ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ- 92 - 10112	89110000204	3/22/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI

334117

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

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

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11 MAR 22 AM 6:03

Re: Declassification Activity-Health and Safety Filing
8EHQ-0892-10112 (EPA DCN 88920008413)

Dear Sir/Madam:

The Procter & Gamble Company (P&G) provides this submission to amend the Public Display Version of our submission pursuant to the TSCA Section 8(e) Compliance Audit Program (CAP) under terms of CAP Agreement # 8ECAP-0003.

This amended submission is composed of the following:

(a) new information provided in this cover letter and its attachment(s); and
(b) the unaltered original submission which directly follows.

Any CBI substantiation which appears in the original submission is no longer applicable as the information which was originally claimed CBI is disclosed in this revised submission.

Should you have any questions concerning this amended submission, please contact me at (513) 983-2531 or froelicher.jm@pg.com.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Julie Froelicher
NA Regulatory & Technical Relations Manager
The Procter & Gamble Company
One Procter & Gamble Plaza
Cincinnati, OH 45202
(513) 983-2531
froelicher.jm@pg.com

8 9 1 1 0 0 0 0 2 0 4

Attachment 1

Public Display Version

Chemical Identity	CAS RN
Sulfuric acid disodium salt	
Triphosphoric acid, pentasodium salt	7758-29-4
Silicic acid, sodium salt	1344-09-8
Benzenesulfonic acid, C10-16-alkyl derivatives	68584-22-5
C.I. Pigment Green 7- sulfophenyl)azo]-4-hydroxy-, disodium salt	1328-53-6
Benzenesulfonic acid, 2,5-dichloro-4-[4,5-dihydro-3-methyl-5-oxo-4-[(4-sulfophenyl)azo]-1H-pyrazol-1-yl]-, disodium salt	6359-98-4
Fragrance	
Water	

8EHQ-0892-10112s
COMPANY SANITIZED

Procter & Gamble

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

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August 25, 1992

8EHQ-92-10112s INIT
88920008413

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M St. S.W.
Washington, D.C. 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

This submission is being made pursuant to the TSCA Section 8(e) Compliance Audit Program and the terms of CAP Agreement # 8ECAP-0003. This report discharges our Company obligation to report the attached data under TSCA Section 8(e). The filing of these studies does not indicate that we agree that "substantial risk" exists. We are following the agency's guidance and the terms of the CAP agreement, but we expressly disclaim that the filings reflect a decision that these materials pose any significant human or environmental safety risks.

The material identified in the attached report as B0723-01 is a confidential mixture. The composition of the mixture is appended as Attachment 1. The report is titled "28-Day Subchronic Percutaneous Toxicity Study of B0723-01 (BSBTS 862S)". Any correspondence relating to this submission should reference study # 1333-32209.

This study reports the effects of dermal application of the test material as a 10% w/v aqueous suspension at a dose volume of 0.2 g/kg to abraded skin 5 days per week for four weeks. Treatment produced slight erythema, edema, and desquamation. No treatment-related signs of toxicity were observed during the in-life phase of the study. Treated males showed increased absolute and relative liver weights with an associated increase in centrilobular hepatocytic swelling. Similar changes with less severity were also observed in the control group. Hepatocyte swelling is believed to reflect glycogen accumulation, but this was not confirmed in the present study. A repeat study with the same test material did not produce comparable changes.

We do not believe findings in this report reasonably support a conclusion of substantial risk to human health or the environment. Nevertheless, we are submitting this report to discharge any potential liability under TSCA Section 8(e).

To our knowledge, this report has not been the subject of a prior submission to EPA under the provisions of TSCA.

The specific chemical constituents and percentage composition of this mixture is claimed as confidential business information. A sanitized version of this submission containing generic chemical names has been included as part of this submission. Answers to the seven questions required to substantiate this claim of confidentiality are provided below:

1. Confidentiality of the chemical constituents and their percentages should be maintained indefinitely. There are no plans for this information to be otherwise disclosed, and this technology has significant commercial value.

2. To our knowledge, there have been no government confidentiality determinations made for this mixture.

Procter&Gamble

3. The specific chemical identity and exact proportions of the constituents of this mixture have not been disclosed outside the Company. There are no plans to disclose publicly the exact composition of this mixture at any time in the future.

4. Measures for protection of the compositional information include "need to know" internal restriction within the Company. An internal code is used to protect the identity of the material. Information is maintained in locked files. Employees leaving the Company are contractually bound not to disclose Company secrets.

5. The exact composition of this mixture has not appeared in advertising or promotional literature, MSD sheets, any publications or any other media available to the general public or competitors.

6. Disclosure of the information claimed as CBI would result in substantial harm to the Company's competitive position. This formula provides an important commercial opportunity for a competitor. Knowledge of the exact composition of this mixture could enable a competitor to duplicate the formula without R&D cost, thus providing an unfair competitive disadvantage to the Procter & Gamble Company. Development of this formula required many technically trained personnel, hundreds of hours of research and development, and significant capital investment valued in aggregate at . Any competitor would normally be required to make a similar investment to duplicate the formula. Disclosure of this information would allow a competitor to duplicate the formula without incurring significant R&D costs thus doing substantial harm to our competitive position.

7. The information we have identified as confidential is not health or safety data.

Any questions concerning this submission, may be directed to me at (513) 627-5551.

Sincerely,

THE PROCTER AND GAMBLE COMPANY

Richard H. Hall, Ph.D.
Manager
Regulatory & Government Affairs
The Procter & Gamble Company

Procter&Gamble

Attachment I

Public Display Copy

Sodium sulfate

Complex sodium phosphate

Sodium silicate

Water

Alkyl benzene sulfonic acid

Fragrance

Colorant

1333-32209

HAZLETON LABORATORIES AMERICA, INC.

3301 KINSMAN BLVD. • P.O. BOX 7545 • MADISON, WI 53707 • (608) 241-4471 • TLX 703856 HAZRAL MDS UD

FINAL REPORT

28-Day Subchronic Percutaneous Toxicity Study of B0723-01 (BSBTS 862S) in Rabbits

Study No. 6114-119

for

The Procter and Gamble Company
Cincinnati, Ohio

by

Hazleton Laboratories America, Inc.
Life Sciences Division
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Reviewed and Accepted by BS&HOP/PS&RS
W. B. Gibson Date 3/7/86
W. B. GIBSON

April 23, 1985

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OPERATIONS SECTION

COPY SENT TO:
W. B. Gibson
DATE: 5/8/85

Chemical & BioMedical Sciences Division

HAZLETON LABORATORIES AMERICA, INC.
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28-Day Subchronic Percutaneous Toxicity Study of B0723-01 (BSBTS 862S) in Rabbits

HLA Study No. 6114-119

Sponsor	Contractor
The Procter & Gamble Company 11520 Reed Hartman Highway Cincinnati OH 45241	Hazleton Laboratories America, Inc. Life Sciences Division 3301 Kinsman Boulevard Madison WI 53704
Divisional Toxicologist	Study Director
W. Bruce Gibson, PhD	Wayne A. Madison

Final Report Amendment No. 1
Effective May 22, 1985

This amendment modifies the following portions of the final report.

1) Page 7, Anatomical Pathology, paragraph 2, sentence 1. To clarify the significance of the centrolobular lesions seen in the liver tissues, add the underlined.

> The only potentially treatment-related microscopic lesion was the severe centrolobular hepatocytic swelling in the Group II male animals.

2) Page 7, Organ Weights, sentence 1. To correct a typographical error, substitute the underlined for "Tables 10".

> The group mean absolute and relative organ weights are presented in Table 10.

3) Page 7, Conclusion, sentence 4. To clarify the significance of the centrolobular lesions seen in the liver tissues, add the underlined.

> Potentially treatment-related lesions were limited to the Group II (0.2 g.kg) males, in which significantly increased absolute and relative liver weights with an associated increase in severity of centrolobular hepatocytic swelling were noted.

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UPDATING SECTION
OCT 9 1985

4) Page 9, Pathology Report, Microscopic Lesions and Summary paragraphs. To clarify the significance of the hepatocytic swelling seen by our pathologists the following have been rewritten.

Microscopic Lesions

SUMMARY

5) Page 29, Table 8, RBC value heading. The units of measurement were incorrectly stated, substitute the underlined.

RBC ($x10^6$/cumm)

6) Page 104, (Addendum No. 1). This was inadvertently omitted from the final report.

Addendum No. 1 is to be added to the protocol section of the final report.

7) To include the summary of Dr. Field's review in the final report.

The results of Dr. Field's blind review of the liver sections will be on page 64A.

Corrected pages with these changes are attached.

AMENDMENT APPROVAL

Wayne A. Madison — 9/24/85
Wayne A. Madison
Study Director
Hazleton Laboratories America, Inc.
Date

Karen M. MacKenzie — 9-24-85
Karen M. MacKenzie, PhD
Director, Toxicology
Hazleton Laboratories America, Inc.
Date

Diana E. Skalitzky — 9/26/85
Diana E. Skalitzky
Inspector, Quality Assurance Unit
Hazleton Laboratories America, Inc.
Date

(0863t/mkk)

QUALITY ASSURANCE STATEMENT

28-Day Subchronic Percutaneous Toxicity Study
of BO723-01 in Rabbits

Study No. 6114-119

The final report as herein attached for the above-mentioned study has been reviewed by the assigned Quality Assurance Unit of Hazleton Laboratories America, Inc. in accordance with the Good Laboratory Practice Regulations as set forth in 40 CFR 160.35 (b) (6) (7). It has been found to accurately identify and/or describe the authorized methods and standard operating procedures followed in the conduct of the study and that the reported data accurately reflect the raw data of the laboratory study. Furthermore, the Quality Assurance Unit has conducted the following inspections of the testing facilities utilized in the conduct of this study and has submitted written reports of said inspections to the study director and/or management.

Date of Inspection	Type of Inspection	Date Issued to Management
7/30/84	Animal/Cage ID/Animal Care Test Article Administration	7/30/84
8/14/84	Test Material Preparation	8/14/84
8/28/84	Pathology/Necropsy/Recording	8/28/84
1/02/85	Report Review	1/02/85

Diana E. Skalitzky

Diana E. Skalitzky
Inspector, Quality Assurance Unit

DATE 4/24/85

The Procter and Gamble Company
Cincinnati, Ohio

FINAL REPORT

28-Day Subchronic Percutaneous Toxicity Study
of B0723-01 (BSBTS 862S) in Rabbits

Test Article	B0723-01 (BSBTS 862S)
Divisional Toxicologist	W. Bruce Gibson
Hazleton Study Director	Wayne A. Madison
Starting Date	July 30, 1984
Termination Date	August 28, 1984

Personnel

Director of Toxicology	Karen M. MacKenzie, PhD
Study Director	Wayne A. Madison
Study Supervisor	Steven M. Glaza
Pathologist	Wallace K. Hauck, DVM

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CORRECTED PAGE

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Wayne A. Madison 9/24/85

Wayne A. Madison
Study Director
Section Supervisor, Acute Toxicology

Date

(10195/kk)

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OBJECTIVES

The purpose of this investigation was to assess the cutaneous and systemic toxicity of test material B0723-01 (BSBTS 862S) when it is repeatedly applied to abraded skin over a period of 28 days.

TEST ARTICLE

Purity, Stability, and Identification

The test article, B0723-01 (BSBTS 862S), was received from the Procter and Gamble Company, Cincinnati, Ohio, and assigned HLA Sample No. 40701902. Information on the strength, purity, and stability was to be determined and documented by the Sponsor. The test article was received as a green crystalline solid and was stored in a clear, screw-cap, glass container. The sample container was stored at room temperature.

Preparation of Test and Vehicle Control Solutions (Suspensions)

The vehicle and test solution were prepared fresh daily throughout the 28-day study period.

To prepare the 10% (w/w) mixture of B0723-01, the appropriate amount of test material was placed into either a 50- or 100-mL volumetric flask and distilled water was added to the appropriate final volume. The test mixture was shaken vigorously then transferred to a suitably sized glass beaker.

Each sample was continuously stirred using a Teflon®-coated magnetic stir bar and stir plate during the dosing procedure. After dosing the unused portion was discarded.

TEST SYSTEM

Animal Model

Young adult rabbits of the New Zealand White strain, an equal number of both sexes, were obtained from Hazleton Dutchland, Inc., Denver, Pennsylvania. Rabbits were selected from animals weighing 1.9 to 2.6 kg that had been acclimated in the laboratory for a minimum of 7 days (Hazleton Laboratories America, Inc. (HLA) Standard Operating Procedure OP-LAR 135). Those rabbits judged to be of acceptable health status were selected for hematology screening. Only animals with an acceptable health status and normal hemogram were randomized into study groups.

Identification

Each rabbit was assigned an individual ear tag identification number. That number accompanied all data collected from that animal throughout the study (HLA Standard Operating Procedure OP-CEN 24).

Housing and Maintenance

The rabbits were housed individually in screen-bottom stainless-steel cages (heavy gauge) in a room with a controlled environment at 22°C (±2°), 50% to 78% relative humidity, and with a 12-hour light, 12-hour dark lighting cycle. The collecting pans for urine and feces were cleaned daily and washed once every 2 weeks in a tunnel washer at 80°C. Both collecting pans and cages were acid cleaned prior to washing in the tunnel washer.

Feed and Water

Feed and water were provided *ad libitum* throughout the course of the study. Tap water, partially demineralized by reverse osmosis, was available from an automatic watering system (Systems Engineering, Napa California), while feed was offered from food hoppers on the cage doors. Fresh feed was provided daily and monitored periodically during the day. The diet for all treatment and control animals was Purina Certified Rabbit Chow® No. 5322 (Lot Nos. JUN 1984 1B and JUN 2684 2A).

PROCEDURE

This study was conducted according to the protocol (Procter and Gamble No. C11 issued 6/21/82) and protocol amendment presented in the Protocol Appendix.

Study Design

Identification of Groups in the 28-Day Subchronic Percutaneous Toxicity Study

Group Number	Treatment	Dose Level (g/kg)	Number of Rabbits Male	Number of Rabbits Female
I	Distilled Water	0.0	5	5
II	B0723-01	0.2	5	5

Treatment

Dermal application was daily, 5 days per week for 4 weeks (20 applications), at a dosage volume of 2.0 mL/kg of body weight. The vehicle control, distilled water, was applied following the same regimen.

All animals were randomly assigned to each test group by use of a computer-generated random numbers list based upon individual body weights taken just prior to initiation of treatment. The hair was clipped from the back of each animal, from shoulder to rump, approximately 15-cm wide. This was done just prior to initiation of the study and as needed throughout the study before application of the test material.

The application site of each animal was abraded with a clipper head prior to each treatment by penetrating the horny layer of the epidermis without causing bleeding. The test material was applied through a syringe onto the abraded back and spread evenly over the test site with gentle inunction using a glass rod. Care was taken to prevent runoff from accumulating along the hairline of the application site. The animals were restrained with collars to prevent oral ingestion of the test material. The collars were removed approximately 7 hours post-treatment and the animals were washed with tepid tap water, patted dry with clean cloth towels and returned to their cages. The control animals were handled in the same manner as the test animals except the vehicle was applied to the test site. Treatment was initiated on July 30, 1984 and all rabbits were euthanatized and necropsied on August 28, 1984.

Observations

All rabbits were examined daily for gross pharmacotoxic signs and mortality (7 days/week) and any abnormalities were recorded. Daily dermal irritation readings were read immediately prior to each application of the test material (5 days/week) and again just prior to necropsy. All animals were weighed at initiation, once weekly to adjust the dosages, and at study termination.

