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REPORT

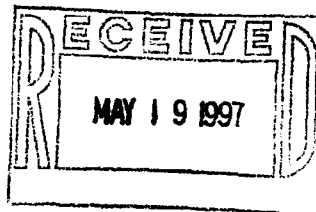
Twenty-eight-day Repeated Dose Oral  
Toxicity Study of Sample D-1 in Rats

(BMR143C)

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Bio-Medical Research Laboratories  
Co., Ltd.

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**Exhibit  
2797**

State of Minnesota v. 3M Co.,  
Court File No. 27-CV-10-28862

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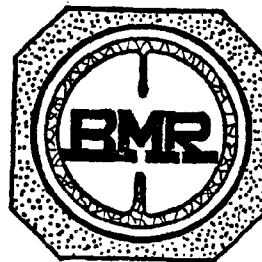
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REPORT

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

(BMR143C)

-TRANSLATION-



Pure free life

February 16, 1993

Bio-Medical Research Laboratories  
Co., Ltd.

3M\_MN01649988

2797.0002

## 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 author, the study director Mr. Michio Otsuka.

April 23, 1997

Translator :

*M. Tennichi*

Makoto Tennichi

General Manager

Bio-Medical Research Laboratories Co., Ltd.

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# 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

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(Makoto Tennichi)

General Manager

Bio-Medical Research Laboratories Co., Ltd.

(iv)

3M\_MN01649993

2797.0007

# 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 | 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    |

(v)

3M\_MN01649994

2797.0008

## 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

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(Michio Otsuka)

Study Director

Bio-Medical Research Laboratories Co., Ltd.

(vi)

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2797.0009

## 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.

## MATERIALS AND METHODS

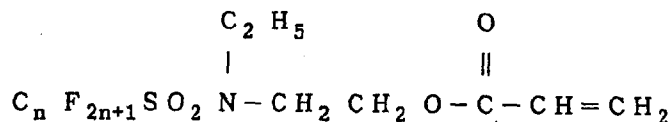
### 1. Test Substance

#### 1-1 Name

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

(Abbreviation) Sample D-1

#### 1-2 Structural formula



(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 Storage 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 °C 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 °C                                                 |
| Humidity    | : 30 - 70% RH                                                |
| Ventilation | : 13 times/hour (all fresh air)                              |
| Lighting    | : Light /dark cycle of 12 hours<br>(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 December 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    | Main Groups(*1)             | Recovery Groups(*2)         |
|----------------|---------|-----------------------------|-----------------------------|
| dose levels    | (mg/kg) | (Sex and Number of animals) |                             |
| 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 administration.

(\*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 intermediate-1 group |
|                           | 3, | the intermediate-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 thromboplastin 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 |

#### Instruments

- (1)-(8) : Automatic cell counter, Sysmex model CC-180A, TOA Medical Electronics Co.,Ltd.
- (9) : Optical microscopy
- (10)-(11) : Blood coagulator, 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 °C, 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) $\gamma$ -GPT              | $\gamma$ -Glutamyl-p-nitroanilide substrate method<br>(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,<br>Ketone bodies, Urobilinogen, Bilirubin | Paper test, MULTISTIX ®<br>(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), thyroid (with parathyroid), 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-embedded 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 changes 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, Appendix 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 observed 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.

Microgranuloma 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 myocardial 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 microgranuloma 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 control. 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 observed 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 abnormalities were 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<br>(mg/kg) | 0.1            | 1 | 10     | 30         | 30       |
| Clinical signs (*1)---reduced spontaneous movement,<br>bradypnea, anemia, salivation, convulsion; sup-<br>pression of body weight gain and food consump-<br>tion |                 |                |   |        | m<br>f     | m<br>f   |
| death occurred (number of the animal)                                                                                                                            |                 |                |   |        |            | m (1)    |
| Hematological findings---inclination to anemia,<br>abnormal change of blood coagulation                                                                          |                 |                |   | m<br>f | m          | m<br>f   |
| Biochemical findings---Abnormal changes in lipids,<br>protein, and in enzymes or in electrolytes                                                                 |                 |                |   |        | m<br>f f f | m<br>f   |
| Urinalysis (*2)---acidic urine                                                                                                                                   |                 |                |   |        | m<br>f     | m        |
| Organ weight---change in absolute weight of the<br>liver;                                                                                                        |                 |                |   | m<br>f | m          | m<br>f   |
| change in relative weight of the liver and kid-<br>neys                                                                                                          |                 |                |   | m<br>f | m          | m<br>f   |
| Macroscopic findings---greyish dot or patch and<br>hypertrophy in the liver                                                                                      |                 |                |   |        | m<br>f     | m<br>f   |
| Histological findings---such changes as eosinophil-<br>ic swelling and focal necrosis in the liver,<br>fatty change in peripheral lobule                         |                 |                |   | m<br>f | m<br>m     | m<br>f   |

(\*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  $\gamma$ -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  $\gamma$ -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 histological 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)**

3M\_MN01650025

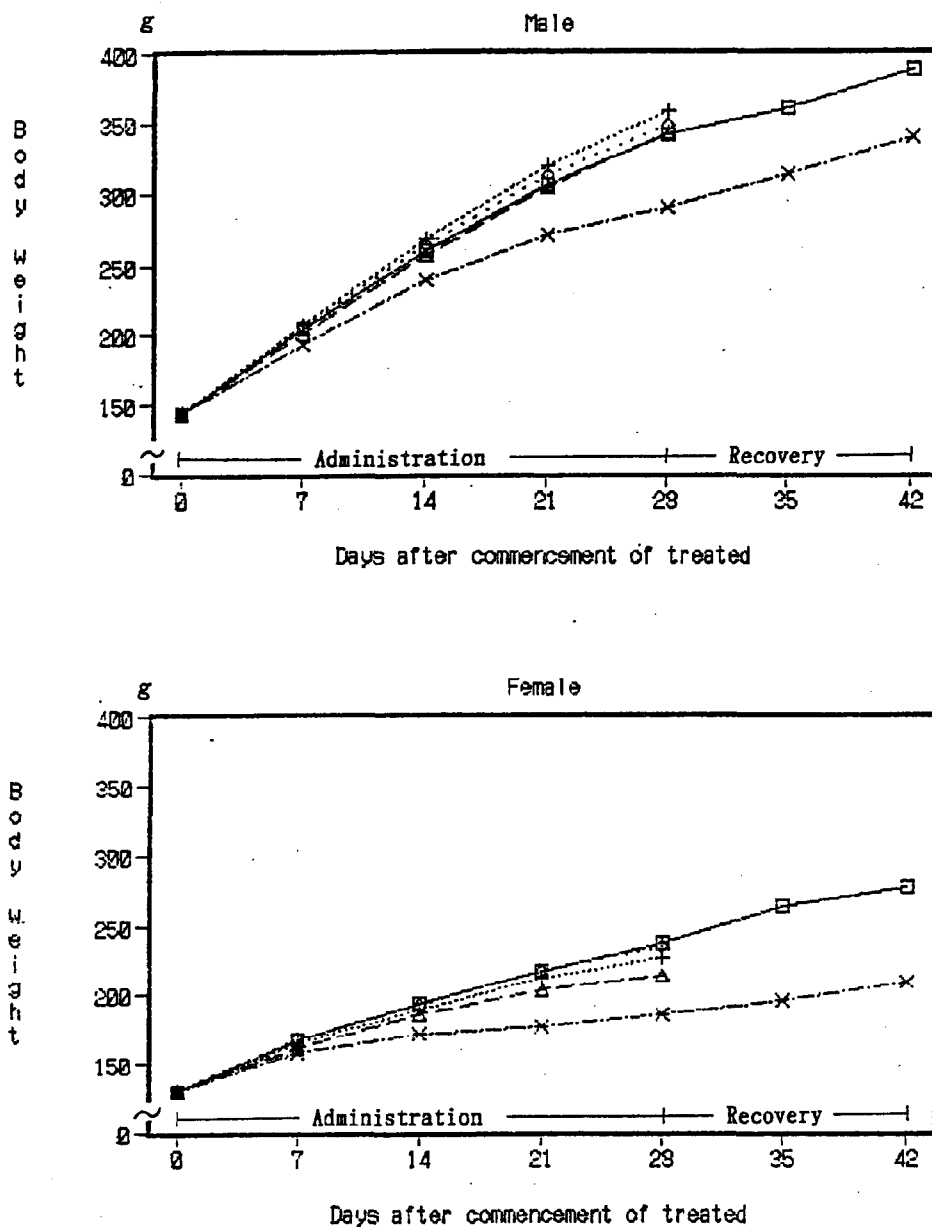


Fig. 1 Changes in mean body weight of male and female rats during 28 days of oral administration of Sample D-1 and 14 days recovery period.

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

Study No. BMR143C

3M\_MN01650027

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

Study No. BMR143C

| Sex    | Dose level<br>(mg/kg) | Clinical signs          | Days after commencement / cessation of treatment |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Female | 0                     | No abnormality observed | 12                                               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Table 2 - H  
 Body weight - Group mean values  
 Sex : Male  
 Test article : Sample D-1  
 Study No. BMRI43C  
 Unit : g

