T-6322

REPORT

Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

(BMR143C)

Bio-Medical Research Laboratories Co., Ltd.

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Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

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-TRANSLATION-

Pure free life

February 16, 1993

Bio-Medical Research Laboratories
Co., Ltd.

PREFACE BY TRANSLATOR

This is a total translation of the original report in Japanese language. On this work, I have paid close attention to transfer the real facts and the correct meaning in the text, confirming scientific matters to the original auther, the study director Mr. Michio Otsuka.

April 23, 1997

Translator : M. Tennichi

Makoto Tennichi

General Manager

Bio-Medical Research Laboratories Co., Ltd.

CONTENTS

STATEMENT ON GLP

Title : Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study Number : BMR143C

The said study has been conducted in compliance with the "GLP Standard for Industrial Chemicals" in Japan (1984, amended 1988).

(Signature)	(Date)
Signed	February 16, 1993

(Makoto Tennichi)

General Manager

Bio-Medical Research Laboratories Co., Ltd.

CERTIFICATION

Title : Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study Number : BMR143C

Having audited the final report, I, the undersigned, assure that the study has been conducted in compliance with Japanese "GLP Standard for Industrial Chemicals", and accomplished with the protocol and appropriate standard operating procedures of the testing facility, and the report has been prepared exactly based on the experimental results.

(Signature) (Date)

Signed February 16, 1993

(Yutaka Kambara)

Quality Assurance Unit
Bio-Medical Research Laboratories Co., Ltd.

Dates of Inspection

Object	Dates of Inspection	Dates of Report to Study Director	Dates of Report to Management
Protocol	1992. 6.23	1992. 6.23	1992. 6.23
Testing Procedures	1992. 7. 3	1992. 7. 3	1992. 7. 3
	1992. 7. 7	1992. 7. 7	1992. 7. 7
	1992. 8. 4	1992. 8. 4	1992. 8. 4
	1992. 8.18	1992. 8.20	1992. 8.20
Records, Raw Data	1992.12.17	1992.12.17	1992.12.17
Final Report	1993. 2.16	1993. 2.16	1993. 2.16

SIGNATURE

Title: Twenty-eight-day Repeated Dose Oral Toxicity Study of Sample D-1 in Rats

Study No.: BMR143C

The said study has been conducted under the responsibility of the undersigned, and this report has been prepared so as to reflect whole study correctly.

(Signature)	(Date)
Signed	February 16, 1993

(Michio Otsuka)

Study Director

Bio-Medical Research Laboratories Co., Ltd.

GENERAL MATTERS

1. Title

Twenty-eight-day repeated dose oral toxicity study of Sample D-1 in rats

2. Study Number BMR143C

3. Purpose

To investigate toxicological potential of the test substance, Sample D-1, through serial oral administration to rats for 28 days. It was intended to meet Japanese legal regulation for industrial new chemical substances.

4. GLP Application

The study was conducted in compliance with the Japanese "GLP Standard for Industrial Chemicals" (1984, ammended 1988).

5. Testing Guidelines

The testing methods conformed to the Japanese "Guidelines for Screening Toxicity Testings of Chemicals" (1988).

6. Sponsor

Sumitomo 3M Co., Ltd.

3-8-8, Minami-hashimoto, Sagamihara, Kanagawa, Japan

(Responcible Person) Nobushige Murakami

Manager, Technical Department,

Chemicals Division

7. Testing Facilities

Key Facility

① Bio-Medical Research Laboratories Co., Ltd.

3079 Susugaya, Kiyokawa-mura, Aikoh-gun, Kanagawa, Japan

Partial Contributor

(Blood Biochemical Examination)

② Kashima Laboratory, Mitsubishi-Kasei Institute of Toxicological and Environmental Sciences (*)

14, Sunayama, Hasaki-machi, Kashima-gun, Ibaraki, Japan

*)The company name has altered to Mitsubishi Chemical Safety Institute.

(Histopathological Specimens Preparation)

③ Nara Pathological Research

Kinomine, Hayama, Tuge-mura, Yamabe-gun, Nara, Japan

(Histopathological Examination)

④ Hatano Research Institute, Food and Drug Safety Center

729-5 Ochiai, Hadano-city, Kanagawa, Japan

8. Responsible Personnel

(Circled figure after the name indicates each belonging facility cited above.)

General Manager	Makoto Tennichi,	①
Study Director	Michio Otsuka,	①
General Participants	Hiroyuki Ishii,	①
	Naoto Ichikawa,	①
	Osamu Tanaka,	①
	Mikiko Kawanabe,	①
Quality Assurance	Yutaka Kambara,	①

Partial Participants

(Responsible to biochemical determination)

Naoto Toyota, ②

(Responsible to histopathological specimens reparation)

Yoshimi Tatsumi, ③

(Director for histopathological examination)

Shinsuke Yoshimura, ④

(Participant to histopathological examination)

Fumie Kawashima, ④

9. Dates in the Study

(Initiation of the study)	June 23, 1992
(Animals reception)	July 1, 1992
(Administration period)	
-Male-	July 6 - Aug. 2, 1992
-Female-	July 7 - Aug. 3, 1992
(Termination of observation, blood sampling and necropsy)	
-Male, main groups-	Aug. 3, 1992
-Female, main groups-	Aug. 4, 1992
-Male, recovery groups-	Aug. 17, 1992
-Female, recovery groups-	Aug. 18, 1992
(Completion of the study)	Feb. 16, 1993

10. Retention of Records and Samples

All documentation records and samples (including specimens) of the study are retained in the archives of Bio-Medical Research Laboratories Co., Ltd. for 10 years after the completion of the study. As to further retention, it will be decided on consultation with the sponsor and the contractor.

SUMMARY

1. Sample D-1 was administered to both sexes of rats with doses of 0.1, 1, 10, and 30 mg/kg for 28 days. A group of rats given the vehicle (olive oil) alone was included as the control. Besides the main groups for nonrecovery study, a satellite group for 14-day recovery study was added to each of the highest dose and the control groups.

2. No death occurred throughout the administration period. One male of the 30 mg/kg group, however, died during the recovery period; the death was considered to be caused by the test substance.

3. No abnormal clinical signs were found in all rats of the control (including those for the recovery study) and the 10 mg/kg or lower dose groups throughout the whole of the observation period. In the 30 mg/kg group, however, such signs as the followings were observed during the administration and the recovery periods: reduced spontaneous movement, tonic-clonic convulsion, lying or crouching, bradypnea or cyanosis, salivation, reddish salivation, brown urine, loss of hair, and coat staining. These were considered to be caused by the test substance.

4. Body weight gain was suppressed during the administration period in both males and females of the 30 mg/kg group from the second week and after; the suppression continued throughout the recovery period.

5. Food consumption was suppressed during the administration period in both males and females of the 30 mg/kg group from the second week and after; it tended to return during the recovery period, however.

6. Hematological examination at the end of the administration period revealed

decreased hemoglobin concentration in males of the 10 and 30 mg/kg groups, and reduced prothrombin time in females given 30 mg/kg. Moreover, at the end of the recovery period, the followings were still detected in the 30 mg/kg group: decrease of erythrocyte count and hematocrit, shortening of prothrombin time, and increase of leukocyte count, in males; decrease of hemoglobin concentration and mean corpuscular hemoglobin concentration, shortening of activated partial thromboplastin time, and increase of mean corpuscular volume, in females.

7. Biochemical examination revealed the the followings at the end of the administration period: decrease of GOT in females of the 1 mg/kg and higher dose groups; increase of albumin in females of the 10 mg/kg and higher dose groups; increase of GPT and chloride, and decrease of total cholesterol in both sexes, decrease of total protein and increase of alkaline phosphatase and of A/G ratio in males, increase of urea nitrogen in females, all these in the 30 mg/kg group.

At the end of the recovery period, the followings were observed in the 30 mg/kg group: decrease of triglyceride and increase of A/G ratio, in males; increase of urea nitrogen, total protein, albumin, and calcium, and decrease of glucose and triglycerides, in females.

Besides, reddish change of serum was recognized in both sexes with the 10 mg/kg or higher dose main groups, and in the 30 mg/kg recovery group.

8. By urinalysis, acidic shift in both sexes and decrease of protein in females were noted in the 30 mg/kg group during the administration period. Acidic shift remained in males during the recovery period.

9. As for absolute organ weight, the administration resulted in increase of the liver weight in both sexes of the 10 mg/kg or higher dose groups and decrease in the kidneys weight of males given 30 mg/kg. After the recovery

period, increase in the liver of both sexes and decrease in the kidneys of females were still noted in the 30 mg/kg group.

Relative organ weight increased in the liver of both sexes of the 10 mg/kg or higher dose and increased in the kidneys in females of the 10 mg/kg or higher dose. After the recovery period, increase in the liver of both sexes and increase in the kidneys of females remained in the 30 mg/kg group.

10. Autopsy for the male died during the recovery period revealed atrophy and dark reddish patch in the thymus, hemorrhage and tarry contents in the stomach, tarry contents in the small intestine, and grayish patch in the liver.

In the scheduled necropsy at the end of the administration period, the following findings were detected by macroscopic examination: dark reddish change in the liver of females receiving 30 mg/kg; grayish dot or patch and hypertrophy in the liver and blackish change in the kidneys in males given 30 mg/kg; dark reddish change, yellowish change, grayish patch, and hypertrophy in the liver of females receiving 30 mg/kg.

The examination at the end of the recovery period revealed grayish patch, dark reddish change, and hypertrophy in the liver of both sexes of the 30 mg/kg dose.

11. Histopathological examination at the end of the administration period revealed dose-dependent changes as eosinophilic degeneration in centrilobular hepatocytes and swelling in the liver in males of the 1 mg/kg or higher doses and in females of the 10 mg/kg or higher dose. Other findings: focal necrosis in hepatocytes in both sexes given 30 mg/kg and in males given 10 mg/kg; somewhat remarkable fatty degeneration in peripheral lobule in males receiving 30 mg/kg.

No abnormal change was detected in the heart, kidneys, spleen, adrenals, brain, and testes or ovaries.

At the end of the recovery period, eosinophilic degeneration in centrilobular hepatocytes turned slighter; swelling in the liver, however, did not recover in both sexes given 30 mg/kg, and focal necrosis also remained.

In case of one male given 30 mg/kg and died during the recovery period, in addition to the same changes as found in the liver of the main groups, the followings were detected: hemorrhagic foci in the brain, ulcer and hemorrhage in the glandular stomach, and congestion and hemorrhage in the thymus.

12. Judging from the above, the toxicological no-observed-effect level (NOEL) of the test substance, Sample D-1, was considered to be 0.1 mg/kg for both male and female rats.

MTERIALS AND METHODS

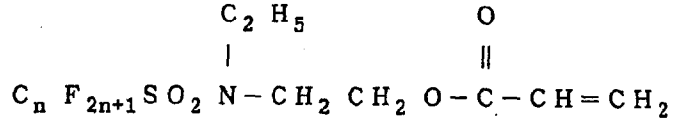
1. Test Substance

1-1 Name

(Chemical Name) 2-[N-Ethyl-N-perfluoroalkyl(C=1-8)sulfonylamino] ethyl acrylate

(Abbreviation) Sample D-1

1-2 Structural formula



$$C_n F_{2n+1} SO_2 N(C_2H_5) CH_2 CH_2 O-C(=O)-CH=CH_2$$

(n ranges from 1 to 8)

(Composition) about 78% for n=8 component,
about 21% for n=1-7 components.

1-3 Molecular weight 625

1-4 Lot number 101 (supplied by the sponsor)

1-5 Appearance Amber-colored waxy solid

1-6 Purity 99% or above

1-7 Strage conditions Stored at room temperature

2. Preparation of Dosing Solution

2-1 Vehicle Olive oil

2-2 Procedure Required amount of the test substance was weighed and suspended homogeneously in the vehicle mentioned above. The dosing solution was divided into daily batches and stored in a refrigerator at 4 ℃ until just before use.

2-3 Frequency of preparation The dosing solution was prepared once a week, because the stability of the test substance in the mixture for eight days was confirmed in Japan Food Research Laboratories (Tokyo) by

our request.

3. Laboratory Animals and Reason for Choice

The animals used were SPF Crj:CD(SD) rats of both sexes. They were purchased from Charles River Japan, Inc. (795 Shimo-furusawa, Atsugi, Kanagawa, Japan) at four weeks of age on July 1, 1992. After five (male) or six (female) days of acclimatization, animals that apparently healthy and showed normal weight gain were selected for the study at five weeks of age. They were grouped to be uniform for the mean body weight based on the last weighing during the acclimatization. The weight ranged from 132 to 151 g for males and 121 to 141 g for females at the initiation of administration.

Reason for choice: Having appropriate nature for laboratory animals and being bred under good genetic and microbial control, this species and strain are widely used in toxicological studies; our testing facility, besides, has accumulated back ground data on this animal.

4. Animal Housing

Five or two (during or after the acclimatization, respectively) animals of the same sex were housed together in a stainless steel wire mesh cage of the hanging type (26×38×18 cm). The animal care room was a barriered facility that was automatically controlled to keep the following conditions:

Temperature	:	22 - 26 ℃
Humidity	:	30 - 70% RH
Ventilation	:	13 times/hour (all fresh air)
Lighting	:	Light /dark cycle of 12 hours (lights on 6:00 to 18:00)

A little deviation of temperature and humidity occurred during the animal keeping; it was, however, judged not to affect to the reliability of the study.

The diet was MF pelleted food for laboratory animals (Oriental Yeast Co.,

Ltd.) and drinking water was tap water subjected to filtration and UV irradiation. Animals were allowed access to food and water ad libitum except for fasting from the evening before necropsy. Analysis of the ingredients and microbial contamination of the diet was performed by the manufacturer, and toxic contaminants were examined by Japan Food Research Laboratories (Tokyo) at the manufacturer's responsibility. The quality of the tap water was periodically examined by Atsugi Public Health Center by our request. These data were checked and stored by us.

Cages were replaced with freshly autoclaved ones once a week.

5. Identification of Animals

Each animal was identified by marking a number on the tail with a saturated alcoholic solution of picric acid. To identify the dose group to which each animal belonged, a colored mark was painted on the tail with an oil-based felt-tip pen.

6. Identification of Cages

Each cage was identified with an attached card on which the study number, abbreviated name of the test substance, dosage, and individual animal number were listed.

7. Test Procedures

The testing methods conformed to the Japanese "Guidelines for Screening Toxicity Testing of Chemicals " (amended on Decenber 5, 1986).

7-1 Dose levels and reason for selection

Prior to the principal study, preliminary dose-finding studies ranged between 4 and 14 days in administration period was performed with such doses as 20, 40, 50, 100, 200, 500, and 1000 mg/kg, each in a few (three to five) male and female rats. It resulted death of more than half number of rats in

1000 mg/kg for 14 days repeated administration; suppression of body weight gain was observed in 40 mg/kg dose, though none of changes found in 20 mg/kg dose. Hence, the highest dose was decided at 30 mg/kg in the principal study and the lower doses were set at 10 mg/kg, 1 mg/kg, and 0.1 mg/kg for both sexes. A group of rats given the vehicle alone was included as the control.

7-2 Number of animals

Forty-two rats of each sex were used.

7-3 Route, frequency, and duration of administration

Administration was performed via the oral route, once a day for 28 days.

7-4 Method of administration

The dosing mixture was intubated directly into the stomach via a plastic gavage tube. The volume administered was 1 ml per 100 g of body weight based on the most recent weight data.

7-5 Grouping

Four dose groups mentioned above and the control group were set. Besides, to monitor the reversibility of any toxic effects, satellite groups were added to the control and the highest dose groups for a 14-day recovery study.

Grouping by dose levels	Dose (mg/kg)	Main Groups(*1) (Sex and Number of animals)	Recovery Groups(*2)
Control	0	male & female, 6 rats each	male & female, 6 rats each
Lowest dose	0.1	male & female, 6 rats each	
Intermediate-1	1	male & female, 6 rats each	
Intermediate-2	10	male & female, 6 rats each	
Highest dose	30	male & female, 6 rats each	male & female, 6 rats each
Total		male & female,30 rats each	male & female,12 rats each

(*1) Animals were necropsied on the next day of the last administratrion.

(*2) Animals were necropsied immediately after the recovery period was over.

Note. Individual animal number. Each animal was numbered with four-digit figure.

First digit, Dose groups:
- 0, the control group
- 1, the lowest dose group
- 2, the intemediate-1 group
- 3, the intemediate-2 group
- 4, the highest dose group

Second digit, Sexes:
- 1, males
- 2, females

Third and fourth digits, individual animal of main or recovery groups;
- 01-06, animals of the main groups
- 07-12, animals of the recovery groups

8. Parameters Assessed

8-1 General condition

8-1-1 Clinical signs

The appearance, behavior, and excreta of every animal were observed daily throughout the administration and the recovery periods.

8-1-2 Body weight

Every animal was weighed with an electric balance at the commencement of the administration, once a week thereafter.

8-1-3 Food consumption

Leftover food from each cage was weighed on day 0 and once a week thereafter, and the daily average consumption per animal was calculated for each group.

8-2 Laboratory tests

8-2-1 Hematology

Blood samples were collected from the inferior vena cava under ether anesthesia just before the scheduled time of sacrifice. Blood sampling was

done under non-fasting condition. The hematological parameters determined are listed below.

The anticoagulant used was ethylenediaminetetraacetic acid dipotassium salt (EDTA-2K), except that 3.13% sodium citrate was used to determine the prothrombin time and the activated partial thromboplastine time.

Parameters		Method
(1) Leukocyte count	(WBC)	Electrical resistance method
(2) Erythrocyte count	(RBC)	Electrical resistance method
(3) Platelet count	(PLT)	Electrical resistance method
(4) Hemoglobin concentration	(Hgb)	Photo-electric colorimetry
(5) Hematocrit	(Hct)	Pulse detection method
(6) Mean corpuscular volume	(MCV)	Calculated from (2) and (5)
(7) Mean corpuscular hemoglobin	(MCH)	Calculated from (2) and (4)
(8) Mean corpuscular hemoglobin concentration	(MCHC)	Calculated from (4) and (5)
(9) Differential leukocyte count		Giemsa-stained smear
(10) Prothrombin time	(PT)	Quick's one-stage test
(11) Activated partial thromboplastin time	(APTT)	Activated cefaroplastin method

Insturuments

(1)-(8) : Automatic cell counter, Sysmex model CC-180A, TOA Medical Electronics Co.,Ltd.

(9) : Optical microscopy

(10)-(11) : Blood coagulater, Model KC-1, Amelung Co.,Ltd.

Among these data, PT and APTT of one male in the recovery group (animal no. 0111) were missing owing to coagulation at blood sampling. On the other hand, reticulocyte counting was added in the main groups after sequential staining with new methylene blue process and May-Gruenwald-Giemsa process, because anemia was suspected in animals of this group.

8-2-2 Biochemistry

The residual blood sample was let stand at room temperature for 30 min and

then centrifuged at 3000 rpm for 10 min to separate serum. The serum, being frozen to -20 ℃, was sent to Kashima Laboratory of Mitsubishi-Kasei Institute of Toxicological and Environmental Sciences for biochemical examination. Parameters examined were as follows:

Parameters	Method
(1) Total protein	Biuret's method
(2) Albumin	Bromocresol green method
(3) A/G ratio	Calculated from (1) and (2)
(4) Glucose	Enzymatic UV-spectrophotometry (Hexokinase-G6-PDH)
(5) Triglycerides	Enzymatic method (LPL-GK-G3PO-POD)
(6) Total cholesterol	Enzymatic method (CES-CO-POD)
(7) Urea nitrogen	Enzymatic UV-spectrophotometry (Urease-GLDH)
(8) Creatinine	Jaffe method
(9) Calcium	o-Cresolphthalein complexone method
(10) Inorganic phosphorous	Phosphomolybdate-UV spectrophotometry
(11) GOT (AST)	UV spectrophotometry-rate method (Modified SSCC)
(12) GPT (ALT)	UV spectrophotometry-rate method (Modified SSCC)
(13) γ-GPT	γ-Glutamyl-p-nitroanilide substrate method (Modified SSCC)
(14) Alkaline phosphatase (ALP)	p-Nitrophenyl phosphate substrate method
(15) Sodium	Ion selective electrodes method
(16) Potassium	Ion selective electrodes method
(17) Chloride	Ion selective electrodes method

Instrument: Automatic analyser (Hitachi 736-10 type)

8-2-3 Urinalysis

Fresh urine was collected from all animals at six or seven days before the completion of administration, and four or five days before the end of the recovery period. (In each of two successive days, the former and the latter days were for male and for female respectively.) These were tested for the following parameters.

Parameter	Method
pH, Occult blood, Protein, Glucose, Ketone bodies, Urobilinogen, Bilirubin	Paper test, MULTISTIX ® (Miles-Sankyo Co.,Ltd.)

8-3 Pathological examination

8-3-1 Necropsy and macroscopic examination

On the next day of the last administration, all survived animals except those assigned for the recovery test were sacrificed for necropsy after blood sampling; whereas for animals of the recovery groups, the necropsy was held on the scheduled day just after the recovery period was over.

After careful investigation for any macroscopic abnormalities, the following organs were removed and fixed in 10% neutral buffered formalin: brain, pituitary, eye ball, (with Harderian glands), thyloid (with parathyloid), heart, lungs, liver, kidneys, spleen, adrenals, stomach, testes or ovaries, urinary bladder, and right femur (with bone marrow).

8-3-2 Organ weight

The following organs were weighed before fixation, then the relative organ weight (ratio of organ weight to body weight on the day of necropsy) was calculated: brain, liver, kidneys, adrenals, and testes or ovaries.