Hematology and Clinical Chemistry

Blood samples were taken, via the marginal ear vein, once before initiation of treatment (baseline) and once at termination (4 days prior to necropsy). The following hematology values were determined on these samples.

Hematology

Test	Abbreviation	Units
White blood cell count	WBC	($x10^3$/cu mm)
Neutrophils	N	(%)
Lymphocytes	L	(%)
Monocytes	M	(%)
Eosinophils	E	(%)
Basophils	B	(%)
Neutrophil-bands (total % open)	BANDS N	(%)

Hematology

Test	Abbreviation	Units
Mature neutrophils	M-SEG	(%)
RBC count	RBC	($x10^6$/cu mm)
NRBC count	NRBC	(/100 WBC)
Hematocrit	HCT	(g/dL)
Hemoglobin	HGB	(%)
Mean corpuscular volume	MCV	(cu u)
Mean corpuscular hemoglobin	MCH	(pg)
Mean corpuscular hemoglobin concentration	MCHC	(%)

Pathology

Prior to initiation of the study, the animals were scheduled for necropsy. Randomization procedures were used to determine the order in which the animals were sacrificed. All animals were sacrificed 4 days after completion of dosing. The animals were euthanatized with an intravenous overdose of sodium pentobarbital, and exsanguinated prior to cessation of heart beat by severing the femoral and brachial arteries. Necropsy was started within 10 minutes after euthanasia. A complete necropsy was performed on all animals and all gross lesions were noted. The following tissues were collected, with the trimmed tissues being placed in 10% neutral buffered formalin at an estimated volume dilution of 1 part tissue to 15 parts formalin, and prepared for histopathological examinations. Zenker's fixative was used for preserving the eyes.

Tissues Collected for Histopathological Examinations

Lung
Heart
Aorta
Tongue
Trachea, esophagus, thyroid
Submandibular lymph node
Ileocecal lymph node
Stomach (fundic, cardiac, and pyloric regions)
Liver and gall bladder*
Duodenum
Jejunum
Ileum
Cecum, colon
Urinary bladder
Kidneys*

*Organs weighed at time of necropsy.

Reproductive: Male - prostate, seminal vesicle, epididymis, and testes
Female - vagina, both uterine horns, and ovaries
Adrenals
Thymus
Psoas muscle
Spleen
Pancreas
Bone (costochondral junction)
Bone (with marrow - 5th costochondral junction)
Skin (test site)
Brain
Lumbar spinal cord
Sciatic nerve
Submandibular salivary gland
Pituitary gland
Eyes (both)
Lesions

Statistical Analysis

Body weight, body weight gain, organ weight, the ratio of organ weights to terminal body weight and hematology data were analyzed using analysis of variance. Data were analyzed separately for each sex. Differences were considered statistically significant at $p < 0.05$. Provided that Bartlett's test for homogeneity of variance was not significant, treated groups were compared to the control group by the least significant difference (LSD) criterion. If Bartlett's test was significant, multiple comparisons were made by Wilcoxon's test.

Location of Raw Data, Tissues, and Slides

All the records, raw data, wet tissues, paraffin blocks, and microscope slides with stained tissue sections will be retained in the archives of Hazleton Laboratories America, Inc. at 3301 Kinsman Boulevard, Madison, Wisconsin until transfer is requested by Procter and Gamble.

RESULTS

Dermal Irritation and Pharmacotoxic Signs

Summaries of the dermal irritation observations are presented in Tables 1 and 2. The daily dermal irritation observations with the number of animals affected and categorized according to group, sex and study day are presented in Appendix A. The summary of observed pharmacotoxic signs is presented in Table 3.

Group I - Vehicle Control (0.0 g/kg/day)

No dermal irritation was produced by the distilled water control during the study.

All animals appeared clinically normal throughout the study with the exception of one animal (F05324, male) which appeared thin on Days 29 and 30 of the study.

Group II - B0723-01 (10% w/v), 0.2 g/kg/day

Slight dermal irritation (erythema, eccma and/or desquamation) was observed in four animals during the first week of the study. With the exception of a slight erythema response seen in one animal on Study Day 16, no dermal irritation was observed during Weeks 2, 3, and 4 of the study.

All animals appeared clinically normal throughout the study.

Body Weights

A summary of group mean body weights and body weight gains is presented in Table 4. Individual animal body weight data are presented in Appendix B. Increasing group mean body weights were exhibited by both groups throughout the study. There were no significant differences in the mean body weights between the two groups. A significantly lower mean body weight gain was detected during Week 4 for the Group II (0.2 g/kg) female animals when compared to that of the control group.

Clinical Pathology

A complete discussion of the clinical pathology data is in the Pathology Report. Individual hematology values are listed in Appendix D; mean values for each group are in Tables 7 and 8. A summary of the hematological changes (terminal from baseline) is presented in Table 9.

The Group II (0.2 g/kg) females had a significantly lower absolute basophil mean value at termination when compared to their respective control group. Significant increases were detected in the change from baseline to terminal mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values for the Group II (0.2 g/kg) female animals when compared to those of the control. These changes, although statistically significant, are not considered biologically important.

Anatomical Pathology

Individual values for macroscopic and microscopic findings are listed in Appendix E. Summaries of the macroscopic and microscopic findings are in Tables 5 and 6, respectively.

CORRECTED PAGE

All macroscopic findings were incidental and not apparently treatment related.

The only potentially treatment-related microscopic lesion was the severe centrolobular hepatocytic swelling in the Group II male animals. All other microscopic lesions were incidental and not treatment related.

Organ Weights

The group mean absolute and relative organ weights are presented in Table 10. Individual organ weights are presented in Appendix C. Significantly higher absolute and relative liver weights ($p < 0.05$) were noted for the Group II males when compared to their respective control group. No other statistically significant differences were seen in the organ weights or organ-to-body-weight ratios for test animals when compared to those of the control (Group I).

CONCLUSION

The test material B0723-01, when applied as a 10% w/v aqueous suspension to abraded skin, 5 days/week for 4 weeks at a dosage level of 0.2 g/kg, resulted in macroscopic changes in the skin and microscopic changes in the liver. No treatment-related signs of toxicosis were seen during the in-life phase of the study. Macroscopic observations during the in-life portion of the study included slight erythema, edema and desquamation. Potentially treatment-related lesions were limited to the Group II (0.2 g/kg) males in which significantly increased absolute and relative liver weights with an associated increase in severity of centrolobular hepatocytic swelling were noted. However, since similar lesions were observed in all study groups including controls, a definative cause and effect relationship with the test material could not be determined. The biological significance of this lesion is unknown. A few hematologic changes were found to be statistically significant, but none were considered biologically important or caused by treatment.

Wayne A. Madison — 9/24/85
Wayne A. Madison
Study Director
Section Supervisor, Acute Toxicology
Date

Karen M. MacKenzie — 9-24-85
Karen M. MacKenzie, PhD
Director, Toxicology
Date

by and for Hazleton Laboratories America, Inc.

(10198/sl)

All macroscopic findings were incidental and not apparently treatment related.

The only treatment-related microscopic lesion was the severe centrolobular hepatocytic swelling in the Group II male animals. All other microscopic lesions were incidental and not treatment related.

Organ Weights

The group mean absolute and relative organ weights are presented in Tables 10. Individual organ weights are presented in Appendix C. Significantly higher absolute and relative liver weights ($p \leq 0.05$) were noted for the Group II males when compared to their respective control group. No other statistically significant differences were seen in the organ weights or organ-to-body-weight ratios for test animals when compared to those of the control (Group I).

CONCLUSION

The test material, B0723-01, when applied as a 10% w/v aqueous suspension to abraded skin, 5 days/week for 4 weeks at a dosage level of .2 g/kg resu[illegible] in macroscopic changes in the skin and microscopic changes in the liver. No treatment-related signs of toxicosis were seen during the in-life phase of the study. Macroscopic observations during the in-life portion of the study included slight erythema, edema and desquamation. Treatment-related lesions were limited to the Group II (0.2 g/kg) males in which significantly increased absolute and relative liver weights with an associated increase in severity of centrolobular hepatocytic swelling were noted. However, since similar lesions were observed in all study groups including controls, a definative cause and effect relationship with the test material could not be determined. The biological significance of this lesion is unknown. A few hematologic changes were found to be statistically significant, but none were considered biologically important or caused by treatment.

Wayne A. Madison
Study Director
Section Supervisor, Acute Toxicology

4/29/85
Date

Karen M. MacKenzie, PhD
Director, Toxicology

4-30-85
Date

by and for Hazleton Laboratories America, Inc.

(10198/tji)

Study No. 6114-119

PATHOLOGY REPORT

INTRODUCTION

The purpose of this study was to assess the cutaneous and systemic toxicity of B0723-01 which was repeatedly applied to abraded skin for 28 days. New Zealand albino rabbits weighing 2.0 - 3.0 kg were randomly assigned to either the control or the treatment group so that each group contained 5 rabbits of each sex. Distilled water was applied to the abraded skin of control rabbits and B0723-01 in a 10% weight/volume suspension was applied to abraded skin of treated rabbits.

All rabbits were bled, sacrificed and necropsied at the termination of the study, hematology tests were performed; selected tissues were collected, preserved in formalin, processed, and examined histologically.

RESULTS/CLINICAL PATHOLOGY

Individual hematology values for the baseline and terminal sacrifices are in Appendix D; summaries of statistics are in Tables 7 and 8, respectively. A statistics summary of differences in baseline and terminal mean values is in Table 9.

The significantly lower absolute basophil mean in terminally sacrificed females was within normal limits. There were significant increases in two erythrocyte indices in the comparison of baseline to terminal hematology values; however, all values were within normal limits.

Slight deviations from normal ranges present in mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) baseline values and hemoglobin (HGB) terminal sacrifice values were probably caused by small sample numbers for the normal value ranges. These deviations, the significant change in basophil mean, and the significant changes in baseline to terminal comparisons, were not considered biologically important.

RESULTS/ANATOMICAL PATHOLOGY

Individual values for terminal body weights, organ weights, and macroscopic observations with correlating microscopic lesions are in Appendix E.

The quality and quantity of tissues taken were adequate to evaluate this study.

Organ Weights

Individual absolute and relative organ weight values are in Appendix C; mean values of absolute and relative organ weights are summarized in Table 10. In treated males, absolute and relative liver weight means were significantly higher, according to the least significant difference (LSD) analysis.

Macroscopic Observations

An incidence summary of macroscopic observations is in Table 5. All findings were considered incidental to the study and not treatment related.

Microscopic Lesions

An expanded incidence summary of microscopic lesions is in Table 6. Centrilobular hepatocytic swelling was more severe in treated males and correlated with the higher absolute and relative liver weights. Because the severity of centrilobular hepatocellular swelling appeared to be treatment-related, a second pathologist was asked to read the liver sections from all animals.* The sections were read blind and the results were in general agreement with those of the study pathologist. Although the centrilobular swelling is possibly treatment-related, healthy, untreated rabbits often have variable amounts of glycogen stored in hepatocytes and this may be responsible for the swollen hepatocytes in this study. All other lesions were clearly incidental to the study.

The morphology of granulomatous inflammations in brain, heart, and kidneys was compatible with a diagnosis of encephalitozoonosis.

SUMMARY

The severity of centrilobular hepatocytic swelling was more severe in treated males and correlated with higher absolute and relative liver weights. Although the hepatocellular swelling is possibly treatment related, the lesion was also seen in control males and females. The specific cause of the swelling could not be established but healthy, untreated rabbits often have variable amounts of glycogen in enlarged hepatocytes.

Other organ weight and microscopic lesions and all hematology and macroscopic changes were clearly incidental to the study and not treatment related.

Wallace W. Haucke, DVM
Pathologist

24 Sept 1985
Date

(976)

* A summary of Dr. Field's review is in Appendix D.

Microscopic Lesions

An expanded incidence summary of microscopic lesions is in Table 6. Centrilobular hepatocytic swelling was more severe in treated males. This lesion correlated with the higher absolute and relative liver weights. All other lesions were considered incidental to the study and not treatment related.

The morphology of granulomatous inflammations in brain, heart, and kidneys was compatible with a diagnosis of encephalitozoonosis.

SUMMARY

Treatment-related effects were limited to higher male absolute and relative liver weights and a microscopic correlate, higher severity of centrilobular hepatocytic swelling. Because there were only five rabbits per group and the same lesion was present in reduced severity in control males, a definitive cause-effect relationship with BC723-01 could not be ascertained.

Other organ weight and microscopic lesions and all hematology and macroscopic changes were considered incidental to the study and not treatment related.

Wallace N. Hauck, DVM
Pathologist

4/29/85
Date

(976)

Study No. 6114-119

Table 1

Summary of Dermal Irritation Scores - Group 1
Vehicle Control
0.0 g/kg/day

	Males					Females				
	Week 1	Week 2	Week 3	Week 4	Final Observation	Week 1	Week 2	Week 3	Week 4	Final Observation
Erythema										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0
Edema										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0
Atonia										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0
Desquamation										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0
Fissuring										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0

Study No. 6114-119

Table 2

Summary of Dermal Irritation Scores - Group 11
B0723-01 (10% w/v) 0.20g/kg/day

	Males					Females				
	Week 1	Week 2	Week 3	Week 4	Final Observation	Week 1	Week 2	Week 3	Week 4	Final Observation
Erythema										
Average	0.24	0	0.04	0	0	0.40	0	0	0	0
Range	0-1	0	0-1	0	0	0-1	0	0	0	0
Edema										
Average	0.08	0	0	0	0	0	0	0	0	0
Range	0-1	0	0	0	0	0	0	0	0	0
Atonia										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0
Desquamation										
Average	0.04	0	0	0	0	0	0	0	0	0
Range	0-1	0	0	0	0	0	0	0	0	0
Fissuring										
Average	0	0	0	0	0	0	0	0	0	0
Range	0	0	0	0	0	0	0	0	0	0

Study No. 6114-119

Table 3

Summary of Pharmacotoxic Signs
(Number of Animals Affected)

Observation	Study Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Males																														
Group I - Vehicle Control, 0.0 g/kg/day																														
Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4	4
Appears thin	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	0	1	1
Group II - M0723-01 (10% w/v) 0.20 g/kg/day																														
Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Females																														
Group I - Vehicle Control, 0.0 g/kg/day																														
Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Group II - M0723-01 (10% w/v) 0.20 g/kg/day																														
Normal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Study No. 6114-119

Table 4

Summary of Mean Body Weights and Mean Body Weight Gains (g)

Males/Females

Week	Body Weights: Group I Vehicle Control (0.0 g/kg/day)	Body Weights: Group II B0723-01 10% w/v (0.20 g/kg/day)	Body Weight Gains: Group I Vehicle Control (0.0 g/kg/day)	Body Weight Gains: Group II B0723-01 10% w/v (0.20 g/kg/day)
Males				
Initial	2,382	2,335	-	-
1	2,591	2,473	209	138
2	2,735	2,621	143	148
3	2,789	2,774	54	153
4	2,831	2,902	42	129
Females				
Initial	2,324	2,382	-	-
1	2,520	2,569	196	187
2	2,701	2,707	181	138
3	2,848	2,833	146	126
4	3,001	2,909	153	76*

*Statistically different from the control (Group I) at $p < 0.05$. All other means are not significantly different from the control.