| Dose level | Weeks after commencement/ cessation of treatment |                  |                   |                      |                      |                                                                  |
|------------|--------------------------------------------------|------------------|-------------------|----------------------|----------------------|------------------------------------------------------------------|
|            | 0                                                | 1                | 2                 | 3                    | 4                    | 5/1 6/2                                                          |
| 0 mg/kg    | Mean<br>S.D.<br>N                                | 204<br>8.8<br>12 | 260<br>12.2<br>12 | 307<br>15.4<br>12    | 342<br>21.8<br>12    | 361<br>26.8<br>6<br>389<br>34.4<br>6                             |
| 0.1 mg/kg  | Mean<br>S.D.<br>N                                | 143<br>4.6<br>6  | 207<br>6.6<br>6   | 269<br>16.7<br>6     | 320<br>24.7<br>6     | 359<br>31.8<br>6                                                 |
| 1 mg/kg    | Mean<br>S.D.<br>N                                | 144<br>4.2<br>6  | 206<br>7.1<br>6   | 265<br>9.9<br>6      | 314<br>13.2<br>6     | 349<br>17.7<br>6                                                 |
| 10 mg/kg   | Mean<br>S.D.<br>N                                | 143<br>5.8<br>6  | 201<br>8.8<br>6   | 257<br>14.2<br>6     | 305<br>19.6<br>6     | 343<br>24.5<br>6                                                 |
| 30 mg/kg   | Mean<br>S.D.<br>N                                | 143<br>3.7<br>12 | 193<br>7.0<br>12  | 239 **<br>10.2<br>12 | 272 **<br>14.5<br>12 | 290 **<br>16.2<br>12<br>315 *<br>13.4<br>5<br>341 *<br>18.5<br>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<br>S.D.<br>N                                | 130<br>5.4<br>12 | 166<br>8.1<br>12 | 193<br>13.1<br>12   | 217<br>16.5<br>12   | 237<br>18.6<br>12    |
| 0.1 mg/kg  | Mean<br>S.D.<br>N                                | 129<br>3.4<br>6  | 164<br>2.3<br>6  | 189<br>5.0<br>6     | 212<br>9.6<br>6     | 227<br>10.5<br>6     |
| 1 mg/kg    | Mean<br>S.D.<br>N                                | 131<br>6.6<br>6  | 167<br>13.7<br>6 | 192<br>14.2<br>6    | 217<br>15.2<br>6    | 235<br>15.9<br>6     |
| 10 mg/kg   | Mean<br>S.D.<br>N                                | 130<br>5.9<br>6  | 161<br>7.9<br>6  | 185<br>9.8<br>6     | 203<br>13.4<br>6    | 214<br>14.4<br>6     |
| 30 mg/kg   | Mean<br>S.D.<br>N                                | 130<br>3.9<br>12 | 158<br>7.0<br>12 | 171 **<br>7.2<br>12 | 176 **<br>7.8<br>12 | 185 **<br>10.9<br>12 |
|            |                                                  |                  |                  |                     | 195 **<br>9.9<br>6  | 208 **<br>14.5<br>6  |

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

Table 3 - M  
Food consumption - Group mean values  
Sex : Male  
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<br>S.D.<br>N                                | 18.8<br>0.85<br>6 | 19.1<br>0.92<br>6    | 18.9<br>0.77<br>6   | 16.8<br>1.27<br>6   | 21.8<br>1.26<br>3 |
| 0.1 mg/kg  | Mean<br>S.D.<br>N                                | 18.0<br>1.26<br>3 | 20.6<br>1.88<br>3    | 20.2<br>2.96<br>3   | 18.8<br>2.52<br>3   | 23.0<br>0.75<br>3 |
| 1 mg/kg    | Mean<br>S.D.<br>N                                | 17.0<br>0.75<br>3 | 19.3<br>0.57<br>3    | 18.1<br>1.00<br>3   | 17.3<br>0.65<br>3   |                   |
| 10 mg/kg   | Mean<br>S.D.<br>N                                | 16.6<br>1.25<br>3 | 18.3<br>1.61<br>3    | 19.5<br>2.77<br>3   | 17.8<br>2.63<br>3   |                   |
| 30 mg/kg   | Mean<br>S.D.<br>N                                | 15.4<br>0.72<br>6 | 15.8 **<br>0.68<br>6 | 15.3 *<br>0.36<br>6 | 12.7 *<br>0.64<br>6 | 20.4<br>2.46<br>3 |
|            |                                                  |                   |                      |                     |                     | 21.2<br>2.12<br>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<br>S.D.<br>N                                | 13.8<br>1.15<br>6 | 13.1<br>1.36<br>6   | 13.9<br>1.50<br>6   | 12.7<br>1.42<br>6   | 19.4<br>0.20<br>3   |
| 0.1 mg/kg  | Mean<br>S.D.<br>N                                | 13.7<br>0.40<br>3 | 12.6<br>0.80<br>3   | 13.4<br>1.42<br>3   | 12.4<br>1.12<br>3   | 20.0<br>0.35<br>3   |
| 1 mg/kg    | Mean<br>S.D.<br>N                                | 14.0<br>2.35<br>3 | 12.3<br>1.55<br>3   | 12.9<br>1.07<br>3   | 11.9<br>0.79<br>3   |                     |
| 10 mg/kg   | Mean<br>S.D.<br>N                                | 12.7<br>1.10<br>3 | 11.5<br>0.81<br>3   | 11.2<br>0.75<br>3   | 9.7<br>0.36<br>3    |                     |
| 30 mg/kg   | Mean<br>S.D.<br>N                                | 12.9<br>0.78<br>6 | 10.3 *<br>0.72<br>6 | 8.1 **<br>0.82<br>6 | 8.0 **<br>1.09<br>6 | 14.3 *<br>1.51<br>3 |
|            |                                                  |                   |                     |                     |                     | 15.4<br>1.97<br>3   |

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

Table 4 - M - 1

Hematology - Group mean values

Sex : Male

Test article : Sample D-1

Animals killed on schedule (4 weeks)

| Dose level |      | RBC count<br>( $\times 10^6/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%)† |
|------------|------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|---------------------------------|
| 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

## Hematology - Group mean values

Sex : Male

Test article : Sample D-1

Animals killed on schedule (Recovery)

| Dose level |           | RBC count<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht (%)    | MCV ( $\mu\text{m}^3$ ) | MCH (pg)  | MCHC (%)  | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT (sec)  | APTT (sec) | Reticulo-<br>cyte count<br>(%) |
|------------|-----------|--------------------------------------------|--------------------|-----------|-------------------------|-----------|-----------|-------------------------------------------------|-----------|------------|--------------------------------|
| 0 mg/kg    | Mean      | 798                                        | 14.1               | 45.5      | 57                      | 17.7      | 31.0      | 88.4                                            | 13.8      | 16.0       | 25                             |
|            | S.D.<br>N | 54.4<br>6                                  | 0.39<br>6          | 2.82<br>6 | 2.2<br>6                | 0.88<br>6 | 1.44<br>6 | 16.90<br>6                                      | 0.11<br>5 | 0.79<br>5  | 4.9<br>6                       |
| 30 mg/kg   | Mean      | 717 *                                      | 12.7 **            | 41.6 *    | 58                      | 17.7      | 30.4      | 95.5                                            | 13.4 *    | 15.2       | 31                             |
|            | S.D.<br>N | 22.6<br>5                                  | 0.50<br>5          | 1.68<br>5 | 2.2<br>5                | 0.67<br>5 | 1.15<br>5 | 11.28<br>5                                      | 0.47<br>5 | 1.28<br>5  | 6.2<br>5                       |

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

Table 4 - F - 1

Hematology - Group mean values

Sex : Female

Test article : Sample D-1

Animals killed on schedule (4 weeks)

| Dose level |      | RBC count<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|------------|------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 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&lt;0.01.

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Table 4 - F - 2

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

| Dose level |           | RBC count<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|------------|-----------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 0 mg/kg    | Mean      | 715                                        | 13.7               | 43.1      | 60                         | 19.2        | 31.8        | 93.8                                            | 13.5        | 15.5          | 24                             |
|            | S.D.<br>N | 24.6<br>6                                  | 0.28<br>6          | 1.68<br>6 | 2.3<br>6                   | 0.38<br>6   | 1.12<br>6   | 13.44<br>6                                      | 0.37<br>6   | 1.62<br>6     | 3.3<br>6                       |
| 30 mg/kg   | Mean      | 678                                        | 12.6 **            | 42.7      | 63 *                       | 18.7        | 29.6 **     | 110.3                                           | 13.1        | 12.3 **       | 25                             |
|            | S.D.<br>N | 33.3<br>6                                  | 0.29<br>6          | 1.62<br>6 | 1.3<br>6                   | 0.61<br>6   | 0.80<br>6   | 17.87<br>6                                      | 0.46<br>6   | 1.35<br>6     | 2.6<br>6                       |

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

Hematology - Group mean values

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

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

\$ : Statistical analysis impossible.

## Animals killed on schedule (Recovery)

\* : 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 <sup>2</sup> /mm <sup>3</sup> ) |           | Differential count of leukocytes ( % of total counted cells ) |                          |                  |                | \$       |          |
|------------|------------------------------------------------|-----------|---------------------------------------------------------------|--------------------------|------------------|----------------|----------|----------|
|            |                                                |           | Lympho-<br>cytes                                              | Segmented<br>Neutrophils | Eosino-<br>phils | Baso-<br>phils |          |          |
| 0 mg/kg    | Mean                                           | 75        | 86                                                            | 10                       | 1                | 0              | 0        | 3        |
|            | S.D.<br>N                                      | 10.8<br>6 | 3.0<br>6                                                      | 2.1<br>6                 | 0.8<br>6         | 0.0<br>6       | 0.0<br>6 | 2.0<br>6 |
| 0.1 mg/kg  | Mean                                           | 101       | 88                                                            | 7                        | 0                | 0              | 0        | 4        |
|            | S.D.<br>N                                      | 30.7<br>6 | 4.7<br>6                                                      | 4.0<br>6                 | 0.5<br>6         | 0.4<br>6       | 0.0<br>6 | 2.5<br>6 |
| 1 mg/kg    | Mean                                           | 86        | 88                                                            | 10                       | 0                | 0              | 0        | 2        |
|            | S.D.<br>N                                      | 21.9<br>6 | 4.4<br>6                                                      | 3.7<br>6                 | 0.5<br>6         | 0.5<br>6       | 0.0<br>6 | 1.3<br>6 |
| 10 mg/kg   | Mean                                           | 85        | 89                                                            | 5                        | 0                | 0              | 0        | 5        |
|            | S.D.<br>N                                      | 22.3<br>6 | 3.1<br>6                                                      | 2.1<br>6                 | 0.4<br>6         | 0.5<br>6       | 0.0<br>6 | 1.7<br>6 |
| 30 mg/kg   | Mean                                           | 77        | 87                                                            | 8                        | 0                | 0              | 0        | 5        |
|            | S.D.<br>N                                      | 15.6<br>6 | 4.4<br>6                                                      | 4.8<br>6                 | 0.4<br>6         | 0.4<br>6       | 0.0<br>6 | 2.4<br>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<br>(x10 <sup>2</sup> /mm <sup>3</sup> ) | Differential count of leukocytes |                          |          |                  | ( % of total counted cells ) |                |          |  |
|------------|---------------------------------------------------|----------------------------------|--------------------------|----------|------------------|------------------------------|----------------|----------|--|
|            |                                                   | Lympho-<br>cytes                 | Segmented<br>Neutrophils | Band     | Eosino-<br>phils | Baso-<br>phils               | Mono-<br>cytes |          |  |
| 0 mg/kg    | Mean                                              | 85                               | 86                       | 9        | 0                | 1                            | 0              | 5        |  |
|            | S.D.<br>N                                         | 23.9<br>6                        | 6.3<br>6                 | 5.3<br>6 | 0.4<br>6         | 1.3<br>6                     | 0.0<br>6       | 3.1<br>6 |  |
| 30 mg/kg   | Mean                                              | 86                               | 91                       | 5        | 0                | 0                            | 0              | 4        |  |
|            | S.D.<br>N                                         | 18.1<br>6                        | 2.3<br>6                 | 2.2<br>6 | 0.4<br>6         | 0.4<br>6                     | 0.0<br>6       | 1.9<br>6 |  |

\$ : Statistical analysis impossible.

