTUM - SUMMARY - F1 GENERATION PUPS - PART II

		I	III	IV
MATERNAL DOSAGE GROUP		0	250	200
MATERNAL DOSAGE (MG/KG/DAY)a		VEHICLE	RE-0981.05	RE-1122.01
MATERNAL DESCRIPTOR		28	29	27
LITTERS EXAMINED (N)				
TRANSIENT CLINICAL OBSERVATIONS: b		TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS		
PORTION OF TAIL BLACK	N/N	3/ 1	0/ 0	0/ 0
BACK: LESION	N/N	2/ 1	0/ 0	0/ 0
WHITE AREA SURROUNDING GENITALIA	N/N	1/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES WERE RESTRICTED TO THE NUMBER OF LITTERS WITH OBSERVATIONS.
a. Dosage occurred on days 7 through 11 of gestation.
b. Tabulation restricted to adverse observations; all other pups appeared normal.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C9 (PAGE 2): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 4 POSTPARTUM - SUMMARY - F1 GENERATION PUPS - PART II

DOSAGE GROUP		II	V	VI
DOSAGE (MG/KG/DAY)a		0	1000	1000
DESCRIPTOR		VEHICLE	RE-1123.01	RE-1125.01
LITTERS EXAMINED (N)		29	28	28
PERSISTENT CLINICAL OBSERVATIONS: b		TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS		
PORTION OF TAIL MISSING	N/N	4/ 1	0/ 0	0/ 0
TRANSIENT CLINICAL OBSERVATIONS: b		TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS		
MUZZLE: PURPLE	N/N	0/ 0	2/ 1	4/ 1

STATISTICAL ANALYSES WERE RESTRICTED TO THE NUMBER OF LITTERS WITH OBSERVATIONS.
a. Dosage occurred on days 7 through 11 of gestation.
b. Tabulation restricted to adverse observations; all other pups appeared normal.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C10 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION PUPS

MATERNAL DOSAGE GROUP		I	III	IV
MATERNAL DOSAGE (MG/KG/DAY)a		0	250	200
MATERNAL DESCRIPTOR		VEHICLE	RE-0981.05	RE-1122.01
TOTAL PUPS STILLBORN OR FOUND DEAD b	N	21	7	3
STILLBORN	N	12	5	2
FOUND DEAD	N	9	2	1
NO MILK IN STOMACH c	N(%)	6(66.7)	0(0.0)	1(100.0)
SKULL: DEFECT	N(%)	0(0.0)	0(0.0)	1(33.3)**
PUPS SACRIFICED AND NECROPSIED ON DAY 4 POSTPARTUM				
LITTERS EVALUATED	N	29	19	16
PUPS EVALUATED	N	417	279	254
APPEARED NORMAL				
LITTER INCIDENCE	N(%)	29(100.0)	19(100.0)	15(93.8)
PUP INCIDENCE	N(%)	417(100.0)	279(100.0)	253(99.6)
LIVER: MULTIPLE TAN AREAS				
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(6.3)
PUP INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.4)

a. Dosage occurred on days 7 through 11 of gestation.
b. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
c. Analysis restricted to pups found dead and necropsied.
** Significantly different from the vehicle control group value ($P \leq 0.01$).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C10 (PAGE 2): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION PUPS

MATERNAL DOSAGE GROUP		II	V	VI
MATERNAL DOSAGE (MG/KG/DAY)a		0	1000	1000
MATERNAL DESCRIPTOR		VEHICLE	RE-1123.01	RE-1125.01
TOTAL PUPS STILLBORN OR FOUND DEAD b	N	17	18	5
STILLBORN	N	5	12	2
FOUND DEAD	N	12	6	3
NO MILK IN STOMACH c	N(%)	1(11.1)	3(50.0)	2(66.7)
PUPS SACRIFICED AND NECROPSIED ON DAYS 2, 3 OR 4 POSTPARTUM				
LITTERS EVALUATED	N	29	28	27
PUPS EVALUATED	N	445	421	427
APPEARED NORMAL				
LITTER INCIDENCE	N(%)	29(100.0)	28(100.0)	26(96.3)
PUP INCIDENCE	N(%)	445(100.0)	421(100.0)	426(99.8)
KIDNEYS: LEFT PELVIS, MODERATE DILATION				
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(3.7)
PUP INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.2)

a. Dosage occurred on days 7 through 11 of gestation.
b. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
c. Analysis restricted to pups found dead and necropsied.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP I VEHICLE 0 MG/KG/DAY

RAT #		DESCRIPTION
9301		NO ADVERSE FINDINGS
9302		NO ADVERSE FINDINGS
9303		NO ADVERSE FINDINGS
9304	DG(13- 20)	LOCALIZED ALOPECIA: LIMBS
	DG(20)	ALOPECIA NO LONGER APPARENT
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9305		NO ADVERSE FINDINGS
9306	DG(17- 20)	SWOLLEN SNOUT
	DG(21)	SWELLING RESOLVED
	DG(17- 21)	MOUTH: LESION (0.2 CM IN DIAMETER)
	DL(1- 3)	MOUTH: LESION (0.2 CM IN DIAMETER)
	DL(4)	LESION HEALED
9307		NO ADVERSE FINDINGS
9308		NO ADVERSE FINDINGS
9309		NO ADVERSE FINDINGS
9310	DG(0)	LOCALIZED ALOPECIA: LIMBS
	DG(7- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9311		NO ADVERSE FINDINGS
9312		NO ADVERSE FINDINGS
9313		NO ADVERSE FINDINGS
9314	DG(17- 21)	LOCALIZED ALOPECIA: LIMBS
	DG(21)	ALOPECIA NO LONGER APPARENT
9315		NO ADVERSE FINDINGS
9316		NO ADVERSE FINDINGS
9317		NO ADVERSE FINDINGS
9318		NO ADVERSE FINDINGS
9319		NO ADVERSE FINDINGS
9320		NO ADVERSE FINDINGS
9321		NO ADVERSE FINDINGS
9322		NO ADVERSE FINDINGS
9323	DL(4)	LOCALIZED ALOPECIA: LIMBS a
9324		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP I VEHICLE 0 MG/KG/DAY

RAT #		DESCRIPTION
9325		NO ADVERSE FINDINGS
9326	DG(10- 17)	LOCALIZED ALOPECIA: LIMBS
9327	DG(7- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9328		NO ADVERSE FINDINGS
9329		NO ADVERSE FINDINGS
9330	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP II VEHICLE 0 MG/KG/DAY

RAT #		DESCRIPTION
9331		NO ADVERSE FINDINGS
9332		NO ADVERSE FINDINGS
9333	DG(7- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9334		NO ADVERSE FINDINGS
9335		NO ADVERSE FINDINGS
9336		NO ADVERSE FINDINGS
9337	DG(7- 15)	LOCALIZED ALOPECIA: LIMBS
	DG(16)	ALOPECIA NO LONGER APPARENT
9338		NO ADVERSE FINDINGS
9339	DG(9- 15)	INCISORS: MISSING/BROKEN
	DG(16)	INCISORS GROWN IN
9340		NO ADVERSE FINDINGS
9341		NO ADVERSE FINDINGS
9342		NO ADVERSE FINDINGS
9343		NO ADVERSE FINDINGS
9344		NO ADVERSE FINDINGS
9345		NO ADVERSE FINDINGS
9346	DG(7- 21)	LOCALIZED ALOPECIA: NECK
	DL(1- 4)	LOCALIZED ALOPECIA: NECK a
9347	DG(7- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9348		NO ADVERSE FINDINGS
9349		NO ADVERSE FINDINGS
9350		NO ADVERSE FINDINGS
9351		NO ADVERSE FINDINGS
9352		NO ADVERSE FINDINGS
9353		NO ADVERSE FINDINGS
9354		NO ADVERSE FINDINGS
9355		NO ADVERSE FINDINGS
9356		NO ADVERSE FINDINGS
9357		NO ADVERSE FINDINGS
9358		NO ADVERSE FINDINGS
9359		NO ADVERSE FINDINGS
9360		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP III RE-0981.05 250 MG/KG/DAY

RAT #		DESCRIPTION
9361	DG(7)	TACHYPNEA
	DG(10)	CONVULSION: CLONIC
	DG(10- 11)	TACHYPNEA
9362	DG(7)	TACHYPNEA
	DG(10- 11)	TACHYPNEA
9363	DG(7- 8)	CONVULSION: CLONIC
	DG(7- 8)	TACHYPNEA
	DG(7- 8)	LOCALIZED ALOPECIA: LIMBS
	DG(8)	LOST RIGHTING REFLEX
	DG(8)	TWITCHES
	DG(8)	LACRIMATION
	DG(8)	EXCESS SALIVATION
	DG(8)	FOUND DEAD
9364	DG(9- 10)	TACHYPNEA
9365	DG(8)	TWITCHES
	DG(8)	LACRIMATION
	DG(8)	EXCESS SALIVATION
	DG(8- 10)	TACHYPNEA
9366	DG(0)	LOCALIZED ALOPECIA: LIMBS
	DG(7- 9)	LOCALIZED ALOPECIA: LIMBS
	DG(9)	FOUND DEAD
9367	DG(11)	CONVULSION: CLONIC
	DG(11)	TWITCHES
	DG(11)	VOCALIZATION
	DG(11)	CHROMODACRYORRHEA
	DG(11)	DILATED PUPIL
	DG(11)	EXCESS SALIVATION
	DG(11)	PILOERECTION
	DG(11)	FOUND DEAD
9368	DG(8)	CONVULSION: CLONIC
	DG(8)	TWITCHES
	DG(8)	FOUND DEAD

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP III RE-0981.05 250 MG/KG/DAY

RAT #		DESCRIPTION
9369	DG(8- 9)	TACHYPNEA
	DG(10)	FOUND DEAD
9370	DG(8- 9)	TACHYPNEA
9371	DG(8- 9)	TACHYPNEA
	DG(10)	CONVULSION: CLONIC
	DG(10)	TWITCHES
	DG(10)	VOCALIZATION
	DG(10)	EXCESS SALIVATION
	DG(10)	PILOERECTION
	DG(10)	FOUND DEAD
9372		NO ADVERSE FINDINGS
9373		NO ADVERSE FINDINGS
9374	DG(8)	TACHYPNEA
9375		NO ADVERSE FINDINGS
9376	DG(8)	TACHYPNEA
9377	DG(10- 11)	EXCESS SALIVATION
	DG(10- 11)	TACHYPNEA
	DG(11)	DECREASED MOTOR ACTIVITY
	DG(11)	CONVULSION: CLONIC
	DG(11)	TWITCHES
	DG(11)	LACRIMATION
	DG(11)	URINE-STAINED ABDOMINAL FUR
	DG(12)	FOUND DEAD
9378		NO ADVERSE FINDINGS
9379	DG(10)	TACHYPNEA
	DG(10- 11)	EXCESS SALIVATION
9380	DG(10- 11)	EXCESS SALIVATION
9381		NO ADVERSE FINDINGS
	DG(8)	FOUND DEAD
9382	DG(10- 11)	TACHYPNEA
9383		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 6): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP III	RE-0981.05	250 MG/KG/DAY

RAT #		DESCRIPTION
9384	DG(10- 11)	EXCESS SALIVATION
9385	DG(7)	CONVULSION: CLONIC
	DG(7)	TWITCHES
	DG(7)	EXCESS SALIVATION
	DG(7)	FOUND DEAD
9386	DG(7)	CONVULSION: CLONIC
	DG(7- 8)	TWITCHES
	DG(10)	TACHYPNEA
	DG(10- 11)	EXCESS SALIVATION
	DG(13)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(14)	ALOPECIA NO LONGER APPARENT
	DL(4)	LOCALIZED ALOPECIA: UNDERSIDE a
9387	DG(7)	CONVULSION: CLONIC
	DG(7)	FOUND DEAD
9388	DG(7)	CONVULSION: CLONIC
	DG(7)	TWITCHES
	DG(7)	FOUND DEAD
9389	DG(8)	EXCESS SALIVATION
9390	DG(8)	TACHYPNEA
	DG(10)	TACHYPNEA

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 7): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP IV RE-1122.01 200 MG/KG/DAY

RAT #		DESCRIPTION
9391		NO ADVERSE FINDINGS
	DG(9)	FOUND DEAD
9392		NO ADVERSE FINDINGS
	DG(10)	FOUND DEAD
9393	DG(7- 12)	LOCALIZED ALOPECIA: LIMBS a
	DG(9- 12)	DECREASED MOTOR ACTIVITY
	DG(11- 12)	CHROMODACRYORRHEA
	DG(11- 12)	EMACIATION
	DG(11- 12)	URINE-STAINED ABDOMINAL FUR
	DG(13)	FOUND DEAD
9394	DG(9- 10)	DECREASED MOTOR ACTIVITY
	DG(10- 11)	URINE-STAINED ABDOMINAL FUR
	DG(11- 12)	EMACIATION
9395		NO ADVERSE FINDINGS
9396		NO ADVERSE FINDINGS
9397	DG(9)	TACHYPNEA
	DG(9- 10)	DECREASED MOTOR ACTIVITY
	DG(10)	CHROMODACRYORRHEA
	DG(10)	CHROMORHINORRHEA
	DG(10)	EMACIATION
	DG(11)	FOUND DEAD
9398	DG(9- 11)	DECREASED MOTOR ACTIVITY
	DG(11- 13)	RED PERIORAL SUBSTANCE
9398	DG(11- 14)	URINE-STAINED ABDOMINAL FUR
9399	DG(9- 10)	CHROMORHINORRHEA
	DG(10)	FOUND DEAD
9400	DG(9- 10)	DECREASED MOTOR ACTIVITY
	DG(10)	CONVULSION: CLONIC
	DG(10)	TWITCHES
	DG(10)	VOCALIZATION
	DG(10)	EXCESS SALIVATION
	DG(10)	FOUND DEAD
9401	DG(10- 18)	URINE-STAINED ABDOMINAL FUR

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 8): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP IV RE-1122.01 200 MG/KG/DAY

RAT #		DESCRIPTION
9402	DG(10- 13)	URINE-STAINED ABDOMINAL FUR
	DG(11)	BROWN PERIVAGINAL SUBSTANCE
9403	DG(9)	DECREASED MOTOR ACTIVITY
	DG(9)	VOCALIZATION
	DG(9- 10)	CHROMORHINORRHEA
9404	DG(7- 8)	LOCALIZED ALOPECIA: LIMBS
	DG(8)	FOUND DEAD
9405	DG(10)	FOUND DEAD
9406	DG(9)	DECREASED MOTOR ACTIVITY
9407	DG(0)	LOCALIZED ALOPECIA: LIMBS
	DG(9)	DECREASED MOTOR ACTIVITY
	DG(9)	EXCESS SALIVATION
	DG(9)	INCISORS: MISSING/BROKEN
	DG(9)	URINE-STAINED ABDOMINAL FUR
	DG(10)	FOUND DEAD
9408	DG(9- 16)	URINE-STAINED ABDOMINAL FUR
	DG(10- 12)	ABDOMEN: RED SUBSTANCE
	DG(16- 19)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(20)	ALOPECIA NO LONGER APPARENT
9409	DG(9- 16)	URINE-STAINED ABDOMINAL FUR
9410		NO ADVERSE FINDINGS
9411	DG(8)	DECREASED MOTOR ACTIVITY
	DG(10)	EXCESS SALIVATION
9412	DG(8)	DECREASED MOTOR ACTIVITY
	DG(10- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(2- 4)	LOCALIZED ALOPECIA: LIMBS a
9413	DG(9)	TWITCHES
	DG(9)	FOUND DEAD

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 9): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP IV	RE-1122.01	200 MG/KG/DAY
RAT #		DESCRIPTION
9414	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
9415	DG(9- 12)	URINE-STAINED ABDOMINAL FUR
	DG(12- 14)	LOCALIZED ALOPECIA: HEAD
	DG(15)	ALOPECIA NO LONGER APPARENT
9416	DG(12- 15)	CHROMODACRYORRHEA
9417	DG(9)	LACRIMATION
9418	DG(11)	DECREASED MOTOR ACTIVITY
	DG(11)	TWITCHES
	DG(12)	HYPERACTIVITY
	DG(12)	URINE-STAINED ABDOMINAL FUR
9419	DG(12- 15)	URINE-STAINED ABDOMINAL FUR
9420	DG(10)	DECREASED MOTOR ACTIVITY
	DG(11)	FOUND DEAD

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 10): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP V RE-1123.01 1000 MG/KG/DAY

RAT #		DESCRIPTION
9421	DG(8)	CHROMODACRYORRHEA
9422		NO ADVERSE FINDINGS
9423		NO ADVERSE FINDINGS
9424		NO ADVERSE FINDINGS
9425	DG(11- 16)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(17)	ALOPECIA NO LONGER APPARENT
9426		NO ADVERSE FINDINGS
9427		NO ADVERSE FINDINGS
9428		NO ADVERSE FINDINGS
9429		NO ADVERSE FINDINGS
9430		NO ADVERSE FINDINGS
9431		NO ADVERSE FINDINGS
9432		NO ADVERSE FINDINGS
9433		NO ADVERSE FINDINGS
9434		NO ADVERSE FINDINGS
9435		NO ADVERSE FINDINGS
9436		NO ADVERSE FINDINGS
9437		NO ADVERSE FINDINGS
9438	DG(11- 14)	LOCALIZED ALOPECIA: UNDERSIDE
	DG(15)	ALOPECIA NO LONGER APPARENT
9439	DG(8)	CHROMORHINORRHEA
9440		NO ADVERSE FINDINGS
9441	DG(13- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS
9442		NO ADVERSE FINDINGS
9443	DG(11- 21)	LOCALIZED ALOPECIA: LIMBS
9444	DG(10- 17)	HEAD: LESION (0.2 CM X 0.1 CM)
	DG(18)	LESION HEALED
9445		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 11): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP V RE-1123.01 1000 MG/KG/DAY

RAT #		DESCRIPTION
9446	DG(9- 21)	LOCALIZED ALOPECIA: NECK
	DG(10- 21)	LOCALIZED ALOPECIA: LIMBS
	DL(1- 4)	LOCALIZED ALOPECIA: LIMBS a
	DL(1- 4)	LOCALIZED ALOPECIA: NECK a
9447	DG(12- 19)	LOCALIZED ALOPECIA: UNDERSIDE
	DL(1- 2)	LOCALIZED ALOPECIA: LIMBS
	DL(3)	ALOPECIA NO LONGER APPARENT
	DL(1- 4)	LOCALIZED ALOPECIA: UNDERSIDE a
9448		NO ADVERSE FINDINGS
9449		NO ADVERSE FINDINGS
9450		NO ADVERSE FINDINGS

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

ARGUS 916-014
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ARGUS 916-014
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DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

RAT #	DOSAGE GROUP VI	DESCRIPTION
9451	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(7- 14)	LOCALIZED ALOPECIA; LIMBS
	DG(15)	ALOPECIA NO LONGER APPARENT
	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(11)	CHROMORHINORRHEA
9452	DG(8)	NO ADVERSE FINDINGS
	DG(7)	LACRIMATION
	DG(7- 9)	DECREASED MOTOR ACTIVITY
	DG(12- 14)	URINE-STAINED ABDOMINAL FUR
9453	DG(7- 8)	DECREASED MOTOR ACTIVITY
9454	DG(7- 8)	LACRIMATION
9455	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(7- 9)	NO ADVERSE FINDINGS
9456	DG(7)	LACRIMATION
	DG(7)	DECREASED MOTOR ACTIVITY
	DG(9)	LACRIMATION
9457	DG(7)	DECREASED MOTOR ACTIVITY
	DG(7)	DECREASED MOTOR ACTIVITY
9458	DG(7)	PTOSIS
9459	DG(9)	FOUND DEAD
	DG(11)	DECREASED MOTOR ACTIVITY
	DG(11)	DECREASED MOTOR ACTIVITY
9460	DG(7)	DECREASED MOTOR ACTIVITY
	DG(12)	FOUND DEAD
	DG(7- 8)	DECREASED MOTOR ACTIVITY
9461	DG(11)	DECREASED MOTOR ACTIVITY
	DG(12)	CHROMORHINORRHEA
	DG(8)	DECREASED MOTOR ACTIVITY
9462	DG(9)	DECREASED MOTOR ACTIVITY
	DG(11)	DECREASED MOTOR ACTIVITY

TABLE C11 (PAGE 12): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

1000 MG/KG/DAY

RE-1125.01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C11 (PAGE 13): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DOSAGE GROUP VI RE-1125.01 1000 MG/KG/DAY

RAT #		DESCRIPTION
9463	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(11)	DECREASED MOTOR ACTIVITY
9464	DG(8)	DECREASED MOTOR ACTIVITY
	DG(11)	DECREASED MOTOR ACTIVITY
9465	DG(7)	LACRIMATION
	DG(7- 8)	DECREASED MOTOR ACTIVITY
9466	DG(7)	LACRIMATION
	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(10)	DECREASED MOTOR ACTIVITY
9467	DG(7)	DECREASED MOTOR ACTIVITY
9468	DG(7)	DECREASED MOTOR ACTIVITY
	DG(10- 11)	DECREASED MOTOR ACTIVITY
9469	DG(7)	DECREASED MOTOR ACTIVITY
	DG(12- 19)	URINE-STAINED ABDOMINAL FUR
9470	DG(7)	DECREASED MOTOR ACTIVITY
9471	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DL(4)	LOCALIZED ALOPECIA: LIMBS a
9472	DG(7- 8)	DECREASED MOTOR ACTIVITY
	DG(7- 13)	INCISORS: MISSING/BROKEN
	DG(14)	INCISORS GROWN IN
	DG(8)	CHROMORHINORRHEA
9473	DG(7)	DECREASED MOTOR ACTIVITY
9474	DG(7- 11)	DECREASED MOTOR ACTIVITY
9475	DG(7)	DECREASED MOTOR ACTIVITY
9476	DG(7)	DECREASED MOTOR ACTIVITY
9477	DG(7- 9)	DECREASED MOTOR ACTIVITY
9478	DG(8- 9)	DECREASED MOTOR ACTIVITY
9479	DG(8)	DECREASED MOTOR ACTIVITY
	DG(11)	EXCESS SALIVATION
9480	DG(7- 8)	DECREASED MOTOR ACTIVITY

DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

a. Observation confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
I 0 VEHICLE	9301	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9302	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9303	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9304	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9305	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9306	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9307	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9308	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9309	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9310	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9311	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9312	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9313	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9314	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9315	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9316	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9317	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9318	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9319	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9320	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9321	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9322	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9323	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9324	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9325	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9326	DL 4	P	5	OBSERVATIONS WERE NOT RECORDED.
	9327	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9328	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9329	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9330	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
II 0 VEHICLE	9331	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9332	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9333	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9334	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9335	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9336	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9337	DL 1	P	5	ALL TISSUES APPEARED NORMAL.
	9338	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9339	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9340	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9341	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9342	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9343	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9344	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9345	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9346	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9347	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9348	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9349	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9350	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9351	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9352	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9353	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9354	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9355	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9356	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9357	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9358	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9359	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9360	DL 3	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
III 250 RE-0981.05	9361	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9362	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9363	DG 8	NP	2	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION. ALL TISSUES APPEARED NORMAL.
	9364	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9365	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9366	DG 9	P	3	FOUND DEAD ON DAY 9 OF GESTATION. STOMACH: CONTAINED APPROXIMATELY 3 ML CLEAR YELLOW FLUID. ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 15 IMPLANTATION SITES (15 EMBRYOS).
	9367	DG 11	P	5	FOUND DEAD ON DAY 11 OF GESTATION. TRACHEA: PERFORATION, POSSIBLY DAMAGED DURING NECROPSY ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 20 IMPLANTATION SITES (19 EMBRYOS ONE EARLY RESORPTION).b
	9368	DG 8	P	2	FOUND DEAD ON DAY 8 OF GESTATION. STOMACH: DISTENDED WITH AIR, CONTAINED APPROXIMATELY 2 ML CLEAR FLUID. ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 18 IMPLANTATION SITES (18 EMBRYOS).

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
III (cont.) 250 RE-0981.05	9369	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 17 IMPLANTATION SITES (17 EMBRYOS).b
	9370	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9371	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 16 IMPLANTATION SITES (16 EMBRYOS).b
	9372	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9373	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9374	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9375	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9376	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9377	DG 12	P	5	FOUND DEAD ON DAY 12 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 12 IMPLANTATION SITES (12 EMBRYOS).
	9378	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9379	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9380	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 5): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
III (cont.) 250 RE-0981.05	9381	DG 8	P	2	FOUND DEAD ON DAY 8 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 14 IMPLANTATION SITES (14 EMBRYOS).
	9382	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9383	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9384	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9385	DG 7	P	1	FOUND DEAD ON DAY 7 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 18 IMPLANTATION SITES (18 EMBRYOS).
	9386	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9387	DG 7	P	1	FOUND DEAD ON DAY 7 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 16 IMPLANTATION SITES (16 EMBRYOS).
	9388	DG 7	P	1	FOUND DEAD ON DAY 7 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 17 IMPLANTATION SITES (17 EMBRYOS).b
	9389	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9390	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 6): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
IV 200 RE-1122.01	9391	DG 9	P	2	FOUND DEAD ON DAY 9 OF GESTATION. ALL TISSUES APPEARED NORMAL FOR DEGREE OF AUTOLYSIS (SLIGHT). UTERINE CONTENTS: 14 IMPLANTATION SITES (14 EMBRYOS).
	9392	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION. STOMACH: CONTAINED APPROXIMATELY 3 ML CLEAR YELLOW FLUID. ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 16 IMPLANTATION SITES (16 EMBRYOS).
	9393	DG 13	P	5	FOUND DEAD ON DAY 13 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 14 IMPLANTATION SITES (14 EMBRYOS).
	9394	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9395	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9396	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9397	DG 11	P	4	FOUND DEAD ON DAY 11 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 19 IMPLANTATION SITES (19 EMBRYOS).
	9398	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9399	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 20 IMPLANTATION SITES (20 EMBRYOS).b
	9400	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION: LUNGS: CONTAINED WHITE, FROTHY FLUID. ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 20 IMPLANTATION SITES (20 EMBRYOS).b

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 7): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
IV (cont.) 200 RE-1122.01	9401	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9402	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9403	DL 4	P	5	SPLEEN: LARGE (2.19 G). ALL OTHER TISSUES APPEARED NORMAL.
	9404	DG 8	P	2	FOUND DEAD ON DAY 8 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 19 IMPLANTATION SITES (19 EMBRYOS).
	9405	DG 10	P	4	FOUND DEAD ON DAY 10 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 16 IMPLANTATION SITES (16 EMBRYOS).b
	9406	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9407	DG 10	P	3	FOUND DEAD ON DAY 10 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 17 IMPLANTATION SITES (17 EMBRYOS).
	9408	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9409	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9410	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9411	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9412	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 8): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
IV (cont.) 200 RE-1122.01	9413	DG 9	P	3	FOUND DEAD ON DAY 9 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 10 IMPLANTATION SITES (10 EMBRYOS).b
	9414	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9415	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9416	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9417	DL 4	P	5	OBSERVATIONS WERE NOT RECORDED.
	9418	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9419	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9420	DG 11	P	4	FOUND DEAD ON DAY 11 OF GESTATION. ALL TISSUES APPEARED NORMAL. UTERINE CONTENTS: 15 IMPLANTATION SITES (15 EMBRYOS).

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.
b. Conceptuses appeared normal for their developmental ages.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 9): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
V 1000 RE-1123.01	9421	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9422	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9423	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9424	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9425	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9426	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9427	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9428	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9429	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9430	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9431	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9432	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9433	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9434	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9435	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9436	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9437	DL 4	P	5	SPLEEN: DARK RED. ALL OTHER TISSUES APPEARED NORMAL.
	9438	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9439	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9440	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9441	DL 4	P	5	SPLEEN: DARK RED AND LARGE (1.22 G). ALL OTHER TISSUES APPEARED NORMAL.
	9442	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9443	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9444	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9445	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9446	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9447	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9448	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9449	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9450	DL 3	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 10): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
VI 1000 RE-1125.01	9451	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9452	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9453	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9454	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9455	DG 23	NP	5	ALL TISSUES APPEARED NORMAL.
	9456	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9457	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9458	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9459	DG 12	P	5	FOUND DEAD ON DAY 12 OF GESTATION. EXTERNAL OBSERVATIONS: VENTRAL ABDOMEN AND PERIORAL SURFACE, RED SUBSTANCE. ALL OTHER TISSUES APPEARED NORMAL. UTERINE CONTENTS: 15 IMPLANTATION SITES (15 EMBRYOS).
	9460	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9461	DG 12	NP	5	FOUND DEAD ON DAY 12 OF GESTATION. EXTERNAL OBSERVATIONS: VENTRAL ABDOMEN, PERIORAL SURFACE AND FOREPAWS, RED SUBSTANCE. ALL OTHER TISSUES APPEARED NORMAL.
	9462	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9463	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9464	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9465	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9466	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9467	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9468	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9469	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9470	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C12 (PAGE 11): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - PART II

DOSAGE GROUP DOSAGE (MG/KG/DAY) DESCRIPTOR	RAT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DOSAGES ADMINISTERED	OBSERVATIONS a
VI (cont.) 1000 RE-1125.01	9471	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9472	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9473	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9474	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9475	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9476	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9477	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9478	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9479	DL 4	P	5	ALL TISSUES APPEARED NORMAL.
	9480	DL 4	P	5	ALL TISSUES APPEARED NORMAL.

P = PREGNANT NP = NOT PREGNANT
DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Refer to the individual clinical observations table (Table C11) for external observations confirmed at necropsy.

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TABLE C13 (PAGE 1): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP I			VEHICLE		0 MG/KG/DAY							
9301 NP	251.	298.	303.	307.	308.	312.	311.	308.	312.	316.	304.	299.	306.
9302 P	315.	369.	360.	385.	391.	399.	407.	408.	418.	430.	455.	474.	501.
9303 P	271.	317.	320.	318.	323.	327.	335.	335.	340.	344.	347.	361.	361.
9304 P	223.	269.	264.	268.	272.	276.	280.	282.	288.	296.	304.	316.	331.
9305 P	274.	315.	322.	333.	337.	348.	344.	352.	362.	371.	389.	400.	414.
9306 P	297.	338.	336.	346.	351.	362.	362.	363.	375.	391.	401.	421.	441.
9307 P	244.	276.	281.	286.	294.	300.	304.	310.	318.	324.	334.	351.	366.
9308 P	248.	266.	268.	274.	275.	282.	284.	288.	290.	298.	307.	315.	328.
9309 P	255.	288.	289.	293.	297.	303.	308.	315.	324.	334.	343.	358.	380.
9310 P	273.	303.	307.	310.	323.	325.	330.	338.	346.	354.	366.	385.	411.
9311 P	252.	286.	288.	291.	296.	303.	305.	308.	317.	321.	328.	343.	364.
9312 P	309.	358.	358.	368.	377.	381.	391.	401.	417.	422.	438.	454.	469.
9313 P	265.	293.	295.	301.	306.	311.	315.	320.	328.	331.	340.	349.	366.
9314 P	261.	307.	310.	318.	323.	334.	338.	341.	351.	357.	369.	390.	415.
9315 P	277.	322.	324.	326.	337.	341.	345.	349.	362.	368.	383.	402.	428.
9316 P	287.	330.	330.	333.	338.	342.	344.	350.	356.	367.	383.	394.	419.
9317 P	301.	355.	353.	353.	366.	378.	383.	397.	402.	414.	427.	445.	472.
9318 P	258.	304.	305.	310.	314.	326.	327.	340.	349.	355.	368.	382.	406.
9319 P	260.	292.	292.	296.	306.	312.	308.	324.	325.	332.	347.	363.	381.
9320 P	268.	318.	322.	326.	330.	336.	339.	347.	358.	369.	387.	403.	425.
9321 P	283.	341.	341.	348.	360.	366.	370.	381.	393.	404.	423.	434.	459.
9322 P	240.	299.	299.	310.	314.	327.	334.	346.	351.	361.	376.	387.	408.
9323 P	286.	326.	332.	335.	339.	349.	355.	368.	372.	382.	392.	417.	423.
9324 P	245.	272.	277.	280.	281.	286.	294.	297.	302.	309.	321.	338.	336.
9325 P	259.	315.	323.	328.	332.	340.	350.	358.	363.	370.	383.	405.	369.
9326 P	293.	317.	321.	328.	328.	336.	340.	348.	352.	365.	374.	391.	400.
9327 P	280.	311.	314.	321.	328.	338.	340.	350.	354.	366.	383.	393.	407.
9328 P	267.	329.	333.	335.	344.	353.	365.	363.	373.	387.	403.	404.	421.
9329 P	277.	314.	317.	315.	319.	319.	332.	336.	345.	351.	366.	373.	388.
9330 P	263.	289.	290.	294.	295.	305.	314.	320.	328.	341.	343.	365.	380.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 2): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP I		VEHICLE		0 MG/KG/DAY
9301 NP	309.	307.	295.	294.	302.
9302 P	529.	544.	568.		
9303 P	369.	385.	376.	370.	
9304 P	341.	361.			
9305 P	436.	458.	465.		
9306 P	462.	496.	504.		
9307 P	386.	395.	421.		
9308 P	346.	350.	360.		
9309 P	390.	407.	420.		
9310 P	416.	438.	444.		
9311 P	331.	361.	384.		
9312 P	490.	513.	533.		
9313 P	375.	385.	406.		
9314 P	424.	446.	463.		
9315 P	423.	449.			
9316 P	422.	446.	457.		
9317 P	482.	512.	529.		
9318 P	413.	429.	454.		
9319 P	387.	409.	423.		
9320 P	435.	463.			
9321 P	474.	496.	530.		
9322 P	415.	435.	459.	470.	
9323 P	440.	455.	464.		
9324 P	358.	369.			
9325 P	417.	438.	446.		
9326 P	417.	430.	447.		
9327 P	425.	440.	460.		
9328 P	444.	461.	471.		
9329 P	404.	426.	440.		
9330 P	398.	415.			

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE C13 (PAGE 3): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP II		VEHICLE		0 MG/KG/DAY								
9331 P	260.	286.	289.	294.	299.	306.	307.	312.	319.	331.	343.	355.	372.
9332 P	259.	287.	292.	303.	305.	308.	315.	315.	328.	336.	352.	364.	383.
9333 P	254.	290.	296.	304.	307.	312.	314.	327.	332.	344.	355.	372.	391.
9334 P	258.	295.	294.	298.	302.	309.	317.	321.	329.	341.	355.	366.	387.
9335 P	228.	245.	245.	252.	256.	255.	263.	264.	272.	284.	291.	307.	316.
9336 P	262.	308.	309.	323.	332.	340.	351.	351.	360.	369.	384.	400.	422.
9337 P	282.	308.	314.	317.	329.	328.	334.	335.	343.	353.	364.	377.	396.
9338 NP	272.	280.	280.	283.	280.	285.	287.	287.	284.	292.	299.	299.	296.
9339 P	266.	304.	305.	310.	315.	321.	324.	333.	346.	362.	382.	392.	416.
9340 P	262.	295.	304.	302.	310.	316.	321.	331.	340.	351.	358.	380.	406.
9341 P	251.	295.	303.	308.	314.	319.	326.	335.	343.	350.	365.	385.	404.
9342 P	255.	300.	301.	310.	320.	328.	333.	342.	352.	358.	371.	384.	409.
9343 P	250.	304.	310.	310.	313.	318.	317.	326.	336.	343.	353.	367.	376.
9344 P	318.	352.	355.	357.	365.	369.	372.	384.	394.	406.	416.	434.	457.
9345 P	283.	323.	325.	331.	339.	352.	352.	363.	370.	383.	382.	393.	413.
9346 P	269.	306.	307.	308.	316.	323.	328.	340.	347.	352.	363.	370.	398.
9347 P	280.	313.	317.	324.	328.	335.	341.	351.	358.	369.	381.	402.	416.
9348 P	244.	288.	292.	293.	299.	310.	308.	320.	328.	336.	350.	373.	378.
9349 P	277.	306.	310.	316.	319.	326.	334.	340.	346.	349.	365.	383.	396.
9350 P	267.	306.	312.	316.	323.	332.	333.	343.	348.	352.	364.	362.	385.
9351 P	291.	319.	324.	332.	338.	350.	356.	367.	374.	390.	393.	424.	431.
9352 P	302.	344.	347.	353.	355.	365.	371.	379.	385.	396.	406.	401.	428.
9353 P	293.	336.	336.	340.	345.	355.	358.	364.	366.	372.	385.	401.	410.
9354 P	271.	310.	313.	309.	319.	322.	324.	335.	342.	349.	357.	380.	382.
9355 P	300.	343.	344.	348.	343.	360.	362.	370.	377.	391.	409.	422.	440.
9356 P	308.	349.	294.	303.	310.	326.	339.	349.	353.	368.	383.	394.	419.
9357 P	274.	307.	309.	313.	316.	324.	329.	337.	341.	347.	372.	379.	399.
9358 P	276.	308.	315.	322.	329.	332.	337.	345.	352.	366.	367.	384.	403.
9359 P	244.	283.	289.	293.	296.	302.	305.	311.	323.	330.	336.	347.	366.
9360 P	278.	311.	314.	323.	326.	332.	331.	342.	341.	350.	362.	372.	388.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 4): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP II		VEHICLE		0 MG/KG/DAY
9331 P	388.	414.	408.		
9332 P	399.	423.	424.		
9333 P	405.	430.	439.		
9334 P	409.	434.	431.		
9335 P	329.	346.	352.		
9336 P	442.	467.			
9337 P	412.	430.	428.	439.	
9338 NP	301.	312.	297.	298.	302.
9339 P	434.	456.	456.		
9340 P	418.	438.	458.		
9341 P	416.	442.			
9342 P	416.	439.	459.		
9343 P	399.	417.			
9344 P	463.	484.	499.		
9345 P	424.	449.	466.		
9346 P	406.	422.	440.		
9347 P	431.	448.	468.		
9348 P	399.	418.			
9349 P	415.	434.	454.		
9350 P	403.	415.	432.		
9351 P	452.	466.	481.		
9352 P	442.	458.			
9353 P	432.	449.	466.		
9354 P	401.	416.			
9355 P	458.	478.			
9356 P	436.	453.			
9357 P	415.	434.	456.		
9358 P	415.	432.	445.		
9359 P	379.	394.			
9360 P	365.	409.			

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE C13 (PAGE 5): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP III			RE-0981.05		250 MG/KG/DAY							
9361 P	280.	317.	321.	324.	327.	327.	331.	337.	344.	354.	359.	373.	385.
9362 P	242.	278.	280.	284.	288.	292.	296.	300.	307.	315.	324.	337.	350.
9363 NP	270.	299.	287.	FOUND DEAD ON DAY 8 OF GESTATION									
9364 P	260.	282.	288.	288.	293.	302.	304.	314.	322.	334.	346.	365.	387.
9365 P	240.	262.	260.	263.	265.	265.	266.	272.	278.	289.	302.	316.	328.
9366 P	247.	284.	288.	286.	FOUND DEAD ON DAY 9 OF GESTATION								
9367 P	303.	352.	352.	359.	370.	368.	FOUND DEAD ON DAY 11 OF GESTATION						
9368 P	257.	296.	293.	FOUND DEAD ON DAY 8 OF GESTATION									
9369 P	285.	329.	331.	332.	335.	FOUND DEAD ON DAY 10 OF GESTATION							
9370 P	226.	264.	265.	265.	271.	277.	280.	289.	294.	303.	314.	327.	348.
9371 P	259.	292.	299.	298.	297.	FOUND DEAD ON DAY 10 OF GESTATION							
9372 P	275.	316.	318.	320.	323.	324.	329.	335.	345.	350.	364.	379.	402.
9373 P	280.	331.	329.	331.	334.	339.	351.	359.	370.	379.	394.	406.	432.
9374 P	266.	311.	309.	314.	312.	323.	328.	331.	344.	352.	364.	376.	405.
9375 P	250.	281.	283.	285.	288.	293.	300.	304.	315.	326.	339.	359.	376.
9376 P	265.	321.	329.	331.	326.	335.	338.	345.	361.	370.	377.	395.	412.
9377 P	254.	282.	280.	278.	282.	284.	FOUND DEAD ON DAY 12 OF GESTATION						
9378 P	273.	328.	328.	332.	336.	348.	348.	360.	365.	373.	390.	413.	413.
9379 P	277.	298.	297.	306.	310.	313.	316.	324.	332.	333.	349.	367.	370.
9380 P	262.	302.	304.	305.	309.	311.	319.	329.	334.	342.	352.	373.	377.
9381 P	252.	287.	283.	FOUND DEAD ON DAY 8 OF GESTATION									
9382 P	296.	342.	341.	351.	351.	357.	363.	374.	376.	382.	397.	416.	420.
9383 P	274.	309.	308.	307.	308.	313.	322.	333.	337.	345.	360.	384.	378.
9384 P	272.	310.	309.	312.	315.	322.	325.	333.	341.	348.	360.	377.	387.
9385 P	262.	296.	FOUND DEAD ON DAY 7 OF GESTATION										
9386 P	252.	272.	270.	272.	280.	283.	281.	286.	290.	296.	309.	320.	339.
9387 P	303.	339.	FOUND DEAD ON DAY 7 OF GESTATION										
9388 P	289.	309.	FOUND DEAD ON DAY 7 OF GESTATION										
9389 P	329.	364.	366.	368.	375.	381.	390.	397.	406.	421.	421.	435.	451.
9390 P	296.	327.	329.	333.	336.	340.	341.	347.	360.	364.	380.	397.	412.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 6): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP III	RE-0981.05	250 MG/KG/DAY		
9361 P	398.	417.	413.	411.	
9362 P	365.	389.	400.		
9363 NP	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION				
9364 P	407.	422.	443.		
9365 P	349.	349.	361.		
9366 P	FOUND DEAD ON DAY 9 OF GESTATION				
9367 P	FOUND DEAD ON DAY 11 OF GESTATION				
9368 P	FOUND DEAD ON DAY 8 OF GESTATION				
9369 P	FOUND DEAD ON DAY 10 OF GESTATION				
9370 P	350.	375.	445.		
9371 P	FOUND DEAD ON DAY 10 OF GESTATION				
9372 P	409.	429.	446.		
9373 P	437.	458.			
9374 P	412.	436.	466.		
9375 P	388.	406.	423.		
9376 P	417.	438.	445.		
9377 P	FOUND DEAD ON DAY 12 OF GESTATION				
9378 P	433.	450.			
9379 P	386.	401.			
9380 P	393.	412.			
9381 P	FOUND DEAD ON DAY 8 OF GESTATION				
9382 P	434.	455.	481.		
9383 P	409.	427.			
9384 P	407.	428.	442.		
9385 P	FOUND DEAD ON DAY 7 OF GESTATION				
9386 P	350.	368.			
9387 P	FOUND DEAD ON DAY 7 OF GESTATION				
9388 P	FOUND DEAD ON DAY 7 OF GESTATION				
9389 P	461.	488.	512.		
9390 P	436.	449.			

