CERI

Receipt No. 827-06-D-3208

STUDY CODE: B11-0838

FINAL REPORT

TWENTY-EIGHT-DAY REPEATED-DOSE ORAL TOXICITY STUDY OF 13F-OLE IN RATS

August 2007

Hita Laboratory
Chemicals Evaluation and Research Institute
Japan

STATEMENT

I, the undersigned, hereby declare that this report provides correct English translation of the final report (Study Code B11-0838, issued on August 24, 2007).

November 9, 2009

Date

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

GLP STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Sponsor: DAIKIN INDUSTRIES, LTD.

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of 13F-OLE in Rats

Study Code: B11-0838

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP [Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)].

And, I confirmed that this report accurately reflects the raw data obtained and that data of the study has reliability.

Study Director: Signed in original August 24, 2007

QUALITY ASSURANCE STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Sponsor: DAIKIN INDUSTRIES, LTD.

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of 13F-OLE in Rats

Study Code: B11-0838

This study was audited and inspected by Quality Assurance Section of Hita Laboratory, Chemicals Evaluation and Research Institute, Japan. The dates audited and/or inspected and the dates reported of these results to the study director and management are as follows.

Items of Inspections and Audits	Dates of Inspections and Audits	Dates of Inspections and Audits Reports
Protocol	March 2, 2007	March 3, 2007
Preparation of test substance	March 9, 2007	March 9, 2007
Administration and clinical sign observation	March 13, 2007	March 13, 2007
Amendment to protocol	March 14, 2007	March 14, 2007
Re-inspection of protocol	March 23, 2007	January 23, 2007
Amendment to protocol (2^{nd})	May 9, 2007	May 9, 2007
Clinical chemistry data	June 29, 2007	June 29, 2007
Re-inspection of clinical chemistry data	July 2, 2007	July 2, 2007
Pathological data	July 11, 2007	July 11, 2007
Animal data	July 18, 2007	July 18, 2007
Detailed clinical observation and sensorimotor function data	July 18, 2007	July 18, 2007
Re-inspection of animal data	July 31, 2007	July 31, 2007
Re-inspection of detailed clinical observation and sensorimotor function data	July 31, 2007	July 31, 2007
Documents of test substance and housing conditions	August 16, 2007	August 16, 2007
Draft of final report	August 16, 2007	August 16, 2007
Re-inspection of test substance and animal data	August 21, 2007	August 22, 2007
Re-inspection of draft final report	August 24, 2007	August 24, 2007
Draft of final report (2^{nd})	August 24, 2007	August 24, 2007
Re-inspection of draft final report (2^{nd})	August 24, 2007	August 24, 2007
Final report	August 24, 2007	August 24, 2007

Following items were reported to the study director and management on the basis of the audit of facility or audit results in other studies.

Items of Audits	Dates of Audits	Dates of Audits Reports
Animal receipt	January 16, 2007	June 27, 2007
Quarantine and acclimatization	December 7, 2006	June 27, 2007
Body weight measurements	February 23, 2007	June 27, 2007
Food intake measurements	February 23, 2007	June 27, 2007
Detailed clinical observation and sensorimotor function test	March 23, 2007	June 27, 2007
Urine sampling	March 28, 2007	June 27, 2007
Blood sampling	January 16, 2007	June 27, 2007
Dissection, necropsy and organ weight measurements	January 16, 2007	June 27, 2007
Hematology	January 16, 2007	June 27, 2007
Blood chemistry	January 16, 2007	June 27, 2007
Urinalysis	January 16, 2007	June 27, 2007
Pathological preparation	February 6, 9 and 15, 2007	June 27, 2007

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study and that the reported results accurately reflect the raw data obtained.

Section Chief, Quality Assurance: Signed in original August 24, 2007

TABLE OF CONTENTS

Study Code: B11-0838
Test Substance Code: HR6853
Sponsor Code: D-0060

TITLE

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of 13F-OLE in Rats

SPONSOR

DAIKIN INDUSTRIES, LTD.
1-1, Nishihitotsuya, Settsu, Osaka 566-8585, Japan

TESTING FACILITY

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The purpose of this study is to define the type, severity and reversibility of toxicological signs of the test substance by observing the functional and morphological changes in animals receiving repeated doses orally for 28 days.

TESTING METHOD

This study was conducted in accordance with "28-day Repeated Dose Toxicity Study in Mammalian Species" prescribed in "Concerning Testing Methods Relating to the New Chemical Substances" [Notification No. 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 2 (November 13, 2003) of the Manufacturing Industries Bureau, METI & No. 031121002 of the Environmental Health Department, MOE (November 21, 2003)].

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP [Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)].

PERIOD OF STUDY

Commencement of Study:	March 1, 2007
Animal Receipt:	March 6, 2007
Initiation of Examination (Initiation of Dosing):	March 13, 2007
Terminal Necropsy of Dosing Period:	April 10, 2007
Initiation of Recovery Period:	April 10, 2007
Terminal Necropsy of Recovery Period:	April 24, 2007
Termination of Examination (Termination of Histology):	June 25, 2007
Completion of Study:	August 24, 2007

LOCATION AND PERIOD FOR RETENTION OF RAW DATA AND SPECIMENS

The raw data, protocol and amendment, study contract documents, test substance information, final report, other record documents and specimens will be stored in the archive of Hita Laboratory of our organization, and samples of every lot of the test substance will be stored in the test substance storage room, for a period of 10 years from the date of receipt of the notification that they are applicable to Article 4, Paragraphs 1 or 2, Article 4-2, Paragraphs 2, 3 or 8, Article 5-4, Paragraph 2, Article 24, Paragraph 2 or Article 25-3, Paragraph 2 of the Japanese Chemical Substances Control Law No. 117 (1973). The sponsor will inform Hita Laboratory of the date of receipt of the notification. After termination of the retention period, any measures taken will be done so with the approval of the sponsor. Samples and specimens that are liable to deteriorate markedly will be retained for 10 years after receipt of the notification or only for as long as the quality of the preparation permits evaluation, and they will be disposed with approval of the sponsor.

RETENTION OF ORIGINAL PROTOCOL AND FINAL REPORT

An original protocol, original protocol amendments and an original final report will be retained at Hita Laboratory. The copies of their originals that the study director will have been recognized to be accurate copy will be sent to the sponsor.

AUTHOR AND PERSONNEL CONCERNED WITH STUDY

Study Director:

(Planning and management of the study, evaluation of the results, report creation, and over all responsible for the technical conduct of the study)

Study Staff:

(Quarantine, acclimation and housing management of animals, preparation and administration of the test substance, clinical observation, detailed clinical observation, sensorimotor function, body weights and food intakes measurements, and responsible for the animal examination)

Person in charge of Pathologic Examination:

(Necropsy, collection of tissues, organ weight measurements, histopathological examinations, and responsible for the histopathology)

Person in charge of Clinical Chemistry:

(until March 29, 2007)
(from March 30, 2007)

(Hematological and blood chemical examinations, urinalysis, and responsible for the biochemistry of the specimens)

AUTHOR APPROVAL

Study Director: Signed in original August 24, 2007

Section 2 (Toxicology area)
Hita Laboratory

SUMMARY

A 28-day repeated-dose oral toxicity study of 13F-OLE was performed in groups of five male and five female Crl:CD(SD) rats at 5 weeks of age. The high dose was set at 200 mg/kg/day, and altogether three doses including 25 and 5 mg/kg/day were employed. Recovery groups were also set for the 200 mg/kg and vehicle control groups to investigate the reversibility of the effects.

No death occurred in all groups.

No abnormalities were observed in the clinical sings, body weights, food intakes, detailed clinical observations or the sensorimotor function during the dosing period.

In the histopathological examinations at the end of the dosing period, centrilobular lipid droplets in the hepatocytes and microgranuloma of the liver in males of the groups of 25 mg/kg or more, periportal hypertrophy of the hepatocytes and periportal prominent nucleoli of the hepatocytes of the liver in males of the 200 mg/kg group, centrilobular lipid droplets in the hepatocytes of the liver in females of the 200 mg/kg group were observed. In the necropsy, enlargement of the liver was observed in males of the 200 mg/kg group. In the organ weights, relative liver weight in both sexes of the groups of 25 mg/kg or more and absolute liver weight in males of the 200 mg/kg group were increased. No abnormalities were observed in the hematological examinations, blood chemical examinations or the urinalyses at the end of the dosing period.

In the necropsy at the end of the recovery period, mottled teeth were observed in both sexes of the 200 mg/kg recovery group. The changes were recovered. In addition, centrilobular lipid droplets in the hepatocytes and microgranuloma of the liver remained in males of the 200 mg/kg recovery group. There were no clear reversibility of these changes.

Based on these results, it was considered that the effects of 13F-OLE were mainly on the incisor and liver. However, it was not considered that the effect on the liver was reversible clearly. The No-observed-Adverse-Effect Level (NOAEL) of 13F-OLE was considered to be 5 mg/kg/day based on centrilobular lipid droplets in the hepatocytes and microgranuloma of the liver in males given 25 mg/kg.

MATERIALS AND METHODS

1. TEST SUBSTANCE (Information provided by the sponsor)

1.1 Name

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octa-1-ene

Other Name: 13F-OLE

CAS No.: 25291-17-2

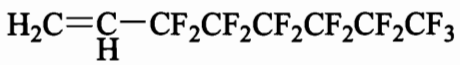
1.2 Lot No.

061024HM

1.3 Supplier

DAIKIN INDUSTRIES, LTD.

1.4 Structural Formula



(Molecular formula: $C_8H_3F_{13}$)

1.5 Purity

99.7%

1.6 Names and Concentration of Impurities

Unknown component 0.3%

1.7 Physicochemical Properties

Appearance at Ordinary Temperature: clear colorless liquid

Molecular Weight: 346.09

Boiling Point: 106°C (760 mmHg)

Density: 1.560 g/cm^3 (20°C)

Hydrolyzability: Unknown

Degree of Solubility: Water; insoluble

DMSO; insoluble

Acetone; soluble (arbitrary mixable)

1.8 Storage Conditions

The test substance was stored at room temperature under a light shielding condition (cabinet No. 1 in the test substance storage room, permissible temperature range: 10-30°C)

1.9 Handling Precaution

Glove, mask, cap and lab coat were put on.

2. ANIMALS

Crl:CD(SD) rats (SPF) of 33 males and 33 females were obtained from Charles River Japan Hino Breeding Center (735, Shimokomatsuki, Hino-cho, Gamo-gun, Shiga 529-1633, Japan) at 4 weeks old. Animals were acclimatized for 7 days including 6 days quarantine. No abnormalities were noted in any animals during the quarantine and acclimation periods. All animals were allocated to groups to ensure homogeneity of mean body weights using body weight-stratified randomization on one day before the start of administration. The animals not treated were excluded from the study and euthanized under ether anesthesia. At the onset of treatment, the animals were five weeks old with body weight ranges of 127.3-146.1 g and 111.4-130.7 g for males and females, respectively. Animals were identified by means of a marker on the tail before grouping and ear-tags after grouping.

3. HOUSING CONDITIONS

All animals were bred at the barrier-system animal rooms (room No. 4 during the quarantine period, room No. 7 after the quarantine), which were maintained at a stable temperature (21-25°C) and relative humidity (40-70%) with 10-15 air changes per hour and artificial light-dark cycle of 12-12 hours (light on: 7:00 and light off: 19:00), in the biotron (1) throughout the whole feeding period including the quarantine and acclimation periods. The actual temperature and humidity were 22.5-24.1°C and 47.9-58.6%, respectively.

The rats were housed in hanging stainless steel cages with wire-mesh floor at three or five animals/cage (260 W×380 D×180 H mm, TOKIWA KAGAKU KIKAI) for quarantine and acclimation, and at one animal/cage (165 W×300 D×150 H mm, TOKIWA KAGAKU KIKAI) after grouping. Undertrays were changed once a week before grouping, and twice a week after grouping. In addition, the undertrays of the animals which diarrhea was observed were changed. Feeders, cages and racks were changed once at grouping, and once at termination of the dosing period for the recovery group. Racks and cages were identified by individual cards.

The animals had free access to an MF pelleted diet (Lot No. 061204, Oriental Yeast) and chlorinated water from Hita City supply via automatic watering system with sipper tubes. The diet and housing materials were autoclaved at 121°C for 30 min prior to use. Analysis of the diet was performed in Japan Food Research laboratories, and the analytical data were provided by the manufacturer. The tested parameters met the requirements in our laboratories according to the "Toxic Substances Control Act of US-EPA". Contaminants in drinking water were analyzed twice yearly in Oita Prefecture Pharmaceutical Association according to the water regulations of the "Notification No. 101 of Environmental Health Bureau, MHLW"

except for test of the taste in our laboratory. Contaminants in the water were in the stated ranges in our laboratory.

4. GROUPING

Grouping was as follows.

Group	Dose	Volume	Concentration of dosing formulation	Number of Animals (Animal No.)	
	(mg/kg/day)	(mL/kg)	(w/v%)	Male	Female
Vehicle control	0	10	0	5 (1 - 5)	5 (31 - 35)
Vehicle control (recovery)	0	10	0	5 (6 - 10)	5 (36 - 40)
Low dose	5	10	0.05	5 (11 - 15)	5 (41 - 45)
Intermediate dose	25	10	0.25	5 (16 - 20)	5 (46 - 50)
High dose	200	10	2.0	5 (21 - 25)	5 (51 - 55)
High dose (recovery)	200	10	2.0	5 (26 - 30)	5 (56 - 60)

Rationale for dosage selection: A range finding study of 7-day repeated oral treatment was performed at 0, 25, 250, 500 and 1,000 mg/kg/day in our Hita Labolatory. Enlargement of the liver and increases in liver weight were noted in the groups given 250 mg/kg or more. Accordingly, the high dose was set at 200 mg/kg/day and lower doses of 25 and 5 mg/kg were set for the present study. Recovery groups were also set for the 200 mg/kg and vehicle control groups.

5. STABILITY OF TEST SUBSTANCE

Stability of the test substance during the dosing period was confirmed with infrared (IR) spectrophotometer in our Hita Laboratory (See APPENDIX 1, Study code: X18-0838). IR spectrum of the test substance within 4000 cm^{-1}-400 cm^{-1} was compared with that provided by the sponsor before dosing to determine the identity. The test substance was also analyzed to confirm the stability before and after the dosing period to confirm the stability.

6. PREPARATION OF FORMULATIONS

6.1 Vehicle

Since the hydrolyzability of the test substance was unknown, olive oil (Lot No. 038OHS, Fujimi Pharmaceutical) including 1.0 w/v% Tween 80 (Lot No. DPK6694, Wako Pure Chemical Industries) was selected as the vehicle.

6.2 Preparation and Storage

The test substance was accurately weighed in an agate mortar and mixed with olive oil (including 1.0 w/v% Tween 80) to prepare the 2.0 w/v% formulation under a light shielding condition. The lower concentration formulations of the 0.05 and 0.25 w/v% were prepared by diluting the 2.0 w/v% formulation with the vehicle. The formulations were stored at the dark and cold place (cool box No. 15 in the test substance preparation room).

6.3 Homogeneity and Stability Analyses

The homogeneity and stability analyses were performed in our Hita Laboratory (See APPENDIX 1, Study code: X18-0838). In the homogeneity analysis, top, middle and bottom layers of the 10.0 and 0.04 w/v% formulations were taken (n=1) immediately after preparation, and quantitatively analyzed (n=1) by Gas chromatography (GC) after sample pretreatment. The homogeneity of the test substance in the formulations was confirmed. In the stability test, the formulations for homogeneity samples were stored at the dark and cold place. Then, middle layers of the formulations were taken (n=1) after 9 days, and quantitatively analyzed (n=1) by GC after sample pretreatment. The test substance in the formulations was confirmed to be stable for 8 days.

6.4 Concentration Analysis

The concentration analysis was performed in our Hita Laboratory (See APPENDIX 1, Study code: X18-0838). The concentrations of the 2.0, 0.25 and 0.05 w/v% formulations were confirmed to be within 100±10% of each nominal concentration at the first preparation of the dosing period.

7. ADMINISTRATION

The formulations were repeatedly administered daily in the morning by oral gavage using a syringe (Terumo) connected to a Nelaton catheter (Terumo) for 28 days. Thereafter, a 14-day recovery period was set.

8. OBSERVATIONS

Concerning the numbering of day and week, the day of initiation of dosing was regarded as day 1, the day before initiation of dosing as day −1 and the week of initiation of dosing as week 1. The day after the last dosing was regarded as day 1 (recovery period) and the week of initiation of recovery as week 1 (recovery period).

8.1 Clinical Signs

During the dosing period, all animals were observed three times a day, i.e., before dosing, during and immediately after dosing, and in the afternoon, daily from day 1 to day 28. During the recovery period, observation was performed twice daily i.e., in the morning and in the afternoon.

8.2 Detailed Clinical Observations

The detailed examinations in all animals were performed once before dosing. Thereafter, the examinations were performed once weekly during the dosing and recovery periods on a blind test basis. The blind test was performed using the random numbers and observation labels without identifying the dosing group. The detailed examination about the incisors was not performed since it was not included in the items of the detailed clinical observation.

1) Observations at removal from cage

Animal reactions such as excitement from external stimuli (holding animals or bringing a hand close to animals to hold, etc.) were observed.

Observation items: Ease of removal, Vocalization

2) Handling observations

Observation items: Muscle tone, Hypothermia, Piloerection, Hair appearance (staining and unkempt hair), Skin and mucous color (paleness, reddening and cyanosis), Eyes (lacrimation, exophthalmos and pupillary size), Salivation, Secretion

3) Observation in arena

Animals were placed in a standard arena (on an observation platform) and observed for 1 min or more, and the frequencies of defecation (number of feces) and urination (number of pools) were recorded for 1 min.

Observation items: Posture, Motor activity level, Respiration, Lid closure, Gait characteristics, Tremor, Twitch, Convulsion, Stereotypical behavior, Abnormal behavior

8.3 Sensorimotor Function

All animals were examined in week 4 of the dosing period, but not in the recovery period, since no abnormalities were noted in week 4 of the dosing period.

1) Reflex

Reactions of animals were observed and made a score when proper stimuli were given their test subjected sensory organs. The examinations were also performed on a blind test basis.

(1) Approach contact/touch response

The animal's response when a blunt probe was brought approximately 3 cm from the animal's nose for 4 seconds was assessed.

(2) Pinna response

The animal's response when a sudden sound of a finger snap was produced was assessed.

(3) Pain response

The animal's response when the animal's tail was pinched with a clothespin between one-third and base of the tail was assessed.

(4) Pupillary reflex

Following darkness adaptation of the animal's eyes, pupil constriction in response to a bright beam of a penlight was observed.

(5) Air righting reflex

The animal's response when the animal was held with ventral surface uppermost approximately 30 cm height from the flat surface and released was assessed.

2) Grip strength

The forelimbs and hindlimbs grip strengths were measured with the automated grip strength meter (COLUMBUS) on a blind test basis. Two trials were performed, and the mean values of the forelimbs or hindlimbs were calculated for each animal.

3) Locomotor activity counts

Locomotor activity level of each animal was counted with the activity monitoring system (SCANET: MV-10, MAYTES) by the number of crossing IR beam for 1 hour at 10 min intervals.

8.4 Body Weights

Body weights were measured on day -1 (allocation to groups), and on days 1, 3, 8, 12, 17, 21, 26 and 28 during the dosing period and on days 1, 5, 10 and 14 (recovery period). In addition, immediately before necropsy, body weights were measured for calculation of the relative organ weights.

8.5 Food Intakes

Food intakes were measured on day -1 (allocation to groups), and on days 1, 3, 8, 15, 22 and 28 during the dosing period and on days 1, 4, 8 and 14 (recovery period). Mean food intakes per day were calculated from their remainders for each period.

8.6 Hematological Examinations

Blood or plasma samples were obtained by blood sampling from the abdominal aorta under ether anesthesia after overnight fasting (16 to 20 hr) at completion of the dosing period (excluding the recovery groups) and at completion of the recovery period. The samples were determined for the following items. In addition, the blood smears were made for unmeasurable cases. As an anticoagulant, 3.2% sodium citrate aqueous solution (Lot No. LTR3558, Wako Pure Chemical Industries) was used for the determination of prothrombin time and activated partial thromboplastin time, and EDTA-2K (Lot No. G5071, Sysmex) for other measurements.

	Parameters		Method
1)	Red blood cell count (RBC)	($\times 10^4/\mu L$)	Electrical resistance detection
2)	White blood cell count (WBC)	($\times 10^2/\mu L$)	Electrical resistance detection
3)	Hemoglobin conc. (Hb)	(g/dL)	Noncyanhemoglobin method
4)	Hematocrit value (Ht)	(%)	$\frac{RBC \times MCV}{10^3}$
5)	Mean corpuscular volume (MCV)	(fL)	Electrical resistance detection
6)	Mean corpuscular hemoglobin (MCH)	(pg)	$\frac{Hb}{RBC} \times 10^3$
7)	Mean corpuscular hemoglobin conc. (MCHC)	(g/dL)	$\frac{Hb}{Ht} \times 10^2$
8)	Platelet count (Platelet)	($\times 10^4/\mu L$)	Electrical resistance detection
9)	Reticulocyte ratio (Reticulo)	(%)	RNA staining
10)	Prothrombin time (PT)	(sec)	Magnetic sensor
11)	Activated partial thromboplastin time (APTT)	(sec)	Magnetic sensor
12)	Differentiation of leukocytes	(%)	Flow cytometry technique
	Neutrophils (Neutro)		
	Eosinophils (Eosino)		
	Basophils (Baso)		
	Lymphocytes (Lymph)		
	Monocytes (Mono)		
	Large unstained cells (LUC)		

1) - 8) CELL-DYN3500, Abbott Laboratories

9), 12) ADVIA 120, Bayer Medical

10), 11) KC-10A, AMELUNG

8.7 Blood Chemical Examinations

Serum samples were separated from blood samples collected at the same times as those described in section 8.6, and the following items were determined in the obtained serum samples.

	Parameters		Method
1)	Aspartate aminotransferase (AST)	(IU/L)	UV method (method based on JSCC)
2)	Alanine aminotransferase (ALT)	(IU/L)	UV method (method based on JSCC)
3)	Alkaline phosphatase (ALP)	(IU/L)	*p*-Nitrophenyl phosphate method
4)	Cholinesterase (ChE)	(IU/L)	Butyrylthiocholine iodide method
5)	γ-Glutamyl transpeptidase (γ-GTP)	(IU/L)	L-γ-glutamyl-3-carboxy-4-nitroanilide method
6)	Total cholesterol (T-Cho)	(mg/dL)	COD·ADPS method
7)	Triglyceride (TG)	(mg/dL)	GPO·ADPS glycerol blocking method
8)	Glucose	(mg/dL)	Hexokinase·G-6-PDH method
9)	Total protein (T-Protein)	(g/dL)	Biuret method
10)	Albumin	(g/dL)	Bromocresol green method
11)	A/G ratio		$\frac{\text{Albumin}}{\text{T - Protein} - \text{Albumin}}$ (calculated value)
12)	Blood urea nitrogen (BUN)	(mg/dL)	Urease·GlDH method
13)	Creatinine	(mg/dL)	Creatininase·F-DAOS method
14)	Total bilirubin (T-Bil)	(mg/dL)	Enzyme method
15)	Calcium (Ca)	(mg/dL)	OCPC method
16)	Inorganic phosphorus (IP)	(mg/dL)	Fiske-Subbarow method
17)	Sodium (Na)	(mEq/L)	Crown-Ether membrane electrode method
18)	Potassium (K)	(mEq/L)	Crown-Ether membrane electrode method
19)	Chloride (Cl)	(mEq/L)	Coulometric titration method

1), 2), 4), 9), 10), 14)	7150 Automatic Analyzer, Hitachi
3), 5)-8), 12), 13), 15), 16)	7170 Automatic Analyzer, Hitachi
17)-19)	PVA-αIII, A & T

8.8 Urinalyses

Urinalysis was performed once (day 28) during the dosing period (excluding the recovery groups) and once (day 14 (recovery)) during the recovery period. Urine samples (accumulated for 15-17 hr) collected in individual metabolic cages (150 W×200 D×263 H mm) were determined with drinking water *ad libitum*. The urine sediments were stained and examined in males and females of the vehicle control and 200 mg/kg groups at the end of the dosing period. The urine sediments were not examined at the end of the recovery period since no abnormalities were noted at the end of the dosing period.

	Parameters		Method
1)	Urine volume	(m/L)	Volumetric method
2)	Color		Macroscopy
3)	Turbidity		Macroscopy
4)	Urine specific gravity (Sp.Gr.)		Refractive index
5)	pH		Test paper
6)	Protein		Test paper
7)	Glucose		Test paper
8)	Occult blood		Test paper
9)	Urinary sediments		Sternheimer modified

1) Measuring cylinder

4) SPR-N, ATAGO

9) Biological microscope, BH2, OLYMPUS

5)-8) Hema-Combistix, Bayer Medical

8.9 Pathological Examinations

1) Necropsy

All animals were subjected to the detailed gross necropsy including body surface, all orifices, cranial, thoracic and abdominal cavities, and these contents.

2) Organ weights

The weights of the following organs were measured in all animals. The relative organ weight was calculated based on the body weight at the time of necropsy.

* Left and right organs were measured totally.

Liver(g), heart(g), kidneys*(g), testes*(g), epididymides*(g), ovaries*(mg), brain(g), spleen(g), thymus(mg) and adrenals*(mg)

3) Histopathological examinations

(1) The following organs and tissues were taken in all animals.

Category	Organs and Tissues
Respiratory system	Trachea, lungs
Digestive system	Incisors, stomach, intestine (duodenum to rectum, with Peyer's patches), liver
Cardiovascular system	Heart
Urinary system	Kidneys, urinary bladder
Reproductive system	Testes, epididymides, prostate, seminal vesicles, ovaries, uterus, vagina
Nervous system	Brain (cerebrum, cerebellum and pons), spinal cord, sciatic nerve
Hematopoietic and lymphatic systems	Bone marrow (femur), axillar and mesenteric lymph nodes, spleen, thymus
Endocrine system	Pituitary gland, thyroid (with parathyroids), adrenals
Special sense organ	Eye balls

The trachea, lungs and urinary bladder were filled with 10% neutralized buffered formalin before taken. The stomach and intestine were filled and fixed with 10% neutralized buffered formalin and were washed with water. All organs/tissues were preserved in 10% neutralized buffered formalin. However, the testes and epididymides were fixed in Bouin's solution.

(2) The following organs/tissues were taken as macroscopic lesions.