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)     | $\gamma$ -GTP (IU/l) | ALP (IU/l)    | Urea nitrogen (mg/dl) | Creatinin (mg/dl) | Glucose (mg/dl)  | Total chol. (mg/dl) | Trigly- ceride (mg/dl) |
|------------|-------------------|----------------|----------------------|---------------|-----------------------|-------------------|------------------|---------------------|------------------------|
| 0 mg/kg    | Mean<br>S.D.<br>N | 68<br>7.0<br>6 | 30<br>4.6<br>6       | 0<br>0.0<br>6 | 711<br>129.3<br>6     | 12.4<br>1.62<br>6 | 0.5<br>0.00<br>6 | 140<br>9.4<br>6     | 58<br>18.2<br>6        |
| 0.1 mg/kg  | Mean<br>S.D.<br>N | 65<br>9.0<br>6 | 30<br>5.1<br>6       | 0<br>0.0<br>6 | 677<br>84.9<br>6      | 10.6<br>2.18<br>6 | 0.5<br>0.05<br>6 | 150<br>10.5<br>6    | 57<br>3.5<br>6         |
| 1 mg/kg    | Mean<br>S.D.<br>N | 71<br>8.1<br>6 | 31<br>4.5<br>6       | 0<br>0.0<br>6 | 734<br>127.7<br>6     | 13.3<br>2.34<br>6 | 0.5<br>0.04<br>6 | 140<br>6.9<br>6     | 49<br>4.3<br>6         |
| 10 mg/kg   | Mean<br>S.D.<br>N | 65<br>3.9<br>6 | 34<br>3.2<br>6       | 0<br>0.0<br>6 | 780<br>130.2<br>6     | 12.4<br>2.56<br>6 | 0.5<br>0.05<br>6 | 142<br>9.0<br>6     | 38<br>11.1<br>6        |
| 30 mg/kg   | Mean<br>S.D.<br>N | 73<br>9.5<br>6 | 53 **<br>13.2<br>6   | 0<br>0.0<br>6 | 1191 **<br>243.7<br>6 | 14.1<br>1.93<br>6 | 0.6<br>0.12<br>6 | 142<br>11.5<br>6    | 9 **<br>2.0<br>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&lt;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<br>(IU/l)     | GPT<br>(IU/l)  | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l)     | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(mg/dl) |
|------------|-------------------|----------------|-------------------------|-------------------|-----------------------------|----------------------|--------------------|---------------------------|------------------------------|
| 0 mg/kg    | Mean<br>S.D.<br>N | 34<br>4.5<br>6 | 0<br>0.0<br>6           | 613<br>65.2<br>6  | 18.7<br>2.42<br>6           | 0.5<br>0.05<br>6     | 148<br>5.9<br>6    | 50<br>14.1<br>6           | 85<br>45.0<br>6              |
| 30 mg/kg   | Mean<br>S.D.<br>N | 76<br>6.5<br>5 | 0<br>0.0<br>5           | 716<br>105.4<br>5 | 21.8<br>3.61<br>5           | 0.5<br>0.08<br>5     | 152<br>12.8<br>5   | 29<br>11.3<br>5           | 10 **<br>4.2<br>5            |

\* : Significantly different from control value , \*\* : p&lt;0.01.

\$ : Statistical analysis impossible.

Table 6 - N - 4 Study No. BMRI43C

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

| Dose level | Mean | S.D.  | N | 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    | 6.42 | 0.167 | 6 | 3.85                 | 1.50           | 0.072     | 9.6             | 8.7                     | 141        | 4.2       | 104        |
|            |      |       |   |                      |                |           | 0.28            | 0.18                    | 1.5        | 0.28      | 1.5        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |
| 30 mg/kg   | 6.57 | 0.288 | 5 | 4.14                 | 1.70 *         | 0.109     | 9.7             | 8.9                     | 142        | 4.2       | 106        |
|            |      |       |   |                      |                |           | 0.08            | 0.63                    | 1.1        | 0.20      | 2.5        |
|            |      |       |   |                      |                |           | 5               | 5                       | 5          | 5         | 5          |

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

Table 6 - F - I

Study No. BMR143C

## Clinical chemistry - Group mean values

Sex : Female

Test article : Sample D-1

Animals killed on schedule (4 weeks)

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

\* : Significantly different from control value , \*\* : p&lt;0.01.

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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 | Mean | S.D.  | N | 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    | 6.83 | 0.173 | 6 | 4.18                 | 0.060          | 1.72      | 9.4             | 8.4                     | 141        | 4.1       | 104        |
|            |      |       |   |                      |                |           | 0.15            | 1.09                    | 0.8        | 0.27      | 0.5        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |
| 0.1 mg/kg  | 6.61 | 0.320 | 6 | 4.19                 | 0.154          | 1.74      | 9.8             | 9.7                     | 141        | 4.5       | 102        |
|            |      |       |   |                      |                |           | 0.59            | 1.01                    | 0.9        | 0.58      | 1.4        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |
| 1 mg/kg    | 6.45 | 0.335 | 6 | 4.15                 | 0.125          | 1.82      | 9.6             | 8.7                     | 141        | 4.4       | 104        |
|            |      |       |   |                      |                |           | 0.18            | 0.31                    | 1.2        | 0.48      | 1.9        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |
| 10 mg/kg   | 6.91 | 0.255 | 6 | 4.42 *               | 0.143          | 1.77      | 9.7             | 7.9                     | 142        | 4.1       | 106        |
|            |      |       |   |                      |                |           | 0.35            | 0.73                    | 1.5        | 0.45      | 1.2        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |
| 30 mg/kg   | 7.01 | 0.327 | 6 | 4.59 **              | 0.140          | 1.90      | 9.9             | 8.6                     | 142        | 4.9       | 106 **     |
|            |      |       |   |                      |                |           | 0.49            | 0.93                    | 1.1        | 0.72      | 1.5        |
|            |      |       |   |                      |                |           | 6               | 6                       | 6          | 6         | 6          |

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

**Clinical chemistry - Group mean values**

**Sex : Female**

Test article : Sample D-1

### Animals killed on schedule (Recovery)

| Dose level | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(mg/dl) |
|------------|---------------|---------------|-------------------------|---------------|-----------------------------|----------------------|--------------------|---------------------------|------------------------------|
| 0 mg/kg    | Mean<br>S.D.  | 71<br>8.8     | 30<br>7.7               | 0<br>0.0      | 323<br>63.4                 | 17.3<br>2.55         | 0.6<br>0.05        | 61<br>10.1                | 48<br>31.1                   |
|            | N             | 6             | 6                       | 6             | 6                           | 6                    | 6                  | 6                         | 6                            |
| 30 mg/kg   | Mean<br>S.D.  | 61<br>10.6    | 30<br>5.9               | 0<br>0.0      | 387<br>52.4                 | 24.1 **<br>2.99      | 0.6<br>0.04        | 51<br>7.3                 | 18 **<br>2.4                 |
|            | N             | 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<br>S.D.<br>N    | 4.34<br>0.142<br>6   | 1.62<br>0.064<br>6 | 9.6<br>0.16<br>6     | 7.3<br>0.54<br>6        | 140<br>0.6<br>6    | 4.1<br>0.12<br>6 | 105<br>1.2<br>6 |
| 30 mg/kg   | Mean<br>S.D.<br>N    | 4.72 *<br>0.204<br>6 | 1.70<br>0.123<br>6 | 10.2 **<br>0.19<br>6 | 8.1 *<br>0.31<br>6      | 141 **<br>0.4<br>6 | 4.3<br>0.39<br>6 | 105<br>1.0<br>6 |

\* : Significantly different from control value, \* ; p&lt;0.05 ; \*\* ; p&lt;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 |    |   |    |    |     |      |     |     |     |     |     |
|------------|---|----------------------|---|---|---|--------------|----|-----------|----|-----------------------|---|----------------|---|-----------------|-----|----|----|---|----|----|-----|------|-----|-----|-----|-----|-----|
|            |   | 0.1                  | 1 | 2 | 4 | ≥8           | TR | 1+        | 2+ | 3+                    | — | 1              | 0 | 0.25            | 0.5 |    | ≥1 | — | TR | 30 | 100 | ≥300 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |
|            |   |                      |   |   |   |              |    |           |    |                       |   |                |   |                 |     |    |    |   |    |    |     |      |     |     |     |     |     |

— : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe

\$ : Statistical analysis impossible.

\* : Significantly different from control value, \* ; p&lt;0.05, \*\* ; p&lt;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 $\geq 8$   | TR 1+ 2+ 3+  | - 1+ 2+ 3+ | - 5 15 40 $\geq 80$   | - 0.1 0.25 0.5 $\geq 1$ | TR 30 100 $\geq 300$ | 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 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 0             | 5 0 0 0 0               | 5 0 0 0 0            | 0 2 3 0 0               |

- : Negative, TR : Trace, 1+ : Slight, 2+ : Moderate, 3+ : Severe

\$ : Statistical analysis impossible.

\* : Significantly different from control value, \*\* ; p&lt;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 $\geq 8$    | TR 1+ 2+ 3+  | 1+ 2+ 3+   | 5 15 40 $\geq 80$     | 0.1 0.25 0.5 $\geq 1$ | TR 30 100 $\geq 300$ | 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 0   | 9 3 0 0 0  | 12 0 0 0 0 0          | 0 0 0 0 0             | 0 10 0 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 0    | 5 1 0 0 0  | 6 0 0 0 0 0           | 0 0 0 0 0             | 0 4 0 0 0            | 0 0 0 1 3 2             |
| 1          | 6  | 6 0 0 0 0 2 2 2 0 0   | 6 0 0 0 0    | 2 4 0 0 0  | 6 0 0 0 0 0           | 0 0 0 0 0             | 1 5 0 0 0            | 0 0 1 3 2 0             |
| 10         | 6  | 6 0 0 0 0 5 1 0 0 0   | 6 0 0 0 0    | 3 3 0 0 0  | 6 0 0 0 0 0           | 0 0 0 0 0             | 4 0 0 0              | 0 1 1 1 2 1             |
| 30         | 12 | 12 0 0 0 0 7 3 2 0 0  | 12 0 0 0 0   | 10 2 0 0 0 | 12 0 0 0 0 0          | 0 0 0 0 0             | 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&lt;0.05, \*\* ; p&lt;0.01.