8-4 Histological examination

From the following fixed organs of all rats in the control and the highest dose (30 mg/kg) groups, histological sections of paraffin-embeded specimens were cut and subjected to hematoxylin-eosin staining, then histological changes were surveyed: heart, liver, spleen, kidneys, adrenals, brain, and testes or ovaries. (typical seven organs)

The survey of the liver was expanded to animals of the other dose groups since some chages were found in case of 30 mg/kg dose group.

Additional histological survey was conducted to the following cases in which any macroscopic changes were observed at the necropsy: lung in one case (animal no. 0105), kidneys in two cases (animal nos. 1103, 2102), and testes in one case (animal no. 0111).

Concerning the dead animal which occurred during the recovery period in one male (animal no. 4109), histological survey was performed in the typical seven organs and in thymus and stomach, the latter two were additional because of the macroscopic changes found at the necropsy. In this animal, tarry intestinal contents were found between duodenum and ileum at autopsy; however, preparation of the specimen and histological examination were not performed because of post-mortem autolysis

All through the histopathology, histological specimens were prepared in Nara Pathological Research, whereas the microscopic examination was carried out in Hatano Research Institute of Food and Drug Research Center, both at our quest.

9. Statistical Analysis

For metrical data, homogeneity of variance among all groups was first tested by Bartlett's method. Then the homogeneity of all group means was tested by one-way layout analysis or Kruskal-Wallis H-test, depending on whether the group variance was homogeneous or not, respectively. When group means were significantly heterogeneous and each group had the same number of data items, differences in mean values between any group and the control were tested by Dunnett's multiple range test or Dunnett's rank sum test, according to whether the group variance was homogeneous or not, respectively. When group means were heterogeneous and the number of data items in each group was unequal, the above-mentioned procedures were replaced by Scheffe's multiple range test or Scheffe's rank sum test, respectively. Armitage's chi-squared test was used to assess discrete data such as urinalysis findings.

RESULTS

1. Mortality

All rats survived to the end of administration period; during the recovery period, however, one male given 30 mg/kg died on day 32 (viz. day 4 of recovery *).

*) Each day throughout the study is indicated with such way as the day of commencement of the administration is named "day 0 " ; and the next day of the last administration (viz. day 28), that is the first day of recovery period, is expressed as "day 0 of recovery " .

2. Clinical Signs (Table 1, and Appendix 1)

2-1 During the administration period

No abnormal signs were noted in all rats of the control and the 10 mg/kg or lower dose groups. With rats receiving 30 mg/kg (inclusive of the recovery group), however, the following findings were detected:

Salivation---a considerable number of animals of both sexes, in the latter half of administration period; and in one male on day 0, besides;

Reddish salivation---in a few males and females, occasionally;

Tonic-clonic convulsion, lying, bradypnea---in one male on day 26;

Reduced spontaneous movement, clonic or tonic-clonic convulsion, lying or crouching, bradypnea or cyanosis---in one and two females on day 20 and from day 25 to 27, respectively;

Loss of hair and coat staining---in three and one females respectively, on day 17 and after.

2-2 During the recovery period

No abnormal signs appeared in both males and females of the control group as well as in the administration period. In case of the male given 30

mg/kg and died during the recovery period, reduced spontaneous movement, lying, bradypnea, reddish salivation and brownish urine were found on day 31 (viz. day 3 of recovery), then died on the next day. Loss of hair found in females of the 30 mg/kg group during the administration period lasted until the termination of the recovery period, whereas the coat staining in one female disappeared after day 34 (viz. day 6 of recovery).

3. Body Weight (Fig.1, Table 2, Appendix 2)

3-1 During the administration period

Body weight gain in the 10 mg/kg or lower dose groups was similar to that of the control throughout the administration period. Significant suppression of weight gain, however, appeared in both males and females receiving 30 mg/kg (rats of the recovery group inclusive) from week 2 and after.

3-2 During the recovery period

The above-mentioned suppression of weight gain during the administration period lasted until the end of recovery period.

4. Food Consumption (Table 3, Apendix 3)

4-1 During the administration period

Food consumption in the 10 mg/kg or lower dose groups was similar to that of the control throughout the administration period. Significant suppression of the consumption, however, was observed in both sexes receiving 30 mg/kg (rats of the recovery group inclusive) from week 2 and after.

4-2 During the recovery period

The suppression in females of the 30 mg/kg group lasted one more week after the finish of the administration.

5. Hematological Findings (Table 4 and 5, Appendix 4 and 5)

5-1 At the end of the administration period

Hematological examination with animals of the main groups performed on the scheduled necropsy-day revealed the following changes: decreased hemoglobin concentration in males of the 10 mg/kg and higher dose groups; reduced prothrombin time in females receiving 30 mg/kg.

5-2 At the end of the recovery period

After-recovery examination with animals of the 30 mg/kg recovery group revealed the following changes: in males, decrease of erythrocyte count, hemoglobin concentration, and hematocrit, shortening of prothrombin time, and increase of leukocyte count; in females, decrease of hemoglobin concentration and mean corpuscular hemoglobin concentration, shortening of activated partial thromboplastin time, and increase of mean corpuscular volume.

6. Biochemical Findings (Table 6, Appendix 6)

6-1 At the end of the administration period

The examination with animals of the main groups resulted in decrease of GOT in females of the 1 mg/kg and higher dose group, and increase of albumin in also females of the 10 mg/kg and higher dose groups. Moreover, in the 30 mg/kg group, the following changes were significant: increase of GPT and of chloride, and decrease of total cholesterol, all these in both sexes; decrease of total protein and increase of alkaline phosphatase and of A/G ratio, all these in males; and increase of urea nitrogen in females.

In addition, reddish change of serum was visually recognized in two males (animal nos. 3102, 3103) and in one female (animal no. 3205) given 10 mg/kg, and in five males (animal nos. 4101, 4102, 4103, 4105, 4106) and in all females given 30 mg/kg.

6-2 At the end of the recovery period

Significant changes detected in the 30 mg/kg recovery group were as follows: lowering of triglycerides and increase of A/G ratio in males; increase of urea nitrogen, total protein, albumin, calcium, inorganic phosphorous and sodium, and decrease of glucose and triglycerides, all these in females.

And besides, reddish change of serum was recognized in four males (animal nos. 4108, 4110, 4111, 4112) and in three females (animal nos. 4207, 4210, 4211).

7. Urinalysis (Table 7, Appendix 7)

7-1 During the administration period

The examination performed with rats (inclusive of the recovery group) one week before the end of administration period resulted in the following changes: pH shift to alkaline side in males of the 1 mg/kg and 10 mg/kg groups and in females receiving 0.1 mg/kg; pH shift to acidic side in both sexes receiving 30 mg/kg; decrease of occult blood in males receiving 30 mg/kg; decrease of protein in females receiving 30 mg/kg.

7-2 During the recovery period

Shift of pH to acidic side was noted in males of the 30 mg/kg recovery group in the examination conducted one week before the end of the period.

8. Pathological Findings

8-1 Organ weight (Table 8 and 9; Appendix 8 and 9)

8-1-1 Absolute organ weight

1) At the end of the administration period

With the animals of the main groups, liver weight increased in both males

and females of the 10 mg/kg and higher dose groups; whereas weight decreased in kidneys of males and ovaries of females, both in the 30 mg/kg group.

2) At the end of the recovery period

Changes noted in the 30 mg/kg recovery group were as follows: increase of the liver weight in both sexes; increase in the testes of males; decrease in the kidneys, in the adrenals and in the ovaries, all these of females.

8-1-2 Relative organ weight

1) At the end of the administration period

Increase of liver weight found in the absolute weight with the 10 mg/kg and higher dose groups was also detected in the relative weight in both males and females. In addition, the followings were observed: increase in the brain of both sexes receiving 30 mg/kg; increase in the adrenals and the testes of males receiving 30 mg/kg; increase in the kidneys of females given 10 mg/kg and higher dose.

2) At the end of the recovery period

Changes detected in the 30 mg/kg recovery group were as follows: increase in the liver and the brain of both sexes; increase in the testes of males; increase in the kidneys of females.

8-2 Macroscopic findings at necropsy (Table 10; Appendix 10 and 12)

8-2-1 Macroscopic findings in the dead animal

Autopsy on the male died during the recovery period (animal no. 4109) revealed the following changes: atrophy and dark reddish patch in the thymus; hemorrhage and tarry contents in the stomach; tarry contents in the small intestine; grayish patch in the liver.

8-2-2 Macroscopic findings at scheduled necropsy

Gross pathological findings observed were listed below.

1) At the end of the administration period

Males of the 30 mg/kg group---greyish dot or patch in the liver and hypertrophy of the liver, in all six rats; blackish change in the kidneys and dark reddish change in the adrenals, in one rat.

Females of the 30 mg/kg group---dark reddish change, yellowish change and grayish patch in the liver, in four, one and one rats respectively; hypertrophy of the liver, in all six rats; pyelectasis in the kidneys of one rat.

Females of the 10 mg/kg group---dark reddish change in the liver in one rat.

Others---graysh patch in the kidneys of one male of the 1 mg/kg group; pyelectasis in the kidneys of one male of the 0.1 mg/kg group; cyst in the kidneys and dark reddish patch in the lung, each in one male of the control group.

2) At the end of the recovery period

Males of the 30 mg/kg group---grayish patch and dark reddish change, and hypertrophy in the liver, all these in two rats.

Females of the 30 mg/kg group---dark reddish change and grayish patch, and hypertrophy in the liver, in five, one, and one rat respectively.

Others---atrophy of the testes in one male of the control.

8-3 Histological findings (Table 11; Appendix 11 and 12)

8-3-1 Histological findings in the dead animal

Histopathological examination with the male died during the recovery period (animal no.4109) revealed the following findings: eosinophilic degeneration in centrilobular hepatocytes, focal necrosis and peripheral fatty change in the liver; dilated tubules in restricted part of the

kidneys; hemorrhagic foci in the brain; ulcer and hemorrhage in the glandular stomach; congestion and hemorrhage in the thymus. No abnormality was obvserved in the heart, spleen, adrenals and testes.

8-3-2 Histological findings at scheduled necropsy

Histological findings observed were listed below.

1) At the end of the administration period

① Liver

In centrilobular hepatocytes, cytoplasm appeared to be granular and eosinophilic, and swelling was recognized in all males and females of the 30 mg/kg group; in the 10 mg/kg group, the similar changes, though slightly, were found in all males; and in females, either the swelling or eosinophilic change was observed in four rats even slighter in incidence and intensity than in male; in the 1 mg /kg group, the similar change was slighter in intensity and incidence than in 10 mg/kg group. (Photo 1 and 2).

Focal necrosis in hepatocytes was found in five males and two females of the 30 mg/kg group, and in two males of the 10 mg/kg group. The necrosis was found also in one male of the control.

Fatty change in peripheral lobule was remarkable in males of the 30 mg/kg group (Photo 4); in females, however, the incidence and intensity was similar to that in the control. Localized fatty change was also observed in one male of the control.

Microglanuloma was found in a few males and females of all groups, though clear difference in incidence and intensity was not noticed between each dose group and the control group.

② Heart

No abnormalities were found except extremely localized myocardinal degeneration in two male of the control group.

③ Spleen

No abnormalities were found except extramedullary hematopoiesis in three male of the control group.

④ Kidneys

Regenerated tubules were found in both males and females of the 30 mg/kg and the control groups though no difference in incidence and intensity between two groups was noted. Other findings: dilated tubules in one male of the control; infiltration of lymphocytes in the interstitial tissue in one male of the 30 mg/kg group and three male and female of the control; dilation of pelvis in two males and in one female of the 30 mg/kg group.

⑤ Adrenals, brain and testes or ovaries

No abnormalities were observed.

2) At the end of the recovery period

① Liver

Centrilobular hepatocytes were eosinophilic and showed swelling in all males and females given 30 mg/kg. As compared to the main group animals, eosinophilic intensity turned slighter in both sexes; however, the intensity of swelling was similar to that in the main group.

Focal necrosis in hepatocytes was found in three males and two females of the 30 mg/kg group, though none in the control.

Other findings: fatty change in peripheral lobule and microglanuloma were observed, the former was somewhat definite in males given 30 mg/kg, the latter, however, no difference was found with the control.

② Heart

Very slight myocardial fibrosis was found in one male of each of the 30 mg/kg and the control group, and myocardial degeneration was found in one female of the cotrol. No other abnormal findings were noted.

③ Spleen

No abnormal findings were found except extramedullary hematopoiesis in one

male of each of the 30 mg/kg and control groups.

④ Kidneys

Regenerated tubules were found in both sexes of every group; infiltration of lymphocytes in interstitial tissue was observerd in one male and in two female of the 30 mg/kg and the control group, respectively; very slight chronic nephropathy was found in one male given 30 mg/kg. No other abnornmalities was found.

⑤ Testes

No abnormal findings were noticed except atrophy in one male of the control group.

⑥ Adrenals, brain and ovaries

No abnormalities were observed.

3) Histological findings for gross pathological abnormalities

Swelling of cytoplasm of centrilobular hepatocytes and focal necrosis were found corresponding to the macroscopic findings of hypertrophy and grayish patch, respectively.

DISCUSSION AND CONCLUSION

Major findings obtained through repeated oral administration of the test substance to rats for 28 days were summarized below. Those changes were considered to be affected by the test substance.

m: male, f: female

Examination / Findings	Period	Administration				Recovery
	Dose (mg/kg)	0.1	1	10	30	30
Clinical signs (*1)---reduced spontaneous movement, bradypnea, anemia, salivation, convulsion; suppression of body weight gain and food consumption					m f	m f
death occurred (number of the animal)						m (1)
Hematological findings---inclination to anemia, abnormal change of blood coagulation				m	m f	m f
Biochemical findings---Abnormal changes in lipids, protein, and in enzymes or in electolytes			f	f	m f	m f
Urinalysis (*2)---acidic urine					m f	m
Organ weight---change in absolute weight of the liver;				m f	m f	m f
change in relative weight of the liver and kidneys				m f	m f	m f
Macroscopic findings---greyish dot or patch and hypertrophy in the liver					m f	m f
Histological findings---such changes as eosinophilic swelling and focal necrosis in the liver,			m	m f	m f	m f
fatty change in peripheral lobule					m	

(*1) Observation during each of the administration and the recovery period.

(*2) Examination one week before each end of the administration and the recovery period.

The other examination was practised at each end of the administration and the recovery period.

[Changes suggesting relation with the liver]

Among the changes detected, decrease of serum cholesterol was remarkable. Though the mechanism of the reaction is not clear, it is generally accepted that cholesterol is produced through synthesis in the liver and absorption of lipid in the intestine and is controlled through accumulation in tissues, conversion into energy and excretion from the body. As decrease of total protein and increase of A/G ratio in males or increase of albumin in females were found, considering the connection among protein and lipoprotein and cholesterol, influence of the test substance on globulin or effect to decrease lipoprotein was suggested; hence, for the reduction of serum cholesterol, concern of the liver was suspected.

Lowering of triglyceride found in both males and females of the 30 mg/kg recovery group was also considered to be affected by the test substance; because the same tendency was observed in the main group though statistically insignificant and the facts that the test substance was suspected to affect to lipids as mentioned above.

Moreover, changes in enzymes relating to the liver, increase of the liver weight such macroscopic findings in the necropsy as grayish dot/patch and hypertrophy, and histopathological pictures such as eosinophilic swelling and focal necrosis in centrilobular hepatocytes which were considered to be connected with the macroscopic findings, all these changes suggested that the test substance affected to the liver parenchyma.

Additional changes suggesting relation with the liver were shortened prothrombin time in females of the 30 mg/kg main group and in males of the same dose of the recovery group, shortened activated partial thromboplastine time in females of the 30 mg/kg recovery group. Changes of calcium and glucose observed in females of the 30 mg/kg recovery group, though not found in the main group, were a little remarkable comparing with level of physiological variation, and connection with the administ-

ration of the test substance was presumed.

[Changes suggesting relation with other organs]

As to the increase of leukocyte count observed in the 30 mg/kg recovery group, the mechanism was unclear; the same tendency, however, was noticed in the main group though statistically insignificant. Therefore the connection with the test substance was suspected.

For the increase of urea nitrogen found in females given 30 mg/kg in both the main and the recovery groups, it was not clear whether the change was caused by degradation of protein or by excretion disturbance in the kidneys; however, considering such facts as the increase of chloride in both sexes of the 30 mg/kg main group and the increase of the kidneys weight in females of the 10 mg/kg or higher dose main groups and of the 30 mg/kg recovery group, effect of the test substance to the kidneys was suspected, though no histological changes were found.

As to reddish change of serum recognized visually in both sexes of the 10 and 30 mg/kg groups, sometimes γ-GTP activity does not change apparently when reddish serum was caused by hemolysis. In this case of the study, however, the relation among the reddish serum and hemolysis and γ-GTP was unclear.

[Changes considered not to be related to the test substance]

The following changes were considered not to be related to the effect of the test substance.

Changes of inorganic phosphorous and sodium observed in females of the 30 mg/kg recovery group were unconnected to the test substance, because the magnitude of the changes was within limit of physiological variation and the changes were not found in the main group.

In urinalysis, significant decrease of occult blood was recorded in males of the 30 mg/kg main group; it was, however, considered to be apparent,

because one case of occult blood occurred in the control accidentally, hence the change was detected statistically.

Urine pH shifted to alkaline side with the administration in males receiving 1 and 10 mg/kg and in females receiving 0.1 mg/kg; the change, however, was not dose-dependent, and the change was considered not to be related to the test substance, therefore.

Weight increase of the brain and the testes and decrease of the ovaries were observed in males or females given 30 mg/kg in both the main and the recovery groups; no histological findings, however, were detected. Therefore, the changes were considered to be apparent caused by decrease of the body weight and to have no toxicological significance.

As for the macroscopic changes in the adrenals found in males or females given 30 mg/kg, no histological findings were detected; they were judged to have little toxicological significance, therefore.

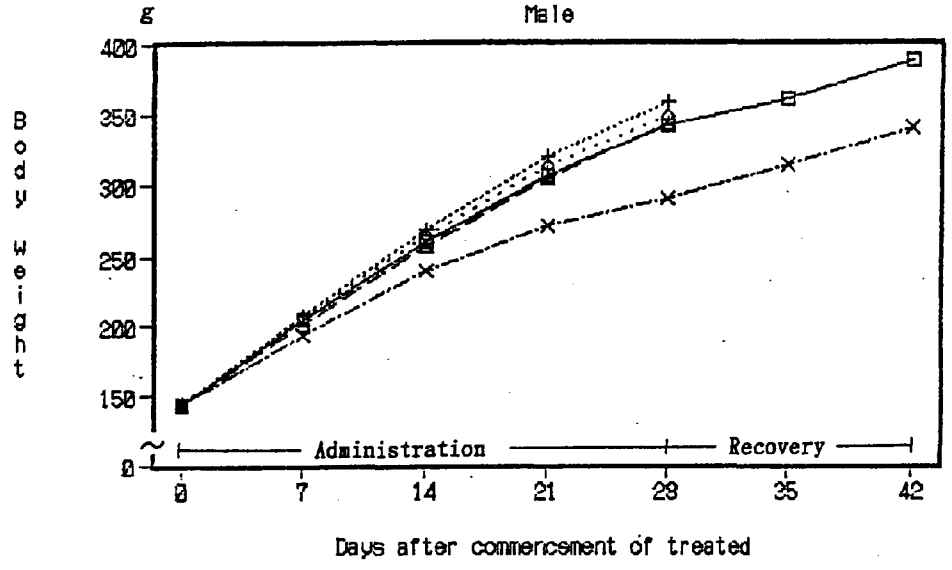
Concerning any other changes such as gross pathological findings having no dose dependency and no histologocal findings except above-mentioned incidents, they were judged to be unconnected with the test substance.

[Conclusion]

As mentioned above, significant response was found in the liver by administering the test substance to both sexes of rats with 1 mg/kg or higher dose. Whereas none of response was observed in the 0.1 mg/kg group with both male and female.

Therefore the toxicological no-observed-effect level (NOEL) of the test substance, Sample D-1, was concluded to be 0.1 mg/kg for both male and female of rats.

FIGURES AND TABLES (Group Mean Data)



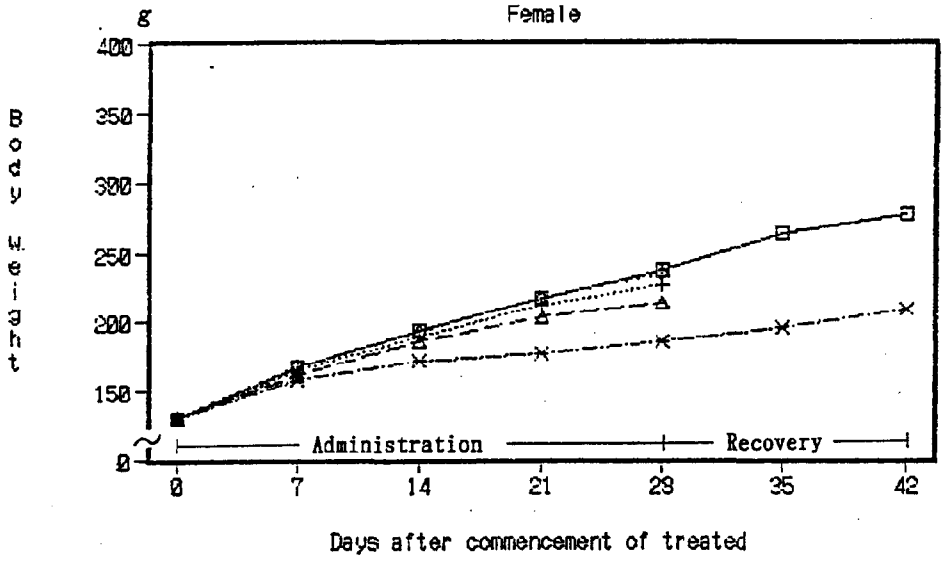


Fig. 1 Changes in mean body weight of male and female rats during 28 days of oral administration of Sample D-1 and 14 days recovery period.