Group (Animal No.)	Organs and tissues
Vehicle control group (No. 2)	Skin
Vehicle control group (No. 32)	Skin
Vehicle control recovery group (No. 36)	Skin
200 mg/kg recovery group (No. 58)	Skin

(3) Light microscopic examinations were performed for the organs and tissues of the following groups after embedding in paraffin, sectioning and hematoxylin and eosin (HE) staining. Decalcification was done for incisors and bone marrow (femur) with 10% formic acid formalin before cutting. In the table, parentheses show that HE specimens were not prepared although paraffin blocks was prepared since no abnormality was noted histopathologically in the 200 mg/kg group.

Organ and tissue	Vehicle control group	Vehicle control recovery group	5 mg/kg group	25 mg/kg group	200 mg/kg group	200 mg/kg recovery group
Trachea	♂♀	-	-	-	♂♀	-
Lungs	♂♀	-	-	-	♂♀	-
Incisors [a)]	♂♀	♂♀	(♂♀)	(♂♀)	♂♀	♂♀
Forestomach [b)]	♂♀	♀	♀	♀	♂♀	♀
Glandular stomach [b)]	♂♀	♀	♀	♀	♂♀	♀
Duodenum-ileum	♂♀	-	-	-	♂♀	-
Cecum- rectum	♂♀	-	-	-	♂♀	-
Liver [b)]	♂♀	♂♀	♂♀	♂♀	♂♀	♂♀
Heart	♂♀	-	-	-	♂♀	-
Kidneys [c)]	♂♀	♂	-	-	♂♀	♂
Urinary bladder	♂♀	-	-	-	♂♀	-
Testes [b)]	♂	♂	♂	♂	♂	♂
Epididymides [b)]	♂	♂	♂	♂	♂	♂
Prostate	♂	-	-	-	♂	-
Seminal vesicle	♂	-	-	-	♂	-
Ovaries	♀	-	-	-	♀	-
Uterus	♀	-	-	-	♀	-
Vagina	♀	-	-	-	♀	-

a) Since changes suspected to be effects of the test substance were noted in the necropsy in both sexes of the 200 mg/kg recovery group, histopathological examinations for the vehicle control group, 200 mg/kg group and these recovery groups were done. Paraffin blocks for other all groups were prepared.

b) Since changes suspected to be effects of the test substance were noted in males or females of the 200 mg/kg group, histopathological examinations for each sex of all groups including the recovery groups were done.

c) Since changes suspected to be effects of the test substance were noted in the organ weights in males of the 200 mg/kg recovery group, histopathological examinations for the recovery groups were done.

Organ and tissue	Vehicle control group	Vehicle control recovery group	5 mg/kg group	25 mg/kg group	200 mg/kg group	200 mg/kg recovery group
Cerebrum, cerebellum, pons	♂♀	-	-	-	♂♀	-
Spinal cord	♂♀	-	-	-	♂♀	-
Sciatic nerve	♂♀	-	-	-	♂♀	-
Bone marrow	♂♀	-	-	-	♂♀	-
Axillar lymph nodes	♂♀	-	-	-	♂♀	-
Mesenteric lymph nodes	♂♀	-	-	-	♂♀	-
Spleen	♂♀	-	-	-	♂♀	-
Thymus	♂♀	-	-	-	♂♀	-
Pituitary gland	♂♀	-	-	-	♂♀	-
Thyroid	♂♀	-	-	-	♂♀	-
Parathyroid	♂♀	-	-	-	♂♀	-
Adrenals	♂♀	-	-	-	♂♀	-
Eye ball	♂♀	-	-	-	♂♀	-

(4) The following organs/tissues were examined as macroscopic lesions.

Group (Animal No.)	Organs and tissues
Vehicle control group (No. 2)	Skin
5 mg/kg group (No. 11)	Spleen
25 mg/kg group (No. 20)	Pituitary gland
Vehicle control group (No. 32)	Skin
Vehicle control recovery group (No. 36)	Skin
200 mg/kg recovery group (No. 58)	Skin

(5) The special staining of the following organs/tissues was performed.

Group (Animal No.)	Organs and tissues	Method
Vehicle control group (No. 1)	Liver [d)]	Oil red O staining
200 mg/kg group (No. 22)	Liver [d)]	Oil red O staining
Vehicle control group (No. 34)	Liver [d)]	Oil red O staining
25 mg/kg group (No. 47)	Liver [d)]	Oil red O staining
200 mg/kg group (No. 55)	Liver [d)]	Oil red O staining

d) Since vacuolization of the hepatocytes suspected to be accumulation of fat was noted in the HE specimens, Oil red O staining was done.

9. STATISTICAL ANALYSIS

Data regarding body weights (excluding those at the time of necropsy), food intakes, hematological examinations, blood chemical examinations, urine volume, urine specific gravity, organ weights, grip strength and locomotor activity counts were analyzed by using the Bartlett's test for homogeneity of variance. If the variances were homogeneous at a significance level of 5%, one way analysis of variance was performed. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the Dunnett's test. If the variances were not homogeneous, the Kruskal-Wallis's test was used. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the nonparametric Dunnett's test.

The frequencies of defecation (number of feces) and urination (number of pools) were analyzed by using the Kruskal-Wallis's test. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the nonparametric Dunnett's test.

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED THE RELIABILITY OF STUDY RESULTS

There were no environmental factors that might have affected the reliability of the study results.

RESULTS

1. CLINICAL SIGNS (Table 1, Addendum 1)

1.1 During Dosing Period

Males: Salivation was noted in eight animals of the vehicle control group, in five animals of the 5 mg/kg group, in four animals of the 25 mg/kg group and in nine animals of the 200 mg/kg group, respectively. Soft stool was noted in three animals of the 200 mg/kg group. Loss of hair (ventral neck) in one animal was noted in the vehicle control group. The salivation disappeared at the observation in the afternoon.

Females: Salivation was noted in three animals of the vehicle control group, in one animal of the 5 mg/kg group, in three animals of the 25 mg/kg group and in 10 animals of the 200 mg/kg group, respectively. Soft stool was noted in one animal of the 5 mg/kg group, in one animal of the 25 mg/kg group, in four animals of the 200 mg/kg group, respectively. Diarrhea was noted in one animal of the 5 mg/kg group, in one animal of the 25 mg/kg group, in one animal of the 200 mg/kg group, respectively. Loss of hair (shoulder) and scab formation (shoulder) were noted in one animal of the vehicle control group. Loss of hair (forelimb) was noted in one animal of the vehicle control group, in one animal of the 5 mg/kg group, in one animal of the 200 mg/kg group, respectively. The salivation disappeared at the observation in the afternoon.

1.2 During Recovery Period

Males: Mottled teeth in two animals were noted in the 200 mg/kg recovery group from day 11 (recovery period) to day 14 (recovery period).

Females: Loss of hair (forelimb) was noted in one animal of the vehicle control recovery group and in one animal of the 200 mg/kg recovery group.

2. DETAILED CLINICAL OBSERVATIONS (Table 2, Addendum 2)

2.1 During Dosing Period

No abnormalities attributable to the test substance were noted in either sex of any treatment groups.

2.2 During Recovery Period

No abnormalities attributable to the test substance were noted in either sex of the 200 mg/kg recovery group.

3. SENSORIMOTOR FUNCTION (Tables 3, 4 and 5, Addenda 3, 4 and 5)

3.1 During Dosing Period

Males: Hyper reaction of the pain response was noted in one animal of the 5 mg/kg group in week 4.

Females: Hyper reaction of the pinna response was noted in one animal of the 5 mg/kg group in week 4.

3.2 During Recovery Period

Males or females were not examined since no abnormalities attributable to the test substance were noted in week 4 during the dosing period.

4. BODY WEIGHTS (Fig.1, Table 6, Addendum 6)

4.1 During Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

4.2 During Recovery Period

No statistically significant changes attributable to the test substance were noted in either sex of the 200 mg/kg recovery group.

5. FOOD INTAKES (Fig.2, Table 7, Addendum 7)

5.1 During Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

5.2 During Recovery Period

No statistically significant changes attributable to the test substance were noted in either sex of the 200 mg/kg recovery group.

6. HEMATOLOGICAL EXAMINATIONS (Table 8, Addendum 8)

6.1 At Termination of Dosing Period

Males: No statistically significant changes attributable to the test substance were noted in any treatment groups.

Females: A statistically significant increase in WBC was noted in the 5 mg/kg group.

6.2 At Termination of Recovery Period

Males: As for the differentiation of leukocytes, a statistically significant increase in the ratio of neutrophils, statistically significant decreases in the ratio of lymphocytes and large unstained cells were noted in the 200 mg/kg recovery group.

Females: No statistically significant changes attributable to the test substance were noted in the 200 mg/kg recovery group.

7. BLOOD CHEMICAL EXAMINATIONS (Table 9, Addendum 9)

7.1 At Termination of Dosing Period

No statistically significant changes attributable to the test substance were noted in either sex of any treatment groups.

7.2 At Termination of Recovery Period

No statistically significant changes attributable to the test substance were noted in either sex of 200 mg/kg recovery group.

8. URINALYSES (Table 10, Addendum 10)

8.1 At Termination of Dosing Period

No abnormalities attributable to the test substance were noted in either sex of any treatment groups.

8.2 At Termination of Recovery Period

No abnormalities attributable to the test substance were noted in either sex of the 200 mg/kg recovery group.

9. ORGAN WEIGHTS (Tables 11 and 12, Addenda 11 and 12)

9.1 At Termination of Dosing Period

Males: Relative liver weight was significantly increased in the groups given 25 mg/kg or more. A statistically significant increase in absolute weight of the liver, a statistically significant decrease in absolute weight of the heart and statistically significant decreases in absolute and relative spleen weights were noted in the 200 mg/kg group.

Females: Relative liver weight was significantly increased in the groups given 25 mg/kg or more. Relative kidney weight was significantly increased in the group given 200 mg/kg. Absolute liver weight was significantly increased in the group given 25 mg/kg.

9.2 At Termination of Recovery Period

Males: Statistically significant increases in absolute weight of the kidney and absolute weight of the epididymis were noted in the 200 mg/kg recovery group.

Females: No statistically significant changes attributable to the test substance were noted in the 200 mg/kg recovery group.

10. NECROPSY (Table 13, Addendum 13)

10.1 At Termination of Dosing Period

Males: Enlargement of the liver in all animals (Nos. 21-25) of the 200 mg/kg group was noted. In addition, sparsed fur of the skin in one animal (No. 2) of the vehicle

control group, whitish region on the capsule of the spleen in one animal (No. 11) of the 5 mg/kg group, cyst of the pituitary gland in one animal (No. 20) of the 25 mg/kg group were noted.

Females: Elevated region of the mucosa in the forestomach in one animal (No. 51) of the 200 mg/kg group was noted. In addition, scab formation of the skin in one animal (No. 32) was noted in the vehicle control group.

10.2 At Termination of Recovery Period

Males: Mottled teeth were noted in three animals (Nos. 27, 28 and 30) of the 200 mg/kg recovery group.

Females: Mottled teeth were noted in one animal (No. 59) of the 200 mg/kg recovery group. In addition, loss of hair of the forelimb in one animal (No. 36) of the vehicle control recovery group, loss of hair of the forelimb in one animal (No. 58) of the 200 mg/kg recovery group were noted.

11. HISTOPATHOLOGICAL EXAMINATIONS (Table 14, Addendum 13)

11.1 At Termination of Dosing Period

Males: Centrilobular lipid droplets in the hepatocytes of the liver in one animal (No. 19), microgranuloma of the liver in one animal (No. 20) of the 25 mg/kg group were noted. And, centrilobular lipid droplets in the hepatocytes of the liver in all animals (Nos. 21-25, Photos. 1 and 2), periportal hypertrophy of the hepatocytes and periportal prominent nucleoli of the hepatocytes of the liver in one animal (No. 21, Photos. 3 and 4), microgranuloma of the liver in four animals (Nos. 22-25), degeneration of the spermatocytes of the testis in one animal (No. 25), germ cell debris in the lumen of the epididymis in one animal (No. 25) of the 200 mg/kg group were noted.

In addition, focal necrosis in the Peyer's patches of the jejunum in one animal (No. 2) of the vehicle control group, capsulitis of the spleen in one animal (No. 11) of the 5 mg/kg group, cyst formation in the pars intermedia of the pituitary gland in one animal (No. 20) of the 25 mg/kg group were noted.

Females: Microgranuloma of the liver in one animal (No. 47), centrilobular lipid droplets in the hepatocytes of the liver in one animal (No. 47) of the 25 mg/kg group, centrilobular lipid droplets in the hepatocytes of the liver in one animal (No. 55), microgranuloma of the liver in two animals (Nos. 52 and 53), lymphocyte infiltration in the submucosal layer of the forestomach in one animal (No. 51), edema in the submucosal layer of the glandular stomach in one animal (No. 51), mineralization in the cortico-medullary junction of the kidney in one animal (No. 54) of the 200 mg/kg group were noted.

In addition, focal inflammation of the rectum in one animal (No. 32), ulcer of the skin in one animal (No. 32), microgranuloma of the liver in one animal (No. 35) of the vehicle control group were noted.

11.2 At Termination of Recovery Period

Males: Centrilobular lipid droplets in the hepatocytes of the liver in four animals (Nos. 26 and 28-30), microgranuloma of the liver in three animals (Nos. 26, 28 and 30) were noted in the 200 mg/kg recovery group.

In addition, mineralization in the medulla of the kidneys in one animal (No. 9), inhibited spermiation and deep retention of the spermatids of the testis in one animal (No. 10) were noted in the vehicle control recovery group.

Females: Microgranuloma of the liver in one animal (No. 40) was noted in the vehicle control recovery group.

Centrilobular lipid droplets in the hepatocytes of the liver and microgranuloma of the liver were mentioned as changes that exceeded a normal range. In addition, increases in positive substance were found in the vacuolating area of the hepatocyte with the oil red O staining in the representative animals (Nos. 22, 47 and 55) in which centrilobular lipid droplets in the hepatocytes or periportal lipid droplets in the hepatocytes of the liver were observed.

DISCUSSION

A 28-day repeated-dose oral toxicity study of 13F-OLE with Crl:CD(SD) rats was carried out at doses of 5, 25, and 200 mg/kg/day. A 14-day recovery test was also performed to investigate the reversibility of the effects.

No death occurred in all groups. No abnormalities attributable to the test substance were observed in the sensorimotor function, body weights or food intakes during the dosing period. In addition, no abnormalities were observed in the blood chemical examinations or the urinalyses at the end of the dosing period.

The test substance caused changes suggesting effects on the incisor and liver.
As the effects on the liver, centrilobular lipid droplets of the hepatocytes in males of the groups of 25 mg/kg or more and in females of the 200 mg/kg group, periportal hypertrophy of the hepatocytes and periportal prominent nucleoli of the hepatocytes in males of the 200 mg/kg group were observed in the histopathological examinations at the end of the dosing period. In the necropsy, enlargement of the liver was observed in males of the 200 mg/kg group. As the related changes in the organ weights, relative liver weight in both sexes of the groups of 25 mg/kg or more and absolute liver

weight in males of the 200 mg/kg group were increased. In addition, microgranuloma of the liver in males of the groups of 25 mg/kg or more was dose-relatedly observed. Since this change remained at the end of the recovery period, this suggested the secondary change to the liver caused by the test substance. As for the centrilobular lipid droplets in the hepatocytes of the liver, the oil red O staining revealed that positive substance was increased in the vacuolating area of the hepatocytes, indicating that the vacuolization was caused by the accumulation of the fat.

As the effect on the incisor, mottled teeth in the clinical signs were observed in males at the latter term of the recovery period. These changes in females were also observed by detailed observation in the necropsy. It was suggested that impaired iron-pigment secretion to the enamel occurred, since this test substance includes the fluorine and it was also reported that decreased iron pigments, degeneration and necrosis of the ameloblasts were found in the animals including rats with brown enamel surface of the teeth by fluoride administration[1) 2)]. Therefore, it was suggested that these changes were caused by the test substance. In addition, no clear chage in the histopathological examinations was found in the incisor at the end of the recovery period. Therefore, it was considered that the impairments occurred at the end of the dosing period and at the first term of the recovery period were recovered.

As other changes, salivation was observed in both sexes in all groups including the vehicle control group during the dosing period. However, this change disappeared at the observation in the afternoon and no change related to the neural system was observed in the histopathological examinations, detailed clinical observations or the sensorimotor function. Therefore, this change was not considered to be toxicologically significant. In addition, soft stool or diarrhea in females of the groups of 5 mg/kg or more, soft stool in males of the 200 mg/kg group were observed. However, these changes were single occurrence and no histopathological change was observed. Therefore, these changes were considered to be incidental. Furthermore, loss of the hair in the forelimbs was observed in females of the 5 mg/kg group, the 200 mg/kg group and the 200 mg/kg recovery group. However, this occurred only in one animal each and it was found in the vehicle control group. Therefore, this change was considered to be no treatment related.

In the sensorimotor function, hyper reaction of the pain response in one male of the 5 mg/kg group on week 4, hyper reaction of the pinna response in one female of the 5 mg/kg group were observed. However, they were no dose-related and found only in the 5 mg/kg group. Therefore, these changes were considered to be incidental.

In the hematological examinations, increased WBC was observed in males of the 5 mg/kg group at the end of the dosing period. However, no dose-related change was observed. Therefore, this change was considered to be incidental.

In the organ weights, decreased absolute and relative spleen weights in males of the 200 mg/kg group were observed at the end of the dosing period. However, there were no abnormal changes in the histopathological examinations and no changes that indicated anemia in the hematological examinations. Therefore, these changes were not considered to be toxicologically significant. In addition, decreased absolute heart weight in males of the 200 mg/kg group, increased relative kidney weights in females of the 200 mg/kg group were observed at the end of the dosing period. However, there were no abnormal changes in the histopathological examinations and they were changes only in either absolute weight or relative weight. Therefore, they were not considered to be toxicologically significant. Furthermore, increased absolute liver weight in females of the 25 mg/kg group was observed. However, no dose-related change was observed. Therefore, this change was considered to be incidental.

In the necropsy, elevated region of the mucosa of the forestomach in females of the 200 mg/kg group was observed at the end of the dosing period, and lymphocyte infiltration in the submucosal layer of the forestomach and edema in the submucosal layer of the glandular stomach were observed in the histopathological examinations in the same animal. However, there were no other effects that indicate irritable effects of the test substance and these changes were the slight focal changes found only in one animal. Therefore, they were considered to be no treatment related. In addition, whitish region on the capsule of the spleen in males of the 5 mg/kg group, cyst of the pituitary gland in one male of the 25 mg/kg group were observed. They were observed as capsulitis of the spleen and cyst formation in the pars intermedia of the pituitary gland respectively in the histopathological examinations. However, they were found in only one animal and no dose-related changes. Therefore, these changes were considered to be incidental.

In the histopathological examinations, microgranuloma of the liver in females of the 25 mg/kg group and 200 mg/kg group was observed. However, the change was also found in the vehicle control group. Therefore, this change was considered to be no treatment related. Periportal lipid droplets in the hepatocytes of the liver was observed only in females of the 25 mg/kg group. However, it was a slight change and found in only one animal. Therefore, this change was considered to be no treatment related. In addition, mineralization in the cortico-medullary junction of the kidney in females of the 200 mg/kg group was observed. However, it was found in only one animal and it has been observed in historical data[3)] frequently. Therefore, this change was considered to be no treatment related. Furthermore, degeneration of the spermatocytes of the testes and germ cell debris in the lumen of the epididymides in males of the 200 mg/kg group were observed. However, they were slight changes, they were found in only one animal and they have been observed in historical data[3)]. Therefore, these changes were considered to be incidental.

In the recovery group, centrilobular lipid droplets in the hepatocytes of the liver and microgranuloma of the liver as the treatment related changes remained in the 200 mg/kg recovery group. Therefore, there were no clear reversibility. In addition, increased ratio of the neutrophils, decreased ratio of the lymphocytes and large unstained cells as for the differentiation of leukocytes, and increased relative kidney weight were newly observed in males of the 200 mg/kg recovery group. However, these changes were not found at the end of the dosing period. Therefore, these changes were considered to be incidental. Furthermore, an increase in absolute weight of the epididymis was observed in males of the 200 mg/kg recovery group. However, there were no changes in relative weight or the histopathological examinations. Therefore, they were not considered to be toxicologically significant.

In conclusion, it was considered that the effects of 13F-OLE were mainly on the incisor and liver. It was also considered that the effects on the liver were not reversible clearly. The No-observed-Adverse-Effect Level (NOAEL) of 13F-OLE was considered to be 5 mg/kg/day based on centrilobular lipid droplets in the hepatocytes and microgranuloma of the liver in males given 25 mg/kg.

1) The Japanese Society of Toxicologic Pathology, 2000, Toxicological Histopathology, 137-152, Secretariat of the Japanese Society of Toxicological Pathology, Tokyo.

2) Hideaki Ogura and Keiichi Ohya, 1995, Study on Physiology and Pharmacology in Hard Tissue −Effects of chemicals on formation and resorption mechanism of tooth and bone−, *Folia Pharmacol. Jpn.*, 105, 305-318.

3) Historical data of histopathology of Crl:CD(SD) rats in Hita Laboratory (9-16 weeks old)

Items	Sex	Incidence
Mineralization in the cortico-medullary junction in the kidney	female	70/484
Degeneration of spermatocytes in the testes	male	4/407
Germ cell debris in the lumen in the epididymides	male	7/485