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Table 5
Incidence Summary of Macroscopic Observations
Terminal Sacrifice

PRINTED: 08-NOV-84
PAGE: 1

STUDY NUMBER: 4114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		-FEMALE-	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
** TOP OF LIST **					
BRAIN (BR)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
LUNG (LU)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	4	4	3
RED FOCUS(1)/AREA(S)		0	1	1	1
CYST(S)		0	0	0	1
KIDNEY(S) (KD)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	3	5	5	4
LIGHT FOCUS(1)/AREA(S)		0	0	0	1
DEPRESSED FOCUS(1)/AREA(S)		2	0	0	0
HEART (HT)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
LIVER (LI)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	4
LIGHT FOCUS(1)/AREA(S)		0	0	0	1
GALL BLADDER (GB)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
SPLEEN (SP)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	4	5	5
RAISED FOCUS(1)/AREA(S)		0	1	0	0

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MADISON, WISCONSIN 53707

Table 5 (Continued)
Incidence Summary of Macroscopic Observations
Terminal Sacrifice

PRINTED: 05-NOV-84
PAGE: 2
STUDY NUMBER: 6114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

DRONN AND KEYWORD(S) OF PHRASE		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		-FEMALE-	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
EYE(S) (EY)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
TONGUE (TO)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
TRACHEA (TR)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
ESOPHAGUS (ES)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
THYROID(S) (TY)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
PARATHYROID(S) (PT)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
PITUITARY (PI)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
ADRENAL(S) (AD)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
AORTA (AO)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5

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Table 5 (Continued)
Incidence Summary of Macroscopic Observations
Terminal Sacrifice

STUDY NUMBER: 6114019

TABLE INCLUDES:
SEX=ALL:GROUP=ALL:WEEKS=ALL
DEATH=T:SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
PANCREAS (PAN)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
STOMACH (ST)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
DUODENUM (DU)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
JEJUNUM (JE)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
ILEUM (IL)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
CECUM (CE)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
COLON (CO)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
PSOAS MUSCLE (SM)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
SCIATIC NERVE (SN)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5

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Table 5 (Continued)
Incidence Summary of Macroscopic Observations
Terminal Sacrifice

STUDY NUMBER: 6114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
SALIVARY GLANDS (SG)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	4	5	5
DIFFUSELY RED		0	1	0	0
SUBMANDIBULAR LN (MN)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
THYMUS (TM)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
MESENTERIC L.N. (MN)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
ZG WHITE-5TH COS (RL)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
SPINAL CORD (TL) (SC)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5
TREATED SKIN (TS)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	4	5	5	5
THICKENED		1	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	5	5	5	5

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DEPARTMENT OF PATHOLOGY
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Table 5 (Continued)
Incidence Summary of Macroscopic Observations
Terminal Sacrifice

STUDY NUMBER: 6114139

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
PROSTATE (PRO)	NUMBER EXAMINED:	5	5	0	0
	NOT REMARKABLE:	5	5	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	5	5	0	0
	NOT REMARKABLE:	5	5	0	0
TESTES (TES)	NUMBER EXAMINED:	5	5	0	0
	NOT REMARKABLE:	5	5	0	0
EPIDIDYMIDES (EP)	NUMBER EXAMINED:	5	5	0	0
	NOT REMARKABLE:	5	5	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	5	5
	NOT REMARKABLE:	0	0	4	5
THICKENED WALLS		0	0	1	0
DIFFUSELY RED		0	0	1	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	5	5
	NOT REMARKABLE:	0	0	5	5
OVARIES (OV)	NUMBER EXAMINED:	0	0	5	5
	NOT REMARKABLE:	0	0	5	5
GENERAL COMMENT (GC)	NUMBER EXAMINED:	5	5	5	5
	NOT REMARKABLE:	2	2	2	3
ALL TISSUES, ORGANS NORMAL		3	3	3	2

** END OF LIST **

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Table 6
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

PRINTED: 09-NOV-84
PAGE: 1

STUDY NUMBER: 6114219

TABLE INCLUDES:
SEX=ALL:GROUP=ALL:SCREEN=ALL:WEEKS=ALL
DEAT=T:FIND=ALL:SUBSET=ALL

ORGAN/TISSUE EXAMINED		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
** TOP OF LIST **					
BRAIN (CNS)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—ENCEPHALITIS, GRANULOMATOUS	→	2	4	3	4
	D	1	0	1	0
	D	0	0	1	1
	D	2	1	0	0
	TD	5	5	5	5
LUNG (CNS)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA	→	4	3	3	3
	D	0	1	0	1
	D	1	1	2	1
	TD	5	5	5	5
—HETEROPHIL INFILTRATION	→	5	5	5	4
	D	0	0	0	1
	TD	5	5	5	5
—PNEUMONITIS, GRANULOMATOUS	→	2	3	3	3
	D	3	2	0	2
	D	0	0	2	0
	TD	5	5	5	5
—MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES	→	5	4	2	4
	D	0	1	3	1
	TD	5	5	5	5
—HEMORRHAGE	→	4	5	5	5
	D	1	0	0	0
	TD	5	5	5	5

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Table 6 (Continued)
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

PRINTED: 05-NOV-84
PAGE: 2
STUDY NUMBER: 6114139

TABLE INCLUDES:
SEX=ALL:GROUP=ALL:SCREEN=ALL:WEEKS=ALL
DEATH=T:FDXO=ALL:SUBSET=ALL

ORGAN/TISSUE EXAMINED		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		-FEMALE-	
	GROUP:	-1-	-2-	-1-	-2-
	NUMBER:	5	5	5	5
KIDNEY(S) (KD)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—INTERSTITIAL NEPHRITIS, GRANULOMATOUS	→	2	3	3	4
	1>	0	1	0	0
	2>	2	0	2	0
	3>	1	1	0	0
	4>	0	0	0	1
	TL>	5	5	5	5
—TUBULAR DILATATION	→	4	4	5	4
	P>	1	1	0	1
	TL>	5	5	5	5
—REGENERATIVE TUBULAR EPITHELIUM	→	4	4	5	4
	P>	1	1	0	1
	TL>	5	5	5	5
—INFARCT(S)	→	5	5	5	4
	P>	0	0	0	1
	TL>	5	5	5	5
—MINERALIZATION	→	5	5	4	5
	P>	0	0	1	0
	TL>	5	5	5	5
HEART (HT)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—MYOCARDITIS, GRANULOMATOUS	→	4	5	3	5
	1>	1	0	2	0
	TL>	5	5	5	5

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MADISON, WISCONSIN 53707

Table 6 (Continued)
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

STUDY NUMBER: 6114139

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		— NUMBER-OF-ANIMALS-AFFECTED —			
	SEX:	—MALE—		-FEMALE-	
	GROUP:	-1-	-2-	-1-	-2-
ORGAN/TISSUE EXAMINED	NUMBER:	5	5	5	5
LIVER (LI)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—HEPATOCYTIC SWELLING, CENTROLOBULAR	->	1	0	0	0
	1>	1	0	0	0
	2>	1	0	2	2
	3>	2	0	1	2
	4>	0	4	1	1
	5>	0	1	1	0
	TL>	5	5	5	5
—MONONUCLEAR CELL INFILTRATE, PORTAL	->	0	3	2	2
	1>	2	5	1	1
	2>	3	2	1	2
	3>	0	0	1	0
	TL>	5	5	5	5
GALL BLADDER (GB)	NUMBER THAT CAN BE EXAMINED:	5	4	5	4
SPLEEN (SP)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—CONGESTION/HEMORRHAGE	->	3	3	3	5
	P>	2	2	2	0
	TL>	5	5	5	5
—MYELOID HYPERPLASIA, HETEROPHILIC	->	5	4	5	5
	3>	0	1	0	0
	TL>	5	5	5	5
EYE(S) (EY)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
TONGUE (TO)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
TRACHEA (TR)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
ESOPHAGUS (ES)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5

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Table 6 (Continued)
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

PRINTED: 05-NOV-84
PAGE: 4
STUDY NUMBER: 6114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-3-	-1-	-3-
ORGAN/TISSUE EXAMINED	NUMBER:	5	5	5	5
THYROID(S) (TY)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
PARATHYROID(S) (PT)	NUMBER THAT CAN BE EXAMINED:	4	5	5	4
PITUITARY (PT)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
ADRENAL(S) (AD)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
AORTA (AO)	NUMBER THAT CAN BE EXAMINED:	4	5	5	5
PANCREAS (PA)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
STOMACH (ST)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
DUODENUM (DU)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—MONONUCLEAR CELL INFILTRATION, LAMINA PROPRIA	→	4	5	5	5
	2>	1	0	0	0
	TL>	5	5	5	5
JEJUNUM (JE)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—MONONUCLEAR CELL INFILTRATION, LAMINA PROPRIA	→	4	5	5	5
	2>	1	0	0	0
	TL>	5	5	5	5
ILEUM (IL)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
CECUM (CE)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
COLON (CO)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
PSOAS MUSCLE (SM)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
SCIATIC NERVE (SN)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5

HAZLETON LABORATORIES AMERICA, INC.
DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

Table 6 (Continued)
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

PRINTED: 09-NOV-84
PAGE: 5
STUDY NUMBER: 6124119

TABLE INCLUDES:
SEX=ALL:GROUP=ALL:SCREEN=ALL:WEEKS=ALL
DEATH=TERMINAL:SUBSET=ALL

		—NUMBER-OF-ANIMALS-AFFECTED—			
	SEX:	—MALE—		—FEMALE—	
	GROUP:	-1-	-2-	-1-	-2-
ORGAN/TISSUE EXAMINED	NUMBER:	5	5	5	5
SALIVARY GLD(S) (SG)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
SUBMANDIBULAR LN (MN)	NUMBER THAT CAN BE EXAMINED:	5	5	4	5
—LYMPHORETICULAR HYPERPLASIA	→	5	4	4	5
	2>	0	1	0	0
	TL>	5	5	4	5
THYMUS (TH)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
ILEOCECAL LN. (IC)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
—LYMPHORETICULAR HYPERPLASIA	→	1	1	0	2
	2>	0	0	3	1
	3>	1	2	1	2
	4>	3	2	1	0
	TL>	5	5	5	5
RX WANG-5TH DIS (RI)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
SPINAL CORD (TL) (SC)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
TREATED SKIN (TS)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
URINARY BLADDER (UB)	NUMBER THAT CAN BE EXAMINED:	5	5	5	5
PROSTATE (PR)	NUMBER THAT CAN BE EXAMINED:	5	5	0	0
SEMINAL VESICLE (SV)	NUMBER THAT CAN BE EXAMINED:	5	5	0	0
TESTES (TE)	NUMBER THAT CAN BE EXAMINED:	5	5	0	0
EPIDIDYMIDES (EP)	NUMBER THAT CAN BE EXAMINED:	5	5	0	0
UTERUS (UT)	NUMBER THAT CAN BE EXAMINED:	0	0	5	5

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Table 6 (Continued)
Incidence Summary of Microscopic Diagnoses
Terminal Sacrifice

PRINTED: 19-NOV-84
PAGE: 6

STUDY NUMBER: 4114139

TABLE INCLUDES:
SEX=ALL:GROUP=ALL:SCREEN=ALL:WEEKS=ALL
DEATH=T:FIND=ALL:SUBSET=ALL

		NUMBER OF ANIMALS AFFECTED			
	SEX:	MALE		FEMALE	
	GROUP:	1	2	1	2
ORGAN/TISSUE EXAMINED	NUMBER:	5	5	5	5
VAGINA (VAG)	NUMBER THAT CAN BE EXAMINED:	0	0	5	5
OVARIES (OVY)	NUMBER THAT CAN BE EXAMINED:	0	0	5	5

** END OF LIST **

Study No. 6114-119

Table 7

Summary of Base-line Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)
RBC (x 10^6/cmm)				
N	5	5	5	5
Mean	5.78	5.77	5.18	5.31
S	0.562	0.345	0.382	0.175
NRBC/100 WBC				
N	5	5	5	5
Mean	4	4	2	0
S	3.6	3.0	2.8	0.5
HGB (g/dL)				
N	5	5	5	5
Mean	12.4	12.4	11.9	11.8
S	0.53	0.37	0.65	0.29
HCT (%)				
N	5	5	5	5
Mean	35.3	35.5	34.7	34.7
S	1.51	0.94	2.15	1.31
MCV (cubic microns)				
N	5	5	5	5
Mean	61	62	67	65
S	4.9	5.1	2.9	1.4

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p \leq 0.05$.

Study No. 5114-119

Table 7 (Continued)

Summary of Base-line Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/v (0.20 g/kg/day)
MCH (picograms)				
N	5	5	5	5
Mean	21.5	21.5	23.0	22.3
S	1.41	1.04	0.81	0.30
MCHC (%)				
N	5	5	5	5
Mean	35.1	35.0	34.4	34.2
S	0.79	1.29	0.78	0.58
WBC (x 10^3/cmm)				
N	5	5	5	5
Mean	6.5	7.5	7.7	6.8
S	1.83	1.55	2.02	0.61
Mature neutrophils (%)				
N	5	5	5	5
Mean	33	26	28	38
S	9.2	11.0	13.7	14.6
Band immature neutrophils (%)				
N	5	5	5	5
Mean	0	0	0	0
S	0.0	0.0	0.0	0.0

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

Study No. 6114-119

Table 7 (Continued)

Summary of Base-line Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)
Lymphocytes (%)				
N	5	5	5	5
Mean	62	71	67	57
S	10.2	12.6	14.3	15.9
Monocytes (%)				
N	5	5	5	5
Mean	1	0	1	1
S	1.4	0.5	0.8	1.3
Eosinophils (%)				
N	5	5	5	5
Mean	1	1	0	1
S	0.5	0.7	0.5	0.5
Basophils (%)				
N	5	5	5	5
Mean	3	2	3	3
S	1.7	1.9	1.8	2.2
Mature neutrophils ($x 10^3$/cumm)				
N	5	5	5	5
Mean	2.06	1.90	2.03	2.52
S	0.337	0.795	0.761	0.964

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

Table 7 (Continued)

Summary of Base-line Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)
Band immature neutrophils (x 10^3/cumm)				
N	5	5	5	5
Mean	0	0	0	0
S	0	0	0	0
Lymphocytes (x 10^3/cumm)				
N	5	5	5	5
Mean	4.17	5.32	5.34	3.89
S	1.881	1.630	2.138	1.269
Monocytes (x 10^3/cumm)				
N	5	5	5	5
Mean	0.06	0.03	0.06	0.08
S	0.082	0.044	0.058	0.066
Eosinophils (x 10^3/cumm)				
N	5	5	5	5
Mean	0.03	0.08	0.03	0.04
S	0.029	0.049	0.042	0.040
Basophils (x 10^3/cumm)				
N	5	5	5	5
Mean	0.18	0.13	0.25	0.23
S	0.078	0.128	0.114	0.153

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

CORRECTED PAGE

Study No. 6114-119

Table 8

Summary of Terminal Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)
RBC (x 10^6/cmm)				
N	5	5	5	5
Mean	6.88	6.67	6.30	6.34
S	0.548	0.363	0.568	0.255
NRBC/100 WBC				
N	5	5	5	5
Mean	0	1	2	1
S	0.0	0.8	2.2	0.7
HGB (g/dL)				
N	5	5	5	5
Mean	14.5	14.6	13.5	14.1
S	0.79	0.47	1.18	0.79
HCT (%)				
N	5	5	5	5
Mean	44.8	45.0	41.7	43.5
S	2.65	1.77	3.56	2.54
MCV (cubic microns)				
N	5	5	5	5
Mean	66	67	66	68
S	2.3	3.8	3.7	2.1

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

Wayne A. Madison

Wayne A. Madison
Study Director
Section Supervisor, Acute Toxicology

9/24/85
Date

Study No. 6114-119

Table 8

Summary of Terminal Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)
RBC (x 10^6 cumm)				
N	5	5	5	5
Mean	6.80	6.67	6.30	6.34
S	0.548	0.363	0.568	0.255
NRBC/100 WBC				
N	5	5	5	5
Mean	0	1	2	1
S	0.0	0.8	2.2	0.7
HGB (g/dL)				
N	5	5	5	5
Mean	14.5	14.6	13.5	14.1
S	0.79	0.47	1.18	0.79
HCT (%)				
N	5	5	5	5
Mean	44.8	45.0	41.7	43.5
S	2.65	1.77	3.56	2.54
MCV (cubic microns)				
N	5	5	5	5
Mean	66	67	66	68
S	2.3	3.8	3.7	2.1

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p \leq 0.05$.