□ 0 mg/kg + 0.1 mg/kg ◇ 1 mg/kg △ 10 mg/kg × 30 mg/kg

Table 1-M
Group incidence of clinical signs
Test article : Sample D-1
Sex : Male

Study No. BMR143C

Sex	Dose level (mg/kg)	Clinical signs	Days after commencement / cessation of treatment: 0	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	/D	29	30	31	32	33	34	35/7	42/14
Male	0	No abnormality observed	12	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	→12	6	.....	.....	.....	.....	.....	.....	.....	>6
	0.1	No abnormality observed	6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	→6									
	1	No abnormality observed	6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	→6									
	10	No abnormality observed	6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	→6									
	30	Reduced spontaneous movement																																1					
		Tonic-clonic/Clonic convulsion																											1					1					
		Lying																											1					1					
		Crouching																																					
		Salivation	1																2	2	2	2	5	5	5	3	2	3	4	3									
		Reddish salivation																			1									1									
		Reddish snivel																																1					
		Bradypnea																											1					1					
		Cyanosis																																					
		Brownish urine																																1					
		Loss of hair																																					
		Coat staining																																					
		No abnormality observed	11	12	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	→ 12	10	10	9	10	7	7	7	9	10	9	7	8	12	6	6	6	5	5	.....	.....	>5
		Death																																	1				

Table 1-F
Group incidence of clinical signs
Test article : Sample D-1
Sex : Female

Study No. BMR143C

Sex	Dose level (mg/kg)	Clinical signs	Days after commencement / cessation of treatment: 0 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 /0 29 30 31 32 33 34 35/7 42/14
Female	0	No abnormality observed	12 ····→ 12 6 ····→ >6
	0.1	No abnormality observed	6 ····→ >6
	1	No abnormality observed	6 ····→ >6
	10	No abnormality observed	6 ····→ >6
	30	Reduced spontaneous movement	2 1 1 2
		Tonic-clonic/Clonic convulsion	2 1 2 1
		Lying	2
		Crouching	2 1
		Salivation	1 1 1 2 2 3 4 5 2 2 1 3
		Reddish salivation	1 1
		Reddish snivel	
		Bradypnea	
		Cyanosis	1
		Brownish urine	
		Loss of hair	3 ····→ >3
		Coat staining	1 ····→ >1
		No abnormality observed	12 ····→ 11 11 11 8 6 6 5 5 4 7 5 7 7 4 8 2 2 2 2 2 2 3 ····→ >3
		Death	

Table 2 - M

Body weight - Group mean values
Sex : Male
Test article : Sample D-1

Study No. BMR143C

Unit : g

Dose level		Weeks after commencement/ cessation of treatment						
		0	1	2	3	4	5/1	6/2
0 mg/kg	Mean	143	204	260	307	342	361	389
	S.D.	5.6	8.8	12.2	15.4	21.8	26.8	34.4
	N	12	12	12	12	12	6	6
0.1 mg/kg	Mean	143	207	269	320	359		
	S.D.	4.6	6.6	16.7	24.7	31.8		
	N	6	6	6	6	6		
1 mg/kg	Mean	144	206	265	314	349		
	S.D.	4.2	7.1	9.9	13.2	17.7		
	N	6	6	6	6	6		
10 mg/kg	Mean	143	201	257	305	343		
	S.D.	5.8	8.8	14.2	19.6	24.5		
	N	6	6	6	6	6		
30 mg/kg	Mean	143	193	239 **	272 **	290 **	315 *	341 *
	S.D.	3.7	7.0	10.2	14.5	16.2	13.4	18.5
	N	12	12	12	12	12	5	5

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 2 - F

Body weight - Group mean values
Sex : Female
Test article : Sample D-1

Study No. BMR143C

Unit : g

Dose level		Weeks after commencement/ cessation of treatment						
		0	1	2	3	4	5/1	6/2
0 mg/kg	Mean	130	166	193	217	237	264	277
	S.D.	5.4	8.1	13.1	16.5	18.6	20.7	24.8
	N	12	12	12	12	12	6	6
0.1 mg/kg	Mean	129	164	189	212	227		
	S.D.	3.4	2.3	5.0	9.6	10.5		
	N	6	6	6	6	6		
1 mg/kg	Mean	131	167	192	217	235		
	S.D.	6.6	13.7	14.2	15.2	15.9		
	N	6	6	6	6	6		
10 mg/kg	Mean	130	161	185	203	214		
	S.D.	5.9	7.9	9.8	13.4	14.4		
	N	6	6	6	6	6		
30 mg/kg	Mean	130	158	171 **	176 **	185 **	195 **	208 **
	S.D.	3.9	7.0	7.2	7.8	10.9	9.9	14.5
	N	12	12	12	12	12	6	6

* : Significantly different from control value , ** ; $p<0.01$.

Table 3 - M

Study No. BMR143C

Food consumption - Group mean values
Sex : Male
Test article : Sample D-1

Unit : g/Animal/Day

Dose level		Weeks after commencement/ cessation of treatment					
		1	2	3	4	5/1	6/2
0 mg/kg	Mean	16.8	19.1	18.9	16.8	21.8	23.0
	S.D.	0.85	0.92	0.77	1.27	1.26	0.75
	N	6	6	6	6	3	3
0.1 mg/kg	Mean	18.0	20.6	20.2	18.8		
	S.D.	1.26	1.88	2.96	2.52		
	N	3	3	3	3		
1 mg/kg	Mean	17.0	19.3	18.1	17.3		
	S.D.	0.75	0.57	1.00	0.65		
	N	3	3	3	3		
10 mg/kg	Mean	16.6	18.3	19.5	17.8		
	S.D.	1.25	1.61	2.77	2.63		
	N	3	3	3	3		
30 mg/kg	Mean	15.4	15.8 **	15.3 *	12.7 *	20.4	21.2
	S.D.	0.72	0.68	0.36	0.64	2.46	2.12
	N	6	6	6	6	3	3

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 3 - F

Food consumption - Group mean values
Sex : Female
Test article : Sample D-1

Study No. BMR143C

Unit : g/Animal/Day

Dose level		Weeks after commencement/ cessation of treatment					
		1	2	3	4	5/1	6/2
0 mg/kg	Mean	13.8	13.1	13.9	12.7	19.4	20.0
	S.D.	1.15	1.36	1.50	1.42	0.20	0.35
	N	6	6	6	6	3	3
0.1 mg/kg	Mean	13.7	12.6	13.4	12.4		
	S.D.	0.40	0.80	1.42	1.12		
	N	3	3	3	3		
1 mg/kg	Mean	14.0	12.3	12.9	11.9		
	S.D.	2.35	1.55	1.07	0.79		
	N	3	3	3	3		
10 mg/kg	Mean	12.7	11.5	11.2	9.7		
	S.D.	1.10	0.81	0.75	0.36		
	N	3	3	3	3		
30 mg/kg	Mean	12.9	10.3 *	8.1 **	8.0 **	14.3 *	15.4
	S.D.	0.78	0.72	0.82	1.09	1.51	1.97
	N	6	6	6	6	3	3

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 4 - M - 1 Study No. BMR143C

Hematology - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0 mg/kg	Mean	735	14.2	47.3	65	19.3	30.0	96.6	14.3	16.4	26
	S.D.	46.0	0.39	2.66	2.9	1.02	1.66	12.88	0.59	1.16	3.9
	N	6	6	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	698	14.0	46.7	67	20.1	30.1	93.8	14.0	16.7	29
	S.D.	33.7	0.18	2.74	1.0	0.91	1.54	10.51	0.44	1.57	5.3
	N	6	6	6	6	6	6	6	6	6	6
1 mg/kg	Mean	737	14.0	47.2	64	19.0	29.7	103.7	14.0	15.5	28
	S.D.	38.8	0.43	3.21	1.9	0.69	1.34	18.92	0.31	1.60	2.1
	N	6	6	6	6	6	6	6	6	6	6
10 mg/kg	Mean	728	13.4 *	46.2	64	18.4	28.9	103.7	13.9	15.6	27
	S.D.	31.4	0.33	2.15	2.4	0.80	1.20	11.79	0.30	1.26	5.6
	N	6	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	700	13.3 *	46.1	66	19.1	29.0	89.9	14.4	18.1	20
	S.D.	53.3	0.85	3.30	1.5	1.01	1.63	6.76	0.29	2.29	5.0
	N	6	6	6	6	6	6	6	6	6	6

* : Significantly different from control value , * ; $p<0.05$.

Table 4 - M - 2 Study No. BMR143C

Hematology - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0 mg/kg	Mean	798	14.1	45.5	57	17.7	31.0	88.4	13.8	16.0	25
	S.D.	54.4	0.39	2.82	2.2	0.88	1.44	16.90	0.11	0.79	4.9
	N	6	6	6	6	6	6	6	5	5	6
30 mg/kg	Mean	717 *	12.7 **	41.6 *	58	17.7	30.4	95.5	13.4 *	15.2	31
	S.D.	22.6	0.50	1.68	2.2	0.67	1.15	11.28	0.47	1.28	6.2
	N	5	5	5	5	5	5	5	5	5	5

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 4 - F - 1 Study No. BMR143C

Hematology - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0 mg/kg	Mean	705	13.3	42.8	61	18.9	31.3	115.7	14.3	14.0	22
	S.D.	51.2	0.43	3.36	2.5	1.00	1.70	15.64	0.20	1.64	3.1
	N	6	6	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	691	13.6	42.0	61	19.7	32.4	103.1	14.3	14.8	22
	S.D.	25.2	0.18	1.40	3.4	0.66	1.24	12.27	0.46	1.19	2.9
	N	6	6	6	6	6	6	6	6	6	6
1 mg/kg	Mean	701	13.3	41.3	60	19.4	32.2	107.9	14.2	15.7	22
	S.D.	52.0	0.29	1.79	2.3	1.09	1.19	6.81	0.57	1.66	2.5
	N	6	6	6	6	6	6	6	6	6	6
10 mg/kg	Mean	716	13.7	43.8	61	19.2	31.4	105.9	14.0	15.2	21
	S.D.	35.6	0.30	2.06	2.7	0.96	1.00	13.81	0.42	0.99	2.1
	N	6	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	722	13.0	43.1	60	18.0	30.1	103.2	13.4 **	14.6	20
	S.D.	54.6	0.49	2.95	1.5	1.16	1.92	11.39	0.21	2.12	2.8
	N	6	6	6	6	6	6	6	6	6	6

* : Significantly different from control value , ** ; $p<0.01$.

Table 4 - F - 2 Study No. BMR143C

Hematology - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0 mg/kg	Mean	715	13.7	43.1	60	19.2	31.8	93.8	13.5	15.5	24
	S.D.	24.6	0.28	1.68	2.3	0.38	1.12	13.44	0.37	1.62	3.3
	N	6	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	678	12.6 ‡‡	42.7	63 ‡	18.7	29.6 ‡‡	110.3	13.1	12.3 ‡‡	25
	S.D.	33.3	0.29	1.62	1.3	0.61	0.80	17.87	0.46	1.35	2.6
	N	6	6	6	6	6	6	6	6	6	6

‡ : Significantly different from control value , ‡ ; $p<0.05$, ‡‡ ; $p<0.01$.

Table 5 - M - 1 Study No. BMR143C

Hematology - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
0 mg/kg	Mean	88	86	8	1	0	0	6
	S.D.	22.6	5.7	3.2	0.5	0.5	0.0	2.9
	N	6	6	6	6	6	6	6
0.1 mg/kg	Mean	106	87	8	0	1	0	4
	S.D.	24.8	5.7	3.9	0.5	1.2	0.0	2.2
	N	6	6	6	6	6	6	6
1 mg/kg	Mean	118	88	8	0	1	0	3
	S.D.	23.3	4.3	3.1	0.4	0.5	0.0	1.3
	N	6	6	6	6	6	6	6
10 mg/kg	Mean	97	85	10	0	1	0	5
	S.D.	17.4	5.6	3.5	0.0	1.0	0.0	2.8
	N	6	6	6	6	6	6	6
30 mg/kg	Mean	137	86	9	1	0	0	5
	S.D.	65.5	2.8	2.4	0.8	0.0	0.0	3.0
	N	6	6	6	6	6	6	6

$: Statistical analysis impossible.

Table 5 - M - 2 Study No. BMR143C

Hematology - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
						$	$	
0 mg/kg	Mean	97	85	11	0	0	0	5
	S.D.	13.9	6.5	6.1	0.5	0.0	0.0	1.6
	N	6	6	6	6	6	6	6
30 mg/kg	Mean	126 **	87	8	1	0	0	5
	S.D.	11.6	4.6	1.8	0.5	0.0	0.0	3.2
	N	5	5	5	5	5	5	5

* : Significantly different from control value , ** ; $p<0.01$.
$: Statistical analysis impossible.

Table 5 - F - 1 Study No. BMR143C

Hematology - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
0 mg/kg	Mean	75	86	10	1	0	0	3
	S.D.	10.8	3.0	2.1	0.8	0.0	0.0	2.0
	N	6	6	6	6	6	6	6
0.1 mg/kg	Mean	101	88	7	0	0	0	4
	S.D.	30.7	4.7	4.0	0.5	0.4	0.0	2.5
	N	6	6	6	6	6	6	6
1 mg/kg	Mean	86	88	10	0	0	0	2
	S.D.	21.9	4.4	3.7	0.5	0.5	0.0	1.3
	N	6	6	6	6	6	6	6
10 mg/kg	Mean	85	89	5	0	0	0	5
	S.D.	22.3	3.1	2.1	0.4	0.5	0.0	1.7
	N	6	6	6	6	6	6	6
30 mg/kg	Mean	77	87	8	0	0	0	5
	S.D.	15.6	4.4	4.8	0.4	0.4	0.0	2.4
	N	6	6	6	6	6	6	6

$: Statistical analysis impossible.

Table 5 - F - 2 Study No. BMR143C

Hematology - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
0 mg/kg	Mean	85	86	9	0	1	0 $	5
	S.D.	23.9	6.3	5.3	0.4	1.3	0.0	3.1
	N	6	6	6	6	6	6	6
30 mg/kg	Mean	86	91	5	0	0	0	4
	S.D.	18.1	2.3	2.2	0.4	0.4	0.0	1.9
	N	6	6	6	6	6	6	6

$: Statistical analysis impossible.

Table 6 - M - 1 Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
				$						
0 mg/kg	Mean	68	30	0	711	12.4	0.5	140	58	49
	S.D.	7.0	4.6	0.0	129.3	1.62	0.00	9.4	6.9	18.2
	N	6	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	65	30	0	677	10.6	0.5	150	57	55
	S.D.	9.0	5.1	0.0	84.9	2.18	0.05	10.5	3.5	11.8
	N	6	6	6	6	6	6	6	6	6
1 mg/kg	Mean	71	31	0	734	13.3	0.5	140	49	60
	S.D.	8.1	4.5	0.0	127.7	2.34	0.04	6.9	4.3	28.6
	N	6	6	6	6	6	6	6	6	6
10 mg/kg	Mean	65	34	0	780	12.4	0.5	142	38	48
	S.D.	3.9	3.2	0.0	130.2	2.56	0.05	9.0	11.1	28.0
	N	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	73	53 **	0	1191 **	14.1	0.6	142	9 **	21
	S.D.	9.5	13.2	0.0	243.7	1.93	0.12	11.5	2.0	9.6
	N	6	6	6	6	6	6	6	6	6

* : Significantly different from control value , ** ; p<0.01.
$: Statistical analysis impossible.

Table 6 - M - 2 Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0 mg/kg	Mean	6.51	3.98	1.58	9.8	10.2	142	4.1	102
	S.D.	0.212	0.125	0.110	0.46	0.70	0.5	0.08	2.2
	N	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	6.38	3.96	1.63	9.8	9.5	142	4.0	102
	S.D.	0.166	0.103	0.076	0.28	0.98	0.4	0.08	0.8
	N	6	6	6	6	6	6	6	6
1 mg/kg	Mean	6.22	3.84	1.63	9.8	9.5	142	4.2	103
	S.D.	0.190	0.079	0.149	0.31	0.72	0.8	0.20	1.2
	N	6	6	6	6	6	6	6	6
10 mg/kg	Mean	6.20	3.93	1.74	9.8	9.3	142	4.3	104
	S.D.	0.099	0.146	0.141	0.30	0.82	0.9	0.33	1.4
	N	6	6	6	6	6	6	6	6
30 mg/kg	Mean	6.01 **	4.01	2.04 **	9.4	10.0	144	4.2	106 **
	S.D.	0.368	0.166	0.264	0.54	3.06	1.9	0.35	1.3
	N	6	6	6	6	6	6	6	6

* : Significantly different from control value , ** ; $p<0.01$.

Table 6 - M - 3

Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
				$						
0 mg/kg	Mean	85	34	0	613	18.7	0.5	148	50	85
	S.D.	12.7	4.5	0.0	65.2	2.42	0.05	5.9	14.1	45.0
	N	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	76	44	0	716	21.8	0.5	152	29	10 **
	S.D.	6.5	10.1	0.0	105.4	3.61	0.08	12.8	11.3	4.2
	N	5	5	5	5	5	5	5	5	5

* : Significantly different from control value , ** ; $p<0.01$.
$: Statistical analysis impossible.

Table 6 - M - 4

Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0 mg/kg	Mean	6.42	3.85	1.50	9.6	8.7	141	4.2	104
	S.D.	0.167	0.056	0.072	0.28	0.18	1.5	0.28	1.5
	N	6	6	6	6	6	6	6	6
30 mg/kg	Mean	6.57	4.14	1.70 ‡	9.7	8.9	142	4.2	106
	S.D.	0.288	0.195	0.109	0.08	0.63	1.1	0.20	2.5
	N	5	5	5	5	5	5	5	5

‡ : Significantly different from control value , * ; $p<0.05$.

Table 6 - F - 1 Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
0 mg/kg	Mean	80	23	0	472	11.9	0.5	133	58	24
	S.D.	8.0	3.5	0.4	65.2	1.33	0.04	7.6	10.5	4.9
	N	6	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	70	25	0	419	13.2	0.6	140	57	28
	S.D.	5.0	4.8	0.0	84.6	3.41	0.08	22.0	6.2	9.4
	N	6	6	6	6	6	6	6	6	6
1 mg/kg	Mean	60 **	20	0	437	13.1	0.5	143	59	30
	S.D.	7.4	2.9	0.4	82.1	2.89	0.06	8.3	5.1	6.2
	N	6	6	6	6	6	6	6	6	6
10 mg/kg	Mean	60 **	24	0	451	13.5	0.5	135	48	21
	S.D.	12.5	3.2	0.0	81.8	2.59	0.04	11.7	8.1	2.9
	N	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	56 **	36 **	0	590	18.0 **	0.5	126	25 **	20
	S.D.	4.1	7.2	0.0	170.9	3.43	0.05	15.0	5.1	4.7
	N	6	6	6	6	6	6	6	6	6

* : Significantly different from control value , ** : $p<0.01$.

Table 6 - F - 2 Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0 mg/kg	Mean	6.63	4.18	1.72	9.4	8.4	141	4.1	104
	S.D.	0.173	0.060	0.099	0.15	1.09	0.8	0.27	0.5
	N	6	6	6	6	6	6	6	6
0.1 mg/kg	Mean	6.61	4.19	1.74	9.8	9.7	141	4.5	102
	S.D.	0.320	0.154	0.095	0.59	1.01	0.9	0.58	1.4
	N	6	6	6	6	6	6	6	6
1 mg/kg	Mean	6.45	4.15	1.82	9.6	8.7	141	4.4	104
	S.D.	0.335	0.125	0.191	0.18	0.31	1.2	0.48	1.9
	N	6	6	6	6	6	6	6	6
10 mg/kg	Mean	6.91	4.42 *	1.77	9.7	7.9	142	4.1	106
	S.D.	0.255	0.143	0.072	0.35	0.73	1.5	0.45	1.2
	N	6	6	6	6	6	6	6	6
30 mg/kg	Mean	7.01	4.59 **	1.90	9.9	8.6	142	4.9	106 **
	S.D.	0.327	0.140	0.143	0.49	0.93	1.1	0.72	1.5
	N	6	6	6	6	6	6	6	6

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 6 - F - 3

Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
				$						
0 mg/kg	Mean	71	30	0	323	17.3	0.6	150	61	48
	S.D.	8.8	7.7	0.0	63.4	2.55	0.05	6.9	10.1	31.1
	N	6	6	6	6	6	6	6	6	6
30 mg/kg	Mean	61	30	0	387	24.1 **	0.6	126 **	51	18 **
	S.D.	10.6	5.9	0.0	52.4	2.99	0.04	9.6	7.3	2.4
	N	6	6	6	6	6	6	6	6	6

* : Significantly different from control value , ** ; p<0.01.
$: Statistical analysis impossible.