Table 7 - F - 2

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 $\geq 8$   | TR 1+ 2+ 3+  | - 1+ 2+ 3+ | - 5 15 40 $\geq 80$   | - 0.1 0.25 0.5 $\geq 1$ | TR 30 100 $\geq 300$ | 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 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 0  | 6 0 0 0 0             | 6 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  
Organ weight (Absolute) - Group mean values  
Sex : Male  
Test article : Sample D-1  
Animals killed on schedule (4 weeks)  
Study No. BMR143C

| Dose level |           | F.B.W<br>(g) | Brain<br>(g) | Liver<br>(g) | Kidneys<br>(g) | Adrenals<br>(mg) | Testes<br>(g) |
|------------|-----------|--------------|--------------|--------------|----------------|------------------|---------------|
| 0 mg/kg    | Mean      | 351          | 1.96         | 13.60        | 2.43           | 50.5             | 2.99          |
|            | S.D.<br>N | 22.0<br>6    | 0.117<br>6   | 1.180<br>6   | 0.156<br>6     | 3.19<br>6        | 0.265<br>6    |
| 0.1 mg/kg  | Mean      | 359          | 1.98         | 14.50        | 2.55           | 54.3             | 3.14          |
|            | S.D.<br>N | 31.8<br>6    | 0.094<br>6   | 1.194<br>6   | 0.257<br>6     | 4.90<br>6        | 0.196<br>6    |
| 1 mg/kg    | Mean      | 349          | 1.94         | 13.88        | 2.26           | 52.9             | 3.14          |
|            | S.D.<br>N | 17.7<br>6    | 0.045<br>6   | 1.459<br>6   | 0.170<br>6     | 3.71<br>6        | 0.194<br>6    |
| 10 mg/kg   | Mean      | 343          | 1.94         | 16.93 **     | 2.39           | 49.5             | 3.01          |
|            | S.D.<br>N | 24.5<br>6    | 0.078<br>6   | 1.179<br>6   | 0.101<br>6     | 5.14<br>6        | 0.189<br>6    |
| 30 mg/kg   | Mean      | 292 **       | 1.97         | 20.36 **     | 2.11 **        | 50.4             | 3.08          |
|            | S.D.<br>N | 17.6<br>6    | 0.072<br>6   | 2.228<br>6   | 0.084<br>6     | 4.15<br>6        | 0.250<br>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<br>(g)      | Brain<br>(g)       | Liver<br>(g)           | Kidneys<br>(g)     | Adrenals<br>(mg)  | Testes<br>(g)        |
|------------|-------------------|--------------------|------------------------|--------------------|-------------------|----------------------|
| 0 mg/kg    | Mean<br>S.D.<br>N | 2.05<br>0.051<br>6 | 13.57<br>1.768<br>6    | 2.47<br>0.151<br>6 | 53.1<br>6.85<br>6 | 2.74<br>0.942<br>6   |
| 30 mg/kg   | Mean<br>S.D.<br>N | 341 *<br>18.5<br>5 | 20.66 **<br>1.693<br>5 | 2.40<br>0.157<br>5 | 51.5<br>7.31<br>5 | 3.38 *<br>0.117<br>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.V<br>(g)      | Brain<br>(g)       | Liver<br>(g)           | Kidneys<br>(g)     | Adrenals<br>(mg)  | Ovaries<br>(mg)      |
|------------|-------------------|--------------------|------------------------|--------------------|-------------------|----------------------|
| 0 mg/kg    | Mean<br>S.D.<br>N | 1.85<br>0.067<br>6 | 8.76<br>0.471<br>6     | 1.62<br>0.177<br>6 | 60.1<br>5.46<br>6 | 83.7<br>10.13<br>6   |
| 0.1 mg/kg  | Mean<br>S.D.<br>N | 227<br>10.5<br>6   | 8.65<br>0.679<br>6     | 1.61<br>0.162<br>6 | 59.8<br>6.93<br>6 | 83.7<br>7.86<br>6    |
| 1 mg/kg    | Mean<br>S.D.<br>N | 235<br>15.9<br>6   | 9.07<br>0.852<br>6     | 1.67<br>0.081<br>6 | 62.6<br>7.79<br>6 | 92.0<br>15.11<br>6   |
| 10 mg/kg   | Mean<br>S.D.<br>N | 214<br>14.4<br>6   | 10.58 **<br>0.973<br>6 | 1.70<br>0.109<br>6 | 60.8<br>8.01<br>6 | 75.8<br>8.53<br>6    |
| 30 mg/kg   | Mean<br>S.D.<br>N | 190 **<br>9.5<br>6 | 13.78 **<br>0.816<br>6 | 1.50<br>0.126<br>6 | 55.6<br>6.28<br>6 | 62.6 **<br>7.57<br>6 |

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

F.B.W : Final body weight

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

Table 9 - M - 1  
 Organ weight (Relative : percentage of body weight)  
 - Group mean values  
 Sex : Male  
 Test article : Sample D-1  
 Animals killed on schedule (4 weeks)  
 Study No. BMR143C

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

F.B.W : Final body weight

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

Table 9 - M - 2 Study No. BMRI43C

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<br>(g)      | Brain              | Liver                 | Kidneys            | Adrenals<br>(x10 <sup>-3</sup> ) | Testes                |
|------------|-------------------|--------------------|-----------------------|--------------------|----------------------------------|-----------------------|
| 0 mg/kg    | Mean<br>S.D.<br>N | 0.53<br>0.044<br>6 | 3.48<br>0.160<br>6    | 0.64<br>0.058<br>6 | 13.7<br>1.82<br>6                | 0.70<br>0.231<br>6    |
| 30 mg/kg   | Mean<br>S.D.<br>N | 341 *<br>18.5<br>5 | 6.06 **<br>0.482<br>5 | 0.70<br>0.029<br>5 | 15.2<br>2.67<br>5                | 0.99 **<br>0.069<br>5 |

F.B.W : Final body weight

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

Table 9 - F - I Study No. BMRI43C

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<br>(g) | Brain      | Liver      | Kidneys    | Adrenals<br>( $\times 10^{-3}$ ) | Ovaries<br>( $\times 10^{-3}$ ) |
|------------|-----------|--------------|------------|------------|------------|----------------------------------|---------------------------------|
| 0 mg/kg    | Mean      | 230          | 0.80       | 3.81       | 0.70       | 26.2                             | 36.4                            |
|            | S.D.<br>N | 17.4<br>6    | 0.037<br>6 | 0.198<br>6 | 0.043<br>6 | 2.76<br>6                        | 4.28<br>6                       |
| 0.1 mg/kg  | Mean      | 227          | 0.79       | 3.81       | 0.71       | 26.4                             | 36.9                            |
|            | S.D.<br>N | 10.5<br>6    | 0.053<br>6 | 0.148<br>6 | 0.042<br>6 | 2.89<br>6                        | 2.90<br>6                       |
| 1 mg/kg    | Mean      | 235          | 0.81       | 3.85       | 0.71       | 26.6                             | 39.3                            |
|            | S.D.<br>N | 15.9<br>6    | 0.047<br>6 | 0.237<br>6 | 0.043<br>6 | 2.73<br>6                        | 5.90<br>6                       |
| 10 mg/kg   | Mean      | 214          | 0.87       | 4.95 **    | 0.79 **    | 28.4                             | 35.4                            |
|            | S.D.<br>N | 14.4<br>6    | 0.055<br>6 | 0.255<br>6 | 0.015<br>6 | 2.54<br>6                        | 3.23<br>6                       |
| 30 mg/kg   | Mean      | 190 **       | 0.96 **    | 7.24 **    | 0.79 **    | 29.2                             | 33.0                            |
|            | S.D.<br>N | 9.5<br>6     | 0.034<br>6 | 0.321<br>6 | 0.053<br>6 | 2.50<br>6                        | 4.37<br>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<br>(g) | Brain      | Liver      | Kidneys    | Adrenals<br>( $\times 10^{-3}$ ) | Ovaries<br>( $\times 10^{-3}$ ) |
|------------|-----------|--------------|------------|------------|------------|----------------------------------|---------------------------------|
| 0 mg/kg    | Mean      | 277          | 0.70       | 3.28       | 0.64       | 25.6                             | 32.5                            |
|            | S.D.<br>N | 24.8<br>6    | 0.059<br>6 | 0.157<br>6 | 0.035<br>6 | 4.10<br>6                        | 2.25<br>6                       |
| 30 mg/kg   | Mean      | 208 **       | 0.90 **    | 6.00 **    | 0.76 **    | 25.9                             | 33.0                            |
|            | S.D.<br>N | 14.5<br>6    | 0.047<br>6 | 0.358<br>6 | 0.033<br>6 | 2.43<br>6                        | 3.18<br>6                       |

F.B.W : Final body weight

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

Table 10-N.F  
Group Incidence of macroscopic findings  
Test article : Sample D-1

| Organ                           | Period<br>Sex        | 28 days |     |   |    |    |        |     |   |    |    | Recovery |    | Dead animal |    |
|---------------------------------|----------------------|---------|-----|---|----|----|--------|-----|---|----|----|----------|----|-------------|----|
|                                 |                      | Male    |     |   |    |    | Female |     |   |    |    | Male     |    | Female      |    |
|                                 |                      | 0       | 0.1 | 1 | 10 | 30 | 0      | 0.1 | 1 | 10 | 30 | 0        | 30 | 0           | 30 |
| Findings                        | Dose level (mg/kg) : | 6       | 6   | 6 | 6  | 6  | 6      | 6   | 6 | 6  | 6  | 6        | 5  | 6           | 6  |
|                                 | Number of animals :  | 6       | 6   | 6 | 6  | 6  | 6      | 6   | 6 | 6  | 6  | 6        | 5  | 6           | 6  |
| Thymus                          |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Dark reddish patch              |                      | 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           | 1  |
| Lungs                           |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Dark reddish patch              |                      | 1       | 0   | 0 | 0  | 0  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Liver                           |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Scattering of greyish dot/patch |                      | 0       | 0   | 0 | 0  | 5  | 0      | 0   | 0 | 0  | 0  | 1        | 0  | 0           | 1  |
| Hypertrophy                     |                      | 0       | 0   | 0 | 0  | 6  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 1           | 0  |
| Greyish patch                   |                      | 0       | 0   | 0 | 0  | 1  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 1           | 0  |
| Dark reddish change             |                      | 0       | 0   | 0 | 0  | 0  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Yellowish change                |                      | 0       | 0   | 0 | 0  | 0  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Kidneys                         |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Cyst                            |                      | 1       | 0   | 0 | 0  | 0  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Pyelectasis                     |                      | 0       | 1   | 0 | 0  | 0  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Greyish patch                   |                      | 0       | 0   | 1 | 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  |
| Adrenals                        |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Dark reddish change             |                      | 0       | 0   | 0 | 0  | 1  | 0      | 0   | 0 | 0  | 0  | 0        | 0  | 0           | 0  |
| Stomach                         |                      |         |     |   |    |    |        |     |   |    |    |          |    |             |    |
| Tarry contents/haemorrhage      |                      | 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 II-X  
Group Incidence of microscopic findings (28days)  
Sex : Male  
Test article : Sample D-1