Study No. 6114-119

Table 8 (Continued)

Summary of Terminal Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)
MCH (picograms)				
N	5	5	5	5
Mean	21.4	21.9	21.4	22.2
S	0.55	1.09	0.97	0.48
MCHC (%)				
N	5	5	5	5
Mean	32.4	32.4	32.3	32.4
S	0.77	0.87	0.92	0.61
WBC (x 10^3/cumm)				
N	5	5	5	5
Mean	7.5	6.7	6.5	5.9
S	1.21	0.71	0.66	1.15
Mature neutrophils (%)				
N	5	5	5	5
Mean	36	31	31	35
S	9.4	15.3	14.1	11.2
Band immature neutrophils (%)				
N	5	5	5	5
Mean	0	0	0	0
S	0.0	0.0	0.0	0.0

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

Study No. 5114-119

Table 8 (Continued)

Summary of Terminal Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/w (0.20 g/kg/day)
Lymphocytes (%)				
N	5	5	5	5
Mean	58	61	64	61
S	10.7	14.8	15.4	9.4
Monocytes (%)				
N	5	5	5	5
Mean	1	1	1	2
S	1.0	0.4	1.3	2.1
Eosinophils (%)				
N	5	5	5	5
Mean	1	1	1	1
S	0.0	0.5	0.8	0.7
Basophils (%)				
N	5	5	5	5
Mean	4	6	4	2
S	5.0	1.7	1.9	1.1
Mature neutrophils ($\times 10^3$/cumm)				
N	5	5	5	5
Mean	2.71	2.00	2.08	2.14
S	0.862	0.884	1.149	1.106

N = Number of samples.
S = Standard deviation.

All means are not significantly different from the control (Group I) at $p < 0.05$.

Study No. 5114-119

Table 8 (Continued)

Summary of Terminal Hematology

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II B0723-01 10% w/v (0.20 g/kg/day)
Band immature neutrophils (x 10^3/cmm)				
N	5	5	5	5
Mean	0	0	0	0
S	0	0	0	0
Lymphocytes (x 10^3/cmm)				
N	5	5	5	5
Mean	4.37	4.15	4.12	3.51
S	0.936	1.305	0.684	0.338
Monocytes (x 10^3/cmm)				
N	5	5	5	5
Mean	0.08	0.05	0.04	0.09
S	0.087	0.031	0.089	0.117
Eosinophils (x 10^3/cmm)				
N	5	5	5	5
Mean	0.07	0.04	0.05	0.06
S	0.011	0.037	0.050	0.043
Basophils (x 10^3/cmm)				
N	5	5	5	5
Mean	0.28	0.43	0.25	0.10*
S	0.372	0.163	0.137	0.056

N = Number of samples.
S = Standard deviation.

*Significantly different from the control (Group I) at $p < 0.05$.

All other means are not significantly different from the control.

Study No. 6114-119

Table 9

Summary of Differences in Baseline and Terminal Mean Values

Male

Parameter	Group I Vehicle Control		Group II B0723-01 10% w/v 0.2 g/kg/day	
	mean	std. dev.	mean	std. dev.
RBC	1.02	0.28	0.90	0.55
HGB	2.16	0.64	2.18	0.77
HCT	9.56	3.04	9.50	2.64
MCV	4.80	4.21	5.80	7.89
MCH	-0.12	0.90	0.40	1.61
MCHC	-2.62	1.23	-2.52	2.08
WBC	1.02	0.96	-0.78	1.96

Female

Parameter	Group I Vehicle Control		Group II B0723-01 10% w/v 0.2 g/kg/day	
	mean	std. dev.	mean	std. dev.
RBC	1.12	0.61	1.03	0.11
HGB	1.56	1.38	2.22	0.58
HCT	6.98	4.10	8.80	1.62
MCV	-0.40	1.52	3.20*	1.30
MCH	-1.64	1.14	-0.14*	0.60
MCHC	-2.06	1.11	-1.80	0.74
WBC	-1.18	2.31	-0.86	1.62

* Significantly different from Control Mean Values at $P<0.05$ according to Least Significant Difference test.

(961)

Study No. 6114-119

Table 10

Summary of Absolute and Relative Organ Weights

	Males		Females	
	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/v (0.20 g/kg/day)	Group I Vehicle Control (0.0 g/kg/day)	Group II BO723-01 10% w/v (0.20 g/kg/day)
Terminal body weight (g)				
N	5	5	5	5
Mean	2,855.8	2,899.8	3,022.8	2,952.0
S	307.1	345.0	102.7	194.2
Liver (g)				
N	5	5	5	5
Mean	79.836	110.459*	112.576	90.449
S	13.989	13.980	28.023	3.929
Left kidney (g)				
N	5	5	5	5
Mean	8.110	9.123	8.692	7.204
S	1.10*	1.932	1.512	0.685
Right kidney (g)				
N	5	5	5	5
Mean	8.006	8.933	8.708	7.926
S	1.023	1.524	1.563	1.037
Liver (%)				
N	5	5	5	5
Mean	2.7960	3.8196*	3.7457	3.0724
S	0.3837	0.3421	1.0339	0.2033
Left kidney (%)				
N	5	5	5	5
Mean	0.2839	0.3166	0.2873	0.2620
S	0.0197	0.0710	0.0469	0.0299
Right kidney (%)				
N	5	5	5	5
Mean	0.2803	0.3104	0.2879	0.2695
S	0.0182	0.0582	0.0492	0.0404

N = Number of samples.
S = Standard deviation.

*Significantly different from the control (Group I) at $p < 0.05$. All other means are not significantly different from the control.

APPENDIX A

Daily Dermal Irritation

Study No. 6114-119

Table A1

Daily Dermal Irritation Observations
(Number of Animals Affected)

Observation	Study Day 1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26	29	30
Males																						
Group I - Vehicle Control, 0.0 g/kg/day																						
No dermal irritation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group II - B0723-01 (10% w/v) 0.20 g/kg/day																						
No dermal irritation	5	5	3	2	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5	5	5	5
Slight erythema	0	0	2	3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Slight edema	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slight desquamation	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Females																						
Group I - Vehicle Control, 0.0 g/kg/day																						
No dermal irritation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group II - B0723-01 (10% w/v) 0.20 g/kg/day																						
No dermal irritation	5	5	5	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Slight erythema	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

APPENDIX B

Individual Body Weights

Study No. 6114-119

Table B1

Rabbit Body Weights (g)

Animal Number	Initiation	Week 1	Week 2	Week 3	Week 4
Group I - Vehicle Control, 0.0 g/kg/day					
Males					
F05349	2,300	2,473	2,623	2,761	2,842
F05333	2,328	2,672	2,833	2,866	2,983
F05369	2,385	2,562	2,681	2,813	2,760
F05324	2,442	2,640	2,696	2,479	2,386
F05339	2,455	2,609	2,840	3,026	3,186
N	5	5	5	5	5
Mean	2,382	2,591	2,735	2,789	2,831
S	68.2	77.5	97.0	199.7	296.8
Females					
F05366	2,177	2,379	2,503	2,662	2,846
F05323	2,232	2,410	2,584	2,774	2,940
F05370	2,352	2,505	2,727	2,856	3,072
F05334	2,406	2,620	2,778	2,929	3,042
F05352	2,454	2,686	2,915	3,018	3,106
N	5	5	5	5	5
Mean	2,324	2,520	2,701	2,848	3,001
S	116.7	132.1	162.2	137.5	106.6
Group II - B0773-01 (10% w/v) 0.20 g/kg/day					
Males					
F05326	2,109	2,213	2,304	2,361	2,547
F05362	2,321	2,389	2,532	2,635	2,655
F05321	2,334	2,335	2,412	2,656	2,806
F05355	2,453	2,758	3,004	3,186	3,354
F05351	2,456	2,670	2,853	3,030	3,150
N	5	5	5	5	5
Mean	2,335	2,473	2,621	2,774	2,902
S	141.3	231.2	296.9	331.3	339.9

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table E11 (Continued)

Rabbit Body Weights (g)

Animal Number	Initiation	Week 1	Week 2	Week 3	Week 4
		Females			
F05318	2,223	2,373	2,549	2,695	2,790
F05310	2,230	2,584	2,744	2,869	2,969
F05316	2,338	2,469	2,574	2,697	2,743
F05311	2,382	2,603	2,706	2,827	2,876
F05380	2,736	2,817	2,964	3,058	3,166
N	5	5	5	5	5
Mean	2,382	2,569	2,707	2,833	2,909
S	209.2	166.8	165.9	151.1	167.7

N = Number of samples.
S = Standard deviation.

APPENDIX C

Individual Organ Weights

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DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

Table C1

Individual Absolute Organ Weight Values - Males

PRINTED: 30-OCT-84
PAGE: 1

STUDY NUMBER: 6114139

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN ABBREVIATION: KSO - LEFT KIDNEY, KDI - RIGHT KIDNEY, LI - LIVER

SEX	DOSE GROUP	ANIMAL NUMBER	TERMINAL BODY WT (g)	KSO	KDI	LI
M	1	005340	2873.0	7.259	7.229	98.938
M	1	005333	3028.0	8.443	8.427	97.360
M	1	005389	2831.0	8.169	8.531	75.383
M	1	005324	2367.0	6.922	6.674	63.046
M	1	005339	3180.0	9.738	9.169	74.545
NUMBER IN GROUP:			5	5	5	5
MEAN:			2859.0	8.118	8.006	79.836
STANDARD DEV:			302.1	1.188	1.025	13.989
M	2	005326	2548.0	7.183	7.448	98.974
M	2	005342	2677.0	8.375	8.383	109.984
M	2	005321	2754.0	12.841	11.152	98.142
M	2	005355	3336.0	9.980	9.880	112.519
M	2	005351	3192.0	8.196	7.882	132.677
NUMBER IN GROUP:			5	5	5	5
MEAN:			2899.0	9.123	8.933	110.459
STANDARD DEV:			345.0	1.932	1.524	13.988

HAZLETON LABORATORIES AMERICA, INC.
DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

Table C2

Individual Relative Organ Weight Values - Males

PRINTED: 30-OCT-84
PAGE: 1

STUDY NUMBER: 6114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;SUBSET=ALL

ORGAN ABBREVIATION: KOB - LEFT KIDNEY, KO1 - RIGHT KIDNEY, LI - LIVER

SEX	DOSE GROUP	ANIMAL NUMBER	TERMINAL BODY WT (g)	KOB	KO1	LI
M	1	005340	2875.0	.2527	.2516	3.1644
M	1	005333	3028.0	.2882	.2790	3.2241
M	1	005349	2831.0	.2806	.3013	2.5809
M	1	005324	2567.0	.2924	.2828	2.6655
M	1	005339	3180.0	.3055	.2876	2.3389
NUMBER IN GROUP:			5	5	5	5
MEAN:			2895.0	.2839	.2845	2.7968
STANDARD DEV:			307.1	.0197	.0182	.3857
M	2	005326	2548.0	.2796	.2932	3.8946
M	2	005342	2677.0	.3129	.3131	4.1885
M	2	005321	2754.0	.4872	.4649	3.5636
M	2	005355	3336.0	.2994	.2938	3.3729
M	2	005351	3192.0	.2539	.2469	4.1569
NUMBER IN GROUP:			5	5	5	5
MEAN:			2899.0	.3166	.3184	3.8196
STANDARD DEV:			345.0	.0718	.0582	.3421

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Table C3

Individual Absolute Organ Weight Values - Female

PRINTED: 30-OCT-84
PAGE: 2

STUDY NUMBER: 6114119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN ABBREVIATION: KOR - LEFT KIDNEY, KOI - RIGHT KIDNEY, LI - LIVER

SEX	DOSE GROUP	ANIMAL NUMBER	TERMINAL BODY WT (g)	KOR	KOI	LI
F	1	005366	2848.0	8.177	8.448	144.885
F	1	005323	2998.0	7.392	7.156	132.931
F	1	005378	3846.0	10.771	10.802	102.336
F	1	005334	3068.0	7.348	7.574	72.875
F	1	005352	3144.0	9.758	9.760	109.995
NUMBER IN GROUP:			5	5	5	5
MEAN:			3022.0	8.492	8.708	112.576
STANDARD DEV:			102.7	1.512	1.663	28.825
F	2	005318	2784.0	7.370	7.279	87.483
F	2	005318	2974.0	7.888	7.881	92.463
F	2	005316	2825.0	8.089	7.920	86.272
F	2	005311	2983.0	8.678	9.606	96.813
F	2	005308	3274.0	7.591	7.665	98.854
NUMBER IN GROUP:			5	5	5	5
MEAN:			2952.0	7.784	7.926	98.449
STANDARD DEV:			194.2	.605	1.037	3.929

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MADISON, WISCONSIN 53707

Table C4

Individual Relative Organ Weight Values - Female

PRINTED: 30-OCT-84
PAGE: 2
STUDY NUMBER: 6334119

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;SACRIFICE=ALL

ORGAN ABBREVIATION: KDL - LEFT KIDNEY, KDR - RIGHT KIDNEY, LI - LIVER

SEX	DOSE GROUP	ANIMAL NUMBER	TERMINAL BODY WT (g)	KDL	KDR	LI
F	1	005346	2648.0	.2851	.2943	5.8498
F	1	005373	2998.0	.2472	.2395	4.4459
F	1	005378	3844.0	.3538	.3549	3.3619
F	1	005334	3068.0	.2402	.2404	2.5753
F	1	005352	3144.0	.3181	.3187	3.4067
NUMBER IN GROUP:			5	5	5	5
MEAN:			3022.0	.2875	.2879	3.7467
STANDARD DEV:			182.7	.0469	.0492	1.0539
F	2	005318	2784.0	.2575	.2615	3.1423
F	2	005318	2974.0	.2954	.2981	3.1898
F	2	005316	2825.0	.2863	.2884	3.0525
F	2	005311	2983.0	.2987	.3337	3.3074
F	2	005308	3234.0	.2319	.2341	2.7546
NUMBER IN GROUP:			5	5	5	5
MEAN:			2952.0	.2678	.2695	3.0724
STANDARD DEV:			194.2	.0299	.0404	.2033

APPENDIX D

Individual Clinical Hematology Values

Study No. 6114-119

Table D1

Individual Clinical Hematology Values
Baseline - Males

Animal Number	RBC (x 10^6/cu mm)	HGB (g/dL)	HCT (%)	MCV (Cubic Microns)	MCH (Picograms)	MCHC (%)	NRBC (per 100 WBC)
Group I - Vehicle Control - 0.0 g/kg/day							
F05324	6.28	12.8	35.5	57	20.4	36.1	6
F05333	6.29	12.7	35.8	57	20.2	35.5	9
F05339	4.92	11.6	33.3	68	23.6	34.8	2
F05349	5.72	12.7	37.3	65	22.2	34.0	2
F05369	5.69	12.0	34.4	60	21.1	34.9	0
N	5	5	5	5	5	5	5
Mean	5.78	12.4	35.3	61	21.5	35.1	4
S	0.562	0.53	1.51	4.9	1.41	0.79	3.6
Group II - B0723-01 (10% w/w) - 0.20 g/kg/day							
F05321	6.17	12.7	34.8	56	20.6	36.5	6
F05326	5.62	12.6	36.5	65	22.4	34.5	2
F05351	5.62	12.6	36.3	65	22.4	34.7	1
F05355	5.36	11.8	35.5	66	22.0	33.2	2
F05362	6.09	12.3	34.3	56	20.2	35.9	8
N	5	5	5	5	5	5	5
Mean	5.77	12.4	35.5	62	21.5	35.0	4
S	0.345	0.37	0.94	5.1	1.04	1.29	3.0