Table 6 - F - 4

Study No. BMR143C

Clinical chemistry - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0 mg/kg	Mean	7.02	4.34	1.62	9.6	7.3	140	4.1	105
	S.D.	0.286	0.142	0.064	0.16	0.54	0.6	0.12	1.2
	N	6	6	6	6	6	6	6	6
30 mg/kg	Mean	7.50 *	4.72 **	1.70	10.2 **	8.1 *	141 **	4.3	105
	S.D.	0.379	0.204	0.123	0.19	0.31	0.4	0.39	1.0
	N	6	6	6	6	6	6	6	6

* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 7 - M - 1

Study No. BMR143C

Urinalysis - Group mean values
Sex : Male
Test article : Sample D-1
3 weeks after commencement of treatment

Dose level	N	Urobilinogen (EU/dl)					Occult Blood					Bilirubin				Ketone bodies (mg/dl)					Glucose (g/dl)					Protein (mg/dl)				pH					
(mg/kg)		0.1	1	2	4	≧8	−	TR	1+	2+	3+	−	1+	2+	3+	−	5	15	40	≧80	−	0.1	0.25	0.5	≧1	−	TR	30	100	≧300	6.0	6.5	7.0	7.5	8.0	8.5
0	12	12	0	0	0	0	9	2	0	0	1	12	0	0	0	1	10	1	0	0	12	0	0	0	0	0	2	10	0	0	1	0	4	1	6	0
0.1	6	6	0	0	0	0	5	1	0	0	0	6	0	0	0	0	4	1	1	0	6	0	0	0	0	0	0	5	1	0	0	0	0	2	4	0
1	6	6	0	0	0	0	5	1	0	0	0	6	0	0	0	0	5	1	0	0	6	0	0	0	0	0	0	4	2	0	0	0	0	0	4	2 **
10	6	6	0	0	0	0	6	0	0	0	0 *	6	0	0	0	0	6	0	0	0	6	0	0	0	0	0	0	4	2	0	0	0	0	1	5	0 *
30	12	12	0	0	0	0	12	0	0	0	0	12	0	0	0	0	8	2	2	0	12	0	0	0	0	0	1	9	2	0	2	1	4	4	1	0

− : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe
$: Statistical analysis impossible.
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 7 - M - 2

Study No. BMR143C

Urinalysis - Group mean values
Sex : Male
Test article : Sample D-1
5 weeks after commencement of treatment (Recovery)

Dose level	N	Urobilinogen (EU/dl)					Occult Blood					Bilirubin				Ketone bodies (mg/dl)					Glucose (g/dl)					Protein (mg/dl)					pH					
(mg/kg)		0.1	1	2	4	≧8	−	TR	1+	2+	3+	−	1+	2+	3+	−	5	15	40	≧80	−	0.1	0.25	0.5	≧1	−	TR	30	100	≧300	6.0	6.5	7.0	7.5	8.0	8.5
0	6	6	0	0	0	0	$ 2	4	0	0	0	6	0	0	0	$ 1	5	0	0	0	$ 6	0	0	0	0	2	4	0	0	0	0	1	2	3	0
30	6	5	0	0	0	0	4	0	0	1	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	0	0	5	0	0	0	2	3	0	0	‡‡ 0

− : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe
$: Statistical analysis impossible.
‡ : Significantly different from control value , ‡‡ ; $p<0.01$.

Table 7 - F - 1

Study No. BMR143C

Urinalysis - Group mean values
Sex : Female
Test article : Sample D-1
3 weeks after commencement of treatment

Dose level	N	Urobilinogen (EU/dl)					Occult Blood					Bilirubin				Ketone bodies (mg/dl)					Glucose (g/dl)					Protein (mg/dl)					pH					
(mg/kg)		0.1	1	2	4	≧8	−	TR	1+	2+	3+	−	1+	2+	3+	−	5	15	40	≧80	−	0.1	0.25	0.5	≧1	−	TR	30	100	≧300	6.0	6.5	7.0	7.5	8.0	8.5
0	12	12	0	0	0	0	10	2	0	0	0	12	0	0	0	9	3	0	0	0	12	0	0	0	0	0	2	10	0	0	0	1	3	3	4	1
0.1	6	6	0	0	0	0	4	2	0	0	0	6	0	0	0	5	1	0	0	0	6	0	0	0	0	0	2	4	0	0	0	0	1	3	2	
1	6	6	0	0	0	0	2	2	2	0	0	6	0	0	0	2	4	0	0	0	6	0	0	0	0	0	1	5	0	0	0	1	3	2	0	
10	6	6	0	0	0	0	5	1	0	0	0	6	0	0	0	3	3	0	0	0	6	0	0	0	0	0	2	4	0	0	0	1	1	2	1	
30	12	12	0	0	0	0	7	3	2	0	0	12	0	0	0	10	2	0	0	0	12	0	0	0	0	3	5	4	0	0	3	1	6	2	0	0

− : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe
$: Statistical analysis impossible.
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 7 - F - 2

Study No. BMR143C

Urinalysis - Group mean values
Sex : Female
Test article : Sample D-1
5 weeks after commencement of treatment (Recovery)

Dose level	N	Urobilinogen (EU/dl)					Occult Blood					Bilirubin				Ketone bodies (mg/dl)					Glucose (g/dl)					Protein (mg/dl)					pH				
(mg/kg)		0.1	1	2	4	≧8	−	TR	1+	2+	3+	−	1+	2+	3+	−	5	15	40	≧80	−	0.1	0.25	0.5	≧1	−	TR	30	100	≧300	6.0	6.5	7.0	7.5	8.0	8.5
							$								$					$					$										
0	6	6	0	0	0	0	3	2	0	1	0	6	0	0	0	6	0	0	0	0	6	0	0	0	0	1	3	2	0	0	0	0	1	2	3	0
30	6	6	0	0	0	0	2	4	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	0	0	0	4	2	0	0	0	1	3	1	1	0

− : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe
$: Statistical analysis impossible.

Table 8 - M - 1

Study No. BMR143C

Organ weight (Absolute) - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0 mg/kg	Mean	351	1.96	13.60	2.43	50.5	2.99
	S.D.	22.0	0.117	1.180	0.156	3.19	0.265
	N	6	6	6	6	6	6
0.1 mg/kg	Mean	359	1.98	14.50	2.55	54.3	3.14
	S.D.	31.8	0.094	1.194	0.257	4.90	0.196
	N	6	6	6	6	6	6
1 mg/kg	Mean	349	1.94	13.88	2.26	52.9	3.14
	S.D.	17.7	0.045	1.459	0.170	3.71	0.194
	N	6	6	6	6	6	6
10 mg/kg	Mean	343	1.94	16.93 **	2.39	49.5	3.01
	S.D.	24.5	0.078	1.179	0.101	5.14	0.189
	N	6	6	6	6	6	6
30 mg/kg	Mean	292 **	1.97	20.36 **	2.11 **	50.4	3.08
	S.D.	17.6	0.072	2.228	0.084	4.15	0.250
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , ** ; $p<0.01$.

Table 8 - M - 2 Study No. BMR143C

Organ weight (Absolute) - Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0 mg/kg	Mean	389	2.05	13.57	2.47	53.1	2.74
	S.D.	34.4	0.051	1.768	0.151	6.85	0.942
	N	6	6	6	6	6	6
30 mg/kg	Mean	341 *	2.02	20.66 **	2.40	51.5	3.38 *
	S.D.	18.5	0.058	1.693	0.157	7.31	0.117
	N	5	5	5	5	5	5

F.B.W : Final body weight
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 8 - F - 1

Study No. BMR143C

Organ weight (Absolute) - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0 mg/kg	Mean	230	1.85	8.76	1.62	60.1	83.7
	S.D.	17.4	0.067	0.471	0.177	5.46	10.13
	N	6	6	6	6	6	6
0.1 mg/kg	Mean	227	1.79	8.65	1.61	59.8	83.7
	S.D.	10.5	0.054	0.679	0.162	6.93	7.86
	N	6	6	6	6	6	6
1 mg/kg	Mean	235	1.91	9.07	1.67	62.6	92.0
	S.D.	15.9	0.069	0.852	0.081	7.79	15.11
	N	6	6	6	6	6	6
10 mg/kg	Mean	214	1.85	10.58 **	1.70	60.8	75.8
	S.D.	14.4	0.063	0.973	0.109	8.01	8.53
	N	6	6	6	6	6	6
30 mg/kg	Mean	190 **	1.83	13.78 **	1.50	55.6	62.6 **
	S.D.	9.5	0.064	0.816	0.126	6.28	7.57
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , ** : $p<0.01$.

Table 8 - F - 2 Study No. BMR143C

Organ weight (Absolute) - Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0 mg/kg	Mean	277	1.93	9.09	1.78	70.8	89.7
	S.D.	24.8	0.074	1.122	0.100	12.55	9.96
	N	6	6	6	6	6	6
30 mg/kg	Mean	208 **	1.86	12.46 **	1.59 *	54.0 *	68.5 **
	S.D.	14.5	0.131	0.574	0.146	7.39	6.22
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 9 - M - 1

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
0 mg/kg	Mean	351	0.56	3.88	0.69	14.5	0.86
	S.D.	22.0	0.037	0.197	0.026	1.55	0.094
	N	6	6	6	6	6	6
0.1 mg/kg	Mean	359	0.55	4.04	0.71	15.3	0.88
	S.D.	31.8	0.066	0.210	0.018	2.70	0.071
	N	6	6	6	6	6	6
1 mg/kg	Mean	349	0.56	3.97	0.65	15.2	0.90
	S.D.	17.7	0.037	0.272	0.060	1.03	0.057
	N	6	6	6	6	6	6
10 mg/kg	Mean	343	0.57	4.98 **	0.70	14.5	0.88
	S.D.	24.5	0.043	0.611	0.060	1.10	0.075
	N	6	6	6	6	6	6
30 mg/kg	Mean	292 **	0.68 **	6.97 **	0.72	17.3 *	1.06 **
	S.D.	17.6	0.048	0.475	0.035	1.54	0.112
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 9 - M - 2 Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Group mean values
Sex : Male
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($\times 10^{-3}$)	Testes
0 mg/kg	Mean	389	0.53	3.48	0.64	13.7	0.70
	S.D.	34.4	0.044	0.160	0.056	1.82	0.231
	N	6	6	6	6	6	6
30 mg/kg	Mean	341 *	0.59 *	6.06 **	0.70	15.2	0.99 **
	S.D.	18.5	0.030	0.482	0.029	2.67	0.069
	N	5	5	5	5	5	5

F.B.W : Final body weight
* : Significantly different from control value , * ; $p<0.05$, ** ; $p<0.01$.

Table 9 - F - 1 Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (4 weeks)

Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($\times 10^{-3}$)	Ovaries ($\times 10^{-3}$)
0 mg/kg	Mean	230	0.80	3.81	0.70	26.2	36.4
	S.D.	17.4	0.037	0.198	0.043	2.76	4.28
	N	6	6	6	6	6	6
0.1 mg/kg	Mean	227	0.79	3.81	0.71	26.4	36.9
	S.D.	10.5	0.053	0.148	0.042	2.89	2.90
	N	6	6	6	6	6	6
1 mg/kg	Mean	235	0.81	3.85	0.71	26.6	39.3
	S.D.	15.9	0.047	0.237	0.043	2.73	6.90
	N	6	6	6	6	6	6
10 mg/kg	Mean	214	0.87	4.95 **	0.79 **	28.4	35.4
	S.D.	14.4	0.055	0.255	0.015	2.54	3.23
	N	6	6	6	6	6	6
30 mg/kg	Mean	190 **	0.96 **	7.24 **	0.79 **	29.2	33.0
	S.D.	9.5	0.034	0.321	0.053	2.50	4.37
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , ** ; $p<0.01$.

Table 9 - F - 2 Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Group mean values
Sex : Female
Test article : Sample D-1
Animals killed on schedule (Recovery)

Dose level		F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
0 mg/kg	Mean	277	0.70	3.28	0.64	25.6	32.5
	S.D.	24.8	0.059	0.157	0.035	4.10	2.25
	N	6	6	6	6	6	6
30 mg/kg	Mean	208 **	0.90 **	6.00 **	0.76 **	25.9	33.0
	S.D.	14.5	0.047	0.358	0.033	2.43	3.18
	N	6	6	6	6	6	6

F.B.W : Final body weight
* : Significantly different from control value , ** ; $p<0.01$.

Table 10-M.F
Group incidence of macroscopic findings
Test article : Sample D-1

Study No.BMR143C

Organ / Findings	Period / Sex / Dose level(mg/kg) / Number of animals	28 days Male 0	0.1	1	10	30	28 days Female 0	0.1	1	10	30	Recovery Male 0	30	Recovery Female 0	30	Dead animal Male 30
		6	6	6	6	6	6	6	6	6	6	6	5	6	6	1
Thymus																
Dark reddish patch		0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Atrophy		0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Lungs																
Dark reddish patch		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Liver																
Scatterring of greyish dot/patch		0	0	0	0	5	0	0	0	0	0	0	1	0	0	1
Hypertrophy		0	0	0	0	6	0	0	0	0	6	0	2	0	1	0
Greyish patch		0	0	0	0	1	0	0	0	0	1	0	2	0	1	0
Dark reddish change		0	0	0	0	0	0	0	0	0	4	0	2	0	5	0
Yellowish change		0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
kidneys																
Cyst		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pyelectasis		0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Greyish patch		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Blackish change		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Adrenals																
Dark reddish change		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Stomach																
Tarry contents/Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Testes																
Atrophy		0	0	0	0	0						1	0			0

Table 11-M
Group incidence of microscopic findings (28days)
Sex : Male
Test article : Sample D-1

Study No.BMR143C

Findings	Dose level : 0 mg/kg (n=6)					0.1 mg/kg (n=6)					1 mg/kg (n=6)					10 mg/kg (n=6)					30 mg/kg (n=6)				
Grade :	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++
Liver																									
microgranuloma	0	4	2	0	0	0	6	0	0	0	0	4	2	0	0	0	3	3	0	0	0	3	3	0	0
focal necrosis	5	0	1	0	0	6	0	0	0	0	6	0	0	0	0	4	0	2	0	0	1	0	4	1	0
focal fatty change	5	0	1	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0
peripheral fatty change	6	0	0	0	0	5	1	0	0	0	4	2	0	0	0	2	2	2	0	0	1	2	2	1	0
swelling of centrilobular hepatocytes	6	0	0	0	0	6	0	0	0	0	3	3	0	0	0	0	1	5	0	0	0	0	2	4	0
eosinophilic change in centrilobular hepatocytes	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	0	1	2	3	0	0	0	0	6	0
Heart																									
myocardial degeneration	4	2	0	0	0																6	0	0	0	0
myocardial fibrosis	6	0	0	0	0																6	0	0	0	0
Spleen																									
extramedullary hematopoiesis	3	2	1	0	0																6	0	0	0	0
Kidneys																									
regenerated tubules	3	1	2	0	0																3	1	2	0	0
dilated tubules	5	0	1	0	0																6	0	0	0	0
infiltration of lymphocytes	3	2	1	0	0																5	1	0	0	0
dilation of pelvis	6	0	0	0	0																4	0	2	0	0
chronic nephropathy	6	0	0	0	0																6	0	0	0	0
Adrenals																									
abnormality	6	0	0	0	0																6	0	0	0	0
Brain																									
abnormality	6	0	0	0	0																6	0	0	0	0
Testes																									
atrophy	6	0	0	0	0																6	0	0	0	0

− : Negative, ± : Very slight, + : Slight, ++ : Moderate, +++ : Severe

Table 11-F
Group incidence of microscopic findings (28days)
Sex : Female
Test article : Sample D-1

Study No.BMR143C

Dose level :	0 mg/kg (n=6)					0.1 mg/kg (n=6)					1 mg/kg (n=6)					10 mg/kg (n=6)					30 mg/kg (n=6)				
Findings Grade :	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++
Liver																									
microgranuloma	1	5	0	0	0	0	5	1	0	0	2	4	0	0	0	0	5	1	0	0	1	3	1	1	0
focal necrosis	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	4	0	2	0	0
focal fatty change	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0
peripheral fatty change	2	2	2	0	0	0	2	4	0	0	3	2	1	0	0	2	2	2	0	0	3	1	2	0	0
swelling of centrilobular hepatocytes	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	0	0	1	5	0
eosinophilic change in centrilobular hepatocytes	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	0	0	0	6	0
Heart																									
myocardial degeneration	6	0	0	0	0																6	0	0	0	0
myocardial fibrosis	6	0	0	0	0																6	0	0	0	0
Spleen																									
extramedullary hematopoiesis	6	0	0	0	0																6	0	0	0	0
Kidneys																									
regenerated tubules	3	2	1	0	0																3	3	0	0	0
dilated tubules	6	0	0	0	0																6	0	0	0	0
infiltration of lymphocytes	3	2	1	0	0																6	0	0	0	0
dilation of pelvis	6	0	0	0	0																5	0	1	0	0
chronic nephropathy	6	0	0	0	0																6	0	0	0	0
Adrenals																									
abnormality	6	0	0	0	0																6	0	0	0	0
Brain																									
abnormality	6	0	0	0	0																6	0	0	0	0
Ovaries																									
abnormality	6	0	0	0	0																6	0	0	0	0

− : Negative. ± : Very slight. + : Slight. ++ : Moderate. +++ : Severe

Table 11-R-1
Group incidence of microscopic findings (Recovery)
Test article : Sample D-1

Study No.BMR143C

Findings	Sex / Dose level / Grade	Male 0 mg/kg (n=6)					Male 30 mg/kg (n=5)					Female 0 mg/kg (n=6)					Female 30 mg/kg (n=6)				
		−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++	−	±	+	++	+++
Liver																					
microgranuloma		1	3	2	0	0	0	1	4	0	0	0	6	0	0	0	1	3	2	0	0
focal necrosis		6	0	0	0	0	2	0	3	0	0	6	0	0	0	0	4	0	2	0	0
focal fatty change		6	0	0	0	0	5	0	0	0	0	6	0	0	0	0	6	0	0	0	0
peripheral fatty change		6	0	0	0	0	2	1	2	0	0	4	1	1	0	0	5	0	1	0	0
swelling of centrilobular hepatocytes		6	0	0	0	0	0	0	0	5	0	6	0	0	0	0	0	0	2	4	0
eosinophilic change in centrilobular hepatocytes		6	0	0	0	0	0	0	3	2	0	6	0	0	0	0	0	0	6	0	0
Heart																					
myocardial degeneration		6	0	0	0	0	5	0	0	0	0	5	1	0	0	0	6	0	0	0	0
myocardial fibrosis		5	1	0	0	0	4	1	0	0	0	6	0	0	0	0	6	0	0	0	0
Spleen																					
extramedullary hematopoiesis		5	1	0	0	0	4	1	0	0	0	6	0	0	0	0	6	0	0	0	0
Kidneys																					
regenerated tubules		3	3	0	0	0	4	1	0	0	0	2	4	0	0	0	5	1	0	0	0
dilated tubules		6	0	0	0	0	5	0	0	0	0	6	0	0	0	0	6	0	0	0	0
infiltration of lymphocytes		6	0	0	0	0	4	0	1	0	0	4	0	2	0	0	6	0	0	0	0
dilation of pelvis		6	0	0	0	0	5	0	0	0	0	6	0	0	0	0	6	0	0	0	0
chronic nephropathy		6	0	0	0	0	4	1	0	0	0	6	0	0	0	0	6	0	0	0	0
Adrenals																					
abnormality		6	0	0	0	0	5	0	0	0	0	6	0	0	0	0	6	0	0	0	0
Brain																					
abnormality		6	0	0	0	0	5	0	0	0	0	6	0	0	0	0	6	0	0	0	0
Testes																					
atrophy		5	0	0	1	0	5	0	0	0	0										
Ovaries																					
abnormality												6	0	0	0	0	6	0	0	0	0

− : Negative. ± : Very slight. + : Slight. ++ : Moderate. +++ : Severe

Table 11-R-2
Incidence of microscopic findings in died male rat (32 day)
Test article : Sample D-1

Study No.BMR143C

Findings	Sex / Dose level / Grade	Male 30 mg/kg (n=1)				
		−	±	+	++	+++
Liver						
Eosinophilic change in centrilobular hepatocytes		0	0	0	1	0
Swelling of centrilobular hepatocytes		0	0	0	1	0
Focal necrosis		0	0	0	1	0
Peripheral fatty change		0	0	1	0	0
Kidneys						
Dilated tubules		0	0	1	0	0
Brain						
Hemorrhagic foci		0	0	1	0	0
Stomach						
Ulcer and hemorrhage in glandular stomach		0	0	1	0	0
Thymus						
Congestion		0	0	1	0	0
Hemorrhage		0	0	1	0	0
Heart						
No abnormality		1	0	0	0	0
Spleen						
No abnormality		1	0	0	0	0
Adrenals						
No abnormality		1	0	0	0	0
Testes						
No abnormality		1	0	0	0	0

− : Negative, ± : Very slight, + : Slight, ++ : Moderate, +++ : Severe

APPENDICES (Individual Data)

Appendix 1-M-1
Clinical signs - Individual
Test article : Sample D-1
Sex : Male

Study No. BMR143C

Sex	Dose level (mg/kg)	Animal number	Days after commencement 0	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
Male	0	0101 ↓ 0112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.1	1101 ↓ 1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1	2101 ↓ 2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	3101 ↓ 3106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	30	4101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	SA	SA	-	SA	SA	SA	-
		4102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	-
		4103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	-	-
		4104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4105	SA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	-	-	-	-	-	-	-	-	-
		4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	RS	-	SA	SA	SA	SA	SA	SA	SA	SA	-
		4109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	-	SA	SA	SA	-	-	-	TC LY BP	RS	-
		4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	SA	-	-	-	-	-	-
		4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TC : Tonic-clonic/Clonic convulsion, LY : Lying, SA : Salivation, RS : Reddish salivation, BP : Bradypnea,
- : No abnormality observed.

Appendix 1-M-2
Clinical signs - Individual
Test article : Sample D-1
Sex : Male

Study No. BMR143C

Sex	Dose level (mg/kg)	Animal number	Days after commencement/cessation of treatment														
			28/0	29/1	30/2	31/3	32/4	33/5	34/6	35/7	36/8	37/9	38/10	39/11	40/12	41/13	42/14
	0	0107 ↓ 0112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4109	-	-	-	RM	DD										
Male	30					TC											
						LY											
						BP											
						RD											
						BU											
		4110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

RM : Reduced spontaneous movement, TC : Tonic-clonic/Clonic convulsion, LY : Lying, RD : Reddish snivel, BP : Bradypnea,
BU : Brownish urine, DD : Death, - : No abnormality observed.