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

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TABLE C13 (PAGE 7): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP IV			RE-1122.01		200 MG/KG/DAY							
9391 P	274.	320.	318.	FOUND DEAD ON DAY 9 OF GESTATION									
9392 P	258.	303.	300.	298.	296.	FOUND DEAD ON DAY 10 OF GESTATION							
9393 P	241.	287.	266.	269.	245.	235.	225.	FOUND DEAD ON DAY 13 OF GESTATION					
9394 P	233.	271.	248.	248.	232.	236.	244.	251.	259.	268.	281.	296.	308.
9395 P	252.	295.	287.	272.	277.	282.	280.	287.	296.	310.	327.	346.	367.
9396 NP	264.	308.	298.	281.	282.	266.	274.	279.	288.	296.	300.	311.	316.
9397 P	285.	319.	307.	297.	274.	FOUND DEAD ON DAY 11 OF GESTATION							
9398 P	270.	310.	312.	290.	280.	261.	266.	279.	294.	308.	324.	344.	368.
9399 P	277.	306.	305.	293.	283.	FOUND DEAD ON DAY 10 OF GESTATION							
9400 P	280.	318.	316.	293.	305.	FOUND DEAD ON DAY 10 OF GESTATION							
9401 NP	245.	248.	242.	229.	216.	220.	219.	229.	235.	238.	243.	238.	254.
9402 P	253.	291.	280.	254.	265.	261.	257.	274.	294.	304.	323.	342.	377.
9403 P	281.	336.	335.	327.	316.	327.	307.	327.	341.	352.	367.	389.	415.
9404 P	293.	332.	327.	FOUND DEAD ON DAY 8 OF GESTATION									
9405 P	249.	290.	284.	270.	270.	FOUND DEAD ON DAY 10 OF GESTATION							
9406 P	272.	314.	314.	303.	299.	310.	314.	324.	332.	340.	352.	370.	399.
9407 P	260.	297.	296.	270.	FOUND DEAD ON DAY 10 OF GESTATION								
9408 P	261.	304.	293.	253.	250.	266.	272.	286.	296.	309.	319.	341.	353.
9409 NP	254.	288.	282.	269.	250.	261.	259.	263.	265.	266.	269.	277.	272.
9410 P	273.	310.	314.	310.	294.	295.	300.	316.	328.	343.	360.	388.	395.
9411 P	258.	290.	287.	282.	283.	282.	271.	274.	283.	293.	306.	325.	341.
9412 P	263.	301.	296.	285.	275.	281.	280.	284.	297.	304.	321.	344.	354.
9413 P	277.	314.	314.	304.	FOUND DEAD ON DAY 9 OF GESTATION								
9414 P	297.	335.	336.	313.	318.	316.	309.	314.	331.	347.	363.	381.	404.
9415 P	306.	348.	342.	316.	331.	336.	333.	344.	358.	374.	396.	408.	439.
9416 P	266.	304.	284.	277.	285.	272.	262.	258.	279.	297.	319.	338.	358.
9417 P	290.	331.	330.	316.	307.	326.	329.	340.	346.	358.	382.	385.	408.
9418 P	300.	342.	344.	344.	336.	333.	316.	327.	338.	349.	367.	372.	394.
9419 P	318.	346.	328.	317.	300.	307.	281.	293.	310.	320.	328.	345.	363.
9420 P	286.	329.	320.	318.	305.	FOUND DEAD ON DAY 11 OF GESTATION							

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 8): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP IV		RE-1122.01		200 MG/KG/DAY
9391 P	FOUND DEAD ON DAY 9 OF GESTATION				
9392 P	FOUND DEAD ON DAY 10 OF GESTATION				
9393 P	FOUND DEAD ON DAY 13 OF GESTATION				
9394 P	320.	343.	344.		
9395 P	391.	419.			
9396 NP	327.	338.	304.	324.	325.
9397 P	FOUND DEAD ON DAY 11 OF GESTATION				
9398 P	391.	402.	433.		
9399 P	FOUND DEAD ON DAY 10 OF GESTATION				
9400 P	FOUND DEAD ON DAY 10 OF GESTATION				
9401 NP	250.	253.	252.	254.	266.
9402 P	377.	403.	429.		
9403 P	421.	438.			
9404 P	FOUND DEAD ON DAY 8 OF GESTATION				
9405 P	FOUND DEAD ON DAY 10 OF GESTATION				
9406 P	410.	428.	446.		
9407 P	FOUND DEAD ON DAY 10 OF GESTATION				
9408 P	373.	394.	405.		
9409 NP	276.	278.	282.	282.	287.
9410 P	418.	440.	461.		
9411 P	340.	355.	389.		
9412 P	372.	402.	418.		
9413 P	FOUND DEAD ON DAY 9 OF GESTATION				
9414 P	427.	444.	470.		
9415 P	459.	476.	506.		
9416 P	379.	402.			
9417 P	425.	451.	473.		
9418 P	414.	428.	448.		
9419 P	377.	400.	424.		
9420 P	FOUND DEAD ON DAY 11 OF GESTATION				

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 9): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP V			RE-1123.01		1000 MG/KG/DAY							
9421 P	247.	299.	297.	297.	301.	300.	298.	313.	327.	342.	365.	379.	400.
9422 P	296.	337.	317.	314.	320.	320.	326.	333.	344.	357.	375.	390.	403.
9423 NP	275.	306.	290.	296.	292.	297.	286.	277.	297.	300.	300.	304.	315.
9424 NP	226.	340.	337.	345.	338.	329.	323.	338.	345.	358.	363.	369.	372.
9425 P	291.	335.	332.	325.	320.	323.	331.	344.	354.	372.	383.	398.	414.
9426 P	250.	314.	304.	310.	302.	304.	304.	319.	334.	341.	363.	379.	405.
9427 P	266.	286.	274.	270.	273.	275.	285.	296.	312.	324.	334.	353.	380.
9428 P	280.	301.	295.	289.	287.	296.	299.	309.	319.	326.	345.	360.	382.
9429 P	262.	286.	272.	267.	269.	277.	278.	284.	291.	299.	309.	329.	344.
9430 P	264.	290.	284.	282.	282.	292.	292.	307.	303.	321.	330.	350.	378.
9431 P	242.	281.	276.	280.	281.	284.	288.	298.	301.	308.	321.	338.	364.
9432 P	286.	326.	313.	305.	310.	315.	316.	334.	346.	361.	376.	401.	426.
9433 P	271.	314.	297.	294.	289.	307.	309.	325.	335.	351.	371.	393.	419.
9434 P	262.	307.	302.	300.	299.	306.	304.	320.	330.	343.	359.	371.	401.
9435 P	280.	308.	308.	310.	314.	317.	321.	330.	341.	354.	369.	391.	399.
9436 P	256.	285.	275.	280.	283.	288.	291.	300.	303.	313.	324.	337.	346.
9437 P	253.	295.	293.	298.	297.	302.	305.	315.	324.	336.	346.	365.	377.
9438 P	277.	318.	313.	310.	314.	324.	326.	338.	344.	358.	374.	406.	408.
9439 P	309.	354.	352.	355.	354.	345.	353.	370.	388.	401.	414.	440.	455.
9440 P	258.	302.	294.	294.	299.	300.	301.	309.	314.	328.	339.	365.	372.
9441 P	252.	283.	281.	283.	287.	288.	281.	294.	301.	310.	319.	332.	344.
9442 P	276.	311.	309.	313.	314.	322.	327.	335.	341.	352.	365.	389.	398.
9443 P	260.	295.	288.	286.	289.	293.	290.	302.	308.	321.	330.	350.	361.
9444 P	293.	341.	341.	340.	338.	340.	341.	354.	360.	376.	384.	411.	422.
9445 P	300.	330.	325.	328.	331.	342.	339.	353.	364.	374.	395.	396.	416.
9446 P	227.	250.	247.	240.	244.	249.	250.	259.	259.	267.	278.	283.	294.
9447 P	312.	344.	342.	337.	346.	347.	347.	358.	372.	388.	408.	414.	427.
9448 P	274.	310.	306.	311.	314.	317.	322.	328.	339.	356.	359.	381.	394.
9449 P	269.	308.	308.	308.	312.	317.	323.	331.	339.	360.	359.	378.	400.
9450 P	255.	309.	310.	315.	311.	310.	302.	320.	337.	334.	351.	370.	386.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 10): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP V		RE-1123.01		1000 MG/KG/DAY
9421 P	415.	411.	433.		
9422 P	426.	446.	467.		
9423 NP	317.	329.	319.	323.	332.
9424 NP	389.	370.	378.	364.	356.
9425 P	436.	436.	456.		
9426 P	430.	435.	458.		
9427 P	387.	411.	427.		
9428 P	391.	410.	432.		
9429 P	356.	376.	390.		
9430 P	390.	413.	437.		
9431 P	373.	390.	420.		
9432 P	431.	456.	480.		
9433 P	426.	447.	455.		
9434 P	406.	426.	442.		
9435 P	420.	433.	448.		
9436 P	358.	375.	387.		
9437 P	399.	417.	443.		
9438 P	426.	451.			
9439 P	481.	502.	525.		
9440 P	385.	405.			
9441 P	361.	380.	394.		
9442 P	412.	434.	456.		
9443 P	380.	390.			
9444 P	441.	464.	490.		
9445 P	433.	448.	461.		
9446 P	303.	316.	324.		
9447 P	438.				
9448 P	409.	429.	448.		
9449 P	418.	431.	457.		
9450 P	408.	423.	448.	467.	

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 11): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 0	7	8	9	10	11	12	13	14	15	16	17	18
RAT #	DOSAGE GROUP VI			RE-1125.01		1000 MG/KG/DAY							
9451 P	279.	316.	315.	327.	332.	332.	337.	340.	350.	362.	376.	392.	414.
9452 P	261.	313.	311.	310.	315.	316.	319.	326.	339.	345.	359.	364.	380.
9453 P	261.	292.	294.	292.	293.	299.	302.	308.	316.	324.	335.	348.	369.
9454 P	286.	334.	338.	345.	348.	350.	371.	360.	365.	373.	380.	397.	410.
9455 NP	258.	267.	272.	272.	275.	271.	280.	280.	278.	278.	283.	283.	278.
9456 P	245.	278.	275.	272.	274.	278.	283.	286.	301.	311.	328.	346.	362.
9457 P	277.	325.	327.	336.	340.	344.	342.	350.	363.	374.	386.	398.	426.
9458 P	299.	332.	326.	331.	337.	333.	338.	340.	343.	354.	361.	375.	402.
9459 P	254.	274.	276.	276.	284.	281.	FOUND DEAD ON DAY 12 OF GESTATION						
9460 P	307.	367.	378.	382.	386.	395.	403.	416.	419.	426.	440.	456.	484.
9461 NP	254.	288.	288.	294.	294.	296.	FOUND DEAD ON DAY 12 OF GESTATION						
9462 P	252.	294.	290.	299.	309.	313.	323.	327.	335.	350.	364.	383.	407.
9463 P	300.	345.	344.	348.	350.	352.	366.	371.	373.	378.	388.	411.	435.
9464 P	292.	335.	325.	333.	334.	332.	338.	340.	346.	353.	365.	381.	408.
9465 P	243.	275.	269.	274.	281.	281.	285.	285.	295.	304.	312.	323.	342.
9466 P	271.	304.	304.	302.	304.	307.	308.	312.	323.	331.	341.	356.	381.
9467 P	282.	318.	311.	314.	315.	321.	324.	325.	336.	344.	359.	372.	377.
9468 P	266.	299.	301.	305.	310.	311.	312.	327.	326.	336.	352.	379.	386.
9469 P	255.	292.	284.	288.	290.	286.	280.	266.	255.	244.	303.	312.	336.
9470 P	267.	307.	296.	304.	306.	307.	315.	319.	322.	330.	345.	358.	366.
9471 P	291.	326.	328.	334.	333.	344.	350.	355.	362.	372.	387.	399.	408.
9472 P	263.	309.	297.	303.	308.	309.	309.	313.	320.	332.	347.	377.	338.
9473 P	240.	283.	278.	285.	290.	298.	298.	309.	320.	327.	342.	357.	368.
9474 P	249.	263.	274.	281.	282.	290.	293.	296.	303.	309.	324.	344.	357.
9475 P	274.	323.	327.	329.	337.	342.	344.	349.	355.	365.	378.	402.	416.
9476 P	268.	319.	314.	316.	316.	322.	324.	330.	334.	342.	355.	376.	388.
9477 P	273.	299.	297.	294.	304.	310.	307.	316.	325.	338.	356.	360.	386.
9478 P	276.	306.	306.	315.	314.	318.	319.	323.	330.	338.	355.	357.	380.
9479 P	315.	346.	347.	350.	354.	362.	361.	363.	370.	376.	397.	402.	427.
9480 NP	278.	334.	333.	332.	332.	339.	343.	352.	349.	358.	365.	371.	374.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C13 (PAGE 12): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

PREGNANCY STATUS	DAY 19	20	21	22	23
RAT #	DOSAGE GROUP VI		RE-1125.01		1000 MG/KG/DAY
9451 P	434.	456.	471.		
9452 P	394.	414.	408.	409.	
9453 P	387.	414.	419.		
9454 P	427.	456.			
9455 NP	279.	284.	281.	282.	284.
9456 P	388.	417.			
9457 P	440.	435.	463.		
9458 P	413.	439.	456.		
9459 P	FOUND DEAD ON DAY 12 OF GESTATION				
9460 P	492.	517.	534.		
9461 NP	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION				
9462 P	418.	439.	457.		
9463 P	439.	459.	475.		
9464 P	412.	432.	457.		
9465 P	352.	374.	387.		
9466 P	389.	406.	430.		
9467 P	393.	408.	423.		
9468 P	415.	426.	443.		
9469 P	351.	373.	395.	279.	
9470 P	383.	401.			
9471 P	427.	443.	463.	349.	
9472 P	392.	413.		308.	
9473 P	388.	407.			
9474 P	375.	396.	412.	303.	
9475 P	433.	454.	479.	332.	
9476 P	407.	423.	438.	302.	
9477 P	399.	420.	434.		
9478 P	397.	424.	436.		
9479 P	443.	462.	486.		
9480 NP	381.	388.	398.	415.	404.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
DAY = DAY OF PRESUMED GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DAY	1	2	3	4
RAT #	DOSAGE GROUP I		VEHICLE	0 MG/KG/DAY
9301	NOT PREGNANT			
9302	418.	403.	415.	426.
9303	338.	334.	335.	316.
9304	284.	266.	267.	291.
9305	348.	348.	346.	370.
9306	376.	366.	359.	351.
9307	288.	300.	308.	327.
9308	285.	268.	270.	286.
9309	308.	301.	303.	318.
9310	317.	317.	320.	341.
9311	310.	300.	308.	325.
9312	413.	403.	410.	422.
9313	312.	310.	308.	325.
9314	335.	332.	334.	346.
9315	357.	340.	327.	346.
9316	318.	320.	315.	330.
9317	374.	380.	390.	394.
9318	326.	316.	326.	292.
9319	295.	306.	312.	331.
9320	356.	351.	360.	375.
9321	378.	375.	385.	384.
9322	328.	323.	322.	330.
9323	347.	345.	347.	364.
9324	276.	272.	286.	298.
9325	335.	331.	338.	349.
9326	331.	318.	326.	330.
9327	315.	327.	327.	330.
9328	337.	328.	326.	340.
9329	325.	328.	322.	325.
9330	297.	297.	301.	317.

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 2): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DAY	1	2	3	4
RAT #	DOSAGE GROUP II		VEHICLE	0 MG/KG/DAY
9331	301.	300.	314.	325.
9332	309.	313.	317.	336.
9333	313.	303.	312.	331.
9334	309.	303.	307.	323.
9335	263.	264.	268.	279.
9336	366.	348.	340.	352.
9337	349.	NO SURVIVING PUPS ON DAY 1 OF LACTATION		
9338	NOT PREGNANT			
9339	337.	327.	327.	335.
9340	334.	321.	328.	325.
9341	335.	325.	314.	335.
9342	320.	324.	323.	323.
9343	315.	319.	327.	332.
9344	363.	363.	368.	392.
9345	337.	333.	330.	350.
9346	330.	317.	313.	325.
9347	343.	325.	334.	342.
9348	311.	301.	308.	327.
9349	304.	306.	314.	322.
9350	330.	323.	317.	326.
9351	377.	362.	377.	378.
9352	352.	342.	340.	362.
9353	343.	345.	340.	345.
9354	322.	320.	315.	330.
9355	353.	360.	315.	290.
9356	356.	338.	340.	347.
9357	316.	315.	326.	321.
9358	325.	329.	343.	355.
9359	293.	297.	307.	315.
9360	287.	294.	298.	SACRIFICED ON DAY 3 OF LACTATION

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 3): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DAY	1	2	3	4
RAT #	DOSAGE GROUP III	RE-0981.05	250 MG/KG/DAY	
9361	335.	319.	325.	337.
9362	303.	278.	278.	265.
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION			
9364	278.	302.	310.	329.
9365	384.	272.	268.	265.
9366	FOUND DEAD ON DAY 9 OF GESTATION			
9367	FOUND DEAD ON DAY 11 OF GESTATION			
9368	FOUND DEAD ON DAY 8 OF GESTATION			
9369	FOUND DEAD ON DAY 10 OF GESTATION			
9370	276.	273.	280.	300.
9371	FOUND DEAD ON DAY 10 OF GESTATION			
9372	328.	325.	343.	350.
9373	360.	355.	354.	364.
9374	315.	321.	323.	340.
9375	298.	303.	302.	317.
9376	318.	317.	320.	328.
9377	FOUND DEAD ON DAY 12 OF GESTATION			
9378	354.	331.	327.	356.
9379	302.	298.	303.	323.
9380	301.	306.	308.	307.
9381	FOUND DEAD ON DAY 8 OF GESTATION			
9382	352.	355.	363.	378.
9383	317.	316.	311.	326.
9384	316.	314.	317.	335.
9385	FOUND DEAD ON DAY 7 OF GESTATION			
9387	FOUND DEAD ON DAY 7 OF GESTATION			
9388	FOUND DEAD ON DAY 7 OF GESTATION			
9389	377.	386.	395.	392.
9390	358.	330.	339.	337.

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 4): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DAY	1	2	3	4
RAT #	DOSAGE GROUP IV	RE-1122.01	200 MG/KG/DAY	
9391	FOUND DEAD ON DAY 9 OF GESTATION			
9392	FOUND DEAD ON DAY 10 OF GESTATION			
9393	FOUND DEAD ON DAY 13 OF GESTATION			
9394	274.	265.	264.	275.
9395	313.	300.	296.	326.
9396	NOT PREGNANT			
9397	FOUND DEAD ON DAY 11 OF GESTATION			
9398	304.	303.	315.	322.
9399	FOUND DEAD ON DAY 10 OF GESTATION			
9400	FOUND DEAD ON DAY 10 OF GESTATION			
9401	NOT PREGNANT			
9402	291.	288.	291.	296.
9403	325.	326.	322.	316.
9404	FOUND DEAD ON DAY 8 OF GESTATION			
9405	FOUND DEAD ON DAY 10 OF GESTATION			
9406	321.	329.	323.	334.
9407	FOUND DEAD ON DAY 10 OF GESTATION			
9408	315.	309.	312.	306.
9409	NOT PREGNANT			
9410	327.	328.	335.	338.
9411	271.	282.	284.	290.
9412	301.	289.	300.	323.
9413	FOUND DEAD ON DAY 9 OF GESTATION			
9414	352.	357.	366.	361.
9415	358.	368.	368.	381.
9416	300.	294.	295.	302.
9417	336.	320.	326.	340.
9418	330.	328.	334.	347.
9419	321.	315.	318.	330.
9420	FOUND DEAD ON DAY 11 OF GESTATION			

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 5): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

	DAY 1	2	3	4
RAT #	DOSAGE GROUP V		RE-1123.01	1000 MG/KG/DAY
9421	337.	321.	325.	349.
9422	345.	339.	345.	369.
9423	NOT PREGNANT			
9424	NOT PREGNANT			
9425	360.	345.	346.	366.
9426	315.	320.	320.	343.
9427	304.	302.	312.	320.
9428	306.	307.	309.	325.
9429	281.	270.	273.	284.
9430	284.	293.	290.	315.
9431	293.	301.	294.	299.
9432	348.	352.	358.	349.
9433	313.	313.	307.	310.
9434	321.	321.	317.	336.
9435	307.	328.	336.	355.
9436	298.	294.	305.	317.
9437	314.	300.	306.	303.
9438	349.	351.	358.	362.
9439	379.	378.	383.	394.
9440	285.a	286.	282.	291.
9441	293.	287.	283.	290.
9442	325.	327.	328.	347.
9443b	c	c	290.	SACRIFICED ON DAY 4 OF LACTATION
9444	354.	353.	356.	373.
9445	335.	335.	338.	345.
9446	258.	249.	253.	250.
9447	344.	343.	348.	360.
9448	341.	330.	332.	334.
9449	329.	318.	323.	332.
9450	325.	349.	360.	SACRIFICED ON DAY 3 OF LACTATION

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Rat 9440 delivered one additional pup by day 2 of lactation; value excluded from group averages and statistical analyses.
b. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.
c. Value was not recorded.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C14 (PAGE 6): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS - PART II

DAY	1	2	3	4
RAT #	DOSAGE GROUP VI		RE-1125.01	1000 MG/KG/DAY
9451	348.	331.	332.	350.
9452	312.	312.	315.	334.
9453	306.	284.	289.	301.
9454	334.	337.	341.	353.
9455	NOT PREGNANT			
9456	286.	282.	283.	306.
9457	359.	348.	341.	356.
9458	318.	316.	325.	337.
9459	FOUND DEAD ON DAY 12 OF GESTATION			
9460	396.	388.	395.	388.
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION			
9462	311.	319.	317.	334.
9463	350.	338.	327.	341.
9464	331.	325.	327.	342.
9465	271.	280.	287.	289.
9466	307.	300.	304.	315.
9467	312.	306.	310.	313.
9468	312.	314.	321.	338.
9469	279.	282.	290.	304.
9470	310.	293.	298.	304.
9471	349.	337.	358.	362.
9472	308.	303.	311.	331.
9473	312.	300.	295.	317.
9474	303.	288.	287.	312.
9475	332.	326.	329.	350.
9476	302.	308.	312.	323.
9477	285.	316.	314.	315.
9478	304.	297.	303.	314.
9479	342.	343.	340.	347.
9480	NOT PREGNANT			

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 1): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP I VEHICLE 0 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLAN-TATIONS N
9301	NOT PREGNANT								
9302	23	19	2	21	10	9	10	9	21
9303	24	2	0	2	-	2	-	2	6
9304	22	12	0	12	6	6	6	6	12
9305	23	14	0	14	6	8	6	8	17
9306	23	18(1)	1	19	11	6	11	6	19
9307	23	14	0	14	8	6	8	6	15
9308	23	9	1	10	6	3	6	3	14
9309	23	18	0	18	7	11	7	11	19
9310	23	15	0	15	7	8	7	8	14
9311	23	8	0	8	5	3	5	3	9
9312	23	15	0	15	5	10	5	9	17
9313	23	13	0	13	8	5	8	5	15
9314	23	17	0	17	12	5	12	5	17
9315	22	17	0	17	7	10	7	9	17
9316	23	20	0	20	11	9	11	9	21
9317	23	18	1	19	10	8	10	8	21
9318	23	15	0	15	9	6	8	6	18
9319	23	16	0	16	12	4	12	4	16
9320	23	16(1)	0	16	6	9	6	9	17
9321	23	17(1)	0	17	9	7	9	7	20
9322	24	5(3)	6	12[1]	2	-	2	-	20
9323	23	17	1	18	9	8	8	8	18
9324	22	14	0	14	8	6	8	6	16
9325	23	14	0	14	10	4	10	4	16
9326	23	16	0	16	6	10	6	10	16
9327	23	17	0	17	12	5	12	5	17
9328	23	17	0	17	8	9	8	9	18
9329	23	17	0	17	7	10	7	10	17
9330	22	17(1)	0	17	4	12	4	12	17

M = MALE F = FEMALE
( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.
[ ] = NUMBER OF PUPS IN WHICH CANNIBALIZATION AND/OR AUTOLYSIS PRECLUDED THE DETERMINATION OF VIABILITY.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 2): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP II VEHICLE 0 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLAN-TATIONS N
9331	23	16(1)	0	16	6	9	6	9	18
9332	23	16	0	16	3	13	3	13	16
9333	23	17	0	17	11	6	11	6	17
9334	23	16	0	16	5	11	5	11	16
9335	23	14	0	14	8	6	8	6	15
9336	22	14	0	14	9	5	8	5	14
9337	24	9(9)	2	11	-	-	-	-	18
9338	NOT PREGNANT								
9339	23	15	0	15	12	3	12	3	17
9340	23	16	1	17	11	5	11	5	17
9341	22	19	0	19	11	8	10	8	16
9342	23	18	0	18	9	9	9	8	18
9343	22	15	0	15	6	9	6	9	17
9344	23	19(2)	1	20	11	6	11	6	20
9345	23	16	0	16	6	10	6	10	17
9346	23	14	0	14	7	7	7	7	15
9347	23	17	0	17	10	7	10	7	19
9348	22	18	0	18	12	6	12	6	18
9349	23	18	0	18	8	10	8	10	18
9350	23	14	0	14	9	5	9	5	15
9351	23	15	0	15	8	7	8	7	16
9352	22	16	0	16	10	6	9	6	18
9353	23	15	0	15	7	8	7	8	15
9354	22	13	0	13	10	3	10	3	16
9355	22	17	0	17	9	8	9	8	18
9356	22	19	0	19	5	14	5	14	21
9357	23	18	1	19	6	12	6	12	19
9358	23	16	0	16	10	6	10	6	17
9359	22	13	0	13	6	7	6	7	14
9360a	22	18	0	18	9	9	-	-	18

M = MALE F = FEMALE
( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.
a. Rat 9360 was sacrificed on day 3 of lactation.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 3): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP III RE-0981.05 250 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLAN-TATIONS N
9361	24	7	0	7	6	1	6	1	7
9362	23	13	0	13	8	5	8	5	15
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION								
9364	23	18	0	18	10	8	10	8	18
9365	23	10	1	11	2	8	2	8	11
9366	FOUND DEAD ON DAY 9 OF GESTATION								
9367	FOUND DEAD ON DAY 11 OF GESTATION								
9368	FOUND DEAD ON DAY 8 OF GESTATION								
9369	FOUND DEAD ON DAY 10 OF GESTATION								
9370	23	14	0	14	8	6	8	6	14
9371	FOUND DEAD ON DAY 10 OF GESTATION								
9372	23	16	0	16	10	6	10	6	18
9373	22	16	0	16	9	7	9	7	18
9374	23	17	0	17	10	7	10	6	18
9375	23	17	0	17	10	7	10	7	17
9376	23	17	1	18	8	9	8	9	18
9377	FOUND DEAD ON DAY 12 OF GESTATION								
9378	22	17	0	17	7	10	7	10	17
9379	22	13	0	13	4	9	4	9	16
9380	22	16	0	16	10	6	10	6	16
9381	FOUND DEAD ON DAY 8 OF GESTATION								
9382	23	17	0	17	8	9	8	9	18
9383	22	15	0	15	7	8	7	8	16
9384	23	17(1)	0	17	8	8	8	8	19
9385	FOUND DEAD ON DAY 7 OF GESTATION								
9386	22	14	0	14	6	8	6	8	15
9387	FOUND DEAD ON DAY 7 OF GESTATION								
9388	FOUND DEAD ON DAY 7 OF GESTATION								
9389	23	16	1	17	9	7	9	7	17
9390	22	12	2	14	5	7	4	7	15

M = MALE F = FEMALE
( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 4): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP IV RE-1122.01 200 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLAN-TATIONS N
9391	FOUND DEAD ON DAY 9 OF GESTATION								
9392	FOUND DEAD ON DAY 10 OF GESTATION								
9393	FOUND DEAD ON DAY 13 OF GESTATION								
9394	23	10	0	10	7	3	7	3	13
9395	22	15	0	15	6	9	6	9	17
9396	NOT PREGNANT								
9397	FOUND DEAD ON DAY 11 OF GESTATION								
9398	23	18(2)	0	18	11	5	11	5	14
9399	FOUND DEAD ON DAY 10 OF GESTATION								
9400	FOUND DEAD ON DAY 10 OF GESTATION								
9401	NOT PREGNANT								
9402	23	17	1	18	11	6	11	6	18
9403	22	14	1	15	6	8	6	8	18
9404	FOUND DEAD ON DAY 8 OF GESTATION								
9405	FOUND DEAD ON DAY 10 OF GESTATION								
9406	23	19	0	19	6	13	6	13	20
9407	FOUND DEAD ON DAY 10 OF GESTATION								
9408	23	14	0	14	9	5	9	5	14
9409	NOT PREGNANT								
9410	23	18	0	18	7	11	7	11	18
9411	23	14	0	14	5	9	5	9	14
9412	23	15	0	15	8	7	8	7	18
9413	FOUND DEAD ON DAY 9 OF GESTATION								
9414	23	17	0	17	7	10	7	10	19
9415	23	20	0	20	9	11	9	11	20
9416	22	15(1)	0	15	4	10	4	10	15
9417	23	21	0	21	10	11	10	11	22
9418	23	17	0	17	9	8	9	8	17
9419	23	15(2)	0	15	5	8	5	8	16
9420	FOUND DEAD ON DAY 11 OF GESTATION								

M = MALE F = FEMALE

( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 5): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP V RE-1123.01 1000 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLAN-TATIONS N
9421	23	15	0	15	10	5	10	5	15
9422	23	15	1	16	8	7	8	7	19
9423	NOT PREGNANT								
9424	NOT PREGNANT								
9425	23	14	0	14	6	8	6	8	15
9426	23	17	0	17	6	11	6	11	17
9427	23	18	0	18	9	9	9	9	18
9428	23	16	1	17	10	6	10	6	18
9429	23	16	0	16	6	10	6	10	16
9430	23	19	0	19	6	13	6	13	19
9431	23	15	0	15	8	7	8	7	16
9432	23	16	1	17	10	6	10	6	17
9433	23	19	0	19	8	11	7	11	20
9434	23	14(1)	1	15	2	11	2	11	15
9435	23	13	0	13	7	6	7	6	14
9436	23	14	0	14	7	7	7	7	14
9437	23	15	1	16	9	6	9	6	16
9438	22	17	0	17	12	5	12	5	18
9439	23	18	0	18	6	12	6	12	19
9440	22	17	0	17	7	10	7	9	18
9441	23	9(1)	5	14	6	2	6	2	16
9442	23	17(1)	0	17	6	10	6	10	17
9443a	23	11	0	11	5	6	-	-	13
9444	23	15	0	16[1]	8	7	8	7	19
9445	23	17(1)	0	17	10	6	10	6	16
9446	23	10	0	10	5	5	5	5	12
9447	21	12	0	12	4	8	4	8	15
9448	23	14(1)	1	15	9	4	9	4	15
9449	23	17	1	18	8	9	8	9	18
9450b	24	19(1)	0	19	10	8	-	-	22

M = MALE F = FEMALE
( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.
[ ] = NUMBER OF PUPS IN WHICH CANNIBALIZATION AND/OR AUTOLYSIS PRECLUDED THE DETERMINATION OF VIABILITY.
a. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.
b. Rat 9450 was sacrificed on day 3 of lactation.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C15 (PAGE 6): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS/F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP VI RE-1125.01 1000 MG/KG/DAY

RAT/ LITTER NUMBER	DURATION OF GESTATION (DAYS) N	LITTER DELIVERED LIVE BORN N	STILL-BORN N	TOTAL BORN N	NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM 2 M	2 F	4 M	4 F	TOTAL IMPLANTATIONS N
9451	23	16	0	16	7	9	7	9	18
9452	24	10	0	10	5	5	5	5	18
9453	23	16	0	16	8	8	8	8	16
9454	22	17	0	17	6	11	6	11	18
9455	NOT PREGNANT								
9456	22	16(1)	0	16	9	6	9	6	16
9457	23	12	0	12	7	5	7	5	15
9458	23	16	0	16	6	10	6	10	17
9459	FOUND DEAD ON DAY 12 OF GESTATION								
9460	23	20	0	20	9	11	9	11	21
9461	NOT PREGNANT								
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION								
9462	23	20(1)	0	20	9	10	9	10	20
9463	23	18	0	18	8	10	8	10	19
9464	23	15	0	15	7	8	7	8	16
9465	23	16	0	16	8	8	8	8	16
9466	23	18	0	18	11	7	11	7	18
9467	23	15	0	15	8	7	8	7	17
9468	23	14	0	14	9	5	9	5	17
9469	23	17(2)	0	17	6	9	6	9	18
9470	22	16	0	16	10	6	10	6	16
9471	23	17	0	17	5	12	5	12	17
9472	22	17	0	17	9	8	9	8	18
9473	22	17(1)	0	17	8	8	8	8	17
9474	23	16(1)	0	16	8	7	8	7	17
9475	23	19	1	20	11	8	11	8	21
9476	23	17	0	17	9	8	9	8	20
9477	23	20	0	20	12	8	12	8	18
9478	23	17(1)	1	18	9	7	9	7	18
9479	23	17	0	17	9	8	9	8	17
9480	NOT PREGNANT								

M = MALE F = FEMALE

( ) = NUMBER OF PUPS DYING BEFORE WEIGHING ON DAY 2 POSTPARTUM.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 1): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP I VEHICLE 0 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9301	NOT PREGNANT					
9302	7.9	7.3	7.6	10.0	9.1	9.6
9303	---	8.9	8.9	---	10.4	10.4
9304	6.7	6.5	6.6	8.7	8.4	8.6
9305	8.5	7.9	8.1	11.2	10.4	10.7
9306	7.6	7.1	7.4	9.6	9.2	9.4
9307	7.8	7.4	7.6	9.8	9.7	9.8
9308	7.7	7.3	7.6	9.7	9.5	9.6
9309	7.3	6.8	7.0	9.1	8.5	8.8
9310	8.0	7.6	7.8	9.9	9.7	9.8
9311	8.5	8.1	8.4	11.7	11.0	11.5
9312	8.0	7.2	7.5	10.8	10.1	10.3
9313	7.7	7.5	7.6	10.2	9.8	10.0
9314	7.8	7.3	7.6	9.4	9.2	9.3
9315	5.6	5.4	5.5	5.9	5.6	5.7
9316	6.4	6.4	6.4	7.7	7.5	7.6
9317	8.1	7.7	7.9	10.4	10.0	10.3
9318	8.0	7.5	7.8	10.2	9.5	9.9
9319	7.0	6.6	6.9	9.2	8.5	9.0
9320	7.4	7.2	7.2	9.2	9.2	9.2
9321	6.9	6.7	6.8	8.9	8.6	8.8
9322	7.3	---	7.3	9.4	---	9.4
9323	7.2	6.8	7.0	9.2	9.0	9.1
9324	7.1	6.8	7.0	9.2	8.7	9.0
9325	7.7	7.4	7.6	9.4	9.2	9.3
9326	7.3	7.2	7.3	9.0	8.7	8.8
9327	7.4	7.4	7.4	8.5	8.2	8.4
9328	7.8	7.3	7.6	9.3	8.7	9.0
9329	7.7	7.5	7.6	9.0	9.0	9.0
9330	6.6	6.6	6.6	7.2	7.1	7.1

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 2): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP II VEHICLE 0 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9331	7.4	6.9	7.1	9.6	9.0	9.3
9332	7.1	7.4	7.3	9.0	9.4	9.3
9333	7.4	7.0	7.3	9.4	8.8	9.2
9334	8.0	7.6	7.7	10.1	9.6	9.8
9335	7.0	6.7	6.9	8.7	8.7	8.7
9336	6.8	6.8	6.8	8.8	8.5	8.7
9337	NO SURVIVING PUPS					
9338	NOT PREGNANT					
9339	7.1	7.5	7.2	9.6	10.1	9.7
9340	8.3	7.8	8.1	10.8	10.2	10.6
9341	6.6	6.1	6.4	8.0	7.3	7.7
9342	6.9	6.7	6.8	8.0	7.7	7.9
9343	7.0	7.2	7.1	8.8	8.6	8.7
9344	6.9	6.8	6.9	8.8	8.4	8.7
9345	8.1	7.6	7.7	9.1	8.5	8.7
9346	8.1	7.5	7.8	9.3	8.7	9.0
9347	7.6	6.8	7.3	9.9	8.5	9.3
9348	6.2	6.0	6.1	7.0	7.0	7.0
9349	6.8	6.5	6.6	8.6	8.1	8.3
9350	7.1	6.8	7.0	9.0	8.6	8.9
9351	7.4	6.7	7.1	10.0	9.0	9.6
9352	7.1	6.9	7.0	9.6	9.4	9.5
9353	7.4	7.2	7.3	9.5	9.2	9.4
9354	8.2	7.8	8.1	10.9	10.6	10.8
9355	7.6	7.1	7.4	8.6	8.0	8.3
9356	5.9	5.9	5.9	7.5	7.7	7.6
9357	7.4	7.0	7.2	9.5	8.6	8.9
9358	8.0	7.4	7.8	9.8	9.2	9.6
9359	8.8	8.0	8.4	11.2	10.6	10.9
9360a	10.2	12.7	11.5	----	----	----

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Litter 9360 was sacrificed on day 3 of lactation.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 3): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP III RE-0981.05 250 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9361	10.6	10.7	10.6	13.8	14.0	13.8
9362	7.9	7.2	7.6	9.8	8.7	9.4
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION					
9364	7.9	7.5	7.7	9.1	8.7	8.9
9365	7.8	7.4	7.5	9.7	9.2	9.3
9366	FOUND DEAD ON DAY 9 OF GESTATION					
9367	FOUND DEAD ON DAY 11 OF GESTATION					
9368	FOUND DEAD ON DAY 8 OF GESTATION					
9369	FOUND DEAD ON DAY 10 OF GESTATION					
9370	8.0	7.4	7.7	10.2	9.8	10.0
9371	FOUND DEAD ON DAY 10 OF GESTATION					
9372	8.2	7.5	7.9	10.3	9.7	10.1
9373	7.8	7.6	7.7	10.0	9.7	9.9
9374	8.1	7.8	8.0	10.7	10.2	10.5
9375	7.2	6.9	7.0	9.2	9.0	9.1
9376	7.0	6.9	7.0	8.9	8.7	8.8
9377	FOUND DEAD ON DAY 12 OF GESTATION					
9378	6.7	6.2	6.4	8.2	7.7	7.9
9379	7.9	7.3	7.5	10.7	10.0	10.2
9380	7.0	6.7	6.9	8.6	8.3	8.5
9381	FOUND DEAD ON DAY 8 OF GESTATION					
9382	8.6	8.6	8.6	10.4	10.5	10.5
9383	6.5	6.5	6.5	8.4	8.4	8.4
9384	7.1	6.7	6.9	9.1	8.8	8.9
9385	FOUND DEAD ON DAY 7 OF GESTATION					
9386	6.8	6.3	6.5	8.5	8.0	8.2
9387	FOUND DEAD ON DAY 7 OF GESTATION					
9388	FOUND DEAD ON DAY 7 OF GESTATION					
9389	7.3	7.1	7.2	8.8	8.4	8.6
9390	7.0	7.2	7.1	8.8	8.2	8.4

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 4): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP IV RE-1122.01 200 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2			DAY 4		
	M	F	T	M	F	T
9391	FOUND DEAD ON DAY 9 OF GESTATION					
9392	FOUND DEAD ON DAY 10 OF GESTATION					
9393	FOUND DEAD ON DAY 13 OF GESTATION					
9394	7.7	8.0	7.8	9.3	9.7	9.4
9395	7.0	6.5	6.7	8.5	8.1	8.2
9396	NOT PREGNANT					
9397	FOUND DEAD ON DAY 11 OF GESTATION					
9398	7.0	6.5	6.8	8.2	7.8	8.1
9399	FOUND DEAD ON DAY 10 OF GESTATION					
9400	FOUND DEAD ON DAY 10 OF GESTATION					
9401	NOT PREGNANT					
9402	7.7	7.0	7.5	9.1	8.2	8.8
9403	7.5	7.4	7.4	9.3	9.3	9.3
9404	FOUND DEAD ON DAY 8 OF GESTATION					
9405	FOUND DEAD ON DAY 10 OF GESTATION					
9406	7.8	7.2	7.4	9.8	9.1	9.3
9407	FOUND DEAD ON DAY 10 OF GESTATION					
9408	8.3	8.4	8.3	10.4	10.6	10.5
9409	NOT PREGNANT					
9410	8.4	7.8	8.0	9.9	9.4	9.6
9411	7.2	7.0	7.0	8.6	8.3	8.4
9412	8.4	8.1	8.3	10.4	9.8	10.2
9413	FOUND DEAD ON DAY 9 OF GESTATION					
9414	7.6	7.5	7.6	8.7	8.6	8.6
9415	7.4	7.1	7.2	8.4	8.2	8.3
9416	6.6	6.4	6.4	6.8	6.6	6.7
9417	6.8	7.1	7.0	8.3	8.3	8.3
9418	7.8	7.3	7.5	9.6	8.9	9.3
9419	8.1	7.7	7.8	9.7	9.3	9.4
9420	FOUND DEAD ON DAY 11 OF GESTATION					

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 5): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP V RE-1123.01 1000 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9421	7.7	7.1	7.5	9.5	8.8	9.3
9422	8.1	7.6	7.8	10.2	9.7	10.0
9423	NOT PREGNANT					
9424	NOT PREGNANT					
9425	7.9	7.2	7.5	10.1	9.3	9.6
9426	7.8	7.3	7.5	10.1	9.8	9.9
9427	7.5	7.1	7.3	8.7	8.1	8.4
9428	7.5	6.9	7.2	8.4	7.9	8.2
9429	8.5	8.2	8.3	9.4	8.8	9.1
9430	6.4	6.2	6.3	7.7	7.5	7.6
9431	7.1	6.8	7.0	9.7	9.2	9.4
9432	8.2	7.6	8.0	9.7	8.6	9.3
9433	7.2	6.5	6.8	7.4	6.8	7.0
9434	8.2	7.7	7.8	9.8	9.5	9.5
9435	8.7	8.4	8.6	11.2	10.5	10.9
9436	8.5	8.0	8.3	10.5	9.8	10.1
9437	7.6	7.0	7.3	8.4	8.0	8.2
9438	6.7	6.4	6.6	9.1	8.3	8.8
9439	8.3	8.7	8.6	10.5	11.3	11.0
9440	5.9	5.6	5.7	7.2	6.8	7.0
9441	6.8	6.7	6.8	9.2	9.2	9.2
9442	7.8	7.5	7.6	10.0	9.7	9.8
9443a	---	---	---	----	----	----
9444	9.5	8.5	9.0	12.1	10.8	11.5
9445	8.1	8.1	8.1	10.3	9.8	10.1
9446	9.3	7.7	8.5	10.9	9.3	10.1
9447	7.8	7.0	7.2	10.4	9.6	9.8
9448	8.8	8.7	8.7	10.4	10.1	10.3
9449	8.5	8.0	8.2	9.8	9.2	9.5
9450b	7.7	7.3	7.5	----	----	----

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.
b. Litter 9450 was sacrificed on day 3 of lactation.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 6): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP VI RE-1125.01 1000 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9451	7.8	7.5	7.6	10.0	9.2	9.5
9452	9.5	8.2	8.8	12.1	10.5	11.3
9453	7.6	7.1	7.3	8.4	7.9	8.1
9454	7.0	6.8	6.9	9.1	8.6	8.8
9455	NOT PREGNANT					
9456	7.0	6.6	6.8	9.0	8.4	8.7
9457	8.4	7.3	8.0	10.8	9.3	10.1
9458	9.4	8.8	9.0	11.4	10.5	10.8
9459	FOUND DEAD ON DAY 12 OF GESTATION					
9460	8.0	7.2	7.6	9.8	8.6	9.2
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION					
9462	6.9	6.8	6.9	8.0	7.8	7.9
9463	7.3	6.8	7.0	8.3	7.7	8.0
9464	8.1	7.6	7.8	9.2	9.0	9.1
9465	7.4	6.9	7.1	6.0	5.8	5.9
9466	7.4	6.7	7.1	8.8	7.9	8.4
9467	8.8	8.0	8.4	10.4	9.6	10.0
9468	9.4	8.7	9.2	11.7	10.8	11.4
9469	7.0	6.3	6.6	8.9	8.1	8.4
9470	6.4	5.9	6.2	6.8	6.5	6.7
9471	7.6	6.8	7.0	9.4	8.7	8.9
9472	7.0	6.1	6.6	8.7	7.9	8.3
9473	6.3	6.1	6.2	7.7	7.2	7.5
9474	7.1	6.6	6.9	8.6	7.9	8.3
9475	7.3	6.8	7.1	9.4	8.8	9.2
9476	7.9	7.5	7.7	10.0	9.6	9.8
9477	6.6	6.2	6.4	8.1	7.6	7.9
9478	6.6	6.7	6.6	7.8	7.9	7.9
9479	7.8	7.2	7.5	9.4	8.6	9.0
9480	NOT PREGNANT					

M = MALE F = FEMALE T = TOTAL (SUM OF MALE AND FEMALE LITTER AVERAGES)

ARGUS 9
HBE BTS 0

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C16 (PAGE 6): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS - PART II

MATERNAL DOSAGE GROUP VI RE-1125.01 1000 MG/KG/DAY

RAT/ LITTER NUMBER	DAY 2 M	DAY 2 F	DAY 2 T	DAY 4 M	DAY 4 F	DAY 4 T
9451	7.8	7.5	7.6	10.0	9.2	9.5
9452	9.5	8.2	8.8	12.1	10.5	11.3
9453	7.6	7.1	7.3	8.4	7.9	8.1
9454	7.0	6.8	6.9	9.1	8.6	8.8
9455	NOT PREGNANT					
9456	7.0	6.6	6.8	9.0	8.4	8.7
9457	8.4	7.3	8.0	10.8	9.3	10.1
9458	9.4	8.8	9.0	11.4	10.5	10.8
9459	FOUND DEAD ON DAY 12 OF GESTATION					
9460	8.0	7.2	7.6	9.8	8.6	9.2
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION					
9462	6.9	6.8	6.9	8.0	7.8	7.9
9463	7.3	6.8	7.0	8.3	7.7	8.0
9464	8.1	7.6	7.8	9.2	9.0	9.1
9465	7.4	6.9	7.1	6.0	5.8	5.9
9466	7.4	6.7	7.1	8.8	7.9	8.4
9467	8.8	8.0	8.4	10.4	9.6	10.0
9468	9.4	8.7	9.2	11.7	10.8	11.4
9469	7.0	6.3	6.6	8.9	8.1	8.4
9470	6.4	5.9	6.2	6.8	6.5	6.7
9471	7.6	6.8	7.0	9.4	8.7	8.9
9472	7.0	6.1	6.6	8.7	7.9	8.3
9473	6.3	6.1	6.2	7.7	7.2	7.5
9474	7.1	6.6	6.9	8.6	7.9	8.3
9475	7.3	6.8	7.1	9.4	8.8	9.2
9476	7.9	7.5	7.7	10.0	9.6	9.8
9477	6.6	6.2	6.4	8.1	7.6	7.9
9478	6.6	6.7	6.6	7.8	7.9	7.9
9479	7.8	7.2	7.5	9.4	8.6	9.0
9480	NOT PREGNANT					