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D1 (Continued)

Individual Clinical Hematology Values
Baseline - Males

Animal Number	WBC (x 10^3/cu mm)	Mature Neutrophils (x 10^3/cu mm)	Lymphocytes (x 10^3/cu mm)	Monocytes (x 10^3/cu mm)	Eosinophils (x 10^3/cu mm)	Basophils (x 10^3/cu mm)	Band Immature Neutrophils (x 10^3/cu mm)
Group I - Vehicle Control - 0.0 g/kg/day							
F05324	6.0	2.22	3.60	0.00	0.06	0.12	0.00
F05333	6.1	1.59	4.21	0.18	0.00	0.12	0.00
F05339	5.5	2.47	2.80	0.00	0.05	0.17	0.00
F05349	9.7	2.13	7.37	0.00	0.00	0.19	0.00
F05369	5.2	1.87	2.86	0.10	0.05	0.31	0.00
N	5	5	5	5	5	5	5
Mean	6.5	2.06	4.17	0.06	0.03	0.18	0.00
S	1.83	0.337	1.881	0.082	0.029	0.078	0.000
Group II - B0723-01 (10% w/v) - 0.20 g/kg/day							
F05321	6.6	2.18	4.29	0.07	0.00	0.07	0.00
F05326	8.6	1.03	7.40	0.09	0.09	0.00	0.00
F05351	9.6	2.69	6.62	0.00	0.10	0.19	0.00
F05355	6.0	1.08	4.80	0.00	0.06	0.06	0.00
F05362	6.5	2.53	3.51	0.00	0.13	0.32	0.00
N	5	5	5	5	5	5	5
Mean	7.5	1.90	5.32	0.03	0.08	0.13	0.00
S	1.55	0.795	1.630	0.044	0.049	0.128	0.000

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D1 (Continued)

Individual Clinical Hematology Values
Baseline - Males

Animal Number	Mature Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band Immature Neutrophils (%)
Group I - Vehicle Control - 0.0 g/kg/day						
F05324	37	60	0	1	2	0
F05333	26	69	3	0	2	0
F05339	45	51	0	1	3	0
F05349	22	76	0	0	2	0
F05369	36	55	2	1	6	0
N	5	5	5	5	5	5
Mean	33	62	1	1	3	0
S	9.2	10.2	1.4	0.5	1.7	0.0
Group II - B0723-01 (10% w/v) - 0.20 g/kg/day						
F05321	33	65	1	0	1	0
F05326	12	86	1	1	0	0
F05351	28	69	0	1	2	0
F05355	18	80	0	1	1	0
F05362	39	54	0	2	5	0
N	5	5	5	5	5	5
Mean	26	71	0	1	2	0
S	11.0	12.6	0.5	0.7	1.9	0.0

N = Number of samples.
S = Standard deviation.

Study No. 5114-119

Table D2

Individual Clinical Hematology Values
Baseline - Females

Animal Number	RBC (x 10^6/cu mm)	HGB (g/dL)	HCT (%)	MCV (Cubic Microns)	MCH (Picograms)	MCHC (%)	NRBC (per 100 WBC)
Group I - Vehicle Control - 0.0 g/kg/day							
F05323	5.11	12.3	35.8	70	24.1	34.4	0
F05334	5.68	12.6	37.2	65	22.2	33.9	2
F05352	4.62	10.9	32.1	69	23.6	34.0	7
F05366	5.21	11.7	32.8	63	22.5	35.7	1
F05370	5.30	12.0	35.5	67	22.6	33.8	1
N	5	5	5	5	5	5	5
Mean	5.18	11.9	34.7	67	23.0	34.4	2
S	0.382	0.65	2.15	2.9	0.81	0.78	2.8
Group II - BQ723-01 (10% w/v) - 0.20 g/kg/day							
F05310	5.59	12.2	35.8	64	21.8	34.1	1
F05311	5.27	11.8	34.9	66	22.4	33.8	0
F05316	5.11	11.4	32.4	63	22.3	35.2	0
F05318	5.32	11.9	35.2	66	22.4	33.8	1
F05380	5.26	11.9	35.0	67	22.6	34.0	0
N	5	5	5	5	5	5	5
Mean	5.31	11.8	34.7	65	22.3	34.2	0
S	0.175	0.29	1.31	1.6	0.30	0.54	0.5

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D2 (Continued)

Individual Clinical Hematology Values
Baseline - Females

Animal Number	WBC (x 10^3/cu mm)	Mature Neutrophils (x 10^3/cu mm)	Lymphocytes (x 10^3/cu mm)	Monocytes (x 10^3/cu mm)	Eosinophils (x 10^3/cu mm)	Basophils (x 10^3/cu mm)	Band Immature Neutrophils (x 10^3/cu mm)
Group I - Vehicle Control - 0.0 g/kg/day							
F05323	10.3	2.78	7.11	0.10	0.00	0.31	0.00
F05334	9.4	1.22	7.71	0.09	0.09	0.28	0.00
F05352	7.0	1.54	5.39	0.00	0.00	0.07	0.00
F05366	5.8	2.90	2.61	0.00	0.06	0.23	0.00
F05370	6.1	1.71	3.90	0.12	0.00	0.37	0.00
N	5	5	5	5	5	5	5
Mean	7.7	2.03	5.34	0.06	0.03	0.25	0.00
S	2.02	0.761	2.138	0.058	0.042	0.114	0.000
Group II - 80723-01 (10% w/v) - 0.20 g/kg/day							
F05310	7.0	3.71	2.80	0.00	0.07	0.42	0.00
F05311	6.8	3.04	3.20	0.20	0.07	0.27	0.00
F05316	6.0	2.76	3.06	0.00	0.00	0.18	0.00
F05318	7.6	1.67	5.78	0.08	0.08	0.00	0.00
F05380	6.4	1.41	4.61	0.13	0.00	0.26	0.00
N	5	5	5	5	5	5	5
Mean	6.8	2.52	3.89	0.08	0.04	0.23	0.00
S	0.61	0.964	1.269	0.086	0.040	0.153	0.000

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D2 (Continued)

Individual Clinical Hematology Values
Baseline - Females

Animal Number	Mature Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band Immature Neutrophils (%)
Group I - Vehicle Control - 0.0 g/kg/day						
F05323	27	69	1	0	3	0
F05334	13	82	1	1	3	0
F05352	22	77	0	0	1	0
F05366	50	45	0	1	4	0
F05370	28	64	2	0	6	0
N	5	5	5	5	5	5
Mean	28	67	1	0	3	0
S	13.7	14.3	0.8	0.5	1.8	0.0
Group II - 80723-01 (10% w/v) - 0.20 g/kg/day						
F05310	53	40	0	1	6	0
F05311	45	47	3	1	4	0
F05316	46	51	0	0	3	0
F05318	22	76	1	1	0	0
F05380	22	72	2	0	4	0
N	5	5	5	5	5	5
Mean	38	57	1	1	3	0
S	14.6	15.9	1.3	0.5	2.2	0.0

N = Number of samples.
S = Standard deviation.

Study No. 5114-119

Table D3

Individual Clinical Hematology Values
Terminal - Males

Animal Number	RBC (x 10^6/cu mm)	HGB (g/dL)	HCT (%)	MCV (Cubic Microns)	MCH (Picograms)	MCHC (%)	NRBC (per 100 WBC)
Group I - Vehicle Control - 0.0 g/kg/day							
F05324	7.55	15.6	47.2	63	20.7	33.1	0
F05333	7.05	14.8	47.2	67	21.0	31.4	0
F05339	6.15	13.6	42.2	69	22.1	32.2	0
F05349	6.41	13.9	41.8	65	21.7	33.3	0
F05369	6.86	14.7	45.7	67	21.4	32.2	0
N	5	5	5	5	5	5	5
Mean	6.80	14.5	44.8	66	21.4	32.4	0
S	0.548	0.79	2.65	2.3	0.55	0.77	0.0
Group II - 30723-01 (10% w/v) - 0.20 g/kg/day							
F05321	6.55	14.4	45.1	69	22.0	31.9	0
F05326	6.13	14.4	43.7	71	23.5	33.0	1
F05351	6.72	14.0	43.9	65	20.8	31.9	0
F05355	7.11	14.9	44.2	62	21.0	33.7	1
F05362	6.83	15.2	48.0	70	22.3	31.7	2
N	5	5	5	5	5	5	5
Mean	6.67	14.6	45.0	67	21.9	32.4	1
S	0.363	0.47	1.77	3.8	1.09	0.87	0.8

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D3 (Continued)

Individual Clinical Hematology Values
Terminal - Males

Animal Number	WBC (x 10^3/cu mm)	Mature Neutrophils (x 10^3/cu mm)	Lymphocytes (x 10^3/cu mm)	Monocytes (x 10^3/cu mm)	Eosinophils (x 10^3/cu mm)	Basophils (x 10^3/cu mm)	Band Immature Neutrophils (x 10^3/cu mm)
Group I - Vehicle Control - 0.0 g/kg/day							
F05324	7.3	1.53	5.55	0.00	0.07	0.15	0.00
F05333	7.4	2.74	3.70	0.00	0.07	0.89	0.00
F05339	7.7	3.62	3.85	0.15	0.08	0.00	0.00
F05349	9.3	3.44	5.21	0.19	0.09	0.37	0.00
F05369	5.9	2.24	3.54	0.06	0.06	0.00	0.00
N	5	5	5	5	5	5	5
Mean	7.5	2.71	4.37	0.08	0.07	0.28	0.00
S	1.21	0.862	0.936	0.087	0.011	0.372	0.000
Group II - BO723-01 (10% w/v) - 0.20 g/kg/day							
F05321	7.9	1.42	5.61	0.08	0.08	0.71	0.00
F05326	6.3	2.71	3.21	0.00	0.06	0.31	0.00
F05351	6.3	2.14	3.59	0.06	0.06	0.44	0.00
F05355	6.7	0.80	5.69	0.07	0.00	0.33	0.00
F05362	6.2	2.91	2.85	0.06	0.00	0.37	0.00
N	5	5	5	5	5	5	5
Mean	6.7	2.00	4.15	0.05	0.04	0.43	0.00
S	0.71	0.884	1.305	0.031	0.037	0.163	0.000

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D3 (Continued)

Individual Clinical Hematology Values
Terminal - Males

Animal Number	Mature Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band Immature Neutrophils (%)
Group I - Vehicle Control - 0.0 g/kg/day						
F05324	21	76	0	1	2	0
F05333	37	50	0	1	12	0
F05339	47	50	2	1	0	0
F05349	37	56	2	1	4	0
F05369	38	60	1	1	0	0
N	5	5	5	5	5	5
Mean	36	58	1	1	4	0
S	9.4	10.7	1.0	0.0	5.0	0.0
Group II - B0723-01 (10% w/v) - 0.20 g/kg/day						
F05321	18	71	1	1	9	0
F05326	43	51	0	1	5	0
F05351	34	57	1	1	7	0
F05355	12	82	1	0	5	0
F05362	47	46	1	0	6	0
N	5	5	5	5	5	5
Mean	31	61	1	1	6	0
S	15.3	14.8	0.4	0.5	1.7	0.0

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D4

Individual Clinical Hematology Values
Terminal - Females

Animal Number	RBC (x 10^6/cu mm)	HGB (g/dL)	HCT (%)	MCV (Cubic Microns)	MCH (Picograms)	MCHC (%)	NRBC (per 100 WBC)
			Group I - Vehicle Control - 0.0 g/kg/day				
F05323	5.62	12.1	38.6	69	21.5	31.3	3
F05334	7.06	14.9	45.0	64	21.1	33.1	0
F05352	6.64	14.3	45.7	69	21.5	31.3	0
F05366	6.24	12.5	38.0	61	20.0	32.9	5
F05370	5.94	13.5	41.0	69	22.7	32.9	1
N	5	5	5	5	5	5	5
Mean	6.30	13.5	41.7	66	21.4	32.3	2
S	0.568	1.18	3.56	3.7	0.97	0.92	2.2
			Group II - B0723-01 (10% w/v) - 0.20 g/kg/day				
F05310	6.71	15.0	45.9	68	22.4	32.7	1
F05311	6.41	14.6	44.6	70	22.8	32.7	0
F05316	6.01	13.0	39.8	66	21.6	32.7	1
F05318	6.24	13.6	41.9	67	21.8	32.5	2
F05380	6.35	14.1	45.1	71	22.2	31.3	1
N	5	5	5	5	5	5	5
Mean	6.34	14.1	43.5	68	22.2	32.4	1
S	0.255	0.79	2.54	2.1	0.48	0.61	0.7

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D4 (Continued)

Individual Clinical Hematology Values
Terminal - Females

Animal Number	WBC (x 10^3/cu mm)	Mature Neutrophils (x 10^3/cu mm)	Lymphocytes (x 10^3/cu mm)	Monocytes (x 10^3/cu mm)	Eosinophils (x 10^3/cu mm)	Basophils (x 10^3/cu mm)	Band Immature Neutrophils (x 10^3/cu mm)
Group I - Vehicle Control - 0.0 g/kg/day							
F05323	6.5	1.95	4.16	0.00	0.06	0.32	0.00
F05334	6.1	0.79	5.19	0.00	0.06	0.06	0.00
F05352	6.8	2.38	3.60	0.20	0.00	0.41	0.00
F05366	7.5	3.75	3.45	0.00	0.00	0.30	0.00
F05370	5.8	1.33	4.18	0.00	0.12	0.17	0.00
N	5	5	5	5	5	5	5
Mean	6.5	2.08	4.12	0.04	0.05	0.25	0.00
S	0.66	1.149	0.684	0.089	0.050	0.137	0.000
Group II - B0723-01 (10% w/v) - 0.20 g/kg/day							
F05310	5.8	1.57	3.94	0.12	0.06	0.12	0.00
F05311	5.6	1.57	3.58	0.28	0.06	0.11	0.00
F05316	5.9	2.48	3.19	0.00	0.12	0.12	0.00
F05318	4.5	1.17	3.15	0.05	0.00	0.14	0.00
F05380	7.7	3.93	3.70	0.00	0.08	0.00	0.00
N	5	5	5	5	5	5	5
Mean	5.9	2.14	3.51	0.09	0.06	0.10	0.00
S	1.15	1.108	0.338	0.117	0.043	0.056	0.000

N = Number of samples.
S = Standard deviation.

Study No. 6114-119

Table D4 (Continued)

Individual Clinical Hematology Values
Terminal - Females

Animal Number	Mature Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band Immature Neutrophils (%)
Group I - Vehicle Control - 0.0 g/kg/day						
F05323	30	64	0	1	5	0
F05334	13	85	0	1	1	0
F05352	38	53	3	0	6	0
F05366	50	46	0	0	4	0
F05370	23	72	0	2	3	0
N	5	5	5	5	5	5
Mean	31	64	1	1	4	0
S	14.1	15.4	1.3	0.8	1.9	0.0
Group II - BQ723-01 (10% w/w) - 0.20 g/kg/day						
F05310	27	68	2	1	2	0
F05311	28	64	5	1	2	0
F05316	42	54	0	2	2	0
F05318	26	70	1	0	3	0
F05380	51	48	0	1	0	0
N	5	5	5	5	5	5
Mean	35	61	2	1	2	0
S	11.2	9.4	2.1	0.7	1.1	0.0

N = Number of samples.
S = Standard deviation.