Appendix 1-F-1
Clinical signs - Individual
Test article : Sample D-1
Sex : Female

Study No. BMR143C

Sex	Dose level (mg/kg)	Animal number	Days after commencement 0 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
Female	0	0201 ↓ 0212	- -
	0.1	1201 ↓ 1206	- -
	1	2201 ↓ 2206	- -
	10	3201 ↓ 3206	- -

- : No abnormality observed.

Appendix 1-F-2
Clinical signs - Individual
Test article : Sample D-1
Sex : Female

Study No. BMR143C

Sex	Dose level (mg/kg)	Animal number	Days after commencement 0	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
		4201	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	-	-	SA	SA	-	SA	-	-	SA		SA	-
		4202	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4203	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	-	-	SA	SA	-	RS	-	-	RS	-
		4204	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	-	-	SA	SA	SA RM TC CR CY	SA	SA	-	SA	-	-	SA	-
Female	30	4205	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4206	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SA	SA	SA	-	-	SA	-
		4207	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	LH	LH	LH	LH SA	LH SA	LH SA	LH SA	LH	LH	LH	LH	LH
		4208	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	LH	LH	LH	LH	LH SA	LH	LH	LH	LH	LH	LH	LH
		4209	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH
		4210	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	CS	CS	CS	CS	CS	CS	CS	CS	CS RM TC CR	CS RM TC LY	CS TC	CS
		4211	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4212	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	RM TC CR	RM	-	-	-	-	RM TC LY	-	-

RM : Reduced spontaneous movement, TC : Tonic-clonic/Clonic convulsion, LY : Lying, CR : Crouching, SA : Salivation,
RS : Reddish salivation, CY : Cyanosis, LH : Loss of hair, CS : Coat staining, - : No abnormality observed.

Appendix 1-F-3
Clinical signs - Individual
Test article : Sample D-1
Sex : Female

Study No. BMR143C

Sex	Dose level (mg/kg)	Animal number	Days after commencement/cessation of treatment														
			28/0	29/1	30/2	31/3	32/4	33/5	34/6	35/7	36/8	37/9	38/10	39/11	40/12	41/13	42/14
Female	0	0207 ↓ 0212	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	30	4207	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH
		4208	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH
		4209	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH	LH
		4210	CS	CS	CS	CS	CS	CS	CS	-	-	-	-	-	-	-	-
		4211	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		4212	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

LH : Loss of hair, CS : Coat staining, - : No abnormality observed.

Appendix 2 - M - 1

Study No. BMR143C

Body weight - Individual values

Sex : Male

Dose level : Sample D-1 0 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
0101	139	213	268	313	354 KS		
0102	142	196	249	291	318 KS		
0103	136	196	252	301	334 KS		
0104	140	207	265	318	352 KS		
0105	145	208	274	329	377 KS		
0106	148	215	275	327	370 KS		
0107	146	210	263	300	329	345	365 KS
0108	147	207	257	299	331	363	405 KS
0109	151	206	263	319	361	401	438 KS
0110	149	211	268	306	327	352	374 KS
0111	132	185	231	275	304	324	344 KS
0112	143	198	259	308	346	378	410 KS
Mean	143	204	260	307	342	361	389
S.D.	5.6	8.8	12.2	15.4	21.8	26.8	34.4
N	12	12	12	12	12	6	6

KS : Killed on schedule

Appendix 2 - M - 2

Study No. BMR143C

Body weight - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
1101	137	206	277	333	375 KS		
1102	140	200	244	288	321 KS		
1103	141	210	268	318	362 KS		
1104	146	199	254	293	321 KS		
1105	148	214	284	340	376 KS		
1106	148	214	285	347	399 KS		
Mean	143	207	269	320	359		
S.D.	4.6	6.6	16.7	24.7	31.8		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - M - 3

Study No. BMR143C

Body weight - Individual values

Sex : Male

Dose level : Sample D-1 1 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment						
	0	1	2	3	4	5/1	6/2
2101	136	197	255	308	346 KS		
2102	143	206	265	315	345 KS		
2103	142	202	264	296	354 KS		
2104	146	203	254	311	321 KS		
2105	147	213	278	336	376 KS		
2106	147	216	275	318	350 KS		
Mean	144	206	265	314	349		
S.D.	4.2	7.1	9.9	13.2	17.7		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - M - 4

Study No. BMR143C

Body weight - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
3101	135	196	245	293	326 KS		
3102	137	193	252	298	341 KS		
3103	143	195	245	289	320 KS		
3104	145	198	253	301	335 KS		
3105	150	214	282	343	389 KS		
3106	147	210	264	308	345 KS		
Mean	143	201	257	305	343		
S.D.	5.8	8.8	14.2	19.6	24.5		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - M - 5

Study No. BMR143C

Body weight - Individual values

Sex : Male

Dose level : Sample D-1 30 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
4101	140	193	237	273	300 KS		
4102	139	185	229	265	286 KS		
4103	144	200	254	300	321 KS		
4104	147	198	241	268	283 KS		
4105	143	190	231	256	269 KS		
4106	146	196	247	285	293 KS		
4107	147	193	235	265	284	304	326 KS
4108	136	189	233	268	291	311	336 KS
4109	145	193	231	256	261	D	
4110	138	180	228	263	284	308	331 KS
4111	142	194	238	271	292	315	340 KS
4112	146	207	260	297	310	338	373 KS
Mean	143	193	239	272	290	315	341
S.D.	3.7	7.0	10.2	14.5	16.2	13.4	18.5
N	12	12	12	12	12	5	5

KS : Killed on schedule

D : Dead.

Appendix 2 - F - 1

Study No. BMR143C

Body weight - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
0201	128	162	191	211	228 KS		
0202	123	151	177	193	214 KS		
0203	131	160	181	207	221 KS		
0204	140	178	208	235	264 KS		
0205	128	164	186	207	227 KS		
0206	131	165	187	214	227 KS		
0207	138	178	222	255	279	304	325 KS
0208	131	168	201	222	237	254	265 KS
0209	129	168	188	214	237	256	264 KS
0210	128	171	200	228	243	261	270 KS
0211	133	171	196	220	244	262	278 KS
0212	121	156	179	201	225	245	257 KS
Mean	130	166	193	217	237	264	277
S.D.	5.4	8.1	13.1	16.5	18.6	20.7	24.8
N	12	12	12	12	12	6	6

KS : Killed on schedule

Appendix 2 - F - 2

Study No. BMR143C

Body weight - Individual values

Sex : Female

Dose level : Sample D-1 0.1 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
1201	124	159	188	210	224 KS		
1202	125	165	180	196	212 KS		
1203	132	165	192	219	235 KS		
1204	130	164	192	222	242 KS		
1205	128	165	194	217	227 KS		
1206	132	163	189	207	222 KS		
Mean	129	164	189	212	227		
S.D.	3.4	2.3	5.0	9.6	10.5		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - F - 3

Study No. BMR143C

Body weight - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
2201	121	152	177	204	225 KS		
2202	128	157	184	205	226 KS		
2203	130	157	180	201	216 KS		
2204	132	171	202	228	240 KS		
2205	134	185	213	237	259 KS		
2206	141	180	198	225	246 KS		
Mean	131	167	192	217	235		
S.D.	6.6	13.7	14.2	15.2	15.9		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - F - 4

Study No. BMR143C

Body weight - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment 0	1	2	3	4	5/1	6/2
3201	125	156	185	203	216 KS		
3202	125	164	193	218	225 KS		
3203	125	149	166	178	186 KS		
3204	130	159	189	208	221 KS		
3205	136	169	187	203	212 KS		
3206	138	169	191	208	223 KS		
Mean	130	161	185	203	214		
S.D.	5.9	7.9	9.8	13.4	14.4		
N	6	6	6	6	6		

KS : Killed on schedule

Appendix 2 - F - 5

Study No. BMR143C

Body weight - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg

Unit : g

Animal Number	Weeks after commencement/ cessation of treatment						
	0	1	2	3	4	5/1	6/2
4201	131	160	174	179	178 KS		
4202	130	156	169	180	194 KS		
4203	127	151	172	186	194 KS		
4204	136	168	184	179	204 KS		
4205	133	162	173	177	181 KS		
4206	135	159	172	182	191 KS		
4207	129	157	167	162	175	194	201 KS
4208	128	144	158	161	169	188	199 KS
4209	131	160	177	181	190	196	208 KS
4210	129	159	171	169	168	183	193 KS
4211	122	149	159	175	186	197	213 KS
4212	134	167	175	179	187	212	234 KS
Mean	130	158	171	176	185	195	208
S.D.	3.9	7.0	7.2	7.8	10.9	9.9	14.5
N	12	12	12	12	12	6	6

KS : Killed on schedule

Appendix 3 - M - 1

Study No. BMR143C

Food consumption - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	17.8	20.4	18.6	16.3	NA	
2	17.0	19.2	19.6	18.8	NA	
3	16.9	19.6	19.6	17.4	NA	
4	17.4	19.1	17.6	15.0	20.6	22.3
5	16.1	18.5	19.2	17.1	23.1	23.8
6	15.5	17.7	18.5	16.4	21.6	23.0
Mean	16.8	19.1	18.9	16.8	21.8	23.0
S.D.	0.85	0.92	0.77	1.27	1.26	0.75
N	6	6	6	6	3	3

NA : No animal existed.

Appendix 3 - M - 2

Study No. BMR143C

Food consumption - Individual values

Sex : Male

Dose level : Sample D-1 0.1 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	17.8	20.2	19.5	18.1	NA	
2	16.8	18.9	17.6	16.7	NA	
3	19.3	22.6	23.4	21.6	NA	
Mean	18.0	20.6	20.2	18.8		
S.D.	1.26	1.88	2.96	2.52		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - M - 3

Study No. BMR143C

Food consumption - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	16.3	18.8	18.1	17.3	NA	
2	16.9	19.1	17.1	16.6	NA	
3	17.8	19.9	19.1	17.9	NA	
Mean	17.0	19.3	18.1	17.3		
S.D.	0.75	0.57	1.00	0.65		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - M - 4

Study No. BMR143C

Food consumption - Individual values

Sex : Male

Dose level : Sample D-1 10 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	15.7	17.1	16.9	15.9	NA	
2	16.0	17.6	19.1	16.7	NA	
3	18.0	20.1	22.4	20.8	NA	
Mean	16.6	18.3	19.5	17.8		
S.D.	1.25	1.61	2.77	2.63		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - M - 5

Study No. BMR143C

Food consumption - Individual values

Sex : Male

Dose level : Sample D-1 30 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment					
	1	2	3	4	5/1	6/2
1	14.8	14.9	14.7	12.8	NA	
2	15.8	16.3	15.6	12.8	NA	
3	15.8	16.4	15.3	11.7	NA	
4	15.1	15.2	15.6	13.7	17.8	20.2
5	14.5	15.4	15.0	12.5	22.7	19.7
6	16.4	16.4	15.4	12.8	20.6	23.6
Mean	15.4	15.8	15.3	12.7	20.4	21.2
S.D.	0.72	0.68	0.36	0.64	2.46	2.12
N	6	6	6	6	3	3

NA : No animal existed.

Appendix 3 - F - 1

Study No. BMR143C

Food consumption - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	12.4	12.1	12.3	11.2	NA	
2	14.7	13.6	15.1	13.8	NA	
3	12.6	11.4	12.4	10.8	NA	
4	14.8	14.9	15.6	14.3	19.6	20.4
5	14.9	14.3	15.1	13.3	19.2	20.0
6	13.4	12.4	13.1	12.9	19.4	19.7
Mean	13.8	13.1	13.9	12.7	19.4	20.0
S.D.	1.15	1.36	1.50	1.42	0.20	0.35
N	6	6	6	6	3	3

NA : No animal existed.

Appendix 3 - F - 2

Study No. BMR143C

Food consumption - Individual values

Sex : Female

Dose level : Sample D-1 0.1 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	13.3	11.8	12.1	11.4	NA	
2	14.1	13.4	14.9	13.6	NA	
3	13.6	12.7	13.1	12.1	NA	
Mean	13.7	12.6	13.4	12.4		
S.D.	0.40	0.80	1.42	1.12		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - F - 3

Study No. BMR143C

Food consumption - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	11.6	10.5	11.7	11.0	NA	
2	14.1	12.9	13.1	12.2	NA	
3	16.3	13.4	13.8	12.5	NA	
Mean	14.0	12.3	12.9	11.9		
S.D.	2.35	1.55	1.07	0.79		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - F - 4

Study No. BMR143C

Food consumption - Individual values

Sex : Female

Dose level : Sample D-1 10 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment					
	1	2	3	4	5/1	6/2
1	12.6	11.9	11.2	9.6	NA	
2	11.6	10.6	10.4	9.4	NA	
3	13.8	12.1	11.9	10.1	NA	
Mean	12.7	11.5	11.2	9.7		
S.D.	1.10	0.81	0.75	0.36		
N	3	3	3	3		

NA : No animal existed.

Appendix 3 - F - 5

Study No. BMR143C

Food consumption - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg

Unit : g/Animal/Day

Cage Number	Weeks after commencement/ cessation of treatment 1	2	3	4	5/1	6/2
1	12.0	9.6	7.9	6.9	NA	
2	13.4	11.3	8.5	9.6	NA	
3	13.4	10.6	9.0	8.6	NA	
4	11.9	9.8	6.6	8.5	14.1	14.6
5	13.7	10.7	7.9	6.8	12.9	13.9
6	13.2	9.5	8.4	7.6	15.9	17.6
Mean	12.9	10.3	8.1	8.0	14.3	15.4
S.D.	0.78	0.72	0.82	1.09	1.51	1.97
N	6	6	6	6	3	3

NA : No animal existed.

Appendix 4 - M - 1

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0101	774	14.6	50.5	65	18.9	28.9	84.8	13.8	14.7	26
0102	780	13.8	50.6	65	17.7	27.3	104.6	14.1	16.1	29
0103	681	13.7	44.4	65	20.1	30.9	102.6	14.1	17.0	18
0104	775	14.6	45.6	59	18.8	32.0	115.4	13.8	16.7	27
0105	695	14.2	47.3	68	20.4	30.0	88.2	14.9	15.8	28
0106	705	14.0	45.6	65	19.9	30.7	83.7	15.2	18.1	26
Mean	735	14.2	47.3	65	19.3	30.0	96.6	14.3	16.4	26
S.D.	46.0	0.39	2.66	2.9	1.02	1.66	12.88	0.59	1.16	3.9
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - M - 2

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
1101	765	14.1	52.2	68	18.4	27.0	106.1	14.9	15.5	26
1102	683	13.9	46.0	67	20.4	30.2	78.2	13.9	15.7	26
1103	689	13.9	45.4	66	20.2	30.6	88.3	13.9	15.4	21
1104	675	13.8	44.8	66	20.4	30.8	91.0	14.0	16.4	33
1105	679	14.3	46.1	68	21.1	31.0	94.7	13.8	19.4	32
1106	696	14.1	45.6	66	20.3	30.9	104.7	13.7	17.6	35
Mean	698	14.0	46.7	67	20.1	30.1	93.8	14.0	16.7	29
S.D.	33.7	0.18	2.74	1.0	0.91	1.54	10.51	0.44	1.57	5.3
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - M - 3

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
2101	681	13.2	42.3	62	19.4	31.2	97.4	13.9	13.0	27
2102	733	14.0	46.3	63	19.1	30.2	92.1	14.2	14.7	25
2103	794	14.1	51.9	65	17.8	27.2	134.7	14.1	15.8	30
2104	764	14.3	47.7	62	18.7	30.0	112.7	14.1	16.7	30
2105	719	13.8	46.2	64	19.2	29.9	105.4	14.4	17.6	26
2106	728	14.4	49.0	67	19.8	29.4	79.8	13.5	15.4	27
Mean	737	14.0	47.2	64	19.0	29.7	103.7	14.0	15.5	28
S.D.	38.8	0.43	3.21	1.9	0.69	1.34	18.92	0.31	1.60	2.1
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - M - 4

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
3101	681	12.8	43.4	64	18.8	29.5	97.5	14.4	14.8	25
3102	714	13.6	45.1	63	19.0	30.2	111.8	13.9	14.4	30
3103	737	13.5	49.6	67	18.3	27.2	84.3	13.6	14.7	23
3104	756	13.3	45.4	60	17.6	29.3	115.5	13.8	17.2	31
3105	713	13.7	46.2	65	19.2	29.7	100.9	14.0	17.1	34
3106	766	13.2	47.6	62	17.2	27.7	111.9	13.6	15.1	19
Mean	728	13.4	46.2	64	18.4	28.9	103.7	13.9	15.6	27
S.D.	31.4	0.33	2.15	2.4	0.80	1.20	11.79	0.30	1.26	5.6
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - M - 5

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
4101	647	13.1	44.1	68	20.2	29.7	92.1	14.4	15.0	14
4102	665	12.5	43.8	66	18.8	28.5	88.1	14.8	20.4	21
4103	702	13.0	45.9	65	18.5	28.3	96.0	14.6	15.7	22
4104	725	12.9	48.4	67	17.8	26.7	96.3	14.2	18.4	14
4105	667	13.6	43.0	64	20.4	31.6	78.0	14.0	20.2	21
4106	792	14.9	51.6	65	18.8	28.9	89.1	14.2	19.1	27
Mean	700	13.3	46.1	66	19.1	29.0	89.9	14.4	18.1	20
S.D.	53.3	0.85	3.30	1.5	1.01	1.63	6.76	0.29	2.29	5.0
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - M - 6

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0107	790	14.5	45.0	57	18.4	32.2	71.4	13.8	17.3	22
0108	728	13.4	40.4	55	18.4	33.2	97.0	14.0	16.2	30
0109	798	14.2	46.6	58	17.8	30.5	71.0	13.8	15.3	22
0110	896	14.3	48.2	54	16.0	29.7	97.6	13.8	15.9	24
0111	784	13.8	45.2	58	17.6	30.5	80.2	CL	CL	20
0112	791	14.1	47.7	60	17.8	29.6	113.1	13.7	15.5	32
Mean	798	14.1	45.5	57	17.7	31.0	88.4	13.8	16.0	25
S.D.	54.4	0.39	2.82	2.2	0.88	1.44	16.90	0.11	0.79	4.9
N	6	6	6	6	6	6	6	5	5	6

CL : Not measured because clotting.

Appendix 4 - M - 7

Study No. BMR143C

Hematology - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
4107	743	12.7	43.8	59	17.1	29.0	82.8	13.3	14.2	31
4108	688	11.9	39.6	58	17.3	30.1	112.7	13.7	14.3	34
4109	D									
4110	718	12.5	41.5	58	17.4	30.1	96.0	13.7	15.8	22
4111	703	13.2	42.7	61	18.8	30.9	88.6	12.6	14.6	31
4112	735	13.0	40.5	55	17.7	32.1	97.4	13.6	17.2	39
Mean	717	12.7	41.6	58	17.7	30.4	95.5	13.4	15.2	31
S.D.	22.6	0.50	1.68	2.2	0.67	1.15	11.28	0.47	1.28	6.2
N	5	5	5	5	5	5	5	5	5	5

D : Dead.