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 1): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP I					VEHICLE				0 MG/KG/DAY				POSTPARTUM DAY 2						
9301	NOT PREGNANT																			
9302	8.4	7.9	7.8	6.8	7.8	7.2	8.2	7.5	8.6	8.9	MS	US	8.0	6.5	7.0	6.5	7.2	7.6	7.4	7.8
	8.1																			
9303	9.1	8.7																		
9304	6.5	7.2	6.8	6.6	6.7	6.4	6.5	6.2	6.7	6.7	6.6	6.4								
9305	8.0	8.9	8.3	8.3	8.8	8.6	8.0	8.5	7.8	8.2	7.9	7.2	7.6	7.7						
9306	7.7	8.5	6.9	7.7	6.1	7.5	8.1	7.8	7.7	7.5	7.6	MM 2	7.2	7.0	7.5	7.3	6.1	7.3	FS	
9307	7.6	8.0	8.4	7.3	7.8	7.9	7.2	8.0	7.1	7.1	7.7	7.3	7.7	7.4						
9308	7.9	8.9	7.3	7.6	7.5	7.0	MS	7.5	6.5	7.9										
9309	7.9	7.5	7.2	7.0	6.5	7.7	7.4	7.5	7.8	6.6	6.6	6.8	6.6	6.8	7.5	5.3	6.3	6.9		
9310	8.1	8.2	8.1	7.3	8.1	8.0	8.0	8.2	7.5	6.9	7.2	7.2	7.8	7.6	8.3					
9311	8.6	8.8	9.2	7.7	8.3	8.3	7.9	8.1												
9312	8.0	7.8	8.2	8.4	7.8	7.2	6.8	7.6	5.5	7.9	7.2	7.6	7.0	8.7	6.9					
9313	7.9	7.5	7.8	7.6	7.7	7.5	7.9	7.9	7.8	7.5	7.1	7.6	7.6							
9314	7.9	7.2	8.2	8.3	7.5	8.0	8.4	7.5	7.4	7.2	7.6	8.1	7.0	7.6	7.4	7.0	7.4			
9315	5.2	5.8	6.2	4.9	6.3	5.8	5.4	5.8	5.7	5.5	5.4	5.3	4.6	5.5	5.9	5.9	4.8			
9316	6.2	6.4	6.9	5.9	6.8	6.5	6.5	6.5	6.8	6.0	6.4	6.2	7.3	6.6	6.3	5.7	6.5	6.3	6.5	5.9
9317	7.8	7.5	7.8	8.2	8.5	8.7	7.6	8.8	8.3	7.8	7.4	7.4	7.5	7.4	7.8	8.2	7.7	7.9	FS	
9318	8.7	6.9	7.9	8.8	7.9	9.0	7.3	8.7	6.9	7.0	7.5	7.1	7.2	8.4	7.7					
9319	6.9	6.6	6.8	7.2	7.0	7.2	7.0	7.3	7.0	7.5	6.9	7.2	6.7	6.3	6.9	6.5				
9320	7.4	7.1	7.5	7.7	7.3	7.3	6.9	7.3	7.0	6.9	7.1	7.6	6.8	7.4	7.4	FD 1				
9321	7.6	7.0	6.9	7.5	6.7	7.1	7.3	4.7	7.3	MD 2	6.6	6.4	6.3	6.9	6.5	6.8	7.2			
9322	6.9	7.7	MS	MS	MD 1	MD 1	MD 1	MU	FS	FS	FS	FS								
9323	6.4	7.7	7.3	6.9	6.8	7.1	7.8	7.4	7.2	6.6	6.5	6.9	6.6	7.4	6.6	7.8	5.6	FS		
9324	7.6	6.9	6.9	6.7	6.7	7.4	7.3	7.0	6.7	6.9	7.2	6.6	7.1	6.5						
9325	7.7	7.5	8.2	7.5	7.5	7.8	8.3	7.6	7.4	7.6	7.9	7.1	7.4	7.1						
9326	7.6	7.8	6.6	7.9	7.3	6.7	6.8	7.7	7.4	7.4	7.4	7.8	6.9	7.1	6.8	7.0				
9327	7.1	7.9	7.3	7.4	7.0	7.5	7.7	7.4	7.0	7.7	8.4	6.9	7.3	7.5	7.5	7.7	7.1			
9328	7.6	8.2	7.6	8.0	8.2	7.3	7.8	8.0	7.5	7.9	7.0	7.4	7.6	7.1	6.9	7.3	7.4			
9329	7.5	7.8	7.5	7.0	8.4	7.9	7.8	7.6	7.2	7.6	7.8	7.3	7.2	7.3	8.0	7.3	7.4			
9330	7.0	6.2	6.4	6.9	7.0	6.5	5.9	6.6	6.8	6.5	6.8	7.0	6.1	6.4	6.8	6.8	FD 1			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 2): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP II						VEHICLE				0 MG/KG/DAY			POSTPARTUM DAY 2						
9331	7.2	7.6	7.4	7.6	7.3	7.6	MD 1	6.8	6.2	7.4	6.8	7.1	6.9	6.7	7.5	7.1				
9332	7.3	6.8	7.2	7.8	7.2	7.4	7.5	7.3	7.1	7.3	7.3	7.6	7.9	7.0	8.0	6.8				
9333	7.4	7.9	7.1	8.0	7.3	7.7	7.4	7.3	7.6	7.2	7.0	7.5	7.1	6.8	7.1	6.6	7.2			
9334	8.4	7.8	7.8	7.9	8.1	7.7	7.6	7.6	7.4	7.1	7.2	7.5	8.5	7.6	7.5	7.9				
9335	7.6	7.3	6.4	6.8	6.5	7.3	7.4	7.0	6.1	7.3	6.6	7.2	6.4	6.5						
9336	7.5	7.2	6.7	7.0	6.9	5.6	6.8	6.9	6.9	6.9	6.9	6.7	6.7	6.8						
9337	NO SURVIVING PUPS AFTER DAY 1 POSTPARTUM																			
9338	NOT PREGNANT																			
9339	7.6	6.6	7.0	6.8	7.2	7.3	7.7	6.3	7.2	6.6	7.6	7.8	7.6	7.6	7.2					
9340	8.6	9.0	7.8	8.3	8.6	8.3	8.0	8.4	7.8	8.5	7.8	7.9	7.9	8.4	7.6	7.3	FS			
9341	6.0	6.2	7.0	6.4	7.0	6.8	6.5	6.8	6.5	7.0	6.1	6.2	5.6	5.7	5.8	6.6	6.6	6.6	5.9	
9342	6.6	7.4	7.3	6.6	7.3	6.8	6.3	7.0	7.0	6.6	6.7	6.5	6.0	6.3	7.5	6.8	7.0	6.6		
9343	7.5	7.4	7.2	7.3	7.4	5.1	7.4	7.5	7.1	7.3	7.1	7.3	6.4	7.3	7.5					
9344	7.1	6.9	7.1	6.6	7.0	6.8	6.5	7.2	7.1	6.4	7.6	6.6	7.3	6.6	6.7	6.7	6.7	FM 2	FD 1	FS
9345	7.4	8.1	8.2	8.0	8.1	8.6	8.2	7.6	7.8	7.7	7.3	7.2	7.9	7.7	6.9	7.2				
9346	7.8	8.2	8.1	7.9	8.3	8.0	8.5	7.7	7.9	7.5	7.3	7.2	7.8	7.0						
9347	7.6	8.4	6.6	7.1	8.0	7.8	7.5	8.2	7.6	7.6	7.4	7.1	7.3	6.2	7.6	6.1	6.0			
9348	7.0	6.1	6.0	6.1	6.2	6.1	6.2	6.4	5.8	6.4	6.2	6.2	6.1	6.0	5.7	5.8	6.2	6.0		
9349	6.4	7.1	7.1	6.8	6.6	6.5	7.2	7.1	6.3	6.2	6.8	6.8	6.4	6.3	6.6	6.6	6.2	6.6		
9350	8.0	7.4	6.7	6.6	7.4	7.1	6.9	6.7	7.5	6.4	6.8	6.2	7.3	7.4						
9351	7.5	7.3	7.4	7.1	8.0	7.1	7.6	7.6	7.3	7.1	7.1	6.9	7.0	6.0	5.8					
9352	7.7	6.9	6.8	6.6	7.6	6.7	7.5	7.3	7.0	7.0	6.7	6.4	7.1	6.5	7.0	7.7				
9353	7.5	7.5	7.9	7.0	7.7	7.3	7.1	6.9	7.4	6.8	7.3	6.9	7.6	7.3	7.6					
9354	7.7	8.7	8.6	8.3	8.7	8.1	7.7	8.1	8.0	8.0	7.6	7.7	8.1							
9355	7.6	8.7	8.3	6.5	7.2	7.7	7.0	7.6	7.7	7.2	6.8	7.3	7.3	7.1	6.9	7.7	6.6			
9356	6.0	6.4	6.1	5.4	5.7	6.5	6.0	5.7	5.7	6.2	5.7	6.2	6.1	5.8	5.8	6.1	6.1	5.7	5.6	
9357	8.1	6.8	7.2	7.7	6.7	8.2	7.6	6.6	6.5	7.2	7.3	5.9	6.9	7.5	7.9	6.8	7.7	6.8	FS	
9358	7.1	8.4	7.4	8.4	8.2	7.3	7.7	8.4	8.6	8.7	7.3	7.9	6.9	7.8	7.1	7.3				
9359	8.8	8.9	8.8	8.7	9.2	8.2	7.6	8.3	7.6	7.5	8.2	8.7	8.2							
9360	6.4	6.6	6.2	6.6	13.2	13.0	13.3	13.4	13.4	11.5	12.8	12.9	12.6	13.2	13.0	12.8	12.3	13.2		

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 3): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP III						RE-0981.05			250 MG/KG/DAY				POSTPARTUM DAY 2						
9361	9.9	10.2	11.1	10.8	10.9	10.6	10.7													
9362	7.9	7.6	8.2	7.6	8.2	8.0	8.5	7.2	6.8	7.4	7.1	6.9	7.8							
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION																			
9364	8.1	7.2	7.5	8.3	8.4	8.6	7.8	7.8	7.6	7.6	7.2	7.6	8.0	7.4	7.5	6.7	7.5	8.1		
9365	7.9	7.7	MS	7.7	7.5	7.1	7.9	7.2	7.3	7.2	7.1									
9366	FOUND DEAD ON DAY 9 OF GESTATION																			
9367	FOUND DEAD ON DAY 11 OF GESTATION																			
9368	FOUND DEAD ON DAY 8 OF GESTATION																			
9369	FOUND DEAD ON DAY 10 OF GESTATION																			
9370	7.3	7.4	8.4	7.4	8.1	8.6	8.5	7.9	7.1	7.3	7.2	7.8	8.3	6.9						
9371	FOUND DEAD ON DAY 10 OF GESTATION																			
9372	7.3	7.3	8.4	8.6	8.4	8.7	8.0	8.7	8.4	7.8	7.8	7.5	7.0	7.7	7.3	7.7				
9373	7.4	7.7	7.8	8.4	7.8	8.3	8.1	7.4	7.6	7.4	6.6	8.0	8.5	7.8	7.4	7.4				
9374	9.0	8.3	8.4	8.1	8.2	7.1	8.7	7.1	7.7	8.7	7.9	7.8	7.6	6.4	8.1	8.0	8.5			
9375	7.1	6.7	6.8	7.6	7.4	7.4	7.1	6.4	7.5	7.5	6.7	7.2	6.8	7.3	6.5	6.7	7.2			
9376	7.5	7.1	7.1	7.4	6.1	7.5	6.8	6.8	7.4	6.6	6.7	6.6	7.5	6.8	7.2	6.8	6.6	FS		
9377	FOUND DEAD ON DAY 12 OF GESTATION																			
9378	6.8	6.6	6.8	7.0	6.3	6.5	6.8	6.0	6.4	6.6	6.5	6.2	6.4	5.8	6.4	6.3	5.8			
9379	7.7	8.2	7.7	8.0	6.6	7.5	7.0	7.3	8.1	7.7	7.5	6.7	7.5							
9380	7.3	7.4	7.3	6.3	6.9	7.4	7.0	6.8	6.7	7.0	6.2	6.9	6.7	6.9	6.7	6.7				
9381	FOUND DEAD ON DAY 8 OF GESTATION																			
9382	8.9	8.2	8.8	8.0	9.1	8.3	9.4	7.8	8.5	8.7	7.5	8.5	9.2	8.3	8.8	8.8	9.0			
9383	6.2	7.2	6.6	6.3	5.7	7.4	6.3	6.4	6.9	6.2	6.7	6.1	6.5	6.5	6.4					
9384	6.9	7.5	6.8	7.0	7.2	6.9	7.0	7.4	7.0	6.3	6.7	6.4	6.5	6.6	6.8	7.4	FD 2			
9385	FOUND DEAD ON DAY 7 OF GESTATION																			
9386	6.9	6.6	6.7	7.0	6.6	6.7	6.5	6.0	6.5	6.7	6.3	6.0	6.3	6.4						
9387	FOUND DEAD ON DAY 7 OF GESTATION																			
9388	FOUND DEAD ON DAY 7 OF GESTATION																			
9389	7.7	7.4	7.8	7.1	6.7	7.4	6.5	7.9	7.3	7.2	7.2	7.1	6.9	7.1	6.8	7.4	FS			
9390	3.9	8.2	6.9	8.2	MS	8.0	6.9	7.1	6.9	6.9	8.0	7.8	6.8	FS						

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 4): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP IV						RE-1122.01			200 MG/KG/DAY				POSTPARTUM DAY 2						
9391	FOUND DEAD ON DAY 9 OF GESTATION																			
9392	FOUND DEAD ON DAY 10 OF GESTATION																			
9393	FOUND DEAD ON DAY 13 OF GESTATION																			
9394	5.9	7.8	7.1	8.4	8.0	8.6	7.9	8.0	8.0	7.9										
9395	7.0	7.0	6.4	7.0	7.1	7.4	6.8	6.2	6.6	6.6	6.8	5.9	6.4	7.0	6.1					
9396	NOT PREGNANT																			
9397	FOUND DEAD ON DAY 11 OF GESTATION																			
9398	7.2	7.4	7.2	6.7	7.1	5.8	7.0	7.2	7.0	6.4	7.9	MM 2	MD 1	6.3	6.5	7.0	6.2	6.3		
9399	FOUND DEAD ON DAY 10 OF GESTATION																			
9400	FOUND DEAD ON DAY 10 OF GESTATION																			
9401	NOT PREGNANT																			
9402	7.6	7.5	7.7	8.1	7.9	7.8	7.7	7.7	7.9	7.2	7.9	MS	6.7	7.2	6.9	7.3	6.8	7.0		
9403	7.0	7.8	7.2	7.1	8.0	8.0	MS	7.9	7.7	7.3	7.5	7.8	7.2	6.7	7.0					
9404	FOUND DEAD ON DAY 8 OF GESTATION																			
9405	FOUND DEAD ON DAY 10 OF GESTATION																			
9406	7.2	7.8	7.9	7.4	8.8	8.0	6.2	7.7	7.3	8.3	7.1	7.3	7.1	6.9	7.3	7.3	7.5	7.4	6.5	
9407	FOUND DEAD ON DAY 10 OF GESTATION																			
9408	8.3	9.1	8.8	8.5	8.9	8.9	6.3	7.5	8.4	8.9	8.3	8.7	6.9	9.1						
9409	NOT PREGNANT																			
9410	8.7	8.2	9.1	8.8	7.9	8.4	8.1	8.0	7.8	7.7	7.8	8.5	8.0	7.5	8.1	7.5	7.1	7.3		
9411	7.7	7.3	6.6	7.2	7.2	7.0	6.9	6.3	7.3	6.6	7.7	7.0	7.0	6.9						
9412	8.0	8.4	8.8	8.7	8.7	8.0	8.0	8.8	8.4	8.2	8.3	7.8	7.7	8.1	8.4					
9413	FOUND DEAD ON DAY 9 OF GESTATION																			
9414	7.5	7.9	7.4	7.5	8.1	7.6	7.5	8.0	7.7	7.9	7.5	7.4	7.0	7.2	7.5	7.1	7.9			
9415	8.2	7.0	7.0	6.6	7.5	7.0	7.7	8.1	8.0	6.1	7.0	6.0	7.0	7.5	8.0	7.5	7.9	7.3	7.2	6.5
9416	6.3	7.0	6.7	6.4	6.2	6.1	5.8	6.5	6.5	6.3	6.3	6.7	6.4	6.7	FM 2					
9417	7.6	7.6	6.8	7.0	6.4	6.2	6.2	6.9	6.5	6.6	7.1	7.0	6.7	6.9	7.1	7.6	7.4	6.8	7.4	7.5
	7.0																			
9418	8.5	7.4	7.5	8.2	7.8	7.2	7.4	7.7	8.3	7.0	7.0	7.6	7.3	7.4	8.1	6.3	7.4			
9419	8.3	7.5	8.5	8.0	8.3	MM 2	MM 2	7.0	7.7	7.9	7.9	8.0	7.8	7.3	7.7					
9420	FOUND DEAD ON DAY 11 OF GESTATION																			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
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NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 5): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP V						RE-1123.01			1000 MG/KG/DAY				POSTPARTUM DAY 2						
9421	7.8	7.5	7.7	8.2	7.5	7.1	7.5	7.3	8.0	8.2	7.1	7.8	6.8	7.2	6.8					
9422	8.3	9.0	8.2	7.4	7.5	7.6	8.1	8.5	7.4	7.4	8.0	7.3	7.8	7.9	7.3	FS				
9423	NOT PREGNANT																			
9424	NOT PREGNANT																			
9425	8.4	7.7	7.6	7.8	7.9	8.2	6.9	7.3	7.1	7.3	6.9	7.5	7.1	7.8						
9426	8.0	7.8	7.7	7.6	8.6	7.4	7.6	7.1	6.8	7.4	7.4	7.0	7.2	7.4	7.6	7.7	7.4			
9427	7.9	7.6	7.3	7.9	7.9	7.4	7.5	7.0	7.2	6.1	7.3	7.5	7.4	6.7	7.6	7.6	6.6	7.5		
9428	8.2	7.8	7.2	7.3	7.8	7.6	7.5	7.2	7.4	6.7	MS	6.8	7.0	6.9	7.0	6.7	6.9			
9429	9.3	8.8	7.5	8.3	8.5	8.6	8.0	6.3	8.9	7.5	8.6	8.1	8.9	8.4	8.7	8.4				
9430	6.6	6.8	5.6	6.5	6.3	6.5	6.1	5.6	6.6	5.7	6.4	6.2	6.3	6.6	7.0	5.6	6.0	6.3	6.4	
9431	7.4	7.6	7.0	6.6	6.9	7.2	7.4	7.0	7.3	6.3	7.2	6.8	6.7	6.9	6.3					
9432	8.2	8.2	8.0	8.0	7.6	8.1	8.3	8.5	8.6	8.5	8.6	6.0	7.3	7.2	8.6	7.8	FS			
9433	6.7	6.7	7.1	7.6	6.8	7.6	7.7	7.2	7.3	6.4	6.2	6.4	6.2	6.0	6.9	5.5	6.2	7.0	7.1	
9434	8.1	8.4	7.9	7.3	7.9	8.0	7.6	7.7	8.2	7.7	7.1	8.0	7.7	FD 1	FS					
9435	9.0	9.1	8.9	8.5	8.6	8.7	8.3	8.3	8.1	8.2	8.1	8.9	8.5							
9436	8.3	7.8	8.5	9.1	8.5	8.4	8.8	8.5	8.3	7.9	9.0	7.0	7.8	7.8						
9437	7.5	7.2	7.6	7.8	7.7	7.7	7.7	7.0	7.8	7.8	6.9	6.5	7.1	7.4	6.8	7.3				
9438	6.3	6.6	7.6	7.3	6.8	6.2	6.5	7.2	6.3	6.6	6.4	7.1	6.2	6.2	6.1	6.6	6.9			
9439	7.9	8.6	7.7	8.8	8.3	8.6	9.2	9.1	8.6	8.6	7.8	9.7	7.8	9.1	8.2	8.9	9.3	8.0		
9440	6.1	6.3	5.9	5.7	5.9	5.5	6.0	5.6	5.5	5.8	5.7	5.9	5.2	5.7	5.7	5.7	5.2			
9441	6.8	7.1	6.9	6.5	6.8	6.6	MS	MS	MS	6.7	6.7	FS	FD 1	FS						
9442	7.5	8.6	7.6	7.4	7.8	7.9	MD 1	7.7	7.3	8.1	7.7	6.7	7.5	6.9	7.9	7.8	7.5			
9443a	MX 4	MX 4	MX 4	MX 4	MX 4	FX 4	FX 4	FX 4	FX 4	FX 4	FX 4									
9444	9.6	9.7	9.3	9.5	9.7	9.6	10.1	8.7	9.1	9.8	9.6	6.8	6.7	8.2	9.4	UU				
9445	9.7	7.6	7.9	9.1	8.4	8.3	8.1	7.8	5.9	8.5	8.6	8.0	8.6	8.1	7.7	7.4	FD 1			
9446	10.0	9.1	9.4	8.8	9.0	8.0	7.0	8.0	7.8	7.9										
9447	7.7	7.1	8.2	8.1	7.2	6.0	7.4	6.9	7.4	7.3	6.7	7.1								
9448	9.3	9.2	8.5	8.6	9.1	8.5	8.6	8.1	8.9	MS	8.5	8.5	8.5	9.2	FM 2					
9449	8.3	8.8	8.8	8.4	8.4	8.5	8.2	8.5	7.8	8.0	8.3	8.5	7.6	8.2	7.9	7.9	8.0	FS		
9450	7.6	8.0	7.4	7.5	8.2	7.8	7.7	7.8	7.1	8.0	MD 2	6.7	7.2	7.5	6.9	7.6	7.0	8.2	7.3	

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.
a. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 6): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP VI						RE-1125.01			1000 MG/KG/DAY				POSTPARTUM DAY 2						
9451	7.4	7.4	7.8	8.5	7.9	7.8	7.8	7.5	7.2	7.8	7.7	7.2	7.3	7.2	7.8	7.6				
9452	9.6	9.8	9.8	9.2	8.9	9.2	8.9	9.4	8.3	5.3										
9453	8.1	7.2	6.4	7.9	7.9	7.5	7.5	8.0	7.3	7.0	7.3	6.9	6.9	7.0	7.2	7.2				
9454	6.9	6.6	6.8	7.0	7.6	7.1	7.2	6.8	6.7	6.9	6.9	6.3	6.9	6.8	7.0	7.1	6.2			
9455	NOT PREGNANT																			
9456	7.3	7.0	6.6	6.8	7.3	6.6	7.3	7.4	6.9	MM 2	7.1	7.0	5.6	6.5	6.8	6.4				
9457	8.7	9.3	8.2	7.9	8.6	8.2	8.2	7.3	6.5	7.9	7.8	7.1								
9458	10.9	9.5	9.0	8.3	9.8	9.2	8.9	9.0	8.9	8.6	8.1	9.0	9.1	8.6	9.0	8.9				
9459	FOUND DEAD ON DAY 12 OF GESTATION																			
9460	8.7	8.5	8.4	7.6	8.3	7.8	7.9	7.0	7.8	7.6	7.5	7.0	7.3	7.5	7.2	6.5	7.4	6.5	7.8	7.0
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION																			
9462	6.4	6.9	7.2	7.5	7.4	7.3	6.8	6.6	6.4	7.2	7.7	6.8	6.8	6.7	5.9	6.8	6.9	6.8	6.9	FD 2
9463	7.4	7.2	7.2	7.4	8.1	7.1	6.8	7.3	7.5	6.7	7.0	7.7	6.6	6.3	6.3	6.4	6.9	6.4		
9464	7.6	9.0	8.3	7.9	7.8	8.0	7.9	8.2	7.7	6.6	7.7	7.7	8.0	7.7	6.8					
9465	7.5	7.5	7.1	6.6	7.3	7.9	7.1	7.8	7.3	5.9	7.8	6.0	7.6	6.4	7.2	6.7				
9466	7.2	7.0	6.9	8.0	7.8	7.3	8.1	7.8	6.8	7.0	7.6	7.2	6.2	6.0	6.5	6.7	7.0	7.2		
9467	8.7	9.0	9.2	6.1	8.8	9.0	10.1	9.1	8.4	8.0	8.3	9.1	8.3	8.2	6.1					
9468	10.4	10.4	10.2	10.0	9.8	8.5	8.5	8.4	8.3	9.6	8.6	8.3	9.2	7.9						
9469	7.3	6.4	7.4	7.0	7.0	6.6	6.2	5.9	5.7	6.6	6.7	5.6	7.1	6.6	6.3	FM 2	FD 2			
9470	6.5	6.2	6.1	6.7	6.6	6.2	6.5	6.6	6.0	6.2	5.8	6.0	6.1	6.0	5.6	6.0				
9471	7.7	7.4	7.8	7.4	7.7	7.1	6.7	6.0	6.0	6.8	7.5	7.1	7.1	6.4	6.5	7.2	6.6			
9472	7.5	6.7	7.3	7.2	6.7	7.2	6.5	6.8	7.1	6.7	6.5	6.6	6.2	6.0	5.5	5.5	6.1			
9473	6.0	6.6	6.5	6.6	6.3	5.5	6.6	6.4	5.9	6.2	6.1	5.9	6.0	6.4	6.0	6.2	FM 2			
9474	7.2	5.2	6.3	8.4	7.1	7.4	7.7	7.3	4.4	6.9	6.9	6.7	6.6	8.0	7.1	FD 2				
9475	7.7	7.7	7.4	6.9	7.5	7.9	6.7	6.5	7.2	7.3	7.9	7.3	7.7	6.5	7.1	6.9	6.8	7.4	FS	4.9
9476	7.9	8.1	8.1	8.1	7.8	7.5	7.7	7.4	8.2	7.6	7.6	7.8	7.3	7.2	7.7	7.2	7.3			
9477	6.5	6.3	6.3	6.0	7.0	6.7	7.6	6.9	6.3	5.9	6.4	6.7	6.2	6.3	6.8	6.4	6.3	6.4	5.3	6.1
9478	7.0	6.7	7.0	5.9	7.5	6.3	6.4	6.7	6.2	MM 2	6.6	6.1	6.5	6.9	6.9	6.8	7.0	FS		
9479	8.0	7.8	8.0	7.7	8.0	7.0	8.1	7.7	7.7	7.5	7.5	7.6	6.3	7.5	7.1	7.1	6.7			
9480	NOT PREGNANT																			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 7): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP I					VEHICLE				0 MG/KG/DAY				POSTPARTUM DAY 4						
9301	NOT PREGNANT																			
9302	9.7	9.3	11.1	10.5	10.0	10.0	11.2	8.2	10.6	9.5	MS	US	10.2	9.4	9.3	8.2	8.7	10.2	8.8	9.1
	8.0																			
9303	10.0	10.8																		
9304	8.7	8.1	8.5	8.9	9.4	8.6	8.1	9.0	8.7	8.0	8.6	8.3								
9305	11.2	11.4	11.3	10.9	10.8	11.5	10.3	9.8	10.5	11.5	10.4	10.8	10.1	9.4						
9306	10.7	9.6	9.8	9.5	9.8	10.2	8.8	9.7	10.0	9.8	7.8	MM 2	9.5	9.8	9.4	9.4	9.1	7.8	FS	
9307	10.4	9.2	9.8	9.4	10.1	9.9	9.8	9.8	10.0	9.3	9.5	9.2	9.8	10.4						
9308	10.0	8.7	8.9	9.6	11.2	9.6	MS	10.2	8.4	10.0										
9309	9.7	9.4	9.7	8.5	8.0	8.8	9.5	8.2	9.3	8.8	8.5	8.2	7.2	8.3	9.2	7.6	10.0	8.6		
9310	9.7	9.5	10.2	9.0	10.2	10.0	10.5	9.7	9.2	9.0	10.3	9.3	9.8	9.8	10.7					
9311	12.2	10.4	11.6	12.6	11.8	11.3	11.1	10.7												
9312	10.4	10.5	10.6	11.7	10.8	9.6	10.2	10.0	9.1	11.4	10.8	9.6	10.2	9.8	FD 4					
9313	9.8	9.9	10.2	10.6	10.6	10.4	10.2	9.5	9.4	9.8	9.9	10.2	9.8							
9314	9.4	10.2	9.4	8.9	9.1	9.5	9.2	9.0	9.8	9.6	9.0	9.2	8.9	9.2	8.7	9.7	9.3			
9315	6.3	5.7	6.9	5.8	5.4	5.3	5.7	5.5	5.6	5.7	5.9	5.0	6.4	4.9	6.4	4.9	FM 3			
9316	8.3	6.9	8.0	7.4	8.5	7.7	7.4	7.0	7.5	8.1	7.6	7.3	7.7	6.9	7.6	7.8	6.8	7.3	7.7	8.8
9317	11.2	10.1	10.0	10.1	9.9	11.4	10.5	10.6	9.9	10.8	10.3	9.7	10.2	10.8	10.0	9.6	9.6	10.2	FS	
9318	10.5	9.4	11.5	9.1	10.4	9.9	11.5	9.2	MD 4	9.8	9.0	8.6	9.4	10.4	10.0					
9319	9.5	8.5	9.4	9.7	9.2	9.4	9.4	9.5	8.6	8.4	9.7	8.5	8.0	8.6	8.7	8.8				
9320	8.9	9.7	9.6	8.8	9.1	8.9	9.8	9.5	8.8	8.8	9.3	8.9	8.9	9.4	9.7	FD 1				
9321	9.6	9.5	9.3	9.4	10.0	8.9	6.1	8.2	9.2	MD 2	9.4	9.0	8.6	8.2	8.8	8.4	7.9			
9322	8.5	10.2	MS	MS	MD 1	MD 1	MD 1	MU	FS	FS	FS	FS								
9323	9.7	9.2	9.9	8.3	9.2	8.6	8.7	9.7	MD 3	8.9	7.5	10.1	8.7	9.5	9.3	8.9	8.9	FS		
9324	9.1	9.4	8.8	9.5	8.7	8.9	8.9	10.0	8.7	9.2	8.3	8.5	8.8	8.8						
9325	9.3	8.8	10.3	9.3	9.6	8.6	9.4	9.9	9.0	9.3	8.9	8.8	9.6	9.3						
9326	7.8	8.8	8.8	9.8	9.1	9.5	9.0	8.0	8.3	8.3	8.7	9.1	8.9	9.3	8.9	8.9				
9327	8.1	8.1	8.4	8.9	8.9	9.7	8.5	8.4	8.1	8.6	8.1	7.9	8.4	8.3	7.5	8.5	8.2			
9328	9.4	9.8	9.8	9.1	8.9	9.0	9.3	9.4	8.5	9.5	8.9	8.5	8.5	8.2	9.3	8.9	8.1			
9329	9.2	9.1	7.4	9.2	9.6	8.9	9.6	9.0	9.8	8.8	8.6	8.3	9.3	9.4	8.2	9.3	9.3			
9330	7.6	6.9	7.7	6.5	7.3	7.7	6.4	7.2	7.1	6.2	7.6	7.5	6.5	6.9	7.4	7.6	FD 1			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 8): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP II						VEHICLE				0 MG/KG/DAY			POSTPARTUM DAY 4						
9331	10.0	9.4	9.6	9.4	9.9	9.6	MD 1	8.2	9.2	8.9	9.6	9.8	9.3	9.0	8.8	8.5				
9332	9.2	8.8	8.9	8.7	9.8	9.9	8.6	8.7	9.5	9.9	10.0	9.7	9.7	9.4	10.0	8.4				
9333	10.4	8.9	9.6	9.7	9.6	10.2	8.7	9.0	9.1	9.1	8.9	8.8	9.3	9.0	8.8	8.4	8.8			
9334	10.0	9.7	10.3	10.8	9.9	10.0	10.0	9.2	9.2	10.5	10.0	9.0	9.8	9.2	8.9	9.6				
9335	8.3	9.0	8.2	8.7	9.0	8.9	8.6	9.2	8.6	9.2	8.2	9.3	8.5	8.6						
9336	8.8	9.2	8.6	9.3	8.7	8.5	8.8	8.7	MD 3	8.6	8.5	8.3	8.5	8.5						
9337	NO SURVIVING PUPS AFTER DAY 1 POSTPARTUM																			
9338	NOT PREGNANT																			
9339	9.9	9.4	9.3	9.4	9.9	8.9	10.5	9.6	9.1	10.1	8.8	10.1	9.9	10.5	10.0					
9340	10.6	11.6	11.2	10.9	10.0	11.0	10.2	10.6	10.9	10.9	10.7	9.7	10.5	10.6	9.6	10.4	FS			
9341	8.8	7.7	8.1	7.8	7.6	8.7	7.7	8.1	8.6	7.3	MM 4	8.0	7.2	8.0	7.1	7.0	7.4	6.8	6.9	
9342	8.2	8.6	8.0	8.5	8.3	7.1	7.0	8.0	8.5	7.3	8.2	7.8	8.0	7.4	7.5	6.9	8.8	FM 3		
9343	9.6	9.6	9.6	6.3	8.8	9.1	9.0	8.0	9.0	9.2	9.1	7.9	8.9	8.8	7.9					
9344	8.7	8.6	9.6	8.8	7.9	8.9	9.4	8.9	8.7	8.7	8.7	8.3	8.2	8.5	9.2	8.0	8.2	FM 2	FD 1	FS
9345	9.3	8.9	9.2	8.8	9.2	9.1	8.5	9.3	8.9	8.8	7.7	8.0	7.9	9.2	8.4	8.3				
9346	9.0	8.9	9.5	8.9	9.6	10.0	9.1	8.9	9.3	8.5	8.3	8.6	9.0	8.4						
9347	8.8	9.7	10.3	9.7	10.1	11.3	10.4	9.6	9.7	9.5	9.6	9.2	7.7	7.2	8.9	8.2	9.0			
9348	8.3	6.3	6.7	7.9	7.2	6.9	6.9	6.8	6.5	6.8	7.8	6.3	7.1	6.6	7.0	7.7	6.7	6.9		
9349	8.0	8.0	8.3	8.6	9.1	9.7	8.6	8.3	8.5	7.6	7.6	7.6	8.8	8.4	8.0	7.9	8.8	7.9		
9350	10.4	9.6	8.5	8.9	9.4	9.2	8.3	8.0	8.9	7.8	8.9	8.2	9.2	9.0						
9351	9.6	11.0	9.9	10.0	10.1	9.2	10.1	10.0	7.8	9.5	9.4	8.2	9.0	9.7	9.8					
9352	9.6	10.3	9.3	9.7	8.5	10.3	9.2	10.0	9.3	MM 3	8.8	9.8	8.6	9.3	9.6	10.0				
9353	9.8	9.5	9.1	9.3	10.2	9.7	8.9	8.7	10.5	9.5	9.6	9.1	8.5	8.9	9.1					
9354	11.1	10.9	11.9	10.5	10.6	10.7	9.8	11.4	11.0	10.9	10.8	10.5	10.5							
9355	8.2	7.9	9.4	9.0	8.6	7.3	9.6	8.9	8.7	8.2	8.0	8.1	7.6	8.2	7.8	8.4	7.9			
9356	7.7	6.9	8.2	8.1	6.5	8.1	8.1	7.2	8.1	7.5	7.6	8.2	8.1	8.0	7.0	7.6	7.2	7.5	7.1	
9357	9.5	9.1	9.8	9.7	9.1	9.8	9.2	8.4	9.3	9.2	8.4	9.0	8.2	8.5	8.2	8.3	9.5	7.7	FS	
9358	10.6	11.0	10.4	8.1	10.0	9.6	10.5	9.6	9.3	9.1	10.2	8.9	8.9	9.8	8.6	8.6				
9359	11.7	11.2	11.2	10.3	11.4	11.4	11.5	10.9	11.0	10.3	10.8	9.8	9.7							
9360	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3		

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 9): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP III						RE-0981.05			250 MG/KG/DAY				POSTPARTUM DAY 4						
9361	14.1	14.1	13.9	13.5	12.7	14.4	14.0													
9362	9.0	9.4	9.6	10.4	9.8	9.6	10.0	10.5	8.3	8.9	8.5	9.2	8.7							
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION																			
9364	8.2	8.8	10.3	9.7	8.8	9.0	8.5	9.6	9.0	9.4	8.6	8.8	8.6	9.4	9.0	9.1	8.2	8.0		
9365	9.6	9.8	MS	9.4	9.0	9.5	8.2	8.9	9.2	10.1	9.3									
9366	FOUND DEAD ON DAY 9 OF GESTATION																			
9367	FOUND DEAD ON DAY 11 OF GESTATION																			
9368	FOUND DEAD ON DAY 8 OF GESTATION																			
9369	FOUND DEAD ON DAY 10 OF GESTATION																			
9370	8.8	11.1	10.6	11.1	10.6	10.1	9.8	9.7	10.9	10.2	9.5	9.1	9.1	9.7						
9371	FOUND DEAD ON DAY 10 OF GESTATION																			
9372	10.6	11.2	8.9	9.7	10.7	11.0	10.7	10.1	9.8	10.6	9.6	10.0	9.9	9.0	10.0	9.5				
9373	10.1	10.7	9.8	10.2	9.3	10.4	9.4	9.9	10.5	9.8	10.9	10.1	9.6	9.3	8.5	9.7				
9374	10.9	10.1	10.6	11.3	9.5	9.4	12.0	11.0	10.7	11.4	9.5	10.9	10.4	9.9	10.8	9.8	FD 3			
9375	8.3	9.5	9.6	9.4	9.1	9.2	8.7	9.5	9.5	8.9	8.6	8.6	9.3	9.1	8.8	8.8	9.6			
9376	9.8	8.5	10.0	8.9	8.0	7.8	8.9	9.1	9.3	8.0	8.7	9.0	8.7	9.4	8.7	7.8	8.5	FS		
9377	FOUND DEAD ON DAY 12 OF GESTATION																			
9378	8.7	8.6	8.1	8.0	8.1	8.1	8.1	7.3	7.5	8.5	7.4	7.8	7.7	7.4	7.9	7.7	7.7			
9379	9.8	10.9	11.2	10.9	10.0	10.4	9.1	9.8	9.9	10.5	9.8	9.2	11.1							
9380	8.8	8.5	9.1	8.5	7.9	8.7	8.4	9.3	8.1	8.8	8.0	8.9	7.8	8.6	8.3	8.3				
9381	FOUND DEAD ON DAY 8 OF GESTATION																			
9382	9.8	11.4	10.1	10.5	9.7	11.5	10.6	9.7	10.6	11.2	10.1	11.0	11.0	10.9	9.9	9.1	10.8			
9383	8.7	7.5	8.1	8.3	9.0	7.9	9.1	7.9	7.9	8.3	8.1	8.4	8.6	8.6	9.1					
9384	8.6	9.8	9.0	9.1	8.7	8.6	9.0	9.8	8.7	9.3	8.5	8.8	8.5	8.0	8.7	9.8	FD 2			
9385	FOUND DEAD ON DAY 7 OF GESTATION																			
9386	8.7	8.2	8.2	8.7	8.3	8.7	8.0	7.9	8.3	8.1	8.2	7.7	7.6	8.2						
9387	FOUND DEAD ON DAY 7 OF GESTATION																			
9388	FOUND DEAD ON DAY 7 OF GESTATION																			
9389	8.8	8.1	9.2	7.9	9.2	9.3	9.3	8.7	8.6	8.7	8.9	8.4	8.1	8.7	8.2	7.8	FS			
9390	9.2	9.2	9.1	7.6	MS	MM 4	8.9	8.2	7.6	9.3	7.5	8.5	7.8	FS						

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 10): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP IV						RE-1122.01			200 MG/KG/DAY				POSTPARTUM DAY 4						
9391	FOUND DEAD ON DAY 9 OF GESTATION																			
9392	FOUND DEAD ON DAY 10 OF GESTATION																			
9393	FOUND DEAD ON DAY 13 OF GESTATION																			
9394	9.3	9.9	10.5	10.3	9.4	8.7	7.0	9.9	9.7	9.6										
9395	7.8	8.6	8.8	8.1	9.3	8.3	7.9	7.5	8.2	8.2	8.5	7.6	8.5	7.6	8.6					
9396	NOT PREGNANT																			
9397	FOUND DEAD ON DAY 11 OF GESTATION																			
9398	8.2	7.1	7.7	8.4	8.8	8.7	8.2	8.1	7.8	8.4	8.6	MM 2	MD 1	7.9	8.0	8.2	7.8	7.3		
9399	FOUND DEAD ON DAY 10 OF GESTATION																			
9400	FOUND DEAD ON DAY 10 OF GESTATION																			
9401	NOT PREGNANT																			
9402	9.0	9.8	9.0	8.6	9.3	9.1	9.3	8.5	9.5	8.6	9.2	MS	8.1	8.7	8.3	7.7	7.7	8.6		
9403	8.5	9.9	8.8	8.8	9.3	10.5	MS	8.6	8.9	10.1	8.9	10.3	9.4	8.7	9.3					
9404	FOUND DEAD ON DAY 8 OF GESTATION																			
9405	FOUND DEAD ON DAY 10 OF GESTATION																			
9406	10.5	9.1	9.6	8.9	10.0	10.7	9.4	8.8	8.5	8.6	9.5	9.5	8.6	9.1	8.9	9.5	9.6	9.4	8.8	
9407	FOUND DEAD ON DAY 10 OF GESTATION																			
9408	10.8	11.6	11.3	9.7	10.6	10.9	11.3	11.2	6.4	10.9	10.8	10.9	11.6	8.7						
9409	NOT PREGNANT																			
9410	9.4	9.8	10.0	9.9	11.6	10.2	8.7	9.4	9.2	10.3	9.5	9.2	9.2	9.0	9.6	9.0	10.1	9.3		
9411	8.8	8.0	8.6	8.5	8.9	7.7	7.2	9.2	8.7	8.7	8.0	9.2	7.3	8.9						
9412	10.8	10.9	9.6	10.0	10.5	11.0	10.2	10.6	9.8	9.5	10.1	10.2	9.3	9.6	10.3					
9413	FOUND DEAD ON DAY 9 OF GESTATION																			
9414	8.6	8.5	8.8	8.8	8.4	8.2	9.5	8.7	8.8	9.0	7.4	8.3	8.2	8.7	7.8	9.4	9.5			
9415	8.6	9.8	8.1	7.8	9.0	9.3	7.1	7.8	8.6	7.4	7.4	9.1	9.1	8.4	7.1	8.6	8.7	7.8	8.2	8.5
9416	7.4	7.4	6.4	6.2	7.1	6.5	6.8	6.4	6.6	6.7	5.6	7.2	6.7	6.8	FM 2					
9417	7.4	8.8	9.1	7.8	7.9	7.8	8.2	8.8	8.6	8.2	8.0	7.6	8.4	8.6	8.3	8.8	8.7	7.5	8.3	8.0
	8.8																			
9418	8.8	10.0	9.2	10.4	9.3	9.4	10.0	10.1	9.0	8.8	8.8	9.2	7.6	9.1	9.8	9.7	8.4			
9419	10.0	9.6	10.0	9.2	9.8	MM 2	MM 2	9.5	8.7	9.3	9.6	9.4	8.7	9.2	9.8					
9420	FOUND DEAD ON DAY 11 OF GESTATION																			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 11): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP V						RE-1123.01			1000 MG/KG/DAY				POSTPARTUM DAY 4						
9421	10.3	9.8	9.1	9.6	9.1	9.4	9.6	9.5	9.5	9.5	8.7	8.6	9.0	9.5	8.3					
9422	11.2	9.9	9.9	9.8	9.8	10.5	9.4	10.9	9.7	9.0	10.2	9.7	10.0	9.5	10.0	FS				
9423	NOT PREGNANT																			
9424	NOT PREGNANT																			
9425	9.9	9.6	10.1	9.8	10.6	10.6	9.6	9.6	9.2	9.4	9.2	9.1	9.0	9.0						
9426	11.3	9.4	9.8	10.4	9.9	9.6	9.7	10.7	9.2	10.8	10.3	9.4	10.3	9.8	8.7	9.8	9.1			
9427	8.9	8.5	8.9	9.1	8.7	8.5	8.7	7.9	9.1	8.7	8.7	8.3	7.8	6.9	8.2	8.3	8.3	8.0		
9428	9.1	8.5	8.5	7.9	7.6	7.8	8.9	8.4	9.0	8.6	MS	7.7	8.1	8.0	7.8	8.2	7.5			
9429	9.9	9.5	8.4	9.8	9.8	9.1	9.6	6.9	8.7	9.8	9.1	9.1	9.3	9.5	9.2	7.3				
9430	7.7	7.4	7.9	6.8	8.0	8.6	7.8	7.8	7.5	7.5	8.2	7.6	8.2	6.6	7.3	6.3	8.0	6.7	7.7	
9431	9.9	9.5	9.3	9.5	9.7	9.7	10.2	9.5	9.0	8.8	10.4	9.4	8.6	9.2	9.0					
9432	10.1	9.1	10.3	9.7	9.1	10.5	9.5	9.4	10.3	9.2	8.4	8.3	9.7	8.9	10.2	6.4	FS			
9433	6.9	7.9	7.2	7.6	7.4	7.2	7.8	MD 4	6.7	7.5	6.7	6.0	7.2	6.3	6.8	7.5	7.1	6.8	5.7	
9434	9.6	9.9	9.8	9.3	9.9	9.3	10.0	9.1	9.2	8.6	9.4	9.7	10.0	FD 1	FS					
9435	11.7	11.6	11.1	11.2	10.8	11.3	10.8	10.1	10.5	10.3	10.2	10.7	11.3							
9436	10.8	10.7	10.2	10.6	11.0	10.2	10.1	10.3	9.7	10.2	9.7	8.7	10.5	9.3						
9437	8.4	7.8	8.5	8.3	8.1	8.5	8.8	8.9	MS	8.5	8.4	8.2	7.5	8.5	7.5	7.9				
9438	9.3	9.3	8.5	9.4	9.3	8.3	9.2	8.0	9.8	9.5	8.8	9.6	7.6	9.1	8.8	8.1	8.0			
9439	11.0	9.6	10.9	9.9	10.0	11.8	11.4	11.8	11.0	11.2	11.9	10.6	11.8	11.7	11.1	10.8	11.1	10.9		
9440	7.6	6.9	7.8	6.2	7.4	7.3	7.2	7.0	6.7	7.0	7.1	6.4	6.3	7.2	6.8	6.3	FM 3			
9441	8.5	9.2	9.0	9.8	9.5	9.1	MS	MS	MS	9.1	9.3	FS	FD 1	FS						
9442	9.7	10.6	9.3	10.4	10.3	9.6	MD 1	9.8	9.4	9.0	10.0	9.9	9.8	9.6	10.4	9.0	10.1			
9443a	MX 4	MX 4	MX 4	MX 4	MX 4	FX 4	FX 4	FX 4	FX 4	FX 4	FX 4									
9444	11.8	11.8	12.7	13.1	12.3	12.2	12.6	10.3	12.0	11.4	11.6	9.0	9.9	8.6	13.3	UU				
9445	10.7	7.8	11.0	9.8	12.3	10.0	10.7	10.8	9.4	10.9	9.8	10.9	10.4	9.2	10.5	8.1	FD 1			
9446	11.1	11.6	10.7	10.5	10.8	9.7	9.1	9.5	9.6	8.4										
9447	11.0	10.4	10.7	9.4	9.5	9.9	8.9	8.6	9.4	9.9	10.3	10.2								
9448	10.4	11.2	10.8	10.2	10.3	10.0	10.7	9.7	10.4	MS	10.2	9.7	10.2	10.3	FM 2					
9449	9.7	9.5	9.9	9.7	10.5	9.3	9.8	10.0	9.4	9.8	9.0	9.1	8.9	9.3	9.6	9.0	9.0	FS		
9450	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MD 2	MX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.
a. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C17 (PAGE 12): PUP BODY WEIGHTS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	21	22	23																	
RAT/ LITTER #	MATERNAL DOSAGE GROUP VI						RE-1125.01				1000 MG/KG/DAY					POSTPARTUM DAY 4				
9451	9.7	10.1	10.7	10.3	10.0	9.5	9.8	8.5	10.0	9.3	9.0	8.8	9.1	9.4	9.7	8.8				
9452	11.6	12.6	11.4	12.2	12.5	11.5	11.8	10.2	6.1	12.7										
9453	8.3	8.9	7.7	8.6	8.2	9.0	8.4	7.7	8.0	8.4	8.0	7.3	7.9	7.9	8.1	7.8				
9454	8.9	8.2	8.7	10.2	9.0	9.4	8.6	8.5	9.6	8.6	8.5	8.9	8.9	8.8	8.5	7.8	7.9			
9455	NOT PREGNANT																			
9456	8.8	9.2	8.4	8.8	9.4	8.9	9.2	9.8	8.5	MM 2	9.1	8.6	9.0	6.9	8.6	8.0				
9457	11.6	10.9	10.4	10.0	11.0	11.4	10.0	8.9	9.1	8.3	10.1	9.9								
9458	11.0	9.8	10.7	11.6	13.4	11.8	10.4	11.2	10.6	10.7	10.6	9.4	10.2	10.7	10.2	10.7				
9459	FOUND DEAD ON DAY 12 OF GESTATION																			
9460	10.1	9.8	10.4	9.5	9.7	9.9	10.0	8.8	10.4	8.9	9.2	7.3	8.2	8.9	8.7	9.0	9.0	8.8	8.4	8.4
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION																			
9462	8.8	8.0	7.6	7.5	8.1	7.6	7.9	8.3	8.4	6.7	8.2	8.0	8.0	7.6	7.3	8.2	7.6	7.4	8.5	FD 2
9463	8.4	8.2	7.8	9.2	7.7	8.8	8.3	8.2	7.5	6.6	7.6	7.0	7.6	8.7	8.2	7.2	8.5	7.9		
9464	8.7	9.2	10.0	9.3	9.1	9.4	9.0	8.0	9.6	8.0	10.1	9.1	8.9	9.4	8.7					
9465	6.2	5.7	5.4	6.5	6.1	5.8	6.2	6.4	5.5	5.2	5.0	6.9	6.9	5.3	5.5	6.0				
9466	8.7	9.0	7.9	8.1	8.4	9.0	8.4	9.3	8.9	9.7	8.9	8.0	7.5	7.5	8.7	7.8	7.5	8.1		
9467	10.8	10.8	10.4	10.7	11.9	10.7	7.1	11.0	10.4	9.8	10.9	10.4	9.4	9.8	6.3					
9468	12.3	10.9	11.2	12.7	12.2	10.6	12.7	12.6	10.5	10.1	12.4	10.9	10.2	10.4						
9469	8.8	9.4	8.7	8.8	8.0	9.8	7.6	8.4	7.4	9.8	8.4	8.8	7.2	7.4	7.8	FM 2	FD 2			
9470	7.7	7.1	6.4	6.5	7.1	6.1	6.9	6.7	7.0	6.9	6.2	6.2	6.7	6.7	6.4	6.8				
9471	9.7	9.2	9.1	9.6	9.6	7.5	9.4	8.7	8.3	8.2	8.7	9.0	8.8	8.9	9.1	9.2	8.4			
9472	8.5	8.6	7.9	9.4	9.2	8.7	8.7	8.5	8.9	8.2	7.1	7.8	8.6	8.7	7.1	7.8	8.1			
9473	7.9	6.6	7.6	8.3	8.2	8.1	7.4	7.6	7.4	8.0	6.7	6.8	7.2	7.4	7.3	7.0	FM 2			
9474	8.7	6.3	9.0	7.9	9.1	8.4	9.4	9.9	7.6	9.1	8.4	8.3	5.1	8.8	8.1	FD 2				
9475	10.3	9.9	9.8	9.6	8.8	8.8	10.5	9.0	8.8	10.1	8.4	9.2	6.1	8.9	9.3	9.4	9.2	10.0	FS	8.0
9476	10.1	9.5	10.1	9.7	10.5	9.9	9.9	10.1	10.7	9.5	9.9	9.3	9.0	9.3	9.9	9.6	10.2			
9477	8.2	7.3	8.7	8.6	8.1	7.7	9.0	8.2	8.2	7.5	6.5	9.0	7.6	7.4	8.6	8.0	7.9	7.4	7.3	6.6
9478	7.6	8.6	6.8	8.8	6.9	8.2	7.8	7.6	8.0	MM 2	7.7	8.1	7.8	8.0	8.4	7.4	8.1	FS		
9479	9.0	9.7	9.5	10.0	9.8	9.9	8.2	9.7	9.2	8.1	8.6	9.0	8.3	8.5	9.5	7.6	8.9			
9480	NOT PREGNANT																			