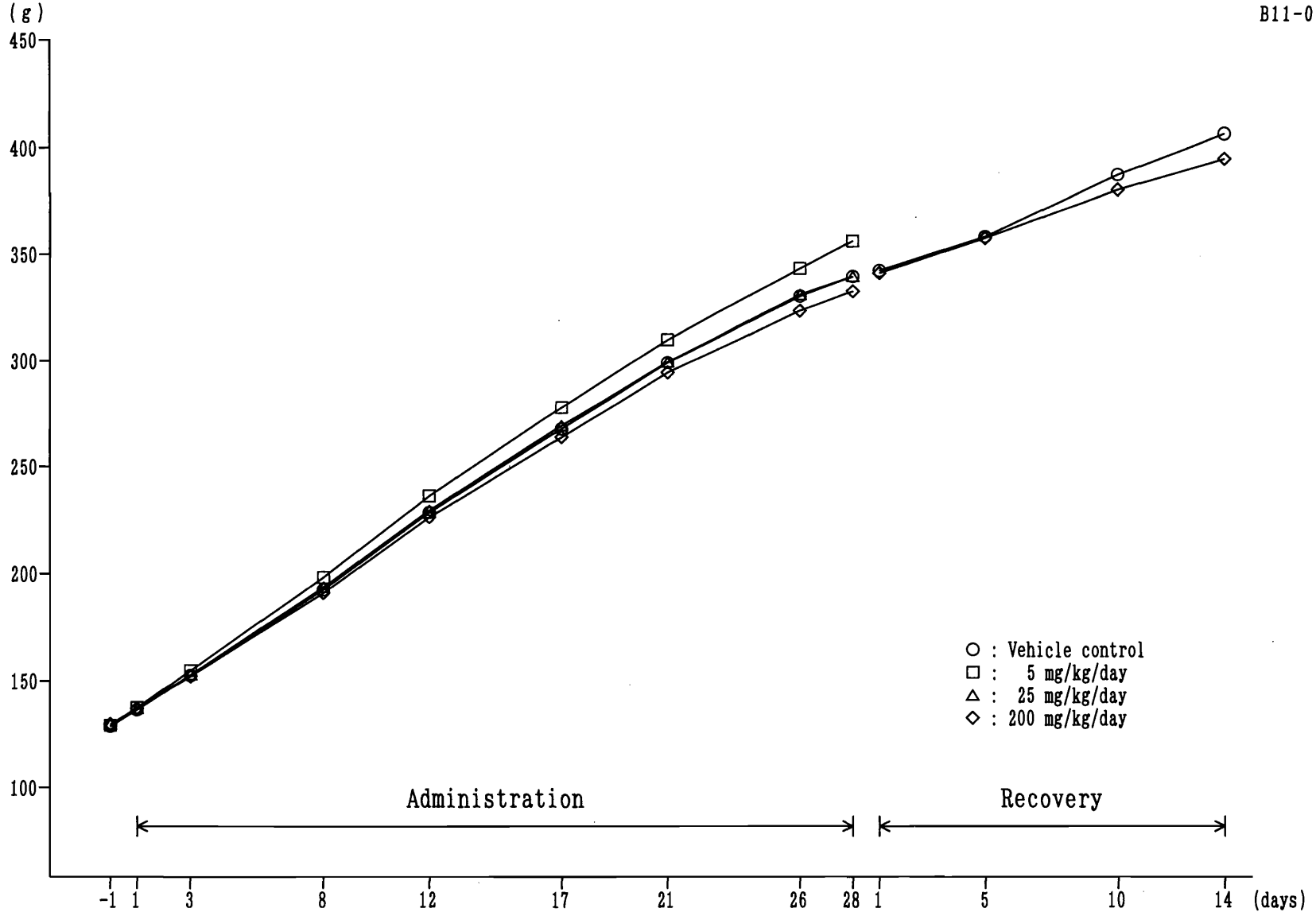


Fig. 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Male

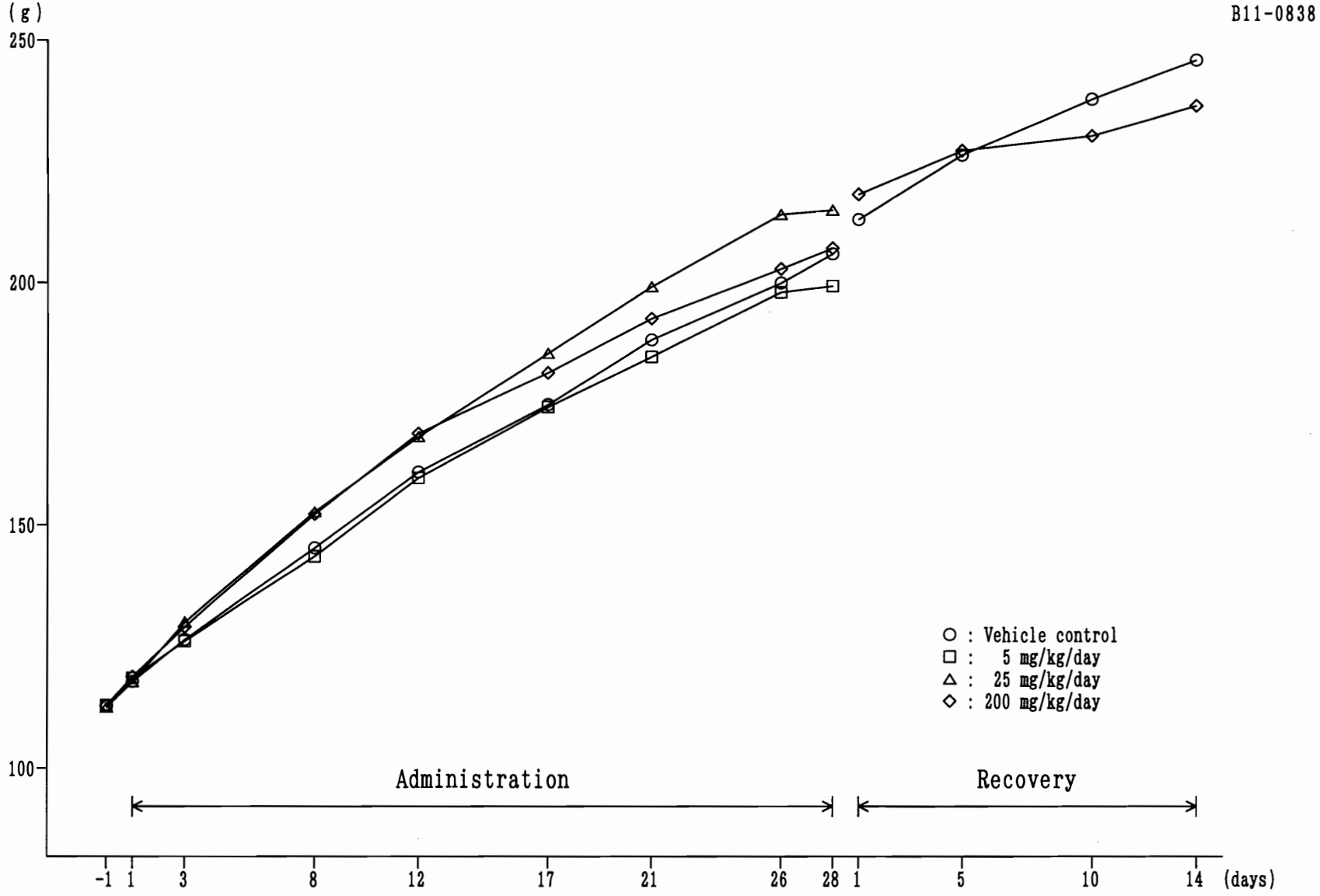


Fig. 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Female

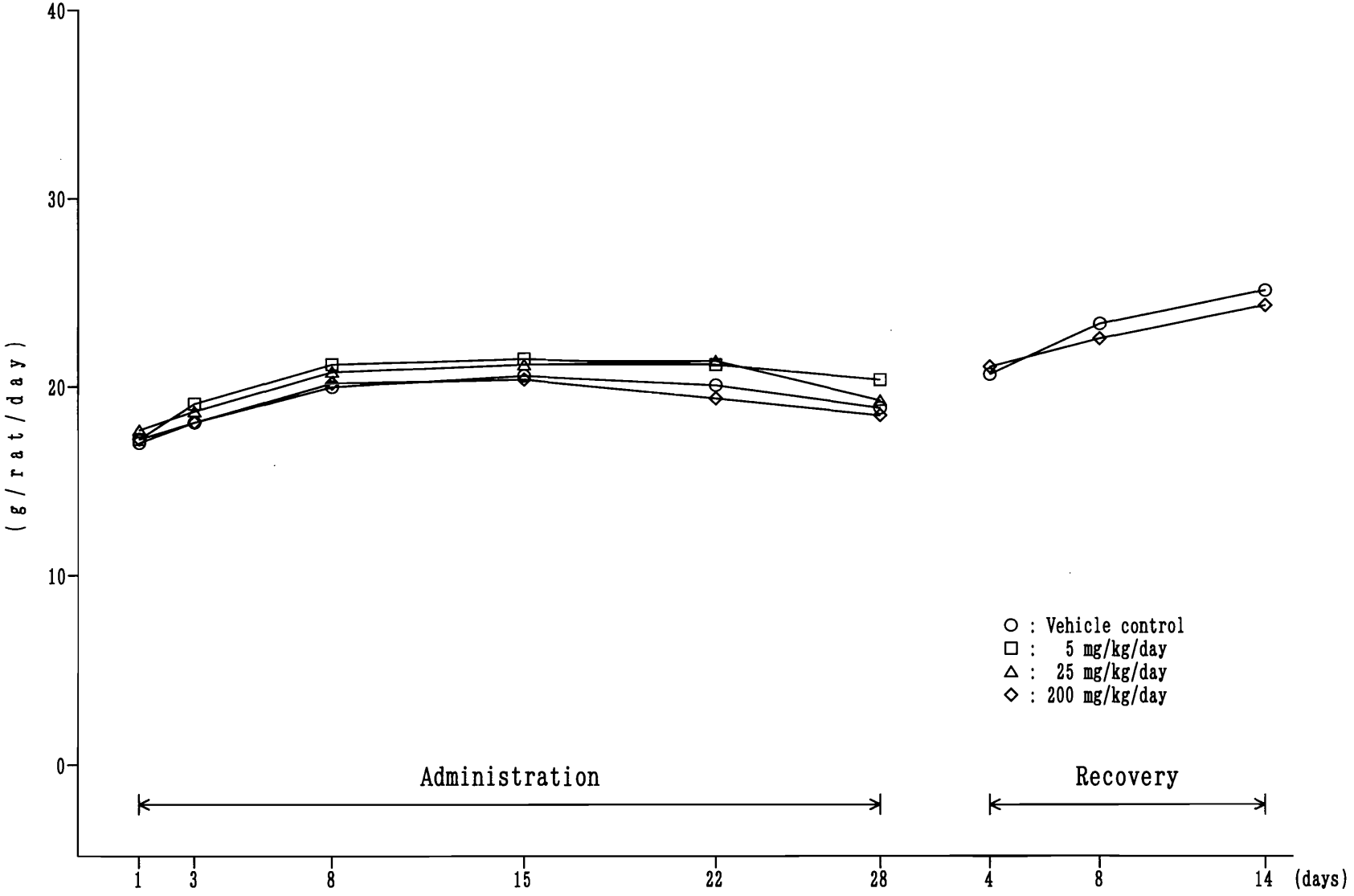


Fig. 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Male

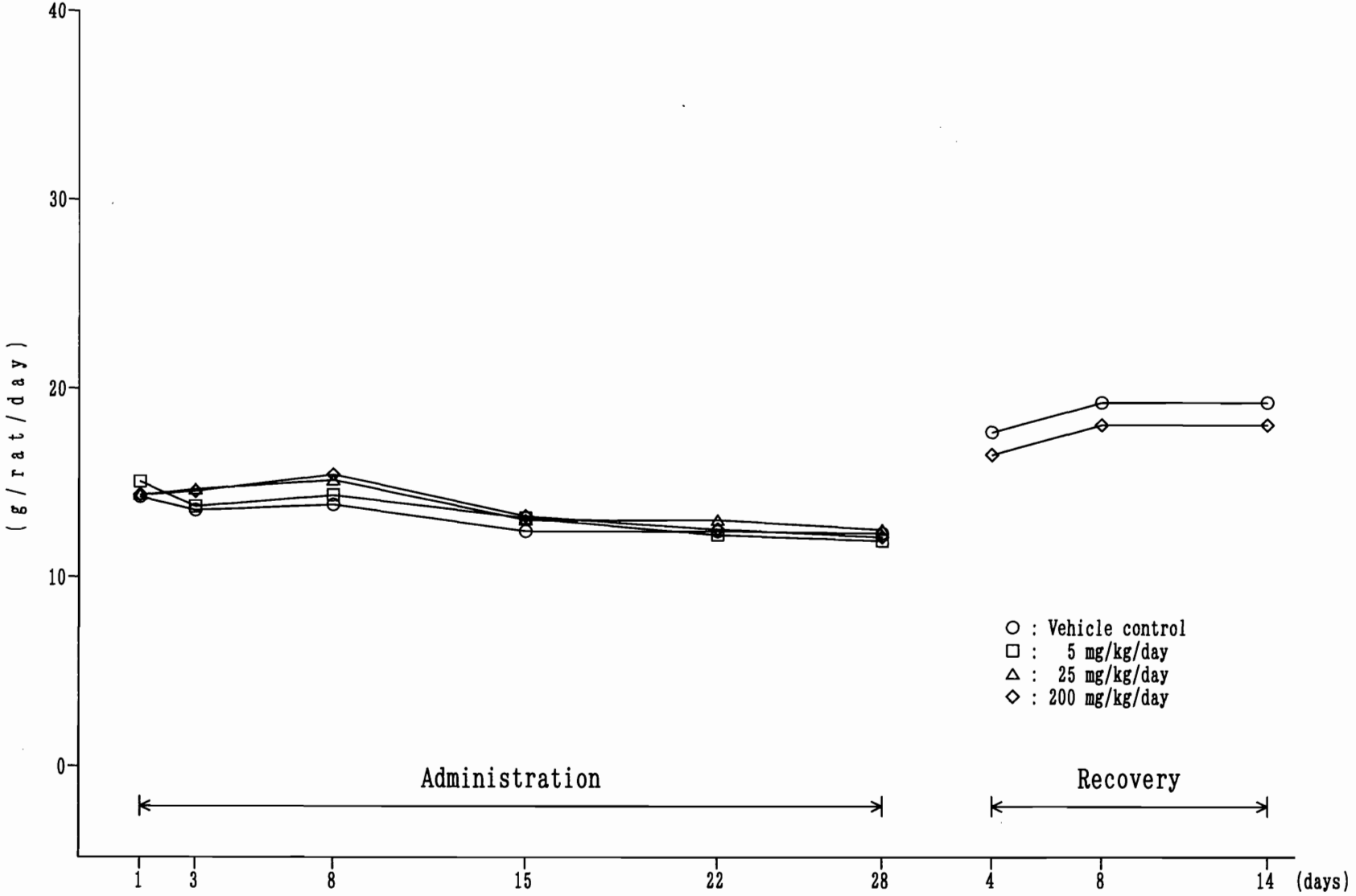


Fig. 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Female

Table 1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of clinical signs

Sex	Signs	Administration Period						Recovery Period	
	mg/kg/day	VC	VC (R)	5	25	200	200 (R)	VC	200
Male		ta 5[a)]	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5
	No abnormalities detected		2		1		1	5	3
	Salivation	5	3	5	4	5	4		
	Soft stool					2	1		
	Mottled teeth								2
	Loss of hair(ventral neck)	1							
Female		ta 5[a)]	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5	ta 5
	No abnormalities detected	1	4	2	2			4	4
	Salivation	3		1	3	5	5		
	Soft stool			1	1	2	2		
	Diarrhea			1	1		1		
	Loss of hair(right shoulder)	1							
	Loss of hair(forelimb)		1				1	1	1
	Loss of hair(left forelimb)			1					
	Scab formation(right shoulder)	1							

a) Number of animals examined.
VC, Vehicle control; (R), Recovery
ta, terminal autopsy.

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

REMOVAL FROM CAGE		
Ease of removal		
	-2	No reaction
	-1	Very easy
	0	Easy (slight resistance)
	+1	Difficult
	+2	Very difficult
Vocalization		
	0	None
	+1	Vocalization during handling
	+2	Continuous vocalization
HANDLING OBSERVATIONS		
Muscle tone		
	-1	Decreased
	0	Normal
	+1	Increased
Subnormal temperature		
	-	Absent
	+	Present
Piloerection		
	-	Absent
	+	Present
Staining hair		
	-	Absent
	+	Present
Unkempt hair		
	-	Absent
	+	Present
Paleness		
	-	Absent
	+	Present
Reddening		
	-	Absent
	+	Present
Cyanosis		
	-	Absent
	+	Present
Lacrimation		
	-	Absent
	+	Present

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

HANDLING OBSERVATIONS-continued		
	Exophthalmos	
	-	Absent
	+	Present
	Pupillary size	
	-1	Miosis
	0	Normal
	+1	Mydriasis
	Salivation	
	-	Absent
	+	Present
	Secretion	
	-	Absent
	+	Present
OBSERVATIONS IN ARENA		
	Posture	
	0	Normal
	+1	Crouching position or hunchback position
	+2	Prone position or lateral position
	Motor activity	
	-2	Significantly decreased
	-1	Decreased
	0	Normal
	+1	Increased
	+2	Significantly increased
	Respiration	
	0	Normal
	+1	Slightly insufficiency
	+2	Moderately insufficiency
	+3	Severely insufficiency
	Lid closure	
	-	Absent
	+	Present
	Gait	
	-	Normal
	S	Staggering gait
	T	Tip toe gait
	P	Shuffling (paralytic) gait
	GD	Gait disturbance

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

OBSERVATIONS IN ARENA-continued	
Tremor/twitch/convulsion	
0	None
+1	Tremor
+2	Twitch or convulsion
+3	Systematic tonic convulsion (opisthotonus or episthotonus etc.)
Stereotypic behavior	
-	None
C	Circling
G	Grooming
S	Sniffing
H	Head bobbing
Abnormal behavior	
-	None
S	Self-biting
B	Backing
C	Circling
R	Rolling
W	Writhing
V	Vocalization
ST	Straub tail
T	Tail lashing behavior

Table 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage							
				Ease of removal					Vocalization		
				-2	-1	0	+1	+2	0	+1	+2
Male	Predosing	Vehicle control	10	0	0	10	0	0	9	1	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	8	2	0
	week 1	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	3	2	0
		200	10	0	0	10	0	0	9	1	0
	week 2	Vehicle control	10	0	0	10	0	0	9	1	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	9	1	0
	week 3	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	5	0	0
		200	10	0	0	10	0	0	8	2	0
	week 4	Vehicle control	10	0	0	10	0	0	8	2	0
		5	5	0	0	5	0	0	3	2	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	9	1	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	4	0	1
		200	5	0	0	5	0	0	5	0	0
	Recovery week 2	Vehicle control	5	0	0	5	0	0	4	1	0
		200	5	0	0	5	0	0	5	0	0

Table 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage							
				Ease of removal					Vocalization		
				-2	-1	0	+1	+2	0	+1	+2
Female	Predosing	Vehicle control	10	0	0	10	0	0	9	1	0
		5	5	0	0	5	0	0	5	0	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	7	3	0
	week 1	Vehicle control	10	0	0	10	0	0	7	3	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	9	1	0
	week 2	Vehicle control	10	0	1	9	0	0	7	3	0
		5	5	0	0	5	0	0	2	3	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	2	8	0	0	9	1	0
	week 3	Vehicle control	10	0	0	10	0	0	6	4	0
		5	5	0	0	5	0	0	4	1	0
		25	5	0	0	5	0	0	5	0	0
		200	10	0	0	10	0	0	6	4	0
	week 4	Vehicle control	10	0	0	10	0	0	7	3	0
		5	5	0	0	5	0	0	3	2	0
		25	5	0	0	5	0	0	4	1	0
		200	10	0	0	10	0	0	10	0	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	4	1	0
		200	5	0	0	5	0	0	3	2	0
	Recovery week 2	Vehicle control	5	0	0	5	0	0	4	1	0
		200	5	0	0	5	0	0	5	0	0

Table 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0

Table 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+1	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0

Table 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		200	5	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0	5	0
		200	5	5	0	5	0	5	0	5	0

*: Yellow staining of whole body

Table 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0	10	0
		5	5	5	0	5	0	5	0	5	0
		25	5	5	0	5	0	5	0	5	0
		200	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		200	5	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0	5	0
		200	5	5	0	5	0	5	0	5	0

*: Yellow staining of whole body

Table 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		200	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		200	5	5	0	5	0	5	0

Table 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		5	5	5	0	5	0	5	0
		25	5	5	0	5	0	5	0
		200	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		200	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		200	5	5	0	5	0	5	0

Table 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0

Table 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		200	5	0	5	0	5	0	5	0

Table 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Male	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 1	Vehicle control	10	10	0	0	0	0	7	3	0
		5	5	5	0	0	0	0	3	2	0
		25	5	5	0	0	0	0	4	1	0
		200	10	10	0	0	0	0	7	3	0
	week 2	Vehicle control	10	10	0	0	0	1	9	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 3	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 4	Vehicle control	10	10	0	0	0	1	9	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	1	4	0	0
		200	10	10	0	0	0	3	7	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	5	0	0
		200	5	5	0	0	0	0	5	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	5	0	0
		200	5	5	0	0	0	0	5	0	0

Table 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Female	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 1	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	9	1	0
	week 2	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 3	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	5	0	0
		25	5	5	0	0	0	0	5	0	0
		200	10	10	0	0	0	0	10	0	0
	week 4	Vehicle control	10	10	0	0	0	0	9	1	0
		5	5	5	0	0	0	0	4	1	0
		25	5	5	0	0	0	1	3	1	0
		200	10	10	0	0	0	0	6	4	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	3	2	0
		200	5	5	0	0	0	0	2	3	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	5	0	0
		200	5	5	0	0	0	0	3	2	0

Table 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Male	Predosing	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		200	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		200	5	5	0	0	0	5	0

Table 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Female	Predosing	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		5	5	5	0	0	0	5	0
		25	5	5	0	0	0	5	0
		200	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		200	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		200	5	5	0	0	0	5	0

Table 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Male	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0

Table 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Female	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0

Table 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a)]	Urination (count/min)[a)]
Male	Predosing	Vehicle control	10	10	0	0	0	0.4 ±0.84	0.5 ±0.71
		5	5	5	0	0	0	0.0 ±0.00	2.8 ±3.35
		25	5	5	0	0	0	0.6 ±1.34	3.0 ±4.80
		200	10	10	0	0	0	0.0 ±0.00	1.2 ±2.53
	week 1	Vehicle control	10	10	0	0	0	0.4 ±0.84	0.9 ±1.10
		5	5	5	0	0	0	0.0 ±0.00	0.4 ±0.55
		25	5	5	0	0	0	0.4 ±0.89	1.0 ±1.41
		200	10	10	0	0	0	0.1 ±0.32	0.5 ±0.97
	week 2	Vehicle control	10	10	0	0	0	0.7 ±0.95	0.7 ±1.06
		5	5	5	0	0	0	0.0 ±0.00	0.4 ±0.89
		25	5	5	0	0	0	0.6 ±0.89	0.6 ±1.34
		200	10	10	0	0	0	0.0 ±0.00	0.4 ±0.70
	week 3	Vehicle control	10	10	0	0	0	0.2 ±0.63	0.0 ±0.00
		5	5	5	0	0	0	0.0 ±0.00	1.0 ±2.24
		25	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	10	10	0	0	0	0.1 ±0.32	0.1 ±0.32
	week 4	Vehicle control	10	10	0	0	0	0.4 ±0.84	0.0 ±0.00
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	0.2 ±0.45
		200	10	10	0	0	0	0.0 ±0.00	0.8 ±2.53
	Recovery week 1	Vehicle control	5	5	0	0	0	0.0 ±0.00	1.0 ±1.22
		200	5	5	0	0	0	0.0 ±0.00	1.0 ±2.24
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	1.0 ±2.24
		200	5	5	0	0	0	0.0 ±0.00	3.6 ±7.50

a) Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a)]	Urination (count/min)[a)]
Female	Predosing	Vehicle control	10	10	0	0	0	0.1 ±0.32	1.2 ±2.15
		5	5	5	0	0	0	0.6 ±1.34	0.8 ±1.30
		25	5	5	0	0	0	0.2 ±0.45	0.8 ±0.84
		200	10	10	0	0	0	0.3 ±0.95	1.8 ±3.16
	week 1	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.3 ±0.95
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
	week 2	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.4 ±0.84
		5	5	5	0	0	0	0.2 ±0.45	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	10	10	0	0	0	0.0 ±0.00	0.1 ±0.32
	week 3	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.2 ±0.63
		5	5	5	0	0	0	0.0 ±0.00	0.4 ±0.89
		25	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	10	10	0	0	0	0.0 ±0.00	0.1 ±0.32
	week 4	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.2 ±0.63
		5	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		25	5	5	0	0	0	0.0 ±0.00	2.6 ±2.07
		200	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
	Recovery week 1	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		200	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00

a) Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Stereotypic behavior				
				-	C	G	S	H
Male	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0

Table 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Stereotypic behavior -	C	G	S	H
Female	Predosing	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		5	5	5	0	0	0	0
		25	5	5	0	0	0	0
		200	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		200	5	5	0	0	0	0

Table 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena								
				Abnormal behavior								
				-	S	B	C	R	W	V	ST	T
Male	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		200	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		200	5	5	0	0	0	0	0	0	0	0

Table 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena								
				Abnormal behavior								
				-	S	B	C	R	W	V	ST	T
Female	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		5	5	5	0	0	0	0	0	0	0	0
		25	5	5	0	0	0	0	0	0	0	0
		200	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		200	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		200	5	5	0	0	0	0	0	0	0	0

Table 3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of reflex (scoring scale for reflex)

SENSORIMOTOR FUNCTION	
Approach contact/touch response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pinna response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pain response (tail pinch)	
-1	No reaction
0	Normal
+1	Hyper reaction
Pupillary reflex	
+	Normal
-	Abnormal reaction
Air righting reflex	
+	Normal
-	Abnormal reaction

Table 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function					
				Approach contact touch response			Pinna response		
				-1	0	+1	-1	0	+1
Male	week 4	Vehicle control	10	0	10	0	0	10	0
		5	5	0	5	0	0	5	0
		25	5	0	5	0	0	5	0
		200	10	0	10	0	0	10	0
Female	week 4	Vehicle control	10	0	10	0	0	10	0
		5	5	0	5	0	0	4	1
		25	5	0	5	0	0	5	0
		200	10	0	10	0	0	10	0

Table 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function						
				Pain response (tail pinch)			Pupillary reflex		Air righting reflex	
				-1	0	+1	+	-	+	-
Male	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	4	1	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0
Female	week 4	Vehicle control	10	0	10	0	10	0	10	0
		5	5	0	5	0	5	0	5	0
		25	5	0	5	0	5	0	5	0
		200	10	0	10	0	10	0	10	0

Table 4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of grip strength

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Forelimb (g)	Hindlimb (g)
Male	week 4	Vehicle control	10	393.0 ±98	380.1 ±50
		5	5	354.4 ±85	414.6 ±72
		25	5	442.0 ±90	374.8 ±72
		200	10	392.8 ±85	421.5 ±62
Female	week 4	Vehicle control	10	348.0 ±103	407.8 ±68
		5	5	365.4 ±101	389.0 ±42
		25	5	367.8 ±94	428.2 ±41
		200	10	305.6 ±58	430.3 ±84

Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Summary of motor activity

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Interval (min) 0-10	10-20	20-30	30-40	40-50	50-60	Total
Male	week 4	Vehicle control	10	3739 ±1244	3577 ±589	2684 ±776	2306 ±1112	2342 ±1559	1267 ±813	15916 ±4414
		5	5	4313 ±504	3796 ±1051	3109 ±1721	2369 ±252	2725 ±2307	1328 ±1478	17639 ±5740
		25	5	3466 ±1810	3610 ±779	2985 ±621	2363 ±667	1979 ±953	1508 ±877	15911 ±4234
		200	10	4212 ±1607	3175 ±1080	2397 ±594	1802 ±797	1861 ±769	1421 ±1053	14868 ±4210
Female	week 4	Vehicle control	10	5003 ±558	3528 ±641	3067 ±1195	3159 ±1413	1876 ±1209	1567 ±1166	18199 ±4192
		5	5	5111 ±1051	3169 ±1683	2045 ±1282	2149 ±1336	1465 ±1406	1178 ±962	15117 ±6724
		25	5	5664 ±1027	4213 ±1800	3225 ±1763	3287 ±2298	2570 ±1831	1720 ±1556	20679 ±9762
		200	10	5243 ±792	3546 ±853	2840 ±1331	2358 ±1892	2222 ±1541	1344 ±1464	17554 ±6145

Mean ±S.D.

* Significantly different from vehicle control at $P<0.05$.