Appendix 4 - F - 1

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
0201	720	13.2	44.5	62	18.3	29.7	117.7	14.3	15.9	22
0202	777	13.7	46.3	60	17.6	29.6	142.0	14.4	13.6	24
0203	658	13.3	40.6	62	20.2	32.8	95.2	14.6	11.8	26
0204	635	12.6	37.6	59	19.8	33.5	107.5	14.2	12.9	18
0205	727	13.4	41.8	57	18.4	32.1	120.4	14.0	15.9	19
0206	714	13.8	45.7	64	19.3	30.2	111.4	14.3	14.1	24
Mean	705	13.3	42.8	61	18.9	31.3	115.7	14.3	14.0	22
S.D.	51.2	0.43	3.36	2.5	1.00	1.70	15.64	0.20	1.64	3.1
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - F - 2

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
1201	720	13.5	40.7	57	18.8	33.2	101.4	14.7	17.0	24
1202	693	13.5	40.8	59	19.5	33.1	97.6	14.5	14.5	18
1203	644	13.4	42.6	66	20.8	31.5	124.0	14.5	15.1	26
1204	699	13.9	41.3	59	19.9	33.7	87.7	13.4	14.0	21
1205	698	13.7	42.3	61	19.6	32.4	99.1	14.2	14.4	20
1206	693	13.5	44.4	64	19.5	30.4	108.6	14.2	13.7	22
Mean	691	13.6	42.0	61	19.7	32.4	103.1	14.3	14.8	22
S.D.	25.2	0.18	1.40	3.4	0.66	1.24	12.27	0.46	1.19	2.9
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - F - 3

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($x10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($x10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
2201	726	13.7	42.6	59	18.9	32.2	106.3	13.9	13.1	22
2202	708	12.9	40.6	57	18.2	31.8	115.6	14.2	16.8	25
2203	724	13.5	44.0	61	18.6	30.7	113.6	14.8	15.1	21
2204	634	13.2	40.7	64	20.8	32.4	111.1	13.2	14.7	24
2205	768	13.1	41.3	61	19.3	31.7	102.7	14.4	17.1	21
2206	643	13.3	38.8	60	20.7	34.3	97.9	14.6	17.3	18
Mean	701	13.3	41.3	60	19.4	32.2	107.9	14.2	15.7	22
S.D.	52.0	0.29	1.79	2.3	1.09	1.19	6.81	0.57	1.66	2.5
N	6	6	6	6	6	6	6	6	6	6

Appendix 4 - F - 4

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	RBC count ($\times 10^4/mm^3$)	HB conc. (g/dl)	Ht (%)	MCV (μm^3)	MCH (pg)	MCHC (%)	Platelet count ($\times 10^4/mm^3$)	PT (sec)	APTT (sec)	Reticulocyte count (‰)
3201	685	14.0	44.0	64	20.4	31.8	88.0	14.3	15.3	22
3202	759	13.5	43.4	57	17.8	31.1	111.0	14.2	14.0	21
3203	764	14.1	47.4	62	18.5	29.7	123.3	14.1	15.2	25
3204	700	13.4	41.0	59	19.1	32.7	93.7	13.5	14.3	20
3205	693	13.5	43.4	63	19.5	31.1	117.7	13.5	15.4	19
3206	695	13.9	43.8	63	20.0	31.7	101.9	14.5	16.8	20
Mean	716	13.7	43.8	61	19.2	31.4	105.9	14.0	15.2	21
S.D.	35.6	0.30	2.06	2.7	0.96	1.00	13.81	0.42	0.99	2.1
N	6	6	6	6	6	6	6	6	6	6

Appendix 5 - F - 3

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
2201	57	86	9	1	0	0	4
2202	94	92	7	0	0	0	1
2203	108	87	10	0	1	0	2
2204	112	81	15	0	1	0	3
2205	77	86	13	0	0	0	1
2206	70	93	5	1	0	0	1
Mean	86	88	10	0	0	0	2
S.D.	21.9	4.4	3.7	0.5	0.5	0.0	1.3
N	6	6	6	6	6	6	6

Appendix 5 - F - 4

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
3201	117	92	4	1	0	0	3
3202	103	87	6	0	0	0	7
3203	61	90	6	0	0	0	4
3204	67	89	6	0	1	0	4
3205	89	92	2	0	0	0	6
3206	70	84	8	0	1	0	7
Mean	85	89	5	0	0	0	5
S.D.	22.3	3.1	2.1	0.4	0.5	0.0	1.7
N	6	6	6	6	6	6	6

Appendix 5 - F - 5

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Band	Eosino-phils	Baso-phils	Mono-cytes
4201	78	89	6	0	0	0	5
4202	66	83	7	1	0	0	9
4203	83	89	7	0	0	0	4
4204	104	87	7	0	1	0	5
4205	60	92	5	0	0	0	3
4206	71	80	18	0	0	0	2
Mean	77	87	8	0	0	0	5
S.D.	15.6	4.4	4.8	0.4	0.4	0.0	2.4
N	6	6	6	6	6	6	6

Appendix 5 - F - 6

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Neutrophils Band	Eosino-phils	Baso-phils	Mono-cytes
0207	69	82	4	1	2	0	11
0208	92	94	2	0	0	0	4
0209	54	87	9	0	0	0	4
0210	114	82	13	0	0	0	5
0211	72	91	7	0	0	0	2
0212	109	77	16	0	3	0	4
Mean	85	86	9	0	1	0	5
S.D.	23.9	6.3	5.3	0.4	1.3	0.0	3.1
N	6	6	6	6	6	6	6

Appendix 5 - F - 7

Study No. BMR143C

Hematology - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	WBC count ($x10^2/mm^3$)	Differential count of leukocytes (% of total counted cells) Lympho-cytes	Neutrophils Segmented	Band	Eosino-phils	Baso-phils	Mono-cytes
4207	105	92	3	1	0	0	4
4208	104	88	6	0	0	0	6
4209	84	88	5	0	1	0	6
4210	76	93	4	0	0	0	3
4211	88	91	8	0	0	0	1
4212	57	93	2	0	0	0	5
Mean	86	91	5	0	0	0	4
S.D.	18.1	2.3	2.2	0.4	0.4	0.0	1.9
N	6	6	6	6	6	6	6

Appendix G - M - 1

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
0101	80	37	0	739	11.2	0.5	134	57	59
0102	70	26	0	667	13.4	0.5	129	52	37
0103	60	33	0	859	14.8	0.5	153	58	81
0104	64	26	0	642	12.2	0.5	138	67	32
0105	65	31	0	841	12.6	0.5	150	63	41
0106	71	26	0	518	10.2	0.5	137	48	43
Mean	68	30	0	711	12.4	0.5	140	58	49
S.D.	7.0	4.6	0.0	129.3	1.62	0.00	9.4	6.9	18.2
N	6	6	6	6	6	6	6	6	6

Appendix 6 - M - 2

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0101	6.36	4.07	1.78	9.5	9.4	142	4.0	103
0102	6.34	3.92	1.62	9.3	9.8	143	4.1	105
0103	6.63	4.00	1.52	10.6	10.8	143	4.1	101
0104	6.68	4.04	1.53	9.6	10.0	142	4.2	99
0105	6.27	3.75	1.49	9.9	11.2	142	4.0	100
0106	6.78	4.08	1.51	9.9	9.7	142	4.1	101
Mean	6.51	3.98	1.58	9.8	10.2	142	4.1	102
S.D.	0.212	0.125	0.110	0.46	0.70	0.5	0.08	2.2
N	6	6	6	6	6	6	6	6

Appendix 6 - M - 3

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
1101	65	29	0	822	11.8	0.4	136	62	71
1102	77	31	0	666	13.2	0.5	138	58	59
1103	69	38	0	713	10.1	0.4	157	59	41
1104	61	26	0	577	11.5	0.4	149	57	61
1105	66	30	0	618	10.4	0.5	159	53	56
1106	50	23	0	666	6.8	0.5	159	53	41
Mean	65	30	0	677	10.6	0.5	150	57	55
S.D.	9.0	5.1	0.0	84.9	2.18	0.05	10.5	3.5	11.8
N	6	6	6	6	6	6	6	6	6

Appendix 6 - M - 4

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
1101	6.29	3.95	1.69	9.6	9.3	142	3.9	102
1102	6.67	4.16	1.66	9.9	9.0	142	4.1	103
1103	6.21	3.93	1.72	10.1	10.4	142	4.1	101
1104	6.31	3.90	1.62	9.8	8.8	142	4.0	101
1105	6.48	3.90	1.51	9.9	10.9	142	4.0	101
1106	6.33	3.89	1.59	9.3	8.4	141	4.0	101
Mean	6.38	3.96	1.63	9.8	9.5	142	4.0	102
S.D.	0.166	0.103	0.076	0.28	0.98	0.4	0.08	0.8
N	6	6	6	6	6	6	6	6

Appendix 6 - M - 5

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
2101	66	26	0	705	11.3	0.5	145	46	41
2102	87	36	0	923	11.1	0.5	129	56	43
2103	69	34	0	537	12.3	0.5	143	52	54
2104	67	33	0	806	12.6	0.5	136	44	39
2105	66	30	0	727	16.8	0.5	139	49	113
2106	70	25	0	703	15.5	0.4	148	48	72
Mean	71	31	0	734	13.3	0.5	140	49	60
S.D.	8.1	4.5	0.0	127.7	2.34	0.04	6.9	4.3	28.6
N	6	6	6	6	6	6	6	6	6

Appendix G - M - 6

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
2101	6.16	3.88	1.70	9.4	8.7	142	4.2	104
2102	6.36	3.92	1.61	9.8	9.0	141	4.4	103
2103	6.35	3.82	1.51	9.9	10.1	141	4.0	101
2104	6.07	3.93	1.84	9.8	10.3	142	4.0	103
2105	6.43	3.77	1.42	10.2	10.1	143	4.5	101
2106	5.95	3.74	1.69	9.4	8.9	141	4.2	103
Mean	6.22	3.84	1.63	9.8	9.5	142	4.2	103
S.D.	0.190	0.079	0.149	0.31	0.72	0.8	0.20	1.2
N	6	6	6	6	6	6	6	6

Appendix 6 - M - 7

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
3101	65	40	0	988	12.8	0.5	131	26	65
3102	66	33	0	755	14.8	0.5	142	35	30
3103	69	32	0	682	14.9	0.5	145	37	60
3104	58	34	0	797	11.0	0.4	145	29	17
3105	67	33	0	615	12.8	0.5	155	54	89
3106	62	31	0	841	8.1	0.4	132	49	25
Mean	65	34	0	780	12.4	0.5	142	38	48
S.D.	3.9	3.2	0.0	130.2	2.56	0.05	9.0	11.1	28.0
N	6	6	6	6	6	6	6	6	6

Appendix 6 - M - 8

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
3101	6.29	4.15	1.94	10.2	9.2	143	4.1	104
3102	6.05	3.84	1.74	9.9	10.8	143	4.8	104
3103	6.28	4.05	1.82	9.9	8.8	141	3.9	102
3104	6.16	3.94	1.77	9.7	8.9	142	4.2	105
3105	6.15	3.75	1.56	9.8	9.6	142	4.6	102
3106	6.29	3.87	1.60	9.3	8.5	141	4.3	105
Mean	6.20	3.93	1.74	9.8	9.3	142	4.3	104
S.D.	0.099	0.146	0.141	0.30	0.82	0.9	0.33	1.4
N	6	6	6	6	6	6	6	6

Appendix G - M - 9

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	r-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
4101	81	46	0	1639	15.1	0.6	139	10	15
4102	77	57	0	1243	15.8	0.5	144	9	13
4103	76	46	0	1036	13.7	0.5	127	12	22
4104	61	47	0	1179	10.4	0.5	140	6	15
4105	62	43	0	940	14.9	0.5	137	10	20
4106	83	78	0	1111	14.5	0.8	162	9	39
Mean	73	53	0	1191	14.1	0.6	142	9	21
S.D.	9.5	13.2	0.0	243.7	1.93	0.12	11.5	2.0	9.6
N	6	6	6	6	6	6	6	6	6

Appendix 6 - M - 10

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
4101	6.06	3.94	1.86	9.3	8.8	142	4.1	107
4102	5.87	3.97	2.09	9.1	8.3	142	4.1	104
4103	6.28	4.06	1.83	9.9	8.9	143	4.7	105
4104	5.45	3.91	2.54	8.8	9.0	144	3.7	107
4105	5.87	3.86	1.92	9.1	8.7	143	4.3	107
4106	6.51	4.32	1.97	10.2	16.2	147	4.5	105
Mean	6.01	4.01	2.04	9.4	10.0	144	4.2	106
S.D.	0.368	0.166	0.264	0.54	3.06	1.9	0.35	1.3
N	6	6	6	6	6	6	6	6

Appendix 6 - M - 11

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
0107	85	28	0	718	22.6	0.5	145	44	144
0108	77	30	0	578	19.9	0.5	152	52	72
0109	80	37	0	621	16.0	0.5	158	77	135
0110	110	36	0	542	16.4	0.4	144	40	39
0111	76	40	0	652	18.6	0.5	145	41	76
0112	81	33	0	564	18.6	0.4	143	43	43
Mean	85	34	0	613	18.7	0.5	148	50	85
S.D.	12.7	4.5	0.0	65.2	2.42	0.05	5.9	14.1	45.0
N	6	6	6	6	6	6	6	6	6

Appendix 6 - M - 12

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0107	6.43	3.82	1.46	10.0	8.7	143	4.0	105
0108	6.23	3.77	1.53	9.7	8.8	142	4.3	105
0109	6.59	3.89	1.44	9.8	8.6	140	4.5	104
0110	6.65	3.90	1.42	9.4	9.0	142	4.2	104
0111	6.34	3.91	1.61	9.3	8.6	142	3.8	105
0112	6.30	3.82	1.54	9.4	8.5	139	4.5	101
Mean	6.42	3.85	1.50	9.6	8.7	141	4.2	104
S.D.	0.167	0.056	0.072	0.28	0.18	1.5	0.28	1.5
N	6	6	6	6	6	6	6	6

Appendix 6 - M - 13

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
4107	78	36	0	792	24.4	0.4	141	22	14
4108	86	42	0	852	21.7	0.5	171	28	15
4109	D								
4110	74	37	0	681	26.1	0.6	159	19	9
4111	71	44	0	671	19.6	0.5	141	48	8
4112	70	61	0	586	17.1	0.4	150	27	5
Mean	76	44	0	716	21.8	0.5	152	29	10
S.D.	6.5	10.1	0.0	105.4	3.61	0.08	12.8	11.3	4.2
N	5	5	5	5	5	5	5	5	5

D : Dead.

Appendix 6 - M - 14

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
4107	6.08	3.80	1.67	9.7	8.3	143	4.1	109
4108	6.81	4.13	1.54	9.8	9.4	141	4.5	108
4109	D							
4110	6.70	4.24	1.72	9.8	9.4	140	4.1	103
4111	6.70	4.25	1.73	9.7	9.4	142	4.3	104
4112	6.57	4.26	1.84	9.6	8.2	142	4.0	106
Mean	6.57	4.14	1.70	9.7	8.9	142	4.2	106
S.D.	0.288	0.195	0.109	0.08	0.63	1.1	0.20	2.5
N	5	5	5	5	5	5	5	5

D : Dead.

Appendix 6 - F - 1

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
0201	75	20	0	364	11.3	0.5	137	48	22
0202	67	26	0	431	10.7	0.6	130	74	29
0203	87	25	0	534	14.2	0.5	143	54	22
0204	79	25	1	473	12.1	0.5	131	53	20
0205	88	23	0	525	12.4	0.5	137	69	21
0206	83	17	0	507	10.7	0.5	121	52	32
Mean	80	23	0	472	11.9	0.5	133	58	24
S.D.	8.0	3.5	0.4	65.2	1.33	0.04	7.6	10.5	4.9
N	6	6	6	6	6	6	6	6	6

Appendix 6 - F - 2

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0201	6.52	4.23	1.85	9.1	7.4	141	4.1	104
0202	6.87	4.24	1.61	9.5	7.0	143	3.8	104
0203	6.63	4.20	1.73	9.4	8.0	141	3.7	104
0204	6.38	4.08	1.77	9.5	9.4	141	4.1	104
0205	6.76	4.15	1.59	9.4	9.2	141	4.3	103
0206	6.62	4.20	1.74	9.5	9.5	141	4.4	103
Mean	6.63	4.18	1.72	9.4	8.4	141	4.1	104
S.D.	0.173	0.060	0.099	0.15	1.09	0.8	0.27	0.5
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 3

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
1201	74	32	0	409	17.0	0.7	126	55	24
1202	64	23	0	504	10.6	0.5	140	56	24
1203	64	25	0	362	16.7	0.5	136	58	36
1204	76	29	0	540	14.9	0.5	182	59	43
1205	71	19	0	366	9.9	0.5	120	67	17
1206	68	22	0	331	9.9	0.6	134	48	26
Mean	70	25	0	419	13.2	0.6	140	57	28
S.D.	5.0	4.8	0.0	84.6	3.41	0.08	22.0	6.2	9.4
N	6	6	6	6	6	6	6	6	6

Appendix 6 - F - 4

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
1201	6.85	4.39	1.78	9.9	9.9	141	3.9	102
1202	6.08	3.94	1.84	9.1	8.9	142	4.3	105
1203	6.61	4.19	1.73	10.1	9.9	140	4.4	102
1204	6.46	4.16	1.81	10.8	11.4	142	5.5	102
1205	6.63	4.14	1.66	9.6	9.5	140	4.7	101
1206	7.00	4.30	1.59	9.5	8.5	141	4.0	102
Mean	6.61	4.19	1.74	9.8	9.7	141	4.5	102
S.D.	0.320	0.154	0.095	0.59	1.01	0.9	0.58	1.4
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 5

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
2201	62	20	0	491	17.7	0.5	156	69	32
2202	66	16	1	504	14.1	0.5	148	57	32
2203	65	20	0	534	13.0	0.4	133	59	32
2204	67	22	0	377	13.6	0.6	136	54	35
2205	51	23	0	342	10.6	0.5	142	58	33
2206	51	16	0	372	9.5	0.5	142	58	18
Mean	60	20	0	437	13.1	0.5	143	59	30
S.D.	7.4	2.9	0.4	82.1	2.89	0.06	8.3	5.1	6.2
N	6	6	6	6	6	6	6	6	6

Appendix G - F - 6

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
2201	6.48	4.17	1.81	9.6	8.5	140	4.4	102
2202	6.08	4.11	2.09	9.9	8.8	143	5.2	106
2203	6.02	4.01	2.00	9.5	9.3	141	4.4	104
2204	6.86	4.38	1.77	9.8	8.7	140	4.0	103
2205	6.68	4.11	1.60	9.5	8.4	142	3.8	103
2206	6.58	4.11	1.66	9.5	8.7	142	4.4	107
Mean	6.45	4.15	1.82	9.6	8.7	141	4.4	104
S.D.	0.335	0.125	0.191	0.18	0.31	1.2	0.48	1.9
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 7

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
3201	65	24	0	567	17.4	0.6	122	36	21
3202	52	21	0	361	11.1	0.5	149	58	19
3203	66	27	0	531	13.7	0.5	148	46	25
3204	79	28	0	429	14.0	0.5	136	44	17
3205	50	24	0	382	14.7	0.5	126	48	23
3206	46	20	0	436	10.2	0.5	127	56	23
Mean	60	24	0	451	13.5	0.5	135	48	21
S.D.	12.5	3.2	0.0	81.8	2.59	0.04	11.7	8.1	2.9
N	6	6	6	6	6	6	6	6	6

Appendix 6 - F - 8

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
3201	6.68	4.35	1.87	9.6	7.0	141	3.7	105
3202	6.84	4.34	1.74	9.2	7.6	140	3.9	106
3203	7.14	4.52	1.73	10.2	7.9	143	4.8	107
3204	6.58	4.24	1.81	9.5	8.0	141	4.5	105
3205	7.21	4.64	1.81	9.9	9.2	144	3.7	104
3206	7.03	4.40	1.67	9.5	7.6	142	4.2	107
Mean	6.91	4.42	1.77	9.7	7.9	142	4.1	106
S.D.	0.255	0.143	0.072	0.35	0.73	1.5	0.45	1.2
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 9

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
4201	62	40	0	826	14.3	0.6	152	24	23
4202	55	31	0	609	20.9	0.6	125	23	15
4203	57	31	0	593	19.8	0.5	111	34	19
4204	55	36	0	717	13.7	0.5	119	21	15
4205	50	29	0	404	21.8	0.5	116	20	27
4206	59	48	0	392	17.3	0.5	135	27	20
Mean	56	36	0	590	18.0	0.5	126	25	20
S.D.	4.1	7.2	0.0	170.9	3.43	0.05	15.0	5.1	4.7
N	6	6	6	6	6	6	6	6	6

Appendix 6 - F - 10

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
4201	7.17	4.61	1.80	9.5	7.0	143	4.4	108
4202	7.32	4.68	1.77	10.0	8.9	142	4.7	107
4203	6.88	4.53	1.93	9.9	9.1	142	4.2	105
4204	6.64	4.36	1.91	9.7	9.3	140	5.5	107
4205	6.67	4.56	2.16	9.5	7.9	143	4.4	107
4206	7.39	4.77	1.82	10.8	9.3	142	6.0	104
Mean	7.01	4.59	1.90	9.9	8.6	142	4.9	106
S.D.	0.327	0.140	0.143	0.49	0.93	1.1	0.72	1.5
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 11

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Trigly-ceride (mg/dl)
0207	57	24	0	266	18.0	0.6	152	76	104
0208	75	30	0	273	19.9	0.6	154	56	65
0209	71	22	0	411	15.0	0.6	149	65	29
0210	66	28	0	283	20.6	0.6	141	66	35
0211	78	29	0	393	14.9	0.5	144	54	26
0212	81	44	0	313	15.5	0.5	160	48	28
Mean	71	30	0	323	17.3	0.6	150	61	48
S.D.	8.8	7.7	0.0	63.4	2.55	0.05	6.9	10.1	31.1
N	6	6	6	6	6	6	6	6	6

Appendix 6 - F - 12

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0207	7.00	4.35	1.64	9.8	7.1	140	4.1	104
0208	7.26	4.41	1.55	9.7	6.7	140	4.0	107
0209	7.01	4.42	1.71	9.5	7.9	141	4.2	106
0210	7.18	4.38	1.56	9.6	6.8	140	4.2	105
0211	6.47	4.05	1.67	9.4	7.9	140	4.0	106
0212	7.17	4.40	1.59	9.8	7.6	139	3.9	104
Mean	7.02	4.34	1.62	9.6	7.3	140	4.1	105
S.D.	0.286	0.142	0.064	0.16	0.54	0.6	0.12	1.2
N	6	6	6	6	6	6	6	6

Appendix 6 - F - 13

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	GOT (IU/l)	GPT (IU/l)	γ-GTP (IU/l)	ALP (IU/l)	Urea nitrogen (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)	Total chol. (mg/dl)	Triglyceride (mg/dl)
4207	62	41	0	404	29.2	0.6	132	47	15
4208	53	29	0	347	22.5	0.6	141	46	22
4209	47	25	0	363	22.6	0.5	123	53	18
4210	78	25	0	486	26.2	0.6	117	62	17
4211	64	28	0	353	22.2	0.6	116	42	17
4212	62	31	0	369	21.7	0.6	129	55	16
Mean	61	30	0	387	24.1	0.6	126	51	18
S.D.	10.6	5.9	0.0	52.4	2.99	0.04	9.6	7.3	2.4
N	6	6	6	6	6	6	6	6	6

Appendix G - F - 14

Study No. BMR143C

Clinical chemistry - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	Total protein (g/dl)	Albumin (g/dl)	A/G ratio	Calcium (mg/dl)	Inorganic phos. (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
4207	7.63	4.72	1.62	10.2	8.2	141	4.7	105
4208	7.51	4.85	1.82	10.4	7.9	141	3.9	107
4209	7.24	4.55	1.69	10.4	7.7	141	4.1	105
4210	8.18	4.99	1.56	10.3	8.1	141	3.9	104
4211	7.12	4.43	1.65	9.9	8.6	141	4.2	106
4212	7.34	4.79	1.88	10.1	8.2	142	4.8	105
Mean	7.50	4.72	1.70	10.2	8.1	141	4.3	105
S.D.	0.379	0.204	0.123	0.19	0.31	0.4	0.39	1.0
N	6	6	6	6	6	6	6	6