ALL WEIGHTS WERE RECORDED IN GRAMS (G).
FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 1): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP I							VEHICLE						0 MG/KG/DAY									
9301	NOT PREGNANT																						
9302	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M S	U S	F A	F A	F A	F A	F A	F A	F A	F A	F A		
9303	F A	F A																					
9304	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A											
9305	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A									
9306	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	MM 2	F A	F A	F A	F A	F A	F A	F S				
9307	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A									
9308	M A	M A	M A	M A	M A	M A	M S	F A	F A	F A													
9309	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9310	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9311	M A	M A	M A	M A	M A	F A	F A	F A															
9312	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FD 4								
9313	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A										
9314	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A					
9315	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FM 3						
9316	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A		
9317	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F S			
9318	M A	M A	M A	M A	M A	M A	M A	M A	MD 4	F A	F A	F A	F A	F A	F A								
9319	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A						
9320	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FD 1							
9321	M A	M A	M A	M A	M A	M A	M A	M A	M A	MD 2	F A	F A	F A	F A	F A	F A	F A						
9322	M A	M A	M S	M S	MD 1	MD 1	MD 1	M U	F S	F S	F S	F S											
9323	M A	M A	M A	M A	M A	M A	M A	M A	MD 3	F A	F A	F A	F A	F A	F A	F A	F A	F S					
9324	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A									
9325	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A									
9326	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9327	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A					
9328	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9329	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9330	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FD 1						

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 2): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP II							VEHICLE						0 MG/KG/DAY									
9331	M A	M A	M A	M A	M A	M A	MD 1	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9332	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9333	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A					
9334	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9335	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A									
9336	M A	M A	M A	M A	M A	M A	M A	M A	MD 3	F A	F A	F A	F A	F A									
9337	M S	MD 1	MD 1	MD 1	MD 1	F S	FD 1	FD 1	FD 1	FD 1	FD 1												
9338	NOT PREGNANT																						
9339	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A									
9340	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F S						
9341	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	MM 4	F A	F A	F A	F A	F A	F A	F A	F A	F A			
9342	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	FM 3				
9343	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9344	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	FM 2	FD 1	F S		
9345	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9346	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A									
9347	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A				
9348	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A				
9349	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9350	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A							
9351	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A							
9352	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	MM 3	F A	F A	F A	F A	F A	F A	F A					
9353	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A							
9354	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A									
9355	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9356	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A		
9357	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F S		
9358	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A					
9359	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A										
9360	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3					

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 3): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP III							RE-0981.05					250 MG/KG/DAY										
9361	M A	M A	M A	M A	M A	M A	F A																
9362	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A										
9363	FOUND DEAD ON DAY 8 OF PRESUMED GESTATION																						
9364	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A					
9365	M A	M A	M S	F A	F A	F A	F A	F A	F A	F A	F A												
9366	FOUND DEAD ON DAY 9 OF GESTATION																						
9367	FOUND DEAD ON DAY 11 OF GESTATION																						
9368	FOUND DEAD ON DAY 8 OF GESTATION																						
9369	FOUND DEAD ON DAY 10 OF GESTATION																						
9370	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A								
9371	FOUND DEAD ON DAY 10 OF GESTATION																						
9372	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A						
9373	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A						
9374	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	FD 3					
9375	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A					
9376	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F S				
9377	FOUND DEAD ON DAY 12 OF GESTATION																						
9378	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9379	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A										
9380	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A						
9381	FOUND DEAD ON DAY 8 OF GESTATION																						
9382	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9383	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A							
9384	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	FD 2					
9385	FOUND DEAD ON DAY 7 OF GESTATION																						
9386	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A									
9387	FOUND DEAD ON DAY 7 OF GESTATION																						
9388	FOUND DEAD ON DAY 7 OF GESTATION																						
9389	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F S					
9390	M A	M A	M A	M A	M S	MM 4	F A	F A	F A	F A	F A	F A	F A	F S									

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 4): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP IV							RE-1122.01					200 MG/KG/DAY										
9391	FOUND DEAD ON DAY 9 OF GESTATION																						
9392	FOUND DEAD ON DAY 10 OF GESTATION																						
9393	FOUND DEAD ON DAY 13 OF GESTATION																						
9394	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A					
9395	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A	
9396	NOT PREGNANT																						
9397	FOUND DEAD ON DAY 11 OF GESTATION																						
9398	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	M	2	M	D	1	F	A	F	A	F	A	F	A
9399	FOUND DEAD ON DAY 10 OF GESTATION																						
9400	FOUND DEAD ON DAY 10 OF GESTATION																						
9401	NOT PREGNANT																						
9402	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	S	F	A	F	A	F	A	F	A	F	A
9403	M	A	M	A	M	A	M	A	M	S	F	A	F	A	F	A	F	A	F	A	F	A	F	A				
9404	FOUND DEAD ON DAY 8 OF GESTATION																						
9405	FOUND DEAD ON DAY 10 OF GESTATION																						
9406	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
9407	FOUND DEAD ON DAY 10 OF GESTATION																						
9408	M	A	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A						
9409	NOT PREGNANT																						
9410	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
9411	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A								
9412	M	A	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A				
9413	FOUND DEAD ON DAY 9 OF GESTATION																						
9414	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A		
9415	M	A	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
9416	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	M	2					
9417	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A	F	A
9418	M	A	M	A	M	A	M	A	M	A	M	A	M	A	F	A	F	A	F	A	F	A	F	A				
9419	M	A	M	A	M	A	M	M	2	M	M	2	F	A	F	A	F	A	F	A	F	A						
9420	FOUND DEAD ON DAY 11 OF GESTATION																						

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 5): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP V							RE-1123.01				1000 MG/KG/DAY											
9421	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A							
9422	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F S							
9423	NOT PREGNANT																						
9424	NOT PREGNANT																						
9425	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A								
9426	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9427	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9428	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M S	F A	F A	F A	F A	F A	F A					
9429	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A						
9430	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9431	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A								
9432	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F S						
9433	M A	M A	M A	M A	M A	M A	M A	MD 4	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9434	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FD 1	F S							
9435	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A									
9436	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A									
9437	M A	M A	M A	M A	M A	M A	M A	M A	M S	M A	F A	F A	F A	F A	F A								
9438	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A						
9439	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9440	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FM 3						
9441	M A	M A	M A	M A	M A	M A	M S	M S	M S	F A	F A	F S	FD 1	F S									
9442	M A	M A	M A	M A	M A	M A	MD 1	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9443a	MX 4	MX 4	MX 4	MX 4	MX 4	FX 4	FX 4	FX 4	FX 4	FX 4	FX 4												
9444	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	U U							
9445	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	FD 1							
9446	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A													
9447	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A											
9448	M A	M A	M A	M A	M A	M A	M A	M A	M A	M S	F A	F A	F A	F A	FM 2								
9449	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F S							
9450	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MX 3	MD 2	MX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3	FX 3				

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.
a. Rat 9443 was sacrificed on day 4 of lactation (day 1 of lactation was incorrectly identified); values excluded from group averages and statistical analyses.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C18 (PAGE 6): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
RAT/ LITTER #	MATERNAL DOSAGE GROUP VI							RE-1125.01				1000 MG/KG/DAY											
9451	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9452	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A													
9453	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A							
9454	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A						
9455	NOT PREGNANT																						
9456	M A	M A	M A	M A	M A	M A	M A	M A	M A	MM 2	F A	F A	F A	F A	F A	F A							
9457	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A											
9458	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A							
9459	FOUND DEAD ON DAY 12 OF GESTATION																						
9460	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A			
9461	FOUND DEAD ON DAY 12 OF PRESUMED GESTATION																						
9462	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	FD 2			
9463	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A					
9464	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A								
9465	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A							
9466	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A						
9467	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A								
9468	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A									
9469	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	FM 2	FD 2							
9470	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A							
9471	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A	F A						
9472	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A						
9473	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	FM 2							
9474	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	FD 2								
9475	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F S	F A				
9476	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A							
9477	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A	F A	F A				
9478	M A	M A	M A	M A	M A	M A	M A	M A	MM 2	F A	F A	F A	F A	F A	F A	F A	F S						
9479	M A	M A	M A	M A	M A	M A	M A	M A	F A	F A	F A	F A	F A	F A	F A								
9480	NOT PREGNANT																						

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED), X-SACRIFICED
NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C19 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 4 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
I 0 VEHICLE	9313	2-4	1/13 PUPS: PORTION OF TAIL BLACK.b
	9315	3	1/17 PUPS: BACK, LESION (3.0 X 0.5 CM).
		4	1/16 PUPS: BACK, LESION (3.0 X 0.5 CM).b
	9330	2	1/16 PUPS: WHITE AREA SURROUNDING GENITALIA.
II 0 VEHICLE	9354	1-4	1/13 PUPS: PORTION OF TAIL MISSING.
III 250 RE-0981.05	----	-	
IV 200 RE-1122.01	----	-	
V 1000 RE-1123.01	9440	1	1/16 PUPS: MUZZLE, PURPLE.
		2	1/17c PUPS: MUZZLE, PURPLE.
VI 1000 RE-1125.01	9474	1	2/16 PUPS: MUZZLE, PURPLE.
		2	1/16 PUPS: MUZZLE, PURPLE.
		3	1/15 PUPS: MUZZLE, PURPLE.

a. Tabulation restricted to adverse observations; all other pups appeared normal.
b. Observation confirmed at necropsy.
c. One additional pup found on day 2 postpartum.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
I 0 VEHICLE	9302	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL. 1 PUP: STILLBORN.
		4	ALL PUPS APPEARED NORMAL.
	9303	4	ALL PUPS APPEARED NORMAL.
	9304	4	ALL PUPS APPEARED NORMAL.
	9305	4	ALL PUPS APPEARED NORMAL.
	9306	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9307	4	ALL PUPS APPEARED NORMAL.
	9308	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9309	4	ALL PUPS APPEARED NORMAL.
	9310	4	ALL PUPS APPEARED NORMAL.
	9311	4	ALL PUPS APPEARED NORMAL.
	9312	4	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL. ALL OTHER PUPS APPEARED NORMAL.
	9313	4	ALL PUPS APPEARED NORMAL.
	9314	4	ALL PUPS APPEARED NORMAL.
	9315	4	ALL PUPS APPEARED NORMAL.
	9316	4	ALL PUPS APPEARED NORMAL.
	9317	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9318	4	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL. ALL OTHER PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
I (cont.) 0 VEHICLE	9319	4	ALL PUPS APPEARED NORMAL.
	9320	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH.
		4	ALL PUPS APPEARED NORMAL.
	9321	2	1 PUP: FOUND DEAD. NO MILK IN STOMACH.
		4	ALL PUPS APPEARED NORMAL.
	9322	1	6 PUPS: STILLBORN. 3 PUPS: FOUND DEAD.
		4	ALL PUPS APPEARED NORMAL.
	9323	1	1 PUP: STILLBORN.
		3	1 PUP: FOUND DEAD. NO MILK IN STOMACH.
	9324	4	ALL PUPS APPEARED NORMAL.
	9325	4	ALL PUPS APPEARED NORMAL.
	9326	4	ALL PUPS APPEARED NORMAL.
	9327	4	ALL PUPS APPEARED NORMAL.
	9328	4	ALL PUPS APPEARED NORMAL.
	9329	4	ALL PUPS APPEARED NORMAL.
	9330	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH.
		4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
II 0 VEHICLE	9331	1	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9332	4	ALL PUPS APPEARED NORMAL.
	9333	4	ALL PUPS APPEARED NORMAL.
	9334	4	ALL PUPS APPEARED NORMAL.
	9335	4	ALL PUPS APPEARED NORMAL.
	9336	3	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9337	1	2 PUPS: STILLBORN. ALL TISSUES APPEARED NORMAL. 9 PUPS: FOUND DEAD. NO MILK IN STOMACH.
	9339	4	ALL PUPS APPEARED NORMAL.
	9340	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9341	4	ALL PUPS APPEARED NORMAL.
	9342	4	ALL PUPS APPEARED NORMAL.
	9343	4	ALL PUPS APPEARED NORMAL.
	9344	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL. 1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
II (cont.) 0 VEHICLE	9345	4	ALL PUPS APPEARED NORMAL.
	9346	4	ALL PUPS APPEARED NORMAL.
	9347	4	ALL PUPS APPEARED NORMAL.
	9348	4	ALL PUPS APPEARED NORMAL.
	9349	4	ALL PUPS APPEARED NORMAL.
	9350	4	ALL PUPS APPEARED NORMAL.
	9351	4	ALL PUPS APPEARED NORMAL.
	9352	4	ALL PUPS APPEARED NORMAL.
	9353	4	ALL PUPS APPEARED NORMAL.
	9354	4	ALL PUPS APPEARED NORMAL.
	9355	4	ALL PUPS APPEARED NORMAL.
	9356	4	ALL PUPS APPEARED NORMAL.
	9357	1	1 PUP: STILLBORN. ALL TISUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9358	4	ALL PUPS APPEARED NORMAL.
	9359	4	ALL PUPS APPEARED NORMAL.
	9360	3	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 5): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
III 250 RE-0981.05	9361	4	ALL PUPS APPEARED NORMAL.
	9362	4	ALL PUPS APPEARED NORMAL.
	9364	4	ALL PUPS APPEARED NORMAL.
	9365	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9370	4	ALL PUPS APPEARED NORMAL.
	9372	4	ALL PUPS APPEARED NORMAL.
	9373	4	ALL PUPS APPEARED NORMAL.
	9374	3	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9375	4	ALL PUPS APPEARED NORMAL.
	9376	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9378	4	ALL PUPS APPEARED NORMAL.
	9379	4	ALL PUPS APPEARED NORMAL.
	9380	4	ALL PUPS APPEARED NORMAL.
	9382	4	ALL PUPS APPEARED NORMAL.
	9383	4	ALL PUPS APPEARED NORMAL.
	9384	2	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9386	4	ALL PUPS APPEARED NORMAL.
	9389	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9390	1	2 PUPS: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 6): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
IV 200 RE-1122.01	9394	4	ALL PUPS APPEARED NORMAL.
	9395	4	ALL PUPS APPEARED NORMAL.
	9398	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9402	1	1 PUP: STILLBORN. DEFECT IN SKULL. NO APPARENT BRAIN TISSUE VISIBLE (0.5 CM IN DIAMETER).
		4	ALL PUPS APPEARED NORMAL.
	9403	1	1 PUP: STILLBORN.
		4	ALL PUPS APPEARED NORMAL.
	9406	4	ALL PUPS APPEARED NORMAL.
	9408	4	1 PUP: LIVER, MULTIPLE TAN AREAS (PINPOINT TO 0.4 CM IN DIAMETER). ALL OTHER TISSUES APPEARED NORMAL. ALL OTHER PUPS APPEARED NORMAL.
	9410	4	ALL PUPS APPEARED NORMAL.
	9411	4	ALL PUPS APPEARED NORMAL.
	9412	4	ALL PUPS APPEARED NORMAL.
	9414	4	ALL PUPS APPEARED NORMAL.
	9415	4	ALL PUPS APPEARED NORMAL.
	9416	4	ALL PUPS APPEARED NORMAL.
	9417	4	ALL PUPS APPEARED NORMAL.
	9418	4	ALL PUPS APPEARED NORMAL.
	9419	4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 7): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
V 1000 RE-1123.01	9421	4	ALL PUPS APPEARED NORMAL.
	9422	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9425	4	ALL PUPS APPEARED NORMAL.
	9426	4	ALL PUPS APPEARED NORMAL.
	9427	4	ALL PUPS APPEARED NORMAL.
	9428	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9429	4	ALL PUPS APPEARED NORMAL.
	9430	4	ALL PUPS APPEARED NORMAL.
	9431	4	ALL PUPS APPEARED NORMAL.
	9432	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9433	4	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL. ALL OTHER PUPS APPEARED NORMAL.
	9434	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL. 1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9435	4	ALL PUPS APPEARED NORMAL.
	9436	4	ALL PUPS APPEARED NORMAL.
	9437	1	1 PUP: STILLBORN.
		4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 8): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
V (cont.) 1000 RE-1123.01	9438	4	ALL PUPS APPEARED NORMAL.
	9439	4	ALL PUPS APPEARED NORMAL.
	9440	4	ALL PUPS APPEARED NORMAL.
	9441	1	5 PUPS: STILLBORN. 1 PUP: FOUND DEAD.
		4	ALL PUPS APPEARED NORMAL.
	9442	1	1 PUP: FOUND DEAD.
		4	ALL PUPS APPEARED NORMAL.
	9443	4	ALL PUPS APPEARED NORMAL.
	9444	4	ALL PUPS APPEARED NORMAL.
	9445	1	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9446	4	ALL PUPS APPEARED NORMAL.
	9447	4	ALL PUPS APPEARED NORMAL.
	9448	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9449	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9450	2	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		3	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

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PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 9): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
VI 1000 RE-1125.01	9451	4	ALL PUPS APPEARED NORMAL.
	9452	4	ALL PUPS APPEARED NORMAL.
	9453	4	ALL PUPS APPEARED NORMAL.
	9454	4	ALL PUPS APPEARED NORMAL.
	9456	4	ALL PUPS APPEARED NORMAL.
	9457	4	ALL PUPS APPEARED NORMAL.
	9458	4	ALL PUPS APPEARED NORMAL.
	9460	4	ALL PUPS APPEARED NORMAL.
	9462	2	1 PUP: FOUND DEAD. NO MILK IN STOMACH.
		4	ALL PUPS APPEARED NORMAL.
	9463	4	ALL PUPS APPEARED NORMAL.
	9464	4	ALL PUPS APPEARED NORMAL.
	9465	4	ALL PUPS APPEARED NORMAL.
	9466	4	ALL PUPS APPEARED NORMAL.
	9467	4	ALL PUPS APPEARED NORMAL.
	9468	4	ALL PUPS APPEARED NORMAL.
	9469	2	1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9470	4	ALL PUPS APPEARED NORMAL.
	9471	4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

ARGUS 916-014
HBE BTS 0679/01

PROTOCOL 916-014: ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

TABLE C20 (PAGE 10): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS - PART II

MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) MATERNAL DESCRIPTOR	LITTER NUMBER	DAY(S) POSTPARTUM	OBSERVATIONS a
VI (cont.) 1000 RE-1125.01	9472	4	1 PUP: KIDNEYS, LEFT PELVIS, MODERATE DILATION. ALL OTHER TISSUES APPEARED NORMAL. ALL OTHER PUPS APPEARED NORMAL.
	9473	4	ALL PUPS APPEARED NORMAL.
	9474	2	1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL OTHER TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9475	1	1 PUP: STILLBORN.
		4	ALL PUPS APPEARED NORMAL.
	9476	4	ALL PUPS APPEARED NORMAL.
	9477	4	ALL PUPS APPEARED NORMAL.
	9478	1	1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL.
		4	ALL PUPS APPEARED NORMAL.
	9479	4	ALL PUPS APPEARED NORMAL.
	9480	4	ALL PUPS APPEARED NORMAL.

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C19) for external clinical observations present at necropsy.

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APPENDIX D

PROTOCOL AND AMENDMENTS

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PROTOCOL 916-014
SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

STUDY TITLE: Oral (Gavage) Chernoff-Kavlock[1] Developmental Toxicity Assay of RE-0981.05, RE-1122.01, RE-1123.01 and RE-1125.01 in Rats

PURPOSE: The purpose of Part I of this study is to determine the minimally toxic dose (MTD) for the selection of dosages to be used in Part II of this study. The purpose of Part II (developmental toxicity assay) is designed to assess the potential of the test substances to induce toxic effects in the conceptus after administration to the dam during gestation.

TESTING FACILITY: Argus Research Laboratories, Inc.
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STUDY DIRECTOR: Raymond G. York, Ph.D., DABT
Associate Director of Research

SPONSOR: Procter & Gamble HABC Europe Ltd.
Lovett House
Lovett Road
Staines
Middlesex TW18 3AZ UK

STUDY MONITOR: Vivienne R. Hoyle, Ph.D.
Telephone: 44-1784-495125
Telefax: 44-1784-495043

ALTERNATE CONTACT: John A. Wisler, Ph.D., DABT
The Procter & Gamble Company
Miami Valley Laboratories
11810 East Miami River Road
Ross, Ohio 45061
Telephone: (513) 627-0992
Telefax: (513) 627-1167

REGULATORY CITATIONS:

U.S. Environmental Protection Agency (1996). Health Effects Test Guidelines; Preliminary Developmental Toxicity Screen. Prevention, Pesticides and Toxic Substances (OPPTS) 870.3500, Public Draft, June 1996.

U.S. Environmental Protection Agency. Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 792.

U.S. Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 160.

REGULATORY COMPLIANCE

All phases of this study, with the exception of homogeneity, stability and concentration analyses of the dosage formulations, will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above. The following description of the Testing Facility's Quality Assurance Unit (QAU) responsibilities refers to those portions of the study conducted at the Testing Facility. GLP compliance for those portions of the study not conducted at the Testing Facility will be the responsibility of the QAU at the laboratory conducting that portion of the study.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The Quality Assurance Unit will audit the protocol, the raw data and the report, and will inspect critical phases of the study in accordance with the Standard Operating Procedures of Argus Research Laboratories, Inc.

The final report will include a statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable Good Laboratory Practice (GLP) regulations were followed in the conduct of the study with the exceptions noted above. Should significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST SUBSTANCES AND VEHICLES:

Information on the identity, composition, strength, purity and stability information of each test substance is on file with the Sponsor. A copy of the characterization reports are on file with the Sponsor.

Identification:

The lot numbers of the test substances are encoded in the last two digits of the identification numbers shown below.

Test Substance:

RE-0981.05

Test Substance:

RE-1122.01

Test Substance:

RE-1123.01

Test Substance:

RE-1125.01

Vehicle 1 (for RE-0981.05 and RE-1122.01):

Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water).

Results of R.O. deionized water analyses will be documented in the raw data and included in the final report.

Vehicle 2 (for RE-1123.01 and RE-1125.01)

Aqueous 0.5% carboxymethylcellulose. (Supplier and lot identification for the bulk vehicle will be documented in the raw data.)

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicles that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, mask, appropriate eye protection and uniform/lab coat to be worn during formulation preparation and dosage. The Material Safety Data Sheets will be maintained in the raw data.

Storage:

Bulk Test Substances:	Airtight; refrigerated.
Vehicle 1:	Room temperature.
Bulk Vehicle 2:	Room temperature.
Prepared Vehicle 2:	Refrigerated.
Prepared Formulations:	Room temperature. Formulations will be stirred continuously (magnetic stir plate with stir bar).

All test substance shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulations, Argus Research Laboratories, Inc., at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of sample shipment.

FORMULATION:

Frequency of Preparation:

Formulations (solutions and suspensions) will be prepared daily at the Testing Facility.

Detailed preparation procedures are attached to this protocol (ATTACHMENT 2).

Adjustment for Purity:

Dosage calculations will be adjusted for the purity of each test substance as follows:

Test Substance	Purity
RE-0981.05	99%
RE-1122.01	99%
RE-1123.01	98%
RE-1125.01	98%

Testing Facility Reserve Samples:

The Testing Facility will reserve a 500 mg sample of each lot of each bulk test substance and a 1 g sample of each lot of bulk Vehicle 2 used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

The Sponsor is responsible for bulk test substance stability.

Bulk Test Substance Sampling:

A 1 g sample of each test substance will be taken on the last day of treatment and retained until the final report is issued. In the event of analysis being required, this sample will be sent to the Sponsor for analysis. If necessary, samples will be shipped (airtight; on wet ice) to:

Vivienne R. Hoyle, Ph.D.
Procter & Gamble HABC Europe Ltd.
Lovett House
Lovett Road
Staines
Middlesex TW18 3AZ UK
Telephone: 44-1784-495125

The recipient will be notified in advance of sample shipment.

Homogeneity and Concentration Analyses of Prepared Formulations:

Homogeneity and concentration of each of the test substances in prepared formulations will not be verified during the course of this study. However, samples will be retained in case analysis is subsequently required. Triplicate samples (2 mL each) will be taken from the top, middle and bottom of the prepared formulations on the first and last days prepared. The triplicate samples will be retained at the Testing Facility until the final report has been issued. Samples will be stored refrigerated and only shipped upon the request of the Sponsor. If necessary, samples will be shipped (on wet ice) to the Study Monitor at the previously cited address. The recipient will be notified in advance of sample shipment.

DISPOSITION:

Prepared formulations will be discarded at the Testing Facility following approval from Sponsor. All remaining bulk test substances will be returned to:

Mrs. A. Sanger
Procter & Gamble HABC Europe Ltd.
Rusham Park, Whitehall Lane
Egham, TW20 9N2, UK
Telephone: 44-1784-474211

The recipient will be notified in advance of shipment.

TEST SYSTEM:

Species/Strain and Reason for Selection:

The Crl:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins and has been widely used throughout industry for reproductive and developmental toxicity evaluations; 2) historical data and experience exist at the Testing Facility[1-3]; and 3) this is one of the preferred species for this assay.

Number:

Initial population acclimated: 415 virgin female rats.
Population selected for study:

Part I	200 nonmated female rats (10 per dosage group).
Part II	180 mated female rats (30 per dosage group).

Body Weight and Age:

Female rats will be ordered to have body weights of 200 g to 225 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

Sex:

Female rats will be given the test substance. Male rats of the same source and strain will be used only as breeders and are not considered part of the Test System.

Source:

Charles River Laboratories, Inc.

The rats will be shipped in filter-topped cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification:

Fo Generation:

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male rats are given unique permanent identification numbers upon assignment to the Testing Facility's breeder male rat population.

Female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study.

F1 Generation:

Pups will not be individually identified during lactation; all parameters will be evaluated in terms of the litter.

ANIMAL HUSBANDRY:

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*[2].

Housing:

Part I:

The rats will be housed in common nesting boxes (two rats per nesting box).

Part II:

Fo generation rats will be individually housed in stainless-steel wire-bottomed cages except during the cohabitation and postpartum periods. During cohabitation, each pair of rats will be housed in the male rat's cage. Beginning no later than day 20 of presumed gestation, Fo generation female rats will be individually housed in nesting boxes. Each dam and delivered litter will be housed in a common nesting box during the postpartum period.

Nesting Material:

Bed-o'cobs®.

Bedding will be changed as often as necessary to keep the animals dry and clean. Analyses for possible contamination are conducted annually and documented in the raw data.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters (Airo Clean® room). Room temperature will be maintained at 70°F to 78°F and monitored constantly. Room humidity will also be monitored constantly and maintained at 40% to 70%.

Light:

An automatically-controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST.

Diet:

Rats will be given Certified Rodent Diet® #5002 (PMI Feeds, Inc.) available *ad libitum* from individual feeders.

Water:

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than 1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet, the drinking water or the nesting material at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

RANDOMIZATION AND COHABITATION:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units.

Part I:

Healthy nonmated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Part II:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units. After acclimation, virgin female rats will be cohabitated with breeder male rats, one male rat per female rat. The cohabitation period will consist of a maximum of five days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ*

will be considered to be at day 0 of presumed gestation and assigned to individual housing.

Healthy mated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Day 1 of lactation (postpartum) is defined as the day of birth (the day on which all pups in a litter are delivered and groomed by the dam).

Litters will not be culled during the lactation period because random selection of pups for culling could result in potential biases in pup viabilities and body weight gains during this period.

ADMINISTRATION:

Route and Reason for Choice:

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it allows the systemic toxic potential of the test substances to be fully characterized.

Method and Frequency:

Dosages will be adjusted daily for body weight changes, and will be given at approximately the same time each day. Formulations will be stirred continuously (magnetic stir plate with stir bar) during dosage administration.

Part I

Female rats will be given one of the test substances once daily for five days.

Part II

Female rats will be given one of the test substances once daily beginning on day 7 of presumed gestation and continuing through day 11 of presumed gestation.

F1 generation pups will not be directly given the test substances but may be possibly exposed to the test substances during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

Rationale for Dosage Selection:

Part I:

Dosages were selected by the Sponsor to cover a broad range of dosages up to and including the limit test dosage.

Part II:

Dosages will be selected on the basis of the minimally toxic dose (MTD) determined in Part I of the study and added by amendment. The dosage level should be high enough to cause overt maternal toxicity as evidenced by significant death, weight loss, or other adverse clinical manifestations, or 1 g/kg, if lower dosage levels fail to induce maternal toxicity.

Dosage Levels, Concentrations and Volumes - Part I:

Group	Number of Female Rats	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Argus Batch Number
I	10	RE-0981.05	25	2.5	10	B-916-014-A(Day.Month.Year)
II	10	RE-0981.05	50	5.0	10	B-916-014-B(Day.Month.Year)
III	10	RE-0981.05	100	10.0	10	B-916-014-C(Day.Month.Year)
IV	10	RE-0981.05	200	20.0	10	B-916-014-D(Day.Month.Year)
V	10	RE-0981.05	300	30.0	10	B-916-014-E(Day.Month.Year)
VI	10	RE-1122.01	25	2.5	10	B-916-014-F(Day.Month.Year)
VII	10	RE-1122.01	50	5.0	10	B-916-014-G(Day.Month.Year)
VIII	10	RE-1122.01	100	10.0	10	B-916-014-H(Day.Month.Year)
IX	10	RE-1122.01	200	20.0	10	B-916-014-I(Day.Month.Year)
X	10	RE-1122.01	300	30.0	10	B-916-014-J(Day.Month.Year)
XI	10	RE-1123.01	50	5.0	10	B-916-014-K(Day.Month.Year)
XII	10	RE-1123.01	150	15.0	10	B-916-014-L(Day.Month.Year)
XIII	10	RE-1123.01	300	30.0	10	B-916-014-M(Day.Month.Year)
XIV	10	RE-1123.01	550	55.0	10	B-916-014-N(Day.Month.Year)
XV	10	RE-1123.01	800	80.0	10	B-916-014-O(Day.Month.Year)
XVI	10	RE-1125.01	250	25.0	10	B-916-014-P(Day.Month.Year)
XVII	10	RE-1125.01	750	75.0	10	B-916-014-Q(Day.Month.Year)
XVIII	10	RE-1125.01	1000	100.0	10	B-916-014-R(Day.Month.Year)
XIX	10	RE-1125.01	1500	150.0	10	B-916-014-S(Day.Month.Year)
XX	10	RE-1125.01	2000	200.0	10	B-916-014-T(Day.Month.Year)

Dosage calculations will be adjusted for the purity of the test substances.

Dosage Levels, Concentrations and Volumes - Part II:

Group	Number of Female Rats	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Argus Batch Number
I	30	Vehicle 1	0	0	10	B-916-014-TBA(Day.Month.Year)
II	30	Vehicle 2	0	0	10	B-916-014-TBA(Day.Month.Year)
III	30	RE-0981.05	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
IV	30	RE-1122.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
V	30	RE-1123.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
VI	30	RE-1125.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)

TBA = To be added by amendment.
Dosage calculations will be adjusted for the purity of the test substances.

TESTS, ANALYSES AND MEASUREMENTS - Fo GENERATION FEMALE RATS:

Viability:

All Periods:	At least twice daily.

Clinical Observations and/or General Appearance:

Predosage Period:	Weekly and on day 0 of presumed gestation (rats assigned to Part II only).
Dosage Period:	Daily before dosage. Postdosage observations will be recorded approximately 60 minutes (±10 minutes) after administration. Observations for signs of toxicity should be recorded as they are observed, including the time of onset, the degree and duration. Cage-side observations should include, but not be limited to: change in skin and fur, eye and mucous membranes, as well as respiratory autonomic and central nervous systems, somatomotor activity and behavioral pattern.
Postdosage Period:	Day of sacrifice (rats assigned to Part I only) and daily on days 12 of presumed gestation through Day 4 postpartum (rats assigned to Part II).
Maternal Behavior:	Days 2 and 4 postpartum (rats assigned to Part II). Observed abnormal behavior recorded daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Body Weights:

Predosage Period:	Weekly and on day 0 of presumed gestation (rats assigned to Part II only).
Dosage Period:	Daily.
Postdosage Period:	Daily (rats assigned to Part II).
Sacrifice:	Terminal weight.

Mating Performance:

Mating will be evaluated daily during the cohabitation period and confirmed by observation of spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed *in situ*.

Duration of Gestation:

The duration of gestation is calculated from day 0 of presumed gestation to the day the first pup is observed.

Natural Delivery Observations:

Rats assigned to Part II of the study will be evaluated for:

Duration of Gestation (day 0 of presumed gestation to the day the first pup is observed).

Delivered Litter Size (all pups).

Live Litter Size (liveborn pups only).

Pup Viability at Birth.

METHOD OF SACRIFICE:

Rats and pups will be sacrificed by carbon dioxide asphyxiation.

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (a table of random units will be used to select one control group female rat from which all tissues examined at necropsy will be retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions). Unless specifically cited below, all other tissues will be discarded.

Scheduled Sacrifice - Female Rats Assigned to Part I:

On the day following the last test substance administration, female rats assigned to Part I of the study will be sacrificed, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed.

Scheduled Sacrifice - Female Rats Assigned to Part II:

After completion of the four-day postpartum period, female rats will be sacrificed, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. The number and distribution of implantation sites will be recorded.

Rats that do not deliver a litter will be sacrificed on day 23 of presumed gestation and examined for pregnancy status and gross lesions.

Dams with No Surviving Pups - Female Rats Assigned to Part II:

Dams with no surviving pups will be sacrificed after the last pup is found dead or missing, presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Postpartum data for these dams will be excluded from summary tables.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Ovaries will be retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[3] and retained in neutral buffered 10% formalin.

TESTS, ANALYSES AND MEASUREMENTS - F1 GENERATION (Part II Only):

Viability:

Postpartum Period:	Litters will be observed for dead pups at least twice daily. The pups in each litter will be counted once daily.

Clinical Observations and/or General Appearance:

Postpartum Period:	Daily.

Body Weights (recorded and tabulated):

Postpartum Period:	Days 2 and 4.

METHOD OF SACRIFICE - F1 GENERATION:

As previously cited for Fo generation rats.

NECROPSY - F1 GENERATION:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation. All other tissues will be discarded.

Scheduled Sacrifice:

At sacrifice on day 4 postpartum, pups will be examined for gross lesions. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

Pups Found Dead on Day 1 Postpartum:

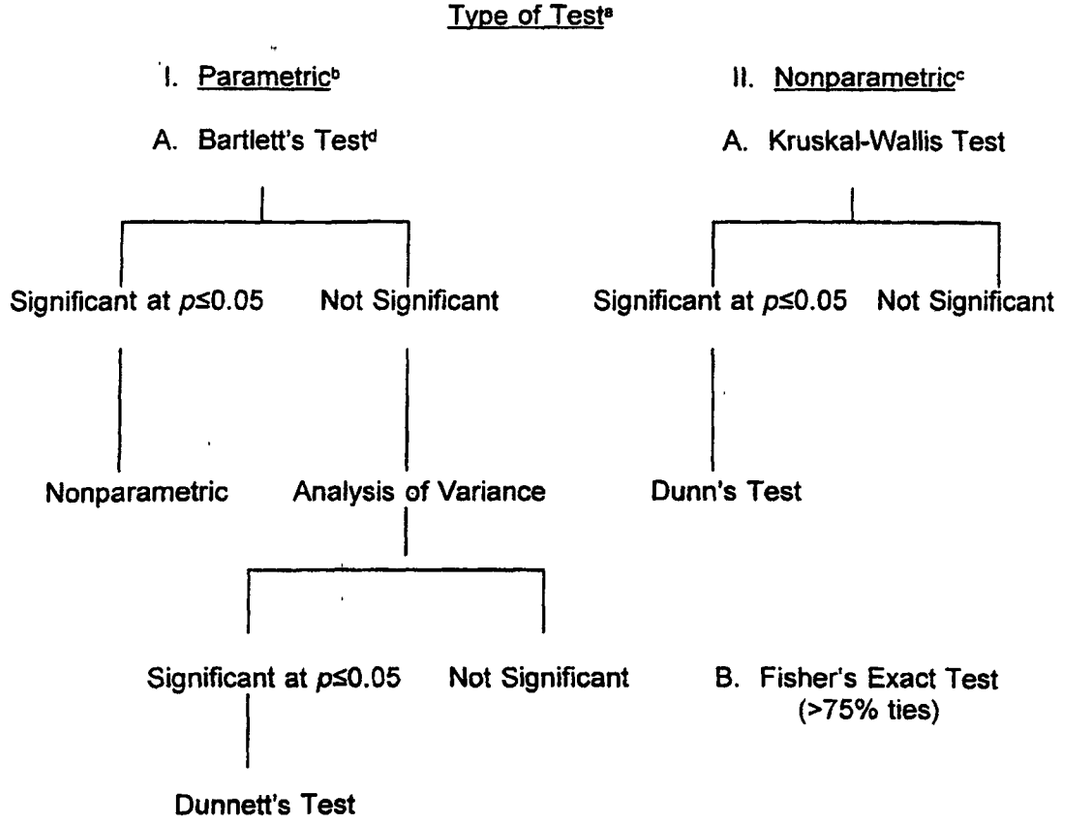
Pups that die before examination of the litter for pup viability will be evaluated for vital status at birth. The lungs will be removed and immersed in water. Pups with lungs that sink will be identified as stillborn; pups with lungs that float will be identified as liveborn and to have died shortly after birth. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

Pups Found Dead or Moribund on Days 2 to 4 Postpartum:

Pups found dead or sacrificed because of moribundity will be examined for gross lesions and for the cause of death or the moribund condition. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

PROPOSED STATISTICAL METHODS:[4-10]

Averages and percentages will be calculated. Litter values will be used where appropriate. Additional procedures and/or analyses may be performed, if appropriate.



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a. All tests evaluated at $p \leq 0.05$ to $p \leq 0.01$.
b. Used only to analyze data with homogeneity of variance.
c. Proportion data are not included in this category.
d. Test for homogeneity of variance.

DATA ACQUISITION, VERIFICATION AND STORAGE:

Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues and all original data and records will be stored at the Testing Facility for twenty years after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED:

All study records will be maintained including:

Protocol and Amendments.
Test Substance, Bulk Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Body Weights.
Natural Delivery Observations.
Litter Observations.
Gross Necropsy Observations.
Organ Weights (if required).
Photographs (if required).
Study Maintenance (room and environmental records).
Feed, Water and Bedding Analyses.
Packing and/or Shipment Lists.

KEY PERSONNEL:

Executive Director of Research: Mildred S. Christian, Ph.D., ATS
Director of Research: Alan M. Hoberman, Ph.D., DABT
Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
Director of Laboratory Operations: John F. Barnett, B.S.
Chairperson, Animal Care Committee: Denise E. Holliday, D.V.M., DABT
Manager of Animal Operations and Member, Animal Care Committee:
Dena C. Lebo, V.M.D.
Manager of Regulatory Compliance: Kathleen A. Moran, B.A.

FINAL REPORT:

A comprehensive audited draft final report will be prepared on completion of the study and will be finalized following consultation with the Sponsor. The report will include the following:

Summary and Conclusion.
Experimental Design and Method.
Evaluation of Test Results.
Appendices: Figures, Summary and Individual Tables Summarizing the Above Data, Protocol and Associated Amendments and Deviations, Study Director's GLP Compliance Statement, Reports of Supporting Data (if appropriate) and Quality Assurance Unit Statement.

ANIMAL CARE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Animal Care Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

Unless otherwise addressed in this protocol, the Testing Facility will not use any paralytics in the course of this study. Information that the test substance is not a paralytic is on file with the Sponsor.

If necessary, animals will be relieved of pain or distress by the use of appropriate sedatives, analgesics or anesthetics unless the withholding of such agent(s) is justified for scientific reasons; the withholding of such agent(s) will continue only for the necessary period of time. Use of such agent(s), if required, will be documented in the raw data.

Animals that would otherwise experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized at the end of the procedure (or, if appropriate, during the procedure) after consultation with the Study Director and/or staff veterinarian. Methods and agents used for euthanasia will be in accordance with acceptable standards, unless a deviation is justified for scientific reasons. The disposition of all animals purchased for this study will be documented in the raw data.

Information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes of the study. Alternative methods to those employed in this study, which may cause more than slight or momentary pain or distress, have been considered but were not available or appropriate for this study.

REFERENCES:

1. Chernoff, N. and Kavlock, R.J. (1982). An *In Vivo* Teratology Screen Utilizing Pregnant Mice. Journal of Toxicology and Environmental Health 10:541-550.

2. U.S. Department of Health and Human Services (1985). *Guide for the Care and Use of Laboratory Animals*. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publication No. 86-23.

3. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Arch. Pathol. Exp. Pharmakol. 247:367.

4. Snedecor, G.W. and Cochran, W.G. (1967). Variance test for homogeneity of the binomial distribution. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 240-241.

5. Sokal, R.R. and Rohlf, F.J. (1969). Bartlett's test of homogeneity of variances. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 370-371.

6. Snedecor, G.W. and Cochran, W.G. (1967). Analysis of Variance. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 258-275.

7. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. J. Amer. Stat. Assoc. 50:1096-1129.

8. Sokal, R.R. and Rohlf, F.J. (1969). Kruskal-Wallis Test. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 388-389.

9. Dunn, O.J. (1964). Multiple comparisons using rank sums. Technometrics 6(3):241-252.

10. Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, pp. 96-104.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY

Alan M. Hoberman, Ph.D., DABT
Director of Research

27-Sep-96
Date

Raymond G. York, Ph.D., DABT
Associate Director of Research
Study Director

27 SEP 96
Date

Dena C. Lebo, V.M.D.
Member, Animal Care Committee

27 Sept 96
Date

FOR THE SPONSOR

VR Hoyle

30 Sept 96
Date

Vivienne R. Hoyle, Ph.D.
Study Monitor

ATTACHMENT 1

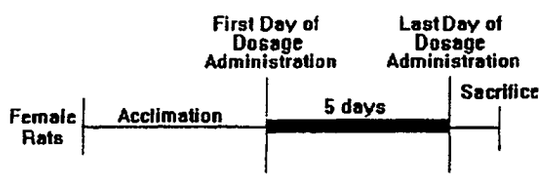
SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

ATTACHMENT 1

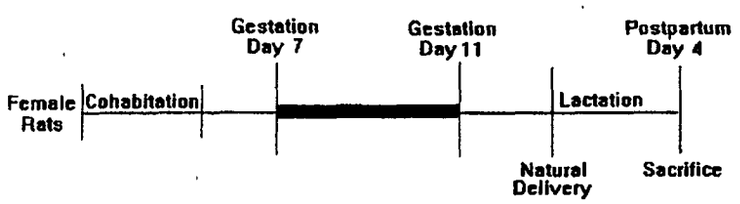
STUDY SCHEMATIC

Chernoff-Kavlock Teratology Screen[a]

Part I



Part II



= Dosage Period

a = For additional details see "Tests, Analyses and Measurements" section of the protocol.

SCHEDULE[a, b]

08 OCT 96	Animal Receipt - Acclimation Begins.
	Part I:
13 OCT 96 - 17 OCT 96	Dosage Period - Female Rats Assigned to Part I.
18 OCT 96	Sacrifice of Female Rats Assigned to Part I.
	Part II:
28 OCT 96 PM - 02 NOV 96 AM	Cohabitation Period.
29 OCT 96	First Possible Day 0 of Presumed Gestation.
02 NOV 96	Last Possible Day 0 of Presumed Gestation.
05 NOV 96 - 13 NOV 96	Dosage Period - Female Rats Assigned to Part II (Days 7 through 11 of presumed gestation).
19 NOV 96	First Possible Delivery (Day 21 of presumed gestation).
25 NOV 96	Last Possible Delivery (Day 23 of presumed gestation).
21 NOV 96	First Possible Day 23 of Presumed Gestation Female Sacrifice.
25 NOV 96	Last Possible Day 23 of Presumed Gestation Female Sacrifice.
22 NOV 96	First Possible Day 4 Postpartum (Dams and litters sacrificed).
28 NOV 96	Last Possible Day 4 Postpartum (Dams and litters sacrificed).
02 DEC 96	Verbal Report.
09 DEC 96	Letter Report.
28 JAN 97	Audited Draft Report.

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a. The study initiation date is the day the Study Director signs the protocol.
b. The day of birth is designated postnatal day 0 (day 0 of lactation) in the Health Effects Test Guidelines (Public Draft) of the U.S. Environmental Protection Agency (EPA). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout this protocol, the day of birth will be designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period will be determined and cited accordingly.

ATTACHMENT 2

TEST SUBSTANCE PREPARATION PROCEDURES

ATTACHMENT 2

TEST SUBSTANCES PREPARATION PROCEDURES

Test Substances: RE-0981.05, RE-1122.01, RE-1123.01, RE-1125.01

Vehicle 1(for RE-0981.05 and RE-1122.01): Reverse osmosis membrane processed deionized water (R.O. deionized water).

Vehicle 2(for RE-1123.01 and RE-1125.01): Aqueous 0.5% carboxymethylcellulose

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage solutions of for oral administration to rats on Argus Study 916-014.

B. General Information:

1. All solution/suspension containers will be labeled and color-coded. Each label will specify the protocol number, Test Substance identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.

2. Solutions/suspensions will be prepared:
   X Daily ___ Weekly ___ For _ days of use
   ___ At least once weekly ___ By Sponsor

3. Solutions/suspensions will be prepared at a final dosage volume of 10 mL/kg.

4. Safety:
   X Gloves, lab coat, goggles or safety glasses and faceshield
   X Dust-Mist Respirator
   ___ Half-Face Respirator
   ___ Full-Face Respirator/Positive Pressure Hood
   ___ Tyvek Suit/Apron

5. Dosage solutions adjusted for % Activity/Purity or Correction Factor:
   X Yes ___ No (Calculations based on 100%)
   99 % Purity (for RE-0981.05 and RE-1122.01)
   98 % Purity (for RE-1123.01 and RE-1125.01)

6. Sampling requirements: Cited in protocol

7. Storage: Cited in protocol

TEST SUBSTANCES PREPARATION PROCEDURES

C. Dosage Solution Preparation: (for RE-0981.05 and RE-1122.01)

1. Into an appropriately sized, labeled container, add the required amount of test substance to prepare the appropriate dosage level (see PREPARATION CALCULATIONS).