** Significantly different from vehicle control at $P<0.01$.

Table 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period								
			-1	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	10	128.7 ± 5.3	136.4 ± 5.8	152.5 ± 7.4	192.6 ± 12.8	228.6 ± 16.1	268.0 ± 23.1	299.2 ± 27.4	330.5 ± 34.1	340.0 ± 35.8
	5	5	129.1 ± 5.0	137.5 ± 4.9	154.8 ± 8.3	198.3 ± 11.7	236.3 ± 14.4	278.2 ± 20.6	310.1 ± 25.9	343.7 ± 33.7	356.4 ± 37.6
	25	5	129.7 ± 4.6	137.0 ± 5.2	152.8 ± 7.4	193.7 ± 10.1	229.6 ± 16.3	269.5 ± 21.2	299.5 ± 25.0	331.3 ± 32.4	340.0 ± 33.2
	200	10	129.7 ± 4.6	137.1 ± 4.9	152.1 ± 5.3	191.0 ± 8.1	226.3 ± 12.7	264.0 ± 15.9	294.5 ± 19.0	323.7 ± 24.2	332.9 ± 24.3
Female	Vehicle control	10	112.9 ± 4.3	118.0 ± 4.7	126.6 ± 6.8	145.3 ± 10.2	160.9 ± 12.4	174.8 ± 14.3	188.2 ± 13.8	200.0 ± 14.8	206.0 ± 14.0
	5	5	113.1 ± 4.1	118.7 ± 4.8	126.3 ± 6.9	143.6 ± 12.3	159.7 ± 14.2	174.3 ± 15.7	184.7 ± 15.8	198.1 ± 14.2	199.4 ± 16.8
	25	5	112.6 ± 3.4	117.9 ± 3.8	130.1 ± 3.7	152.7 ± 5.2	168.2 ± 7.8	185.4 ± 10.4	199.2 ± 12.5	214.1 ± 12.3	215.0 ± 9.2
	200	10	113.0 ± 4.5	119.0 ± 5.9	129.2 ± 6.9	152.2 ± 9.2	168.9 ± 10.5	181.4 ± 12.7	192.6 ± 14.7	202.9 ± 14.6	207.2 ± 18.1

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of body weights(g)

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 1	5	10	14 (days)
Male	Vehicle control	5	342.8 ± 48.6	358.5 ± 50.4	387.8 ± 56.3	406.8 ± 54.6
	200	5	341.6 ± 25.6	357.8 ± 25.1	380.7 ± 22.5	395.2 ± 24.9
Female	Vehicle control	5	213.1 ± 17.2	226.3 ± 19.1	237.8 ± 19.3	246.0 ± 19.3
	200	5	218.2 ± 20.5	227.2 ± 22.1	230.3 ± 22.0	236.5 ± 22.5

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of food intakes(g/rat/day)

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	10	17.0 ± 1.6	18.1 ± 1.3	20.0 ± 1.8	20.6 ± 2.4	20.1 ± 2.8	18.9 ± 2.6
	5	5	17.2 ± 1.7	19.1 ± 1.7	21.2 ± 2.1	21.5 ± 2.1	21.2 ± 2.5	20.4 ± 3.4
	25	5	17.7 ± 1.1	18.7 ± 2.2	20.8 ± 1.4	21.2 ± 2.2	21.4 ± 2.5	19.3 ± 2.5
	200	10	17.2 ± 1.3	18.1 ± 1.6	20.2 ± 1.4	20.4 ± 1.8	19.4 ± 2.0	18.5 ± 2.2
Female	Vehicle control	10	14.2 ± 1.3	13.5 ± 1.5	13.8 ± 1.4	12.4 ± 1.2	12.4 ± 1.1	12.3 ± 1.3
	5	5	15.0 ± 1.6	13.7 ± 1.6	14.3 ± 2.0	13.1 ± 1.0	12.2 ± 0.9	11.9 ± 1.1
	25	5	14.3 ± 1.4	14.6 ± 1.0	15.1 ± 0.7	13.0 ± 1.3	13.0 ± 0.7	12.5 ± 0.7
	200	10	14.3 ± 1.6	14.5 ± 1.2	15.4 ± 1.1	13.2 ± 1.0	12.5 ± 1.5	12.1 ± 1.5

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of food intakes(g/rat/day)

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 4	8	14 (days)
Male	Vehicle control	5	20.7 ± 4.2	23.4 ± 4.0	25.2 ± 2.9
	200	5	21.1 ± 2.9	22.6 ± 3.1	24.4 ± 3.1
Female	Vehicle control	5	17.7 ± 1.4	19.3 ± 1.6	19.3 ± 1.2
	200	5	16.5 ± 2.0	18.1 ± 2.3	18.1 ± 1.6

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	5	724 ± 38	116 ± 39	14.6 ± 0.5	42.9 ± 1.4	59.3 ± 1.5	20.2 ± 0.5	34.0 ± 0.2	101.8 ± 13.5	3.0 ±0.5	15.2 ± 0.5	25.2 ± 3.7
	5	5	708 ± 43	122 ± 23	14.4 ± 0.6	42.9 ± 1.9	60.7 ± 1.9	20.4 ± 0.5	33.7 ± 0.3	95.6 ± 8.0	2.9 ±0.4	14.2 ± 0.7	25.2 ± 3.2
	25	5	712 ± 36	119 ± 18	14.3 ± 0.9	42.7 ± 2.8	59.9 ± 1.4	20.1 ± 0.5	33.6 ± 0.3	99.7 ± 8.0	2.6 ±0.3	14.4 ± 0.7	22.4 ± 2.8
	200	5	735 ± 32	116 ± 16	14.4 ± 0.5	42.8 ± 2.0	58.2 ± 0.9	19.6 ± 0.4	33.7 ± 0.5	100.8 ± 13.3	2.4 ±0.5	14.7 ± 0.4	22.5 ± 3.1
	Recovery												
	Vehicle control	5	791 ± 15	128 ± 30	15.0 ± 0.4	44.1 ± 1.6	55.8 ± 2.0	18.9 ± 0.5	33.9 ± 0.4	109.2 ± 9.1	2.6 ±0.3	17.2 ± 1.5	27.7 ± 2.7
	200	5	822 ± 34	109 ± 17	15.1 ± 0.5	44.7 ± 1.1	54.5 ± 1.9	18.5 ± 0.8	33.9 ± 0.4	110.3 ± 7.7	2.4 ±0.4	15.9 ± 1.0	24.8 ± 4.0
Female	Vehicle control	5	742 ± 17	100 ± 12	14.6 ± 0.4	43.1 ± 1.1	58.1 ± 0.9	19.7 ± 0.4	33.9 ± 0.5	111.0 ± 2.3	2.1 ±0.4	13.8 ± 0.3	21.7 ± 2.0
	5	5	763 ± 55	134* ± 29	14.8 ± 0.7	43.9 ± 2.1	57.7 ± 1.8	19.5 ± 0.6	33.7 ± 0.2	113.6 ± 12.1	2.1 ±0.3	13.5 ± 0.8	22.1 ± 2.6
	25	5	745 ± 35	118 ± 18	14.7 ± 0.6	43.2 ± 2.0	58.1 ± 1.3	19.8 ± 0.6	34.1 ± 0.4	107.0 ± 9.1	2.2 ±0.4	13.8 ± 0.7	20.7 ± 1.1
	200	5	766 ± 51	94 ± 17	14.9 ± 0.6	44.1 ± 2.1	57.6 ± 1.4	19.5 ± 0.5	33.9 ± 0.3	104.0 ± 6.9	1.7 ±0.4	13.7 ± 0.4	22.2 ± 2.3
	Recovery												
	Vehicle control	5	773 ± 23	112 ± 27	15.1 ± 0.6	42.8 ± 2.0	55.3 ± 1.5	19.5 ± 0.6	35.2 ± 0.6	130.1 ± 10.5	2.1 ±0.3	14.6 ± 0.8	22.0 ± 2.0
	200	5	789 ± 55	93 ± 23	15.0 ± 0.6	43.0 ± 1.9	54.6 ± 1.7	19.1 ± 0.7	34.9 ± 0.3	120.3 ± 14.0	2.1 ±0.4	14.1 ± 0.6	21.7 ± 1.9

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of hematological examinations

Sex	Exp.group (mg/kg/day)	Number of animals	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	5	19.5 ± 5.6	1.2 ±0.3	1.2 ±0.6	74.8 ± 6.1	2.5 ±0.6	0.8 ±0.3
	5	5	19.2 ± 5.4	1.8 ±0.5	0.9 ±0.9	75.1 ± 5.4	2.4 ±1.2	0.6 ±0.1
	25	5	21.1 ± 4.5	1.3 ±0.5	1.1 ±0.6	72.5 ± 3.8	2.9 ±0.7	1.1 ±0.5
	200	5	24.9 ± 7.0	1.3 ±0.4	1.2 ±0.9	68.2 ± 6.5	3.4 ±0.7	1.1 ±0.6
	Recovery							
	Vehicle control	5	14.6 ± 2.9	1.1 ±0.3	0.3 ±0.1	81.0 ± 2.9	2.2 ±0.3	0.8 ±0.3
	200	5	19.7* ± 3.2	1.1 ±0.3	0.5 ±0.2	75.8* ± 3.2	2.5 ±0.9	0.5* ±0.2
Female	Vehicle control	5	19.3 ± 5.2	0.9 ±0.3	0.2 ±0.1	77.0 ± 5.9	1.8 ±1.1	0.7 ±0.4
	5	5	22.6 ± 5.0	0.9 ±0.2	0.2 ±0.0	73.6 ± 5.7	1.8 ±0.6	0.9 ±0.4
	25	5	18.4 ± 5.1	1.0 ±0.4	0.2 ±0.1	77.7 ± 4.8	2.0 ±0.6	0.8 ±0.2
	200	5	18.2 ± 7.2	0.8 ±0.2	0.2 ±0.1	77.7 ± 8.1	2.0 ±1.1	1.0 ±0.2
	Recovery							
	Vehicle control	5	18.8 ± 5.9	1.7 ±0.7	0.2 ±0.1	76.2 ± 5.8	2.4 ±0.8	0.8 ±0.2
	200	5	19.9 ± 6.2	1.6 ±0.5	0.2 ±0.1	76.2 ± 6.8	1.6 ±0.4	0.5 ±0.2

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	5	65 ±11	20 ± 2	501 ± 67	41 ± 7	0.5 ±0.1	54 ± 7	76 ±26	138 ± 14	5.4 ±0.0	2.7 ±0.1	0.98 ±0.07
	5	5	66 ± 4	20 ± 2	539 ± 38	41 ± 6	0.5 ±0.2	56 ±13	80 ±30	131 ± 14	5.4 ±0.2	2.7 ±0.1	0.97 ±0.06
	25	5	60 ± 9	21 ± 4	546 ± 48	36 ± 7	0.3 ±0.1	48 ± 9	76 ±23	145 ± 15	5.4 ±0.1	2.7 ±0.1	0.98 ±0.05
	200	5	75 ±11	27 ± 7	511 ± 50	40 ± 6	0.7 ±0.3	50 ±12	74 ±26	125 ± 7	5.4 ±0.2	2.6 ±0.1	0.92 ±0.06
	Recovery												
	Vehicle control	5	62 ± 5	25 ± 4	323 ± 51	43 ± 11	0.4 ±0.1	62 ±19	67 ±26	144 ± 24	5.6 ±0.3	2.8 ±0.1	0.99 ±0.16
	200	5	71 ±12	26 ± 6	344 ± 93	42 ± 4	0.3 ±0.2	50 ± 9	64 ±15	144 ± 5	5.7 ±0.3	2.8 ±0.1	0.94 ±0.05
Female	Vehicle control	5	63 ±11	17 ± 3	225 ± 61	233 ± 46	0.6 ±0.3	63 ± 9	22 ±12	114 ± 7	5.7 ±0.3	3.0 ±0.2	1.08 ±0.06
	5	5	68 ± 8	18 ± 4	270 ± 63	201 ± 95	0.6 ±0.3	61 ± 9	20 ± 7	106 ± 14	5.7 ±0.4	2.9 ±0.2	1.02 ±0.10
	25	5	70 ±10	17 ± 4	292 ± 94	179 ± 36	0.6 ±0.3	64 ± 5	26 ± 7	122 ± 16	6.0 ±0.5	3.0 ±0.2	1.00 ±0.05
	200	5	63 ± 7	16 ± 3	275 ± 45	183 ± 59	0.6 ±0.5	65 ±14	22 ± 7	113 ± 12	5.8 ±0.2	2.9 ±0.2	1.01 ±0.12
	Recovery												
	Vehicle control	5	67 ± 8	20 ± 3	180 ± 57	279 ±106	0.7 ±0.2	68 ±12	20 ± 7	125 ± 8	6.1 ±0.4	3.0 ±0.2	1.00 ±0.07
	200	5	66 ± 6	19 ± 2	180 ± 50	295 ± 53	0.7 ±0.1	77 ±14	23 ± 9	143 ± 22	6.3 ±0.1	3.1 ±0.2	0.98 ±0.10

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	5	9.8 ± 1.2	0.26 ±0.04	0.06 ±0.02	9.1 ±0.1	8.0 ±0.4	143 ± 1	4.6 ±0.3	105.8 ± 1.9
	5	5	9.1 ± 1.1	0.24 ±0.03	0.05 ±0.01	9.3 ±0.1	8.1 ±0.6	144 ± 0	4.5 ±0.3	106.4 ± 1.1
	25	5	9.6 ± 0.8	0.23 ±0.04	0.05 ±0.01	9.2 ±0.3	8.1 ±0.8	144 ± 1	4.3 ±0.3	106.1 ± 1.1
	200	5	9.2 ± 2.1	0.23 ±0.04	0.05 ±0.01	9.4 ±0.5	8.0 ±0.8	143 ± 1	4.5 ±0.3	106.4 ± 1.3
	Recovery									
	Vehicle control	5	14.4 ± 1.8	0.25 ±0.04	0.06 ±0.02	8.9 ±0.2	7.1 ±0.2	144 ± 1	4.3 ±0.1	105.2 ± 1.3
	200	5	13.0 ± 1.8	0.24 ±0.01	0.05 ±0.02	8.9 ±0.2	6.8 ±0.3	143 ± 1	4.3 ±0.4	105.3 ± 1.8
Female	Vehicle control	5	11.3 ± 0.7	0.26 ±0.03	0.05 ±0.02	9.2 ±0.5	7.6 ±0.4	141 ± 1	4.2 ±0.5	107.4 ± 2.3
	5	5	11.8 ± 2.3	0.25 ±0.03	0.05 ±0.02	9.2 ±0.2	7.5 ±0.2	142 ± 1	4.1 ±0.2	106.8 ± 1.0
	25	5	12.1 ± 1.7	0.27 ±0.00	0.05 ±0.00	9.3 ±0.3	8.1 ±0.3	142 ± 1	4.3 ±0.4	107.3 ± 1.0
	200	5	11.5 ± 1.4	0.25 ±0.02	0.04 ±0.01	9.3 ±0.1	8.0 ±0.7	141 ± 1	4.2 ±0.3	108.4 ± 2.3
	Recovery									
	Vehicle control	5	16.1 ± 1.2	0.27 ±0.03	0.06 ±0.01	8.8 ±0.2	5.7 ±0.4	142 ± 1	4.1 ±0.2	107.0 ± 2.6
	200	5	16.3 ± 1.8	0.27 ±0.01	0.06 ±0.01	8.9 ±0.2	6.1 ±0.4	142 ± 1	4.2 ±0.5	107.1 ± 1.3

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Summary of urinalyses

Sex	Exp.group (mg/kg/day)	Number of animals	Urine volume (mL)	Sp.Gr.
Male	Vehicle control	5	5 ± 3	1.051 ±0.028
	5	5	6 ± 4	1.050 ±0.029
	25	5	11 ± 9	1.037 ±0.029
	200	5	5 ± 3	1.051 ±0.027
	Recovery			
	Vehicle control	5	11 ± 6	1.041 ±0.021
	200	5	14 ± 7	1.030 ±0.014
Female	Vehicle control	5	4 ± 3	1.047 ±0.028
	5	5	4 ± 2	1.038 ±0.025
	25	5	6 ± 5	1.035 ±0.020
	200	5	6 ± 2	1.027 ±0.011
	Recovery			
	Vehicle control	5	12 ± 6	1.027 ±0.012
	200	5	7 ± 2	1.033 ±0.008

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	Color SY	Color Y	Turbidity NT	pH 6.0	pH 6.5	pH 7.0	Protein ±	Protein 1+	Protein 2+	Glucose −	Occult blood −	Occult blood ±
Male	Vehicle control	5	1	4	5	3	2	0	0	3	2	5	5	0
	5	5	1	4	5	3	2	0	0	3	2	5	5	0
	25	5	2	3	5	2	2	1	2	1	2	5	5	0
	200	5	1	4	5	3	2	0	0	3	2	5	5	0
	Recovery													
	Vehicle control	5	2	3	5	0	4	1	2	2	1	5	5	0
	200	5	2	3	5	0	3	2	2	3	0	5	5	0
Female	Vehicle control	5	1	4	5	2	3	0	1	2	2	5	5	0
	5	5	0	5	5	2	3	0	0	4	1	5	5	0
	25	5	1	4	5	3	2	0	2	2	1	5	5	0
	200	5	1	4	5	1	4	0	1	3	1	5	5	0
	Recovery													
	Vehicle control	5	2	3	5	0	4	1	3	2	0	5	5	0
	200	5	1	4	5	0	4	1	1	4	0	5	4	1

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.

Table 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses (Urinary sediment)

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	Red blood cells[a]	White blood cells[a]		Epithelial cells[a]		Casts[b]	Crystals[c]	
			0	0	1-5	0	1-5	0	−	±
Male	Vehicle control	5	5	4	1	2	3	5	3	2
	5	0	-	-	-	-	-	-	-	-
	25	0	-	-	-	-	-	-	-	-
	200	5	5	4	1	2	3	5	4	1
	Recovery									
	Vehicle control	0	-	-	-	-	-	-	-	-
	200	0	-	-	-	-	-	-	-	-
Female	Vehicle control	5	5	4	1	1	4	5	4	1
	5	0	-	-	-	-	-	-	-	-
	25	0	-	-	-	-	-	-	-	-
	200	5	5	4	1	1	4	5	4	1
	Recovery									
	Vehicle control	0	-	-	-	-	-	-	-	-
	200	0	-	-	-	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.

Table 11 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of absolute organ weights

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight [a] (g)
Male	Vehicle control	5	10.07 ± 1.02	1.14 ± 0.10	2.37 ± 0.20	2.81 ± 0.29	0.66 ± 0.05	- -	1.93 ± 0.04	0.70 ± 0.14	627.9 ± 136.5	49.5 ± 7.4	326.1 ± 25.2
	5	5	11.08 ± 1.51	1.16 ± 0.05	2.41 ± 0.23	2.80 ± 0.16	0.69 ± 0.05	- -	1.98 ± 0.05	0.60 ± 0.07	525.5 ± 99.1	46.0 ± 3.8	338.8 ± 34.1
	25	5	11.39 ± 1.69	1.08 ± 0.10	2.33 ± 0.28	2.95 ± 0.18	0.72 ± 0.07	- -	1.97 ± 0.06	0.58 ± 0.06	521.6 ± 96.4	42.5 ± 6.3	324.0 ± 32.7
	200	5	13.03** ± 1.08	1.00* ± 0.07	2.38 ± 0.24	2.91 ± 0.36	0.68 ± 0.10	- -	1.97 ± 0.06	0.48** ± 0.07	442.2 ± 132.1	42.1 ± 4.8	309.0 ± 24.1
	Recovery												
	Vehicle control	5	10.85 ± 2.73	1.23 ± 0.16	2.65 ± 0.22	3.05 ± 0.25	0.95 ± 0.04	- -	2.06 ± 0.09	0.65 ± 0.12	452.5 ± 105.8	51.7 ± 10.9	380.4 ± 52.6
	200	5	11.17 ± 1.07	1.24 ± 0.12	2.86 ± 0.17	3.26 ± 0.08	1.05** ± 0.05	- -	2.05 ± 0.02	0.56 ± 0.04	391.7 ± 80.7	53.5 ± 6.0	371.3 ± 24.6
Female	Vehicle control	5	5.84 ± 0.89	0.72 ± 0.04	1.44 ± 0.10	- -	- -	64.5 ± 4.0	1.84 ± 0.09	0.41 ± 0.04	419.4 ± 73.6	53.8 ± 7.0	193.1 ± 8.1
	5	5	5.82 ± 0.85	0.72 ± 0.09	1.43 ± 0.15	- -	- -	74.5 ± 14.6	1.84 ± 0.08	0.41 ± 0.08	386.1 ± 64.0	55.6 ± 12.0	191.9 ± 15.6
	25	5	7.08* ± 0.66	0.76 ± 0.06	1.53 ± 0.11	- -	- -	82.2 ± 9.9	1.86 ± 0.05	0.49 ± 0.03	446.0 ± 32.7	58.6 ± 6.1	205.8 ± 11.8
	200	5	6.59 ± 0.23	0.70 ± 0.04	1.54 ± 0.06	- -	- -	73.3 ± 9.8	1.80 ± 0.11	0.39 ± 0.05	402.9 ± 85.5	59.8 ± 10.7	189.9 ± 9.3
	Recovery												
	Vehicle control	5	6.43 ± 0.84	0.83 ± 0.08	1.60 ± 0.21	- -	- -	89.1 ± 12.4	1.88 ± 0.04	0.55 ± 0.07	467.3 ± 81.0	64.6 ± 10.5	229.9 ± 18.6
	200	5	6.64 ± 0.93	0.84 ± 0.08	1.60 ± 0.22	- -	- -	82.1 ± 12.6	1.88 ± 0.07	0.49 ± 0.10	402.6 ± 129.1	64.7 ± 4.7	222.7 ± 22.9

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 12 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of relative organ weights

B11-0838

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight [a] (g)
Male	Vehicle control	5	3.09 ±0.24	0.35 ±0.01	0.73 ±0.06	0.87 ±0.12	0.20 ±0.01	- -	0.59 ±0.04	0.22 ±0.05	193.6 ± 45.4	15.2 ± 2.1	326.1 ± 25.2
	5	5	3.26 ±0.12	0.34 ±0.02	0.72 ±0.06	0.83 ±0.09	0.21 ±0.03	- -	0.59 ±0.05	0.18 ±0.02	154.2 ± 16.0	13.7 ± 1.8	338.8 ± 34.1
	25	5	3.50** ±0.19	0.33 ±0.01	0.72 ±0.04	0.91 ±0.05	0.22 ±0.01	- -	0.61 ±0.06	0.18 ±0.02	160.7 ± 22.5	13.2 ± 1.6	324.0 ± 32.7
	200	5	4.22** ±0.13	0.33 ±0.03	0.77 ±0.05	0.94 ±0.11	0.22 ±0.04	- -	0.64 ±0.05	0.16* ±0.02	142.6 ± 39.7	13.6 ± 0.9	309.0 ± 24.1
	Recovery												
	Vehicle control	5	2.83 ±0.34	0.32 ±0.04	0.70 ±0.04	0.82 ±0.15	0.25 ±0.03	- -	0.55 ±0.05	0.17 ±0.01	118.5 ± 20.3	13.6 ± 1.6	380.4 ± 52.6
	200	5	3.00 ±0.15	0.33 ±0.02	0.77* ±0.04	0.88 ±0.07	0.28 ±0.03	- -	0.55 ±0.04	0.15 ±0.02	105.1 ± 17.7	14.4 ± 0.9	371.3 ± 24.6
Female	Vehicle control	5	3.01 ±0.33	0.37 ±0.01	0.75 ±0.03	- -	- -	33.4 ± 2.3	0.96 ±0.06	0.21 ±0.02	216.6 ± 32.2	27.8 ± 2.9	193.1 ± 8.1
	5	5	3.02 ±0.20	0.38 ±0.03	0.74 ±0.05	- -	- -	38.7 ± 5.5	0.96 ±0.05	0.21 ±0.03	200.8 ± 23.0	28.8 ± 4.3	191.9 ± 15.6
	25	5	3.44* ±0.29	0.37 ±0.03	0.74 ±0.04	- -	- -	40.2 ± 7.2	0.90 ±0.05	0.24 ±0.02	216.9 ± 15.7	28.5 ± 2.3	205.8 ± 11.8
	200	5	3.47* ±0.09	0.37 ±0.02	0.81* ±0.04	- -	- -	38.6 ± 4.6	0.95 ±0.05	0.20 ±0.02	210.9 ± 35.1	31.6 ± 6.1	189.9 ± 9.3
	Recovery												
	Vehicle control	5	2.79 ±0.20	0.36 ±0.03	0.70 ±0.07	- -	- -	38.8 ± 4.5	0.83 ±0.07	0.24 ±0.02	202.8 ± 29.8	28.0 ± 3.4	229.9 ± 18.6
	200	5	2.98 ±0.24	0.38 ±0.02	0.72 ±0.04	- -	- -	36.8 ± 2.7	0.85 ±0.06	0.22 ±0.03	178.1 ± 40.0	29.2 ± 2.6	222.7 ± 22.9

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 13 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of macroscopic examinations

Findings	Male						Female						(mg/kg/day)
	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
	5[a)]	5	5	5	5	5	5	5	5	5	5	5	
No abnormalities detected	4	5	4	4	0	2	4	4	5	5	4	3	
Oral cavity													
Mottled teeth	0	0	0	0	0	3	0	0	0	0	0	1	
Forestomach													
Elevated region of mucosa	0	0	0	0	0	0	0	0	0	0	1	0	
Liver													
Enlargement	0	0	0	0	5	0	0	0	0	0	0	0	
Spleen													
Whitish region on capsule	0	0	1	0	0	0	0	0	0	0	0	0	
Pituitary gland													
Cyst	0	0	0	1	0	0	0	0	0	0	0	0	
Skin													
Loss of hair	0	0	0	0	0	0	0	1	0	0	0	1	
Scab formation	0	0	0	0	0	0	1	0	0	0	0	0	
Sparsed fur	1	0	0	0	0	0	0	0	0	0	0	0	

ta, terminal autopsy.

a) Number of animals examined.

Table 14-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	5	5	5	
Trachea														
No abnormalities detected		5/5[b)]	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Lung														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Incisor														
No abnormalities detected		5/5	5/5	—	—	5/5	5/5	5/5	5/5	—	—	5/5	5/5	
Forestomach														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	5/5	5/5	5/5	4/5	5/5	
Lymphocyte infiltration in submucosal layer	+	0/5	—	—	—	0/5	—	0/5	0/5	0/5	0/5	1/5	0/5	
Glandular stomach														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	5/5	5/5	5/5	4/5	5/5	
Edema in submucosal layer	+	0/5	—	—	—	0/5	—	0/5	0/5	0/5	0/5	1/5	0/5	
Duodenum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Jejunum														
No abnormalities detected		4/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Focal necrosis in Peyer's patches	+	1/5	—	—	—	0/5	—	0/5	—	—	—	0/5	—	
Ileum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Cecum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight.

Table 14-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	5	5	5	
Colon														
No abnormalities detected		5/5[b)]	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Rectum														
No abnormalities detected		5/5	—	—	—	5/5	—	4/5	—	—	—	5/5	—	
Focal inflammation	+	0/5	—	—	—	0/5	—	1/5	—	—	—	0/5	—	
Liver														
No abnormalities detected		5/5	5/5	5/5	3/5	0/5	1/5	4/5	4/5	5/5	4/5	2/5	5/5	
Centrilobular lipid droplets in hepatocytes	+	0/5	0/5	0/5	1/5	3/5	3/5	0/5	0/5	0/5	0/5	1/5	0/5	
	++	0/5	0/5	0/5	0/5	2/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	
Microgranuloma	+	0/5	0/5	0/5	0/5	4/5	3/5	1/5	1/5	0/5	1/5	2/5	0/5	
	++	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	
Periportal hypertrophy of hepatocytes	+	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	
Peliportal lipid droplets in hepatocytes	+	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/5	0/5	
Periportal prominent nucleoli of hepatocytes	+	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	
Heart														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate.

Table 14-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	5	5	5	
Kidney														
No abnormalities detected		5/5[b)]	4/5	—	—	5/5	5/5	5/5	—	—	—	4/5	—	
Mineralization in cortico-medullary junction	+	0/5	0/5	—	—	0/5	0/5	0/5	—	—	—	1/5	—	
Mineralization in medulla	+	0/5	1/5	—	—	0/5	0/5	0/5	—	—	—	0/5	—	
Urinary bladder														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Testis														
No abnormalities detected		5/5	4/5	5/5	5/5	4/5	5/5							
Degeneration of spermatocytes	+	0/5	0/5	0/5	0/5	1/5	0/5							
Inhibited spermiation and deep retention of spermatids	++	0/5	1/5	0/5	0/5	0/5	0/5							
Epididymis														
No abnormalities detected		5/5	5/5	5/5	5/5	4/5	5/5							
Germ cell debris in lumen	+	0/5	0/5	0/5	0/5	1/5	0/5							
Prostate														
No abnormalities detected		5/5	—	—	—	5/5	—							
Seminal vesicle														
No abnormalities detected		5/5	—	—	—	5/5	—							

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate.

Table 14-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	5	5	5	
Ovary														
No abnormalities detected								5/5[b)]	—	—	—	5/5	—	
Uterus														
No abnormalities detected								5/5	—	—	—	5/5	—	
Vagina														
No abnormalities detected								5/5	—	—	—	5/5	—	
Cerebrum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Cerebellum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Pons														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Spinal cord														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Sciatic nerve														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Bone marrow														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Axillar lymph node														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Mesenteric lymph node														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.

Table 14-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	Vehicle control	Vehicle control (Recovery)	5	25	200	200 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a)]	5	5	5	5	5	5	5	5	5	5	5	
Spleen														
No abnormalities detected		5/5[b)]	—	0/1	—	5/5	—	5/5	—	—	—	5/5	—	
Capsulitis	+	0/5	—	1/1	—	0/5	—	0/5	—	—	—	0/5	—	
Thymus														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Pituitary gland														
No abnormalities detected		5/5	—	—	0/1	5/5	—	5/5	—	—	—	5/5	—	
Cyst formation in pars intermedia	++	0/5	—	—	1/1	0/5	—	0/5	—	—	—	0/5	—	
Thyroid														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Parathyroid														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Adrenal														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Eye ball														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Skin														
No abnormalities detected		1/1	—	—	—	—	—	0/1	1/1	—	—	—	1/1	
Ulcer	+	0/1	—	—	—	—	—	1/1	0/1	—	—	—	0/1	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate.