APPENDIX E

Individual Animal Histopathology Findings

Independent Review of Liver Slides for
Study No. 6114-119

Slides from rabbit livers were submitted for blind reading. The severity grades as listed below were obtained from this reading. In those instances where a higher severity of hepatocytic swelling was seen, the distribution of the swelling was diffuse. With hepatocytic swelling severities of 3 or less, the distribution was centrolobular. The changes noted are, in my experience, common in the rabbit and I usually consider them to be non-treatment related.

Hepatocytic Swelling - Severity Grades

Group 1			Group 2		
Animal Number	Sex	Grade	Animal Number	Sex	Grade
F05324	M	0	F05321	M	3 (3)
F05333	M	2	F05326	M	4
F05339	M	0	F05351	M	5
F05349	M	3	F05355	M	3
F05369	M	0 (1)	F05362	M	4
F05323	F	5	F05310	F	2
F05334	F	0	F05311	F	3 (5)
F05352	F	3 (3)	F05316	F	3
F05366	F	5	F05318	F	2
F05370	F	0	F05380	F	1

( ) indicates the second reading of duplicate slides.

William E. Field

W. E. Field, DVM, MS
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9/5/85
Date

(11785/kk)

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*** PATH/TOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
TOXICITY IN RABBITS
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 1

STUDY NUMBER: 6114119

ANIMAL NUMBER: 85346 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/29/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2873.0 GRAMS
DATE AND TIME OF NECROPSY: 08/29/84 PROSECTOR: TERRI LIEDHY RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KD8)	7.259	.2527 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KD1)	7.229	.2516 %	———	WEIGHT TAKEN
LIVER (LI)	90.910	3.1646 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS PRE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
AORTA (AO)		
		** NECROPSY NOTE: >LOST AT NECROPSY
	*MICRO: -TISSUE MISSING	
BRAIN (BR)		
	*MICRO: -MODERATE, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
ILEOCECAL L.N. (IC)		
	*MICRO: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KE)		
	*GROSS: -DEPRESSED FOCUS(I)/AREA(S)	-BILATERAL, ON CORTICAL SURFACE, MULTIPLE DARK BROWN DEPRESSED AREAS UP TO 1 X 2 MM
	*MICRO: -SLIGHT, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
LIVER (LI)		
	*MICRO: -MODERATE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
SPLEEN (SP)		
	*MICRO: -PRESENT	-CONGESTION/HEMOPHAGE
TREATED SKIN (TS)		
	*GROSS: -THICKENED	
	** SPECIAL HISTOPATHOLOGICAL COMMENT: >UNSEVERABLE	

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STUDY NUMBER: 811439

ANIMAL NUMBER: 005333 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/29/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3026.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JANELLE RASCHEIN RECORDER: ANN FISHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE WALCK WEIGHER: ANN FISHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K30)	8.463	.2802 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	8.427	.2790 %	———	WEIGHT TAKEN
LIVER (LI)	97.368	3.2241 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
BLEEDEAL L.N. (LC)		
	*HIST: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*HIST: -MODERATE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-MINIMAL, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
SPLEEN (SP)		
	*HIST: -PRESENT	-CONGESTION/HEMORRHAGE

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*** PATH/TOX SYSTEM OUTPUT ***
26-DAY SUBCHRONIC PERCUTANEOUS
TOXICITY IN RABBITS
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 3

STUDY NUMBER: 6124119

ANIMAL NUMBER: 85369 SEX: MALE DOSE GROUP: I SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2831.6 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JACK SEFFORT RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	8.169	.2886 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	8.531	.3013 %	———	WEIGHT TAKEN
LIVER (LI)	73.383	2.5893 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
DUODENUM (DU)		
	*MICRO: -SLIGHT	-MONONUCLEAR CELL INFILTRATION, LAMINA PROPRIA
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
JEJUNUM (JE)		
	*MICRO: -SLIGHT	-MONONUCLEAR CELL INFILTRATION, LAMINA PROPRIA
LIVER (LI)		
	*MICRO: -MINIMAL	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-MINIMAL, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, FOCAL	-HEMORRHAGE

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*** PATH TOX SYSTEM OUTPUT ***
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TOXICITY IN RABBITS
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-8-
PAGE: 4

STUDY NUMBER: 6154119

ANIMAL NUMBER: 005724 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06/28/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2367.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JACK SEFFORT RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HALCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	6.922	.2924 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	6.674	.2820 %	———	WEIGHT TAKEN
LIVER (LI)	63.846	2.6635 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
HEART (HT)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-MYOCARDITIS, GRANULOMATOUS
ILEOCECAL L.N. (IC)		
	*MICRO: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KD)		
	*MICRO: -MODERATE, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
	-PRESENT	-TUBULAR DILATATION
	-PRESENT	-DEGENERATIVE TUBULAR EPITHELIUM
LIVER (LI)		
	*MICRO: -SLIGHT	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS

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*** PATH/TOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
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INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-AUG-94
PAGE: 5

STUDY NUMBER: 611A219

ANIMAL NUMBER: 105375 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/26/94 STUDY DAY OF DEATH: 39 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3166.0 GRAMS
DATE AND TIME OF NECROPSY: 08/26/94 PROSECTOR: JACK SEPPORT RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HALOX WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K0)	9.798	.3095 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	9.169	.2896 %	———	WEIGHT TAKEN
LIVER (LI)	74.545	2.3543 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -MODERATE, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
MESENTERIC LYMPH NODE (LM)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (K0)		
	*GROSS: -DEPRESSED FOCUS(1)/AREA(S)	-BILATERAL, ON CORTICAL SURFACE, MULTIPLE FOCI UP TO 2 MM IN DIAMETER.
	*MICRO: -SLIGHT, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
LIVER (LI)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
	-SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
PARATHYROID(S) (PT)		
	*MICRO: -TISSUE MISSING	

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*** PATH/TOX SYSTEM OUTPUT ***
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PRINTED: 27-NOV-8-
PAGE: 6

STUDY NUMBER: 6114119

ANIMAL NUMBER: 85726 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/25/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2540.8 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JANELLE FASCHEIN RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	7.183	.2796 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	7.440	.2932 %	———	WEIGHT TAKEN
LIVER (LI)	98.974	3.896[illegible] %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
SUBMAXILLARY LN (BC)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KO)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
LIVER (LI)		
	*MICRO: -MODERATELY SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
SUBMANDIBULAR LN (MN)		
	*MICRO: -SLIGHT	-LYMPHORETICULAR HYPERPLASIA

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*** PATH/TOX SYSTEM OUTPUT ***
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INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 7

STUDY NUMBER: 114119

ANIMAL NUMBER: 005362 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2677.8 GRAMS
DATE AND TIME OF NECROPSY: 06/28/84 PROSECTOR: JANELLE RASCHEIN RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	8.379	.3129 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	8.383	.3131 %	———	WEIGHT TAKEN
LIVER (LI)	109.984	4.1095 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
ILEOCECAL L.N. (ILC)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*MICRO: -SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR

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*** PATHVTOX SYSTEM OUTPUT ***
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INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
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STUDY NUMBER: 6114119

ANIMAL NUMBER: 195721 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2754.0 GRAMS
DATE AND TIME OF NECROPSY: 06/28/84 PROSECTOR: DENNIS HOFFMAN RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	12.841	.4372 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	11.152	.4049 %	———	WEIGHT TAKEN
LIVER (LI)	98.142	3.5636 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS PRE-TOX COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -MODERATE, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS.
LATERAL L.N. (LC)		
	*MICRO: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KD)		
	*MICRO: -MODERATE, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
	-PRESENT	-TUBULAR DILATATION
	-PRESENT	-REGENERATIVE TUBULAR EPITHELIUM
LIVER (LI)		
	*MICRO: -MODERATELY SEVERE	-HEPATOCYTE SWELLING, CONTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*GROSS: -RED FOCUS(1)/AREA(S)	-ALL LOBES, MULTIPLE DARK RED FOCI, PINPOINT TO 1 MM IN DIAMETER
	*MICRO: -MINIMAL, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
	-SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
SPLEEN (SP)		
	*MICRO: -PRESENT	-CONGESTION/HEMORRHAGE

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STUDY NUMBER: 6114119

ANIMAL NUMBER: 085555 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3336.2 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: TERRI LIEDTKY RECORDER: NANCY DIERRION
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HRUDK WEIGHER: NANCY DIERRION

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	9.998	.2996 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	9.859	.2958 %	———	WEIGHT TAKEN
LIVER (LI)	112.919	3.3729 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	MEASURES, SEVERITY, DISTRIBUTION	GROSS PRE-TOX COMMENTS / HISTOPATHOLOGIC FINDINGS
GALL BLADDER (GB)		
	**MICRO: -TISSUE MISSING	
GENERAL COMMENT (GC)		
	**GROSS: -ALL TISSUES, ORGANS NORMAL	
LIVER (LI)		
	**MICRO: -MODERATELY SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
LUNG (LU)		
	**MICRO: -SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
	-SLIGHT, MULTI-FOCAL	-MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES
SPLEEN (SP)		
	**MICRO: -PRESENT	-CONGESTION/HEMORRHAGE

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*** PATH/TOX SYSTEM OUTPUT ***
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STUDY NUMBER: c114219

ANIMAL NUMBER: 885551 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/25/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3171.0 GRAMS
DATE AND TIME OF NECROPSY: 08/25/84 PROSECTOR: TERRI LEDDITY RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KD0)	8.184	.2579 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KD1)	7.982	.2517 %	———	WEIGHT TAKEN
LIVER (LI)	132.677	4.1845 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
ILEOCECAL L.N. (IC)		
	*MICRO: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*MICRO: -MODERATELY SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
SALIVARY GLN(S) (SG)		
	*GROSS: -DIFFUSELY RED	-RIGHT
	** SPECIAL HISTOPATHOLOGICAL COMMENT: >UNREMARKABLE	
SPLEEN (SP)		
	*GROSS: -RAISED FOCUS(1)/AREA(S)	-TRIMMING COMMENT- ON PARIETAL SURFACE, SINGLE FAN FOCUS 3 MM IN DIAMETER
	*MICRO: -MODERATE, FOCAL	-MYELOID HYPERPLASIA, HETEROPHILIC
THYROID(S) (TY)		
	** NECROPSY NOTE: >TRIMMING COMMENT- ONLY ONE PARATHYROID FOUND IN WET TISSUE	

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*** PATHTOX SYSTEM OUTPUT ***
29-DAY SUBCHRONIC PERCUTANEOUS
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PRINTED: 27-NOV-84
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STUDY NUMBER: 612411?

ANIMAL NUMBER: 805366 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/26/84 STUDY DAY OF DEATH: 29 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2562.0 GRAMS
DATE AND TIME OF NECROPSY: 08/26/84 PROSECTOR: JACK SEMPONT RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	8.177	.2851 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	8.448	.2943 %	———	WEIGHT TAKEN
LIVER (LI)	144.505	5.8492 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
MESENTERIC LN. (MC)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*MICRO: -SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES
SPLEEN (SP)		
	*MICRO: -PRESENT	-CONGESTION/HEMORRHAGE
SUBMANDIBULAR LN (MN)		
	*MICRO: -TISSUE MISSING	

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DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

*** PATH/TOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
TOXICITY IN RABBITS
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 12
STUDY NUMBER: o114119

ANIMAL NUMBER: 005323 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/29/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2990.0 GRAMS
DATE AND TIME OF NECROPSY: 08/29/84 PROSECTOR: DENNIS HOFFMAN RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	7.392	.2472 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	7.156	.2393 %	———	WEIGHT TAKEN
LIVER (LI)	132.931	4.4457 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORD, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
HEART (HT)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-MYOCARDITIS, GRANULOMATOUS
ILEOCECAL L.N. (IC)		
	*MICRO: -SLIGHT	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KD)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
LIVER (LI)		
	*MICRO: -MODERATELY SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
	-MODERATE, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS

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*** PATHVTOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
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PRINTED: 27-NOV-84
PAGE: 13

STUDY NUMBER: 6114239

ANIMAL NUMBER: 885378 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 05/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3844.3 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: DENNIS HOFFMAN RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	10.771	.3538 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	10.882	.3549 %	———	WEIGHT TAKEN
LIVER (LI)	102.336	3.3619 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
ILEOCECAL L.N. (IC)		
	*MICRO: -SLIGHT	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KD)		
	*MICRO: -PRESENT	-MINERALIZATION
LIVER (LI)		
	*MICRO: -SLIGHT	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-MINIMAL, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*GROSS: -RED FOCUS(I)/AREA(S)	-ALL LOBES, MULTIPLE DARK RED FOCI, PINPOINT TO 2 MM IN DIAMETER
	*MICRO: -SLIGHT, MULTI-FOCAL	-MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES

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*** PATHTOX SYSTEM OUTPUT ***
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PRINTED: 27-NOV-84
PAGE: 14

STUDY NUMBER: a114119

ANIMAL NUMBER: 005334 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3365.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JANELLE RASCHEIN RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE NAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (KDL)	7.368	.2192 %	———	WEIGHT TAKEN
RIGHT KIDNEY (KDR)	7.376	.2484 %	———	WEIGHT TAKEN
LIVER (LI)	72.873	2.3753 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
HEART (HT)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-MYOCARDITIS, GRANULOMATOUS
ILEOCECAL L.N. (IC)		
	*MICRO: -SLIGHT	-LYMPHORETICULAR HYPERPLASIA
KIDNEY(S) (KD)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
LIVER (LI)		
	*MICRO: -SLIGHT	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-MODERATE, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
	-MODERATE, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
SPLEEN (SP)		
	*MICRO: -PRESENT	-CONGESTION/HEMORRHAGE
UTERUS (UT)		
	*GROSS: -THICKENED WALLS	-BILATERAL
	-DIFFUSELY RED	-BILATERAL, INNER WALLS
	** SPECIAL HISTOPATHOLOGICAL COMMENT: UNREMARKABLE	

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STUDY NUMBER: 6114119

ANIMAL NUMBER: 805952 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3[illegible] GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: JACK SERFORT RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K08)	9.758	.3181 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	9.768	.3187 %	———	WEIGHT TAKEN
LIVER (LI)	109.935	3.4967 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
ILEOCECAL LYM. (IC)		
	*MICRO: -MODERATELY SEVERE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*MICRO: -MODERATE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES

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DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

*** PATH/TOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
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INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 16

STUDY NUMBER: a114319

ANIMAL NUMBER: 255318 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2784.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: DENNIS HOFFMAN RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE WAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K08)	7.178	.2579 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	7.279	.2615 %	———	WEIGHT TAKEN
LIVER (L1)	87.483	3.1423 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
ILEOCECAL LNL (E)		
	*MICRO: -SLIGHT	-LYMPHORETICULAR HYPERPLASIA
LIVER (L1)		
	*MICRO: -SLIGHT	-HEPATOCYTIC SWELLING, CENTROLOBULAR
LUNG (LU)		
	*GROSS: -RED FOCI(S)/AREA(S)	-ALL LOBES, MULTIPLE DARK RED FOCI, UP TO 2 MM IN DIAMETER
	*MICRO: -SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS
	-SLIGHT	-MEDIAL HYPERTROPHY/HYPERPLASIA, PULMONARY ARTERIES
PARATHYROID(S) (PT)		
	*MICRO: -TISSUE MISSING	