2. Add the total required amount of vehicle 1 (see PREPARATION CALCULATIONS).

3. If necessary, mix the test substance and vehicle thoroughly with an homogenizer to ensure the test substance is dispersed evenly throughout the solution.

4. Add a magnetic stirbar to the vessel, place on a magnetic stirplate and agitate until uniform prior to and during dosage administration and/or sampling.

5. Repeat steps (1) through (4) for each concentration.

D. Dosage Suspension Preparation: (for RE-1123.01 and RE-1125.01)

1. Into an appropriately sized, labeled container, add the required amount of test substance to prepare the appropriate dosage level (see PREPARATION CALCULATIONS).

2. Add the total required amount of vehicle 2 (see PREPARATION CALCULATIONS).

3. If necessary, mix the test substance and vehicle thoroughly with an homogenizer to ensure the test substance is dispersed evenly throughout the suspension.

4. Add a magnetic stirbar to the vessel, place on a magnetic stirplate and agitate until uniform prior to and during dosage administration and/or sampling.

5. Repeat steps (1) through (4) for each concentration.

Written By: [signature]

Approved by: [signature] Date: 27-SEP-96

Modification: X No ___ Yes [see attached modification form]

Initials/Date: [initials] 12-6-96

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
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PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 1 - October 16, 1996

---

1. Dosage Levels, Concentrations and Volumes - Part I (page 11 of the protocol):

   Revise dosage level for Groups XI and XII to 1000 and 1200 mg/kg/day (RE-1123.01), respectively.

   Reason for Change:

   Higher dosages are needed for RE-1123.01 to select a minimally toxic dose.

16-OCT-96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

16-OCT-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VRHoyle 23 Oct 96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

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PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 2 - October 21, 1996

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1. Dosage Levels, Concentrations and Volumes - Part I (page 11 of the protocol):

   [Effective Date: October 18, 1996] Revise dosage level for Groups XI and XII to 1500 and 2000 mg/kg/day (RE-1123.01), respectively. Rats will receive these dosages for three consecutive days.

   Reason for Change:

   Higher dosages are needed for RE-1123.01 to select a minimally toxic dose.

21OCT96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

21-OCT-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 23 Oct 96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

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PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 3 - November 1, 1996

---

1. Dosage Levels, Concentrations and Volumes - Part II (page 11 of the protocol):

Group	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)
III	RE-0981.05	250	25.0
IV	RE-1122.01	200	20.0
V	RE-1123.01	1000	100.0
VI	RE-1125.01	1000	100.0

Reason for Change:

This change was made as a result of the establishment of dosages by the Sponsor for the definitive Chernoff-Kavlock test (Part II) following consideration of the data produced from the range-finding study (Part I).

01-NOV-96

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

01-NOV-96

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 11-11-96.

Vivienne R. Hoyle, Ph.D. Date
Study Monitor

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PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 4 - November 22, 1996

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1. Dosage Levels, Concentrations and Volumes - Part II (page 11 of the protocol):

   [Effective Date: November 5, 1996] The batch numbers for Phase II will be as follows:

Group	Number of Female Rats	Descriptor	Batch Number
I	30	Vehicle 1	B-916-014-A(MM.DD.YY)ii
II	30	Vehicle 2	B-916-014-B(MM.DD.YY)ii
III	30	RE-0981.05	B-916-014-C(MM.DD.YY)ii
IV	30	RE-1122.01	B-916-014-D(MM.DD.YY)ii
V	30	RE-1123.01	B-916-014-E(MM.DD.YY)ii
VI	30	RE-1125.01	B-916-014-F(MM.DD.YY)ii

   Reason for Change:

   This change was made to clarify Amendment 3 of the protocol.

for Amdt 22 Nov 96 — 22 Nov 96

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 27 Nov 96

Vivienne R. Hoyle, Ph.D. Date
Study Monitor

APPENDIX E

DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY

DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY

1. Room Conditions:

   13 NOV 96, the automatic watering system was not checked. This deviation did not adversely affect the outcome or interpretation of the study because the system was working properly on the previous day and on the day after the deviation occurred.

   Humidity was not recorded for 1½ to 2 hours on two days because of recorder malfunction. Temperature was not recorded for 6 to 15 hours on two days. These deviations did not adversely affect the outcome or interpretation of the study.

2. Dosage:

   DGs 7 through 11 (09 NOV 96), Group III (RE-0981.05, Part II) rats 9361 through 9387 were administered Vehicle 1 rather than the test article. The error was discovered and the rats were administered the test article. These deviations did not adversely affect the outcome or interpretation of the study because the rats were dosed with the correct dosage of RE-0981.05.

3. Postdosage Observations:

14 OCT 96 (DS 2), postdosage observations for several rats in Part I were recorded slightly later than the targeted interval of 50 to 70 minutes, as tabulated below:

Assigned Numbers	Minutes out of Range
Group X	
8197	4
8198	10
8199	11
8200	10
Group XI	
8201	6
8202	3
8203	4
8204	3
8205	2

These deviations did not adversely affect the outcome or interpretation of the study because the postdosage observations were recorded and the observations affected were a small proportion of the total observations for these rats.

DS 3 (15 OCT 96) and DS 4 (17 OCT 96), body weights were not recorded at necropsy for Part I Group X rats 8197 and 8191, 8192 and 8194, respectively. These deviations did not adversely affect the outcome or interpretation of the study because sufficient body weight data were available for evaluation of this group.

4. On DL 1 (23 NOV 96), the delivery status of Part II Group V rat 9443 was not documented. As a result, lactation body weights, pup observations and pup body weights were not recorded on the correct lactation days. Values for this litter were excluded from the summary tables and values for the dam were excluded from lactation body weight summaries. This deviation did not adversely affect the outcome or interpretation of the study because sufficient data were available for evaluation.

5. Necropsy:

DS 2 (14 OCT 96), Part I Group X rat 8196 was necropsied approximately 24 minutes after sacrifice, rather than within 20 minutes of sacrifice. This deviation did not adversely affect the outcome or interpretation of the study because no data were lost.

DG 8 (06 NOV 96), the trachea, esophagus and lungs were not retained from Part II Group III rat 9363. This deviation did not adversely affect the outcome or interpretation of the study because these tissues were evaluated at necropsy and no further evaluations were necessary.

DL 4 (26 NOV 96), the tail (tip missing) was not retained from one male pup in Part II Group II (Vehicle 2) litter 9354. This deviation did not adversely affect the outcome or interpretation of the study because this gross lesion would not have been evaluated further.

Part II Group II (Vehicle 2) dam and litter 9360 and Group V (RE-1123.01) dam and litter 9450 were sacrificed on DL 3 (29 NOV 96), rather than on DL 4. This deviation did not adversely affect the outcome or interpretation of the study because there were sufficient litters available for evaluation.

All deviations are documented in the raw data.

Raymond G. York 07-NOV-97

Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

APPENDIX F

HISTORICAL CONTROL DATA

SUMMARY OF REPRODUCTIVE INDICES
CD RAT

PERIOD	JUNE 1994 - JUNE 1996
NUMBER OF STUDIES	43
NUMBER OF RATS:	
TESTED	860
PREGNANT	803
FOUND DEAD	1
ABORTED	0
DELIVERED	0
NUMBER OF RATS PREGNANT AT CAESAREAN-SECTIONING	800
NUMBER OF RATS WITH SINGLE CONCEPTUS LITTER:	
LIVE	5
RESORBED	0
ABORTED	0

	MEAN or %	RANGE/STUDY MEAN or %
% PREGNANT	93.8	(76.0-100)
AVERAGE # CORPORA LUTEA	17.5	(13.8-19.4)
AVERAGE # IMPLANTATIONS	15.6	(13.1-17.5)
AVERAGE LITTER SIZE		
AVERAGE # LIVE FETUSES	14.8	(12.4-17.0)
AVERAGE # DEAD FETUSES	0.0	(0-0.1)
AVERAGE # RESORPTIONS	0.8	(0-1.3)
AVERAGE # EARLY RESORPTIONS	0.8	(0-1.3)
AVERAGE # LATE RESORPTIONS	0.0	(0-0.2)

SUMMARY OF REPRODUCTIVE INDICES
CD RAT

	MEAN or %	RANGE/STUDY MEAN or %
AVERAGE % DAMS WITH ANY RESORPTIONS	50.0	(0-88.9)
AVERAGE % DAMS WITH ALL CONCEPTUSES RESORBED	0.0	--
AVERAGE % DAMS WITH ONE OR MORE LIVE FETUSES	100.0	--
AVERAGE SEX RATIO, (% MALES/LITTER)	50.1	(42.1-56.7)
AVERAGE FETAL BODY WEIGHT (G)	3.46	(3.10-3.72)
AVERAGE FOR MALES (G)	3.55	(3.20-3.86)
AVERAGE FOR FEMALES (G)	3.36	(3.00-3.60)
AVERAGE % DEAD OR RESORBED CONCEPTUSES/LITTER	5.4	(0-10.4)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
CD RAT

PERIOD	JUNE 1994 - JUNE 1996
# STUDIES	58
# RATS TESTED	1168
# RATS PREGNANT	1071
# RATS DIED	2
# RATS ABORTED	0
# RATS DELIVERED	220
# RATS WITH 100% RESORPTION	0

EXTERNAL OBSERVATIONS	N	MEAN %	RANGE N	/STUDY %
Red substance around nose and/or mouth	1	0.08	0-1	(0-3.3)
Alopecia	1	0.08	0-1	(0-3.3)
GROSS LESIONS				
SUBMANDIBULAR LYMPH NODES				
Dark red	1	0.08	0-1	(0-3.3)
JUGULAR VEIN				
Distended with blood	1	0.08	0-1	(0-3.3)
CHEST				
Subcutaneous fat, dark red on ventral side	1	0.08	0-1	(0-3.3)
THYMUS				
Discolored areas	2	0.17	0-2	(0-6.7)
AXILLA				
Mass present	1	0.08	0-1	(0-4.0)
STOMACH/INTESTINE				
Stomach, dicolored areas in fundic portion	1	0.08	0-1	(0-3.3)
Stomach, erosion	1	0.08	0-1	(0-3.3)
Stomach, fluid-filled	1	0.08	0-1	(0-4.0)
Intestines, empty	1	0.08	0-1	(0-4.0)

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS
CD RAT

GROSS LESIONS	MEAN N	MEAN %	RANGE /STUDY N	RANGE /STUDY %
BACK				
Lesion present at injection site	1	0.08	0-1	(0-4.0)
KIDNEY(S)				
Pelvis, slight/moderate dilation with or without fluid	14	1.20	0-4	(0-16.0)
Pelvis, marked/extreme dilation	3	0.26	0-1	(0-4.0)
Mottled	1	0.08	0-1	(0-4.0)
SPLEEN				
Accessory tissue present	1	0.08	0-1	(0-4.0)
BLADDER				
Fluid-filled	1	0.08	0-1	(0-4.0)
VAGINA/CERVIX				
Cervix distended with fluid	1	0.08	0-1	(0-4.0)
Cervix contained a thick brown substance	1	0.08	0-1	(0-4.0)
UTERUS				
Distended with fluid	2	0.17	0-1	(0-4.0)
Placenta(s), enlarged	1	0.08	0-1	(0-4.0)
Right horn, mass, firm and black	1	0.08	0-1	(0-3.3)
Contained red-brown fluid and one dead, brown fetus	1	0.08	0-1	(0-4.0)

SUMMARY OF FETAL EXTERNAL ALTERATIONS
CD RAT

PERIOD JUNE 1994 - JUNE 1996

# STUDIES INCLUDED	42
# LITTERS EXAMINED	796
# LIVE FETUSES EXAMINED	11737

ALTERATION			N	%	RANGE /STUDY N	%
HEAD						
	Exencephaly	L	4	0.50	0-1	(0-11.1)
		F	4	0.03	0-1	(0-0.8)
EYES						
	Eye bulges	L	7	0.88	0-1	(0-4.3)
	depressed	F	8	0.07	0-2	(0-0.5)
EARS						
	Low set	L	1	0.13	0-1	(0-4.0)
		F	1	0.01	0-1	(0-0.2)
SNOUT						
	Short	L	2	0.25	0-1	(0-4.2)
		F	2	0.02	0-1	(0-0.3)
PALATE						
	Cleft	L	4	0.50	0-1	(0-4.5)
		F	4	0.03	0-1	(0-0.3)
TONGUE						
	Protrudes	L	1	0.13	0-1	(0-4.2)
		F	1	0.01	0-1	(0-0.3)
JAWS						
	Micrognathia	L	3	0.38	0-1	(0-4.5)
		F	3	0.02	0-1	(0-0.3)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL EXTERNAL ALTERATIONS
CD RAT

ALTERATION					RANGE /STUDY	
			N	%	N	%
BODY						
	Edema	L	1	0.13	0-1	(0-11.1)
		F	1	0.01	0-1	(0-0.8)
	Umbilical hernia	L	4	0.50	0-1	(0-4.8)
		F	4	0.03	0-1	(0-0.4)
	Chest, mass	L	1	0.13	0-1	(0-11.1)
	present	F	1	0.01	0-1	(0-0.8)
	Gastroschisis	L	1	0.13	0-1	(0-4.0)
		F	1	0.01	0-1	(0-0.2)
	Trunk short	L	1	0.13	0-1	(0-4.0)
		F	1	0.01	0-1	(0-0.2)
	Spina bifida	L	1	0.13	0-1	(0-4.0)
		F	1	0.01	0-1	(0-0.2)
PLACENTA						
	Enlarged	L	1	0.13	0-1	(0-16.7)
		F	1	0.01	0-1	(0-1.1)
HINDLIMBS						
	Rotated	L	1	0.13	0-1	(0-4.0)
		F	1	0.01	0-1	(0-0.2)
TAIL						
	Threadlike	L	3	0.38	0-1	(0-4.5)
		F	3	0.02	0-1	(0-0.3)
	Agenesis	L	3	0.38	0-1	(0-4.3)
		F	3	0.02	0-1	(0-0.3)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SOFT TISSUE ALTERATIONS
CD RAT

PERIOD	JUNE 1994 - JUNE 1996
# STUDIES INCLUDED	17
# LITTERS EXAMINED	387
# FETUSES EXAMINED	2837

	ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
EYE(S)						
	Microphthalmia	L	4	1.03	0-1	(0-4.2)
		F	4	0.14	0-1	(0-0.6)
PALATE						
	Cleft	L	3	0.78	0-1	(0-4.2)
		F	3	0.10	0-1	(0-0.6)
VESSELS						
	Innominate, absent	L	5	1.29	0-2	(0-8.0)
		F	5	0.18	0-2	(0-1.2)
	Truncus arteriosus	L	1	0.26	0-1	(0-4.2)
		F	1	0.04	0-1	(0-0.6)
SPLEEN						
	Absent	L	1	0.26	0-1	(0-4.0)
		F	1	0.04	0-1	(0-0.5)
BLADDER						
	Umbilical artery, displaced	L	5	1.29	0-1	(0-4.8)
		F	5	0.18	0-1	(0-0.7)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

PERIOD	JUNE 1994 - JUNE 1996
# STUDIES INCLUDED	16
# LITTERS EXAMINED	380
# FETUSES EXAMINED	2899

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
SKULL					
Frontal(s): incompletely or not ossified	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Parietal(s): not ossified	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Nasal(s): short	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Basisphenoid: incompletely ossified	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Sphenoid: irregularly shaped	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Orbit: small	L	2	0.53	0-1	(0-4.0)
	F	2	0.07	0-1	(0-0.6)
Maxillae and Premaxillae: short	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Skull: not ossified	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Skull: fused	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
VERTEBRAE					
Cervical: Arch, open	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
: Fused	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)
Thoracic: Centrum, bifid	L	27	7.11	0-3	(0-14.3)
	F	28	0.97	0-4	(0-2.2)
: Centra, unilateral ossification	L	2	0.53	0-1	(0-4.3)
	F	2	0.07	0-1	(0-0.6)
: Arch, open	L	1	0.26	0-1	(0-4.0)
	F	1	0.03	0-1	(0-0.5)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

ALTERATION			N	%	RANGE/STUDY N	RANGE/STUDY %
VERTEBRAE (CONT.)						
Lumbar:	Centrum, bifid	L	1	0.26	0-1	(0-3.8)
		F	1	0.03	0-1	(0-0.4)
:	Arches, incompletely	L	5	1.32	0-2	(0-8.0)
	or not ossified	F	7	0.24	0-3	(0-1.9)
:	1, present	L	1	0.26	0-1	(0-4.3)
		F	1	0.03	0-1	(0-0.6)
:	Arch, open	L	1	0.26	0-1	(0-4.0)
		F	1	0.03	0-1	(0-0.5)
Sacral:	None, present	L	1	0.26	0-1	(0-4.3)
		F	1	0.03	0-1	(0-0.6)
:	Arch, open	L	1	0.26	0-1	(0-4.0)
		F	1	0.03	0-1	(0-0.5)
Caudal:	None present	L	1	0.26	0-1	(0-4.3)
		F	1	0.03	0-1	(0-0.6)
RIBS						
Cervical Rib(s) present		L	20	5.26	0-5	(0-20.0)
		F	20	0.69	0-5	(0-2.7)
One or more, wavy		L	14	3.68	0-4	(0-16.0)
		F	21	0.72	0-6	(0-3.3)
One or more, incompletely		L	8	2.11	0-2	(0-8.0)
ossified (hypoplastic),		F	15	0.52	0-4	(0-2.4)
or not ossified						
Fused		L	1	0.26	0-1	(0-4.0)
		F	1	0.03	0-1	(0-0.5)
Split		L	1	0.26	0-1	(0-4.0)
		F	1	0.03	0-1	(0-0.5)
MANUBRIUM						
Duplicated		L	1	0.26	0-1	(0-3.8)
		F	1	0.03	0-1	(0-0.4)
STERNEBRAE						
One or more incompletely		L	53	13.95	0-7	(0-28.0)
ossified or not ossified		F	78	2.69	0-11	(0-6.7)
Duplicated		L	1	0.26	0-1	(0-3.8)
		F	1	0.03	0-1	(0-0.4)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL SKELETAL ALTERATIONS
CD RAT

ALTERATION		N	%	RANGE/STUDY N	RANGE/STUDY %
PELVIS					
Pubis(es) and/or Ischium(a): incompletely or not ossified	L	66	17.37	0-9	(0-39.1)
	F	97	3.35	0-13	(0-8.2)
Pubis(es): incompletely ossified	L	59	15.53	0-9	(0-39.1)
	F	90	3.14	0-13	(0-8.2)
Pubis(es): not ossified	L	6	1.58	0-3	(0-13.6)
	F	6	0.21	0-3	(0-1.6)
Ischium(a): incompletely or not ossified	L	23	6.05	0-4	(0-18.2)
	F	28	0.97	0-5	(0-2.9)

L: LITTER INCIDENCE
F: FETAL INCIDENCE

SUMMARY OF FETAL OSSIFICATION SITES
SKELETAL AVERAGES
CD RAT
(CAESAREAN-SECTIONED DAY 20 GESTATION)

PERIOD:	JUNE 1994 - JUNE 1996
# STUDIES INCLUDED	14
# LITTERS EXAMINED	331
# FETUSES EXAMINED	2551

SKELETAL AVERAGES	FETUS/LITTER MEAN	RANGE/STUDY
HYOID	0.85	(0.74-0.93)
VERTEBRAE		
CERVICAL	7.00	--
THORACIC	13.04	(13.00-13.15)
LUMBAR	5.96	(5.84-6.00)
SACRAL	3.00	--
CAUDAL	4.82	(4.66-4.98)
RIBS (pairs)	13.03	(13.00-13.12)
STERNUM		
MANUBRIUM	1.00	--
STERNAL CENTERS	3.62	(3.38-3.85)
XIPHOID	0.99	(0.95-1.00)
FOREPAWS (Calculated as average per limb)		
CARPALS	0.00	--
METACARPALS	3.48	(3.36-3.57)
DIGITS	5.00	--
PHALANGES	5.03	(4.93-5.08)
HINDPAWS (Calculated as average per limb)		
TARSALS	0.00	--
METATARSALS	3.99	(3.98-4.00)
DIGITS	5.00	--
PHALANGES	4.96	(4.77-5.00)

SUMMARY OF FETAL OSSIFICATION SITES
SKELETAL AVERAGES
CD RAT
(CAESAREAN-SECTIONED DAY 21 GESTATION)

PERIOD:	JUNE 1994 - JUNE 1996
# STUDIES INCLUDED	2
# LITTERS EXAMINED	48
# FETUSES EXAMINED	341

	FETUS/LITTER	
SKELETAL AVERAGES	MEAN	RANGE/STUDY
HYOID	0.98	(0.97-1.00)
VERTEBRAE		
CERVICAL	7.00	--
THORACIC	13.02	(13.01-13.02)
LUMBAR	5.98	(5.97-5.98)
SACRAL	3.00	--
CAUDAL	7.89	(7.67-8.13)
RIBS (pairs)	13.01	--
STERNUM		
MANUBRIUM	1.00	--
STERNAL CENTERS	3.98	(3.98-3.99)
XIPHOID	1.00	--
FOREPAWS (Calculated as average per limb)		
CARPALS	0.00	--
METACARPALS	3.99	(3.98-4.00)
DIGITS	5.00	--
PHALANGES	7.87	(7.75-8.00)
HINDPAWS (Calculated as average per limb)		
TARSALS	0.02	(0.01-0.02)
METATARSALS	4.71	(4.60-4.82)
DIGITS	5.00	--
PHALANGES	6.26	(5.89-6.67)

APPENDIX G

QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

Study Director: Raymond G. York, Ph.D., DABT

Executive Director of Research: Mildred S. Christian, Ph.D., ATS

Protocol 916-014: Oral (Gavage) Chernoff-Kavlock[1] Developmental Toxicity Assay of RE-0981.05, RE-1122.01, RE-1123.01 and RE-1125.01 in Rats
Sponsor's Study Number: HBE BTS 0679/01

The draft protocol for this study was audited for adherence to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards and U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards on 27 Sep 97.

Critical phases of this study were inspected eight times; study information and raw data were audited twice (see tables 1 and 2 for dates and phases/data).

The draft final report and the raw data for this study were compared and audited for accuracy, for adherence to protocol requirements, and for adherence to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards and U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards between 25 Jan and 30 Jan 97, and for revisions requested by the Sponsor on 03 Oct 97 and 07 Nov 97.

This study was conducted according to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards and U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards.

Heather L. Rabuttino 7 Nov 97
for Kathleen A. Moran, B.A. Date
Manager of Regulatory Compliance

Heather L. Rabuttino 7 Nov 97
Heather L. Rabuttino, B.S. Date
Quality Assurance Auditor
and Principal Auditor

TABLE 1

CRITICAL PHASES INSPECTED

Test Substance Administration - Gavage

Dates of inspection: 14 Oct, 08 Nov 96

Dates results reported to the Study Director and Management:
15 Oct 96 and 27 Jan 97

Test Substance Preparation

Dates of inspection: 15 Oct, 13 Nov 96

Dates results reported to the Study Director and Management:
16 Oct, 14 Nov 96

Necropsy

Date of inspection: 18 Oct 96

Date results reported to the Study Director and Management: 21 Oct 96

Cohabitation

Date of inspection: 30 Oct 96

Date results reported to the Study Director and Management: 07 Nov 96

Litter Observations

Date of inspection: 21 Nov 96

Date results reported to the Study Director and Management: 22 Nov 96

Dam and Litter Sacrifice

Date of inspection: 22 Nov 96
Date results reported to the Study Director and Management: 22 Nov 96

TABLE 2

RAW DATA AUDIT(S)

The following study information and raw data were audited on 11 Dec and 12 Dec 96:

Protocol.
Protocol amendments.
List of personnel.
Animal receipt, randomization, physical examination and acclimation.
In-life transaction record.
Pup body weights and status.
Necropsy.
Tissue packing lists.
Male breeder colony records.
General comments.
Study maintenance records.
Tempscribes.
Feed, water and bedding analyses.
Edit requests.
Dosage volumes.
Deviations.
Data review page.

The results of this audit were reported to the Study Director and Management on 13 Dec 96.

The following study information and raw data were audited on 15 Dec 96:

Control receipt, preparation and use.
Test substance receipt, preparation and use.
Test substance packing lists.
Data review page.

The results of this audit were reported to the Study Director and Management on 16 Dec 96.

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 916-014
SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

STUDY TITLE: Oral (Gavage) Chernoff-Kavlock(1) Developmental Toxicity Assay of RE-0981.05, RE-1122.01, RE-1123.01 and RE-1125.01 in Rats

PURPOSE: The purpose of Part I of this study is to determine the minimally toxic dose (MTD) for the selection of dosages to be used in Part II of this study. The purpose of Part II (developmental toxicity assay) is designed to assess the potential of the test substances to induce toxic effects in the conceptus after administration to the dam during gestation.

TESTING FACILITY: Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297 USA
Telephone: (215) 443-8710
Telefax: (215) 443-8587

STUDY DIRECTOR: Raymond G. York, Ph.D., DABT
Associate Director of Research

SPONSOR: Procter & Gamble HABC Europe Ltd.
Lovett House
Lovett Road
Staines
Middlesex TW18 3AZ UK

STUDY MONITOR: Vivienne R. Hoyle, Ph.D.
Telephone: 44-1784-495125
Telefax: 44-1784-495043

ALTERNATE CONTACT: John A. Wisler, Ph.D., DABT
The Procter & Gamble Company
Miami Valley Laboratories
11810 East Miami River Road
Ross, Ohio 45061
Telephone: (513) 627-0992
Telefax: (513) 627-1167

REGULATORY CITATIONS:

U.S. Environmental Protection Agency (1996). Health Effects Test Guidelines; Preliminary Developmental Toxicity Screen. Prevention, Pesticides and Toxic Substances (OPPTS) 870.3500, Public Draft, June 1996.

U.S. Environmental Protection Agency. Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 792.

U.S. Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 160.

REGULATORY COMPLIANCE

All phases of this study, with the exception of homogeneity, stability and concentration analyses of the dosage formulations, will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above. The following description of the Testing Facility's Quality Assurance Unit (QAU) responsibilities refers to those portions of the study conducted at the Testing Facility. GLP compliance for those portions of the study not conducted at the Testing Facility will be the responsibility of the QAU at the laboratory conducting that portion of the study.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The Quality Assurance Unit will audit the protocol, the raw data and the report, and will inspect critical phases of the study in accordance with the Standard Operating Procedures of Argus Research Laboratories, Inc.

The final report will include a statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable Good Laboratory Practice (GLP) regulations were followed in the conduct of the study with the exceptions noted above. Should significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST SUBSTANCES AND VEHICLES:

Information on the identity, composition, strength, purity and stability information of each test substance is on file with the Sponsor. A copy of the characterization reports are on file with the Sponsor.

Identification:

The lot numbers of the test substances are encoded in the last two digits of the identification numbers shown below.

Test Substance:

RE-0981.05

Test Substance:

RE-1122.01

Test Substance:

RE-1123.01

Test Substance:

RE-1125.01

Vehicle 1 (for RE-0981.05 and RE-1122.01):

Reverse Osmosis Membrane Processed Deionized Water (R.O. Deionized Water).

Results of R.O. deionized water analyses will be documented in the raw data and included in the final report.

Vehicle 2 (for RE-1123.01 and RE-1125.01)

Aqueous 0.5% carboxymethylcellulose. (Supplier and lot identification for the bulk vehicle will be documented in the raw data.)

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicles that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, mask, appropriate eye protection and uniform/lab coat to be worn during formulation preparation and dosage. The Material Safety Data Sheets will be maintained in the raw data.

Storage:

Bulk Test Substances:	Airtight; refrigerated.
Vehicle 1:	Room temperature.
Bulk Vehicle 2:	Room temperature.
Prepared Vehicle 2:	Refrigerated.
Prepared Formulations:	Room temperature. Formulations will be stirred continuously (magnetic stir plate with stir bar).

All test substance shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulations, Argus Research Laboratories, Inc., at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of sample shipment.

FORMULATION:

Frequency of Preparation:

Formulations (solutions and suspensions) will be prepared daily at the Testing Facility.

Detailed preparation procedures are attached to this protocol (ATTACHMENT 2).

Adjustment for Purity:

Dosage calculations will be adjusted for the purity of each test substance as follows:

Test Substance	Purity
RE-0981.05	99%
RE-1122.01	99%
RE-1123.01	98%
RE-1125.01	98%

Testing Facility Reserve Samples:

The Testing Facility will reserve a 500 mg sample of each lot of each bulk test substance and a 1 g sample of each lot of bulk Vehicle 2 used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

The Sponsor is responsible for bulk test substance stability.

Bulk Test Substance Sampling:

A 1 g sample of each test substance will be taken on the last day of treatment and retained until the final report is issued. In the event of analysis being required, this sample will be sent to the Sponsor for analysis. If necessary, samples will be shipped (airtight; on wet ice) to:

Vivienne R. Hoyle, Ph.D.
Procter & Gamble HABC Europe Ltd.
Lovett House
Lovett Road
Staines
Middlesex TW18 3AZ UK
Telephone: 44-1784-495125

The recipient will be notified in advance of sample shipment.

Homogeneity and Concentration Analyses of Prepared Formulations:

Homogeneity and concentration of each of the test substances in prepared formulations will not be verified during the course of this study. However, samples will be retained in case analysis is subsequently required. Triplicate samples (2 mL each) will be taken from the top, middle and bottom of the prepared formulations on the first and last days prepared. The triplicate samples will be retained at the Testing Facility until the final report has been issued. Samples will be stored refrigerated and only shipped upon the request of the Sponsor. If necessary, samples will be shipped (on wet ice) to the Study Monitor at the previously cited address. The recipient will be notified in advance of sample shipment.

DISPOSITION:

Prepared formulations will be discarded at the Testing Facility following approval from Sponsor. All remaining bulk test substances will be returned to:

Mrs. A. Sanger
Procter & Gamble HABC Europe Ltd.
Rusham Park, Whitehall Lane
Egham, TW20 9N2, UK
Telephone: 44-1784-474211

The recipient will be notified in advance of shipment.

TEST SYSTEM:

Species/Strain and Reason for Selection:

The Crl:CD®BR VAF/Plus® (Sprague-Dawley) rat was selected as the Test System because: 1) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins and has been widely used throughout industry for reproductive and developmental toxicity evaluations; 2) historical data and experience exist at the Testing Facility[1-3]; and 3) this is one of the preferred species for this assay.

Number:

Initial population acclimated: 415 virgin female rats.
Population selected for study:

Part I	200 nonmated female rats (10 per dosage group).
Part II	180 mated female rats (30 per dosage group).

Body Weight and Age:

Female rats will be ordered to have body weights of 200 g to 225 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

Sex:

Female rats will be given the test substance. Male rats of the same source and strain will be used only as breeders and are not considered part of the Test System.

Source:

Charles River Laboratories, Inc.

The rats will be shipped in filter-topped cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification:

Fo Generation:

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male rats are given unique permanent identification numbers upon assignment to the Testing Facility's breeder male rat population.

Female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study.

F1 Generation:

Pups will not be individually identified during lactation; all parameters will be evaluated in terms of the litter.

ANIMAL HUSBANDRY:

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*[2].

Housing:

Part I:

The rats will be housed in common nesting boxes (two rats per nesting box).

Part II:

Fo generation rats will be individually housed in stainless-steel wire-bottomed cages except during the cohabitation and postpartum periods. During cohabitation, each pair of rats will be housed in the male rat's cage. Beginning no later than day 20 of presumed gestation, Fo generation female rats will be individually housed in nesting boxes. Each dam and delivered litter will be housed in a common nesting box during the postpartum period.

Nesting Material:

Bed-o'cobs®.

Bedding will be changed as often as necessary to keep the animals dry and clean. Analyses for possible contamination are conducted annually and documented in the raw data.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters (Airo Clean® room). Room temperature will be maintained at 70°F to 78°F and monitored constantly. Room humidity will also be monitored constantly and maintained at 40% to 70%.

Light:

An automatically-controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST.

Diet:

Rats will be given Certified Rodent Diet® #5002 (PMI Feeds, Inc.) available *ad libitum* from individual feeders.

Water:

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than 1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet, the drinking water or the nesting material at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

RANDOMIZATION AND COHABITATION:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units.

Part I:

Healthy nonmated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Part II:

Upon arrival, male and female rats will be assigned to individual housing on the basis of computer-generated random units. After acclimation, virgin female rats will be cohabitated with breeder male rats, one male rat per female rat. The cohabitation period will consist of a maximum of five days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ*

will be considered to be at day 0 of presumed gestation and assigned to individual housing.

Healthy mated female rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Day 1 of lactation (postpartum) is defined as the day of birth (the day on which all pups in a litter are delivered and groomed by the dam).

Litters will not be culled during the lactation period because random selection of pups for culling could result in potential biases in pup viabilities and body weight gains during this period.

ADMINISTRATION:

Route and Reason for Choice:

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it allows the systemic toxic potential of the test substances to be fully characterized.

Method and Frequency:

Dosages will be adjusted daily for body weight changes, and will be given at approximately the same time each day. Formulations will be stirred continuously (magnetic stir plate with stir bar) during dosage administration.

Part I

Female rats will be given one of the test substances once daily for five days.

Part II

Female rats will be given one of the test substances once daily beginning on day 7 of presumed gestation and continuing through day 11 of presumed gestation.

F1 generation pups will not be directly given the test substances but may be possibly exposed to the test substances during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

Rationale for Dosage Selection:

Part I:

Dosages were selected by the Sponsor to cover a broad range of dosages up to and including the limit test dosage.

Part II:

Dosages will be selected on the basis of the minimally toxic dose (MTD) determined in Part I of the study and added by amendment. The dosage level should be high enough to cause overt maternal toxicity as evidenced by significant death, weight loss, or other adverse clinical manifestations, or 1 g/kg, if lower dosage levels fail to induce maternal toxicity.

Dosage Levels, Concentrations and Volumes - Part I:

Group	Number of Female Rats	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Argus Batch Number
I	10	RE-0981.05	25	2.5	10	B-916-014-A(Day.Month.Year)
II	10	RE-0981.05	50	5.0	10	B-916-014-B(Day.Month.Year)
III	10	RE-0981.05	100	10.0	10	B-916-014-C(Day.Month.Year)
IV	10	RE-0981.05	200	20.0	10	B-916-014-D(Day.Month.Year)
V	10	RE-0981.05	300	30.0	10	B-916-014-E(Day.Month.Year)
VI	10	RE-1122.01	25	2.5	10	B-916-014-F(Day.Month.Year)
VII	10	RE-1122.01	50	5.0	10	B-916-014-G(Day.Month.Year)
VIII	10	RE-1122.01	100	10.0	10	B-916-014-H(Day.Month.Year)
IX	10	RE-1122.01	200	20.0	10	B-916-014-I(Day.Month.Year)
X	10	RE-1122.01	300	30.0	10	B-916-014-J(Day.Month.Year)
XI	10	RE-1123.01	50	5.0	10	B-916-014-K(Day.Month.Year)
XII	10	RE-1123.01	150	15.0	10	B-916-014-L(Day.Month.Year)
XIII	10	RE-1123.01	300	30.0	10	B-916-014-M(Day.Month.Year)
XIV	10	RE-1123.01	550	55.0	10	B-916-014-N(Day.Month.Year)
XV	10	RE-1123.01	800	80.0	10	B-916-014-O(Day.Month.Year)
XVI	10	RE-1125.01	250	25.0	10	B-916-014-P(Day.Month.Year)
XVII	10	RE-1125.01	750	75.0	10	B-916-014-Q(Day.Month.Year)
XVIII	10	RE-1125.01	1000	100.0	10	B-916-014-R(Day.Month.Year)
XIX	10	RE-1125.01	1500	150.0	10	B-916-014-S(Day.Month.Year)
XX	10	RE-1125.01	2000	200.0	10	B-916-014-T(Day.Month.Year)

Dosage calculations will be adjusted for the purity of the test substances.

Dosage Levels, Concentrations and Volumes - Part II:

Group	Number of Female Rats	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Argus Batch Number
I	30	Vehicle 1	0	0	10	B-916-014-TBA(Day.Month.Year)
II	30	Vehicle 2	0	0	10	B-916-014-TBA(Day.Month.Year)
III	30	RE-0981.05	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
IV	30	RE-1122.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
V	30	RE-1123.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)
VI	30	RE-1125.01	TBA	TBA	10	B-916-014-TBA(Day.Month.Year)

TBA = To be added by amendment.
Dosage calculations will be adjusted for the purity of the test substances.

TESTS, ANALYSES AND MEASUREMENTS - Fo GENERATION FEMALE RATS:

Viability:

All Periods:	At least twice daily.

Clinical Observations and/or General Appearance:

Predosage Period:	Weekly and on day 0 of presumed gestation (rats assigned to Part II only).
Dosage Period:	Daily before dosage. Postdosage observations will be recorded approximately 60 minutes (±10 minutes) after administration. Observations for signs of toxicity should be recorded as they are observed, including the time of onset, the degree and duration. Cage-side observations should include, but not be limited to: change in skin and fur, eye and mucous membranes, as well as respiratory autonomic and central nervous systems, somatomotor activity and behavioral pattern.
Postdosage Period:	Day of sacrifice (rats assigned to Part I only) and daily on days 12 of presumed gestation through Day 4 postpartum (rats assigned to Part II).
Maternal Behavior:	Days 2 and 4 postpartum (rats assigned to Part II). Observed abnormal behavior recorded daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Body Weights:

Predosage Period:	Weekly and on day 0 of presumed gestation (rats assigned to Part II only).
Dosage Period:	Daily.
Postdosage Period:	Daily (rats assigned to Part II).
Sacrifice:	Terminal weight.

Mating Performance:

Mating will be evaluated daily during the cohabitation period and confirmed by observation of spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed *in situ*.

Duration of Gestation:

The duration of gestation is calculated from day 0 of presumed gestation to the day the first pup is observed.

Natural Delivery Observations:

Rats assigned to Part II of the study will be evaluated for:

Duration of Gestation (day 0 of presumed gestation to the day the first pup is observed).

Delivered Litter Size (all pups).

Live Litter Size (liveborn pups only).

Pup Viability at Birth.

METHOD OF SACRIFICE:

Rats and pups will be sacrificed by carbon dioxide asphyxiation.

NECROPSY:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation (a table of random units will be used to select one control group female rat from which all tissues examined at necropsy will be retained, in order to provide control tissues for any possible histopathological evaluations of gross lesions). Unless specifically cited below, all other tissues will be discarded.

Scheduled Sacrifice - Female Rats Assigned to Part I:

On the day following the last test substance administration, female rats assigned to Part I of the study will be sacrificed, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed.

Scheduled Sacrifice - Female Rats Assigned to Part II:

After completion of the four-day postpartum period, female rats will be sacrificed, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. The number and distribution of implantation sites will be recorded.

Rats that do not deliver a litter will be sacrificed on day 23 of presumed gestation and examined for pregnancy status and gross lesions.

Dams with No Surviving Pups - Female Rats Assigned to Part II:

Dams with no surviving pups will be sacrificed after the last pup is found dead or missing, presumed cannibalized. A gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Postpartum data for these dams will be excluded from summary tables.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Ovaries will be retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[3] and retained in neutral buffered 10% formalin.

TESTS, ANALYSES AND MEASUREMENTS - F1 GENERATION (Part II Only):

Viability:

Postpartum Period:	Litters will be observed for dead pups at least twice daily. The pups in each litter will be counted once daily.

Clinical Observations and/or General Appearance:

Postpartum Period:	Daily.

Body Weights (recorded and tabulated):

Postpartum Period:	Days 2 and 4.

METHOD OF SACRIFICE - F1 GENERATION:

As previously cited for Fo generation rats.

NECROPSY - F1 GENERATION:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation. All other tissues will be discarded.

Scheduled Sacrifice:

At sacrifice on day 4 postpartum, pups will be examined for gross lesions. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

Pups Found Dead on Day 1 Postpartum:

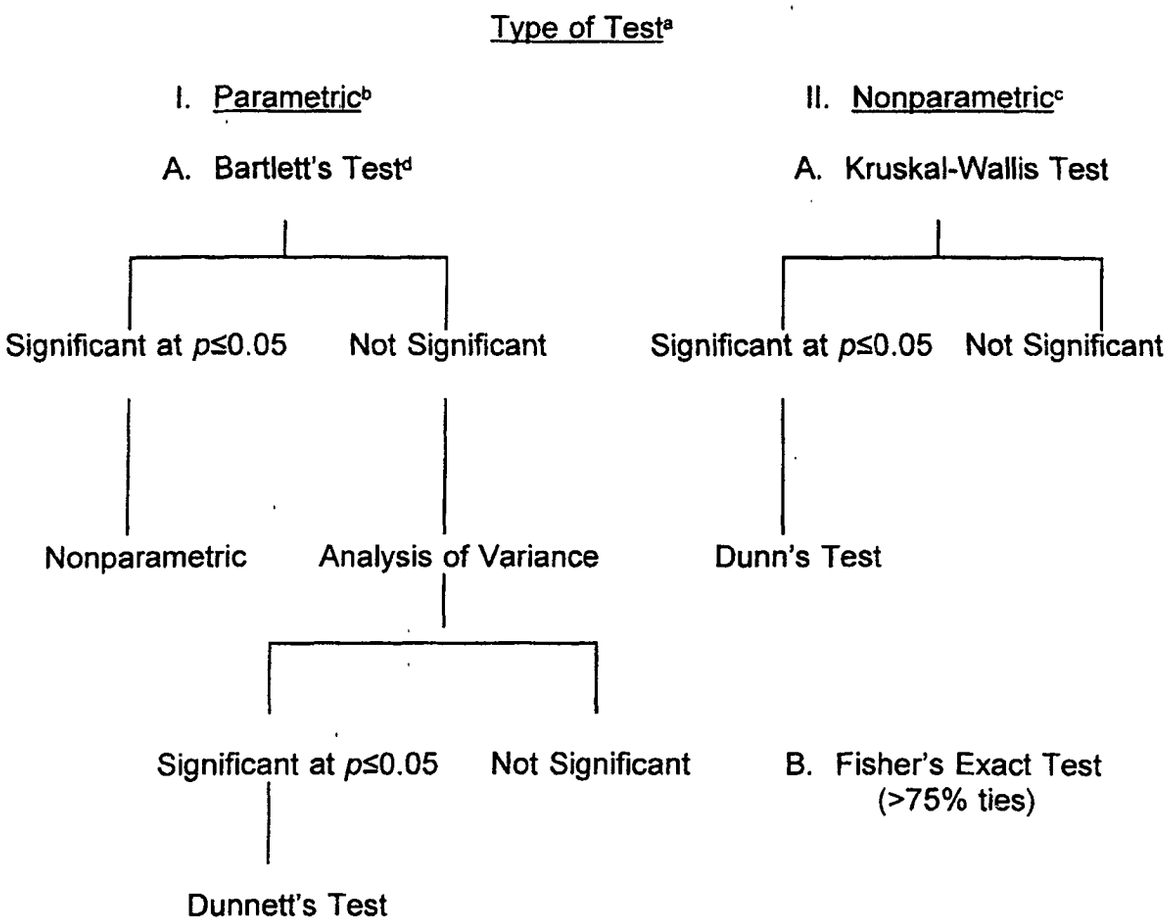
Pups that die before examination of the litter for pup viability will be evaluated for vital status at birth. The lungs will be removed and immersed in water. Pups with lungs that sink will be identified as stillborn; pups with lungs that float will be identified as liveborn and to have died shortly after birth. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

Pups Found Dead or Moribund on Days 2 to 4 Postpartum:

Pups found dead or sacrificed because of moribundity will be examined for gross lesions and for the cause of death or the moribund condition. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

PROPOSED STATISTICAL METHODS:(4-10)

Averages and percentages will be calculated. Litter values will be used where appropriate. Additional procedures and/or analyses may be performed, if appropriate.



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a. All tests evaluated at $p \leq 0.05$ to $p \leq 0.01$.
b. Used only to analyze data with homogeneity of variance.
c. Proportion data are not included in this category.
d. Test for homogeneity of variance.

DATA ACQUISITION, VERIFICATION AND STORAGE:

Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues and all original data and records will be stored at the Testing Facility for twenty years after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED:

All study records will be maintained including:

Protocol and Amendments.
Test Substance, Bulk Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Body Weights.
Natural Delivery Observations.
Litter Observations.
Gross Necropsy Observations.
Organ Weights (if required).
Photographs (if required).
Study Maintenance (room and environmental records).
Feed, Water and Bedding Analyses.
Packing and/or Shipment Lists.

KEY PERSONNEL:

Executive Director of Research: Mildred S. Christian, Ph.D., ATS
Director of Research: Alan M. Hoberman, Ph.D., DABT
Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
Director of Laboratory Operations: John F. Barnett, B.S.
Chairperson, Animal Care Committee: Denise E. Holliday, D.V.M., DABT
Manager of Animal Operations and Member, Animal Care Committee:
Dena C. Lebo, V.M.D.
Manager of Regulatory Compliance: Kathleen A. Moran, B.A.

FINAL REPORT:

A comprehensive audited draft final report will be prepared on completion of the study and will be finalized following consultation with the Sponsor. The report will include the following:

Summary and Conclusion.
Experimental Design and Method.
Evaluation of Test Results.
Appendices: Figures, Summary and Individual Tables Summarizing the Above Data, Protocol and Associated Amendments and Deviations, Study Director's GLP Compliance Statement, Reports of Supporting Data (if appropriate) and Quality Assurance Unit Statement.

ANIMAL CARE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Animal Care Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

Unless otherwise addressed in this protocol, the Testing Facility will not use any paralytics in the course of this study. Information that the test substance is not a paralytic is on file with the Sponsor.

If necessary, animals will be relieved of pain or distress by the use of appropriate sedatives, analgesics or anesthetics unless the withholding of such agent(s) is justified for scientific reasons; the withholding of such agent(s) will continue only for the necessary period of time. Use of such agent(s), if required, will be documented in the raw data.

Animals that would otherwise experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized at the end of the procedure (or, if appropriate, during the procedure) after consultation with the Study Director and/or staff veterinarian. Methods and agents used for euthanasia will be in accordance with acceptable standards, unless a deviation is justified for scientific reasons. The disposition of all animals purchased for this study will be documented in the raw data.

Information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes of the study. Alternative methods to those employed in this study, which may cause more than slight or momentary pain or distress, have been considered but were not available or appropriate for this study.

REFERENCES:

1. Chernoff, N. and Kavlock, R.J. (1982). An *In Vivo* Teratology Screen Utilizing Pregnant Mice. Journal of Toxicology and Environmental Health 10:541-550.

2. U.S. Department of Health and Human Services (1985). *Guide for the Care and Use of Laboratory Animals*. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publication No. 86-23.

3. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Arch. Pathol. Exp. Pharmakol. 247:367.