Addendum 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
Vehicle control

Signs	Sex	Administration Period				Recovery Period		(week)
		1	2	3	4	1	2	
No abnormalities detected	Male	1,[a] 2, 3, 4, 5, 6, 7, 8, 9, 10	1, 2, 3, 4, 6, 7, 9	6, 7	1, 6, 7, 8	6, 7, 8, 9, 10	6, 7, 8, 9, 10	
	Female	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	32, 33, 34, 35, 36, 37, 38, 39, 40	32, 33, 34, 37, 38, 39, 40	33, 37, 38, 39, 40	37, 38, 39, 40	37, 38, 39, 40	
Salivation	Male		5, 8, 10	1, 2, 3, 4, 5, 8, 9, 10	3, 4, 5, 9, 10			
	Female		31	31, 35	31, 34, 35			
Loss of hair(ventral neck)	Male				2			
	Female							
Loss of hair(right shoulder)	Male							
	Female				32			
Loss of hair(forelimb)	Male							
	Female			36	36	36	36	
Scab formation(right shoulder)	Male							
	Female				32			

a) Animal number.

Addendum 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
5 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	11,[a] 12, 14	11, 12, 14	11, 13				
	Female	42, 43, 44, 45	42, 43, 45	42, 43, 45	43, 44, 45			
Salivation	Male	13, 15	13, 15	12, 14, 15	11, 12, 13, 14, 15			
	Female	41	41	41	41			
Soft stool	Male							
	Female		44	44				
Diarrhea	Male							
	Female		44					
Loss of hair(left forelimb)	Male							
	Female				42			

a) Animal number.

Addendum 1-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
25 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	16,[a] 17, 20	16, 17	16, 17	16			
	Female	47, 48, 49	47, 48	47, 48, 49	46, 47, 48, 49, 50			
Salivation	Male	18, 19	18, 19, 20	18, 19, 20	17, 18, 19, 20			
	Female	46, 50	46, 49, 50	46, 50				
Soft stool	Male							
	Female	46						
Diarrhea	Male							
	Female	50						

a) Animal number.

Addendum 1-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
200 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		(week)
		1	2	3	4	1	2	
No abnormalities detected	Male	25,[a] 26, 27, 30	25, 26, 29, 30	26	26, 29	26, 27, 28, 29, 30	27, 29, 30	
	Female	51, 54	54, 58, 60	55	53, 55, 57	56, 57, 59, 60	56, 57, 59, 60	
Salivation	Male	21, 22, 23, 24, 28	21, 22, 23, 24, 27, 28	21, 22, 23, 24, 25, 27, 28, 29, 30	21, 22, 23, 24, 25, 27, 28, 30			
	Female	52, 53, 56, 57, 58, 59, 60	51, 52, 53, 55, 56, 57, 59	51, 52, 53, 54, 56, 57, 58, 59, 60	51, 52, 54, 56, 58, 59, 60			
Soft stool	Male	21, 22, 29	22					
	Female	53, 55, 56, 59	55	59				
Diarrhea	Male							
	Female	59						
Mottled teeth	Male						26, 28	
	Female							
Loss of hair(forelimb)	Male							
	Female				58	58	58	

a) Animal number.

Addendum 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	+1
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	+1
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	200	21	0	0
		22	0	+1
		23	0	0
		24	0	0
		25	0	+1
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	0
		35	0	0
		36	0	+1
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	5	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	25	46	0	0
		47	0	+1
		48	0	0
		49	0	0
		50	0	0
	200	51	0	0
		52	0	0
		53	0	+1
		54	0	0
		55	0	0
		56	0	+1
		57	0	+1
		58	0	0
		59	0	0
		60	0	0

Addendum 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	+1
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	+1
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	+1
		17	0	+1
		18	0	0
		19	0	0
		20	0	0
	200	21	0	0
		22	0	0
		23	0	+1
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	0
		34	0	0
		35	0	0
		36	0	+1
		37	0	0
		38	0	0
		39	0	+1
		40	0	0
	5	41	0	0
		42	0	0
		43	0	0
		44	0	+1
		45	0	0
	25	46	0	0
		47	0	+1
		48	0	0
		49	0	0
		50	0	0
	200	51	0	0
		52	0	0
		53	0	+1
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	+1
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	+1
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	200	21	0	0
		22	0	0
		23	0	+1
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	+1
		34	0	0
		35	0	0
		36	0	+1
		37	0	0
		38	0	0
		39	-1	0
		40	0	0
	5	41	0	0
		42	0	+1
		43	0	0
		44	0	+1
		45	0	+1
	25	46	0	0
		47	0	0
		48	0	+1
		49	0	0
		50	0	0
	200	51	0	0
		52	0	0
		53	-1	+1
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	-1	0
		60	0	0

Addendum 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	+1
		6	0	0
		7	0	0
		8	0	0
		9	0	+1
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	25	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	200	21	0	0
		22	0	0
		23	0	+1
		24	0	0
		25	0	+1
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	+1
		34	0	0
		35	0	0
		36	0	+1
		37	0	0
		38	0	0
		39	0	0
		40	0	+1
	5	41	0	0
		42	0	0
		43	0	0
		44	0	+1
		45	0	0
	25	46	0	0
		47	0	0
		48	0	0
		49	0	0
		50	0	0
	200	51	0	0
		52	0	0
		53	0	0
		54	0	+1
		55	0	0
		56	0	+1
		57	0	+1
		58	0	0
		59	0	0
		60	0	+1

Addendum 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	+1
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	+1
		10	0	0
	5	11	0	0
		12	0	0
		13	0	0
		14	0	+1
		15	0	+1
	25	16	0	+1
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	200	21	0	0
		22	0	0
		23	0	+1
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	+1
		33	0	0
		34	0	0
		35	0	0
		36	0	+1
		37	0	0
		38	0	0
		39	0	0
		40	0	+1
	5	41	0	0
		42	0	0
		43	0	0
		44	0	+1
		45	0	+1
	25	46	0	0
		47	0	0
		48	0	+1
		49	0	0
		50	0	0
	200	51	0	0
		52	0	0
		53	0	0
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	0
		9	0	+2
		10	0	0
	200	26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	+1
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	200	56	0	0
		57	0	0
		58	0	+1
		59	0	0
		60	0	+1

Addendum 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	+1
		9	0	0
		10	0	0
	200	26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	+1
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	200	56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	200	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	200	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	200	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	200	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	200	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	200	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	200	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	200	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-23 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	5	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	25	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	200	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-24 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	5	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	25	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	200	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-25 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	200	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-26 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	200	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-27 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	200	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-28 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	200	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-29 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	200	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-30 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	200	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-31 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	200	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-32 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	200	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-33 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	200	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-34 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	200	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-35 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	200	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-36 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	200	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-37 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	5	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	25	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	200	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-38 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	5	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	25	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	200	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-39 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	200	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-40 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	200	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-41 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	200	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-42 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	200	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-43 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-44 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-45 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	+1	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	+1	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	+1	0	-	-
	5	11	0	0	0	-	-
		12	0	+1	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	+1	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	+1	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	+1	0	-	-
		25	0	+1	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	+1	0	-	-

Addendum 2-46 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	+1	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	+1	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-47 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	-1	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-48 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	+1	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-49 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-50 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	+1	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-51 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	-1	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	-1	0	-	-
	200	21	0	-1	0	-	-
		22	0	0	0	-	-
		23	0	-1	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	-1	0	-	-

Addendum 2-52 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	+1	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	+1	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	-1	0	-	-
		47	0	0	0	-	-
		48	0	+1	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	+1	0	-	-
		53	0	+1	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	+1	0	-	-
		57	0	+1	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-53 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	200	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-54 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	+1	0	-	-
		39	0	0	0	-	-
		40	0	+1	0	-	-
	200	56	0	+1	0	-	-
		57	0	+1	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	+1	0	-	-

Addendum 2-55 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	200	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-56 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	200	56	0	+1	0	-	-
		57	0	+1	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-57 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	2	0	-	-
		2	0	2	1	-	-
		3	0	0	1	-	-
		4	0	0	2	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	1	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	2	-	-
		12	0	0	8	-	-
		13	0	0	0	-	-
		14	0	0	4	-	-
		15	0	0	0	-	-
	25	16	0	3	11	-	-
		17	0	0	4	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	8	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	2	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	2	-	-
		30	0	0	0	-	-

Addendum 2-58 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	1	0	-	-
		32	0	0	7	-	-
		33	0	0	1	-	-
		34	0	0	2	-	-
		35	0	0	1	-	-
		36	0	0	1	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	1	-	-
		44	0	3	3	-	-
		45	0	0	0	-	-
	25	46	0	0	1	-	-
		47	0	0	0	-	-
		48	0	0	1	-	-
		49	0	1	0	-	-
		50	0	0	2	-	-
	200	51	0	0	0	-	-
		52	0	0	2	-	-
		53	0	0	6	-	-
		54	0	0	1	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	3	9	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-59 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	2	1	-	-
		2	0	0	1	-	-
		3	0	0	3	-	-
		4	0	2	2	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	2	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	1	-	-
		13	0	0	1	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	2	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	2	3	-	-
		20	0	0	0	-	-
	200	21	0	0	1	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	3	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	1	1	-	-
		30	0	0	0	-	-

Addendum 2-60 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	3	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-61 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	2	1	-	-
		3	0	0	0	-	-
		4	0	2	2	-	-
		5	0	2	3	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	1	1	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	2	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	3	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	1	0	-	-
		20	0	2	0	-	-
	200	21	0	0	2	-	-
		22	0	0	0	-	-
		23	0	0	1	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	1	-	-
		30	0	0	0	-	-

Addendum 2-62 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	2	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	2	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	1	0	-	-
		45	0	0	0	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	1	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-63 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	2	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	5	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	1	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	1	0	-	-
		30	0	0	0	-	-

Addendum 2-64 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	2	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	2	-	-
	25	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	1	-	-
		60	0	0	0	-	-

Addendum 2-65 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	2	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	2	0	-	-
		10	0	0	0	-	-
	5	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	25	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	1	-	-
		20	0	0	0	-	-
	200	21	0	0	0	-	-
		22	0	0	8	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-66 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	2	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	5	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	25	46	0	0	3	-	-
		47	0	0	5	-	-
		48	0	0	0	-	-
		49	0	0	4	-	-
		50	0	0	1	-	-
	200	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-67 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	3	-	-
		7	0	0	0	-	-
		8	0	0	1	-	-
		9	0	0	0	-	-
		10	0	0	1	-	-
	200	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	5	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-68 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	200	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-69 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	5	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	200	26	0	0	1	-	-
		27	0	0	0	-	-
		28	0	0	17	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-70 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	200	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Male	Vehicle control	1	0	0	0	+	+
		2	0	0	0	+	+
		3	0	0	0	+	+
		4	0	0	0	+	+
		5	0	0	0	+	+
		6	0	0	0	+	+
		7	0	0	0	+	+
		8	0	0	0	+	+
		9	0	0	0	+	+
		10	0	0	0	+	+
	5	11	0	0	+1	+	+
		12	0	0	0	+	+
		13	0	0	0	+	+
		14	0	0	0	+	+
		15	0	0	0	+	+
	25	16	0	0	0	+	+
		17	0	0	0	+	+
		18	0	0	0	+	+
		19	0	0	0	+	+
		20	0	0	0	+	+
	200	21	0	0	0	+	+
		22	0	0	0	+	+
		23	0	0	0	+	+
		24	0	0	0	+	+
		25	0	0	0	+	+
		26	0	0	0	+	+
		27	0	0	0	+	+
		28	0	0	0	+	+
		29	0	0	0	+	+
		30	0	0	0	+	+

Addendum 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Female	Vehicle control	31	0	0	0	+	+
		32	0	0	0	+	+
		33	0	0	0	+	+
		34	0	0	0	+	+
		35	0	0	0	+	+
		36	0	0	0	+	+
		37	0	0	0	+	+
		38	0	0	0	+	+
		39	0	0	0	+	+
		40	0	0	0	+	+
	5	41	0	0	0	+	+
		42	0	0	0	+	+
		43	0	+1	0	+	+
		44	0	0	0	+	+
		45	0	0	0	+	+
	25	46	0	0	0	+	+
		47	0	0	0	+	+
		48	0	0	0	+	+
		49	0	0	0	+	+
		50	0	0	0	+	+
	200	51	0	0	0	+	+
		52	0	0	0	+	+
		53	0	0	0	+	+
		54	0	0	0	+	+
		55	0	0	0	+	+
		56	0	0	0	+	+
		57	0	0	0	+	+
		58	0	0	0	+	+
		59	0	0	0	+	+
		60	0	0	0	+	+

Addendum 4-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Male	Vehicle control	1	540	397	469	388	314	351
		2	325	466	396	360	451	406
		3	253	468	361	337	236	287
		4	639	566	603	567	327	447
		5	493	323	408	339	389	364
		6	226	265	246	380	405	393
		7	405	411	408	493	360	427
		8	290	390	340	332	328	330
		9	440	373	407	342	519	431
		10	302	282	292	425	304	365
	5	11	249	527	388	406	566	486
		12	541	329	435	343	404	374
		13	273	567	420	533	377	455
		14	259	300	280	325	291	308
		15	249	248	249	444	455	450
	25	16	564	449	507	347	512	430
		17	335	261	298	308	293	301
		18	566	470	518	460	413	437
		19	462	482	472	396	429	413
		20	400	430	415	261	325	293
	200	21	450	487	469	382	413	398
		22	271	282	277	491	410	451
		23	403	260	332	327	358	343
		24	478	557	518	348	469	409
		25	481	431	456	477	405	441
		26	565	410	488	551	373	462
		27	335	378	357	537	567	552
		28	254	421	338	369	508	439
		29	332	461	397	389	347	368
		30	314	278	296	391	312	352

Addendum 4-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Female	Vehicle control	31	206	270	238	267	320	294
		32	412	663	538	560	500	530
		33	260	271	266	430	407	419
		34	308	269	289	487	463	475
		35	324	333	329	420	455	438
		36	211	443	327	412	308	360
		37	379	260	320	310	463	387
		38	394	488	441	518	372	445
		39	207	293	250	336	386	361
		40	402	562	482	309	429	369
	5	41	367	505	436	337	525	431
		42	209	275	242	293	454	374
		43	254	484	369	299	531	415
		44	391	586	489	401	400	401
		45	231	351	291	361	287	324
	25	46	551	376	464	317	517	417
		47	362	399	381	267	537	402
		48	280	442	361	517	475	496
		49	399	436	418	343	522	433
		50	221	208	215	455	330	393
	200	51	268	225	247	270	287	279
		52	380	400	390	459	463	461
		53	239	405	322	340	517	429
		54	345	384	365	502	674	588
		55	362	382	372	432	586	509
		56	212	244	228	496	302	399
		57	277	268	273	503	364	434
		58	205	429	317	489	423	456
		59	200	402	301	331	449	390
		60	220	261	241	357	358	358

Addendum 5-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Interval (min)						
			0-10	10-20	20-30	30-40	40-50	50-60	Total
Male	Vehicle control	1	3483	2580	1473	1093	1492	429	10550
		2	3158	3139	1576	1891	1578	642	11984
		3	4104	4369	3255	3817	2534	2678	20757
		4	2240	3173	2615	713	1064	28	9833
		5	3596	4148	4087	3228	1954	1380	18393
		6	4344	3418	2269	1918	2005	1918	15872
		7	4414	3180	2682	3735	1963	1377	17351
		8	5773	3849	3080	3207	6619	680	23208
		9	1490	3585	2848	1994	1907	1653	13477
		10	4789	4329	2959	1465	2305	1888	17735
	5	11	4513	5219	3236	2800	6526	3927	26221
		12	3830	3313	2401	2148	1224	938	13854
		13	3869	2572	1534	2350	649	960	11934
		14	4301	4495	5993	2259	2972	405	20425
		15	5051	3380	2381	2286	2252	412	15762
	25	16	276	2635	2217	1409	1497	1509	9543
		17	3900	2928	2578	2176	1795	1856	15233
		18	4731	4403	3468	2775	3094	1995	20466
		19	4100	3958	3727	2283	2761	2178	19007
		20	4322	4124	2934	3173	749	2	15304
	200	21	3607	3768	2602	2675	3101	2907	18660
		22	3064	925	1190	344	369	217	6109
		23	1868	2429	2271	1707	1434	1668	11377
		24	2090	3310	3101	1966	2113	331	12911
		25	7130	4491	2865	2156	1208	3257	21107
		26	4616	2394	2468	1076	1651	1573	13778
		27	5376	3748	2640	2060	2268	185	16277
		28	4637	4506	1574	1484	2074	1214	15489
		29	5369	3255	2846	3148	1743	1660	18021
		30	4360	2922	2413	1400	2651	1200	14946

Addendum 5-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Interval (min)						
			0-10	10-20	20-30	30-40	40-50	50-60	Total
Female	Vehicle control	31	4125	4280	3110	2876	2982	2083	19456
		32	4551	3161	3903	3325	2339	2360	19639
		33	4716	2446	1103	846	775	654	10540
		34	6231	3610	1329	587	104	6	11867
		35	5123	3377	4494	4668	746	2819	21227
		36	4841	3111	3071	4559	1132	2043	18757
		37	5294	3727	2171	3702	2526	801	18221
		38	4881	4666	4307	3780	3592	3516	24742
		39	4957	3078	4005	3101	1320	1123	17584
		40	5312	3827	3172	4141	3240	264	19956
	5	41	6398	4669	3550	3244	2999	2226	23086
		42	4361	2616	1095	2720	1761	1709	14262
		43	5680	4762	2732	3146	2558	1630	20508
		44	3764	672	385	1552	4	325	6702
		45	5353	3125	2465	84	2	0	11029
	25	46	5132	2845	2752	3252	2332	1583	17896
		47	4892	3020	1654	2120	2008	725	14419
		48	4750	3106	1591	359	91	239	10136
		49	6923	6972	4681	6504	5081	4266	34427
		50	6623	5122	5449	4198	3340	1787	26519
	200	51	5354	3034	1922	95	2862	1899	15166
		52	6506	3274	1257	411	1277	541	13266
		53	4952	3871	2601	3077	2714	2886	20101
		54	5155	4119	3869	3519	1679	81	18422
		55	3665	3380	1835	1651	75	2	10608
		56	5162	1913	2429	1366	2753	142	13765
		57	5798	3929	2861	4112	2867	4336	23903
		58	4617	3488	3022	1809	2750	1528	17214
		59	5125	3228	2572	1260	12	36	12233
		60	6100	5227	6034	6279	5234	1989	30863

Addendum 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-1	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	1	127.8	136.6	154.0	191.6	231.6	277.3	309.8	340.8	351.3
		2	137.6	145.3	165.0	210.1	249.8	293.0	327.4	361.3	371.4
		3	131.7	138.3	155.4	200.3	239.2	284.4	312.6	347.0	352.9
		4	121.7	128.6	142.6	179.9	212.7	250.3	283.9	317.9	327.4
		5	126.3	135.4	151.9	186.8	216.8	245.5	269.1	296.5	302.9
		6	121.9	127.3	141.7	174.1	207.7	239.4	267.0	289.8	299.7
		7	126.3	133.5	149.0	189.2	225.7	258.0	285.9	308.1	316.2
		8	131.0	138.0	153.8	192.3	223.8	268.8	303.1	332.8	344.9
		9	127.4	136.3	149.2	186.1	221.0	252.3	279.9	308.4	316.4
		10	135.5	144.3	162.1	215.1	257.8	310.8	353.1	402.6	417.2
	5	11	135.7	142.0	163.6	206.2	237.9	273.1	299.7	329.0	334.8
		12	126.4	135.5	147.3	183.7	220.6	255.6	282.7	307.8	321.3
		13	128.5	137.9	155.0	204.1	248.3	298.7	342.2	387.9	409.8
		14	122.8	130.2	145.7	187.7	222.6	263.0	293.3	323.8	334.6
		15	132.1	142.0	162.4	209.6	251.9	300.7	332.8	369.9	381.6
	25	16	131.5	135.1	148.2	186.3	219.2	253.2	283.6	305.2	315.1
		17	127.5	134.8	149.7	190.0	222.4	268.2	294.8	331.1	340.5
		18	136.9	146.1	165.9	211.4	258.6	306.0	342.7	385.4	395.6
		19	126.1	135.4	150.9	191.1	223.2	256.6	281.1	307.4	314.4
		20	126.5	133.4	149.4	189.7	224.8	263.6	295.4	327.2	334.3
	200	21	129.5	137.3	151.1	181.9	212.9	245.5	271.1	289.6	299.7
		22	138.4	144.7	161.1	198.3	224.7	255.9	278.2	301.7	303.3
		23	130.6	137.7	155.1	192.4	231.9	275.6	314.0	345.6	360.2
		24	126.1	132.4	147.6	186.7	221.8	261.3	293.9	325.0	332.3
		25	124.6	130.8	147.0	186.9	222.6	259.6	288.9	321.7	332.3
		26	123.8	130.3	143.3	182.5	215.7	251.8	286.2	321.3	333.0
		27	126.6	134.4	151.0	186.4	217.1	251.4	282.1	309.0	323.0
		28	135.2	141.3	157.9	206.3	255.6	299.7	336.7	375.6	381.5
		29	130.4	140.9	153.5	200.0	237.7	274.5	299.3	312.7	323.3
		30	131.4	140.9	153.0	188.5	223.4	264.6	295.0	334.4	340.5

Addendum 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Body weights of individual animals(g)

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-1	1	3	8	12	17	21	26	28 (days)
Female	Vehicle control	31	111.9	115.9	128.9	149.5	165.9	179.1	188.5	193.9	200.5
		32	107.3	111.4	120.7	139.4	155.6	161.7	176.4	184.8	194.7
		33	115.1	123.2	128.2	148.2	163.4	181.0	193.7	201.9	212.2
		34	110.7	115.2	123.1	137.3	147.8	159.0	173.3	182.0	192.6
		35	118.1	123.5	133.8	155.9	172.1	184.1	196.8	208.3	208.2
		36	114.2	118.1	129.9	151.8	167.9	190.8	203.6	218.9	218.2
		37	107.0	114.1	120.3	133.6	148.6	156.9	170.8	191.4	196.9
		38	116.2	123.9	130.6	149.7	165.0	187.0	200.1	207.5	218.6
		39	109.2	113.3	114.4	128.0	141.3	157.3	172.3	186.3	186.9
		40	118.9	121.5	136.2	159.7	181.4	190.8	206.1	225.2	231.1
	5	41	110.0	116.4	126.9	152.3	170.0	181.1	189.7	201.2	206.5
		42	118.0	124.9	134.0	158.9	178.5	196.0	208.0	218.6	224.3
		43	108.1	112.0	115.4	127.5	144.1	157.7	172.2	190.0	181.7
		44	115.8	120.8	129.6	141.3	155.2	176.2	185.6	200.0	197.1
		45	113.5	119.2	125.6	138.2	150.5	160.6	168.1	180.7	187.4
	25	46	110.9	114.6	128.9	152.3	169.4	185.3	200.9	216.9	217.5
		47	116.3	122.8	135.7	157.3	176.5	199.0	215.7	229.0	225.7
		48	116.1	120.8	131.8	157.4	168.8	187.0	198.1	206.5	211.8
		49	108.7	114.3	126.8	144.8	155.3	169.7	180.5	197.5	201.1
		50	111.2	117.1	127.4	151.7	171.2	185.9	200.7	220.5	218.8
	200	51	109.1	112.8	120.7	138.4	155.5	167.3	177.1	189.3	186.1
		52	114.6	119.3	130.9	154.7	174.3	186.4	199.7	212.9	213.2
		53	110.7	117.1	123.9	144.1	160.0	174.7	190.2	204.5	203.7
		54	116.6	125.0	134.7	158.8	173.7	179.7	187.1	200.3	197.4
		55	111.3	115.5	123.4	149.3	166.4	173.8	184.4	188.3	190.4
		56	116.1	124.5	137.4	167.6	183.2	204.9	218.3	232.6	240.7
		57	110.9	117.2	125.1	144.8	156.1	173.3	181.7	193.1	195.0
		58	109.6	114.3	126.7	148.8	164.8	175.0	184.2	194.1	203.4
		59	108.5	113.1	126.8	151.4	169.7	176.2	185.2	194.0	206.3
		60	122.9	130.7	141.9	164.3	185.7	202.2	218.1	219.7	235.6

Addendum 6-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Body weights of individual animals(g)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 1	5	10	14 (days)
Male	Vehicle control	6	303.2	324.4	354.1	375.3
		7	315.9	327.3	348.2	360.8
		8	350.7	363.3	390.0	407.0
		9	320.5	333.0	362.1	391.6
		10	423.9	444.3	484.4	499.5
	200	26	333.1	349.8	368.8	386.6
		27	322.4	342.3	369.7	385.9
		28	384.9	393.9	404.1	406.1
		29	324.1	330.9	355.7	365.6
		30	343.6	371.9	405.0	431.7
Female	Vehicle control	36	227.1	242.7	257.5	265.3
		37	196.7	208.7	223.8	232.0
		38	222.8	239.8	243.0	249.7
		39	192.0	202.6	212.0	220.8
		40	226.7	237.7	252.5	262.4
	200	56	243.0	254.8	262.2	266.0
		57	198.0	209.4	218.8	227.9
		58	203.4	208.4	209.2	212.4
		59	209.4	216.0	217.7	222.3
		60	237.2	247.2	243.6	254.0

Addendum 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	1	16.9	18.7	20.3	21.7	21.9	20.1
		2	19.7	20.1	22.4	23.3	22.6	20.7
		3	17.7	19.0	20.8	21.5	21.2	18.8
		4	13.8	17.1	18.3	19.6	19.3	18.6
		5	16.9	17.5	18.9	18.4	16.2	15.8
		6	15.2	15.5	17.6	18.4	16.8	16.6
		7	17.8	17.3	20.2	19.6	18.3	16.8
		8	16.2	17.9	18.9	19.2	20.5	18.2
		9	17.8	18.2	19.0	18.8	18.8	18.6
		10	17.7	19.4	23.1	25.5	25.2	24.8
	5	11	17.6	20.9	21.8	20.6	19.7	18.1
		12	16.5	17.2	18.8	18.7	17.9	16.6
		13	17.4	19.0	21.9	23.6	24.5	25.3
		14	15.0	17.8	19.5	21.0	21.4	20.5
		15	19.7	20.8	24.1	23.7	22.4	21.6
	25	16	17.0	16.7	19.7	19.6	20.1	17.4
		17	17.1	17.4	19.9	20.8	21.4	19.8
		18	18.6	22.3	23.2	25.0	25.3	23.1
		19	19.2	18.7	20.4	19.7	18.7	16.9
		20	16.7	18.6	20.7	20.8	21.5	19.3
	200	21	17.2	16.9	17.7	17.7	16.2	15.3
		22	19.3	21.2	21.5	19.6	17.1	16.0
		23	16.5	18.6	19.8	21.5	20.6	20.1
		24	17.2	18.2	20.0	19.4	19.2	18.0
		25	16.1	17.4	19.9	21.2	21.6	19.8
		26	15.1	15.7	19.1	18.6	19.3	19.1
		27	17.2	18.2	19.4	20.4	19.5	19.7
		28	16.9	19.7	22.4	24.1	22.4	21.4
		29	19.5	18.4	21.7	21.0	17.9	15.5
		30	17.2	16.6	20.1	20.7	20.6	20.1