Study No. BMR143C

| Findings                                         | Grade | 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) |   |   |
|--------------------------------------------------|-------|---------------|---|---|-----------------|---|---|---------------|---|---|----------------|---|---|----------------|---|---|
|                                                  |       | -             | ± | + | -               | ± | + | -             | ± | + | -              | ± | + | -              | ± | + |
| Liver                                            |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| microgranuloma                                   |       | 0             | 4 | 2 | 0               | 0 | 0 | 0             | 4 | 2 | 0              | 0 | 0 | 0              | 3 | 3 |
| focal necrosis                                   |       | 5             | 0 | 1 | 0               | 0 | 0 | 0             | 6 | 0 | 0              | 0 | 0 | 1              | 0 | 4 |
| focal fatty change                               |       | 5             | 0 | 1 | 0               | 0 | 0 | 0             | 6 | 0 | 0              | 0 | 0 | 6              | 0 | 0 |
| peripheral fatty change                          |       | 6             | 0 | 0 | 0               | 0 | 0 | 0             | 4 | 2 | 0              | 0 | 0 | 1              | 2 | 2 |
| swelling of centrilobular hepatocytes            |       | 6             | 0 | 0 | 0               | 0 | 0 | 0             | 3 | 3 | 0              | 0 | 0 | 0              | 0 | 2 |
| eosinophilic change in centrilobular hepatocytes |       | 6             | 0 | 0 | 0               | 0 | 0 | 0             | 2 | 4 | 0              | 0 | 0 | 0              | 0 | 0 |
| Heart                                            |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| myocardial degeneration                          |       | 4             | 2 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| myocardial fibrosis                              |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| Spleen                                           |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| extramedullary hematopoiesis                     |       | 3             | 2 | 1 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| Kidneys                                          |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| regenerated tubules                              |       | 3             | 1 | 2 | 0               | 0 | 0 |               |   |   |                |   |   | 3              | 1 | 2 |
| dilated tubules                                  |       | 5             | 0 | 1 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| infiltration of lymphocytes                      |       | 3             | 2 | 1 | 0               | 0 | 0 |               |   |   |                |   |   | 5              | 1 | 0 |
| dilation of pelvis                               |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 4              | 0 | 2 |
| chronic nephropathy                              |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| Adrenals                                         |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| abnormality                                      |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| Brain                                            |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| abnormality                                      |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |
| Testes                                           |       |               |   |   |                 |   |   |               |   |   |                |   |   |                |   |   |
| atrophy                                          |       | 6             | 0 | 0 | 0               | 0 | 0 |               |   |   |                |   |   | 6              | 0 | 0 |

- : Negative. ± : Very slight. + : Slight. ++ : Moderate. HH : Severe

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

Study No. DMRI43C

| 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               | 5 | 1 | 0 | 0             | 0 | 0 | 0 | 0              | 5 | 1 | 0 | 0              | 1 | 3 | 1 | 1 |
| focal necrosis                                   |       | 6             | 0 | 0 | 0 | 0               | 6 | 0 | 0 | 0             | 0 | 0 | 0 | 6              | 0 | 0 | 0 | 4              | 0 | 2 | 0 |   |
| focal fatty change                               |       | 6             | 0 | 0 | 0 | 0               | 6 | 0 | 0 | 0             | 0 | 0 | 0 | 6              | 0 | 0 | 0 | 6              | 0 | 0 | 0 |   |
| peripheral fatty change                          |       | 2             | 2 | 2 | 0 | 0               | 0 | 2 | 4 | 0             | 0 | 3 | 2 | 1              | 0 | 0 | 2 | 2              | 3 | 1 | 2 | 0 |
| swelling of centrilobular hepatocytes            |       | 6             | 0 | 0 | 0 | 0               | 6 | 0 | 0 | 0             | 0 | 6 | 0 | 0              | 0 | 2 | 4 | 0              | 0 | 1 | 5 |   |
| eosinophilic change in centrilobular hepatocytes |       | 6             | 0 | 0 | 0 | 0               | 6 | 0 | 0 | 0             | 0 | 6 | 0 | 0              | 0 | 2 | 4 | 0              | 0 | 0 | 6 |   |
| Heart                                            |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   |                |   |   |   |   |
| myocardial degeneration                          |       | 6             | 0 | 0 | 0 | 0               | 6 | 0 | 0 | 0             | 0 | 6 | 0 | 0              | 0 | 2 | 4 | 0              | 0 | 0 | 6 |   |
| myocardial fibrosis                              |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| Spleen                                           |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| extramedullary hematopoiesis                     |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| Kidneys                                          |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   |                |   |   |   |   |
| regenerated tubules                              |       | 3             | 2 | 1 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 3              | 3 | 0 | 0 |   |
| dilated tubules                                  |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| infiltration of lymphocytes                      |       | 3             | 2 | 1 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| dilation of pelvis                               |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 1 | 0 |   |
| chronic nephropathy                              |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| Adrenals                                         |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| abnormality                                      |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| Brain                                            |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   |                |   |   |   |   |
| abnormality                                      |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |
| Ovaries                                          |       |               |   |   |   |                 |   |   |   |               |   |   |   |                |   |   |   |                |   |   |   |   |
| abnormality                                      |       | 6             | 0 | 0 | 0 | 0               |   |   |   |               |   |   |   |                |   |   |   | 6              | 0 | 0 | 0 |   |

- : Negative. ± : Very slight. + : Slight. # : Moderate. ## : Severe

Table II-R-1  
Group Incidence of microscopic findings (Recovery)  
Test article : Sample D-1  
Study No. BMR143C

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

- : Negative, ± : Very slight, + : Slight, # : Moderate, HH : Severe

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

| Findings                                            | Sex<br>Dose level | Grade | Male<br>30 mg/kg (n=1) |   |   |   |    |
|-----------------------------------------------------|-------------------|-------|------------------------|---|---|---|----|
|                                                     |                   |       | -                      | ± | + | # | ## |
| Liver                                               |                   |       |                        |   |   |   |    |
| Eosinophilic change in<br>centrilobular hepatocytes |                   |       | 0                      | 0 | 0 | 1 | 0  |
| Swelling of centrilobular<br>hepatocytes            |                   |       | 0                      | 0 | 0 | 1 | 0  |
| Focal necrosis                                      |                   |       | 0                      | 0 | 0 | 1 | 0  |
| Peripherai 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<br>glandular stomach        |                   |       | 0                      | 0 | 1 | 0 | 0  |
| Thyroid                                             |                   |       |                        |   |   |   |    |
| 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)

3M\_MN01650066

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

Study No. BMR143C

| Sex  | Dose level<br>(mg/kg) | Animal<br>number | Sex : Male              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Study No. BMR143C |    |       |
|------|-----------------------|------------------|-------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-------------------|----|-------|
|      |                       |                  | 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 | -     |
|      |                       | 4104             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | -  | -     |
|      |                       | 4105             | SA                      | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | -  | -     |
|      |                       | 4106             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | -  | -     |
|      |                       | 4107             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | -  | -     |
|      |                       | 4108             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | SA | SA | RS | -  | SA | SA | SA | SA                | SA | SA    |
|      |                       | 4109             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | SA | SA | SA | SA | -  | SA | SA                | -  | TC ES |
|      |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | LY                |    |       |
|      |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   | BP |       |
|      |                       | 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

Study No. BMR143C

Sex : Male

| Sex  | Dose level<br>(mg/kg) | Animal<br>number | Days after commencement/cessation of treatment |      |      |      |      |      |      |      |      |      |       |       |       |       | Study no. 2411400 |
|------|-----------------------|------------------|------------------------------------------------|------|------|------|------|------|------|------|------|------|-------|-------|-------|-------|-------------------|
|      |                       |                  | 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 |                   |
| Male | 0                     | 0107             | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -     | -                 |
|      |                       | ↓                |                                                |      |      |      |      |      |      |      |      |      |       |       |       |       |                   |
|      |                       | 0112             | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -     | -                 |
|      |                       | 4107             | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -     | -                 |
|      | 30                    | 4108             | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -     | -                 |
|      |                       | 4109             | -                                              | -    | -    | RM   | DD   |      |      |      |      |      |       |       |       |       |                   |
|      |                       |                  |                                                |      |      | 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<br>(mg/kg) | Animal<br>number | Sex : female            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Study No. BHR143C |   |
|--------|-----------------------|------------------|-------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-------------------|---|
|        |                       |                  | Days after commencement |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |   |
| Female | 0                     | 0201             | 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                |   |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        | 0.1                   | 0212             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        | 1                     | 1201             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        | 10                    | 2201             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | 2206             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | - |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | 3201             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | - |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |
|        |                       | 3206             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | - |
|        |                       | ↓                | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 |   |

- : No abnormality observed.