Appendix 7 - M - 1

Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
0101	0.1	-	-	5	-	30	7.0
0102	0.1	-	-	5	-	30	8.0
0103	0.1	-	-	15	-	30	7.5
0104	0.1	-	-	5	-	30	8.0
0105	0.1	-	-	5	-	30	7.0
0106	0.1	-	-	5	-	Trace	8.0
0107	0.1	-	-	5	-	30	8.0
0108	0.1	+++	-	5	-	30	7.0
0109	0.1	Trace	-	-	-	30	8.0
0110	0.1	Trace	-	5	-	30	6.0
0111	0.1	-	-	5	-	Trace	7.0
0112	0.1	-	-	5	-	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 2

Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
1101	0.1	-	-	5	-	30	7.5
1102	0.1	-	-	5	-	30	8.0
1103	0.1	-	-	15	-	30	8.0
1104	0.1	Trace	-	5	-	30	7.5
1105	0.1	-	-	40	-	30	8.0
1106	0.1	-	-	5	-	100	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 3

Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
2101	0.1	-	-	15	-	30	8.0
2102	0.1	-	-	5	-	30	8.5
2103	0.1	-	-	5	-	30	8.0
2104	0.1	-	-	5	-	100	8.5
2105	0.1	Trace	-	5	-	100	8.0
2106	0.1	-	-	5	-	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 4

Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
3101	0.1	-	-	5	-	30	8.0
3102	0.1	-	-	5	-	30	7.5
3103	0.1	-	-	5	-	100	8.0
3104	0.1	-	-	5	-	30	8.0
3105	0.1	-	-	5	-	100	8.0
3106	0.1	-	-	5	-	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 5

Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
4101	0.1	-	-	15	-	30	7.5
4102	0.1	-	-	5	-	100	8.0
4103	0.1	-	-	40	-	30	7.5
4104	0.1	-	-	5	-	30	7.0
4105	0.1	-	-	5	-	30	7.0
4106	0.1	-	-	5	-	Trace	6.0
4107	0.1	-	-	5	-	30	7.5
4108	0.1	-	-	5	-	30	7.5
4109	0.1	-	-	15	-	30	6.5
4110	0.1	-	-	5	-	30	7.0
4111	0.1	-	-	40	-	100	7.0
4112	0.1	-	-	5	-	30	6.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 6 Study No. BMR143C

Urinalysis - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
5 weeks after commencement of treatment (Recovery)

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
0107	0.1	-	-	5	-	Trace	8.0
0108	0.1	Trace	-	5	-	30	7.5
0109	0.1	Trace	-	-	-	30	8.0
0110	0.1	-	-	5	-	Trace	7.0
0111	0.1	Trace	-	5	-	30	7.5
0112	0.1	Trace	-	5	-	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - M - 7 Study No. BMR143C

Urinalysis - Individual values

Sex : Male

Dose level : Sample D-1 30 mg/kg

5 weeks after commencement of treatment (Recovery)

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
4107	0.1	-	-	5	-	30	7.0
4108	0.1	++	-	5	-	30	7.0
4109	D						
4110	0.1	-	-	5	-	30	6.5
4111	0.1	-	-	5	-	30	6.5
4112	0.1	-	-	5	-	30	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

D : Dead.

Appendix 7 - F - 1

Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
0201	0.1	-	-	5	-	30	8.0
0202	0.1	-	-	-	-	30	6.5
0203	0.1	-	-	-	-	30	8.5
0204	0.1	-	-	-	-	30	8.0
0205	0.1	-	-	-	-	30	8.0
0206	0.1	-	-	5	-	30	8.0
0207	0.1	-	-	5	-	30	7.0
0208	0.1	-	-	-	-	30	7.5
0209	0.1	Trace	-	-	-	Trace	7.5
0210	0.1	-	-	-	-	30	7.0
0211	0.1	-	-	-	-	30	7.5
0212	0.1	Trace	-	-	-	Trace	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 2

Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 0.1 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobili-nogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
1201	0.1	Trace	-	-	-	30	8.5
1202	0.1	-	-	-	-	Trace	8.5
1203	0.1	-	-	-	-	30	7.5
1204	0.1	Trace	-	-	-	30	8.0
1205	0.1	-	-	-	-	Trace	8.0
1206	0.1	-	-	5	-	30	8.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 3 Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
2201	0.1	-	-	-	-	30	8.0
2202	0.1	Trace	-	5	-	30	8.0
2203	0.1	Trace	-	-	-	Trace	7.5
2204	0.1	-	-	5	-	30	7.5
2205	0.1	+	-	5	-	30	7.5
2206	0.1	+	-	5	-	30	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 4 Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
3201	0.1	-	-	-	-	30	8.5
3202	0.1	-	-	-	-	Trace	8.0
3203	0.1	-	-	5	-	Trace	6.5
3204	0.1	Trace	-	5	-	30	8.0
3205	0.1	-	-	-	-	30	7.0
3206	0.1	-	-	5	-	30	7.5

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 5

Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
3 weeks after commencement of treatment

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
4201	0.1	+	-	-	-	Trace	7.0
4202	0.1	-	-	-	-	Trace	7.0
4203	0.1	-	-	5	-	30	6.5
4204	0.1	-	-	-	-	-	7.0
4205	0.1	-	-	-	-	30	7.5
4206	0.1	Trace	-	-	-	30	6.0
4207	0.1	Trace	-	-	-	-	6.0
4208	0.1	+	-	-	-	Trace	6.0
4209	0.1	-	-	5	-	Trace	7.0
4210	0.1	-	-	-	-	30	7.0
4211	0.1	-	-	-	-	-	7.5
4212	0.1	Trace	-	-	-	Trace	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 6

Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
5 weeks after commencement of treatment (Recovery)

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
0207	0.1	Trace	-	-	-	Trace	8.0
0208	0.1	-	-	-	-	30	8.0
0209	0.1	++	-	-	-	-	7.5
0210	0.1	-	-	-	-	Trace	7.5
0211	0.1	-	-	-	-	Trace	8.0
0212	0.1	Trace	-	-	-	30	7.0

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 7 - F - 7

Study No. BMR143C

Urinalysis - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
5 weeks after commencement of treatment (Recovery)

Animal Number	Urobilinogen (EU/dl)	Occult Blood	Bilirubin	Ketone bodies (mg/dl)	Glucose (g/dl)	Protein (mg/dl)	pH
4207	0.1	Trace	-	-	-	30	6.5
4208	0.1	Trace	-	-	-	Trace	7.0
4209	0.1	Trace	-	-	-	Trace	7.0
4210	0.1	-	-	-	-	30	7.0
4211	0.1	Trace	-	-	-	Trace	8.0
4212	0.1	-	-	-	-	Trace	7.5

- : Negative, + : Slight, ++ : Moderate, +++ : Severe

Appendix 8 - M - 1

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0101	354	1.90	13.07	2.38	51.2	3.01
0102	318	2.00	12.17	2.16	53.1	3.23
0103	334	1.77	13.50	2.45	47.5	2.54
0104	352	1.95	12.92	2.45	54.4	3.07
0105	377	2.03	14.52	2.50	46.1	3.24
0106	370	2.11	15.42	2.63	50.4	2.84
Mean	351	1.96	13.60	2.43	50.5	2.99
S.D.	22.0	0.117	1.180	0.156	3.19	0.265
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 2

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
1101	375	2.06	16.05	2.75	52.2	2.92
1102	321	2.13	13.25	2.19	55.6	2.92
1103	362	1.90	13.55	2.60	50.4	3.20
1104	321	1.94	13.52	2.27	63.4	3.18
1105	376	1.92	15.24	2.71	53.9	3.17
1106	399	1.92	15.37	2.78	50.3	3.44
Mean	359	1.98	14.50	2.55	54.3	3.14
S.D.	31.8	0.094	1.194	0.257	4.90	0.196
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 3

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
2101	346	1.99	14.63	2.42	50.6	2.85
2102	345	1.89	12.98	2.24	47.1	3.10
2103	354	1.95	14.84	2.46	57.4	3.04
2104	321	2.00	12.15	2.25	52.4	3.15
2105	376	1.91	15.90	2.18	55.3	3.40
2106	350	1.92	12.75	1.99	54.8	3.30
Mean	349	1.94	13.88	2.26	52.9	3.14
S.D.	17.7	0.045	1.459	0.170	3.71	0.194
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 4

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
3101	326	1.83	17.23	2.46	46.3	2.78
3102	341	1.92	18.33	2.28	46.6	2.84
3103	320	1.96	17.38	2.35	52.2	3.23
3104	335	2.07	17.50	2.56	47.6	3.11
3105	389	1.95	15.01	2.33	58.8	3.18
3106	345	1.92	16.10	2.37	45.5	2.91
Mean	343	1.94	16.93	2.39	49.5	3.01
S.D.	24.5	0.078	1.179	0.101	5.14	0.189
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 5. Study No. BMR143C

Organ weight (Absolute) - Individual values

Sex : Male

Dose level : Sample D-1 30 mg/kg

Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
4101	300	1.92	19.22	2.02	44.3	2.62
4102	286	2.11	20.73	2.16	48.5	3.30
4103	321	1.97	24.20	2.21	54.0	3.26
4104	283	1.97	18.08	2.04	49.4	3.03
4105	269	1.92	18.72	2.03	50.3	3.21
4106	293	1.93	21.22	2.17	56.0	3.06
Mean	292	1.97	20.36	2.11	50.4	3.08
S.D.	17.6	0.072	2.228	0.084	4.15	0.250
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 6

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
0107	365	2.07	12.43	2.29	48.5	3.00
0108	405	1.98	13.98	2.35	54.0	3.36
0109	438	2.10	15.91	2.50	46.9	2.89
0110	374	2.01	12.82	2.62	59.0	3.24
0111	344	2.04	11.18	2.41	46.8	0.85
0112	410	2.11	15.12	2.67	63.1	3.12
Mean	389	2.05	13.57	2.47	53.1	2.74
S.D.	34.4	0.051	1.768	0.151	6.85	0.942
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - M - 7

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Testes (g)
4107	326	1.96	17.69	2.23	53.4	3.26
4108	336	2.09	21.36	2.30	61.5	3.40
4109	D					
4110	331	2.05	21.91	2.33	53.9	3.54
4111	340	1.96	20.99	2.56	45.0	3.43
4112	373	2.04	21.35	2.57	43.6	3.27
Mean	341	2.02	20.66	2.40	51.5	3.38
S.D.	18.5	0.058	1.693	0.157	7.31	0.117
N	5	5	5	5	5	5

F.B.W : Final body weight
D. : Dead.

Appendix 8 - F - 1 Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0201	228	1.87	8.53	1.59	50.8	95.2
0202	214	1.78	8.75	1.36	58.4	89.2
0203	221	1.86	8.93	1.62	66.6	75.7
0204	264	1.96	9.60	1.88	63.4	93.7
0205	227	1.84	8.40	1.72	59.1	72.7
0206	227	1.78	8.32	1.52	62.5	75.6
Mean	230	1.85	8.76	1.62	60.1	83.7
S.D.	17.4	0.067	0.471	0.177	5.46	10.13
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - F - 2

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
1201	224	1.83	8.57	1.49	60.5	78.0
1202	212	1.85	7.83	1.42	50.3	79.7
1203	235	1.81	9.52	1.63	55.8	93.0
1204	242	1.72	9.41	1.89	60.9	85.5
1205	227	1.81	8.38	1.65	71.3	92.1
1206	222	1.73	8.18	1.60	60.1	73.7
Mean	227	1.79	8.65	1.61	59.8	83.7
S.D.	10.5	0.054	0.679	0.162	6.93	7.86
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - F - 3

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
2201	225	1.87	9.55	1.72	48.1	75.9
2202	226	1.92	8.39	1.71	66.5	93.7
2203	216	1.81	7.95	1.57	59.1	93.8
2204	240	2.02	9.33	1.62	66.8	116.1
2205	259	1.90	10.32	1.79	68.3	75.5
2206	246	1.91	8.85	1.63	66.5	96.8
Mean	235	1.91	9.07	1.67	62.6	92.0
S.D.	15.9	0.069	0.852	0.081	7.79	15.11
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - F - 4

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
3201	216	1.96	10.04	1.69	62.6	90.1
3202	225	1.83	11.96	1.81	71.4	72.6
3203	186	1.77	9.06	1.51	48.4	63.7
3204	221	1.86	10.75	1.76	55.0	76.8
3205	212	1.84	11.01	1.64	63.9	74.7
3206	223	1.82	10.68	1.76	63.7	76.7
Mean	214	1.85	10.58	1.70	60.8	75.8
S.D.	14.4	0.063	0.973	0.109	8.01	8.53
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - F - 5 Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
4201	178	1.79	12.25	1.28	55.9	66.0
4202	194	1.80	14.65	1.46	60.0	61.6
4203	194	1.80	14.18	1.51	55.5	76.2
4204	204	1.96	14.04	1.62	64.6	56.4
4205	181	1.81	13.81	1.53	47.0	56.7
4206	191	1.82	13.73	1.62	50.8	58.6
Mean	190	1.83	13.78	1.50	55.6	62.6
S.D.	9.5	0.064	0.816	0.126	6.28	7.57
N	6	6	6	6	6	6

F.B.W : Final body weight

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
0207	325	1.91	11.30	1.92	80.7	106.4
0208	265	1.85	8.12	1.63	51.1	86.3
0209	264	1.93	8.55	1.72	60.3	78.3
0210	270	2.04	8.97	1.84	82.7	95.7
0211	278	1.99	8.81	1.78	77.7	83.6
0212	257	1.86	8.80	1.76	72.0	88.1
Mean	277	1.93	9.09	1.78	70.8	89.7
S.D.	24.8	0.074	1.122	0.100	12.55	9.96
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 8 - F - 7

Study No. BMR143C

Organ weight (Absolute) - Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Ovaries (mg)
4207	201	1.71	11.92	1.44	50.1	61.8
4208	199	1.72	13.04	1.62	53.7	59.3
4209	208	1.90	12.90	1.57	45.7	72.7
4210	193	1.90	11.64	1.47	53.0	73.6
4211	213	1.89	12.40	1.57	53.6	71.2
4212	234	2.06	12.85	1.85	67.7	72.1
Mean	208	1.86	12.46	1.59	54.0	68.5
S.D.	14.5	0.131	0.574	0.146	7.39	6.22
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - M - 1

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
0101	354	0.54	3.69	0.67	14.5	0.85
0102	318	0.63	3.83	0.68	16.7	1.02
0103	334	0.53	4.04	0.73	14.2	0.76
0104	352	0.55	3.67	0.70	15.5	0.87
0105	377	0.54	3.85	0.66	12.2	0.86
0106	370	0.57	4.17	0.71	13.6	0.77
Mean	351	0.56	3.88	0.69	14.5	0.86
S.D.	22.0	0.037	0.197	0.026	1.55	0.094
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - M - 2 Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
1101	375	0.55	4.28	0.73	13.9	0.78
1102	321	0.66	4.13	0.68	17.3	0.91
1103	362	0.52	3.74	0.72	13.9	0.88
1104	321	0.60	4.21	0.71	19.8	0.99
1105	376	0.51	4.05	0.72	14.3	0.84
1106	399	0.48	3.85	0.70	12.6	0.86
Mean	359	0.55	4.04	0.71	15.3	0.88
S.D.	31.8	0.066	0.210	0.018	2.70	0.071
N	6	6	6	6	6	6

F.B.W : Final body weight

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
2101	346	0.58	4.23	0.70	14.6	0.82
2102	345	0.55	3.76	0.65	13.7	0.90
2103	354	0.55	4.19	0.69	16.2	0.86
2104	321	0.62	3.79	0.70	16.3	0.98
2105	376	0.51	4.23	0.58	14.7	0.90
2106	350	0.55	3.64	0.57	15.7	0.94
Mean	349	0.56	3.97	0.65	15.2	0.90
S.D.	17.7	0.037	0.272	0.060	1.03	0.057
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - M - 4

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
3101	326	0.56	5.29	0.75	14.2	0.85
3102	341	0.56	5.38	0.67	13.7	0.83
3103	320	0.61	5.43	0.73	16.3	1.01
3104	335	0.62	5.22	0.76	14.2	0.93
3105	389	0.50	3.86	0.60	15.1	0.82
3106	345	0.56	4.67	0.69	13.2	0.84
Mean	343	0.57	4.98	0.70	14.5	0.88
S.D.	24.5	0.043	0.611	0.060	1.10	0.075
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - M - 5 Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
4101	300	0.64	6.41	0.67	14.8	0.87
4102	286	0.74	7.25	0.76	17.0	1.15
4103	321	0.61	7.54	0.69	16.8	1.02
4104	283	0.70	6.39	0.72	17.5	1.07
4105	269	0.71	6.96	0.75	18.7	1.19
4106	293	0.66	7.24	0.74	19.1	1.04
Mean	292	0.68	6.97	0.72	17.3	1.06
S.D.	17.6	0.048	0.475	0.035	1.54	0.112
N	6	6	6	6	6	6

F.B.W : Final body weight

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
0107	365	0.57	3.41	0.63	13.3	0.82
0108	405	0.49	3.45	0.58	13.3	0.83
0109	438	0.48	3.63	0.57	10.7	0.66
0110	374	0.54	3.43	0.70	15.8	0.87
0111	344	0.59	3.25	0.70	13.6	0.25
0112	410	0.51	3.69	0.65	15.4	0.76
Mean	389	0.53	3.48	0.64	13.7	0.70
S.D.	34.4	0.044	0.160	0.056	1.82	0.231
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - M - 7

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Male
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Testes
4107	326	0.60	5.43	0.68	16.4	1.00
4108	336	0.62	6.36	0.68	18.3	1.01
4109	D					
4110	331	0.62	6.62	0.70	16.3	1.07
4111	340	0.58	6.17	0.75	13.2	1.01
4112	373	0.55	5.72	0.69	11.7	0.88
Mean	341	0.59	6.06	0.70	15.2	0.99
S.D.	18.5	0.030	0.482	0.029	2.67	0.069
N	5	5	5	5	5	5

F.B.W : Final body weight
D : Dead.

Appendix 9 - F - 1

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
0201	228	0.82	3.74	0.70	22.3	41.8
0202	214	0.83	4.09	0.64	27.3	41.7
0203	221	0.84	4.04	0.73	30.1	34.3
0204	264	0.74	3.64	0.71	24.0	35.5
0205	227	0.81	3.70	0.76	26.0	32.0
0206	227	0.78	3.67	0.67	27.5	33.3
Mean	230	0.80	3.81	0.70	26.2	36.4
S.D.	17.4	0.037	0.198	0.043	2.76	4.26
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - F - 2

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values

Sex : Female
Dose level : Sample D-1 0.1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
1201	224	0.82	3.83	0.67	27.0	34.8
1202	212	0.87	3.69	0.67	23.7	37.6
1203	235	0.77	4.05	0.69	23.7	39.6
1204	242	0.71	3.89	0.78	25.2	35.3
1205	227	0.80	3.69	0.73	31.4	40.6
1206	222	0.78	3.68	0.72	27.1	33.2
Mean	227	0.79	3.81	0.71	26.4	36.8
S.D.	10.5	0.053	0.148	0.042	2.89	2.88
N	6	6	6	6	6	6

F.B.W : Final body weight

Organ weight (Relative : percentage of body weight)
- Individual values

Sex : Female
Dose level : Sample D-1 1 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
2201	225	0.83	4.24	0.76	21.4	33.7
2202	226	0.85	3.71	0.76	29.4	41.5
2203	216	0.84	3.68	0.73	27.4	43.4
2204	240	0.84	3.89	0.68	27.8	48.4
2205	259	0.73	3.98	0.69	26.4	29.2
2206	246	0.78	3.60	0.66	27.0	39.3
Mean	235	0.81	3.85	0.71	26.6	39.3
S.D.	15.9	0.047	0.237	0.043	2.73	6.90
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - F - 4

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Female
Dose level : Sample D-1 10 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
3201	216	0.91	4.65	0.78	29.0	41.7
3202	225	0.81	5.32	0.80	31.7	32.3
3203	186	0.95	4.87	0.81	26.0	34.2
3204	221	0.84	4.86	0.80	24.9	34.8
3205	212	0.87	5.19	0.77	30.1	35.2
3206	223	0.82	4.79	0.79	28.6	34.4
Mean	214	0.87	4.95	0.79	28.4	35.4
S.D.	14.4	0.055	0.255	0.015	2.54	3.23
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - F - 5

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (4 weeks)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
4201	178	1.01	6.88	0.72	31.4	37.1
4202	194	0.93	7.55	0.75	30.9	31.8
4203	194	0.93	7.31	0.78	28.6	39.3
4204	204	0.96	6.88	0.79	31.7	27.6
4205	181	1.00	7.63	0.85	26.0	31.3
4206	191	0.95	7.19	0.85	26.6	30.7
Mean	190	0.96	7.24	0.79	29.2	33.0
S.D.	9.5	0.034	0.321	0.053	2.50	4.37
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - F - 6

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Female
Dose level : Sample D-1 0 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
0207	325	0.59	3.48	0.59	24.8	32.7
0208	265	0.70	3.06	0.62	19.3	32.6
0209	264	0.73	3.24	0.65	22.8	29.7
0210	270	0.76	3.32	0.68	30.6	35.4
0211	278	0.72	3.17	0.64	27.9	30.1
0212	257	0.72	3.42	0.68	28.0	34.3
Mean	277	0.70	3.28	0.64	25.6	32.5
S.D.	24.8	0.059	0.157	0.035	4.10	2.27
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 9 - F - 7