Addendum 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Female	Vehicle control	31	12.5	13.8	14.5	11.4	11.3	11.2
		32	12.6	12.8	12.9	10.8	11.0	10.3
		33	15.7	13.1	14.2	13.2	13.1	13.6
		34	13.4	11.7	12.2	11.0	12.6	12.6
		35	14.5	13.2	15.4	12.8	11.5	10.7
		36	13.6	15.0	15.2	13.5	12.4	12.3
		37	14.9	13.0	12.4	12.0	13.0	12.8
		38	16.0	15.6	14.6	13.8	14.4	13.9
		39	13.0	11.3	11.8	11.4	11.7	11.7
		40	15.6	15.8	15.1	13.9	13.2	13.7
	5	41	15.3	14.4	16.3	13.9	12.4	11.8
		42	17.4	14.4	16.6	14.2	13.4	13.5
		43	13.1	11.2	12.3	11.8	11.3	10.5
		44	14.4	15.4	13.4	13.5	12.5	12.0
		45	14.8	13.1	12.9	12.3	11.4	11.6
	25	46	12.7	14.4	14.9	12.4	12.0	11.6
		47	15.7	16.2	16.1	14.9	13.9	13.1
		48	14.3	14.1	14.7	12.5	13.0	12.2
		49	15.6	15.0	14.2	11.6	12.8	12.5
		50	13.2	13.5	15.4	13.8	13.4	13.2
	200	51	12.7	12.4	13.2	12.0	12.2	10.4
		52	12.6	15.5	15.4	14.6	13.8	14.1
		53	13.5	13.1	14.0	11.7	11.6	11.5
		54	15.5	15.6	15.9	12.8	11.3	11.3
		55	12.6	13.5	16.2	13.2	10.8	9.8
		56	16.6	15.5	16.9	13.9	14.1	13.4
		57	14.3	14.7	14.8	13.1	13.5	12.1
		58	14.3	15.2	15.6	13.0	11.4	11.8
		59	13.7	13.7	15.6	13.0	10.9	12.1
		60	17.1	15.8	16.0	14.8	14.9	14.4

Addendum 7-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 4	8	14 (days)
Male	Vehicle control	6	18.9	21.6	24.1
		7	17.4	19.9	22.6
		8	19.0	22.2	23.6
		9	20.3	23.2	25.6
		10	28.0	30.2	30.1
	200	26	20.3	20.6	23.1
		27	24.6	25.7	27.6
		28	20.4	19.3	21.3
		29	17.1	21.2	22.0
		30	23.3	26.1	27.9
Female	Vehicle control	36	18.3	18.5	19.2
		37	17.8	19.2	19.1
		38	18.8	21.7	21.0
		39	15.4	17.4	17.7
		40	18.4	19.5	19.4
	200	56	17.4	19.5	18.8
		57	17.4	19.1	19.5
		58	13.6	15.2	15.7
		59	15.5	16.1	17.2
		60	18.6	20.6	19.3

Addendum 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	1	661	115	13.8	40.9	61.8	20.9	33.8	107.4	3.3	15.8	23.7
		2	726	183	14.6	42.6	58.7	20.2	34.4	105.5	3.0	15.2	22.7
		3	728	92	14.7	43.3	59.5	20.2	34.0	97.9	2.8	14.5	21.5
		4	747	91	14.7	43.3	58.0	19.7	34.0	81.0	3.6	15.1	27.4
		5	760	97	15.1	44.6	58.7	19.8	33.8	117.0	2.2	15.6	30.5
		Recovery											
		6	810	91	15.6	46.5	57.4	19.3	33.6	105.2	2.5	17.7	25.9
		7	804	146	14.6	42.5	52.9	18.2	34.4	108.0	2.2	14.8	25.9
		8	775	133	15.0	44.6	57.6	19.3	33.5	113.6	2.4	16.8	26.1
		9	788	105	15.0	44.3	56.2	19.0	33.9	97.6	2.9	18.7	32.2
		10	780	166	14.6	42.7	54.8	18.7	34.1	121.8	2.8	17.9	28.2
	5	11	671	108	13.8	40.6	60.5	20.6	34.1	91.7	2.4	15.1	24.7
		12	694	161	14.1	42.1	60.8	20.4	33.6	105.4	2.9	14.3	20.3
		13	680	107	14.1	42.1	61.9	20.7	33.4	95.5	3.2	13.2	25.1
		14	780	126	15.3	45.1	57.8	19.6	33.9	100.6	3.3	14.3	27.9
		15	713	107	14.9	44.7	62.7	20.9	33.3	84.6	2.9	14.2	28.2
	25	16	708	145	14.7	43.8	61.9	20.8	33.5	98.3	2.3	15.5	25.4
		17	674	109	13.2	39.3	58.3	19.6	33.7	100.3	3.0	14.7	22.3
		18	751	116	15.0	45.2	60.2	20.0	33.1	99.0	2.8	13.5	18.1
		19	748	128	15.2	44.9	60.0	20.3	33.9	111.7	2.4	14.1	21.7
		20	681	99	13.5	40.1	58.9	19.9	33.7	89.3	2.7	14.2	24.5
	200	21	729	122	14.2	42.2	57.8	19.5	33.7	97.6	2.0	15.0	20.1
		22	764	91	14.8	44.5	58.3	19.3	33.2	79.8	1.8	15.2	27.8
		23	725	129	14.7	43.3	59.8	20.3	34.0	110.0	3.0	14.4	21.2
		24	690	110	13.6	39.6	57.4	19.7	34.4	113.9	2.7	14.3	20.9
		25	768	128	14.8	44.4	57.8	19.3	33.4	102.7	2.5	14.7	22.4
		Recovery											
		26	813	124	14.8	44.3	54.4	18.2	33.5	112.1	2.2	15.3	20.5
		27	857	104	15.4	45.5	53.1	18.0	33.9	97.1	2.7	16.3	30.1
		28	778	114	15.4	44.9	57.7	19.8	34.3	111.6	2.7	14.5	23.2
		29	856	120	15.7	45.9	53.5	18.3	34.2	117.4	1.8	17.1	27.9
		30	804	82	14.4	43.0	53.6	18.0	33.5	113.3	2.7	16.3	22.2

Sex	Exp.group (mg/kg/day)	Animal No.	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Female	Vehicle control	31	738	106	14.8	43.9	59.5	20.1	33.7	109.1	2.6	14.0	21.1
		32	741	100	14.1	42.7	57.6	19.0	33.1	113.6	1.8	13.8	24.2
		33	733	115	14.3	41.9	57.1	19.6	34.3	113.4	2.0	13.5	20.7
		34	728	97	14.6	42.5	58.4	20.0	34.2	110.2	2.4	13.6	23.2
		35	771	83	15.2	44.5	57.7	19.7	34.0	108.7	1.5	14.1	19.2
		Recovery											
		36	759	115	15.0	41.8	55.1	19.8	35.9	140.3	2.4	14.4	21.1
		37	790	96	16.1	45.8	58.0	20.4	35.1	117.9	1.7	15.5	21.1
		38	755	152	14.7	41.1	54.5	19.5	35.7	141.1	2.0	13.5	25.2
		39	806	80	15.1	43.7	54.2	18.8	34.6	129.2	2.3	15.3	22.6
		40	756	116	14.4	41.4	54.8	19.1	34.8	121.8	1.9	14.2	19.9
	5	41	737	115	14.4	42.9	58.3	19.6	33.6	111.0	1.8	14.7	21.8
		42	781	169	15.0	44.2	56.6	19.2	33.9	125.8	1.8	13.8	23.9
		43	686	145	13.8	40.9	59.6	20.2	33.8	103.0	2.5	12.7	20.7
		44	777	148	15.3	45.6	58.7	19.7	33.5	126.6	2.2	13.4	25.2
		45	833	95	15.5	46.0	55.2	18.6	33.7	101.6	2.3	12.8	18.7
	25	46	752	142	14.3	42.1	56.0	19.0	34.0	119.4	1.8	14.5	19.3
		47	763	120	15.1	43.9	57.6	19.8	34.3	110.0	2.1	13.6	22.2
		48	691	98	14.2	40.9	59.2	20.6	34.7	101.7	2.0	14.3	20.0
		49	783	104	15.7	46.2	59.0	20.1	34.0	95.3	2.8	13.8	20.8
		50	734	126	14.4	43.1	58.7	19.7	33.5	108.6	2.1	12.7	21.3
	200	51	735	96	14.6	43.2	58.7	19.9	33.9	96.8	1.9	13.6	20.6
		52	739	117	14.6	42.7	57.8	19.7	34.2	99.3	1.7	14.1	21.1
		53	740	86	14.7	43.8	59.2	19.9	33.7	101.9	2.1	14.0	26.1
		54	855	100	16.0	47.7	55.8	18.8	33.6	108.3	1.8	13.2	20.8
		55	763	70	14.7	43.1	56.5	19.2	34.1	113.7	1.0	13.6	22.5
		Recovery											
		56	774	132	14.6	42.2	54.5	18.9	34.6	126.7	2.7	14.7	20.7
		57	783	72	15.1	42.6	54.4	19.2	35.4	124.3	2.2	14.1	25.0
		58	824	78	15.6	45.1	54.7	19.0	34.7	100.4	2.1	14.7	21.0
		59	855	93	15.6	44.7	52.3	18.2	34.9	136.9	1.7	14.0	21.1
		60	709	89	14.2	40.6	57.2	20.1	35.1	113.0	1.6	13.2	20.6

Addendum 8-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	1	21.9	1.3	2.2	70.5	2.9	1.2
		2	17.0	0.9	1.2	77.9	2.4	0.6
		3	14.0	1.1	1.0	81.6	1.5	0.7
		4	28.2	1.0	0.9	66.6	2.9	0.4
		5	16.6	1.6	0.7	77.5	2.6	1.0
		Recovery						
		6	16.7	1.3	0.4	79.0	1.9	0.7
		7	11.0	1.0	0.4	85.0	1.8	0.8
		8	11.9	1.0	0.2	83.1	2.3	1.4
		9	16.6	1.5	0.3	78.6	2.5	0.6
		10	16.6	0.7	0.3	79.2	2.5	0.7
	5	11	17.6	2.0	2.6	75.3	1.8	0.6
		12	23.5	1.7	0.7	71.7	2.0	0.5
		13	14.4	2.4	0.6	77.7	4.3	0.6
		14	26.1	1.8	0.6	68.4	2.4	0.7
		15	14.4	1.1	0.2	82.3	1.3	0.8
	25	16	21.5	0.9	1.7	73.5	1.9	0.5
		17	15.3	2.2	1.9	75.2	3.7	1.6
		18	22.4	1.1	0.6	71.1	3.3	1.5
		19	27.5	1.1	0.9	66.5	3.0	1.0
		20	18.7	1.2	0.6	76.1	2.7	0.7
	200	21	14.1	1.4	2.6	77.1	3.5	1.2
		22	28.6	1.2	1.1	65.8	3.0	0.3
		23	30.9	1.4	1.6	60.4	4.4	1.2
		24	21.5	0.7	0.3	72.2	3.5	1.9
		25	29.3	1.8	0.4	65.5	2.4	0.7
		Recovery						
		26	18.6	0.7	0.6	75.5	4.0	0.7
		27	20.0	1.1	0.5	75.7	2.3	0.4
		28	23.9	1.0	0.4	72.1	2.2	0.4
		29	20.9	1.1	0.7	74.9	2.1	0.3
		30	15.1	1.4	0.1	80.9	1.9	0.6

Addendum 8-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Female	Vehicle control	31	14.3	1.2	0.3	82.5	1.1	0.5
		32	26.4	1.3	0.1	69.2	2.3	0.7
		33	22.7	0.8	0.2	74.4	1.4	0.5
		34	14.6	0.5	0.2	83.3	0.8	0.5
		35	18.4	0.8	0.3	75.4	3.5	1.4
		Recovery						
		36	13.5	1.2	0.2	81.1	3.3	0.7
		37	14.8	0.9	0.1	81.5	1.6	1.1
		38	21.5	2.1	0.3	72.6	3.0	0.6
		39	27.9	1.6	0.3	67.9	1.6	0.8
		40	16.4	2.7	0.1	77.7	2.4	0.7
	5	41	20.8	1.1	0.2	75.6	1.7	0.6
		42	28.7	1.1	0.3	67.0	2.3	0.7
		43	25.4	0.9	0.2	69.7	2.4	1.5
		44	22.9	0.8	0.2	73.8	1.4	0.9
		45	15.3	0.8	0.2	81.7	1.1	0.8
	25	46	25.8	0.8	0.3	70.4	1.9	0.8
		47	17.1	0.9	0.2	77.8	2.9	1.0
		48	11.7	1.6	0.2	83.9	1.7	0.9
		49	19.6	0.7	0.1	77.9	1.3	0.5
		50	17.6	0.8	0.2	78.6	2.0	0.7
	200	51	27.5	0.9	0.3	67.8	2.3	1.2
		52	16.2	1.0	0.3	80.6	0.9	0.9
		53	22.9	0.5	0.2	71.8	3.5	1.1
		54	15.7	0.7	0.2	80.2	2.4	0.8
		55	8.7	0.8	0.2	88.3	1.0	1.0
		Recovery						
		56	17.6	0.9	0.2	79.3	1.4	0.6
		57	25.1	2.1	0.1	70.4	1.9	0.4
		58	26.6	2.0	0.2	68.8	2.2	0.3
		59	19.0	1.7	0.2	77.1	1.4	0.5
		60	11.1	1.3	0.1	85.4	1.3	0.8

Addendum 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	1	51	21	495	49	0.5	57	46	144	5.4	2.8	1.08
		2	59	21	491	35	0.6	64	117	157	5.3	2.5	0.89
		3	66	17	416	46	0.5	49	81	138	5.4	2.7	1.00
		4	82	22	603	41	0.5	52	69	118	5.4	2.6	0.93
		5	65	18	498	34	0.3	47	65	135	5.4	2.7	1.00
		Recovery											
		6	66	30	410	60	0.3	96	56	116	5.3	2.9	1.21
		7	53	22	300	34	0.5	58	48	183	5.6	2.9	1.07
		8	66	23	321	47	0.5	52	62	140	5.8	2.7	0.87
		9	62	28	307	36	0.3	49	56	144	5.5	2.7	0.96
		10	61	22	277	37	0.5	55	113	139	6.0	2.7	0.82
	5	11	62	18	538	40	0.7	64	72	141	5.4	2.8	1.08
		12	68	18	505	39	0.5	56	110	114	5.5	2.7	0.96
		13	61	21	514	51	0.4	72	111	121	5.2	2.5	0.93
		14	68	23	601	39	0.1	43	60	132	5.6	2.7	0.93
		15	69	21	535	35	0.6	43	45	149	5.5	2.7	0.96
	25	16	53	23	493	25	0.2	39	72	158	5.3	2.6	0.96
		17	56	15	588	42	0.3	44	65	139	5.4	2.7	1.04
		18	58	24	597	32	0.5	53	98	162	5.5	2.6	0.90
		19	75	21	501	40	0.3	62	99	140	5.6	2.8	1.00
		20	58	24	552	42	0.2	44	46	124	5.4	2.7	1.00
	200	21	61	24	498	37	0.8	58	59	129	5.4	2.7	1.00
		22	74	40	562	39	1.0	46	79	134	5.5	2.6	0.90
		23	81	23	507	47	0.9	66	113	119	5.6	2.6	0.87
		24	89	23	436	45	0.5	45	75	122	5.1	2.5	0.96
		25	70	24	553	33	0.2	35	45	119	5.4	2.5	0.86
		Recovery											
		26	62	22	503	40	0.3	38	70	147	5.7	2.8	0.97
		27	67	33	342	37	0.4	47	46	140	5.9	2.9	0.97
		28	67	21	262	48	0.1	54	72	147	5.8	2.7	0.87
		29	92	32	307	42	0.2	47	51	137	5.9	2.8	0.90
		30	68	24	305	41	0.6	62	80	147	5.2	2.6	1.00

Addendum 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Female	Vehicle control	31	62	17	214	257	0.3	54	20	123	5.8	3.1	1.15
		32	57	18	206	286	0.7	66	14	110	5.8	2.9	1.00
		33	50	13	151	216	0.3	73	20	120	5.3	2.7	1.04
		34	80	22	319	164	0.8	53	12	106	5.6	2.9	1.07
		35	67	15	236	240	1.0	67	42	111	6.2	3.3	1.14
		Recovery											
		36	72	20	201	269	0.8	51	19	133	6.1	3.0	0.97
		37	56	18	146	168	0.8	61	20	117	5.9	3.1	1.11
		38	62	25	100	421	0.8	81	32	122	6.7	3.3	0.97
		39	67	20	244	189	0.4	72	18	120	5.8	2.9	1.00
		40	76	19	207	346	0.7	73	13	133	6.0	2.9	0.94
	5	41	62	16	235	335	0.3	57	21	119	5.8	3.1	1.15
		42	71	15	183	265	0.4	56	9	98	6.2	2.9	0.88
		43	61	15	333	108	0.8	66	28	89	5.0	2.5	1.00
		44	67	17	270	161	0.7	50	19	103	5.6	2.8	1.00
		45	81	25	328	138	0.9	74	22	121	5.8	3.0	1.07
	25	46	64	18	275	146	0.3	57	34	124	5.4	2.7	1.00
		47	87	23	245	205	0.4	68	15	95	6.2	3.0	0.94
		48	69	17	410	152	0.6	63	22	122	5.7	2.8	0.97
		49	64	13	359	163	0.9	62	30	130	6.0	3.1	1.07
		50	64	15	173	228	0.9	69	27	137	6.6	3.3	1.00
	200	51	60	17	225	176	0.1	79	26	119	5.9	2.8	0.90
		52	56	20	299	150	0.2	81	24	124	5.9	2.9	0.97
		53	73	18	298	116	1.3	50	31	102	5.4	2.6	0.93
		54	66	12	230	274	1.0	53	15	97	5.9	3.2	1.19
		55	60	14	323	198	0.5	64	14	122	5.8	3.0	1.07
		Recovery											
		56	73	18	236	219	0.9	86	13	148	6.3	3.0	0.91
		57	63	23	229	272	0.7	77	36	178	6.4	3.4	1.13
		58	62	18	125	319	0.7	57	20	124	6.1	3.1	1.03
		59	62	19	149	361	0.6	71	19	131	6.3	3.0	0.91
		60	72	19	163	306	0.7	92	29	133	6.2	3.0	0.94

Addendum 9-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	1	10.5	0.26	0.08	9.1	8.5	142	4.6	107.0
		2	11.0	0.31	0.06	9.1	7.9	141	4.4	103.6
		3	10.5	0.26	0.05	9.0	8.0	144	4.9	107.8
		4	8.8	0.24	0.09	9.1	7.3	143	4.7	104.0
		5	8.2	0.21	0.04	9.0	8.1	144	4.2	106.5
		Recovery								
		6	13.5	0.27	0.07	8.7	6.9	144	4.3	106.7
		7	15.5	0.29	0.07	9.0	6.8	143	4.1	104.5
		8	15.7	0.27	0.07	9.1	7.3	143	4.4	105.7
		9	11.6	0.19	0.06	8.8	7.1	143	4.2	105.5
		10	15.8	0.24	0.03	9.1	7.2	145	4.3	103.4
	5	11	10.1	0.26	0.04	9.2	7.4	144	4.8	107.1
		12	7.7	0.28	0.07	9.1	7.5	144	4.4	107.6
		13	8.3	0.21	0.04	9.3	8.5	144	4.5	105.1
		14	10.1	0.22	0.06	9.3	8.3	144	4.8	105.4
		15	9.5	0.24	0.06	9.4	8.9	145	4.2	106.6
	25	16	10.2	0.28	0.06	9.0	6.9	143	3.8	106.7
		17	10.5	0.23	0.04	9.2	7.7	142	4.7	106.9
		18	9.2	0.24	0.04	9.6	8.5	144	4.3	104.7
		19	9.8	0.23	0.04	9.0	8.3	145	4.4	107.2
		20	8.4	0.18	0.07	9.4	9.0	145	4.4	105.1
	200	21	7.3	0.25	0.04	9.2	7.6	144	4.4	108.5
		22	10.7	0.28	0.05	8.9	7.0	143	4.2	107.0
		23	9.9	0.23	0.06	9.8	9.1	143	4.8	105.2
		24	11.5	0.23	0.05	9.0	8.5	142	4.8	105.6
		25	6.7	0.17	0.05	10.0	8.0	145	4.5	105.8
		Recovery								
		26	12.4	0.23	0.06	8.7	6.9	142	4.3	105.8
		27	14.0	0.23	0.08	8.9	7.2	142	3.8	102.9
		28	13.4	0.25	0.04	8.8	6.6	143	4.6	106.4
		29	10.3	0.23	0.03	9.1	6.4	143	4.2	104.1
		30	14.9	0.25	0.06	9.2	6.8	144	4.7	107.2

Addendum 9-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Female	Vehicle control	31	11.7	0.28	0.05	9.2	7.8	141	4.8	108.6
		32	11.9	0.28	0.04	8.9	7.8	140	3.6	103.9
		33	11.3	0.24	0.04	9.3	7.7	142	3.8	106.3
		34	10.2	0.27	0.07	8.7	7.0	142	4.1	108.8
		35	11.6	0.21	0.07	10.0	7.9	140	4.5	109.4
		Recovery								
		36	14.4	0.31	0.05	8.9	5.2	141	4.2	105.8
		37	16.3	0.26	0.04	8.5	5.4	143	4.0	110.0
		38	17.5	0.26	0.07	9.1	5.9	141	3.8	104.4
		39	15.3	0.22	0.07	8.7	5.6	144	4.2	109.5
		40	16.9	0.28	0.06	9.0	6.2	142	4.4	105.2
	5	41	15.1	0.27	0.04	9.6	7.6	142	3.9	105.4
		42	10.9	0.28	0.04	9.0	7.4	141	4.3	107.2
		43	11.5	0.24	0.05	9.1	7.7	143	3.9	106.8
		44	8.8	0.23	0.03	9.3	7.6	142	4.3	108.0
		45	12.5	0.21	0.08	9.2	7.2	142	3.9	106.5
	25	46	11.6	0.27	0.05	9.0	8.0	141	3.9	106.2
		47	11.4	0.27	0.05	9.2	8.3	142	3.9	108.9
		48	13.1	0.27	0.05	9.4	8.3	141	4.7	107.1
		49	14.5	0.27	0.05	9.1	7.5	141	4.3	107.4
		50	10.1	0.28	0.04	9.7	8.3	143	4.7	106.7
	200	51	12.7	0.23	0.04	9.3	7.9	141	4.6	110.3
		52	12.8	0.27	0.05	9.2	7.2	141	3.9	106.2
		53	10.7	0.27	0.04	9.3	8.9	142	4.0	109.1
		54	11.9	0.24	0.05	9.5	8.4	140	4.3	110.6
		55	9.5	0.23	0.04	9.3	7.7	140	4.3	105.7
		Recovery								
		56	17.3	0.27	0.05	9.1	5.8	142	3.6	105.5
		57	16.5	0.26	0.05	8.6	5.7	143	3.9	107.3
		58	13.2	0.27	0.07	9.1	6.1	143	4.6	108.5
		59	16.4	0.28	0.06	9.0	6.2	141	4.8	106.2
		60	17.9	0.28	0.08	8.8	6.6	143	4.0	108.1

Addendum 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Sp.Gr.
Male	Vehicle control	1	3	1.054
		2	6	1.046
		3	2	1.096
		4	7	1.032
		5	9	1.025
		Recovery		
		6	9	1.040
		7	4	1.070
		8	18	1.018
		9	15	1.025
		10	7	1.054
	5	11	8	1.026
		12	2	1.084
		13	7	1.042
		14	3	1.075
		15	12	1.021
	25	16	3	1.066
		17	3	1.072
		18	16	1.017
		19	24	1.008
		20	11	1.024
	200	21	6	1.027
		22	4	1.054
		23	10	1.023
		24	2	1.090
		25	4	1.060
		Recovery		
		26	11	1.026
		27	25	1.015
		28	8	1.040
		29	18	1.020
		30	9	1.050

Addendum 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0838
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Sp.Gr.
Female	Vehicle control	31	4	1.031
		32	4	1.038
		33	2	1.062
		34	1	1.087
		35	9	1.017
		Recovery		
		36	21	1.012
		37	11	1.023
		38	12	1.023
		39	7	1.035
		40	7	1.042
	5	41	3	1.038
		42	2	1.081
		43	4	1.028
		44	6	1.021
		45	7	1.022
	25	46	5	1.034
		47	14	1.009
		48	7	1.022
		49	3	1.054
		50	2	1.056
	200	51	9	1.011
		52	3	1.040
		53	5	1.032
		54	7	1.021
		55	5	1.031
		Recovery		
		56	6	1.032
		57	4	1.038
		58	10	1.020
		59	6	1.033
		60	7	1.042

Addendum 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Male	Vehicle control	1	Y	NT	6.0	2+	−	−
		2	Y	NT	6.0	1+	−	−
		3	Y	NT	6.0	2+	−	−
		4	Y	NT	6.5	1+	−	−
		5	SY	NT	6.5	1+	−	−
		Recovery						
		6	Y	NT	6.5	1+	−	−
		7	Y	NT	6.5	2+	−	−
		8	SY	NT	6.5	±	−	−
		9	SY	NT	7.0	±	−	−
		10	Y	NT	6.5	1+	−	−
	5	11	Y	NT	6.5	1+	−	−
		12	Y	NT	6.0	2+	−	−
		13	Y	NT	6.0	1+	−	−
		14	Y	NT	6.0	2+	−	−
		15	SY	NT	6.5	1+	−	−
	25	16	Y	NT	6.0	2+	−	−
		17	Y	NT	6.0	2+	−	−
		18	SY	NT	6.5	±	−	−
		19	SY	NT	7.0	±	−	−
		20	Y	NT	6.5	1+	−	−
	200	21	Y	NT	6.5	1+	−	−
		22	Y	NT	6.0	2+	−	−
		23	SY	NT	6.5	1+	−	−
		24	Y	NT	6.0	2+	−	−
		25	Y	NT	6.0	1+	−	−
		Recovery						
		26	Y	NT	6.5	1+	−	−
		27	SY	NT	7.0	±	−	−
		28	Y	NT	6.5	1+	−	−
		29	SY	NT	6.5	±	−	−
		30	Y	NT	7.0	1+	−	−

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.