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

| Sex    | Dose level<br>(mg/kg) | Animal<br>number | Sex : Female            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Study No. BMR149C |    |  |
|--------|-----------------------|------------------|-------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-------------------|----|--|
|        |                       |                  | 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 | 30                    | 4201             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | SA | -  | -  | -  | SA | SA | -  | SA | -  | -  | SA | -  | -  | SA                | -  |  |
|        |                       | 4202             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -                 | -  |  |
|        |                       | 4203             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | SA | -  | SA | SA | -  | RS | -  | -  | RS | -                 | -  |  |
|        |                       | 4204             | -                       | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | SA | SA | -  | -  | SA | SA | SA | SA | -  | SA | -  | SA | -  | SA                | -  |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | RM |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | TC |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | CR |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    | CY |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |
|        |                       |                  |                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                   |    |  |

RM : Reduced spontaneous movement, TC : Tonic-clonic/Clonic convulsion, LY : Lying, CR : Crouching, SA : Salivation,  
RS : Reddish salivation, CY : Cyanosis, LL : 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<br>(mg/kg) | Animal<br>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             | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -           |
|        |                       | ↓                | -                                              | -    | -    | -    | -    | -    | -    | -    | -    | -    | -     | -     | -     | -           |
|        | 30                    | 4207             | 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          |
|        |                       | 4209             | LH                                             | LH   | LH   | LH   | LH   | LH   | LH   | LH   | LH   | LH   | LH    | LH    | LH    | LH          |
|        |                       | 4210             | CS                                             | 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

## Weeks after commencement/ cessation of treatment

| Animal Number | 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<br>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. BMRI43C

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

Weeks after commencement/ cessation of treatment

| Animal Number | 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

Weeks after commencement/ cessation of treatment

| Animal Number | 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    | 325 KS  |
| 0208          | 131                                              | 168 | 201  | 222  | 237    | 265 KS  |
| 0209          | 129                                              | 168 | 188  | 214  | 256    | 264 KS  |
| 0210          | 128                                              | 171 | 200  | 228  | 261    | 270 KS  |
| 0211          | 133                                              | 171 | 196  | 220  | 262    | 278 KS  |
| 0212          | 121                                              | 156 | 179  | 201  | 245    | 257 KS  |
| Mean          | 130                                              | 166 | 193  | 217  | 237    | 277     |
| S.D.          | 5.4                                              | 8.1 | 13.1 | 16.5 | 18.6   | 24.8    |
| N             | 12                                               | 12  | 12   | 12   | 12     | 6       |

KS : Killed on schedule

Appendix 2 - F - 2  
 Body weight - Individual values  
 Sex : Female  
 Dose level : Sample D-1 0.1 mg/kg  
 Study No. BMR143C  
 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<br>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. BMRI43C

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. BMRI43C

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    |            |
| 4208          | 128                                              | 144 | 158 | 161 | 169    | 194 201 KS |
| 4209          | 131                                              | 160 | 177 | 181 | 190    | 188 199 KS |
| 4210          | 129                                              | 159 | 171 | 169 | 168    | 196 208 KS |
| 4211          | 122                                              | 149 | 159 | 175 | 186    | 183 193 KS |
| 4212          | 134                                              | 167 | 175 | 179 | 187    | 197 213 KS |
|               |                                                  |     |     |     |        | 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<br>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<br>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<br>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.

Food consumption - Individual values

**Sex : Male**

Dose level : Sample D-1 10 mg/kg

Unit : g/Animal/Day

| Cage<br>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<br>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. BMRI43C

Food consumption - Individual values

Sex : Female

Dose level : Sample D-1 0 mg/kg

Unit : g/Animal/Day

Weeks after commencement/ cessation of treatment

| Cage Number | 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<br>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.

## Food consumption - Individual values

**Sex : Female**

| Dose level : | Sample D-1 | 10 mg/kg |
|--------------|------------|----------|
|--------------|------------|----------|

Unit : g/Animal/Day

| Cage<br>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<br>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 ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht. (%) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC (%) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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 ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht ( % ) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC ( % ) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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. BM143C

## Hematology - Individual values

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

| Animal Number | RBC count<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|---------------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 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 - N - 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<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|---------------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 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 ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht (%) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC (%) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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 - H - 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 ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht ( % ) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC ( % ) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|---------------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 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          | 0                                          |                    |           |                            |             |             |                                                 |             |               |                                |
| 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                              |
| 0 : Dead.     |                                            |                    |           |                            |             |             |                                                 |             |               |                                |

## Appendix 4 - F - I

Study No. BMR143C

## Hematology - Individual values

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

| Animal Number | RBC count<br>( $\times 10^4/\text{mm}^3$ ) | HB conc.<br>(g/dl) | Ht<br>(%) | MCV<br>( $\mu\text{m}^3$ ) | MCH<br>(pg) | MCHC<br>(%) | Platelet count<br>( $\times 10^4/\text{mm}^3$ ) | PT<br>(sec) | APTT<br>(sec) | Reticulo-<br>cyte count<br>(%) |
|---------------|--------------------------------------------|--------------------|-----------|----------------------------|-------------|-------------|-------------------------------------------------|-------------|---------------|--------------------------------|
| 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 ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht (%) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC (%) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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 0-1 1 mg/kg  
 Animals killed on schedule (4 weeks)

| Animal Number | RBC count ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht ( % ) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC ( % ) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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. BNRI43C

## Hematology - Individual values

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

| Animal Number | RBC count ( $\times 10^4/\text{mm}^3$ ) | HB conc. (g/dl) | Ht ( % ) | MCV ( $\mu\text{m}^3$ ) | MCH (pg) | MCHC ( % ) | Platelet count ( $\times 10^4/\text{mm}^3$ ) | PT (sec) | APTT (sec) | Reticulo-cyte 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 <sup>2</sup> /mm <sup>3</sup> ) | Differential count of leukocytes ( % of total counted cells ) |                       |      |              |            |
|---------------|------------------------------------------------|---------------------------------------------------------------|-----------------------|------|--------------|------------|
|               |                                                | Lymphocytes                                                   | Segmented Neutrophils | Band | Eosino-phils | Baso-phils |
| 2201          | 57                                             | 86                                                            | 9                     | 1    | 0            | 0          |
| 2202          | 94                                             | 92                                                            | 7                     | 0    | 0            | 0          |
| 2203          | 108                                            | 87                                                            | 10                    | 0    | 1            | 0          |
| 2204          | 112                                            | 81                                                            | 15                    | 0    | 1            | 0          |
| 2205          | 77                                             | 86                                                            | 13                    | 0    | 0            | 0          |
| 2206          | 70                                             | 93                                                            | 5                     | 1    | 0            | 0          |
| Mean          | 86                                             | 88                                                            | 10                    | 0    | 0            | 0          |
| S.D.          | 21.9                                           | 4.4                                                           | 3.7                   | 0.5  | 0.5          | 0.0        |
| N             | 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<br>(x10 <sup>2</sup> /mm <sup>3</sup> ) | Differential count of leukocytes ( % of total counted cells ) |                          |      |                  |                |                |
|---------------|---------------------------------------------------|---------------------------------------------------------------|--------------------------|------|------------------|----------------|----------------|
|               |                                                   | Lympho-<br>cytes                                              | Segmented<br>Neutrophils | Band | Eosino-<br>phils | Baso-<br>phils | Mono-<br>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 <sup>2</sup> /mm <sup>3</sup> ) | Differential count of leukocytes ( % of total counted cells ) |                          |      |                  |
|---------------|------------------------------------------------|---------------------------------------------------------------|--------------------------|------|------------------|
|               |                                                | Lympho-<br>cytes                                              | Segmented<br>Neutrophils | Band | Eosino-<br>phils |
| 4201          | 78                                             | 89                                                            | 6                        | 0    | 0                |
| 4202          | 66                                             | 83                                                            | 7                        | 1    | 0                |
| 4203          | 83                                             | 89                                                            | 7                        | 0    | 0                |
| 4204          | 104                                            | 87                                                            | 7                        | 0    | 1                |
| 4205          | 60                                             | 92                                                            | 5                        | 0    | 0                |
| 4206          | 71                                             | 80                                                            | 18                       | 0    | 0                |
| Mean          | 77                                             | 87                                                            | 8                        | 0    | 0                |
| S.D.          | 15.6                                           | 4.4                                                           | 4.8                      | 0.4  | 0.4              |
| N             | 6                                              | 6                                                             | 6                        | 6    | 6                |
|               |                                                |                                                               |                          |      | 2.4              |
|               |                                                |                                                               |                          |      | 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<br>Number | WBC<br>count<br>(x10 <sup>2</sup> /mm <sup>3</sup> ) | Differential count of leukocytes ( % of total counted cells ) |                          |      |                  |                |                |
|------------------|------------------------------------------------------|---------------------------------------------------------------|--------------------------|------|------------------|----------------|----------------|
|                  |                                                      | Lympho-<br>cytes                                              | Neutrophils<br>Segmented | Band | Eosino-<br>phils | Baso-<br>phils | Mono-<br>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<br>Number | WBC<br>count<br>( $\times 10^2/\text{mm}^3$ ) | Differential count of leukocytes ( % of total counted cells ) |                               |                  |                |                |     |
|------------------|-----------------------------------------------|---------------------------------------------------------------|-------------------------------|------------------|----------------|----------------|-----|
|                  |                                               | Lympho-<br>cytes                                              | Neutrophils<br>Segmented Band | Eosino-<br>phils | Baso-<br>phils | Mono-<br>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 - N - 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<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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 G - M - 2

Study No. BMR143C

## Clinical chemistry - Individual values

Sex : Male  
 Dose level : Sample 0-1 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 - N - 3

Study No. BMR143C

## Clinical chemistry - Individual values

Sex : Male  
 Dose level : Sample 0-1 0.1 mg/kg  
 Animals killed on schedule (4 weeks)

| Animal Number | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(mg/dl) |
|---------------|---------------|---------------|-------------------------|---------------|-----------------------------|----------------------|--------------------|---------------------------|------------------------------|
| 1101          | 65            | 29            | 0                       | 822           | 11.8                        | 0.4                  | 136                | 62                        | 71                           |
| 1102          | 77            | 31            | 0                       | 686           | 13.2                        | 0.5                  | 138                | 58                        | 59                           |
| 1103          | 69            | 38            | 0                       | 713           | 10.1                        | 0.4                  | 157                | 59                        | 41                           |
| 1104          | 81            | 26            | 0                       | 577           | 11.5                        | 0.4                  | 149                | 57                        | 61                           |
| 1105          | 68            | 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 - N - 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<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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 - H - 6

Study No. BMRI43C

## Clinical chemistry - Individual values

Sex : Male  
 Dose level : Sample 0-1 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 - N - 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<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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 6 - N - 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<br>(IU/l) | GPT<br>(IU/l) | r-GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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) | $\gamma$ -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 - N - 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          |

## 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) | $\gamma$ -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          |            |            |                      |            |                       |                   |                 |                     |                        |
| 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          | 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          |

0 : Dead.