4. Snedecor, G.W. and Cochran, W.G. (1967). Variance test for homogeneity of the binomial distribution. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 240-241.

5. Sokal, R.R. and Rohlf, F.J. (1969). Bartlett's test of homogeneity of variances. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 370-371.

6. Snedecor, G.W. and Cochran, W.G. (1967). Analysis of Variance. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 258-275.

7. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. J. Amer. Stat. Assoc. 50:1096-1129.

8. Sokal, R.R. and Rohlf, F.J. (1969). Kruskal-Wallis Test. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 388-389.

9. Dunn, O.J. (1964). Multiple comparisons using rank sums. Technometrics 6(3):241-252.

10. Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, pp. 96-104.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY

Alan M. Hoberman, Ph.D., DABT
Director of Research

27-SEP-96
Date

Raymond G. York, Ph.D., DABT
Associate Director of Research
Study Director

27 SEP 96
Date

Dena C. Lebo, V.M.D.
Member, Animal Care Committee

27 Sept 96
Date

FOR THE SPONSOR

Vivienne R. Hoyle, Ph.D.
Study Monitor

30 Sept 96
Date

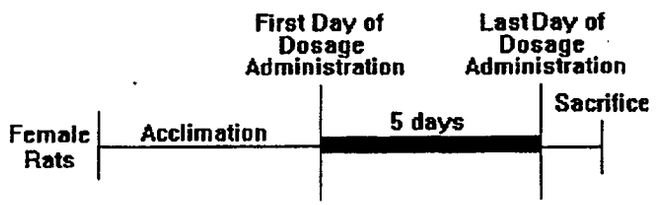
ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

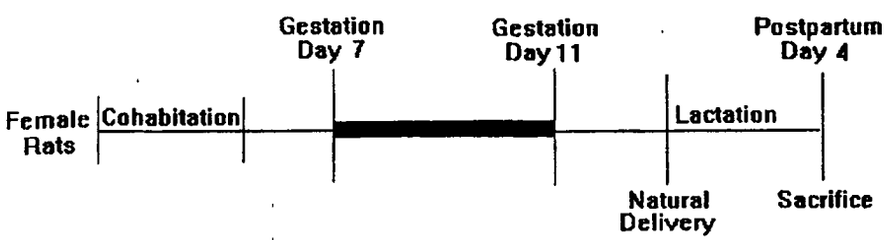
STUDY SCHEMATIC

Chernoff-Kavlock Teratology Screen[a]

Part I



Part II



■ = Dosage Period

a = For additional details see "Tests, Analyses and Measurements" section of the protocol.

SCHEDULE[a, b]

08 OCT 96	Animal Receipt - Acclimation Begins.
	Part I:
13 OCT 96 - 17 OCT 96	Dosage Period - Female Rats Assigned to Part I.
18 OCT 96	Sacrifice of Female Rats Assigned to Part I.
	Part II:
28 OCT 96 PM - 02 NOV 96 AM	Cohabitation Period.
29 OCT 96	First Possible Day 0 of Presumed Gestation.
02 NOV 96	Last Possible Day 0 of Presumed Gestation.
05 NOV 96 - 13 NOV 96	Dosage Period - Female Rats Assigned to Part II (Days 7 through 11 of presumed gestation).
19 NOV 96	First Possible Delivery (Day 21 of presumed gestation).
25 NOV 96	Last Possible Delivery (Day 23 of presumed gestation).
21 NOV 96	First Possible Day 23 of Presumed Gestation Female Sacrifice.
25 NOV 96	Last Possible Day 23 of Presumed Gestation Female Sacrifice.
22 NOV 96	First Possible Day 4 Postpartum (Dams and litters sacrificed).
28 NOV 96	Last Possible Day 4 Postpartum (Dams and litters sacrificed).
02 DEC 96	Verbal Report.
09 DEC 96	Letter Report.
28 JAN 97	Audited Draft Report.

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a. The study initiation date is the day the Study Director signs the protocol.
b. The day of birth is designated postnatal day 0 (day 0 of lactation) in the Health Effects Test Guidelines (Public Draft) of the U.S. Environmental Protection Agency (EPA). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout this protocol, the day of birth will be designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period will be determined and cited accordingly.

ATTACHMENT 2

TEST SUBSTANCE PREPARATION PROCEDURES

TEST SUBSTANCES PREPARATION PROCEDURES

Test Substances: RE-0981.05, RE-1122.01, RE-1123.01, RE-1125.01

Vehicle 1(for RE-0981.05 and RE-1122.01): Reverse osmosis membrane processed deionized water (R.O. deionized water).

Vehicle 2(for RE-1123.01 and RE-1125.01): Aqueous 0.5% carboxymethylcellulose

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage solutions of for oral administration to rats on Argus Study 916-014.

B. General Information:

1. All solution/suspension containers will be labeled and color-coded. Each label will specify the protocol number, Test Substance identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.

2. Solutions/suspensions will be prepared:
   X Daily ___ Weekly ___ For _ days of use
   ___ At least once weekly ___ By Sponsor

3. Solutions/suspensions will be prepared at a final dosage volume of 10 mL/kg.

4. Safety:
   X Gloves, lab coat, goggles or safety glasses and faceshield
   X Dust-Mist Respirator
   ___ Half-Face Respirator
   ___ Full-Face Respirator/Positive Pressure Hood
   ___ Tyvek Suit/Apron

5. Dosage solutions adjusted for % Activity/Purity or Correction Factor:
   X Yes ___ No (Calculations based on 100%)
   99 % Purity (for RE-0981.05 and RE-1122.01)
   98 % Purity (for RE-1123.01 and RE-1125.01)

6. Sampling requirements: Cited in protocol

7. Storage: Cited in protocol

TEST SUBSTANCES PREPARATION PROCEDURES

C. Dosage Solution Preparation: (for RE-0981.05 and RE-1122.01)

1. Into an appropriately sized, labeled container, add the required amount of test substance to prepare the appropriate dosage level (see PREPARATION CALCULATIONS).

2. Add the total required amount of vehicle 1 (see PREPARATION CALCULATIONS).

3. If necessary, mix the test substance and vehicle thoroughly with an homogenizer to ensure the test substance is dispersed evenly throughout the solution.

4. Add a magnetic stirbar to the vessel, place on a magnetic stirplate and agitate until uniform prior to and during dosage administration and/or sampling.

5. Repeat steps (1) through (4) for each concentration.

D. Dosage Suspension Preparation: (for RE-1123.01 and RE-1125.01)

1. Into an appropriately sized, labeled container, add the required amount of test substance to prepare the appropriate dosage level (see PREPARATION CALCULATIONS).

2. Add the total required amount of vehicle 2 (see PREPARATION CALCULATIONS).

3. If necessary, mix the test substance and vehicle thoroughly with an homogenizer to ensure the test substance is dispersed evenly throughout the suspension.

4. Add a magnetic stirbar to the vessel, place on a magnetic stirplate and agitate until uniform prior to and during dosage administration and/or sampling.

5. Repeat steps (1) through (4) for each concentration.

Written By: Julian Gallinich

Approved by: Raymond G. Jon Date: 27-SEP-96

Modification: ___ No ___ Yes [see attached modification form]

Initials/Date: _____

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 1 - October 16, 1996

---

1. Dosage Levels, Concentrations and Volumes - Part I (page 11 of the protocol):

   Revise dosage level for Groups XI and XII to 1000 and 1200 mg/kg/day (RE-1123.01), respectively.

   Reason for Change:

   Higher dosages are needed for RE-1123.01 to select a minimally toxic dose.

A Hoberman 16Oct96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 16-OCT-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VRHoyle 23 Oct 96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK[1] DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 2 - October 21, 1996

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1. Dosage Levels, Concentrations and Volumes - Part I (page 11 of the protocol):

   [Effective Date: October 18, 1996] Revise dosage level for Groups XI and XII to 1500 and 2000 mg/kg/day (RE-1123.01), respectively. Rats will receive these dosages for three consecutive days.

   Reason for Change:

   Higher dosages are needed for RE-1123.01 to select a minimally toxic dose.

A. Hoberman 21 Oct 96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 21-Oct-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 23 Oct 96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
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PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 3 - November 1, 1996

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1. Dosage Levels, Concentrations and Volumes - Part II (page 11 of the protocol):

Group	Descriptor	Dosage (mg/kg/day)	Concentration (mg/mL)
III	RE-0981.05	250	25.0
IV	RE-1122.01	200	20.0
V	RE-1123.01	1000	100.0
VI	RE-1125.01	1000	100.0

Reason for Change:

This change was made as a result of the establishment of dosages by the Sponsor for the definitive Chernoff-Kavlock test (Part II) following consideration of the data produced from the range-finding study (Part I).

A. Hoberman 01-NOV-96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 01-NOV-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 11-11-96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 916-014

ORAL (GAVAGE) CHERNOFF-KAVLOCK(1) DEVELOPMENTAL TOXICITY ASSAY OF RE-0981.05, RE-1122.01, RE-1123.01 AND RE-1125.01 IN RATS

SPONSOR'S STUDY NUMBER: HBE BTS 0679/01

Amendment 4 - November 22, 1996

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1. Dosage Levels, Concentrations and Volumes - Part II (page 11 of the protocol):

[Effective Date: November 5, 1996] The batch numbers for Phase II will be as follows:

Group	Number of Female Rats	Descriptor	Batch Number
I	30	Vehicle 1	B-916-014-A(MM.DD.YY)ii
II	30	Vehicle 2	B-916-014-B(MM.DD.YY)ii
III	30	RE-0981.05	B-916-014-C(MM.DD.YY)ii
IV	30	RE-1122.01	B-916-014-D(MM.DD.YY)ii
V	30	RE-1123.01	B-916-014-E(MM.DD.YY)ii
VI	30	RE-1125.01	B-916-014-F(MM.DD.YY)ii

Reason for Change:

This change was made to clarify Amendment 3 of the protocol.

P D Hoberman for AMH 22 Nov 96
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Raymond G. York 22-Nov-96
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

VR Hoyle 27-Nov-96
Vivienne R. Hoyle, Ph.D. Date
Study Monitor

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

***Section I*: P&RS Study Related Reference Numbers (To be completed by P&RS)**

Test Substance Identification Number (TSIN) RE- 1122.01

Divisional Request Document(s) HBE BTS 0675/01, 0676/01, 0679/01

***Section II*: Test Substance General Characteristics**
(To be completed by Originator, helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or Ingredient (or code designation): 4-(N-ethyl-N-2-methanesulphonylaminoethyl)-2-methylphenylenediamine sesquisulphate monohydrate Also called Eastman Color Developing Agent CD-3

Supplier's Name: Eastman

Brand Notebook Reference M217 / 17197 / 17198, 17199, 17200 Lot # G5171
(test substance source, production code if available and date ingredient received or date product made)

Physical Form: Crystals Color: off white/pink pH: _____ at: _____ %

Density/Sp.Gravity: NA Ingredient Mol. Wt.: 436.52 Ingredient Solubility: 380g/L @25° water

Storage Conditions: keep closed, dry, cool Viscosity: NA

Expiration Date (Day/Month/Year): 30/12/96 Ingredient Stability : Stable

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows: Harmful irritant sensitizer

Originator's Section Head:	JC Dunbar	J Dunbar	27/9/96
	Name	Signature	Date

***Section III:* Test Substance Composition and Analytical Information**

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for the safety testing indicated by the Divisional Request Document (s).

Divisional Toxicologist:	VR Hayle	V.R. HOYLE	27-9-96
	Name	Signature	Date

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
CaS # 025646-71-3						ACN° 31860 FTIR reference spectra collected for sample. N1015/47 C. Alexander 24 Sep 96			

Compositional Information Provided by: A Sanger 18/9/96

(ORIGINATOR NAME/SIGNATURE/DATE)
Signature verifies integrity of all data provided (including Section II)

Analytical Verification by: P.J. Greenhill 25/9/96.

(ANALYTICAL MGR NAME/SIGNATURE/DATE)
Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

(NAME/SIGNATURE/DATE) [signature] 25/9/96

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

ssu\tscr.doc

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methyl phenylenediamine
Purity:	99.6%
Remarks:	Test Substance was described as Test Substance # RE-1122.01
Comments:	Report includes RE0981.05 which is not reportable under the 8(d) rule.

Method

GLP:	Yes
Method / Guideline:	Murine Local Lymph Node Assay
Test Type:	Delayed contact hypersensitivity / Skin sensitization
Report Year:	1997
Species:	Mouse
Strain:	CBA/J
Gender:	female
Vehicle:	dimethylsulfoxide (DMSO)
Number of Animals:	25 (5 / group)
Doses:	0, 0.1, 1.0, 5.0 and 10.0%
Study Design:	Animals received 12.5 µl of carrier or one of the test solutions to the ventral and dorsal surface of both pinnae (total of 25 µl per ear, 50 µl per mouse) for 3 consecutive days. Approximately 70 hours after final test article application, each mouse was injected i.v. with titrated thymidine to radiolabel proliferating cells. Lymph nodes were removed five hours later and dissociated. The radioactivity was measured by liquid scintillation spectrometry. Study included carrier and naïve control groups.

Results

Result:	The mean DPM of all groups treated with RE1122.01 were statistically significantly increased compared to the mean DPM of the naïve group. Groups treated with RE1122.01 at 1, 5 and 10% concentrations were significantly increased compared to the mean DPM of the carrier control. In addition, the stimulation indices for groups treated with 1, 5, 10 % RE1122.01 were greater than 3.0 relative to the carrier control. Stimulation Index (SI) 0.1% = 1.21 1.0% = 4.53 5.0% = 5.94 10% = 6.62
Conclusion:	The test material was positive for contact allergenic potential.
Remarks:	No adverse clinical signs and no sign of dermal irritation at the test article application site were observed in test or control animals.

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	L08607 SN15
Reference:	Procter & Gamble, 1997. Murine Local Lymph Node Assay. Accession #40229.

96C295
Acc# 40229

MURINE LOCAL LYMPH NODE ASSAY

FINAL REPORT

IITRI PROJECT NO. L08607
STUDY NO. 15
P&G DRD NO.: HBE BTS 0676/01

Testing Facility:

IIT Research Institute
Life Sciences Research
10 West 35th Street
Chicago, IL 60616-3799

Sponsor:

The Procter and Gamble Company
P & G HABC Europe Ltd.
Lovett House, Lovett Road
Staines, Middlesex, TW18 3AZ, UK

September 1997

RECEIVED BY
OCT 13 1997
OPERATIONS SECTION

I. GLP COMPLIANCE STATEMENT

Study Title: Murine Local Lymph Node Assay

Project Number: L08607

Study Number: 15

Study Director: Jennifer T. Kozak, B.S.

This study was conducted in accordance with U.S. Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations (21 CFR Part 58). .The study was not intended for submission and, as such, was not listed on IITRI's master schedule of regulated studies. All chemical analyses and attendant documentation pertaining to the characterization and stability of the bulk test articles (including the test article/carrier mixtures) were the responsibility of the Sponsor. Information pertaining to the characterization and stability of the test articles are on file with the Sponsor. The raw data have been reviewed by the Study Director, who certifies that the information contained in this report accurately reflects the raw data of the study and represents an appropriate conclusion within the context of the study design and evaluation criteria.

Jennifer T. Kozak 9/25/97

Jennifer T. Kozak, B.S. Date
Study Director
Life Sciences Research

Murine Local Lymph Node Assay

FOREWORD

This report describes a study conducted by the Life Sciences Department, IIT Research Institute, for Procter & Gamble HABC Europe during the period of November 6, 1996 (receipt of test animals) to November 18, 1996 (final in-life date). The study was performed under IITRI Project No. L08607, Study No. 15. Vivienne R. Hoyle, Ph.D., served as representative of Procter & Gamble HABC Europe.

Jennifer T. Kozak, B.S., served as the Study Director. J. Brooks Harder, DVM, and Carolyn J. Kucharz, M.S., also participated in the study. Experimental data are recorded in a ring binder labeled L08607/SN15. All raw data generated at IITRI and a copy of the final report will be archived at IITRI. All chemical analyses of the test and control articles, test article/carrier mixtures, and attendant documentation were the responsibility of the Sponsor. Residual test articles and samples of the dosing solutions were returned to the Sponsor on April 3, 1997.

Respectfully submitted,

Jennifer T Kozak 9/25/97

Jennifer T. Kozak, B.S. Date
Study Director
Laboratory Biologist
Life Sciences Research

Approved by:

RV House 9-25-97

Robert V. House, Ph.D. Date
Senior Scientist
Life Sciences Research

Robert L. Sherwood 9/25/97

Robert L. Sherwood, Ph.D. Date
Program Manager,
Microbiology/Immunology
Life Sciences Research

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II. OBJECTIVE

The objective of this study was to examine the potential of two test articles to induce contact hypersensitivity using the murine local lymph node assay. The end point determination for this assay was proliferation of the auricular lymph node cells as determined by radiolabeled thymidine incorporation.

III. SUMMARY

Five mice per group were treated daily for three consecutive days by the direct epicutaneous application onto each ear of 25 µl of either one of two test articles, RE-0981.05 at concentrations of 0.1, 1, 10 and 15% (w/v) or RE-1122.01 at concentrations of 0.1, 1, 5 and 10%, both in a dimethylsulfoxide (DMSO) carrier. In addition, the carrier control group received DMSO and the naive control group received no treatment. Mice were clinically observed twice daily on dosing days, then once daily, for morbidity, mortality and any signs of toxicity, including signs of alteration in the appearance of the test article application site. Approximately 70 hours following final test article application, the animals were injected intravenously (iv) with radiolabeled thymidine to label proliferating cells. Approximately five hours after this injection, the animals were euthanized by CO_2 asphyxiation, the auricular lymph nodes were removed, and single-cell suspensions were prepared. The cells were washed with phosphate-buffered saline to remove unbound radiolabel, then precipitated with trichloroacetic acid. The total radiolabel incorporation in these precipitates was subsequently quantitated by liquid scintillation spectrometry.

No adverse clinical signs and no sign of dermal irritation at the test article application site (*i.e.*, erythema and/or edema) were observed in any test or control animal.

Statistical comparisons were performed for the two test articles separately. That is comparsions between the two control groups and groups treated with RE-0981.05 were conducted first, followed by comparison of the two control groups with groups treated with RE-1122.01. In statistical analyses comparing RE-0981.05-treated groups and the naive and carrier control groups, Bartlett's test of homogeneity was not significant for the log-transformed data (disintegrations per minute; DPM) and the results of Fisher's LSD test were used to compare the data. The mean DPM of the carrier control group was significantly increased compared to that of the naive control group. The mean DPM of all groups treated with RE-0981.05, were statistically significantly increased compared to the mean DPM of the naive control and groups treated with RE-0981.05 at 1, 10 and 15% concentrations were significantly increased compared to the mean DPM of the carrier control. In addition, the stimulation indices for groups treated with 10 and 15% RE-0981.05 were greater than 3.0 relative to the carrier control. In dose-relationship comparisons, the mean DPM of groups treated at 1, 10 and 15% concentration were significantly increased compared to the 0.1% concentration level; groups treated at the 10 and 15% concentration level were also significantly increased compared to the 1% level.

In the comaprison of the control groups with groups treated with RE-1122.01, the results of Bartlett's test were significant, the results of Wilcoxon's Rank Sum test were used. Based on those comparisons, there were no statistically significant differences between the naive and carrier control group with regard to mean DPM. The mean DPM of all groups treated with RE-1122.01, were statistically significantly increased compared to the mean DPM of the naive control and groups treated with RE-1122.01 at 1, 5 and 10% concentrations were significantly increased compared to the mean DPM of the carrier control. In addition, the stimulation indices for groups treated with 1, 5, and 10% RE-1122.01 were greater than 3.0 relative to the carrier control. In dose-relationship comparisons, the mean DPM of groups treated at 1 and 5% concentration were significantly increased compared to the 0.1% concentration level.

IV. MATERIALS AND METHODS

A. Test and Control Articles

Two test articles, RE-0981.05, a light brown powder, and RE-1122.01, a pink powder, were received on November 13, 1996, and were stored at room temperature. Dimethylsulfoxide (DMSO, Sigma Chemical, St. Louis, MO, Lot. No. 53H0634) was used as the carrier for both test articles. RE-0981.05 was prepared at concentrations of 0.1, 1, 10 and 15% (w/v) and RE-1122.01 was prepared at concentrations of 0.1, 1, 5 and 10% (w/v). The dosing solutions were prepared as follows: The highest concentration solution of each test article was prepared by weighing out an aliquot of the test article and mixing with a suitable aliquot of carrier. The lower concentration solutions were prepared by serial dilution of the highest concentration solution with carrier. The dosing solutions were prepared daily on each of the three dosing days. No analyses for the concentration and stability of the test article/carrier mixtures were required of IITRI. Unused test articles and samples of the dosing solutions were returned to the Sponsor on April 3, 1997. Documentation of the strength, purity, stability and composition of the test articles is on file with and is the responsibility of the Sponsor.

B. Experimental Animals

Female CBA/J mice, approximately 6 weeks of age, were received at IITRI on November 6, 1996, from Jackson Laboratory, Bar Harbor, ME. The animals were housed individually in plastic shoe box type cages, and provided Certified Rodent Chow (Purina 5002) and City of Chicago tap water *ad libitum* via water bottles. After approximately one week of quarantine, overall health status was reviewed by the IITRI Staff Clinical Veterinarian before releasing the animals for use in the study. Fifty animals were placed on study following randomization on November 13, 1996. Each animal received an identification mark by indelible ink on the tail, with number of marks corresponding to the number of the animal

within its respective dose group. Individual cage cards were provided bearing the animal number, project number, study number, and dose group. Body weight range upon randomization was 16 to 23 g. The mean body weight of the exposure and control groups (10 groups/5 mice per group) was 20 g. The animal room was maintained at a temperature between 23°C and 25°C and relative humidity between 3% and 50% during the course of the study. Excursions of relative humidity outside the range specified in the protocol were not considered to have adversely affected the outcome of the study. Fluorescent lighting was provided in a 12 hour on/12 hour off cycle. All cages and water bottles were changed once weekly.

The IITRI animal facilities have been fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1975. The animal facilities are also registered with the U.S. Department of Agriculture in compliance with appropriate laws and are regularly inspected by USDA veterinarians. The animal facilities were operated under the overall supervision of the IITRI Staff Clinical Veterinarian, Dr. J. Brooks Harder.

C. Experimental Design

Five mice per group were dosed with test article solutions RE-0981.05 at concentrations of 0.1, 1, 10 and 15% (w/v) or RE-1122.01 at concentrations of 0.1, 1, 5 and 10% (w/v) in a DMSO carrier. The carrier control group was treated identically to the dosed groups but received only DMSO. The mice were dosed once daily for three consecutive days beginning on November 13, 1996. An additional group of five mice (naive control) did not receive any test article or carrier. Mice were observed twice daily on dosing days immediately prior to and approximately 2-4 hours after test article application, then once daily for morbidity, mortality and any signs of toxicity, including signs of alteration in the appearance of the test article application site. On Day 6 of the assay, the mice were injected with tritiated thymidine, and approximately five hours later, the auricular nodes were excised and processed for experimental end points.

D. Murine Local Lymph Node Assay

For dosing, the animals were restrained by hand, and 12.5 μl of carrier or test article solution was applied to the ventral and dorsal surfaces of both pinnae (a total of 25 μl per ear) daily for three consecutive days. All doses were applied with a positive displacement pipettor (Gilson, Villiers-le-Bel, France, Serial Nos. G10581L and J10689K). Naive control mice did not receive any test or control article. On Day 6 of the study, approximately 70 hours after the last dose, each mouse (including naive controls) was injected intravenously with 20 μCi of tritiated thymidine (specific activity of 6.7 Ci/mmole) (ICN, Gardena, CA, Lot No.

61710812) in a total volume of 0.25 ml of phosphate-buffered saline (Bio-Whittaker, Walkersville, MD, Lot No. 5M1046). Approximately five hours later, the animals were euthanized by CO_2 asphyxiation, and the auricular lymph nodes were removed. The nodes were dissociated by rubbing them through nylon macromesh, washed twice in phosphate-buffered saline, resuspended in 5% trichloroacetic acid (TCA; Sigma Chemical Co., Lot No. 112H03662), and refrigerated. Approximately 47 hours later the cells were centrifuged, resuspended in fresh TCA and added to liquid scintillation cocktail fluid (EcoLume; ICN, Lot No. 60145). The acid-precipitable radioactivity was then measured by liquid scintillation spectrometry.

E. Statistical Analysis and Data Presentation

The observed values of disintegrations per minute (DPM) of acid-precipitated auricular lymph node cells were analyzed, with statistical analyses including both normal distribution and distribution-free techniques. The data were log-transformed and analyzed by Bartlett's test for homogeneity and analysis of variance (ANOVA). Subsequent *post-hoc* tests were performed, including the parametric Fisher's test for least significant difference (LSD) and the non-parametric Wilcoxon's rank sum test (also known as the Mann-Whitney U test). The latter is a t-test analog wherein the carrier and naive control groups were each compared to each test group. Which output to heed for significance (the parametric test or the non-parametric) is dictated by the results of Bartlett's test for homogeneity of data. If Bartlett's is significant (*i.e.*, data are not homogeneous) then non-parametric (Wilcoxon's rank sum) statistics are used. If Bartlett's is not significant (*i.e.*, data are homogeneous) parametric (Fisher's LSD) statistics are used. Statistical analyses were performed using SYSTAT (SPSS, Inc., Chicago, IL, version 5.0, 1990) software. A p value of ≤ 0.01 was considered to be significant.

V. RESULTS AND DISCUSSION

A. Daily Observations

No adverse clinical signs and no sign of dermal irritation at the test article application site (*i.e.*, erythema and/or edema) were observed in any test or control animal.

B. Radiolabel Incorporation

Individual and group mean radiolabel incorporation data are shown in Table 1. These results are presented graphically in Figures 1 and 2.

Statisical comparisons were performed for the two test articles separately. That is comparsions between the two control groups and groups treated with RE-0981.05 were conducted first, followed by comparison of the two control groups with groups treated with RE-1122.01. In statistical analyses comparing RE-0981.05-treated groups and the naive and carrier control groups, Bartlett's test of homogeneity was not significant for the log-transformed data (disintegrations per minute; DPM) and the results of Fisher's LSD test were used to compare the data. The mean DPM of the carrier control group was significantly increased compared to that of the naive control group. The mean DPM of all groups treated with RE-0981.05, were statistically significantly increased compared to the mean DPM of the naive control and groups treated with RE-0981.05 at 1, 10 and 15% concentrations were significantly increased compared to the mean DPM of the carrier control. In addition, the stimulation indices for groups treated with 10 and 15% RE-0981.05 were greater than 3.0 relative to the carrier control. In dose-relationship comparisons, the mean DPM of groups treated at 1, 10 and 15% concentration were significantly increased compared to the 0.1% concentration level; groups treated at the 10 and 15% concentration level were also significantly increased compared to the 1% level.

In the comparison of the control groups with groups treated with RE-1122.01, the results of Bartlett's test were significant, the results of Wilcoxon's Rank Sum test were used. Based on those comparisons, there were no statistically significant differences between the naive and carrier control group with regard to mean DPM. The mean DPM of all groups treated with RE-1122.01, were statistically significantly increased compared to the mean DPM of the naive control and groups treated with RE-1122.01 at 1, 5 and 10% concentrations were significantly increased compared to the mean DPM of the carrier control. In addition, the stimulation indices for groups treated with 1, 5 and 10% RE-1122.01 were greater than 3.0 relative to the carrier control. In dose-relationship comparisons, the mean DPM of groups treated at 1 and 5% concentration were significantly increased compared to the 0.1% concentration level.

C. Stimulation Indices

The stimulation index (SI) is a ratio of the DPM values of cells from test animals relative to the control. The SI was determined by dividing the individual DPM values of the treated groups by the mean DPM value of the carrier control group. The mean SI for each group is presented in Table 2.

VI. QUALITY ASSURANCE STATEMENT

Study Title: Murine Local Lymph Node Assay

Project No.: L08607

Study Number: 15

Study Director: Jennifer T. Kozak, B.S.

This study has been subjected to inspections and the report has been audited by the IITRI Quality Assurance Unit in accordance with the U.S. Food and Drug Administration (FDA) "Good Laboratory Practice (GLP) Regulations" - "CFR Title 21 Section 58.35". The report describes the methods and procedures used in the study and the reported results accurately reflect the raw data.

The following are the inspection dates and the dates inspection findings were reported:

	Findings Reported to:	
Date of Inspection	Study Director	Management
October 30, 1996	October 30, 1996	October 30, 1996
November 13, 1996	November 13, 1996	November 13, 1996
June 9 and 10, 1997	June 10, 1997	June 10, 1997
August 1, 1997	August 1, 1997	August 1, 1997

R. A. Boyne 9-24-97

Ronald A. Boyne, B.S. Date
Manager, Quality Assurance

VII. TABLES

MURINE LOCAL LYMPH NODE ASSAY

TABLE 1

Radiolabel Incorporation Data for Individual Animals

Test Article	Mouse Number Within Group 1	2	3	4	5	Mean ± SEM[a]
Naive Control	159[b]	265	162	208	176	194 ± 20
DMSO Carrier	386	425	406	229	403	370 ± 36*
RE-0981.05						
0.1%	382	325	407	398	317	366 ± 19*
1%	564	620	576	924	481	633 ± 76*†
10%	1070	1676	1732	1681	2717	1775 ± 265*†
15%	1288	3515	2549	2443	2275	2414 ± 355*†
RE-1122.01						
0.1%	362	404	491	444	529	446 ± 30*
1%	2013	1768	1823	1095	1677	1675 ± 155*†
5%	2093	2010	2548	2409	1934	2199 ± 119*†
10%	4563	471	1916	2179	2431	2312 ± 657*†

[a] Standard error of the mean
[b] All values expressed as DPM
* Significantly different from the naive control; $p \leq 0.01$
† Significantly different from the carrier control; $p \leq 0.01$

MURINE LOCAL LYMPH NODE ASSAY

TABLE 2

Stimulation Indices of Thymidine Incorporation in
Auricular Lymph Nodes Following Exposure to Test Articles

Test Article	Dose	Stimulation Index[a]
Naive Control	--	0.52[b]
DMSO Carrier Control	--	1.00
RE-0981.05	0.1%	0.99
	1%	1.71
	10%	4.80
	15%	6.52
RE-1122.01	0.1%	1.21
	1%	4.53
	5%	5.94
	10%	6.25

[a] Mean of Individual DPM/Mean DPM of carrier control
[b] Determined relative to mean DPM of the carrier control

VIII. FIGURES

FIGURE 1

THYMIDINE INCORPORATION INTO AURICULAR LYMPH NODES OF MICE TREATED FOR THREE DAYS WITH RE-0981.05

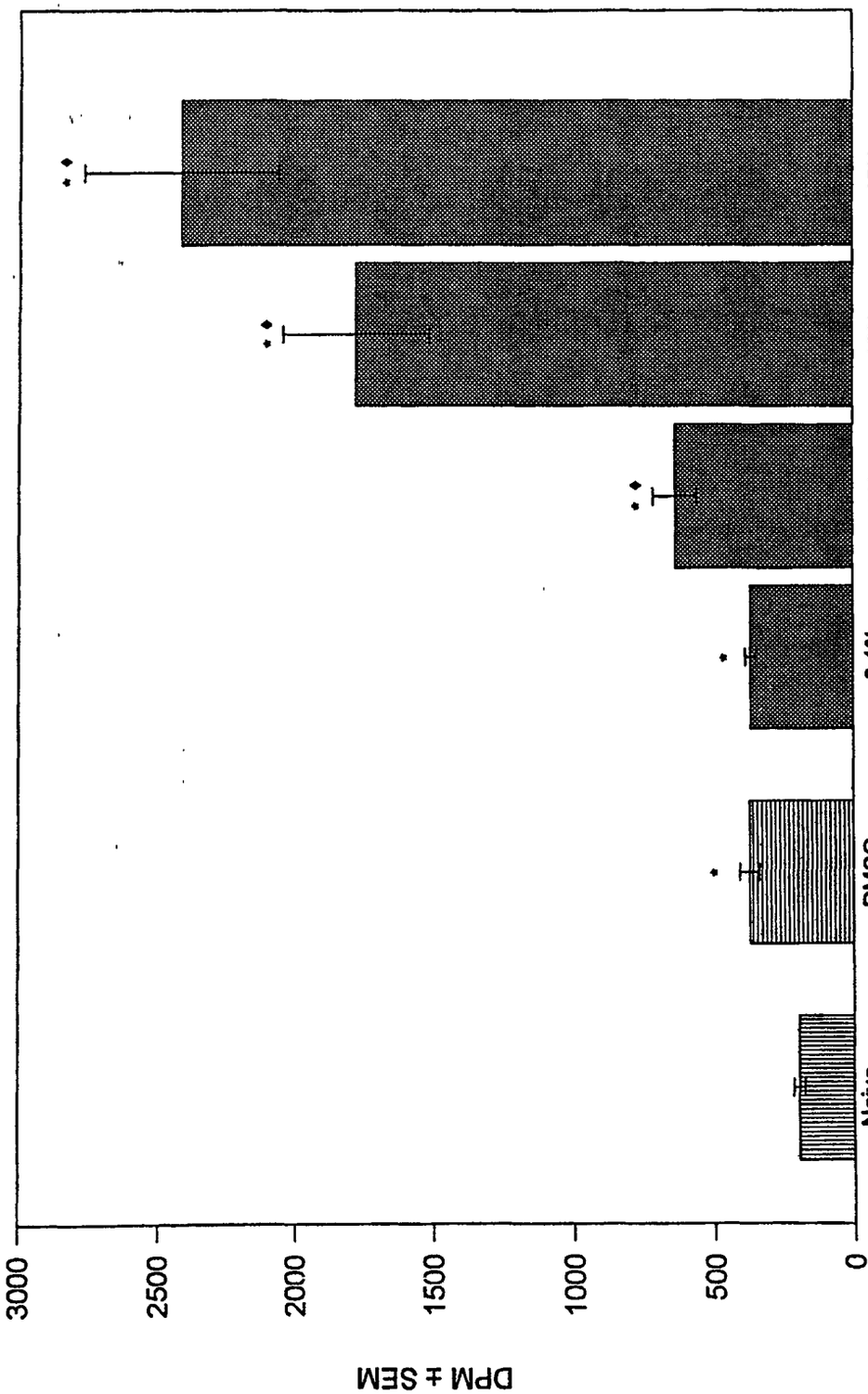
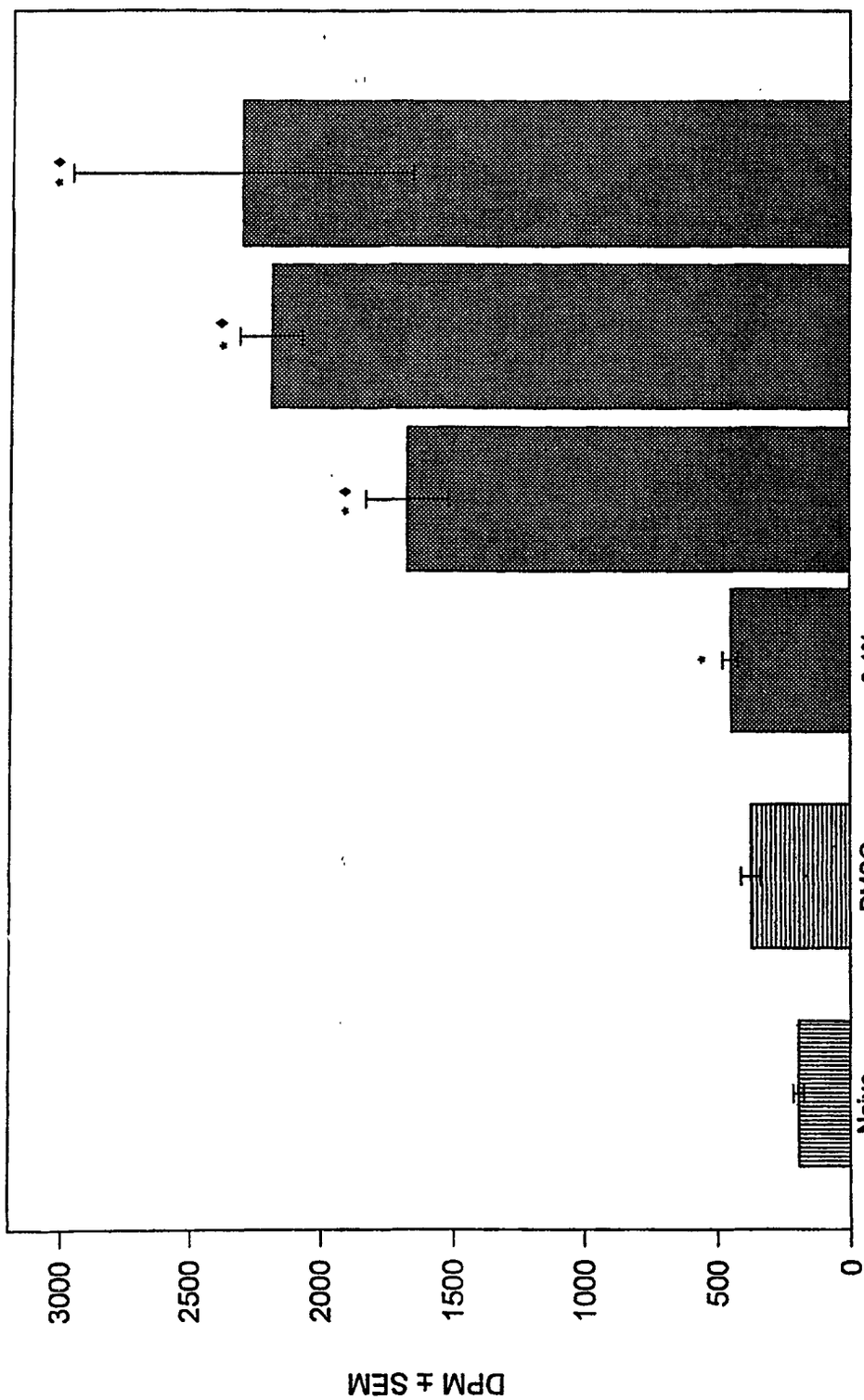


FIGURE 2

THYMIDINE INCORPORATION INTO AURICULAR LYMPH NODES OF MICE TREATED FOR THREE DAYS WITH RE-1122.01



IX. APPENDIX

Protocol
MURINE LOCAL LYMPH NODE ASSAY

Sponsor:

The Procter and Gamble Company
P&G HABC Europe Ltd.
Lovett House, Lovett Rd.
Staines, Middlesex TW18 3AZ, UK

Testing Facility:

IIT Research Institute
10 West 35th Street
Chicago, IL 60616-3799

Purpose:

To evaluate the contact allergenic potential of a test material, under the conditions of this protocol, by its ability to cause lymphocyte proliferation as determined by incorporation of [^{3}H]-thymidine by lymphocytes from the auricular nodes of topically treated mice compared to appropriate controls.

Justification for Selection of Test System:

Tritiated thymidine incorporation into the DNA of lymphocytes isolated from the auricular lymph nodes results from proliferation of the cells after application of a contact sensitizer to the dorsal and ventral sides of the ears. Measurement of [^{3}H]-thymidine uptake by the cells is an objective and quantifiable response. The mouse is the only currently accepted animal model for determining local lymph node proliferative activity following application of sensitizing agents; no *in vitro* alternatives exist.

Route of Administration of Test Material and Reason for Choice:

Direct epicutaneous application to the ears is an appropriate route of administration for assessing the contact allergenic potential of a test material.

Quality Assurance:

This study and final report will be audited by the Quality Assurance Unit in accordance with IITRI's Standard Operating Procedures.

Test Material Characterization:

Information on the methods of formulation and data on the composition or other characteristics that define the test and control materials (including the stability and homogeneity of the test material-carrier mixture(s)) is the Sponsor's responsibility.

Test Material Retention:

Any unused test material will be returned to the Sponsor upon completion of the study.

Animals:

Female CBA/J mice will be obtained from Jackson Laboratory, Bar Harbor, ME. Mice will weigh approximately 17 to 26 grams at randomization for selection for the study. Mice will be 6-9 weeks of age at experiment initiation. The acclimation period will be a minimum of seven days before the animals are placed on test. Five mice per group will be used for all test groups.

Animal Care and Diet:

Mice will be provided access to tap or reverse osmosis (RO) treated water and Certified Rodent Chow 5002 (or equivalent) *ad libitum*.

Note: The animals will be observed daily during treatment for morbidity and mortality. Any animals that exhibit signs of undue stress or discomfort, as judged by the Study Director or the test facility veterinarian, will be euthanized immediately for humane reasons following AAALAC approved guidelines and/or test facility Institutional Animal Care and Use Committee (IACUC) approved procedures. The Sponsor's Divisional Toxicologist will be notified within 24 hours of the animal's euthanasia. Animals which die or are euthanized prior to study termination will be grossly examined. No tissues will be taken for pathology. All findings will be recorded.

Diet and/or Water Analysis Required:

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

Environmental Conditions:

Environmental conditions for the animal room will be observed and recorded daily in accordance with IITRI's Standard Operating Procedures. Animal room temperature will be maintained at 18-26°C, relative humidity will be maintained at 30-70%, and the room will be maintained on a 12-hr on/12-hr off light cycle.

Animal Identification:

Mice will be housed individually in plastic shoe box type cages or in suspended stainless steel cages equipped with an automatic drinking water distribution system and removable food trays for the duration of the study. Control of bias will be addressed by randomization of mice with a computer randomization program prior to initiation of the in-life portion of the study, with each animal assigned a unique number. Animals will be weighed only during the randomization procedure. Each cage will be labeled with the project number, study number, animal number and group number or letter. Each individual animal will be identified by a color code using a water proof felt-tipped pen mark to identify the group and dots of the same color ink on the under side of the tail to identify individual animals within the groups, one dot being animal number 1, two dots indicating animal 2, etc.

Experimental Design:

Each control or treatment group will consist of five animals. The induction period consists of treating the animals once a day for three consecutive days. Approximately 24 ± 2 hours between applications of test material will be maintained. Following the final application of test material the animals will be rested for two days. On day six the animals will be given an intravenous (iv) injection of [^{3}H]-thymidine (66 to 72 hours after the last application of test material to the ears).

Approximately five hours after the iv injections, the animals will be euthanized and the auricular nodes will be removed. Single cell suspensions of the node cells will be prepared and then counted on a liquid scintillation counter to quantitate [^{3}H]-thymidine incorporation.

Dose Preparation and Test Concentrations:

All test material/carrier mixtures will be prepared on the day of use or as indicated in the Protocol Design Specifications and Sponsor Information and Approval form (Attachment 1).

Homogeneity Measurements of Test Material Dilutions/Solutions

Homogeneity measurements are not required for materials that are soluble in the carrier. For suspensions, a sample of top, middle and bottom will be taken and sent to the Sponsor for analysis. Samples will be stored and shipped per the Sponsor's instructions.

Test Material Mixture Concentration

A sample will be taken of each test material mixture/solution used for treatment. These samples will be sent to the Sponsor for analysis. The samples will be stored and shipped per the Sponsor's instructions.

Procedures:

Note: All animal procedures will follow applicable animal welfare procedures, e.g., AAALAC approved guidelines and/or test facility Institutional Animal Care and Use Committee (IACUC) approved procedures. This study will be conducted in accordance with the Testing Facility's Standard Operating Procedures.

A. Application of Test Material:

The animals will be restrained in such a manner as to allow free access to the dorsal and ventral sides of both ears. Using an adjustable push button pipet, 12.5 μl of test material will be applied to the dorsal and ventral sides of each ear, for a total of 25 μl of test material per ear or as otherwise instructed by the Sponsor. Care will be taken to ensure that the test material does not run off the ear during application. Pipets are to be calibrated at least every three months (90 days) to assure accurate delivery of the 0.0125 ml volume.

B. Daily Observations of Test Material Application Sites:

All animals will be observed twice daily at a time immediately prior to, and approximately 2-4 hours subsequent to, test material application for any significant alterations in the appearance of the test material application sites (i.e., erythema and edema). All observations of pinnae appearance will be documented.

C. Intravenous Injection of [^{3}H]-Thymidine:

Each animal will receive 0.250 ml of phosphate buffered saline (PBS) containing 20 μCi of [^{3}H]-thymidine (specific activity of 6.7 Ci/mmol). A heat lamp may be used to dilate the tail veins for easier iv injections. The animal will be restrained in such a manner as to allow complete access to the tail. A 1 cc disposable syringe and 25-27 gauge needle may be used for iv injections. An animal will be excluded from the study if the full 0.250 ml of [^{3}H]-thymidine/PBS is not properly

iv injected. Statistical analysis will not be performed on a group when more than one mouse is excluded from the group.

D. Lymph Node Removal:

Approximately five hours after the [^{3}H]-thymidine injections, the animals will be euthanized with CO_2 and the auricular lymph nodes removed and pooled for each individual animal. Care will be taken to assure that the lymph nodes are removed intact. Once the lymph nodes are removed, they will be placed in a 12x75 mm capped tissue culture tube containing 4 ml of PBS.

E. Single Cell Suspension:

The lymph nodes will be transferred to a 60mm tissue culture dish by pouring the PBS from the tubes containing the lymph nodes. Both the top and bottom of the tissue culture dish may be used for preparing single cell suspensions for each individual animal. The lymph nodes will be placed onto an approximately 1 inch square section of nylon macromesh (mesh opening ~100 microns, ~85 microns thick) with a small amount of PBS (0.5-1.5 ml). The capsule will be snipped with a small pair of pointed surgical scissors and the nodes will be gently rubbed through the nylon screen using the rubber surface of a plunger from a 1 cc disposable syringe. A Pasteur pipet and a small pair of forceps will be used to rinse the screen with PBS into the bottom portion of the tissue culture dish. The nylon filter will be discarded after rinsing and the tissue culture dish rinsed with the PBS. The PBS will be placed back into the 12x75 mm round bottom tube to allow the capsule debris to settle to the bottom. After approximately 5 minutes the PBS will be carefully drawn off with a Pasteur pipet and placed in a 15 ml conical bottom centrifuge tube containing 6 ml of PBS (approximately 10 ml total tube volume) and the cell suspensions centrifuged at 200xg for 10 minutes. After the first wash in PBS the cells will be resuspended in 10 ml of PBS, and a second wash will be performed. After completion of the second wash, the cells will be suspended in 3 ml of 5% trichloroacetic acid (TCA) (w/v, distilled H_2O) and left at approximately 4°C for 18 to 72 hours.

F. Preparation for Scintillation Counting:

The cell suspensions will be centrifuged at 200xg for 10 minutes and resuspended in 1 ml of 5% TCA. Scintillation vials containing 10 ml of Ecolume scintillation cocktail will be appropriately labeled with the individual animal numbers. The individual cell suspensions will be transferred into the appropriate vials along with an additional 1 ml of TCA which has been used to rinse the bottom portion of the tube. The TCA and scintillation fluid will be thoroughly mixed by gently swirling the contents of the vial until the solution becomes clear.

G. Scintillation Counting:

A liquid scintillation system will be used for counting. The samples will be counted for 5-10 minutes and the counts recorded in disintegrations per minute (DPM).