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*** PATH/TOX SYSTEM OUTPUT ***
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PRINTED: 27-NOV-84
PAGE: 17

STUDY NUMBER: 6114119

ANIMAL NUMBER: 005318 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/25/84 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2974.0 GRAMS
DATE AND TIME OF NECROPSY: 08/29/84 PROSECTOR: JANELLE WASCHEIN RECORDER: ANN MOSHER
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: ANN MOSHER

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	7.000	.2354 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	7.001	.2381 %	———	WEIGHT TAKEN
LIVER (L1)	92.463	3.1096 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GALL BLADDER (GB)		
	*GROSS:	** NECROPSY NOTE: >NOT FOUND IN WET TISSUE.
	*MICRO: -TISSUE MISSING	
MESENTERIC LYM. (MC)		
		** NECROPSY NOTE: >TRIMMING COMMENT- NOT POSITIVELY IDENTIFIED AT TRIMMING
LIVER (L1)		
	*GROSS: -LIGHT FOCUS(I)/AREA(S)	-RIGHT LATERAL LOBE, VISCERAL SURFACE, TAN AREA COVERING UP TO 3/4 OF LOBE (CAP 38)
	*MICRO: -MODERATE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
LUNG (LU)		
	*GROSS: -CYST(S)	-ALL LOBES, MULTIPLE GREY CYSTS, PINPOINT TO 1 MM IN DIAMETER, FILLED WITH CLEAR FLUID
	*MICRO: -MINIMAL, FOCAL	-HETEROPHIL INFILTRATION

HAZLETON LABORATORIES AMERICA, INC.
DEPARTMENT OF PATHOLOGY
MADISON, WISCONSIN 53707

*** PATH/TOX SYSTEM OUTPUT ***
28-DAY SUBCHRONIC PERCUTANEOUS
TOXICITY IN RABBITS
INDIVIDUAL ANIMAL DATA SHEET

PRINTED: 27-NOV-84
PAGE: 18
STUDY NUMBER: 611-419

ANIMAL NUMBER: 395316 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 38 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2025.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: DENNIS HOFFMAN RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	8.889	.2863 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	7.920	.2884 %	———	WEIGHT TAKEN
LIVER (L1)	84.232	3.8525 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
MESENTERIC LN. (ME)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
LIVER (L1)		
	*MICRO: -MODERATE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-MINIMAL, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL

HAZLETON LABORATORIES AMERICA, INC.
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*** PATH/TOX SYSTEM OUTPUT ***
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PAGE: 19

STUDY NUMBER: 6114119

ANIMAL NUMBER: 005311 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 28 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2983.0 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: TERRI LIEDITY RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	8.678	.2907 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	9.684	.3337 %	———	WEIGHT TAKEN
LIVER (L1)	96.823	3.3874 %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYWORDS, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
BRAIN (BR)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-ENCEPHALITIS, GRANULOMATOUS
KIDNEY(S) (KD)		
	*GROSS: -LIGHT FOCUS(1)/AREA(S)	-BILATERAL, ON CORTICAL SURFACE EXTENDING INTO MEDULLA, MULTIPLE TAN AREAS UP TO 2 X 4 MM
	*MICRO: -MODERATELY SEVERE, MULTI-FOCAL	-INTERSTITIAL NEPHRITIS, GRANULOMATOUS
	-PRESENT	-TUBULAR DILATATION
	-PRESENT	-REGENERATIVE TUBULAR EPITHELIUM
	-PRESENT	-INFARCT(S)
LIVER (L1)		
	*MICRO: -MODERATELY SEVERE	-HEPATOCYTIC SWELLING, CENTROLOBULAR
	-SLIGHT	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -MINIMAL, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA
	-SLIGHT, MULTI-FOCAL	-PNEUMONITIS, GRANULOMATOUS

HAZLETON LABORATORIES AMERICA, INC.
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MADISON, WISCONSIN 53707

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28-DAY SUBCHRONIC PERCUTANEOUS
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PRINTED: 27-NOV-84
PAGE: 28
STUDY NUMBER: 611431[illegible]

ANIMAL NUMBER: 005[illegible] SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 08/28/84 STUDY DAY OF DEATH: 28 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3274.8 GRAMS
DATE AND TIME OF NECROPSY: 08/28/84 PROSECTOR: TERRI LIECHTY RECORDER: NANCY DIEDRICH
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: WALLACE HAUCK WEIGHER: NANCY DIEDRICH

ORGAN NAME	ABSOLUTE ORGAN WEIGHT (GRAMS)	ORGAN WEIGHT RELATIVE TO BODY WEIGHT (%)	ORGAN TO BRAIN WEIGHT RATIO	ORGAN STATUS
LEFT KIDNEY (K00)	7.591	.2319 %	———	WEIGHT TAKEN
RIGHT KIDNEY (K01)	7.665	.2341 %	———	WEIGHT TAKEN
LIVER (LI)	90.054	2.75[illegible] %	———	WEIGHT TAKEN

*** PATHOLOGY OBSERVATIONS ***

ORGAN NAME	KEYNOTES, SEVERITY, DISTRIBUTION	GROSS FREE-TEXT COMMENTS / HISTOPATHOLOGIC FINDINGS
GENERAL COMMENT (GC)		
	*GROSS: -ALL TISSUES, ORGANS NORMAL	
MESENTERIC LN. (ME)		
	*MICRO: -MODERATE	-LYMPHORETICULAR HYPERPLASIA
LIVER (LI)		
	*MICRO: -SLIGHT	-HEPATOCYTE SWELLING, CENTROLOBULAR
	-SLIGHT, MULTI-FOCAL	-MONONUCLEAR CELL INFILTRATE, PORTAL
LUNG (LU)		
	*MICRO: -SLIGHT, MULTI-FOCAL	-PERIVASCULAR/PERIBRONCHIAL LYMPHOID HYPERPLASIA

APPENDIX F

Study Protocol

HAZLETON LABORATORIES AMERICA, INC.
3301 KINSMAN BLVD. • P.O. BOX 7545 • MADISON, WI 53707 • (608) 241-4471 • TLX 703856 HAZRAL MDS UD

Protocol No. C11
28-Day Subchronic Percutaneous Toxicity with B0723-01
Doc. Req. No.: BSBTS #625

Study No. 6114-119

Sponsor

The Procter & Gamble Company
11520 Reed Hartman Highway
Cincinnati OH 45241

Contractor

Hazleton Laboratories America, Inc.
Life Sciences Division
3301 Kinsman Boulevard
Madison WI 53704

Divisional Toxicologist

W. Bruce Gibson

Study Director

Wayne A. Madison

Amendment No. 1
Effective July 23, 1984

This amendment modifies the following portion of the protocol.

1) Page 5 of 16, Necropsy, paragraph 1, sentence 3. To accommodate the terminal sacrifice of the animals, substitute the underlined below for, "three (3)".

All animals will be sacrificed within four (4) days after completion of dosing.

AMENDMENT APPROVAL

W. Bruce Gibson — Date: 8/20/84
W. Bruce Gibson
Divisional Toxicologist
The Procter & Gamble Company

Steven M. Gloyer for — Date: 8-9-84
Wayne A. Madison
Study Director, Acute Toxicology
Hazleton Laboratories America, Inc.

Diana E. Skalitzky — Date: 8-9-84
Diana E. Skalitzky
Inspector, Quality Assurance Unit
Hazleton Laboratories America, Inc.

SG/cja

THE PROCTER & GAMBLE COMPANY

PROTOCOL NO. C11

28-day Subchronic Percutaneous Toxicity

Issue Date: June 21, 1982
Supersedes Issue Dated: April 15, 1982

Test Substance Identification Number (TSIN) # B0723-01

Divisional Request Document Number (DRD) # RSBTS: 8625

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: (To be filled in by Operations Section)
Hazleton Laboratories America, Inc.
P. O. Box 7545
Madison, Wisconsin 53707

Study # 6114-119 (To be filled in by Testing Facility)

Purpose: To assess the cutaneous and systemic toxicity of a substance when it is repeatedly applied to abraded skin over a period of 28 days.

Justification for Selection of Test System: Historically, the New Zealand albino rabbit has been the animal of choice due to the large amount of background information on this species.

Route of Administration of Test Substance and Reason for Choice: Applied topically to abraded skin. Historical. One of the possible routes of human exposure.

Diet and/or Water Analyses Required: None (no known contaminants expected which would interfere with this study)

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

THE PROCTER & GAMBLE COMPANY

PROTOCOL NO. CT1 (Cont'd)

25-day Subchronic Percutaneous Toxicity

Issue Date: June 21, 1982

Test Substance(s)

TSIN #	DRD Number	Description: Color	Description: Physical Form	Expiration Date
B0723-01	BSB75:8625	Green	Crystalline	3/9/85

Storage Conditions: (Check one)

[X] Room temperature [ ] Refrigerator [ ] Freezer
[X] Other Sealed container

Hazards: (Check one)

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

Special Instructions: (Check one)

[X] None
[ ] As follows:

Animals: Rabbits, New Zealand albino, obtained from a source that has been approved by the Test Facility. There will be at least one test group for each test substance listed above plus one vehicle control group. Each test group will consist of ten (10) animals (5 males, 5 females) weighing 2.0-3.0 kg.

Animal Care and Diet: Follow the approved Standard Operating Procedures of the Test Facility. (Acclimation period must be a minimum of seven (7) days.)

Environmental Conditions: Follow the approved Standard Operating Procedures of the Test Facility.

Animal Identification: Follow the approved Standard Operating Procedures of the Test Facility.

Group Assignment Methods and Pre-Dose Requirements: Rabbits will be selected from animals that have been acclimated in the laboratory a minimum of seven (7) days and have been used in no previous studies. Animals will be given a visual examination by a qualified individual and only those rabbits judged to be of acceptable health status will be selected for hematology screening.

Collect blood samples into collection tubes containing EDTA anti-coagulant, following the approved Standard Operating Procedures of the Test Facility. Specify the method used. Determine hemoglobin, hematocrit, white blood cell count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and differential white blood cell count. Eliminate those animals judged to have an abnormal hemogram as defined by the Standard Operating Procedures of the Test Facility. Dosing will be started within seven (7) days of the baseline blood collections.

Only animals weighing between 2.0-3.0 kg with an acceptable health status and normal hemogram will be randomized into test and control groups. Animals should be randomized into groups by weight and sex with 5 males and 5 females in each group according to the approved Standard Operating Procedures of the Test Facility (Appendix 1 or equivalent).

Test Site Preparation: Clip the area on the back of each animal from shoulder to rump, approximately 15 cm wide, using a small animal clipper. Clip animals as needed while the test is in progress to prevent the test substance from matting in the hair. Abrade the skin of the rabbits following the approved Standard Operating Procedures of the Test Facility prior to each treatment by penetrating the horny layer of the epidermis without causing bleeding. Discontinue abrading if the skin becomes fissured.

Dose Preparation:

Test Group(s): (Check appropriate box)

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

[x] Dose as a 10 % (w/v) solution/suspension of test substance in distilled water.

[ ] Dose per Special Instructions (see page 2)

Note:

If a test substance - vehicle mixture is required, follow directions in Appendix 7.

Control Group

A control group should be [x]; should not be [ ] included in this study. If included, the control substance distilled water should be tested concurrently with the test substance at a dosage level of 2 ml/kg.

Dosing Instructions:

Apply appropriate concentration (see Dose Preparation) of test substance(s) or control substance daily, 5 days per week for 4 weeks (20 applications) at a dosage volume of 2 ml/kg of body weight.

Apply the substances with a syringe. Use Test Facility's Standard Operating Procedures to evenly distribute the substances over the clipped area. Record time of dosing. Weigh the animals once weekly and adjust the dose levels accordingly.

Restraining:

[ ] Do not restrain.

[x] Restrain the animals to prevent oral ingestion. Remove the restraining device approximately 7 hours after the start of treatment.

PROTOCOL NO. C11 (Cont'd)

28-day Subchronic Percutaneous Toxicity

Issue Date: June 21, 1982

Washing:

[ ] Do not wash

[x] Wash all test sites with tepid water approximately 7 hours posttreatment. Gently dry with disposable paper towels or equivalent.

[ ] Wash animals with tepid water if significant amounts of test substance accumulates on the test sites. If any animals require washing, all animals should be washed and gently dried with disposable paper towels or equivalent. Record time and dates when animals are washed.

Grading:

Immediately prior to treatment each day (after day 1), grade the skin sites using the attached scale (Appendix 2), or a similar Draize skin reaction scoring system.

Observations:

Observe all animals daily (7 days/week), up to the day of necropsy, recording all findings including any abnormalities. Necropsy all animals as soon as possible that are found moribund or dead during the course of the experiment. If necropsy is delayed, refrigerate the carcass until prosection begins. Necropsies will be supervised by a veterinarian. Record all observations. If possible, determine the cause of death and notify the Sponsor's Divisional Toxicologist. Collect the tissues listed in Appendix 4 from all animals which either die or are sacrificed prematurely unless the supervising veterinarian judges that autolysis present precludes a meaningful microscopic examination of the tissues. If any deaths occur after start of dosing, no replacement animals will be used without authorization of the Sponsor.

Necropsy:

Prior to initiation of the study, schedule the animals for necropsy with, as nearly as possible, an equal distribution as to sex and group number for each necropsy day. Randomization procedures will be used to determine which animals will be sacrificed each day and the order in which they will be sacrificed (Appendix 3 or equivalent). All animals will be sacrificed within three (3) days after completion of dosing.

Necropsy (Cont'd): Between days 25 and day of necropsy, obtain blood samples via the technique used in the pre-study and analyze as described in the pretreatment hematology screening on page 3. Weigh all animals on the first day of necropsy for use in assessing in-life body weight changes. Obtain a body weight at the time of euthanasia for use in establishing relative organ weights. Sacrifice the animals with an IV overdose of sodium pentobarbital. Exsanguinate prior to cessation of heart beat following the appropriate Standard Operating Procedure of the Test Facility. Necropsy should be started within ten (10) minutes after euthanasia. Necropsy all surviving animals and record all gross observations for all organs following the Standard Operating Procedure of the Test Facility. Lungs shall be perfused with formalin intratracheally at a pressure of approximately 40 cm of water, following the procedure in Appendix 5 or an equivalent procedure. Take tissue specimens and use trimming methods given in Appendix 4. Any deviations from the protocol such as missing tissues, hematology results, etc., should be noted in the raw data. All necropsies will be supervised by a veterinary pathologist. All necropsy room assistants will be trained and qualified.

Organ Weights: Determine absolute weights of liver and kidneys and calculate organ to body weight ratios.

Histopathology: Trim all tissues listed in Appendix 4 and prepare paraffin blocks and H&E slides following the approved Standard Operating Procedures of the Test Facility. Slides of all tissues will be examined microscopically by a veterinary pathologist.

Statistical Analysis: The statistical evaluation should be made by analysis of variance techniques. Provided that Bartlett's test of homogeneity of variance is not significant, treated groups should be compared to the control group using the least significant difference (LSD) criterion. If Bartlett's test is significant, comparisons with the control group should be made by Wilcoxon's rank sum test. If the study includes only one test group and one control group, then they should be compared by the t-test for equal variances provided that the group variances are not significantly different by an F-test.