## Appendix 6 - F - 1

Study No. BMRI43C

## Clinical chemistry - Individual values

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

| Animal Number | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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                            |

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. BMRI43C

## 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) | $\gamma$ -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 8 - F - 5

Study No. BMRI43C

## Clinical chemistry - Individual values

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

| Animal Number | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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. BMRI43C

## 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) | $\gamma$ -GTP (IU/l) | ALP (IU/l) | Urea nitrogen (mg/dl) | Creatinin (mg/dl) | Glucose (mg/dl) | Total chol. (mg/dl) | Trigly-<br>ceride (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 0-1 30 mg/kg  
 Animals killed on schedule (4 weeks)

| Animal Number | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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. BNR143C

## 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) | $\gamma$ -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          |

## Clinical chemistry - Individual values

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

| Animal Number | GOT<br>(IU/l) | GPT<br>(IU/l) | $\gamma$ -GTP<br>(IU/l) | ALP<br>(IU/l) | Urea<br>nitrogen<br>(mg/dl) | Creatinin<br>(mg/dl) | Glucose<br>(mg/dl) | Total<br>chol.<br>(mg/dl) | Trigly-<br>ceride<br>(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 6 - 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. BMRL43C

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. BMRI43C

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. BMRI43C

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

Study No. BMR143C

Appendix 7 - M - 6

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

Study No. BMR143C

Appendix 7 - M - 7

Urinalysis - Individual values

Sex : Male 30 mg/kg  
Dose level : Sample D-1  
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                    | -            | -         | 5                     | -              | 30              | 6.5 |
| 4110          | 0.1                  | -            | -         | 5                     | -              | 30              | 6.5 |
| 4111          | 0.1                  | -            | -         | 5                     | -              | 30              | 7.0 |
| 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

### Urinalysis - Individual values

Sex : Female  
Dose level : Sample D-1  
3 weeks after commencement of treatment

| Animal<br>Number | Urobili-<br>nogen<br>(EU/dl) | Occult<br>Blood | Bilirubin | Ketone<br>bodies<br>(mg/dl) | Glucose<br>(g/dl) | Protein<br>(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

Study No. BMR143C

Appendix 7 - F - 3

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. BMRI43C

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. BMRI43C

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        | 62.2          | 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 |           |           |           |             |               |            |

Study No. BMR143C

Appendix 8 - M - 5.

Organ weight (Absolute) - Individual values

Sex : Male

Dose level : Sample D-1

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. BMRI43C

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. BMRI43C

## 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        | 52.6          | 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        | 53.9          | 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 |           |           |           |             |               |              |

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

Appendix 8 - F - 6 Study No. BMR143C

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 <sup>-3</sup> ) | 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. BMRI43C

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 <sup>-3</sup> ) | 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 <sup>-3</sup> ) | 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 | 0.050   | 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 <sup>-3</sup> ) | 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 <sup>-3</sup> ) | 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 |           |       |       |         |                               |        |

Appendix 9 - M - 6 Study No. BMRI43C

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 <sup>-3</sup> ) | 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. BMRI43C

Organ weight (Relative : percentage of body weight)  
- Individual valuesSex : 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 <sup>-3</sup> ) | 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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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. BMRI43C

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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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. BMRI43C

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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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. BMRI43C

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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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  | 7.53  | 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 valuesSex : 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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 0207                      | 325       | 0.59  | 3.48  | 0.59    | 24.8                          | 32.7                         |
| 0208                      | 265       | 0.70  | 3.05  | 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. BMRI43C

Organ weight (Relative : percentage of body weight)  
- Individual valuesSex : 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 <sup>-3</sup> ) | Ovaries (x10 <sup>-3</sup> ) |
|---------------------------|-----------|-------|-------|---------|-------------------------------|------------------------------|
| 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. BNRI43C

|                                 |               | 0 mg/kg (01-) |    |    |    |    |    | 0.1 mg/kg (11-) |    |    |    |    |    | 1 mg/kg (21-) |    |    |    |    |    | 10 mg/kg (31-) |    |    |    |    |    | 30 mg/kg (41-) |    |    |    |    |    |
|---------------------------------|---------------|---------------|----|----|----|----|----|-----------------|----|----|----|----|----|---------------|----|----|----|----|----|----------------|----|----|----|----|----|----------------|----|----|----|----|----|
| Dose level                      | :             | 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 |
| Findings                        | Animal number | 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                           |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Scattering of greyish dot/patch |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Hypertrophy                     |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Greyish patch                   |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Dark reddish change             |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Yellowish change                |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Kidneys                         |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Cyst                            |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Pylectasis                      |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Greyish patch                   |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Blackish change                 |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Adrenals                        |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Dark reddish change             |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Testes                          |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Atrophy                         |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |

- : No lesion. P : Present

Appendix 10-F  
Individual macroscopic findings (28days)  
Sex : Female  
Test article : Sample D-1  
Study No. DMR143C

| Dose level                      |               | 0 mg/kg (02-) |    |    |    |    |    | 0.1 mg/kg (12-) |    |    |    |    |    | 1 mg/kg (22-) |    |    |    |    |    | 10 mg/kg (32-) |    |    |    |    |    | 30 mg/kg (42-) |    |    |    |    |    |
|---------------------------------|---------------|---------------|----|----|----|----|----|-----------------|----|----|----|----|----|---------------|----|----|----|----|----|----------------|----|----|----|----|----|----------------|----|----|----|----|----|
| Findings                        | Animal number | 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                           |               |               |    |    |    |    |    |                 |    |    |    |    |    |               |    |    |    |    |    |                |    |    |    |    |    |                |    |    |    |    |    |
| Scattering of greyish dot/patch |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Hypertrophy                     |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Greyish patch                   |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Dark reddish change             |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Yellowish change                |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Kidneys                         |               |               |    |    |    |    |    |                 |    |    |    |    |    |               |    |    |    |    |    |                |    |    |    |    |    |                |    |    |    |    |    |
| Cyst                            |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Pyelectasis                     |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Greyish patch                   |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Blackish change                 |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |
| Adrenals                        |               |               |    |    |    |    |    |                 |    |    |    |    |    |               |    |    |    |    |    |                |    |    |    |    |    |                |    |    |    |    |    |
| Dark reddish change             |               | -             | -  | -  | -  | -  | -  | -               | -  | -  | -  | -  | -  | -             | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  | -              | -  | -  | -  | -  | -  |

- : No lesion, P : Present

Appendix 10-R-1  
Individual macroscopic findings (Recovery)  
Test article : Sample 0-1

Study No. BMR143C

| Sex                             | Dose level    | Male          |    |    |    |                |    |    |    |               |    |    |    | Female         |    |    |    |    |    |    |    |    |    |    |  |
|---------------------------------|---------------|---------------|----|----|----|----------------|----|----|----|---------------|----|----|----|----------------|----|----|----|----|----|----|----|----|----|----|--|
|                                 |               | 0 mg/kg (01-) |    |    |    | 30 mg/kg (41-) |    |    |    | 0 mg/kg (02-) |    |    |    | 30 mg/kg (42-) |    |    |    |    |    |    |    |    |    |    |  |
| Findings                        | 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 |  |
| Lungs                           |               |               |    |    |    |                |    |    |    |               |    |    |    |                |    |    |    |    |    |    |    |    |    |    |  |
| Dark reddish patch              |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Liver                           |               |               |    |    |    |                |    |    |    |               |    |    |    |                |    |    |    |    |    |    |    |    |    |    |  |
| Scattering of greyish dot/patch |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Hypertrophy                     |               | -             | -  | -  | -  | -              | -  | -  | P  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Greyish patch                   |               | -             | -  | -  | -  | -              | -  | -  | P  | P             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Dark reddish change             |               | -             | -  | -  | -  | -              | -  | -  | P  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Yellowish change                |               | -             | -  | -  | -  | -              | -  | -  | P  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| kidneys                         |               |               |    |    |    |                |    |    |    |               |    |    |    |                |    |    |    |    |    |    |    |    |    |    |  |
| Cyst                            |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Pyelocystis                     |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Greyish patch                   |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Blackish change                 |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Adrenals                        |               |               |    |    |    |                |    |    |    |               |    |    |    |                |    |    |    |    |    |    |    |    |    |    |  |
| Dark reddish change             |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| Testes                          |               |               |    |    |    |                |    |    |    |               |    |    |    |                |    |    |    |    |    |    |    |    |    |    |  |
| Atrophy                         |               | -             | -  | -  | -  | -              | -  | -  | -  | -             | -  | -  | -  | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |

-- : 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   | Scattering of greyish dot/patch |

3M\_MN01650181

Appendix 11-M  
Individual microscopic findings (28days)  
Sex : Male  
Test article : Sample D-1

Study No. BMR143C

| Dose level :                                     |                 | 0 mg/kg (01-) |    |    |    |    | 0.1 mg/kg (11-) |    |    |    |    | 1 mg/kg (21-) |    |    |    |    | 10 mg/kg (31-) |    |    |    |    | 30 mg/kg (41-) |    |    |    |    |    |    |    |    |    |
|--------------------------------------------------|-----------------|---------------|----|----|----|----|-----------------|----|----|----|----|---------------|----|----|----|----|----------------|----|----|----|----|----------------|----|----|----|----|----|----|----|----|----|
| Findings                                         | Animal number : | 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. DMRL43C

| Dose level                                       |               | 0 mg/kg (02-) |    |    |    |    |    | 1 mg/kg (22-) |    |    |    |    |    | 10 mg/kg (32-) |    |    |    |    |    | 30 mg/kg (42-) |    |    |    |    |    |
|--------------------------------------------------|---------------|---------------|----|----|----|----|----|---------------|----|----|----|----|----|----------------|----|----|----|----|----|----------------|----|----|----|----|----|
| Findings                                         | Animal number | 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

| Sex                                              | Dose level | Animal number | Findings | Male          |    |    |    |                |    |    |    |               |    |    |    | Female         |    |    |    |               |    |    |    |                |    |    |    |
|--------------------------------------------------|------------|---------------|----------|---------------|----|----|----|----------------|----|----|----|---------------|----|----|----|----------------|----|----|----|---------------|----|----|----|----------------|----|----|----|
|                                                  |            |               |          | 0 mg/kg (01-) |    |    |    | 30 mg/kg (41-) |    |    |    | 0 mg/kg (02-) |    |    |    | 30 mg/kg (42-) |    |    |    | 0 mg/kg (02-) |    |    |    | 30 mg/kg (42-) |    |    |    |
|                                                  |            |               |          | 07            | 08 | 09 | 10 | 11             | 12 | 07 | 08 | 09            | 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 II-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. BMR143C