Protocol Changes:

Should it become necessary to change the approved protocol, verbal agreement to make those changes should be made between the Study Director and the Sponsor's Divisional Toxicologist or Alternate Divisional contact. As soon as practical, the change, date of 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:

The report will include how the study was conducted, including any deviations from the protocol, and the dates of study initiation and completion. Data for each animal will be included in the final report. Also, calculation of the group mean DPM ± standard error of the mean (SE) for each group and a graphic representation of the results using the group mean and SE (standard error is to be calculated using n-1) will be included. In addition, the fold increase in the mean of isotope incorporation relative to the control group will be determined and included in the final report. The observed values of disintegrations per minute (DPM) from acid-precipitated murine auricular lymph nodes will be analyzed. Data will be log-transformed, and statistical analyses may include both normal distribution and distribution-free techniques. If Bartlett's test for homogeneity of variance is not significant, comparisons with the control group (and other specific, pairwise comparisons of groups) will be based on the least significant difference criterion. If Bartlett's test is significant, these comparisons will be based on Wilcoxon's rank sum test. All statistical tests shall be conducted at a 1%, two-sided risk level. The report shall conform to all requirements outlined in CFR Title 21, Part 58, Subpart J, Section 58.185, Good Laboratory Practice Regulations.

Maintenance of Raw Data and Records:

Original data or copies thereof, will be available at the testing facility to facilitate auditing of the study during its progress and before acceptance of the final report. When the final report is completed, all experimental data generated by the testing facility and a copy of the final report will be retained in the archive of the testing facility.

Proposed Study Starting Date: 11/13/96
Defined as: First day of dosing

Proposed Study Completion Date: 11/18/96
Defined as: End of in-life phase of study

Study Director: J. T. Kozak J. T. Kozak
(Print Name and Signature)

Date: 11/11/96

Quality Assurance Representative: K. A. Boyne R. A. Boyne
(Print Name and Signature)

Date: 12-4-96

L08607 SN

pg. ~~7~~ 6 of 7
wrong pg
#. JTK 10/

Attachment 1. Murine Local Lymph Node Assay
Protocol Design Specifications and Sponsor Information and Approval

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Alternative contact:
Pauline M. McNamee, PhD
Phone: 44-1784-495125
Fax: 44-1784-

Sponsor's Representative:
Vivienne R. Hoyle, PhD
Procter & Gamble HABC Europe
Lovett House, Lovett Rd,
Staines, Middlesex, TW18 3AZ
Phone: 44-1784-495125
Fax: 44-1784-495043

P&G DRD No.: HBE BTS 0676/01

Regulatory Compliance: This study will be conducted in accordance with (Check all that apply):

[✓] FDA Good Laboratory Practice Regulations (and OECD GLP) JTK 10/15/~~97~~ 96 RE: JTK 7/7/97.
[ ] EPA Good Laboratory Practice Standards
[✓] With the exception that the study will not be listed on the Testing Facility's Master Schedule of GLP regulated studies, as it is not expected to be submitted to a regulatory agency

Test Material(s):

TSIN	Color	Physical Form	Expiration Date
RE-0981.05	off.white/grey brown	crystalline powder	30 Dec 96
RE-1122.01	off.white/pink	crystalline	30 Dec 96

Test Material Storage Condition (Check one):

Bulk Material: [ ] Room Temperature
[✓] Refrigerated
[ ] Frozen

Formulated Material: [ ] Room Temperature
[ ] Refrigerated
[ ] Frozen

[ ] Other: _____

Test Material Hazards:
[ ] None Known
[ ] Unknown (not evaluated)
[✓] As follows: RE-0981.05 : Harmful, Irritant
RE-Ø1122.01 : Harmful, Irritant, Sensitiser
VRH 28 Nov 96

IITRI Project No. L08607
Study No. 15

pg. 6 of 7
wrong pg. # JTK 10/3

Dose Selection:
Dose assay at the following levels:
[✓] 4 concentrations per test material (specify % concentrations w/v, v/v, w/w, etc.)
[✓] carrier control
[✓] naive control

Test Material	Concentration(s)	Carrier
RE-0981.505 VRH 28Nov96	0.1, 1.0, 10.0, 15.0 % (w/v)	DMSO
RE-1122.01	0.1, 1.0, 5.0, 10.0 % (w/v)	DMSO

Other Comments and Instructions:
prepare fresh test article solutions daily.

Test Material Carrier(s):
[ ] Acetone [ ] 80% Ethanol [ ] Dimethylformamide [✓] Dimethylsulfoxide
[ ] Distilled water [ ] Propylene glycol, USP [ ] Other: _____

Test material formulation is a: [ ] suspension [✓] solution [ ] emulsion

Concentration Analyses: Analysis of concentration/stability/homogeneity of the test material-carrier mixture(s):
Will be performed by the Sponsor; volume required n/a ml
Any unused test material(s) will be returned to the Sponsor

Shipping Instruction for Test Solutions/Mixtures:
Send approximately _____ ml of test solution/mixture, [ ] frozen; [ ] under ambient conditions;
[ ] Other n/a to

Return Unused Test Material to:
Mrs. A. Sanger
Procter & Gamble HABC Europe
Rusham Park, Whitehall Lane
Egham, Surrey, TW20 9NZ, UK
9NW VRH 28Nov96

Send Invoices to:
FAO: Ms. T. Martin
Procter & Gamble HABC Europe
Lovett House, Lovett Rd.
Staines, Middlesex, TW18 3AZ

Relevant alternative test procedures were reviewed and no acceptable non-animal method was found to exist. Further, the relevant literature was reviewed and no data were found that would preclude the need to conduct this test.

Divisional Toxicologist: VRHayes Date: 30-9-96

PROTOCOL AMENDMENT NO. 1

Effective Date: 11-13-96

Project No.: L08607

Study No.: 15

Nature of Revision:

Test Materials RE-0981.05 and RE-1122.01 were stored at room temperature instead of refrigerated.

Reason for Change:

On page 6 of the Protocol under *Test Material Storage Condition*, the Sponsor instructed that Test Materials RE-0981.05 and RE-1122.01 were to be stored refrigerated. However, the labeling on the Test Material containers received on 11-13-96 indicated room temperature storage. Sponsor representative Dr. Vivienne Hoyle was contacted by telephone to verify the chemical stability of the Test Materials at room temperature. She stated that room temperature storage of the Test Materials was acceptable.

Study Director: Jennifer A. Kozak Date: 8/4/97

Quality Assurance: K. A. Bayne Date: 8/5/97

Sponsor Representative: V R Hoyle Date: 22-8-97

Protocol Amendment 1
L08607 SN 15
page 1 of 1

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

***Section I*: P&RS Study Related Reference Numbers (To be completed by P&RS)**

Test Substance Identification Number (TSIN) RE- 1122.01

Divisional Request Document(s) HBE BTS 0675/01, 0676/01,0679/01

***Section II*: Test Substance General Characteristics**
(To be completed by Originator, helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or Ingredient (or code designation): 4-(N-ethyl-N-2-methanesulphonylaminoethyl)-2-methylphenylenediamine sesquisulphate monohydrate Also called Eastman Color Developing Agent CD-3

Supplier's Name: Eastman

Brand Notebook Reference M217 / 17197 / 17198, 17199, 17200 LA# G5171
(test substance source, production code if available and date ingredient received or date product made)

Physical Form: Crystals Color: off white/pink pH: _____ at: _____ %

Density/Sp.Gravity: NA Ingredient Mol. Wt.: 436.52 Ingredient Solubility: 380g/L @25°C water

Storage Conditions: keep closed, dry, cool Viscosity: NA

Expiration Date (Day/Month/Year): 30/12/96 Ingredient Stability : Stable

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows: Harmful irritant sensitizer

Originator's Section Head: J C Dunbar (Name) J Dunlop (Signature) 27/9/96 (Date)

***Section III:* Test Substance Composition and Analytical Information**

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for the safety testing indicated by the Divisional Request Document (s).

Divisional Toxicologist: V R Hayle (Name) V. R. HOYLE (Signature) 27-9-96 (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Cas # 025646-71-3						ACN 31860 FTIR reference spectra collected for sample. N1016/47 [signature] 24Sep96			
Compositional Information Provided by: [signature] 18/9/96						Analytical Verification by: P.J. Greenhill 25/9/96.			
(ORIGINATOR NAME/SIGNATURE/DATE) Signature verifies integrity of all data provided (including Section II)						(ANALYTICAL MGR NAME/SIGNATURE/DATE) Signature verifies only Analyzed Value & Reference.			

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

(NAME/SIGNATURE/DATE) [signature] 25/9/96

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methyl phenylenediamine
Purity:	99.6%
Remarks:	Test Substance was identified as RE-1122.02. Group H was the only Group containing the reportable substance alone.
Comments:	Study report includes mixtures or compounds unrelated to the 8(d) rule (Groups A – G).

Method

Method / Guideline:	Murine Local Lymph Node Assay
Test Type:	Delayed contact hypersensitivity / Skin sensitization
Report Year:	1997
GLP:	Yes
Species:	Mouse
Strain:	CBA/J
Gender:	female
Doses:	Group H received 3.81% RE1122.02. Naïve control received no treatment. Carrier control received water.
Number of Animals:	50 (5 / group)
Study Design:	Animals received 12.5 µl of carrier or one of the test solutions to the ventral and dorsal surface of both pinnae (total of 25 µl per ear, 50 ul per mouse) for 3 consecutive days. On day 6, each mouse was injected i.v. with 20 µCi of titrated thymidine (specific activity of 6.7 Ci/mmole) in a total volume of 0.25 ml of phosphate buffered saline. Lymph nodes were removed five hours later and dissociated. The radioactivity was measured by liquid scintillation spectrometry.

Results

Result:	There were no statistically significant differences in DPM between any of the treated and control groups. The stimulation indices for Group H were less than 3.0 relative to the control groups.
Remarks:	No clinical signs were observed in any of the mice and no animals died during the study.
Conclusion:	Under the conditions of this test, the test material (Group H) was negative for contact allergenic potential.

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	L08607 SN23
Reference:	Procter & Gamble, 1997. Murine Local Lymph Node Assay. Accession #43675.

ACC#43675 97C070 R

MURINE LOCAL LYMPH NODE ASSAY

FINAL REPORT

IITRI PROJECT NO. L08607
STUDY NO. 23
HBE BTS 0689/02.

Testing Facility:

IIT Research Institute
Life Sciences Research
10 West 35th Street
Chicago, IL 60616-3799

Sponsor:

The Procter & Gamble Company
Lovett House
Lovett Road
Staines, Middlesex TW18 3AZ, UK

December 1997

RECEIVED BY
DEC 15 1997
OPERATIONS SECTION

IITRI since 1936
COMMITMENT TO EXCELLENCE

I. GLP COMPLIANCE STATEMENT

Study Title:	Murine Local Lymph Node Assay
Project Number:	L08607
Study Number:	23
Study Director:	Jennifer T. Kozak, B.S.

This study was conducted in accordance with U.S. Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations (21 CFR Part 58), except that the study was not intended for submission to a regulatory agency; consequently, the study was not listed on the master schedule of regulated studies. All chemical analyses and attendant documentation pertaining to the characterization and stability of the bulk test articles were the responsibility of the Sponsor. Information pertaining to the characterization and stability of the test articles are on file with the Sponsor. No analyses, except pH adjustment, were performed to confirm concentrations, homogeneity or stability of the test solutions. The raw data have been reviewed by the Study Director, who certifies that the information contained in this report accurately reflects the raw data of the study and represents an appropriate conclusion within the context of the study design and evaluation criteria.

Jennifer T. Kozak 12/09/97

Jennifer T. Kozak, B.S. Date
Study Director
Life Sciences Research

FOREWORD

This report describes a study conducted by Life Sciences Research, IIT Research Institute (IITRI), for The Procter & Gamble Company during the period of May 14, 1997 (receipt of test animals) to June 2, 1997 (final in-life date). The study was performed under IITRI Project No. L08607, Study No. 23. V. R. Hoyle, Ph.D., served as representative of The Procter & Gamble Company.

Jennifer T. Kozak, B.S., served as the Study Director. J. Brooks Harder, DVM, and J. Fred Krueger, M.S., also participated in the study. Experimental data are recorded in a ring binder labeled L08607/SN23. All raw data generated at IITRI and a copy of the final report will be archived at IITRI. All chemical analyses of the test articles and test article/carrier mixtures and attendant documentation were the responsibility of the Sponsor.

Respectfully submitted,

Jennifer T. Kozak, B.S. — 12/09/97 Date
Study Director
Laboratory Biologist
Life Sciences Research

Approved by:

Robert V. House, Ph.D. — 12-9-97 Date
Senior Scientist
Life Sciences Research

Robert L. Sherwood, Ph.D. — 12/9/97 Date
Manager, Microbiology/Immunology
Life Sciences Research

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II. OBJECTIVE

The objective of this study was to examine the contact allergenic potential of three test articles in various mixtures as specified by the Sponsor (see protocol, Appendix), by their abilities to cause lymphocyte proliferation as determined by incorporation of [^{3}H]-thymidine by lymphocytes from the auricular nodes of topically treated mice compared to appropriate controls.

III. SUMMARY

Five mice per group were treated daily for three consecutive days by the direct epicutaneous application onto each ear of 25 µl of the pH-adjusted admixtures of three test articles (RE1122.02, RE1044.04 and RE1142.01) in a ASTM Type 1 water carrier. Another group of five mice received ASTM Type 1 water only and served as a carrier control group. An additional group of five mice received no treatment and served as a naive control. At the request of the sponsor, the dosing admixtures were identified as Test Solutions A through H, with the further stipulation that Test Solution G was to be considered as a control for Test Solutions A through F and H. Mice were clinically observed twice daily on dosing days immediately prior to and approximately 2-4 hours after dosing, then once daily, for morbidity, mortality and any signs of toxicity, including signs of alteration in the appearance of the test article application site. Approximately 68 hours following final test solution application, the animals were injected intravenously (iv) with radiolabeled thymidine to label proliferating cells. Approximately five hours after this injection, the animals were euthanized by CO_2 asphyxiation, the auricular lymph nodes were removed, and single-cell suspensions were prepared. The cells were washed with phosphate-buffered saline to remove unbound radiolabel, then precipitated with trichloroacetic acid. The total radiolabel incorporation in these precipitates was subsequently quantitated by liquid scintillation spectrometry.

No clinical signs were observed in any of the mice and no deaths occurred during the study.

Statistical comparisons were performed by comparing the groups treated with Test Solutions A through F and H with the naive control, carrier control and Test Solution G-treated groups. The results of Bartlett's test of homogeneity were not significant (p=0.011) for the log-transformed data (disintegrations per minute; DPM) and consequently, Fisher's LSD test was used to compare the data.

The results of the overall Analysis of Variance test including all groups were not statistically significant. More specifically, there were no statistically significant differences between any of the treated and control groups and the stimulation indices for the treated groups were less than 3.0 relative to the control groups.

IV. MATERIALS AND METHODS

A. Test and Control Articles

The test article RE1122.02 (an off-white/pinkish solid) was received on March 19, 1997. The test article RE1142.01 (a clear, colorless liquid) was received on April 9, 1997. The test article RE1044.04 (a clear, colorless liquid) was received on April 9, 1997 and May 23, 1997. The test articles were stored at room temperature (RE1122.02 and RE1142.01) or refrigerated (RE1044.04) in the original containers. The Sponsor provided specific instructions for the preparation of dosing admixtures of the three test articles in ASTM Type 1 water (vehicle control). These instructions were stringently adhered to in the daily preparation of the pre-mixes and dosing formulations. The Sponsor's instructions are included as an attachment and amendments (*i.e*, Amendments 1-3) to the protocol (see Appendix 1). The dosing admixtures were identified as Test Solutions A through H. Test Solution C formed a precipitate when prepared on all three dosing days. Remnants of the dosing solutions were discarded following dosing. No analyses for determining the concentration and stability of the test articles or carrier control were required to be performed by IITRI. Unused test articles were discarded at the termination of the treatment phase. Documentation of the strength, purity, stability and composition of the test articles is on file with and is the responsibility of the Sponsor.

B. Experimental Animals

Female CBA/J mice, approximately 6 weeks of age, were received at IITRI on May 14, 1997, from Harlan Sprague Dawley, Indianapolis, IN. (Protocol specification of Jackson Laboratory, Bar Harbor, ME, as the source for animals was not met due to animal availability. Using an alternative source for animals did not adversely affect the outcome of the study.) The animals were housed individually in plastic shoe box type cages and were provided Certified Purina Rodent Chow 5002 (PMI Feeds, Inc., St. Louis, MO) and City of Chicago tap water *ad libitum* via water bottles. After thirteen days of quarantine, overall health status was reviewed by the IITRI Staff Clinical Veterinarian before releasing the animals for use in the study. Fifty animals were placed on study following randomization on May 28, 1997. Each animal received an identification mark by indelible ink on the tail, with the number of marks corresponding to the number of the animal within its respective dose group. Individual cage cards were provided bearing the animal number, project number, study number, and dose group. Body weight range upon randomization was 18 to 23 g. The mean body weights of

the exposure and control groups (10 groups/5 mice per group) were 20.6 to 21.2 g. The animal room was maintained at a temperature between 19°C and 22°C and relative humidity between 44% and 79% during the course of the study. Excursions of relative humidity outside the range specified in the protocol were not considered to have adversely affected the outcome of the study. Fluorescent lighting was provided in a 12 hour on/12 hour off cycle. All cages were changed at least once weekly.

The IITRI animal facilities have been fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1975. The animal facilities are also registered with the U.S. Department of Agriculture in compliance with appropriate laws and are regularly inspected by USDA veterinarians. The animal facilities are operated under the overall supervision of the IITRI Staff Clinical Veterinarian, Dr. J. Brooks Harder.

C. Experimental Design

Five mice per group were dosed with pH-adjusted Test Solutions A through H in ASTM Type 1 water (carrier). The carrier control group was treated identically to the Test Solution-dosed groups and received only ASTM Type 1 water. Mice were dosed once daily for three consecutive days beginning on May 28, 1997. Five naive control mice were not treated with test article or carrier. All mice were observed twice daily on dosing days immediately prior to and approximately 2-4 hours after dosing, then once daily for morbidity, mortality and any signs of toxicity, including signs of alteration in the appearance of the Test Solution application site. On Day 6 of the assay, the mice were injected with tritiated thymidine and approximately five hours later, the auricular nodes were excised and processed for experimental end points.

D. Murine Local Lymph Node Assay

For dosing, the animals were restrained and 12.5 µl of carrier or one of the Test Solutions was applied to the ventral and dorsal surfaces of both pinnae (a total of 25 µl per ear, 50µl per mouse) daily for three consecutive days. All doses were applied with a positive displacement pipettor (Gilson, Villiers-le-Bel, France, Serial No. G10581L). On Day 6 (June 2, 1997) of the study, approximately 68 hours after the last dose, each mouse was injected intravenously with 20 µCi of tritiated thymidine (specific activity of 6.7 Ci/mmole) (ICN, Gardena, CA, Lot No. 61710303) in a total volume of 0.25 ml of phosphate-buffered saline (Bio-Whittaker, Walkersville, MD, Lot No. 7M0166). Approximately five hours later, the animals were euthanized by CO_2 asphyxiation, and the auricular lymph nodes were removed.

The nodes were dissociated by rubbing them through nylon macromesh, washed twice in phosphate-buffered saline, resuspended in trichloroacetic acid (TCA; Sigma Chemical Co., Lot No. 85H06621), and refrigerated (approximately 4°C). Approximately 63 hours later, the cells were centrifuged, resuspended in fresh TCA and added to liquid scintillation cocktail fluid (EcoLume; ICN, Lot No. 60145). The acid-precipitable radioactivity was then measured by liquid scintillation spectrometry.

E. Statistical Analysis and Data Presentation

The observed values of disintegrations per minute (DPM) of acid-precipitated auricular lymph node cells were compared with statistical comparisons including both normal distribution and distribution-free techniques. The data were log-transformed and analyzed by Bartlett's test for homogeneity and analysis of variance (ANOVA). Subsequent *post-hoc* comparisons were performed, including the parametric Fisher's test for least significant difference (LSD) and the non-parametric Wilcoxon's Rank Sum test (also known as the Mann-Whitney U test). The latter is a t-test analog wherein the carrier and naive control groups were each compared to each test group. Which output to heed for significance (the parametric test or the non-parametric) is dictated by the results of Bartlett's test for homogeneity of data. If Bartlett's is significant (*i.e.*, data are not homogeneous) then non-parametric (Wilcoxon's Rank Sum) statistics are used. If Bartlett's is not significant (*i.e.*, data are homogeneous) parametric (Fisher's LSD) statistics are used. Statistical comparisons were performed using SYSTAT (SPSS, Inc., Chicago, IL, version 5.0, 1990) software. A p value of ≤ 0.01 was considered to be significant.

V. RESULTS AND DISCUSSION

A. Daily Observations

No clinical signs were observed in any of the mice and no animals died during the study.

B. Radiolabel Incorporation

Individual and group mean radiolabel incorporation data are shown in Table 1. These results are presented graphically in Figure 1.

Statistical comparisons were performed comparing the groups treated with Test Solutions A through F and H with the naive control, carrier control and Test Solution G-treated groups. The results of Bartlett's test of homogeneity were not significant (p=0.011) for the log-

transformed data (disintegrations per minute; DPM) and Fisher's LSD test were used to compare the data.

The results of the overall Analysis of Variance test including all groups were not statistically significant. More specifically, there were no statistically significant differences between any of the treated and control groups.

C. Stimulation Indices

The stimulation index (SI) is a ratio of the DPM values of cells from the test animals relative to the carrier or Test Solution G controls. Two SI values were determined by dividing the individual DPM values of the treated groups by the mean DPM value of either the carrier control or Test Solution G-treated groups. The two mean SI values (based on the carrier and Test Solution G controls) for each group are presented in Table 2.

VI. QUALITY ASSURANCE STATEMENT

Study Title: Murine Local Lymph Node Assay

Project No.: L08607

Study Number: 23

Study Director: Jennifer T. Kozak, B.S.

This study has been subjected to inspections and the report has been audited by the IITRI Quality Assurance Unit in accordance with the U.S. Food and Drug Administration (FDA) "Good Laboratory Practice (GLP) Regulations" - "CFR Title 21 Section 58.35". The report describes the methods and procedures used in the study and the reported results accurately reflect the raw data.

The following are the inspection dates and the dates inspection findings were reported:

Dates of Inspection	Study Director	Findings Reported To Management
April 1, 1997	April 1, 1997	April 1, 1997
April 18, 1997	April 18, 1997	April 18, 1997
May 14, 1997	May 14, 1997	May 14, 1997
May 21, 1997	May 21, 1997	May 21, 1997
May 27, 1997	May 27, 1997	May 27, 1997
May 28, 1997	May 28, 1997	May 28, 1997
July 30, 1997	July 30, 1997	July 30, 1997
October 7 and 8, 1997	October 9, 1997	October 9, 1997

R. A. Boyne 12-8-97

Ronald A. Boyne, B.S. Date
Manager, Quality Assurance

VII. TABLES

MURINE LOCAL LYMPH NODE ASSAY

TABLE 1

Radiolabel Incorporation Data for Individual Animals

	Mouse Number Within Group					
Test article	1	2	3	4	5	Mean ± SEM[a]
Naive Control	200[b]	111	196	141	179	165 ± 17.2
Carrier Control	251	120	138	143	114	153 ± 25.1
Solution A	159	137	286	177	133	178 ± 28.0
Solution B	528	195	195	150	245	263 ± 68.0
Solution C	873	282	261	155	351	384 ± 126.1
Solution D	177	231	209	221	216	211 ± 9.1
Solution E	229	215	207	1053	117	364 ± 173.5
Solution F	152	627	99	291	254	285 ± 92.2
Solution G	131	186	146	123	113	140 ± 12.8
Solution H	258	215	166	355	152	229 ± 36.7

[a] Standard error of the mean
[b] All values expressed as DPM

MURINE LOCAL LYMPH NODE ASSAY

TABLE 2

Stimulation Indices of Thymidine Incorporation in Auricular Lymph Nodes Following Exposure to Test Articles

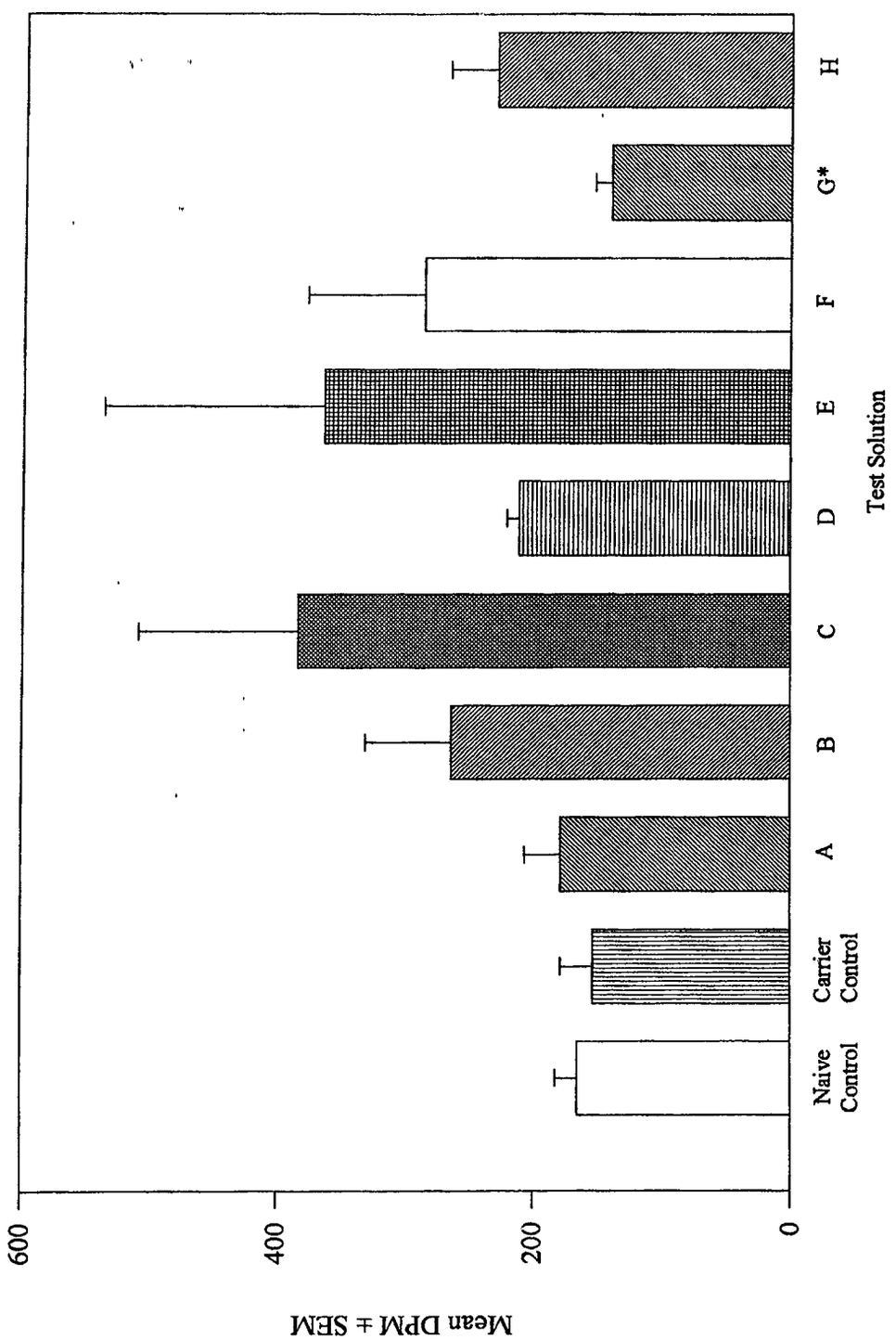
Treatment Group	Stimulation Index[a]	Stimulation Index[c]
Naive Control	1.08[b]	--
Carrier Control	1.00	--
Solution A	1.16	1.27[d]
Solution B	1.71	1.87
Solution C	2.51	2.74
Solution D	1.37	1.50
Solution E	2.37	2.60
Solution F	1.86	2.03
Solution G	0.91	1.00
Solution H	1.49	1.63

[a] Mean of Individual DPM/Mean DPM of the carrier control
[b] Determined relative to mean DPM of the carrier control
[c] Mean of Individual DPM/Mean DPM of Test Solution G
[d] Determined relative to mean DPM of Test Solution G
-- Not determined relative to mean DPM of Test Solution G

VIII. FIGURE

FIGURE 1

THYMIDINE INCORPORATION INTO AURICULAR LYMPH NODES OF MICE TREATED FOR THREE DAYS WITH TEST SOLUTIONS AND CARRIER CONTROL



* = Control for Test Solutions A-F and H

IX. APPENDIX

Protocol
MURINE LOCAL LYMPH NODE ASSAY

Sponsor: The Procter and Gamble Company
DR. V. B. HOYLE
LOVETHE HOUSE, LOVETHE ROAD
STAINES, MIDDLESEX
TW18 3AZ, UK

Testing Facility: IIT Research Institute
10 West 35th Street
Chicago, IL 60616-3799

Purpose:

To evaluate the contact allergenic potential of a test material, under the conditions of this protocol, by its ability to cause lymphocyte proliferation as determined by incorporation of [^{3}H]-thymidine by lymphocytes from the auricular nodes of topically treated mice compared to appropriate controls.

Justification for Selection of Test System:

Tritiated thymidine incorporation into the DNA of lymphocytes isolated from the auricular lymph nodes results from proliferation of the cells after application of a contact sensitizer to the dorsal and ventral sides of the ears. Measurement of [^{3}H]-thymidine uptake by the cells is an objective and quantifiable response. The mouse is the only currently accepted animal model for determining local lymph node proliferative activity following application of sensitizing agents; no *in vitro* alternatives exist.

Route of Administration of Test Material and Reason for Choice:

Direct epicutaneous application to the ears is an appropriate route of administration for assessing the contact allergenic potential of a test material.

Quality Assurance:

This study and final report will be audited by the Quality Assurance Unit in accordance with IITRI's Standard Operating Procedures.

Test Material Characterization:

Information on the methods of formulation and data on the composition or other characteristics that define the test and control materials (including the stability and homogeneity of the test material-carrier mixture(s)) is the Sponsor's responsibility.

Test Material Retention:

Any unused test material will be returned to the Sponsor upon completion of the study.

Animals:

Female CBA/J mice will be obtained from Jackson Laboratory, Bar Harbor, ME. Mice will weigh approximately 17 to 26 grams at randomization for selection for the study. Mice will be 6-9 weeks of age at experiment initiation. The acclimation period will be a minimum of seven days before the animals are placed on test. Five mice per group will be used for all test groups.

Animal Care and Diet:

Mice will be provided access to tap or reverse osmosis (RO) treated water and Certified Rodent Chow 5002 (or equivalent) *ad libitum*.

Note: The animals will be observed daily during treatment for morbidity and mortality. Any animals that exhibit signs of undue stress or discomfort, as judged by the Study Director or the test facility veterinarian, will be euthanized immediately for humane reasons following AAALAC approved guidelines and/or test facility Institutional Animal Care and Use Committee (IACUC) approved procedures. The Sponsor's Divisional Toxicologist will be notified within 24 hours of the animal's euthanasia. Animals which die or are euthanized prior to study termination will be grossly examined. No tissues will be taken for pathology. All findings will be recorded.

Diet and/or Water Analysis Required:

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

Environmental Conditions:

Environmental conditions for the animal room will be observed and recorded daily in accordance with IITRI's Standard Operating Procedures. Animal room temperature will be maintained at 18-26 C, relative humidity will be maintained at 30-70%, and the room will be maintained on a 12-hr on/12-hr off light cycle.

Animal Identification:

Mice will be housed individually in plastic shoe box type cages or in suspended stainless steel cages equipped with an automatic drinking water distribution system and removable food trays for the duration of the study. Control of bias will be addressed by randomization of mice with a computer randomization program prior to initiation of the in-life portion of the study, with each animal assigned a unique number. Animals will be weighed only during the randomization procedure. Each cage will be labeled with the project number, study number, animal number and group number or letter. Each individual animal will be identified by a color code using a water proof felt-tipped pen mark to identify the group and dots of the same color ink on the under side of the tail to identify individual animals within the groups, one dot being animal number 1, two dots indicating animal 2, etc.

Experimental Design:

Each control or treatment group will consist of five animals. The induction period consists of treating the animals once a day for three consecutive days. Approximately 24 ± 2 hours between applications of test material will be maintained. Following the final application of test material the animals will be rested for two days. On day six the animals will be given an intravenous (iv) injection of [^{3}H]-thymidine (66 to 72 hours after the last application of test material to the ears).

Approximately five hours after the iv injections, the animals will be euthanized and the auricular nodes will be removed. Single cell suspensions of the node cells will be prepared and then counted on a liquid scintillation counter to quantitate [^{3}H]-thymidine incorporation.

Dose Preparation and Test Concentrations:

All test material/carrier mixtures will be prepared on the day of use or as indicated in the Protocol Design Specifications and Sponsor Information and Approval form (Attachment 1).

Homogeneity Measurements of Test Material Dilutions/Solutions

Homogeneity measurements are not required for materials that are soluble in the carrier. For suspensions, a sample of top, middle and bottom will be taken and sent to the Sponsor for analysis. Samples will be stored and shipped per the Sponsor's instructions.

Test Material Mixture Concentration

A sample will be taken of each test material mixture/solution used for treatment. These samples will be sent to the Sponsor for analysis. The samples will be stored and shipped per the Sponsor's instructions.

Procedures:

Note: All animal procedures will follow applicable animal welfare procedures, e.g., AAALAC approved guidelines and/or test facility Institutional Animal Care and Use Committee (IACUC) approved procedures. This study will be conducted in accordance with the Testing Facility's Standard Operating Procedures.

A. Application of Test Material:

The animals will be restrained in such a manner as to allow free access to the dorsal and ventral sides of both ears. Using an adjustable push button pipet, 12.5 μl of test material will be applied to the dorsal and ventral sides of each ear, for a total of 25 μl of test material per ear or as otherwise instructed by the Sponsor. Care will be taken to ensure that the test material does not run off the ear during application. Pipets are to be calibrated at least every three months (90 days) to assure accurate delivery of the 0.0125 ml volume.

B. Daily Observations of Test Material Application Sites:

All animals will be observed twice daily at a time immediately prior to, and approximately 2-4 hours subsequent to, test material application for any significant alterations in the appearance of the test material application sites (i.e., erythema and edema). All observations of pinnae appearance will be documented.

C. Intravenous Injection of [^{3}H]-Thymidine:

Each animal will receive 0.250 ml of phosphate buffered saline (PBS) containing 20 μCi of [^{3}H]-thymidine (specific activity of 6.7 Ci/mmol). A heat lamp may be used to dilate the tail veins for easier iv injections. The animal will be restrained in such a manner as to allow complete access to the tail. A 1 cc disposable syringe and 25-27 gauge needle may be used for iv injections. An animal will be excluded from the study if the full 0.250 ml of [^{3}H]-thymidine/PBS is not properly

iv injected. Statistical analysis will not be performed on a group when more than one mouse is excluded from the group.

D. Lymph Node Removal:

Approximately five hours after the [^{3}H]-thymidine injections, the animals will be euthanized with CO_2 and the auricular lymph nodes removed and pooled for each individual animal. Care will be taken to assure that the lymph nodes are removed intact. Once the lymph nodes are removed, they will be placed in a 12x75 mm capped tissue culture tube containing 4 ml of PBS.

E. Single Cell Suspension:

The lymph nodes will be transferred to a 60mm tissue culture dish by pouring the PBS from the tubes containing the lymph nodes. Both the top and bottom of the tissue culture dish may be used for preparing single cell suspensions for each individual animal. The lymph nodes will be placed onto an approximately 1 inch square section of nylon macromesh (mesh opening ~100 microns, ~85 microns thick) with a small amount of PBS (0.5-1.5 ml). The capsule will be snipped with a small pair of pointed surgical scissors and the nodes will be gently rubbed through the nylon screen using the rubber surface of a plunger from a 1 cc disposable syringe. A Pasteur pipet and a small pair of forceps will be used to rinse the screen with PBS into the bottom portion of the tissue culture dish. The nylon filter will be discarded after rinsing and the tissue culture dish rinsed with the PBS. The PBS will be placed back into the 12x75 mm round bottom tube to allow the capsule debris to settle to the bottom. After approximately 5 minutes the PBS will be carefully drawn off with a Pasteur pipet and placed in a 15 ml conical bottom centrifuge tube containing 6 ml of PBS (approximately 10 ml total tube volume) and the cell suspensions centrifuged at 200xg for 10 minutes. After the first wash in PBS the cells will be resuspended in 10 ml of PBS, and a second wash will be performed. After completion of the second wash, the cells will be suspended in 3 ml of 5% trichloroacetic acid (TCA) (w/v, distilled H_2O) and left at approximately 4 C for 18 to 72 hours.

F. Preparation for Scintillation Counting:

The cell suspensions will be centrifuged at 200xg for 10 minutes and resuspended in 1 ml of 5% TCA. Scintillation vials containing 10 ml of Ecolume scintillation cocktail will be appropriately labeled with the individual animal numbers. The individual cell suspensions will be transferred into the appropriate vials along with an additional 1 ml of TCA which has been used to rinse the bottom portion of the tube. The TCA and scintillation fluid will be thoroughly mixed by gently swirling the contents of the vial until the solution becomes clear.

G. Scintillation Counting:

A liquid scintillation system will be used for counting. The samples will be counted for 5-10 minutes and the counts recorded in disintegrations per minute (DPM).

Protocol Changes:

Should it become necessary to change the approved protocol, verbal agreement to make those changes should be made between the Study Director and the Sponsor's Divisional Toxicologist or Alternate Divisional contact. As soon as practical, the change, date of 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:

The report will include how the study was conducted, including any deviations from the protocol, and the dates of study initiation and completion. Data for each animal will be included in the final report. Also, calculation of the group mean DPM ± standard error of the mean (SE) for each group and a graphic representation of the results using the group mean and SE will be included. In addition, the fold increase in the mean of isotope incorporation relative to the control group will be determined and included in the final report. The observed values of disintegrations per minute (DPM) from acid-precipitated murine auricular lymph nodes will be analyzed. Data will be log-transformed, and statistical analyses may include both normal distribution and distribution-free techniques. If Bartlett's test for homogeneity of variance is not significant, comparisons with the control group (and other specific, pairwise comparisons of groups) will be based on the least significant difference criterion. If Bartlett's test is significant, these comparisons will be based on Wilcoxon's rank sum test. All statistical tests shall be conducted at a 1%, two-sided risk level. The report shall conform to all requirements outlined in CFR Title 21, Part 58, Subpart J, Section 58.185, Good Laboratory Practice Regulations.

Maintenance of Raw Data and Records:

Original data or copies thereof, will be available at the testing facility to facilitate auditing of the study during its progress and before acceptance of the final report. When the final report is completed, all experimental data generated by the testing facility and a copy of the final report will be retained in the archive of the testing facility.

Proposed Study Starting Date: 4/9/97
Defined as: First day of dosing

Proposed Study Completion Date: 4/14/97
Defined as: End of in-life phase of study

Study Director: T. T. Horth T. T. Horth
(Print Name and Signature)

Date: 4/2/97

Quality Assurance Representative: R. A. Boyne R. A. Boyne
(Print Name and Signature)

Date: 4/3/97

Attachment 1. Murine Local Lymph Node Assay
Protocol Design Specifications and Sponsor Information and Approval

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Alternative contact:
Mr. Russell Traynor
Phone: 44 1784 495134
Fax: 44 1784 495043

Sponsor's Representative:
V. R. Hoyle, PhD.
Lovett House, Lovett Road,
Staines, Middlesex,
TW18 3AZ, UK.
Phone: 44 1784 495125
Fax: 44 1784 495043

P&G DRD No.: HBE BTS 0689/02

Regulatory Compliance: This study will be conducted in accordance with (Check all that apply):

[✓] FDA Good Laboratory Practice Regulations
[ ] EPA Good Laboratory Practice Standards
[✓] With the exception that the study will not be listed on the Testing Facility's Master Schedule of GLP regulated studies, as it is not expected to be submitted to a regulatory agency

Test Material(s): Note: Test materials RE1122.02, RE1044.04 and RE1142.01 from study HBE BTS 0689/01 are to be used in this study.

TSIN	Color	Physical Form	Expiration Date
RE1122.02	off-white	free-flowing crystals	30-Sept-97
RE1044.04	colourless	clear liquid	28-Jan-98
RE1142.01	colourless	clear liquid	01-Jan-98

Test Material Storage Condition (Check one):

Bulk Material: [✓] Room Temperature [ ] Refrigerated [ ] Frozen
Formulated Material: [✓] Room Temperature [ ] Refrigerated [ ] Frozen
[✓] Other: RE1044.04 must be kept refrigerated, all others - room temperature.
RE1142.01: Store in fume cupboard when undiluted.

Test Material Hazards:

[ ] None Known
[ ] Unknown (not evaluated)
[✓] From MSDS sheets: RE1122.02: Potential skin and eye irritant. Potential sensitiser.
RE1044.04: Corrosive oxidiser. Potentially corrosive to eyes and skin. Potentially explosive.
RE1142.01: Potentially corrosive to eyes and skin. Harmful if swallowed or inhaled. Store in fume cupboard when undiluted.

Dose Selection:

Dose assay at the following levels:
[ ] ____ concentrations per test material (specify % concentrations w/v, v/v, w/w, etc.)
[✓] carrier control
[✓] naive control

The test solutions are made up of a number of pre-mixes. Instructions for making the pre-mixes are given in Table1, whilst the instructions for preparing the test solutions are in Table 2.

Table 1: Instructions to make up pre-mixes. Add the ingredients in the following order, whilst stirring.

Note: Pre-mixes 1-4 are not stable and must be made up on the day of use.

Ingredient	Pre-mix 1	Pre-mix 2	Pre-mix 3	Pre-mix 4
Distilled water	100ml	100ml	150ml	-
RE1122.02	0.197g	1.97g	7.4g	-
RE1044.04	-	-	-	57.75g
Distilled water	-	-	-	make upto 100ml

Table 2: Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test solution A	Test solution B	Test solution C	Test solution D	Test solution E	Test solution F
Pre-mix 1	38.5g	-	-	38.5g	-	-
Pre-mix 2	-	38.5g	-	-	38.5g	-
Pre-mix 3	-	-	38.5g	-	-	38.5g
Pre-mix 4	7g	7g	7g	7g	7g	7g
RE1142.01	adjust to pH 10±0.2 *	adjust to pH 10±0.2 *	adjust to pH 10±0.2 *	adjust to pH 4.5±0.2*	adjust to pH 4.5±0.2*	adjust to pH 4.5±0.2*
Distilled water	make upto 47.5g	make upto 47.5g	make upto 47.5g	make upto 47.5g	make upto 47.5g	make upto 47.5g

* RE1142.01 must be added drop-wise whilst measuring pH (maximum addition = 2ml).

Table 2 (continued): Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test Solution G (control for A to F)	Test Solution H (for comparison to C)
Pre-mix 3	-	38.5g
RE1142.01	2.0ml	adjust to pH 10±0.2 *
Distilled water	make upto 47.5g	make upto 47.5g

* RE1142.01 must be added drop-wise whilst measuring pH (maximum addition = 2ml).

Other Comments and Instructions:
Following addition of Pre-mix 4 to test solutions, the pH should be adjusted (where appropriate) and the solutions then used as promptly as possible.

Test Material Carrier(s):
[ ] Acetone [ ] 80% Ethanol [ ] Dimethylformamide [ ] Dimethylsulfoxide
[✓] Distilled water [ ] Propylene glycol, USP [ ] Other: As above

Test material formulation is a: [ ] suspension [✓] solution [ ] emulsion

Concentration Analyses: Analysis of concentration/stability/homogeneity of the test material-carrier mixture(s):
Concentration analysis will not be performed.
Any unused test material(s) will not be returned to the Sponsor

Shipping Instruction for Test Solutions/Mixtures:
Do not return unused test material.

Return Unused Test Material to:
Do not return unused test material.

Send Invoices to:
Ms Teal Martin,
Lovett House, Lovett Road,
Staines, Middlesex, TW18 3AZ,
UK.

Relevant alternative test procedures were reviewed and no acceptable non-animal method was found to exist. Further, the relevant literature was reviewed and no data were found that would preclude the need to conduct this test.

Divisional Toxicologist: VR Hoyle **Date:** 14-Mar 97

Protocol Amendment No. 1

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Alternative contact:
Mr. Russell Traynor
Phone: 44 1784 495134
Fax: 44 1784 495043

Sponsor's Representative:
V. R. Hoyle, PhD.
Lovett House, Lovett Road,
Staines, Middlesex,
TW18 3AZ, UK.
Phone: 44 1784 495125
Fax: 44 1784 495043

P&G DRD No.: HBE-BTS-0689/02

IITRI Project No: L08607 SN23

Amendment No. 1

Reason for Amendment

The amount of materials supplied to IITRI were not sufficient for the original protocol to be followed. The dose selections have been recalculated, in order that IITRI may use the materials which have been supplied, whilst maintaining the integrity of the test solutions. The amended dosing instructions are shown below. Additionally, Test Solution G is now identified as a control for A to F & H (previously only A to F), and Test Solution H is no longer identified as "for comparison to C", these changes are due to an error on the original protocol.

Test materials
RE1122.02
RE1044.04
RE1142.01

Dose Selection:
Dose assay at the following levels:
[ ] ____ concentrations per test material (specify % concentrations w/v, v/v, w/w, etc.)
[✓] carrier control
[✓] naive control

The test solutions are made up of a number of pre-mixes. Instructions for making the pre-mixes are given in Table 1, whilst the instructions for preparing the test solutions are in Table 2.

Table 1: Instructions to make up pre-mixes. Add the ingredients in the following order, whilst stirring.

Note: Pre-mixes 1-4 are not stable and must be made up on the day of use.

Ingredient	Pre-mix 1	Pre-mix 2	Pre-mix 3	Pre-mix 4
Distilled water	25ml	25ml	37.5ml	-
RE1122.02	0.0493g	0.493g	1.85g	-
RE1044.04	-	-	-	14.44g
Distilled water	-	-	-	make upto 25ml

Table 2: Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test solution A	Test solution B	Test solution C	Test solution D	Test solution E	Test solution F
Pre-mix 1	9.625g	-	-	9.625g	-	-
Pre-mix 2	-	9.625g	-	-	9.625g	-
Pre-mix 3	-	-	9.625g	-	-	9.625g
Pre-mix 4	1.75g	1.75g	1.75g	1.75g	1.75g	1.75g
RE1142.01	adjust to pH 10±0.2 *	adjust to pH 10±0.2 *	adjust to pH 10±0.2 *	adjust to pH 4.5±0.2*	adjust to pH 4.5±0.2*	adjust to pH 4.5±0.2*
Distilled water	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g

* RE1142.01 must be added drop-wise whilst measuring pH (maximum addition = 0.5ml).

Table 2 (continued): Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test Solution G (control for A to F &H)	Test Solution H
Pre-mix 3	-	9.625g
RE1142.01	0.5 ml	adjust to pH 10±0.2 *
Distilled water	make upto 11.875g	make upto 11.875g

* RE1142.01 must be added drop-wise whilst measuring pH (maximum addition = 0.5 ml).