Study No. BMR143C

Organ weight (Relative : percentage of body weight)
- Individual values
Sex : Female
Dose level : Sample D-1 30 mg/kg
Animals killed on schedule (Recovery)

Animal Number	F.B.W (g)	Brain	Liver	Kidneys	Adrenals ($x10^{-3}$)	Ovaries ($x10^{-3}$)
4207	201	0.85	5.93	0.72	24.9	30.7
4208	199	0.86	6.55	0.81	27.0	29.8
4209	208	0.91	6.20	0.75	22.0	35.0
4210	193	0.98	6.03	0.76	27.5	38.1
4211	213	0.89	5.82	0.74	25.2	33.4
4212	234	0.88	5.49	0.79	28.9	30.8
Mean	208	0.90	6.00	0.76	25.9	33.0
S.D.	14.5	0.047	0.358	0.033	2.43	3.18
N	6	6	6	6	6	6

F.B.W : Final body weight

Appendix 10-M
Individual macroscopic findings (28days)
Sex : Male
Test article : Sample D-1

Study No.BHR143C

Findings	Dose level / Animal number	0 mg/kg (01-)						0.1 mg/kg (11-)						1 mg/kg (21-)						10 mg/kg (31-)						30 mg/kg (41-)					
		01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06
Lungs																															
Dark reddish patch		-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver																															
Scatterring of greyish dot/patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	-	P
Hypertrophy		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	P	P
Greyish patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-
Dark reddish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yellowish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
kidneys																															
Cyst		-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pyelectasis		-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Greyish patch		-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blackish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Adrenals																															
Dark reddish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Testes																															
Atrophy		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No lesion. P : Present

Appendix 10-F
Individual macroscopic findings (28days)
Sex : Female
Test article : Sample D-1

Study No.BMR143C

Findings	Dose level / Animal number	0 mg/kg (02-)						0.1 mg/kg (12-)						1 mg/kg (22-)						10 mg/kg (32-)						30 mg/kg (42-)					
		01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06
Lungs																															
Dark reddish patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver																															
·Scatterring of greyish dot/patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypertrophy		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	P	P
Greyish patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-
Dark reddish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-	P	P	P	-
Yellowish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-
kidneys																															
Cyst		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pyelectasis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-
Greyish patch		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blackish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Adrenals																															
Dark reddish change		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- : No lesion, P : Present

Appendix 10-R-1
Individual macroscopic findings (Recovery)
Test article : Sample D-1

Study No.BMR143C

Findings	Sex / Dose level	Animal number	Male 0 mg/kg (01-) 07	08	09	10	11	12	Male 30 mg/kg (41-) 07	08	10	11	12	Female 0 mg/kg (02-) 07	08	09	10	11	12	Female 30 mg/kg (42-) 07	08	09	10	11	12
Lungs																									
Dark reddish patch			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver																									
Scatterring of greyish dot/patch			-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypertrophy			-	-	-	-	-	-	-	P	P	-	-	-	-	-	-	-	-	-	P	-	-	-	-
Greyish patch			-	-	-	-	-	-	P	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	P
Dark reddish change			-	-	-	-	-	-	P	-	-	P	-	-	-	-	-	-	-	P	P	P	P	P	-
Yellowish change			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
kidneys																									
Cyst			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pyelectasis			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Greyish patch			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blackish change			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Adrenals																									
Dark reddish change			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Testes																									
Atrophy			-	-	-	-	P	-	-	-	-	-	-												

- : No lesion, P : Present

Appendix 10-R-2
Individual Macroscopic findings in died male rat (32 days)
Sex : Male
Test article : Sample D-1

Study No.BMR143C

Dose level (mg/kg)	Animal number	Organ	Macroscopic findings
30	4109	Thymus	Dark reddish patch
			Atrophy
		Stomach	Tarry contents
			Hemorrhage
		Liver	Scatterring of greyish dot/patch

Appendix II-M
Individual microscopic findings (28days)
Sex : Male
Test article : Sample D-1

Study No.BMR143C

Findings / Dose level	Animal number	0 mg/kg (01-)						0.1 mg/kg (11-)						1 mg/kg (21-)						10 mg/kg (31-)						30 mg/kg (41-)					
		01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06
Liver																															
microgranuloma		±	±	±	+	+	±	±	±	±	±	±	±	±	±	+	±	±	+	±	+	±	+	±	+	±	±	±	+	+	+
focal necrosis		−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	+	−	+	+	+	##
focal fatty change		−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
peripheral fatty change		−	−	−	−	−	−	−	−	−	−	−	±	−	−	−	±	±	−	±	+	+	±	−	−	−	+	±	±	+	##
swelling of centrilobular hepatocytes		−	−	−	−	−	−	−	−	−	−	−	−	±	±	−	−	−	±	+	+	+	+	±	+	##	##	+	##	##	+
eosinophilic change in centrilobular hepatocytes		−	−	−	−	−	−	−	−	−	−	−	−	−	±	±	±	±	−	##	##	##	+	±	+	##	##	##	##	##	##
Heart																															
myocardial degeneration		−	−	±	±	−	−																			−	−	−	−	−	−
myocardial fibrosis		−	−	−	−	−	−																			−	−	−	−	−	−
Spleen																															
extramedullary hematopoiesis		−	−	−	±	+	±																			−	−	−	−	−	−
Kidneys																															
regenerated tubules		−	±	+	−	−	+																			±	−	+	−	+	−
dilated tubules		−	+	−	−	−	−																			−	−	−	−	−	−
infiltration of lymphocytes		−	±	+	−	−	±																			±	−	−	−	−	−
dilation of pelvis		−	−	−	−	−	−																			+	−	−	+	−	−
chronic nephropathy		−	−	−	−	−	−																			−	−	−	−	−	−
Adrenals																															
abnormality		−	−	−	−	−	−																			−	−	−	−	−	−
Brain																															
abnormality		−	−	−	−	−	−																			−	−	−	−	−	−
Testes																															
atrophy		−	−	−	−	−	−																			−	−	−	−	−	−

− : Negative, ± : Very slight, + : Slight, ## : Moderate.

Appendix II-F
Individual microscopic findings (28days)
Sex : Female
Test article : Sample D-1

Study No.BMR143C

Findings / Dose level / Animal number	0 mg/kg (02-)						0.1 mg/kg (12-)						1 mg/kg (22-)						10 mg/kg (32-)						30 mg/kg (42-)					
	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06	01	02	03	04	05	06
Liver																														
microgranuloma	±	±	±	±	±	−	±	+	±	±	±	±	−	−	±	±	±	±	±	±	±	+	±	±	##	+	±	±	−	±
focal necrosis	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−
focal fatty change	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
peripheral fatty change	−	−	+	±	+	±	+	±	+	±	+	+	−	−	−	±	+	±	+	+	±	±	−	−	−	±	+	−	−	+
swelling of centrilobular hepatocytes	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	±	±	±	##	##	##	+	##	##
eosinophilic change in centrilobular hepatocytes	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	±	±	±	##	##	##	##	##	##
Heart																														
myocardial degeneration	−	−	−	−	−	−																			−	−	−	−	−	−
myocardial fibrosis	−	−	−	−	−	−																			−	−	−	−	−	−
Spleen																														
extramedullary hematopoiesis	−	−	−	−	−	−																			−	−	−	−	−	−
Kidneys																														
regenerated tubules	−	±	−	+	−	±																			−	±	−	±	±	−
dilated tubules	−	−	−	−	−	−																			−	−	−	−	−	−
infiltration of lymphocytes	−	±	−	±	+	−																			−	−	−	−	−	−
dilation of pelvis	−	−	−	−	−	−																			−	−	−	−	+	−
chronic nephropathy	−	−	−	−	−	−																			−	−	−	−	−	−
Adrenals																														
abnormality	−	−	−	−	−	−																			−	−	−	−	−	−
Brain																														
abnormality	−	−	−	−	−	−																			−	−	−	−	−	−
Ovaries																														
abnormality	−	−	−	−	−	−																			−	−	−	−	−	−

− : Negative. ± : Very slight. + : Slight. ## : Moderate.

Appendix 11-R-1
Individual microscopic findings (Recovery)
Test article : Sample D-1

Study No.BMR143C

Findings	Sex / Dose level	Male 0 mg/kg (01-)						Male 30 mg/kg (41-)					Female 0 mg/kg (02-)						Female 30 mg/kg (42-)					
	Animal number	07	08	09	10	11	12	07	08	10	11	12	07	08	09	10	11	12	07	08	09	10	11	12
Liver																								
microgranuloma		±	±	+	−	+	±	+	+	±	+	+	±	±	±	±	±	±	±	±	+	±	+	−
focal necrosis		−	−	−	−	−	−	+	+	−	−	+	−	−	−	−	−	−	−	+	−	−	−	+
focal fatty change		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
peripheral fatty change		−	−	−	−	−	−	−	+	+	−	±	+	−	±	−	−	−	−	−	−	−	−	+
swelling of centrilobular hepatocytes		−	−	−	−	−	−	#	#	#	#	#	−	−	−	−	−	−	#	+	+	#	#	#
eosinophilic change in centrilobular hepatocytes		−	−	−	−	−	−	+	+	+	#	#	−	−	−	−	−	−	+	+	+	+	+	+
Heart																								
myocardial degeneration		−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−	−
myocardial fibrosis		−	−	−	±	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen																								
extramedullary hematopoiesis		−	−	±	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−	−	−
Kidneys																								
regenerated tubules		±	−	±	−	−	±	−	−	−	±	−	−	±	±	±	−	±	±	−	−	−	−	−
dilated tubules		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
infiltration of lymphocytes		−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	+	−	−	−	−	−	−
dilation of pelvis		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
chronic nephropathy		−	−	−	−	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−	−
Adrenals																								
abnormality		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Brain																								
abnormality		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Testes																								
atrophy		−	−	−	−	#	−	−	−	−	−	−												
Ovaries																								
abnormality													−	−	−	−	−	−	−	−	−	−	−	−

− : Negative, ± : Very slight, + : Slight, # : Moderate.

Appendix 11-R-2
Individual Microscopic findings in dicd male rat (32 days)
Sex : Male
Test article : Sample D-1

Study No.BMR143C

Dose level (mg/kg)	Animal number	Organ	Microscopic findings	
30	4109	Liver	Eosinophilic change in centrilobular hepatocytes	+ +
			Swelling of centrilobular hepatocytes	+ +
			Focal necrosis	+
			Peripheral fatty change	+
		Kidneys	Dilated tubules	+
		Brain	Hemorrhagic foci	+
		Stomach	Ulcer and hemorrhage in glandular stomach	+
		Thymus	Congestion	+
			Hemorrhage	
		Heart	No abnormality	
		Spleen	No abnormality	
		Adrenals	No abnormality	
		Testes	No abnormality	

+ : Slight, + + : Moderate

Appendix 12-M
Microscopic findings of the organs showed gross lesion (28 days)
Sex : Male
Test article : Sample D-1

Study No.BHR143C

Dose level (mg/kg)	Animal number	Organ	Macroscopic findings	Microscopic findings
0	0102	Kidneys	Cyst	Dilated tubules(+)
	0105	Lungs	Dark reddish patch	Hemorrhage(+)
0.1	1103	Kidneys	Pyelectasis	Dilation of pelvis(+)
1	2102	Kidneys	Grayish patch	Focal degeneration and calcification in tubules(+). regenerated tubules (+) and infiltration of lymphocytes(+)
30	4101	Liver	Scattering of grayish dot	Focal necrosis(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4102	Liver	Scattering of grayish dot/patch	No abnormality except for microgranuloma (±) peripheral fatty change (+).eosinophilic change in centrilobular hepatocytes(++)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4103	Liver	Scattering of grayish dot	Focal necrosis(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(+)
	4104	Liver	Scattering of grayish dot/patch	Focal necrosis(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4105	Liver	Grayish patch	Focal necrosis(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4106	Liver	Scattering of grayish dot	Focal necrosis(++)
			Hypertrophy	Swelling of centrilobular hepatocytes(+)
		Kidneys	Dark reddish/Blackish dot	No abnormality
		Adrenals	Dark reddish/Blackish dot	No abnormality

± : Very slight , + : Slight, ++ : Moderate

Appendix 12-F
Microscopic findings of the organs showed gross lesion (28 days)
Sex : Female
Test article : Sample D-1 Study No.BMR143C

Dose level (mg/kg)	Animal number	Organ	Macroscopic findings	Microscopic findings
10	3206	Liver	Dark reddish change	No abnormality except for microgranuloma (±) . Swelling of centrilobular hepatocytes(±) and eosi--nophilic change in centrilobular hepatocytes(±)
30	4201	Liver	Dark reddish change	No abnormality except for microgranuloma(++). eosinophilic change in centrilobular hepatocytes (++) and focal necrosis(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4202	Liver	Yellowish change	Peripheral fatty change (±)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4203	Liver	Dark reddish change	No abnormality except for microgranuloma (±) eosinophilic change in centrilobular hepatocytes(++) and peripheral fatty change(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4204	Liver	Dark reddish change	No abnormality except for microgranuloma (±) and eosinophilic change in centrilobular hepatocytes(++)
			Hypertrophy	Swelling of centrilobular hepatocytes(+)
	4205	Liver	Dark reddish change	No abnormality except for eosinophilic change in centrilobular hepatocytes(++)
			Grayish patch	No abnormality except for eosinophilic change in centrilobular hepatocytes(++)
			Hypertrophy	Swelling of centrilobular hepatocytes(++)
		Kidneys	Pyelectasis	Dilation of pelvis(+)
	4206	Liver	Hypertrophy	Swelling of centrilobular hepatocytes(++)

± : Very slight , + : Slight, ++ : Moderate

Appendix 12-R
Microscopic findings of the organs showed gross lesion (Recovery)
Test article : Sample D-1

Study No.BMR143C

Dose level (mg/kg)	Animal number	Organ	Macroscopic findings	Microscopic findings
Male 0	0111	Testes	Atrophy	Atrophy(++)
30	4107	Liver	Dark reddish change	No abnormality except for swelling of centrilobular hepatocytes(++).and eosinophilic change in centrilobular hepatocytes(+) and microgranuloma(+)
			Grayish patch	Focal necrosis(+)
	4108	Liver	Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4109 *	Thymus	Dark reddish patch	Congestion(+) and hemorrhage(+)
			Atrophy	No abnormality
		Stomach	Tarry contents/Hemorrhage	Ulcer and hemorrhage in glandular stomach(+)
		Liver	Scattering of grayish dot/patch	Focal necrosis(++)
	4110	Liver	Hypertrophy	Swelling of centrilobular hepatocytes(++)
	4111	Liver	Dark reddish change	No abnormality except for microgranuloma(+). swelling of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(++)
	4112	Liver	Grayish patch	Focal necrosis(+)
Female 30	4207	Liver	Dark reddish change	No abnormality except for microgranuloma (±).swelling of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(+)
	4208	Liver	Dark reddish change	No abnormality except for microgranuloma (±), focal necrosis(+) and eosinophilic change in cent--rilobular hepatocytes(+)
			Hypertrophy	Swelling of centrilobular hepatocytes(+)
	4209	Liver	Dark reddish change	No abnormality except for microgranuloma(+).swelling of centrilobular hepatocytes(+) and eosinophilic change in centrilobular hepatocytes(+)
	4210	Liver	Dark reddish change	No abnormality except for microgranuloma (±).swelling of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(+)
	4211	Liver	Dark reddish change	No abnormality except for microgranuloma(+).swelling of centrilobular hepatocytes(++) and eosinophilic change in centrilobular hepatocytes(+)
	4212	Liver	Grayish patch	Focal necrosis(+)

± : Very slight , + : Slight, ++ : Moderate
* : Dead animal

PHOTOGRAPHS (Hisopathological Pictures)

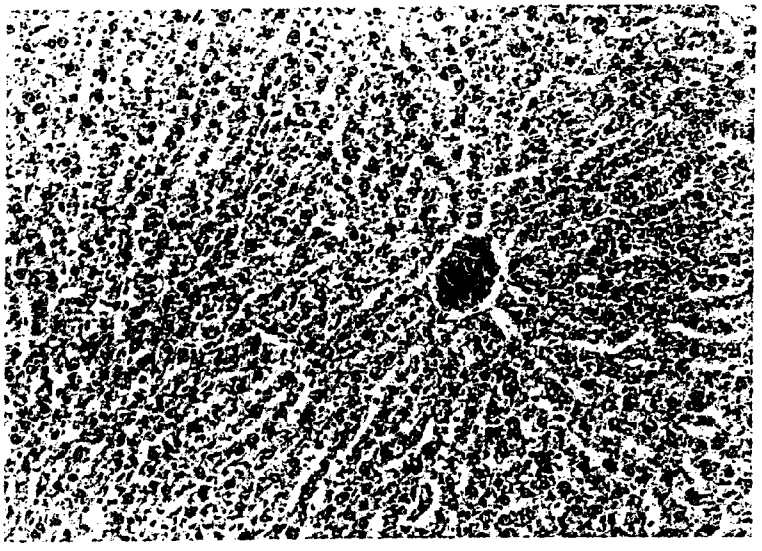


Photo.1 Liver of a male rat of control. (Animal No. 0103)

Showing normal centrilobular region.

H.E.stain ×180

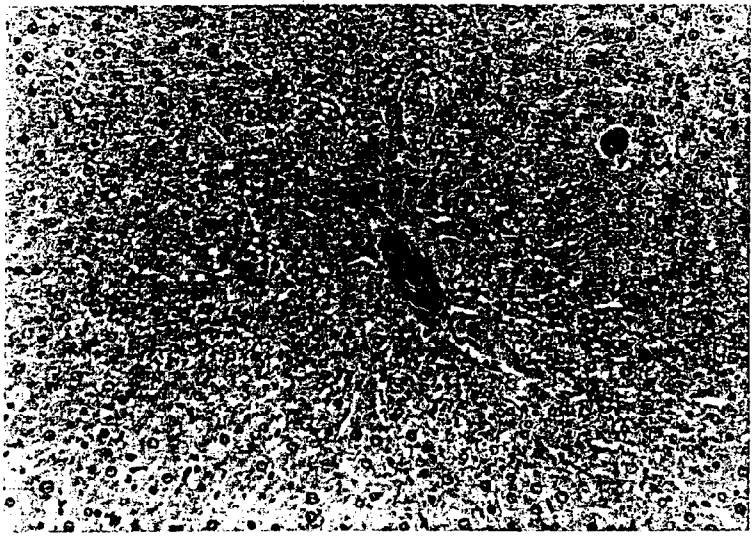


Photo.2 Liver of a male rat given 30 mg/kg. (Animal No. 4105)

Eosinophilic change and swelling of centrilobular hepatocytes are noted.

H.E.stain ×180

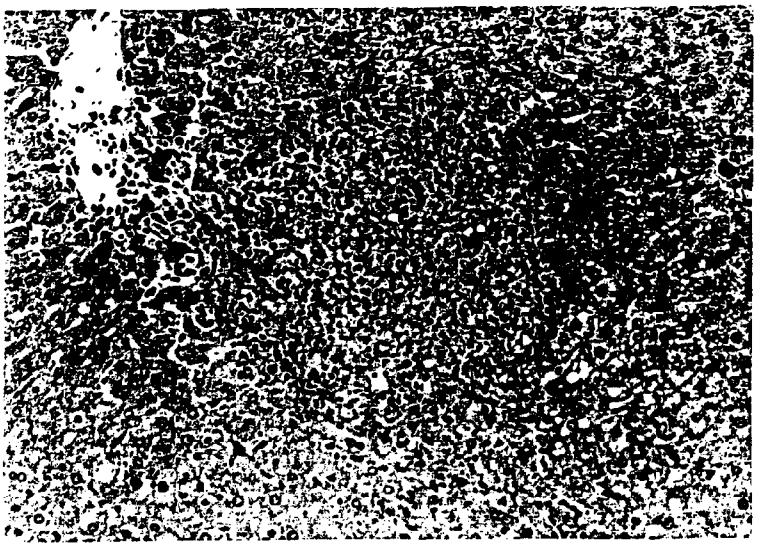


Photo.3 Liver of a male rat given 30 mg/kg. (Animal No. 4105)

Focal necrosis is noted.

H.E.stain ×180

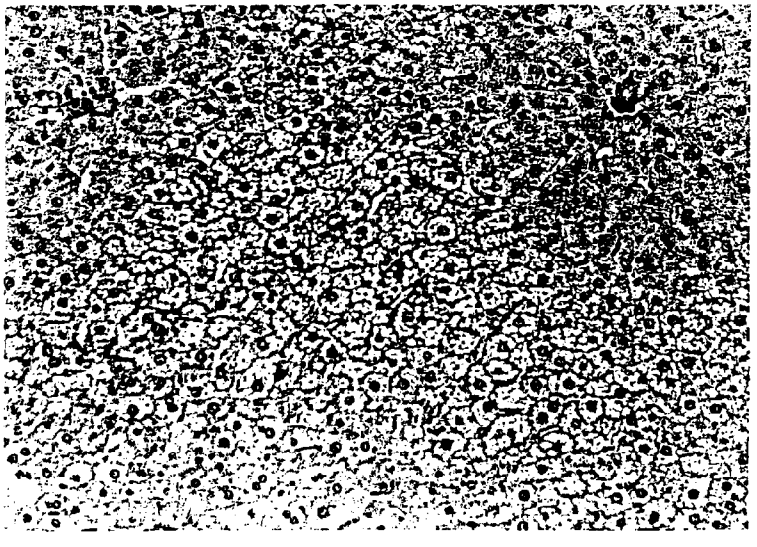


Photo.4 Liver of a male rat given 30 mg/kg. (Animal No. 4106)

Peripheral fatty change is found.

H.E.stain ×180