Addendum 10-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Female	Vehicle control	31	Y	NT	6.5	1+	−	−
		32	Y	NT	6.5	1+	−	−
		33	Y	NT	6.0	2+	−	−
		34	Y	NT	6.0	2+	−	−
		35	SY	NT	6.5	±	−	−
		Recovery						
		36	SY	NT	6.5	±	−	−
		37	Y	NT	7.0	±	−	−
		38	SY	NT	6.5	±	−	−
		39	Y	NT	6.5	1+	−	−
		40	Y	NT	6.5	1+	−	−
	5	41	Y	NT	6.5	1+	−	−
		42	Y	NT	6.0	2+	−	−
		43	Y	NT	6.5	1+	−	−
		44	Y	NT	6.0	1+	−	−
		45	Y	NT	6.5	1+	−	−
	25	46	Y	NT	6.0	1+	−	−
		47	SY	NT	6.5	±	−	−
		48	Y	NT	6.5	±	−	−
		49	Y	NT	6.0	1+	−	−
		50	Y	NT	6.0	2+	−	−
	200	51	SY	NT	6.5	±	−	−
		52	Y	NT	6.0	2+	−	−
		53	Y	NT	6.5	1+	−	−
		54	Y	NT	6.5	1+	−	−
		55	Y	NT	6.5	1+	−	−
		Recovery						
		56	Y	NT	7.0	1+	−	±
		57	Y	NT	6.5	1+	−	−
		58	SY	NT	6.5	±	−	−
		59	Y	NT	6.5	1+	−	−
		60	Y	NT	6.5	1+	−	−

SY, Slightly yellow.
Y, Yellow.
NT, Not turbid.

Addendum 10-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Male	Vehicle control	1	0	0	0	0	−
		2	0	0	2	0	±
		3	0	1	2	0	±
		4	0	0	1	0	−
		5	0	0	0	0	−
		Recovery					
		6 [d]	-	-	-	-	-
		7 [d]	-	-	-	-	-
		8 [d]	-	-	-	-	-
		9 [d]	-	-	-	-	-
		10 [d]	-	-	-	-	-
	5	11 [d]	-	-	-	-	-
		12 [d]	-	-	-	-	-
		13 [d]	-	-	-	-	-
		14 [d]	-	-	-	-	-
		15 [d]	-	-	-	-	-
	25	16 [d]	-	-	-	-	-
		17 [d]	-	-	-	-	-
		18 [d]	-	-	-	-	-
		19 [d]	-	-	-	-	-
		20 [d]	-	-	-	-	-
	200	21	0	0	0	0	−
		22	0	0	3	0	−
		23	0	1	1	0	±
		24	0	0	4	0	−
		25	0	0	0	0	−
		Recovery					
		26 [d]	-	-	-	-	-
		27 [d]	-	-	-	-	-
		28 [d]	-	-	-	-	-
		29 [d]	-	-	-	-	-
		30 [d]	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.

Addendum 10-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Female	Vehicle control	31	0	0	4	0	±
		32	0	1	2	0	−
		33	0	0	3	0	−
		34	0	0	0	0	−
		35	0	0	2	0	−
		Recovery					
		36 [d]	-	-	-	-	-
		37 [d]	-	-	-	-	-
		38 [d]	-	-	-	-	-
		39 [d]	-	-	-	-	-
		40 [d]	-	-	-	-	-
	5	41 [d]	-	-	-	-	-
		42 [d]	-	-	-	-	-
		43 [d]	-	-	-	-	-
		44 [d]	-	-	-	-	-
		45 [d]	-	-	-	-	-
	25	46 [d]	-	-	-	-	-
		47 [d]	-	-	-	-	-
		48 [d]	-	-	-	-	-
		49 [d]	-	-	-	-	-
		50 [d]	-	-	-	-	-
	200	51	0	0	3	0	−
		52	0	0	0	0	−
		53	0	1	4	0	−
		54	0	0	4	0	−
		55	0	0	1	0	±
		Recovery					
		56 [d]	-	-	-	-	-
		57 [d]	-	-	-	-	-
		58 [d]	-	-	-	-	-
		59 [d]	-	-	-	-	-
		60 [d]	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.

Addendum 11-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Male	Vehicle control	1	9.32	1.13	2.33	2.84	0.70	-	1.92	0.64	660.2	44.1	334.6
		2	10.75	1.26	2.34	3.00	0.67	-	1.92	0.68	647.6	50.1	356.4
		3	11.51	1.15	2.54	2.80	0.71	-	1.99	0.59	436.2	62.2	334.6
		4	9.66	1.18	2.55	2.33	0.60	-	1.95	0.94	813.1	45.9	316.1
		5	9.11	0.99	2.07	3.09	0.61	-	1.88	0.63	582.3	45.4	288.9
		Recovery											
		6	8.44	1.03	2.51	2.98	0.91	-	2.05	0.60	411.8	52.0	349.9
		7	9.96	1.34	2.44	3.47	0.96	-	2.01	0.58	365.3	48.4	341.4
		8	9.94	1.26	2.60	3.03	0.97	-	1.99	0.69	578.8	43.7	381.0
		9	10.36	1.09	2.72	2.93	0.92	-	2.03	0.54	354.4	44.0	359.0
		10	15.56	1.41	3.00	2.84	1.00	-	2.21	0.83	552.4	70.2	470.7
	5	11	10.47	1.10	2.06	2.73	0.69	-	1.93	0.51	418.0	43.0	321.7
		12	9.74	1.14	2.42	2.88	0.72	-	2.00	0.63	450.0	50.0	305.7
		13	13.40	1.23	2.69	2.65	0.63	-	2.03	0.64	646.1	43.1	386.1
		14	10.03	1.15	2.41	2.71	0.67	-	1.93	0.53	504.1	43.6	317.8
		15	11.74	1.19	2.49	3.04	0.75	-	2.02	0.68	609.3	50.4	362.8
	25	16	10.46	1.02	2.07	2.72	0.68	-	1.98	0.48	508.9	41.6	296.1
		17	11.63	1.11	2.48	3.01	0.70	-	2.06	0.64	621.0	33.5	326.5
		18	14.24	1.25	2.65	3.15	0.85	-	1.98	0.62	620.8	51.3	377.5
		19	10.14	1.03	2.01	2.82	0.68	-	1.93	0.60	424.9	42.7	298.9
		20	10.48	1.00	2.45	3.07	0.69	-	1.92	0.58	432.6	43.6	321.1
	200	21	12.08	1.00	2.23	2.80	0.72	-	1.92	0.46	351.1	40.5	283.4
		22	12.49	0.93	2.05	3.07	0.81	-	2.00	0.43	327.2	35.3	288.8
		23	14.88	1.00	2.55	3.36	0.67	-	2.02	0.43	436.1	48.4	343.2
		24	12.76	0.98	2.41	2.92	0.63	-	1.90	0.49	434.8	42.1	317.5
		25	12.96	1.11	2.66	2.38	0.55	-	2.01	0.59	661.8	44.0	312.2
		Recovery											
		26	10.84	1.20	2.79	3.31	1.11	-	2.08	0.50	328.4	50.1	358.7
		27	10.43	1.15	3.00	3.20	1.09	-	2.07	0.56	448.9	47.3	360.3
		28	12.61	1.20	2.87	3.15	1.00	-	2.04	0.61	359.5	57.8	388.4
		29	10.05	1.20	2.62	3.33	1.03	-	2.02	0.59	318.7	50.6	344.4
		30	11.92	1.46	3.04	3.29	1.03	-	2.04	0.53	503.2	61.8	404.8

Addendum 11-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

B11-0838

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Female	Vehicle control	31	5.45	0.69	1.37	-	-	60.1	1.74	0.40	473.8	45.5	191.8
		32	5.15	0.71	1.47	-	-	62.5	1.95	0.36	332.8	54.6	186.4
		33	6.93	0.76	1.53	-	-	70.0	1.86	0.46	413.2	58.8	201.2
		34	5.02	0.68	1.32	-	-	67.1	1.77	0.43	366.4	47.9	184.3
		35	6.65	0.75	1.53	-	-	62.8	1.89	0.42	510.9	62.0	201.8
		Recovery											
		36	6.66	0.83	1.51	-	-	110.1	1.84	0.58	477.8	78.3	244.9
		37	5.76	0.73	1.44	-	-	80.1	1.88	0.54	509.6	65.3	214.7
		38	7.47	0.95	1.91	-	-	89.7	1.90	0.63	529.1	68.5	238.3
		39	5.39	0.77	1.41	-	-	84.5	1.86	0.45	326.5	49.4	205.4
		40	6.86	0.86	1.73	-	-	80.9	1.94	0.56	493.6	61.5	246.1
	5	41	5.81	0.70	1.32	-	-	65.2	1.80	0.39	338.3	58.1	196.1
		42	7.24	0.86	1.64	-	-	96.8	1.95	0.54	498.0	71.1	215.6
		43	5.37	0.75	1.32	-	-	76.9	1.75	0.40	374.0	52.2	178.6
		44	5.66	0.67	1.52	-	-	75.2	1.88	0.32	353.5	58.6	192.1
		45	5.01	0.63	1.34	-	-	58.4	1.83	0.38	366.8	38.1	177.1
	25	46	6.39	0.70	1.54	-	-	77.4	1.84	0.45	451.1	52.4	205.8
		47	7.64	0.72	1.72	-	-	79.4	1.90	0.50	423.0	62.3	219.8
		48	6.60	0.79	1.44	-	-	74.4	1.78	0.53	447.1	65.2	205.9
		49	6.87	0.74	1.46	-	-	99.4	1.86	0.46	412.0	51.9	187.4
		50	7.91	0.84	1.48	-	-	80.6	1.91	0.49	496.6	61.4	210.3
	200	51	6.27	0.68	1.50	-	-	65.9	1.64	0.34	304.0	57.6	178.2
		52	6.91	0.70	1.58	-	-	65.7	1.83	0.45	530.2	50.7	200.6
		53	6.61	0.72	1.48	-	-	87.2	1.76	0.37	432.9	50.4	195.1
		54	6.57	0.76	1.63	-	-	80.3	1.95	0.43	392.3	76.1	193.2
		55	6.58	0.65	1.51	-	-	67.6	1.81	0.34	355.3	64.2	182.4
		Recovery											
		56	7.30	0.95	1.89	-	-	101.3	1.98	0.63	610.1	68.4	250.3
		57	6.71	0.79	1.42	-	-	69.4	1.83	0.37	329.6	57.9	204.6
		58	5.32	0.74	1.35	-	-	77.0	1.79	0.50	271.5	63.0	199.8
		59	6.20	0.84	1.65	-	-	75.3	1.89	0.44	377.7	69.6	215.3
		60	7.67	0.86	1.67	-	-	87.5	1.89	0.50	424.3	64.8	243.3

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Male	Vehicle control	1	2.79	0.34	0.70	0.85	0.21	-	0.57	0.19	197.3	13.2	334.6
		2	3.02	0.35	0.66	0.84	0.19	-	0.54	0.19	181.7	14.1	356.4
		3	3.44	0.34	0.76	0.84	0.21	-	0.59	0.18	130.4	18.6	334.6
		4	3.06	0.37	0.81	0.74	0.19	-	0.62	0.30	257.2	14.5	316.1
		5	3.15	0.34	0.72	1.07	0.21	-	0.65	0.22	201.6	15.7	288.9
		Recovery											
		6	2.41	0.29	0.72	0.85	0.26	-	0.59	0.17	117.7	14.9	349.9
		7	2.92	0.39	0.71	1.02	0.28	-	0.59	0.17	107.0	14.2	341.4
		8	2.61	0.33	0.68	0.80	0.25	-	0.52	0.18	151.9	11.5	381.0
		9	2.89	0.30	0.76	0.82	0.26	-	0.57	0.15	98.7	12.3	359.0
		10	3.31	0.30	0.64	0.60	0.21	-	0.47	0.18	117.4	14.9	470.7
	5	11	3.25	0.34	0.64	0.85	0.21	-	0.60	0.16	129.9	13.4	321.7
		12	3.19	0.37	0.79	0.94	0.24	-	0.65	0.21	147.2	16.4	305.7
		13	3.47	0.32	0.70	0.69	0.16	-	0.53	0.17	167.3	11.2	386.1
		14	3.16	0.36	0.76	0.85	0.21	-	0.61	0.17	158.6	13.7	317.8
		15	3.24	0.33	0.69	0.84	0.21	-	0.56	0.19	167.9	13.9	362.8
	25	16	3.53	0.34	0.70	0.92	0.23	-	0.67	0.16	171.9	14.0	296.1
		17	3.56	0.34	0.76	0.92	0.21	-	0.63	0.20	190.2	10.3	326.5
		18	3.77	0.33	0.70	0.83	0.23	-	0.52	0.16	164.5	13.6	377.5
		19	3.39	0.34	0.67	0.94	0.23	-	0.65	0.20	142.2	14.3	298.9
		20	3.26	0.31	0.76	0.96	0.21	-	0.60	0.18	134.7	13.6	321.1
	200	21	4.26	0.35	0.79	0.99	0.25	-	0.68	0.16	123.9	14.3	283.4
		22	4.32	0.32	0.71	1.06	0.28	-	0.69	0.15	113.3	12.2	288.8
		23	4.34	0.29	0.74	0.98	0.20	-	0.59	0.13	127.1	14.1	343.2
		24	4.02	0.31	0.76	0.92	0.20	-	0.60	0.15	136.9	13.3	317.5
		25	4.15	0.36	0.85	0.76	0.18	-	0.64	0.19	212.0	14.1	312.2
		Recovery											
		26	3.02	0.33	0.78	0.92	0.31	-	0.58	0.14	91.6	14.0	358.7
		27	2.89	0.32	0.83	0.89	0.30	-	0.57	0.16	124.6	13.1	360.3
		28	3.25	0.31	0.74	0.81	0.26	-	0.53	0.16	92.6	14.9	388.4
		29	2.92	0.35	0.76	0.97	0.30	-	0.59	0.17	92.5	14.7	344.4
		30	2.94	0.36	0.75	0.81	0.25	-	0.50	0.13	124.3	15.3	404.8

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Female	Vehicle control	31	2.84	0.36	0.71	-	-	31.3	0.91	0.21	247.0	23.7	191.8
		32	2.76	0.38	0.79	-	-	33.5	1.05	0.19	178.5	29.3	186.4
		33	3.44	0.38	0.76	-	-	34.8	0.92	0.23	205.4	29.2	201.2
		34	2.72	0.37	0.72	-	-	36.4	0.96	0.23	198.8	26.0	184.3
		35	3.30	0.37	0.76	-	-	31.1	0.94	0.21	253.2	30.7	201.8
		Recovery											
		36	2.72	0.34	0.62	-	-	45.0	0.75	0.24	195.1	32.0	244.9
		37	2.68	0.34	0.67	-	-	37.3	0.88	0.25	237.4	30.4	214.7
		38	3.13	0.40	0.80	-	-	37.6	0.80	0.26	222.0	28.7	238.3
		39	2.62	0.37	0.69	-	-	41.1	0.91	0.22	159.0	24.1	205.4
		40	2.79	0.35	0.70	-	-	32.9	0.79	0.23	200.6	25.0	246.1
	5	41	2.96	0.36	0.67	-	-	33.2	0.92	0.20	172.5	29.6	196.1
		42	3.36	0.40	0.76	-	-	44.9	0.90	0.25	231.0	33.0	215.6
		43	3.01	0.42	0.74	-	-	43.1	0.98	0.22	209.4	29.2	178.6
		44	2.95	0.35	0.79	-	-	39.1	0.98	0.17	184.0	30.5	192.1
		45	2.83	0.36	0.76	-	-	33.0	1.03	0.21	207.1	21.5	177.1
	25	46	3.10	0.34	0.75	-	-	37.6	0.89	0.22	219.2	25.5	205.8
		47	3.48	0.33	0.78	-	-	36.1	0.86	0.23	192.4	28.3	219.8
		48	3.21	0.38	0.70	-	-	36.1	0.86	0.26	217.1	31.7	205.9
		49	3.67	0.39	0.78	-	-	53.0	0.99	0.25	219.9	27.7	187.4
		50	3.76	0.40	0.70	-	-	38.3	0.91	0.23	236.1	29.2	210.3
	200	51	3.52	0.38	0.84	-	-	37.0	0.92	0.19	170.6	32.3	178.2
		52	3.44	0.35	0.79	-	-	32.8	0.91	0.22	264.3	25.3	200.6
		53	3.39	0.37	0.76	-	-	44.7	0.90	0.19	221.9	25.8	195.1
		54	3.40	0.39	0.84	-	-	41.6	1.01	0.22	203.1	39.4	193.2
		55	3.61	0.36	0.83	-	-	37.1	0.99	0.19	194.8	35.2	182.4
		Recovery											
		56	2.92	0.38	0.76	-	-	40.5	0.79	0.25	243.7	27.3	250.3
		57	3.28	0.39	0.69	-	-	33.9	0.89	0.18	161.1	28.3	204.6
		58	2.66	0.37	0.68	-	-	38.5	0.90	0.25	135.9	31.5	199.8
		59	2.88	0.39	0.77	-	-	35.0	0.88	0.20	175.4	32.3	215.3
		60	3.15	0.35	0.69	-	-	36.0	0.78	0.21	174.4	26.6	243.3

Addendum 13-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control	1	ta	No abnormalities detected	No abnormalities detected
		2	ta	Skin Sparsed fur (neck)	Jejunum Focal necrosis in Peyer's patches + Skin No abnormalities detected
		3	ta	No abnormalities detected	No abnormalities detected
		4	ta	No abnormalities detected	No abnormalities detected
		5	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals, eye ball and macroscopic lesion.

ta, terminal autopsy.

+, slight.

Addendum 13-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control (Recovery)	6	ta	No abnormalities detected	No abnormalities detected
		7	ta	No abnormalities detected	No abnormalities detected
		8	ta	No abnormalities detected	No abnormalities detected
		9	ta	No abnormalities detected	Kidney Mineralization in medulla +
		10	ta	No abnormalities detected	Testis Inhibited spermiation and deep retention of spermatids ++

a) Organs/tissues examined as follows: incisor, liver, kidneys, testes and epididymides.
ta, terminal autopsy.
+, slight; ++, moderate.

Addendum 13-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	5	11	ta	Spleen Whitish region on capsule (multiple, spotty- ϕ 1 mm)	Spleen Capsulitis +
		12	ta	No abnormalities detected	No abnormalities detected
		13	ta	No abnormalities detected	No abnormalities detected
		14	ta	No abnormalities detected	No abnormalities detected
		15	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: liver, testes, epididymides and macroscopic lesion.
ta, terminal autopsy.
+, slight.

Addendum 13-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	25	16	ta	No abnormalities detected	No abnormalities detected
		17	ta	No abnormalities detected	No abnormalities detected
		18	ta	No abnormalities detected	No abnormalities detected
		19	ta	No abnormalities detected	Liver Centrilobular lipid droplets in hepatocytes +
		20	ta	Pituitary gland Cyst (ϕ 1.5 mm)	Liver Microgranuloma ++ Pituitary gland Cyst formation in pars intermedia ++

a) Organs/tissues examined as follows: liver, testes, epididymides and macroscopic lesion.
ta, terminal autopsy.
+, slight; ++, moderate.

Addendum 13-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	200	21	ta	Liver Enlargement	Liver Centrilobular lipid droplets in hepatocytes + Periportal hypertrophy of hepatocytes + Periportal prominent nucleoli of hepatocytes +
		22	ta	Liver Enlargement	Liver Centrilobular lipid droplets in hepatocytes ++ Microgranuloma +
		23	ta	Liver Enlargement	Liver Centrilobular lipid droplets in hepatocytes ++ Microgranuloma +
		24	ta	Liver Enlargement	Liver Centrilobular lipid droplets in hepatocytes + Microgranuloma +
		25	ta	Liver Enlargement	Liver Centrilobular lipid droplets in hepatocytes + Microgranuloma + Testis Degeneration of spermatocytes + Epididymis Germ cell debris in lumen +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight; ++, moderate.

Addendum 13-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	200 (Recovery)	26	ta	No abnormalities detected	Liver Centrilobular lipid droplets in hepatocytes ++ Microgranuloma +
		27	ta	Oral cavity Mottled teeth (lower incisors)	No abnormalities detected Incisor No abnormalities detected
		28	ta	Oral cavity Mottled teeth (lower incisors)	Incisor No abnormalities detected Liver Centrilobular lipid droplets in hepatocytes + Microgranuloma +
		29	ta	No abnormalities detected	Liver Centrilobular lipid droplets in hepatocytes +
		30	ta	Oral cavity Mottled teeth (lower incisors)	Incisor No abnormalities detected Liver Centrilobular lipid droplets in hepatocytes + Microgranuloma +

a) Organs/tissues examined as follows: incisor, liver, kidneys, testes and epididymides.
ta, terminal autopsy.
+, slight; ++, moderate.

Addendum 13-7 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control	31	ta	No abnormalities detected	No abnormalities detected
		32	ta	Skin Scab formation (shoulder, right)	Rectum Focal inflammation + Skin Ulcer +
		33	ta	No abnormalities detected	No abnormalities detected
		34	ta	No abnormalities detected	No abnormalities detected
		35	ta	No abnormalities detected	Liver Microgranuloma +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals, eye ball and macroscopic lesion.

ta, terminal autopsy.

+, slight.

Addendum 13-8 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control (Recovery)	36	ta	Skin	No abnormalities detected
				Loss of hair (forelimbs)	Skin
					No abnormalities detected
		37	ta	No abnormalities detected	No abnormalities detected
		38	ta	No abnormalities detected	No abnormalities detected
		39	ta	No abnormalities detected	No abnormalities detected
		40	ta	No abnormalities detected	Liver
					Microgranuloma +

a) Organs/tissues examined as follows: incisor, forestomach, glandular stomach, liver and macroscopic lesion.
ta, terminal autopsy.
+, slight.

Addendum 13-9 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	5	41	ta	No abnormalities detected	No abnormalities detected
		42	ta	No abnormalities detected	No abnormalities detected
		43	ta	No abnormalities detected	No abnormalities detected
		44	ta	No abnormalities detected	No abnormalities detected
		45	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach and liver.
ta, terminal autopsy.

Addendum 13-10 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	25	46	ta	No abnormalities detected	No abnormalities detected
		47	ta	No abnormalities detected	Liver Microgranuloma + Peliportal lipid droplets in hepatocytes +
		48	ta	No abnormalities detected	No abnormalities detected
		49	ta	No abnormalities detected	No abnormalities detected
		50	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach and liver.
ta, terminal autopsy.
+, slight.

Addendum 13-11 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	200	51	ta	Forestomach Elevated region of mucosa (ϕ 1.5 mm)	Forestomach Lymphocyte infiltration in submucosal layer + Glandular stomach Edema in submucosal layer +
		52	ta	No abnormalities detected	Liver Microgranuloma +
		53	ta	No abnormalities detected	Liver Microgranuloma +
		54	ta	No abnormalities detected	Kidney Mineralization in cortico-medullary junction +
		55	ta	No abnormalities detected	Liver Centrilobular lipid droplets in hepatocytes +

a) Organs/tissues examined as follows: trachea, lungs, incisor, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-12 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	200 (Recovery)	56	ta	No abnormalities detected	No abnormalities detected
		57	ta	No abnormalities detected	No abnormalities detected
		58	ta	Skin Loss of hair (forelimbs)	No abnormalities detected Skin No abnormalities detected
		59	ta	Oral cavity Mottled teeth (lower incisors)	No abnormalities detected Incisor No abnormalities detected
		60	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: incisor, forestomach, glandular stomach, liver and macroscopic lesion.
ta, terminal autopsy.

APPENDIX 1

"STABILITY ANALYSIS OF 13F-OLE, HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION (Study code: X18-0838)"

CERI

Receipt No. 827-06-D-3208

STUDY CODE: X18-0838

FINAL REPORT

STABILITY ANALYSIS OF 13F-OLE, HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

July 2007

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

STATEMENT

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: X18-0838, issued on July 25, 2007).

_____ November 9, 2009

Date

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

GLP STATEMENT

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

Sponsor: DAIKIN INDUSTRIES, LTD.

Title: Stability Analysis of 13F-OLE, Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

Study Code: X18-0838

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP [Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)].

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original July 25, 2007

QUALITY ASSURANCE STATEMENT

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

Sponsor: DAIKIN INDUSTRIES, LTD.

Title: Stability Analysis of 13F-OLE, Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

Study Code: X18-0838

This study was inspected by Quality Assurance Unit of Hita Laboratory, Chemicals Evaluation and Research Institute, Japan The dates inspected and the dates reported these results to the study director and management are as follows

Item of Inspections/Audits	Dates of Inspections/Audits	Dates of Report of Inspections/Audits
Protocol	February 27, 2007	February 27, 2007
Amendment to protocol	February 28, 2007	February 28, 2007
IR spectrum of test substance	February 28, 2007	February 28, 2007
Homogeneity and stability analyses of test substance formulation	February 28, 2007	February 28, 2007
Reinspection of protocol	March 1, 2007	March 1, 2007
Concentration analysis of test substance formulation	March 9, 2007	March 9, 2007
Raw data and draft final report	July 24, 2007	July 24, 2007
Reinspection of raw data and draft final report	July 25, 2007	July 25, 2007
Final report	July 25, 2007	July 25, 2007

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study, and that the reported results accurately reflect obtained raw data.

Head, Quality Assurance Unit: Signed in original July 25, 2007

TABLE OF CONTENTS

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FIGURES

REFERENCE

Study Code: X18-0838
Test Substance Code: HR6853
Sponsor Code: D-0060

TITLE

Stability Analysis of 13F-OLE, Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

SPONSOR

DAIKIN INDUSTRIES, LTD.
1-1, Nishihitotsuya, Settsu, Osaka 566-8585, Japan

TESTING FACILITY

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The purpose of this study is to determine the stability of the test substance during the dosing period, and homogeneity, stability and concentration of the test substance in formulation in "Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of 13F-OLE in Rats" (Study Code: B11-0838).

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP [Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)].

PERIOD OF STUDY

Commencement of Study:	February 26, 2007
Initiation of Examination (Initiation of Analysis):	February 28, 2007
Termination of Examination (Termination of Analysis):	April 23, 2007
Completion of Study:	July 25, 2007

STORAGE AND RETENTION PERIOD OF DATA

The raw data, protocol, amendment to protocol, study contract documents, test substance information, final report and other record documents will be retained in the archive of the Hita Laboratory of our organization for the same period of B11-0838 paper data. After termination of the retention period, any measures taken will be done so with the approval of the sponsor.