Other Comments and Instructions:
Following addition of Pre-mix 4 to test solutions, the pH should be adjusted (where appropriate) and the solutions then used as promptly as possible.

Test Material Carrier(s):
[ ] Acetone [ ] 80% Ethanol [ ] Dimethylformamide [ ] Dimethylsulfoxide
[✓] Distilled water [ ] Propylene glycol, USP [ ] Other: As above

Test material formulation is a: [ ] suspension [✓] solution [ ] emulsion
Note: although the test materials should fully dissolve, some of the test solutions may be a light suspension.

Anticipated effect on study: None

Sponsor's Toxicologist: Vivienne Hoyle/ VR Hoyle 24-4-97
Name Signature Date

Study Supervisor: Robert V. Houre RV Houre 5-8-97
Name Signature Date

Study Director: Jennifer T. Hoyle Jennifer T Hoyle 5/7/97.
Name Signature Date

Quality Assurance Representative: R. A. Boyne R. A. Boyne 5/8/97
Name Signature Date

Protocol Amendment No. 2

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Alternative contact:
Mr. Russell Traynor
Phone: 44-1784-495134
same fax

Sponsor's Representative:
V. R. Hoyle, PhD
Lovett House, Lovett Road
Staines, Middlesex,
TW18 3AZ, UK
Phone: 44-1784-495125
Fax: 44-1784-495043

P&G DRD No: HBEBTS0689/02

IITRI Project no: L08607 SN23

Reason for Amendment
On following the instructions provided in Attachment 1 IITRI personnel were unable to meet the pH specification of pH 10 ± 0.2 pH units on the addition of the specified amount, up to 0.5 ml, of test article RE1142.01. The study was postponed, as an additional quantity of test article RE1044.04 was also required.

Amendment
All test solution make up instructions described in Protocol Amendment 1 remain the same except:

1. pH adjustment with test article RE1142.01
RE1142.01 must be added drop-wise whilst measuring pH, the maximum expected addition is 3.0 ml, however, it is not limited to this value. If the amount of RE1142.01 does exceed 3.0 ml the approximate amount added must be documented.

2. Acceptable pH range
For test solutions A-C and H the acceptable pH range is pH 8.7 - pH 10.2, the actual pH achieved is to be documented in the report.
For test solutions D-F the acceptable pH range is pH 4.2 - pH 4.7, the actual pH achieved is to be documented in the report.

3. Test solution G
The level of RE1142.01 in test solution G, is to be increased to 3.0 ml, to be made up to 11.875g with distilled water. If however, the amount of RE1142.01 used in the pH adjustment of any of test solutions exceeds 3.0 ml, then the amount of test article used to make up test solution G must be increased to the documented level, and then made up to 11.875g with distilled water.

4. Test material formulation
A slight precipitate may form in some test solutions as the target pH is reached.

Anticipated effect of these protocol amendments on study: None

	Name	Signature	Date
Sponsor Toxicologist:	Vivienne Hoyle	VR Hoyle	22 May 97
Study Supervisor:	Robert V. House	RV Hous	29 May 97
Study Director:	Jennifer T. Hozak	Jennifer T. Hozak	5/27/97
Quality Assurance Representative:	R. A. Boyne	R. A. Boyne	5/27/97

Protocol Amendment No. 3

Sponsor:
THE PROCTER & GAMBLE COMPANY
Cincinnati, Ohio

Alternative contact:
Mr. Russell Traynor
Phone: 44 1784 495134
Fax: 44 1784 495043

Sponsor's Representative:
V. R. Hoyle, PhD.
Lovett House, Lovett Road,
Staines, Middlesex,
TW18 3AZ, UK.
Phone: 44 1784 495125
Fax: 44 1784 495043

P&G DRD No.: HBE-BTS-0689/02

IITRI Project No: L08607 SN23

Amendment No. 3

Reason for Amendment

If the instructions for pH adjustment given in Amendment 2 were followed, the total amount of solution would exceed that stated in Table 2 of Amendment 1. In order to maintain the integrity of the dosing solutions, whilst allowing for pH adjustment to occur without exceeding the total volume, it is necessary to alter the instructions for the make-up of the pre-mixes and test solutions. The instructions given in this Amendment replace those given in Amendments 1 and 2.

Test materials
RE1122.02
RE1044.04
RE1142.01

Dose Selection:
Dose assay at the following levels:
[ ] ____ concentrations per test material (specify % concentrations w/v, v/v, w/w, etc.)
[✓] carrier control
[✓] naive control

The test solutions are made up of a number of pre-mixes. Instructions for making the pre-mixes are given in Table 1, whilst the instructions for preparing the test solutions are in Table 2.

Table 1: Instructions to make up pre-mixes. Add the ingredients in the following order, whilst stirring.

Note: Pre-mixes 1-4 are not stable and must be made up on the day of use.

Ingredient	Pre-mix 1	Pre-mix 2	Pre-mix 3	Pre-mix 4
Distilled water	15ml	15ml	22.5ml	-
RE1122.02	0.0493g	0.493g	1.85g	-
RE1044.04	-	-	-	14.44g
Distilled water	-	-	-	make upto 25ml

Table 2: Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test solution A	Test solution B	Test solution C	Test solution D	Test solution E	Test solution F
Pre-mix 1	5.775g	-	-	5.775g	-	-
Pre-mix 2	-	5.775g	-	-	5.775g	-
Pre-mix 3	-	-	5.775g	-	-	5.775g
Pre-mix 4	1.75g	1.75g	1.75g	1.75g	1.75g	1.75g
RE1142.01	adjust to pH 8.7 to 10.2*	adjust to pH 8.7 to 10.2*	adjust to pH 8.7 to 10.2*	adjust to pH 4.2 to 4.7*	adjust to pH 4.2 to 4.7*	adjust to pH 4.2 to 4.7*
Distilled water	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g	make upto 11.875g

* RE1142.01 must be added drop-wise whilst measuring pH, maximum anticipated addition = 3.0 ml, however this may be exceeded if necessary. The approximate amount added must be documented, as must the pH achieved for each test solution.

Table 2 (continued): Instructions to make up test solutions. Add the ingredients/pre-mixes in the following order, whilst stirring, on day of use.

Component	Test Solution G (control for A to F & H)	Test Solution H
Pre-mix 3	-	5.775g
RE1142.01	**	adjust to pH 8.7 to 10.2 *
Distilled water	make upto 11.875g	make upto 11.875g

* RE1142.01 must be added drop-wise whilst measuring pH, maximum anticipated addition = 3.0 ml, however this may be exceeded if necessary. The approximate amount added must be documented, as must the pH achieved for each test solution.

** The amount of RE1142.01 added to solution G must be equal to the maximum amount added to solutions A to F & H.

Other Comments and Instructions:
Following addition of Pre-mix 4 to test solutions, the pH should be adjusted (where appropriate) and the solutions then used as promptly as possible. A slight precipitate may form in Test Solution C as the target pH is reached.

Test Material Carrier(s):
[ ] Acetone [ ] 80% Ethanol [ ] Dimethylformamide [ ] Dimethylsulfoxide
[✓] Distilled water [ ] Propylene glycol, USP [ ] Other: As above

Test material formulation is a: [ ] suspension [✓] solution [ ] emulsion
Note: although the test materials should fully dissolve, some of the test solutions may be a light suspension.

Anticipated effect on study: None

Sponsor's Toxicologist: Vivienne Hoyle/ pp Wendy Tabb 28/5/97.
Name Signature Date

Study Supervisor: Robert House RV Hou 6-3-97
Name Signature Date

Study Director: Jennifer T. Hosek Jennifer T Hosek 5/30/97
Name Signature Date

Quality Assurance Representative: R. A. Boyne R. A. Boyne 6/4/97
Name Signature Date

PROTOCOL AMENDMENT NO. 4

Effective Date: 5/14/97

Project No.: L08607

Study No.: 23

Nature of Revision:

The animals for this study were obtained from Harlan Sprague Dawley, Indianapolis, IN instead of Jackson Laboratory, Bar Harbor, ME.

Reason for Change:

Page 2 of the Protocol specifies that the animals used in the Murine Local Lymph Node Assay be obtained from Jackson Laboratory. At the time the study was placed, mice were unavailable from Jackson. Study Supervisor Robert House contacted Dr. Frank Gerberick from Procter and Gamble who agreed that changing the animal vendor to Harlan Sprague Dawley would be acceptable in cases where animals were not available from Jackson.

Sponsor's Toxicologist: V R Hayes Date: 4 Aug 97

Study Supervisor: R V House Date: 7-31-97

Study Director: Jennifer Bogdanffy Date: 7/31/97

Quality Assurance Representative: R. A. Boyce Date: 7/31/97

TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.02
Divisional Request Document(s) HBE BTS 0689/01

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman
Brand Notebook Reference_N01202/90 M217/18135 M217/18136
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NA at: %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions:_Store at Room temperature Viscosity:_NA
Expiration Date (Day/Month/Year):_30 Sep 97 Ingredient Stability:NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards:[ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: R. Welch (Name) (Signature) 12/3/97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for the sfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: V. R. Hoyle (Name) (Signature) 12-Mar-97 (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	A.C.No. 34617 Spectra collected and matches standard [illegible] N1209-64 7.3.97. Description Tan Powder [illegible] 10.3.97. free from visible contamination			

Compositional Information Provided by:
DOMINIC PRATT [signature] [signature] 12/3/97
(ORIGINATOR NAME/SIGNATURE/DATE)
Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:
[signature] 11/3/97
(ANALYTICAL MGR NAME/SIGNATURE/DATE)
Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

(NAME/SIGNATURE/DATE)
D. Mulligan 11/3/97

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.

COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.

NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.

ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Test Substance

CAS Number:	25646-71-3
Identity:	4-(n-ethyl-n-2-methanesulponylaminoethyl)-2-methylphenylenediamine
Purity:	99.6%
Remarks:	Test substance was identified as RE-1122.03.

Method

Method/Guideline Followed:	Dermal Single-Dose Toxicity (Limit Test)
GLP:	Yes (Japanese)
Report Year:	2000
Species:	Rat
Strain:	SD albino
Gender:	Male and Female
Number of Animals:	5 / sex / group
Vehicle:	0.5 mL water guaze patch
Dose:	0 or 2000 mg/kg
Remarks:	The test substance was administered once to five male and five female rats at 2000 mg/kg. Animals were observed 30 min, 1, 3, and 6 hours following administration, and thereafter once daily for 14 days. A control group was included in the study design. Observations included body weight, mortality, reactivity, behavior, respiration, skin, fur and excrement.

Results

Results:	Dermal LD50 > 2000 mg/kg.
Remarks:	No mortality occurred during the observation period. There were no differences in body weight between test and control animals. No findings ascribed to the test substance were found in any of the animals. In clinical observations, blackish patch and blackish hair in the administered site were found in the treatment group - these were transient changes.

Data Quality

Reliability (Klimisch):	1

Reference

Laboratory Report Number:	7L749
Reference:	Procter & Gamble, 2000. Dermal Single-Dose Toxicity Study of RE1122.03 in Rats. Accession #43695

Submitted to:

Procter & Gamble Far East Inc.

ACC# 43695
HBE BTS 0707/01-06

FINAL REPORT

Dermal Single-Dose Toxicity Study of RE1122.03 in Rats

(Study No. 7L749)

January 26, 2000

Mitsubishi Chemical Safety Institute Ltd.

Statement

Kashima Laboratory
Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Procter & Gamble Far East Inc.

Title: Dermal Single-Dose Toxicity Study of RE1122.03 in Rats

Study No: 7L749

The study in this report was conducted in compliance with the following Good Laboratory Practice Standards.

Japanese GLP Standards for Nonclinical Safety Studies on Drugs (Ministry of Health and Welfare Ordinance No.21, 1997)

Study Director: Kotaro Yamashita (sealed) Date: January 26, 2000

Quality Assurance Statement

Kashima Laboratory

Mitsubishi Chemical Safety Institute Ltd.

Sponsor: Procter & Gamble Far East Inc.

Title: Dermal Single-Dose Toxicity Study of RE1122.03 in Rats

Study No.: 7L749

By the inspections and audits listed below, I hereby certify that this study was carried out in accordance with its protocol and with our Standard Operating Procedures, and that this report faithfully describes the methods and procedures employed, and that the reported results accurately reflect the raw data of the study.

Inspection or audit	Quality Assurance Personal	Date of inspection or audit	Date of reporting to the study director	Date of reporting to the management
Study Protocol	Kunihiko Ofuchi	November 21, 1997	November 21, 1997	November 21, 1997
Protocol Amendment No.1	Hidetsugu Watabe	June 7, 1999	June 7, 1999	June 7, 1999
Study Procedure				
Administration	Hidetsugu Watabe	December 2, 1997	December 2, 1997	December 2, 1997
Observation	Hidetsugu Watabe	December 3, 1997	December 3, 1997	December 4, 1997
Necropsy	Hidetsugu Watabe	December 16, 1997	December 16, 1997	December 16, 1997
Raw Data, Draft Report	Hidetsugu Watabe	February 26, 1998	February 26, 1998	February 26, 1998
Final Report	Hidetsugu Watabe	January 26, 2000	January 26, 2000	January 26, 2000

Quality Assurance Manager: Tamotsu Nishitomi (sealed) Date: January 26, 2000

Study Outline

1. Title: Dermal Single-Dose Toxicity Study of RE1122.03 in Rats
(Study No. 7L749)

2. Purpose: To assess dermal single dose toxicity of RE1122.03 in rats.

3. Guidelines: Japanese Guidelines for Toxicity Studies of Drugs (1993)

4. GLP: Japanese GLP on Drugs (1997)

5. Sponsor: Procter & Gamble Far East Inc.
17, Koyo-cho Naka 1-chome, Higashinada-ku, Kobe, 658-0032, Japan
Responsible Person: Akihiro Kurishita, Ph.D.

6. Organization under contract:
Mitsubishi Chemical Safety Institute Ltd.
1-30, Shiba 2-chome, Minato-ku, Tokyo, 105-0014, Japan

7. Testing facility:
Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd.
14 Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-0255, Japan

8. Study contributor:
Study director: Kotaro Yamashita (sealed) Date: January 26, 2000

9. Study schedule:

Initiation of the study	November 21, 1997
Receipt of animals	November 26, 1997
Administration	December 2, 1997
Necropsy	December 16, 1997
End of the study	January 26, 2000

10. Unforeseeable circumstances that may have adversely affected the reliability of the study and deviation from the protocol: none

11. Retention: The records and documents listed below will be retained in the archives of the Kashima Laboratory. Further retention of the raw data will be discussed with the sponsor 5 years after submission of the final report.

Protocol and its amendment
Test substance
Information on the test substance
Animal care data and facility maintenance data
Record of quarantine and acclimatization
Record of administration
Record of clinical observation
Record of body weight measurement
Record of necropsy finding
Record of inspection by Quality Assurance Unit
Final report
Others

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Summary

Dermal single-dose toxicity of RE1122.03 was evaluated in SD strain rats.

The test substance was administered once to five male and five female rats at the dose level of 2000 mg/kg. The animals were observed for 14 days following administration. A control group was treated in the same manner as the test group, but without the test substance.

No animals died during the observation period. In clinical observation, blackish patch and blackish hair in the administered site were found in the treatment group. However, these were transient changes. No abnormalities ascribed to the test substance were found in any animals at necropsy or body weight measurement.

Under the conditions of this test, the minimum acute dermal lethal dose was greater than 2000 mg/kg, when RE1122.03 is administered dermally at 2000 mg/kg.

Materials and Methods

1. Test substance

Procter & Gamble Far East Inc. supplied RE1122.03 (purity 99.6%, lot no. 75161). The test substance is a paraphenylendiamine derivative, an odorless off-white free flowing crystalline powder with a melting point of 300°C. The sponsor confirmed the stability of the test substance.

Water for injection (Otsuka Pharmaceutical Factory, Inc., lot no. K7B86) was used to moisten the test substance.

2. Experimental animals

SD strain albino rats [Crj:CD(SD)IGS, SPF] were purchased from Charles River Japan, Inc. on November 26, 1997. After quarantine and acclimation for 6 days, healthy rats of both sexes were used in this study. One day before the administration, the animals were grouped by a stratified-by-weight randomization method. At the time of administration, males were 7 weeks old and females were 10 weeks old and weighed 243-265 g in males and 221-240 g in females.

Animals were identified by a marking on the tail with an oil-based ink. Cages were also identified with a label listing the study number, name of the test substance, animal number, sex, dose level, day of administration, the name of species, and strain.

3. Animal husbandry

Throughout the study including quarantine and acclimation, the animal room was maintained at a temperature of 22±2°C (target value), and at a relative humidity of 55±15% (target value). The room was ventilated at about 12 changes per hour (all fresh filtered air) and lit from 7:00 to 19:00.

Animals were housed in polycarbonate cages (265W × 426D × 200H mm, Tokiwa Kagaku Kikai Co., Ltd.) with hard wood chip bedding for experimental animals (Beta-Chip, Charles River Japan, Inc.) on a steel rack (Tokiwa Kagaku Kikai Co., Ltd.). The rats were housed one per cage. A pellet diet and water were supplied with stainless steel feeders (Tokiwa Kagaku Kikai Co., Ltd.) and

polycarbonate bottles (700 mL, Tokiwa Kagaku Kikai Co., Ltd), respectively. The cages (including bedding), feeders and watering bottles were autoclaved and replaced once a week.

A pellet diet for experimental animals (MF, Oriental Yeast Co., Ltd.) and ordinary tap water were given *ad libitum* and replaced once a week. The water was filtered using a 5 μm filter and irradiated with UV.

Analytical reports on hazardous contaminants showed that the diet and bedding met our laboratory's specifications. The water was analyzed periodically in accordance with the Waterworks Law of Japan, and met the required specifications.

4. Administration

The dermal application was selected, as it is the intended exposure route. Approximately 24 hours before the administration, the fur was removed from the dorsal area of the trunk (4 x 5 cm: approximately 10% of the body surface area) by hair clippers (THRIVE 900, Daito Electric Machine Industry Co., Ltd.). Animals without skin lesions from clipping were used. The test substance was applied uniformly on a wet gauze patch moistened with 0.5 mL of water for injection. The gauze patch was applied on the skin where the fur had been removed. The patch was further covered with vinyl film lined tape (ELATEX, ALCARE Co., Ltd.) and then with tape (SILKYTEX, ALCARE Co., Ltd.) to retain the test substance in place. It was confirmed that the patches were tight enough to keep the test substance on the site, but did not give unnecessary pressure to the body. After 24 hours of exposure, the patches were removed and the test site was washed with water.

Dose level was set at 2000 mg/kg as it is the highest dose level in the Japanese Guidelines for Toxicity Studies of Drugs and a control group was treated with wet gauze with water for injection.

5. Constitution of animal groups

Group name	Number of animals	Animal numbers
Control group	5 males	10101～10105
	5 females	50101～50105
RE1122.03 group	5 males	10201～10205
dose: 2000 mg/kg	5 females	50201～50205

6. Observation and measurements

The following items were examined. The day of administration was designated as Day 1.

6.1 Clinical signs

All animals were observed 30 minutes, 1, 3, and 6 hours following the administration, and thereafter once a day for 14 days. Observations included, but were not limited to, mortality, reactivity to irritation, behavior, respiration, convulsion, skin, fur, and excrement.

6.2 Body weight

All rats were weighed shortly before administration and on Days 2, 4, 8, and 15 with an electronic balance (EB-3200S, Shimadzu Corp.).

6.3 Necropsy

All rats were sacrificed after the final observation (Day 15) by exsanguination through the abdominal aorta under anesthesia with thiopental sodium (RAVONAL, Tanabe Seiyaku Co., Ltd.) and were necropsied.

7. Statistical analysis

Body weight data was tested for the presence of a significant difference between the test substance group and control group. In the presence of isovariance as determines according to the F test, data was further tested using Student's *t*-test. In the absence of isovariance, Aspen-Welch's *t*-test was used.

Results and Conclusion

1. Dead animals

No mortality occurred during the observation period.

2. Clinical signs (Table 1, Appendix 1)

Blackish patch in the administered site was observed in 3 males and 2 females of the treatment group on Day 2, and this change became crust from Day 3. Crust was observed until Day 6 in males and Day 12 in females, respectively. Blackish hair was observed in males of the treatment group from Day 3. It is considered that this blackish hair was grown from the site of blackish patch on Day 2 or 3. In observation on Day 4, the root of the blackish hair showed normal white color. No abnormalities were found in any rats except these changes.

3. Body weight (Figure 1, Table 2, Appendix 2)

Body weight in the treatment group progressed similarly to the control group.

Although decreased body weight in both the control and treatment groups was observed on Day 2, this was considered to be the result of stress ascribed to the adhesive tape being attached to protect the administration site.

4. Necropsy findings

No findings ascribed to the test substance were found in any animals.

5. Conclusion

The minimum lethal dose was greater than 2000 mg/kg, when RE1122.03 is administered dermally at 2000 mg/kg under the conditions of this study.

Figure and Tables

Figure 1 Body Weight 1

Table 1 Clinical Sign - Summary 3

Table 2 Body Weight - Summary 4

Figure 1-1 Body Weight - Male

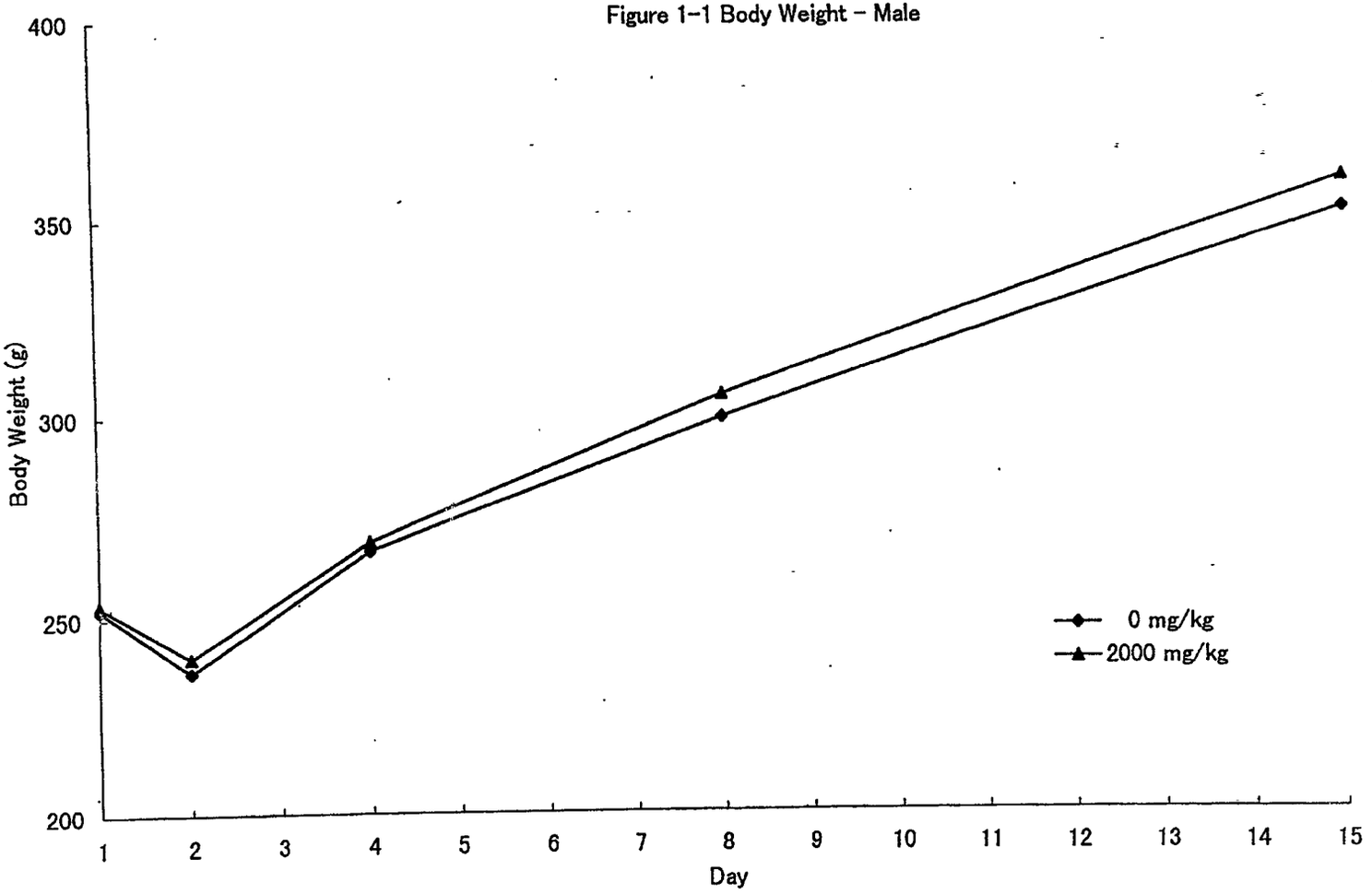

Figure 1-2 Body Weight - Female

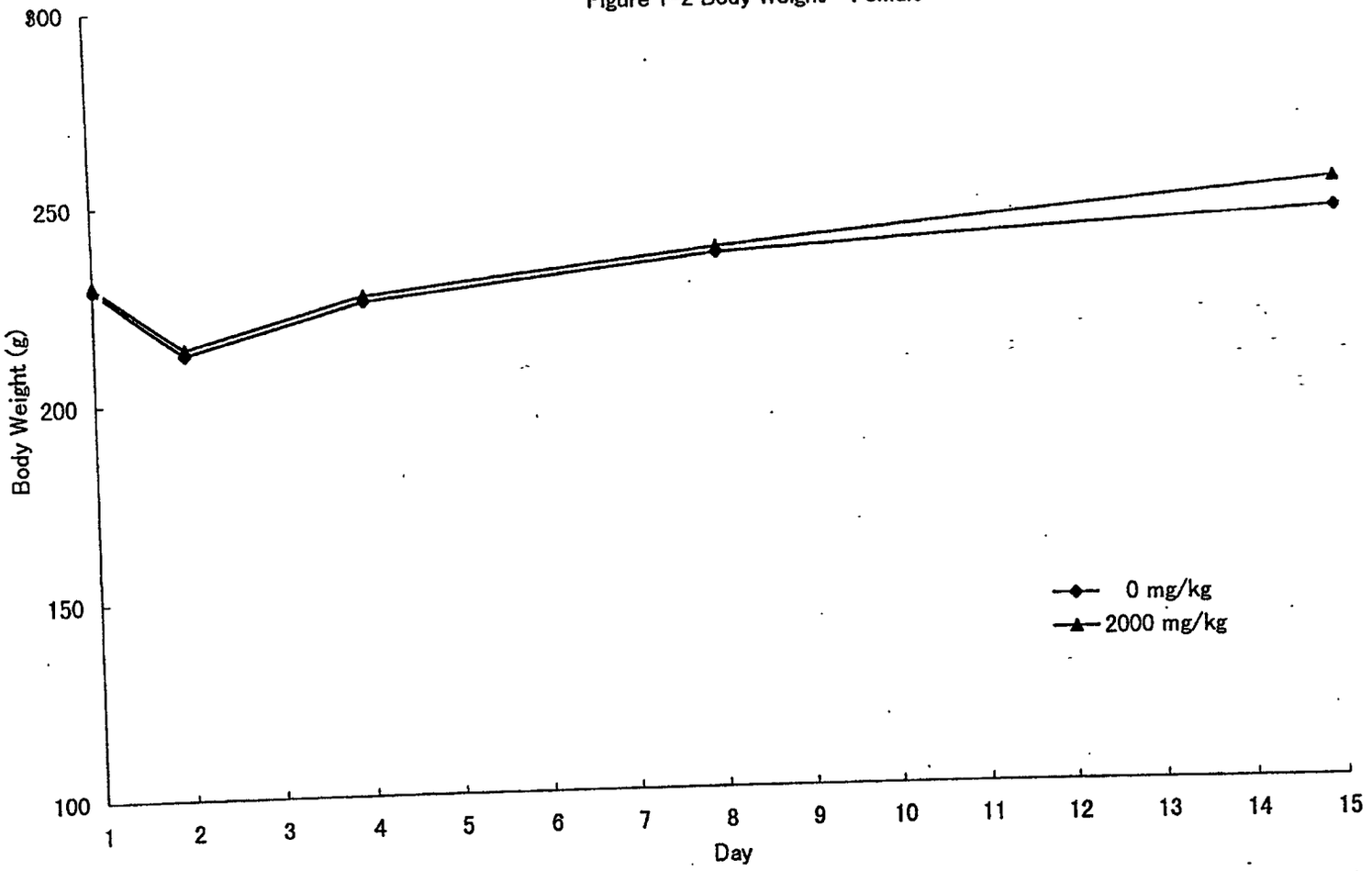

Table 1 Clinical Sign - Summary

Study No. 7L749

Test Substance : RE1122.03

Sex	Dose (mg/kg)	Findings		Day	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
				Time	30m	1h	3h	6h														
Male	0	Number of Animals			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		No Abnormality			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	2000	Number of Animals			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		No Abnormality			5	5	5	5	2	2	2	3	4	5	5	5	5	5	5	5	5	5
		Blackish patch	As		0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
		Crust formation	As		0	0	0	0	0	3	3	2	1	0	0	0	0	0	0	0	0	0
		Blackish of hair	As		0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Female	0	Number of Animals			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		No Abnormality			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	2000	Number of Animals			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
		No Abnormality			5	5	5	5	3	3	3	4	4	4	4	4	4	4	4	5	5	5
		Blackish patch	As		0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
		Crust formation	As		0	0	0	0	0	2	2	1	1	1	1	1	1	1	1	0	0	0

As , Administered site;

Table 2 Body Weight - Summary
Test Substance : RE1122.03

Study No. 7L749
Unit : g

Sex	Dose (mg/kg)	Day	1	2	4	8	15
Male	0	Mean	252.2	236.4	266.4	299.2	352.6
		S.D.	8.6	11.6	10.0	9.2	22.4
		n	5	5	5	5	5
	2000	Mean	253.2	240.0	268.6	305.0	360.6
		S.D.	7.5	5.9	6.7	9.2	14.9
		n	5	5	5	5	5
Female	0	Mean	229.0	212.2	225.0	235.6	245.2
		S.D.	7.0	7.7	6.6	8.7	19.6
		n	5	5	5	5	5
	2000	Mean	230.0	213.8	226.4	237.0	252.8
		S.D.	5.7	7.3	10.6	11.5	14.0
		n	5	5	5	5	5

Significantly different from control : *, $P<0.05$; **, $P<0.01$.

Appendices

Appendix 1 Clinical Sign 1

Appendix 2 Body Weight 2

Appendix 1 Clinical Sign
Test Substance : RE1122.03

Study No. 7L749

Sex	Dose (mg/kg)	Animal Number	Findings		Day 1 Time 30m	1h	3h	6h	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Male	0	10101	No Abnormality																			
		10102	No Abnormality																			
		10103	No Abnormality																			
		10104	No Abnormality																			
		10105	No Abnormality																			
	2000	10201	Blackish patch	As					+													
			Crust formation	As						+	+	+	+									
		10202	No Abnormality																			
		10203	Blackish patch	As					+													
			Crust formation	As						+	+											
			Blackish of hair	As						+												
		10204	Blackish patch	As					+													
			Crust formation	As						+	+	+										
			Blackish of hair	As						+												
		10205	No Abnormality																			
Female	0	50101	No Abnormality																			
		50102	No Abnormality																			
		50103	No Abnormality																			
		50104	No Abnormality																			
		50105	No Abnormality																			
	2000	50201	Blackish patch	As					+													
			Crust formation	As						+	+											
		50202	No Abnormality																			
		50203	No Abnormality																			
		50204	No Abnormality																			
		50205	Blackish patch	As					+													
			Crust formation	As						+	+	+	+	+	+	+	+	+	+			

+ , Present; As , Administered site;

Appendix 2 Body Weight
Test Substance : RE1122.03

Study No. 7L749
Unit : g

Sex	Dose (mg/kg)	Animal Number	Day 1	2	4	8	15
Male	0	10101	243	219	251	287	338
		10102	252	236	269	303	359
		10103	255	235	267	312	388
		10104	265	251	279	297	331
		10105	246	241	266	297	347
	2000	10201	258	246	274	316	380
		10202	245	233	259	291	345
		10203	263	246	276	306	350
		10204	253	239	267	303	356
		10205	247	236	267	309	372
Female	0	50101	238	220	234	248	278
		50102	228	209	229	237	246
		50103	221	206	220	232	233
		50104	234	221	224	237	241
		50105	224	205	218	224	228
	2000	50201	226	210	231	241	258
		50202	227	207	208	221	235
		50203	240	226	233	250	266
		50204	229	212	227	230	241
		50205	228	214	233	243	264

Submitted to:

Procter & Gamble Far East Inc.

ラット 経皮

[PROTOCOL]

Dermal Single-Dose Toxicity Study of

~~FEP19.01~~ in Rats

RE1122.03

(Study No. ~~7L058~~) 7L749 Y.D.

February 21, 1997

Mitsubishi Chemical Safety Institute Ltd.

97-10-24;18:18 ;P&G P&KS/K&CD ;078 845 6949 # 24/ 61

Outline of the study

1. Title : Dermal Single-Dose Toxicity Study of ~~FEP19.01~~ RE1122.03 in Rats
(Study No. 7L058)

2. Purpose : To assess dermal single dose toxicity of FEP19.01 in rats.

3. Guideline : Japanese Guidelines for Toxicity Studies of Drugs (1993)

4. GLP : Japanese GLP on Drugs (1982, 1988)

5. Sponsor : Procter & Gamble Far East Inc.
17, Koyo-cho Naka 1-chome, Higashinada-ku, Kobe, 658, Japan
Responsible person : Akihiro Kurishita, Ph.D.

6. Organization under contract :
Mitsubishi Chemical Safety Institute Ltd.
1-30, Shiba 2-chome, Minato-ku, Tokyo, 105, Japan

7. Testing facility : Kashima Laboratory
14 Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, 314-02, Japan

8. Management : Osamu Fujii

9. Study director : Koutarou Yamashita

10. Quality assurance manager :
Kunihiko Ofuchi

97-10-24;18:18 ;P&G P&RS/R&CD ;078 845 6949 # 25/ 61

11. Study schedule :

Initiation of the study	February	21,	1997
Receipt of animals	March	5,	1997
Administration	March	12,	1997
Necropsy	March	26,	1997
Submission of the draft report	April	11,	1997

12. Amendment : All amendments and the reasons for them shall be documented and they shall be approved by the sponsor.

13. Retention : The following records, data and specimens will be retained in the safekeeping facility of Kashima Laboratory for 5 years after submission of the final report. Retention thereafter will be discussed with the sponsor.

Protocol and its amendments
Test substance
Information on test substance
Animal care data and facility maintenance data
Record of quarantine and acclimatization
Record of administration
Record of clinical observation
Record of body weight measurement
Record of necropsy finding (with photograph, in case of taking a photograph)
Record of histopathological finding (in case of performance)
Record of organ weight measurement (in case of performance)
Organs fixed in formalin (in case of collection)
Paraffin embedded block specimens (in case of making preparation)
Slide specimens of tissues (in case of making preparation)
Photograph of histopathological finding (in case of taking a photograph)
Record of inspection by Quality Assurance Unit
Final report
Others

97-10-24;18:18 ;PBG PBRS/RBCD :078 845 6949 # 26/ 61

Materials and Methods

1. Test materials

1.1 Test substance

Name : ~~FEP19.01~~ RE 1122.03

Lot number : ~~1219B~~ 75161

Physicochemical properties :

appearance ; ~~Poured white sheet~~ Off-white free flowing Crystalline powder

smell ; none

melting point ; ~~122~~ 300 °C

Storage : Room temperature, ~~dark place~~

Stability : The sponsor will confirm the stability of the test substance by analyzing the lot used before and after the study.

Safety precautions : Wear rubber gloves, mask, safety glasses,

1.2 Material using to moisten the test substance

Name : ~~Physiological saline~~ ~~Tap~~ Distilled water for injection

Source : Otsuka Pharmaceutical Factory, Inc.

2. Experimental animals

2.1 Species : Albino rats

2.2 Strain : Sprague-Dawley [Crj:CD(SD)IGS]

2.3 Justification of the test system :

This strain has been widely used in toxicity studies, and much historical data on it and a large number of animals are available.

2.4 Microbial level : SPF

2.5 Supplier : Charles River Japan, Inc.

2.6 Number of animals : 12 animals per sex will be purchased.

2.7 Body weight at receipt of animal:

140-200 g in male and 170-240 g in female

2.8 Quarantine and acclimatization :

Clinical signs of the animals will be observed daily for 7 days.

2.9 Age at administration : Seven weeks in male and 10 weeks in female

97-10-24;18:18 ;PAG PARS/RACD :078 845 6949 # 27/ 61

2.10 Body weight at administration:

The body weights shall be 200 to 300 g and within ±20% of the mean. Animals outside of the above body weights will be excepted.

2.11 Grouping : Animals will be grouped by a stratified-by-weight randomization method to give approximately equal group mean body weights.

2.12 Identification : Animals will be identified by marking on the tail with an oil- based ink. Cages will be also identified with a label listing the study number, name of the test substance, animal numbers, sex, dose level, day of administration, the name of species and strain.

3. Animal husbandry

3.1 Environmental control

1) Room temperature : 22 ± 2 ℃

2) Relative humidity : 55 ± 15%

3) Ventilation : About 12 changes per hour (all fresh filtered air)

4) Lighting period : 12 hours per day (7:00 - 19:00)

3.2 Animal accommodation

1) Cage : Polycarbonate cage (265W× 426D×200H mm, Tokiwa Kagaku Kikai Co., Ltd.); they will be autoclaved and renewed once a week.

2) Feeder : Stainless steel feeder for pellet diet (Tokiwa Kagaku Kikai Co., Ltd.); they will be autoclaved and renewed once a week.

3) Watering bottle : Polycarbonate watering bottle (700 mL, Tokiwa Kagaku Kikai Co., Ltd.); they will be autoclaved and renewed once a week.

4) Cage rack : Steel rack (Tokiwa Kagaku Kikai Co., Ltd.); this will be disinfected with benzalkonium chloride solution (Micro Quat, ECOLAB K.K.).

3.3 Bedding

1) Description : Hardwood chips (Beta-chip, Charles River Japan, Inc.); they will be autoclaved and renewed once a week.

2) Analysis : The hardwood chip is analyzed periodically for contaminants such as pesticide residues and it meets our specifications.

97-10-24;18:18 ;P&G P&RS/R&CD
;U/8 845 6949 # 28/ 61

3.4 Diet

1) Description : Pellet diet for experimental animals (MF, Oriental Yeast Co., Ltd.)

2) Feeding : *ad libitum;* the diet will be renewed once a week.

3) Analysis : The diet shall meet our specifications on contaminants such as pesticide residues.

3.5 Water supply

1) Description : Tap water filtered with a 5 μm filter and UV irradiated

2) Watering : *ad libitum;* the tap water will be renewed once a week.

3) Analysis : The water is analyzed periodically according to the specifications of the Waterworks Law of Japan to ensure that it meets the specifications.

3.6 Animal housing : The rats will be housed in one per cage.

4. Administration

4.1 Route and method : **Dermal administration; Approximately 24 hours before test, fur will be removed from the dorsal area of the trunk (4 cm x 5 cm : approximately 10% of the body surface area) by hair clippers (THRIVE 900 ; Daito Electric Machine Industry Co., Ltd.). Unwounded animal by clipping will be used. After pulverizing in a mortar, the test substance will be applied uniformly on a wet gauze dressing moistened with 0.5 ml of water. The gauze dressing will be applied on removal fur area. The test site will be further covered with gauze and sticking plaster (ELATEX, ALCARE Co., Ltd.) that having a vinyl film backing and with a sticking plaster (SILKYTEX, ALCARE Co., Ltd.) to retain test substance. The sticking plaster is tight enough to keep the test substance at the site, but dose not give unnecessary pressure to the body. After 24 hours exposure, the test site will be washed with the water.**

4.2 Rationale for route selection :

The anticipated clinical route of finished goods

4.3 Rationale for method selection :

This method is decided to be caused by anticipated clinical route of finished goods.

4.4 Frequency : Once

97-10-24;18:18 ;P&G P&RS/R&CD :078 845 6949 # 29/ 61

4.5 Rationale for frequency selection :

It is prescribed in the guidelines.

4.6 Dose : At the request of the sponsor, dose level is approximately 20 cm^3 (4x5cm) and a control group treated with wet gauze with physiological saline. 2000 mg / kg, Dosage will be Calculated based upon body weight measured before treatment.

5. Constitution of groups :

~~Group name~~ Dose (mg/kg)	Number of animals	Animal numbers
Control ~~group~~	5 of male	10101~10105
	5 of female	50101~50105
2000	5 of male	10201~10205
	5 of female	50201~50205

6. Observation and measurements

The following items will be examined. The day of administration will be designated as Day 1.

6.1 Clinical observation (KSOP/ANH/251)

All rats will be observed for mortality and for clinical signs and behavior at least 3 times on the day of administration, and thereafter once a day for 14 days. Observations should include, but not be limited to, death, reactivity to irritation, behavior, respiratory, convulsion, skin and fur, excrement.

6.2 Body weight (KSOP/ANH/402)

Body weights will be measured shortly before administration, and on Days. 2, 4, 8 and 15. When a rat is found dead, it will be weighed immediately.

6.3 Pathological examinations (KSOP/PAT/251, 260)

Dead rats will be necropsied immediately. ~~In case of~~ If necessary, necropsy finding ~~will be taking a photograph~~ recorded photographically. Surviving rats will be sacrificed after the final observation (Day 15) by severing the abdominal aorta under anesthesia with thiopental sodium and will be necropsied. Organ weight measurement and histopathological examination will be discussed with the sponsor. ~~In case of~~ If necessary, histopathological finding ~~will be taking~~ recorded photographically. a photograph.

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7. Statistical analysis

Body weight data will be tested for the presence of a significant difference between the test substance group and control group. In the presence of isovariance as determined according to the F test, data will be tested using Student's t test. In the absence of isovariance, Aspen-Welch's t test will be used.

8. Final report

The draft report including the tables and figure will be presented by April 11, 1997. The sponsor shall review the report and indicate as soon as possible whether it is acceptable as the final report. With the sponsor's approval, the final report will be delivered to the sponsor by May 12, 1997. If more time is needed to discuss the report, the date of the presentation of the final report will be postponed. The report will consist of summary, materials and methods, results and discussions. The table and figure will involved of the following items.

Figure	Body weight
Tables	Clinical sign (if necessary)
	Body weight
	Organ weight (if necessary)
	Necropsy finding (if necessary)
	Histopathological finding (if necessary)
Photographs	Necropsy finding (if necessary)
	Histopathological finding (if necessary)

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Approval

Sponsor : Procter & Gamble Far East Inc.

Title : Dermal Single-Dose Toxicity Study of ~~RE.125.~~ ↑ RE1122.03 in Rats

Study Number : 7L058

Study Director

Koutarou Yamashita sealed February 21, 1997

Quality Assurance Manager

Kunihiko Ofuchi sealed February 21, 1997

Management

Osamu Fujii sealed February 21, 1997

Responsible Person of the Sponsor

Akihiro Kurishita

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TEST SUBSTANCE CHARACTERIZATION REPORT (TSCR)
EUROPEAN OPERATIONS

Section I: P&RS Study Related Reference Numbers (To be completed by P&RS)

Test Substance Identification Number (TSIN) RE -1122.03
Divisional Request Document(s) HBE BTS 0707/01 - 06

Section II: Test Substance General Characteristics
(To be completed by Originator, Helpful instructions are provided on page 2)

No spaces can be left blank. Use "NK" for "not known" and "NA" when "not applicable". NK and NA cannot be used for Notebook references, hazards, or expiration dates.

Name of Product or ingredient (or code designation):4-(n-ethyl-n-2-methanesulphonylaminoethyl)-2-methylphenylenediamine Sesquisulphate Monohydrate Eastman colour developing agent CD-3
Supplier's Name:Eastman LOT # 75161 TM 25-9-97
Brand Notebook Reference_N01511/30 M217/19922 leg M217/19923
(test substance source, production code if available and date ingredient received or product made)
Physical Form:Free flowing crystals Colour:off-white pH NK at: NK %
Density/sp.Gravity:NK Ingredient mol. Wt:872.93 Ingredient Solubility in water @ 25deg: 380g/L
Storage Conditions:_Store at Room temperature Viscosity:_NA
Expiration Date (Day/Month/Year):_01 Sep 98 Ingredient Stability:NK

Enter the hazard classification as provided by the supplier, including P&G (in compliance with EEC 79/831 Directive on Classification and Labelling).

Hazards: [ ] None known. Use normal handling precautions.
[X] As follows:Potential skin and eye irritant. Potential sensitiser.

Originators Section Head: G·GENAIN (Name) G.Genain (Signature) 24-9-97 (Date)

Section III: Test Substance Composition and Analytical Information

The test substance characterization on page 2 of this form has been reviewed and the test material is acceptable for thesfety testing indicated by the Divisional Request Document(s).

Divisional Toxicologist: pp V. Hoyle (Name) P M Mclaren (Signature) 24/09/97. (Date)

TO BE COMPLETED BY ORIGINATOR						TO BE COMPLETED BY ANALYTICAL			
Component	RMS # *	EINECS # *	CAS # *	Nominal Level % by Wt.	Acceptable Range	LIMS Code	Type of Analysis	Analytical Result/ Units	Analytical Reference (EM no.)
Colour developer CD-3			025646-71-3	99.6	99.1-102.9	ARP 2581	I.R	conforms to spec	N1486/113

Description: Tan powder free from any visible contamination
22/9/97 [signature]

Compositional Information Provided by:
[signature] Dominic PRATT 17/09/97
(ORIGINATOR NAME/SIGNATURE/DATE)
Signature verifies integrity of all data provided (including Section II)

Analytical Verification by:
[signature] 24/9/97.
(ANALYTICAL MGR NAME/SIGNATURE/DATE)
Signature verifies only Analyzed Value & Reference.

OPTIONAL: Microbiological Analysis

Cert. of Analysis

CMA #_____

No testing required [✓]

Material approved [ ]

JASON WILLIAMS
(NAME/SIGNATURE/DATE)
[signature]

HELPFUL INSTRUCTIONS TO COMPLETE THE FORM

TO BE COMPLETED BY ORIGINATOR AND VERIFIED BY ANALYTICAL: Originator must check with Divisional Toxicologist which analyses are necessary for the type of testing to be performed. If no analytical work is to be performed, justification must be provided by the Divisional Toxicologist.
COMPONENT: Use chemical name which uniquely identifies component. "Misc." or "balance" is not permitted.
NOMINAL % BY WEIGHT: Target level of each component. "Balance" for fillers or water is not permitted.
ACCEPTABLE RANGE: Range (according to Formula Cards for finished products and RMS for ingredients) for all key components which will be analyzed. Measured levels outside this range will render the material unsuitable for testing.

*Consult RMS-CAS-EINECS list in your department.

Note: Any changes made after TSCR is signed must be made on the original only and must be initialed and dated, and a reason for the change stated (GLP requirement).