Statistical Analysis (Cont'd): If the F-test is significant, then Wilcoxon's rank sum test should be performed. If the test includes two or more concentrations of the same substance, regression analysis on dose level should be performed for each such substance; this analysis should include tests for linear regression and lack of fit. All statistical tests should be conducted at a 5%, two-sided risk level.[1,2]

Protocol Changes: If it becomes necessary to change the approved protocol, verbal agreement to make this change should be made between the Study Director and the Sponsor. As soon as practical this change and the reason for it should be put in writing and signed by both the Study Director and the Sponsor's Divisional Toxicologist. This document is then attached to the protocol as an addendum.

Report: Report dates of study initiation and termination, deaths, skin reactions, body weights, relative and absolute organ weights, gross abnormalities, histopathological and hematological results. Pathologist's report should include a statement that in his opinion the quantity and quality of tissue taken was adequate to evaluate the study. Statistically analyze the final body weights, body weight gains, organ weights, organ to necropsy body weight ratios, and the changes from baseline for hemoglobin, hematocrit, total white blood cell count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration values. Compare each test group, by sex, to the control group. This report shall conform to all requirements outlined in Section 58.185, Subpart J, Good Laboratory Practices Regulations.

(1) Snedecor, G. W. and Cochran, W. G., Statistical Methods, 6th Edition, Iowa State University Press (1967)

Analysis of variance	pp. 277-279
Least significant difference	pp. 271, 272, 278
Bartlett's test	pp. 296-298
Wilcoxon's rank sum test	pp. 130-132
t-test, equal variances	pp. 100-105
F-test	pp. 116-117

(2) Draper, N. R. and Smith, H., Applied Regression Analysis, Wiley (1966)

Regression analysis	pp. 7-26
Lack of fit	pp. 26-32

Retention of Histopathology Materials: All wet tissues, blocks and slides, including blood slides, collected at contract laboratories should be returned to the Sponsor for retention following acceptance of the final report. The Study Director will be notified in writing when the report has been accepted. Instructions for returning these materials are given in Appendix 6.

Sponsor: R. Bruce Gibson, W. Bruce Gibson
Divisional Toxicologist

Date Approved by Sponsor's Divisional Toxicologist 4/25/84

Proposed Starting Date: Week of 7/30/84
Defined as First Compound Administration

Proposed Completion Date: Week of 11/27/84
Defined as Submission of final report (DRAFT)

(To be completed by the Test Facility)

Study Director: Wayne O. Malson
Date: 7/17/84
Study Cost: $16,300

Randomization of Animals into Study Groups

The following procedure will be followed, separately for the male and female animals.

1. Assign a random number (from a table of random numbers or from a computerized pseudo-random number generator) to each animal acceptable under provisions outlined under Group Assignment Method & Pre-Dose Requirements.

2. If there are more acceptable animals than needed to fill the study groups, eliminate the extra animals by one of the following methods:

   a) eliminate the lightest animals.
   b) eliminate the heaviest animals.
   c) eliminate the animals with the largest random numbers.

3. Sort the animals into order from lightest to heaviest.

4. Define the block size (b). If all groups are of equal size, b is the number of study groups. Otherwise, determine the greatest common divisor of the group sizes and divide each of the group sizes by the greatest common divisor. The sum of these quotients is b. For example, suppose three groups of sizes

   15 10 20

   are required. The greatest common divisor is 5 and the resulting quotients obtained by dividing are

   3 2 4

   hence the block size is 3+2+4 = 9.

5. Go through the sorted list of animals b at a time, starting with the lightest animal. Sort each group of b animals into ascending order based upon their random numbers. Then, if the groups are equal in size, assign the first animal to group 1, the second to group 2, etc. If the groups are unequal in size, then the numbers of animals assigned to each successive group are given by the quotients calculated in the preceding step. Continuing the example from above, the first 3 animals would be put in group 1, the next 2 in group 2 and the 4 animals with the highest random numbers would be assigned to group 3. This procedure is repeated for each succeeding group of b animals.

6. Assign individual animal numbers (a) by sorting the animals within each group into order increasing random numbers. The first animal in the sorted group is assigned number 1, the second, number 2, etc.

7. The "computer number" for each animal is now obtained from the formula:

   Group Number x 100
   + Animal Number (a)
   + 50, if female.

This entire procedure may be performed either manually or by computer program. The result of this procedure is to stratify the group assignment on animal weight, provided that b is less than the total number of animals. With certain group sizes, however, b will be equal to the total number of animals and the result, then, is a simple random assignment of animals to groups.

SCALE FOR EVALUATING SKIN REACTIONS

Erythema
- 0 - None
- 1 - Slight (barely perceptible)
- 2 - Moderate (well defined)
- 3 - Severe (beet red)

Edema
- 0 - None
- 1 - Slight (barely perceptible to well defined by definite raising)
- 2 - Moderate (raised approximately 1 mm)
- 3 - Severe (raised more than 1 mm)

Atonia (not including eschar area)
- 0 - Normal
- 1 - Slight (impairment of elasticity)
- 2 - Moderate (slow return to normal)
- 3 - Marked (no elasticity)

Desquamation (not including eschar area)
- 0 - None
- 1 - Slight (slight scaling)
- 2 - Moderate (scabs and flakes)
- 3 - Marked (pronounced flaking with denuded areas)

Fissuring
- 0 - None
- 1 - Slight (definite cracks in epidermis)
- 2 - Moderate (cracks in dermis)
- 3 - Marked (cracks with bleeding)

Eschar
- N - No
- Y - Yes

Exfoliation (sloughing of the eschar tissue)
- N - No
- Y - Yes

Randomization of Animals for Necropsy

The following procedure will be followed for the male and female animals combined.

1. Assign a random number (from a table of random numbers or from a computerized pseudo-random number generator) to each animal in the study. This set of random numbers must not be the same as the set used in group assignment.

2. If all animals will be necropsied on the same day, disregard this step. The animals of each group and sex to be necropsied on the first day will be selected by taking the animals within the group with the lowest computer numbers[1]. The next day's quotas will be filled by taking the next highest numbered animals, etc.

3. For each day of necropsy, the animals will be sorted into order from the lowest to the highest random number. This order will be the order of sacrifice.

This entire procedure may be performed either manually or by computer program.

[1]See Randomization of animals into Study groups for definition of computer number.

Necropsy – Tissue and Trimming Methods

Tissue	Recommended Trimming Method
Lung	Sections to include major anatomic sites from left and right sides. (Lungs shall be perfused intratracheally at a pressure of approximately 40 cm of water following the procedure in Appendix 5 or an equivalent procedure.)
Heart	Sections to include major anatomic sites
Aorta	Transverse section of the straight portion of the thoracic aorta
Tongue	Transverse section midway between tip and base of tongue
Trachea, esophagus, and thyroid (parathyroid)	Obtained together by transversely sectioning at the level of the thyroid. (The parathyroid is collected and viewed histologically if it is included in the plane of sectioning.)
Submandibular lymph node	Intact (Left for section; right for save)
Ileocecumalic lymph node	One for section; one for save
Stomach (cardiac, fundic, pyloric regions)	Open the stomach along its greatest curvature and observe and remove ingesta. Cut a strip of stomach from cardiac, fundic and pyloric regions.
Liver and gall bladder	Transverse section two large lobes of the liver, one containing gall bladder
Duodenum	Transverse section
Jejunum	Transverse section
Ileum	Transverse section
Cecum, colon	Transverse section of each
Urinary bladder	Section
Kidneys	Section of right kidney and of left kidney representing cortex, medulla, and pelvis
Reproductive	Male – Section of the prostate and seminal vesicle. Left testis in toto with tunic nicked and epididymis attached (Right for save). Female – Both ovaries are taken intact. (Save right ovary; section left.) Cross section both uterine horns. Cross section vagina.

Necropsy - Tissue and Trimming Methods

Tissue	Recommended Trimming Method
Adrenals	Left intact adrenal is taken for sectioning; the right for save
Thymus	Section through the greatest dimension
Psoas muscle	Transverse section
Spleen	Section
Pancreas	Section
Bone (with marrow)	Section left 5th costochondral junction (and save right side)
Skin (test site)	Treatment area skin
Brain	Section to include cerebrum, mid brain, cerebellum and stem
Spinal cord	Transverse section taken from thoracolumbar region
Sciatic nerve	Transverse section
Submandibular salivary gland	Save right and section left
Pituitary gland	Take entire gland for processing
Eyes	Both eyes are taken intact. Save right eye and section left.
Lesions	Collect representative section of any gross lesion that would not be represented in the standard samples described above that are considered by the attending pathologist to potentially represent test substance effects.

Duplicate samples of tissues should be collected from each tissue except the pituitary (using one sample for histopathology and one sample as save tissue). Treatment of paired organs, except the kidneys, is mentioned in the Recommended Trimming Methods. Each kidney should be trimmed as stated above, with duplicate samples collected from each - one for histopathology and one for save. Trimmed tissues are placed in 10% neutral buffered formalin at an estimated volume dilution of 1 part tissue to 15 parts formalin.

Note: Save Tissues: (Save tissues are those tissues which are collectively placed in 10% neutral buffered formalin for possible future reference.)

Method for Perfusion of Rabbit Lung

1. The trachea is exposed and the ventral thoracic wall is removed to uncover the ventral aspect of the heart and lungs.

2. A piece of umbilical tape is attached loosely around the trachea.

3. The trachea is cut above the tape and cannulated with tygon tubing. (The size of tubing depends upon the size of the trachea.)

4. The umbilical tape is secured tightly around the tubing.

5. The lungs are perfused with 10% neutral buffered formalin for 1 minute with a constant infusion pressure maintained by a 2 gallon plastic jug with a spiget on it. The tygon tubing is attached to the spiget. The height for infusion is 40 cm.

6. After infusion, the umbilical tape is secured to the trachea after the tygon tubing has been removed.

7. The lungs and heart are carefully dissected free from the thoracic cavity. the heart is separated from the lungs. Sections from the different lobes of the lungs can be immediately taken for histopathology, and stored in buffered formalin at least 24 hours prior to histological processing. Care must be taken to prevent the accidental puncture of the lungs during this removal step.

   NOTE: This method precludes the weighing of the lungs and thus, this information will not be obtained in the study.

INSTRUCTIONS FOR RETURN OF WET TISSUES, PARAFFIN BLOCKS, AND MICROSCOPIC SLIDES TO THE PROCTER & GAMBLE COMPANY

Wet Tissues

Wet tissues must be heat-sealed in plastic bags. Bags such as "Kapak Pouches" by Sintetpak are excellent and available from most scientific supply houses. A 6-1/2" x 8" bag is satisfactory for most laboratory animals. Place only one animal's tissues in a bag together with a small amount of 10% buffered neutral formalin. The amount of formalin should be adequate to thoroughly moisten all tissues. Several seals should be made with an identifying label (study number, group, animal number) between the seals. The label should be written with waterproof ink.

Paraffin Blocks

Blocks should be placed on end (with the label visible listing the study number, group and animal numbers) in numerical order by groups in special tray boxes which consist of a cardboard tray 16" x 9" x 2" plus a protective card board sleeve. These boxes will accomodate approximately 175 to 200 blocks and are available from John Green, Buckeye Box Co., 601 N. Hague Avenue, Columbus, Ohio 43204 (614-274-8488) (Part #UP-1). Label the end of the box to identify the contents. This permanent label should list the study number and groups.

Microscope Slides

Slides must be packed in numerical order by groups in plastic boxes. Individual slides must be labeled to indicate the study number, group and animal number. The boxes to be used must be identical to S.P. #M-6300. Lids should be secured with tape. A packing material such as polyfoam, paper towels, etc. should be placed inside of the lid to prevent breakage. A permanent label should be placed on the outside of the lid identifying the study number and groups.

IMPORTANT

An itemized list should accompany each shipment. This list should indicate the following:

1. The number of units in the shipment; i.e., the number of shipping cartons.

2. The number of slides, blocks, and individual containers of wet tissue in study.

All costs incurred in shipment of these materials to the Sponsor should be included in the fixed study cost.

All materials from contract laboratories should be sent to the attention of; and any questions relating to the implementation of the foregoing guidelines should be referred to:

Mr. George G. Stewart
The Procter & Gamble Company
Miami Valley Laboratories - Rm. 00N220
11810 E. Miami River Road
Ross (Butler County), Ohio 45061

(513) 977-2656

INSTRUCTIONS FOR THE PREPARATION AND HANDLING OF

TEST SUBSTANCE - VEHICLE MIXTURES

1. Test substance - vehicle mixture should be prepared:

   [x] daily; [ ] weekly; [ ] see Special Instructions on page 2

2. Mixtures that are not true solutions should be mixed by use of a magnetic stirring bar while dosing. All mixtures should be shaken or stirred before use.

3. A homogeneity determination [ ] will; [X] will not be required. If a homogeneity determination is required, sample the mixture from the top, middle, and bottom, while stirring, and:

   [ ] Return all three samples, appropriately labeled, to the Sponsor's Divisional Toxicologist for analysis.

   Shipping Instructions

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

   [ ] Analyze all three samples using the analytical method in Appendix _____.

4. A concentration and/or stability analysis of the mixture [ ] will; [x] will not be required. If an analysis is required:

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

   [ ] Analyze the test substance - vehicle mixture for test substance concentration using the analytical method in Appendix _____.

HAZLETON LABORATORIES AMERICA, INC.

3301 KINSMAN BLVD. • P.O. BOX 7545 • MADISON, WI 53707 • (608) 241-4471 • TLX 703856 HAZRAL MDS UD

Protocol No. C11
28-Day Subchronic Percutaneous Toxicity with B0723-01
Doc. Req. No.: BSBTS 4625

Study No. 6114-119

Sponsor	Contractor
The Procter & Gamble Company 11520 Reed Hartman Highway Cincinnati OH 45241	Hazleton Laboratories America, Inc. Life Sciences Division 3301 Kinsman Boulevard Madison WI 53704
Divisional Toxicologist	Study Director
W. Bruce Gibson	Wayne A. Madison

RECEIVED
AUG 30 1984

Amendment No. 1
Effective July 23, 1984

This amendment modifies the following portion of the protocol.

1) Page 5 of 16, Necropsy, paragraph 1, sentence 3. To accommodate the terminal sacrifice of the animals, substitute the underlined below for, "three (3)".

All animals will be sacrificed within four (4) days after completion of dosing.

AMENDMENT APPROVAL

W. Bruce Gibson — 8/20/84
W. Bruce Gibson
Divisional Toxicologist
The Procter & Gamble Company
Date

Steven M. Gloza for — 8-9-84
Wayne A. Madison
Study Director, Acute Toxicology
Hazleton Laboratories America, Inc.
Date

Diana E. Skalitzky — 8-9-84
Diana E. Skalitzky
Inspector, Quality Assurance Unit
Hazleton Laboratories America, Inc.
Date

SG/c 1a

Addendum No. 1
DMED # BSBTS 8625
Hazleton Study # 6114-119

Protocol No. C11
28-Day Percutaneous Toxicity

Test Material B0723-01

Based on a preliminary summary of the histopathology data conveyed to W.B.Gibson by Mr. Wayne Madison (per phone conversation of 11/29/84 and mailing of draft tables 11/30/84) we request that an independent review of the liver slides be made by Dr. William Field (Board Certified Pathologist). This review will be conducted by Dr. Field without his prior knowledge of animal number, group designation and relative or absolute liver weights. A written summary of this review will be appended to the study report.

The above protocol change has been requested for the Procter & Gamble Company by:

W. Bruce Gibson — 12/14/84
W. Bruce Gibson, Ph.D. — Date

The above protocol change has been accepted for Hazleton Laboratories America, Inc. by:

Wayne O. Madison — 2/17/85
Wayne Madison — Date

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