| 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                     | Dilatation of pelvis(+)                                                                                                             |
| 1                  | 2102          | Kidneys  | Grayish patch                   | Focal degeneration and calcification in tubules(+).<br>regenerated tubules (+) and infiltration of<br>lymphocytes(+)                |
| 30                 | 4101          | Liver    | Scattering of grayish dot       | Focal necrosis(+)                                                                                                                   |
|                    | 4102          | Liver    | Hypertrophy                     | Swelling of centrilobular hepatocytes(++)                                                                                           |
|                    |               |          | Scattering of grayish dot/patch | No abnormality except for microgranuloma (±)<br>peripheral fatty change (+).eosinophilic change in<br>centrilobular hepatocytes(++) |
|                    | 4103          | Liver    | Hypertrophy                     | Swelling of centrilobular hepatocytes(++)                                                                                           |
|                    |               |          | Scattering of grayish dot       | Focal necrosis(+)                                                                                                                   |
|                    | 4104          | Liver    | Hypertrophy                     | Swelling of centrilobular hepatocytes(+)                                                                                            |
|                    |               |          | Scattering of grayish dot/patch | Focal necrosis(+)                                                                                                                   |
|                    | 4105          | Liver    | Hypertrophy                     | Swelling of centrilobular hepatocytes(++)                                                                                           |
|                    |               |          | Grayish patch                   | Focal necrosis(+)                                                                                                                   |
|                    | 4106          | Liver    | Hypertrophy                     | Swelling of centrilobular hepatocytes(++)                                                                                           |
|                    |               |          | Scattering of grayish dot       | Focal necrosis(++)                                                                                                                  |
|                    |               | Kidneys  | Hypertrophy                     | Swelling of centrilobular hepatocytes(+)                                                                                            |
|                    |               | Adrenals | Dark reddish/blackish dot       | No abnormality                                                                                                                      |
|                    |               |          | 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. BMRI43C

| Dose level (mg/kg) | Animal number | Organ   | Macroscopic findings               | Microscopic findings                                                                                                                                 |
|--------------------|---------------|---------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10                 | 3208          | Liver   | Dark reddish change                | No abnormality except for microgranuloma (±) .<br>Swelling of centrilobular hepatocytes (±) and eosinophilic change in centrilobular hepatocytes (±) |
| 30                 | 4201          | Liver   | Dark reddish change                | No abnormality except for microgranuloma (±) . eosinophilic change in centrilobular hepatocytes (++) and focal necrosis (±)                          |
|                    | 4202          | Liver   | Hypertrophy<br>Yellowish change    | Swelling of centrilobular hepatocytes (++)<br>Peripheral fatty change (±)                                                                            |
|                    | 4203          | Liver   | Hypertrophy<br>Dark reddish change | Swelling of centrilobular hepatocytes (++)<br>No abnormality except for microgranuloma (±)                                                           |
|                    | 4204          | Liver   | Hypertrophy<br>Dark reddish change | No abnormality except for microgranuloma (±) and eosinophilic change in centrilobular hepatocytes (++)<br>Swelling of centrilobular hepatocytes (±)  |
|                    | 4205          | Liver   | Hypertrophy<br>Dark reddish change | No abnormality except for eosinophilic change in centrilobular hepatocytes (++)<br>Swelling of centrilobular hepatocytes (++)                        |
|                    |               |         | Grayish patch                      | No abnormality except for eosinophilic change in centrilobular hepatocytes (++)                                                                      |
|                    |               | Kidneys | Hypertrophy                        | Swelling of centrilobular hepatocytes (++)                                                                                                           |
|                    | 4206          | Liver   | Pylectasis<br>Hypertrophy          | Dilation of pelvis (±)<br>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(+)                                               |
|                    | 4108          | Liver   | Grayish patch                      | Focal necrosis(+)                                                                                                                                                                               |
|                    | 4109 *        | Thymus  | Hypertrophy<br>Dark reddish patch  | Swelling of centrilobular hepatocytes(++)<br>Congestion(+) and hemorrhage(+)                                                                                                                    |
|                    |               |         | Atrophy                            | No abnormality                                                                                                                                                                                  |
|                    |               | Stomach | Tarry contents/hemorrhage          | Ulcer and hemorrhage in glandular stomach(+)                                                                                                                                                    |
|                    | 4110          | Liver   | Scattering of grayish dot/patch    | Focal necrosis(++)                                                                                                                                                                              |
|                    | 4111          | Liver   | Hypertrophy<br>Dark reddish change | Swelling of centrilobular hepatocytes(++)<br>No abnormality except for microgranuloma(+).<br>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 centrilobular hepatocytes(+)                                                                         |
|                    | 4209          | Liver   | Hypertrophy<br>Dark reddish change | Swelling of centrilobular hepatocytes(+)<br>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)

3M\_MN01650189

2797.0203

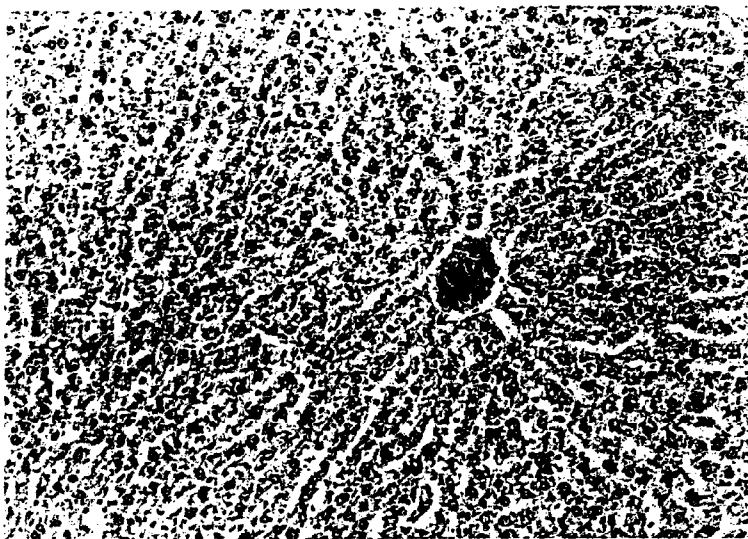


Photo.1 Liver of a male rat of control. (Animal No. 0103)

Showing normal centrilobular region.

H.E.stain  $\times 180$

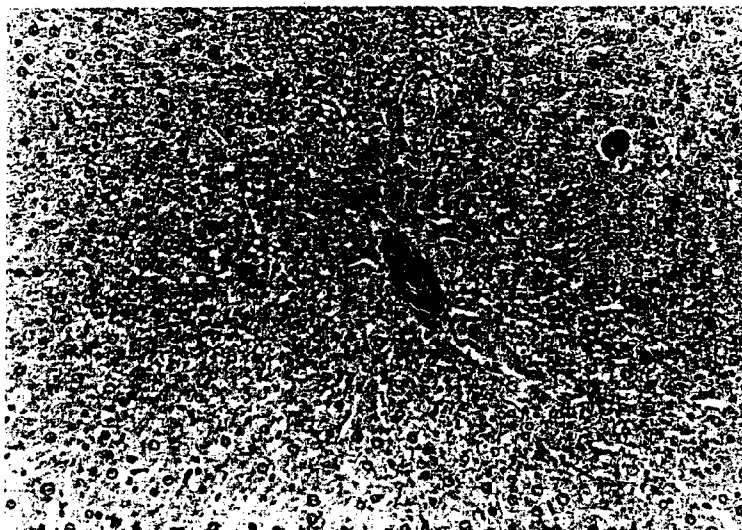


Photo.2 Liver of a male rat given 30 mg/kg. (Animal No. 4105)

Eosinophilic change and swelling of centrilobular hepatocytes are noted.

H.E.stain  $\times 180$

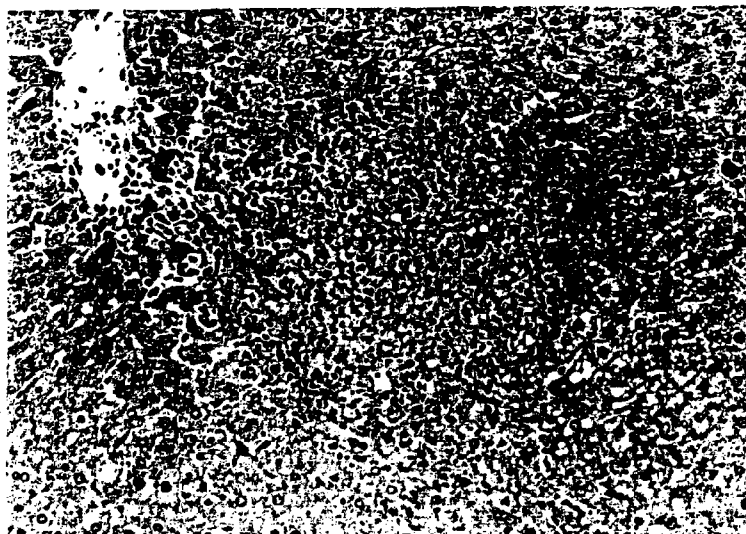


Photo.3 Liver of a male rat given 30 mg/kg. (Animal No. 4105)

Focal necrosis is noted.

H.E. stain  $\times 180$

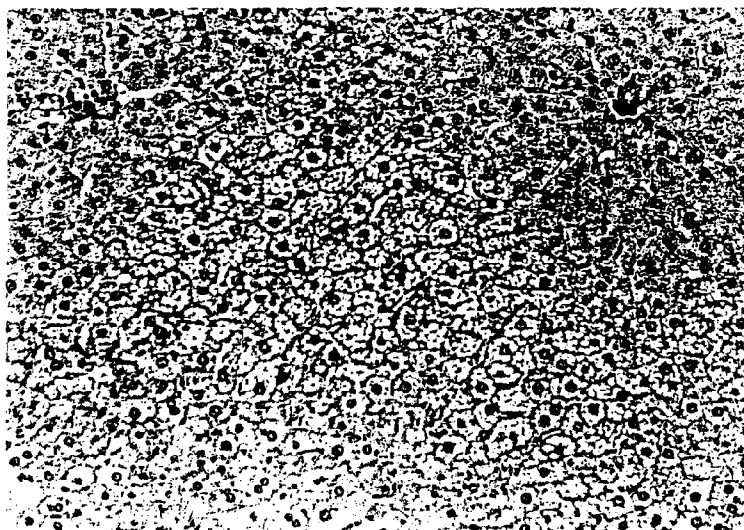


Photo.4 Liver of a male rat given 30 mg/kg. (Animal No. 4106)

Peripheral fatty change is found.

H.E. stain  $\times 180$