RETENTION OF ORIGINAL DOCUMENTS

An original protocol, an original amendment to protocol and an original final report will be retained at Hita Laboratory. The copies of their original that the study director will be recognized to be accurate copy will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study director:

Study staff:

(Analysis of the test substance)

(Preparation of the test substance formulation)

APPROVAL BY AUTHOR

Study director: Signed in original July 25, 2007

Analytical Chemistry Section
Hita Laboratory

SUMMARY

The test substance (13F-OLE) was stable during the dosing period of subject study (Study Code: B11-0838).

The test substance in 10.0 and 0.04 w/v% formulations was stable for 8 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 2.0, 0.25 and 0.05 w/v% dose formulations for subject study was acceptable level.

MATERIALS

1. TEST SUBSTANCE (INFORMATION PROVIDED BY THE SPONSOR)

1.1 Name

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octa-1-ene

Other Name: 13F-OLE

CAS No.: 25291-17-2

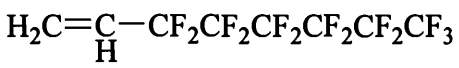
1.2 Lot No.

061024HM

1.3 Supplier

DAIKIN INDUSTRIES, LTD.

1.4 Structural Formula



(Molecular formula: $C_8H_3F_{13}$)

1.5 Purity

99.7%

1.6 Names and Concentration of Impurities

Unknown component	0.3%

1.7 Physicochemical Properties

Appearance at ordinary temperature:	clear colorless liquid
Molecular weight:	346.09
Stability:	—
Melting point:	—
Boiling point:	106°C (760 mmHg)
Vapor pressure:	—
Density:	1.560 g/cm^3 (20°C)
Partition coefficient:	—
Hydrolyzability:	unknown
Solubility:	—
Degree of solubility	
Water:	insoluble
DMSO:	insoluble
Acetone:	soluble (arbitrary mixable)
Others:	—

1.8 Storage Conditions

The test substance was stored at room temperature under a light shielding condition (cabinet No. 1 in the test substance storage room, tolerance temperature: 10-30°C).

1.9 Handling Precaution

Gloves, mask, cap and lab coat were worn.

METHODS

1. SUBJECT STUDY

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of 13F-OLE in Rats (Study Code: B11-0838)

2. STABILITY ANALYSIS OF THE TEST SUBSTANCE

The infrared (IR) spectrum was measured by IR spectrophotometer before and after the dosing period of subject study. Test substance was used under light shield.

2.1 Measurement of IR

1) Instrument

IR spectrophotometer: FT-720 (HORIBA, Ltd.)

2) Condition

Wave number: 4000 cm^{-1} - 400 cm^{-1}

3) Pre-Treatment

Potassium bromide neat

2.2 Criteria for Judgment

IR spectrum of the test substance that measured prior to dosing in our laboratory should be identical with provided from the sponsor. The test substance was judged to be stable when there are no differences in the IR spectrums at before and after dosing period.

3. HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

In the homogeneity analysis, the samples were taken (n=1) from the upper, middle and lower layers of formulations immediately after preparation, respectively. These samples were pretreated and measured (n=1) with gas chromatography (GC).

In the stability analysis, the formulations were stored at cold and dark place for 8 days, and the sample was taken (n=1) from the middle layer of the formulations at point of measurement (5 days and 9 days after preparation). These samples were pretreated and measured (n=1) with GC.

In the concentration analysis, the samples were taken (n=1) from the middle layer of dose

formulations immediately after preparation for subject study. These samples were pretreated and measured (n=1) with GC.

Test substance and formulations were used under light shield.

3.1 The Test Substance Formulation

1) Homogeneity and Stability Analyses

(1) Concentration

10.0 and 0.04 w/v%

(2) Preparation Method

Weighed accurately 10.0 g of test substance was kneaded together with Tween80 (the final concentration of Tween80 in the formulation was 1.0 w/v%) in a mortar and then it was mixed with olive oil to make 100 mL, and used as 10.0 w/v% formulation. Accurate 0.4 mL of 10.0 w/v% formulation was diluted with olive oil (including 1.0 w/v% Tween80) to make 100 mL, and used as 0.04 w/v% formulation.

Vehicle: olive oil (Lot No. 038OHS, Fujimi Pharmaceutical)
Polyoxyethylene (20) sorbitan mono-oleate (Lot No. DPK6694, Tween80, Wako Pure Chemical Industries)

2) Concentration Analysis

The 2.0, 0.25 and 0.05 w/v% dose formulations at first administration for subject study were used.

3.2 Outline of Analytical Method

The analytical method was decided, according to results of validation of the analytical method on non-GLP at the test facility.

1) Validation of the Analytical Method

(1) Preparation for Measurement Sample

a) Standard Stock Solution for Validation of the Analytical Method

Weighed 0.1004 g of the test substance, dissolved in acetone 5000 to make 100 mL, and used this solution as 1004 μg/mL standard stock solution for validation of the analytical method.

b) Sample for Specificity

Weighed 0.1016 g of the test substance, dissolved in acetone 5000 to make 100 mL, and used this solution as 1016 μg/mL standard stock solution for specificity. The standard stock solution for specificity was diluted with acetone 5000 to make 20.3 μg/mL standard solution and 20.3 μg/mL vehicle-containing standard solution (containing 5 v/v% vehicle (olive oil including 1.0 w/v% Tween80)). Acetone 5000 was used as solvent blank, and vehicle blank (containing 5 v/v% vehicle) was prepared.

c) Sample for Linearity

The standard stock solution for validation of the analytical method was diluted with acetone 5000 to make 10.1, 20.1 and 40.2 μg/mL standard solutions.

d) Sample for Accuracy and Repeatability

Standard solutions (concentration: 10.1, 20.1 and 40.2 μg/mL, each concentration: n=3) were prepared in the same way of sample for linearity.

(2) Specificity

Samples for specificity were measured with GC. The variation of detection value (peak area) of the test substance between standard solution with and without vehicle was -2.8%. Therefore, it was confirmed that the result of variation satisfied criteria for judgment (within ±5%). In the results of GC analysis of solvent blank and vehicle blank, it was confirmed there were no background and interfering peaks at the elution peak position of test substance.

(3) Linearity

Samples for linearity were measured with GC. The calibration curve was made by the concentration of the test substance in the horizontal line and the detection value of test substance in the vertical line. The regression formula passed through the origin of the coordinates, and the coefficient of correlation of calibration curve which was obtained from least square was R=0.999. Therefore, it was confirmed that the result of linearity satisfied criteria for judgment (more than 0.999).

(4) Accuracy and Repeatability

Samples for accuracy and repeatability were measured with GC. The concentrations of the test substance were calculated with regression formula that was obtained at linearity. Accuracy and repeatability were calculated with these values.

Accuracy of 10.1 μg/mL standard solution was -3.5, -2.3 and -2.2%.

Accuracy of 20.1 μg/mL standard solution was -3.3, 0.2 and -1.8%.

Accuracy of 40.2 μg/mL standard solution was -3.2, 0.6 and -1.7%.

Repeatability of 10.1, 20.1 and 40.2 μg/mL standard solution was 0.8, 1.8 and 1.9%, respectively.

It was confirmed that the result of accuracy and repeatability satisfied criteria for judgment (accuracy: within ±10%, repeatability: less than 5%).

2) Preparation for Standard Solution

Weighed 0.1000 g of the test substance dissolved in acetone 5000 to make 100 mL, and used this solution as 1000 μg/mL standard stock solution. Accurate 4 mL of standard stock solution diluted with acetone 5000 to make 20 mL, and 200 μg/mL standard solution was prepared. Accurate 2 mL of 200 μg/mL standard solution

diluted with acetone 5000 to make 20 mL, and 20.0 μg/mL standard solution was prepared.

3) Pre-Treatment

Formulations were mixed well using a magnetic stirrer.

(1) Homogeneity and Stability Analyses

a) 10.0 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in acetone 5000 to make 50 mL. Accurate 0.5 mL of this solution was diluted with acetone 5000 to make 25 mL, and served as a GC sample (dilution rate: 5000).

b) 0.04 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in acetone 5000 to make 10 mL, and served as a GC sample (dilution rate: 20).

(2) Concentration Analysis

a) 2.0 w/v% Formulation

Accurate 0.5 mL of formulation was dissolved in acetone 5000 to make 50 mL. Accurate 1 mL of this solution was diluted with acetone 5000 to make 10 mL, and served as a GC sample (dilution rate: 1000).

b) 0.25 w/v% Formulation

Accurate 1 mL of formulation was dissolved in acetone 5000 to make 25 mL. Accurate 2 mL of this solution was diluted with acetone 5000 to make 10 mL, and served as a GC sample (dilution rate: 125).

c) 0.05 w/v% Formulation

Accurate 1 mL of formulation was dissolved in acetone 5000 to make 25 mL, and served as a GC sample (dilution rate: 25).

4) Conditions of GC Analysis

(1) Instruments (HP6890)

Gas chromatograph:	HP6890 Series (Yokogawa Analytical Systems, Inc.)
Controller:	G1512A (Yokogawa Analytical Systems, Inc.)
Auto sampler:	18596C (Yokogawa Analytical Systems, Inc.)
Injector:	18593B (Yokogawa Analytical Systems, Inc.)
Data processor:	GC-Chemstation (Yokogawa Analytical Systems, Inc.)

(2) Conditions

Column:	HP-5MS (F.T. 0.25 μm) 0.25 mm I.D. × 30 m
Column oven temperature:	30°C
Temperature of injection port:	200°C
Carrier gas:	helium
Carrier gas flow rate:	1.0 mL/min
Detector:	FID

Detector temperature:	250°C
Injection method:	split (split ratio 20:1)
Injection volume:	2 μL

3.3 Data Processing

1) Detection Value

A peak area was used as the detection value.

2) Quantitative Analytical Method

In validation of the analytical method, the result of linearity was a straight line range of 10.1, 20.1 and 40.2 μg/mL standard solutions, and it passed through the origin of the coordinates. Therefore, the concentrations of analytical samples were determined by single level calibration.

3) Calculation of the Test Substance Concentration in Formulation

Concentration of test substance in each sample (C: w/v%) was calculated with the equation shown below and rounded off to three significant figures.

$$C = \frac{Cs \times A \times D}{As \times 10000}$$

Cs: Test substance concentration in standard solution (μg/mL)

As: Detection value of test substance in standard solution

A: Detection value of test substance in each GC sample

D: Dilution rate in each GC sample

3.4 Criteria for Judgment

1) Homogeneity Analysis

The test substance was judged as homogeneous dispersion in vehicle if a coefficient of variation (CV) was within 5%. The CV was calculated using the following equation:

$$CV(\%) = \frac{\text{Standard deviation for concentration of test substance in each layer}}{\text{Mean concentration of test substance in each layer}} \times 100$$

2) Stability Analysis

The test substance was judged as stable state in vehicle if a rate to the nominal concentration for the actual concentration (R.N.) and a rate to the mean concentration immediately after preparation for the actual concentration (R.P.) were within the range of 100±10%. The R.N. and R.P. were calculated using the following equation:

$$R.N.(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

$$R.P.(\%) = \frac{\text{Actual concentration}}{\text{Mean concentration immediately after preparation}} \times 100$$

3) Concentration Analysis

It was confirmed that R.N. was within the range of 100±10%. The R.N. was calculated using the following equation:

$$R.N.(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED RELIABILITY OF STUDY RESULTS

There were no factors that might have affected the reliability of the study data.

RESULTS AND DISCUSSION

1. RESULTS

1.1 Stability Analysis of the Test Substance

IR spectrum of test substance provided by the sponsor (Reference 1) was identical with that measured before dosing period for subject study (Figure 1).

There were no differences in the IR spectra between before and after dosing period (Figures 1, 2).

1.2 Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

1) Homogeneity and Stability Analyses

The results of homogeneity and stability analyses of the test substance formulation are shown in Table 1.

(1) Homogeneity Analysis

CV of 10.0 and 0.04 w/v% formulations were 0.7 and 0.3%, respectively. The results satisfied criteria for judgment.

(2) Stability Analysis

a) 10.0 w/v% Formulation

At immediately after preparation, R.N. were 98.0 to 99.4%.

At 5 days after preparation, R.N. was 97.7%, and R.P. was 99.1%.

At 9 days after preparation, R.N. was 98.8%, and R.P. was 100%.

All the results of R.N. and R.P. satisfied criteria for judgment.

b) 0.04 w/v% Formulation

At immediately after preparation, R.N. were 96.8 to 97.3%.

At 5 days after preparation, R.N. was 96.8%, and R.P. was 99.7%.

At 9 days after preparation, R.N. was 97.5%, and R.P. was 101%.

All the results of R.N. and R.P. satisfied criteria for judgment.

2) Concentration Analysis

The results of concentration analysis of the test substance formulation are shown in Table 2.

R.N. of 2.0, 0.25 and 0.05 w/v% dose formulations were 97.5 to 98.4%. All the results satisfied criteria for judgment.

2. DISCUSSION

The test substance was stable during the dosing period of subject study.

The test substance in 10.0 and 0.04 w/v% formulations was stable for 8 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 2.0, 0.25 and 0.05 w/v% dose formulations for subject study was acceptable level.

Table 1 Homogeneity and stability analyses of the test substance formulation

Nominal conc. (w/v%)	Time point of measurement	Layer of measurement	Actual conc. (w/v%)	R.N. (%)	Mean conc. (w/v%)	R.P. (%)	CV (%)
10.0	Immediately after preparation	Upper	9.94	99.4	9.86	-	0.7
		Middle	9.83	98.3			
		Lower	9.80	98.0			
	5 days after preparation	Middle	9.77	97.7	-	99.1	-
	9 days after preparation	Middle	9.88	98.8	-	100	-
0.04	Immediately after preparation	Upper	0.0387	96.8	0.0388	-	0.3
		Middle	0.0389	97.3			
		Lower	0.0387	96.8			
	5 days after preparation	Middle	0.0387	96.8	-	99.7	-
	9 days after preparation	Middle	0.0390	97.5	-	101	-

R.N.: Rate to the nominal concentration

R.P.: Rate to the concentration measured immediately after preparation

CV: Coefficient of variation

Table 2 Concentration analysis of the dose formulation

Date of analysis	Nominal conc. (w/v%)	Actual conc. (w/v%)	R.N. (%)
March 9, 2007	2.0	1.95	97.5
	0.25	0.246	98.4
	0.05	0.0491	98.2

R.N.: Rate to the nominal concentration

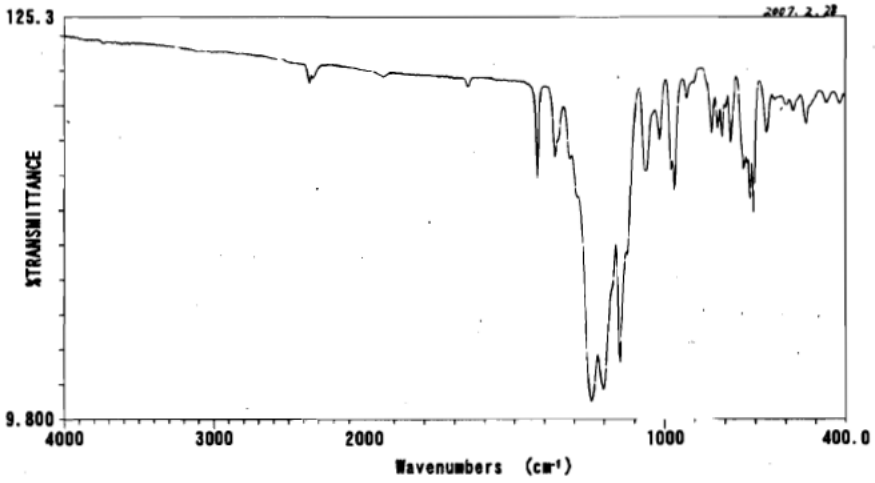


Figure 1 IR spectrum measured prior to the administration period

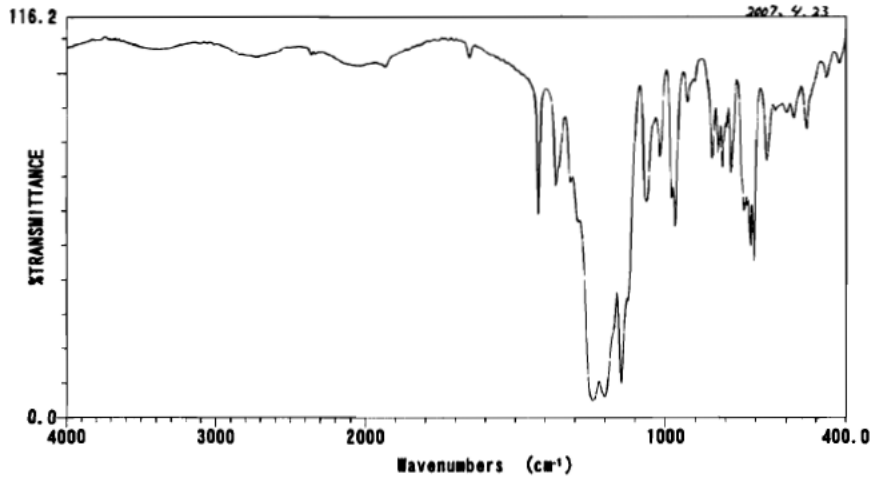
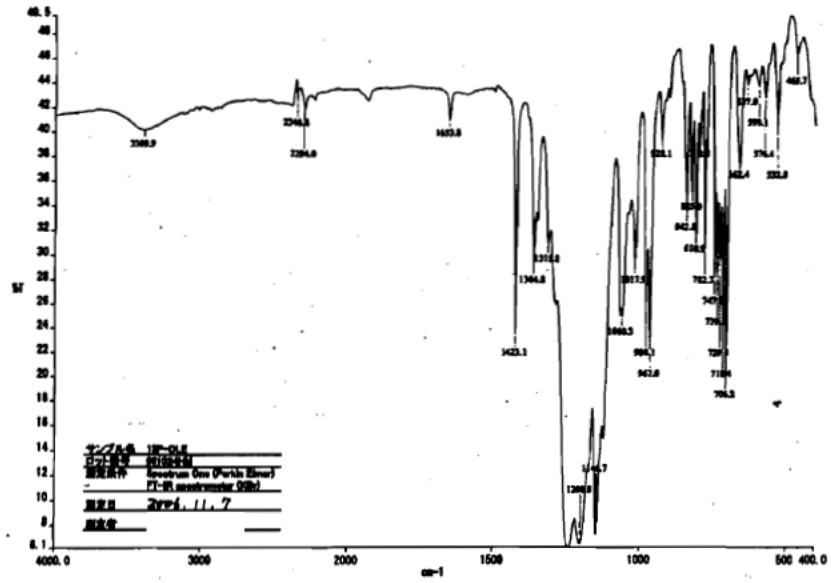


Figure 2 IR spectrum measured after the end of the administration period



Reference 1 IR spectrum provided by the sponsor

APPENDIX 2

"HISTOPATHOLOGICAL PHOTOS"

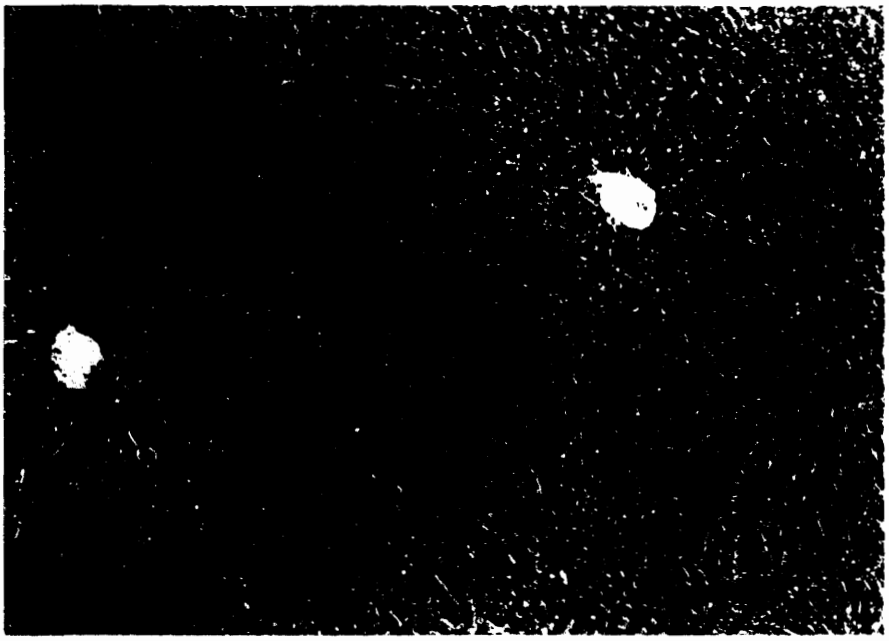


Photo. 1 Liver of a male rat from vehicle control group.
Normal.
No. 5 animal. HE. ×90.

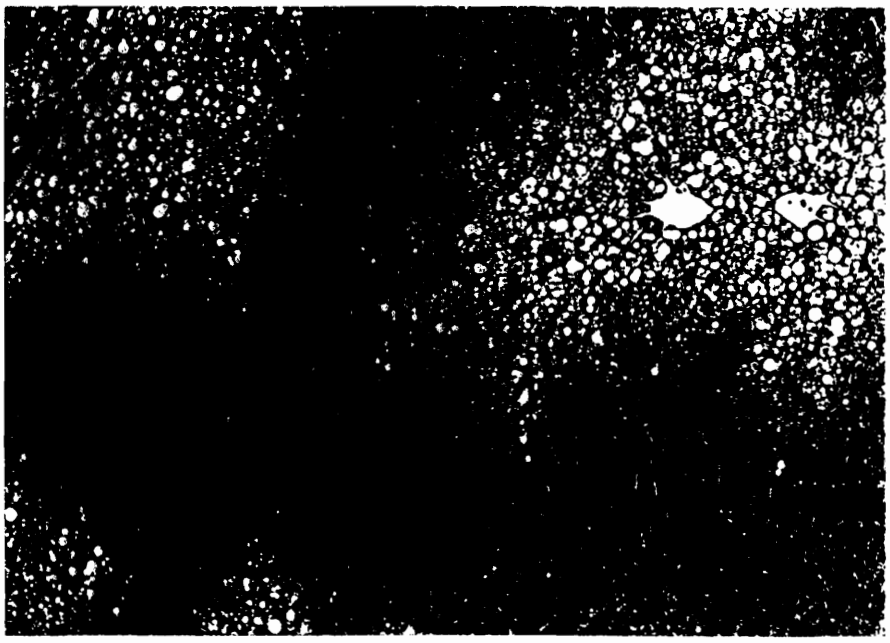


Photo. 2 Liver of a male rat from 200 mg/kg/day group.
Centrilobular lipid droplets in hepatocytes.
No. 23 animal. HE. ×90.

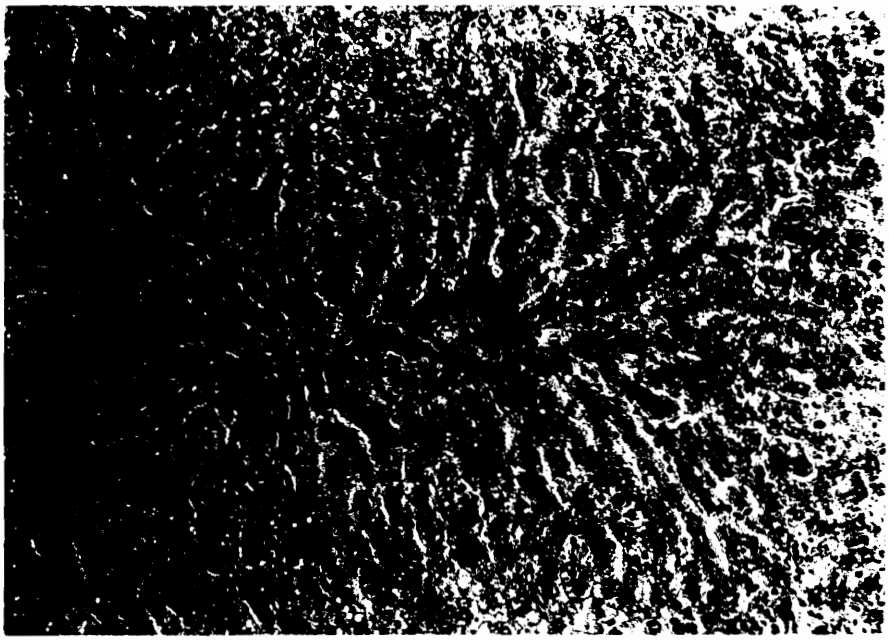


Photo. 3 Liver of a male rat from vehicle control group.
Normal.
No. 5 animal. HE. ×180.

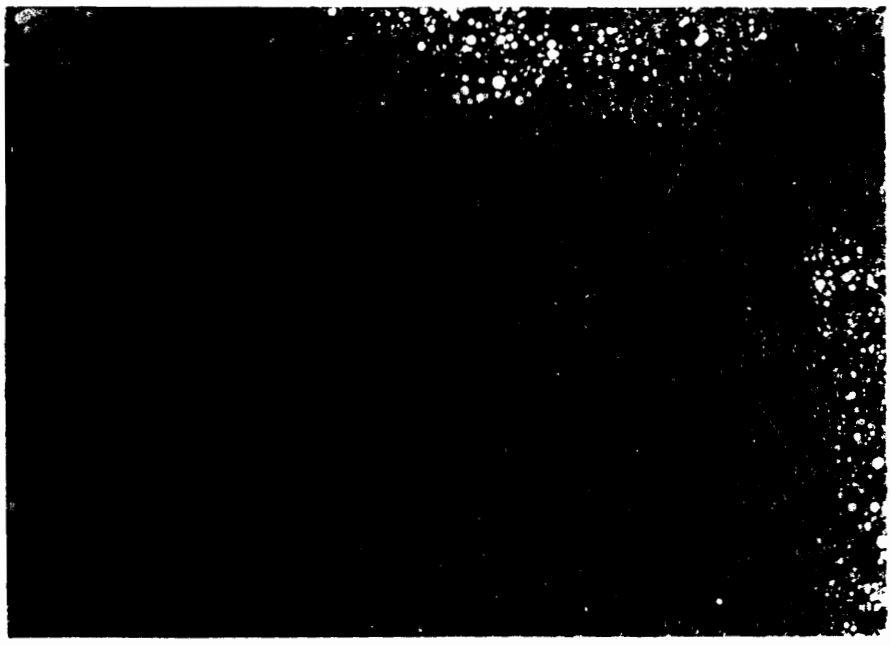


Photo. 4 Liver of a male rat from 200 mg/kg/day group.
Periportal hypertrophy and prominent nucleoli of hepatocytes.
No. 21 animal. HE. ×180.