AR226_3311

Report on the results of 28-day repeated administration toxicity study using a mammal

1. General items

Name of novel chemical substance (IUPAC nomenclature)	[redacted]			
Other name	[redacted]	Physicochemical properties	Molecular weight	[redacted]
Structural formula or rational formula (if neither is known, outline of preparation method) Described in page 2.			State at a room temperature	Brown viscous solid
			Stability	Unknown
			Melting point	–
			Boiling point	–
			Vapor pressure	–
			Partition coefficient	–
			Dissolution	Oil soluble and water soluble
		Solubility	Water	*2
Purity of the novel chemical substance used in the test	[redacted]		DMSO	*3
Name of impurity and concentration	[redacted]		Acetone	–
Lot No.	[redacted]		Other (ethanol)	*4

[Notes]

[redacted]

Company Sanitized. Does not contain TSCA CBI

[redacted]

[redacted]

[redacted]

2. Acute toxicity test

Test No.	Kind of test and term	Animal species	No. of animals per group	Administration path	Dose (mg/kg)	LD50 or NOEL* (mg/kg)	Experiment site
1	14-day repeated administration test	Rat	Male 3 head Female 3 head	Oral administration	(mg/kg/day) 1,000 500 250 50 # control	Abnormal Abnormal Abnormal Normal Normal NOEL 50 mg/kg/day (observation items: bodyweight, general condition, hematological test, hematobiochemical test, organ weight, dissection, histopathological test@)	Chemical Evaluation & Research Institute, Hita Laboratory

* NOEL: No-Observed-Effect Level

Purified water

@ Test carried out on the kidney of the male medium-control group, 50 mg/kg group and 1000 mg/kg group.

General condition

(Male) 250 mg/kg group: soft stool (2/3)
500 mg/kg group: soft stool (2/3)
1,000 mg/kg group: soft stool (3/3)

(Female) 500 mg/kg group: soft stool (3/3)
1,000 mg/kg group: soft stool (3/3)

[redacted]

3. 28-Day repeated administration toxicity test

Test substance administration term	From July 30, Heisei 15 (2003) to August 26, Heisei 15 (2003)	
Animal species and lineage	Rat, Crj: CD (SD) IGS	No. of animals per group
Administration path	Forced oral administration (purified water)	Male: 6 head Female: 6 head

Purity of test substance [redacted]	Dose mg/kg	Control group 0 ♂	♀	Low-dose group 10 ♂	♀	Medium-dose (1) group 40 ♂	♀	Medium-dose (2) group 200 ♂	♀	High-dose group 1,000 ♂	♀	Recovery group 0 ♂	♀	Recovery group 1,000 ♂	♀
Bodyweight (administration term)	day 12			—	—	—	—	—	—	▼	—				
	day 17- day 28			—	—	—	—	—	—	↓	—				
Bodyweight (recovery term)	day 1													▼	—
	day 5、day 10													▽	—
	day 14													▼	—
Feed intake (administration term)				—	—	—	—	—	—	—	—				
Feed intake (recovery term)	day 8													—	△
General condition	soft stool	—	—	—	—	—	—	6/6	2/6	12/12	12/12	—	—	6/6	5/6
Hematological test	Activated partial thromboplastin time			—	—	—	—	▼	—	—	—			—	—
Hematobiochemical test	Alkali phosphatase			—	—	△	—	—	—	—	—			—	—
	Blood glucose			—	—	—	—	—	—	—	—			▽	—
	Albumin			—	—	—	—	▼	—	▽	—			—	—
Urinary test	Amount of urine			—	—	—	—	—	—	—	—			△	—
Organ weight (absolute weight)				—	—	—	—	—	—	—	—			—	—

[redacted]

Purity of test substance [redacted]	Dose mg/kg	Control group 0 ♂	Control group 0 ♀	Low-dose group 10 ♂	Low-dose group 10 ♀	Medium-dose (1) group 40 ♂	Medium-dose (1) group 40 ♀	Medium-dose (2) group 200 ♂	Medium-dose (2) group 200 ♀	High-dose group 1,000 ♂	High-dose group 1,000 ♀	Recovery group 0 ♂	Recovery group 0 ♀	Recovery group 1,000 ♂	Recovery group 1,000 ♀
Organ weight (relative weight)	Liver			—	—	—	—	—	—	—	△			—	—
	Testicles			—		—		—		—				△	
	Brain			—	—	—	—	—	—	—	—			△	—
Dissection	Kidney Pyelectasia	1/6	—	—	—	1/6	—	—	—	—	—	—	—	—	—
	Spleen Node	—	—	—	—	—	—	—	—	—	—	—	—	1/6	—
	White section	—	—	—	—	—	—	1/6	—	—	—	—	—	—	—
Pathohistological Liver test	Centrilobular hepatic cell hypertrophy Small granuloma (+)	—	—	*	*	*	*	—	*	3/6	—	—	*	—	*
	Single cell necrosis (+)	—	—	*	*	*	*	1/6	*	—	—	1/6	*	—	*
	Kidney (+)	—	—	*	*	*	*	—	*	4/6	—	—	*	—	*
	Pyelectasia Localization of medulla (+)	1/6	—	*	*	1/1	*	*	*	—	—	*	*	*	*
	Seminal vesicle vacuole (+)	—	1/6	*	*	0/1	*	*	*	—	—	*	*	*	*
	Spleen Local necrosis (++)	—	—	*	*	*	*	1/1	*	—	—	*	*	0/1	*
	Follicle hypertrophy (++)	—	—	*	*	*	*	0/1	*	—	—	*	*	1/1	*
NOEL (mg/kg)		40 mg/kg/day													
Changes based on NOEL estimation		Soft stool observed in males and females of 200 mg/kg or higher dose													

[redacted]

–: no abnormality
↓ or ↑: tendency
▽or△: risk factor (P) <0.05
▼ or▲: risk factor (P) <0.01
*: not tested

4. Other

Repeated administration toxicity Test implementation facility	Name	Chemical Evaluation & Research Institute, Hita Lab.
	Address	3-822 Ishi-cho, Hita City, Ohita Prefecture, Telephone 0973(24)7211
Test manager	Name	Keiji Shiraishi Seal
Implementation date	From July 16, Heisei 15 (2003) to December 5, Heisei 15 (2003)	

[redacted]

Work assignment table

Title: 28-Day repeated oral administration toxicity test of [redacted] in rats

Name	Work content
Test manager: Keiji Shiraishi	to carry out work such as test planning, test work management, overall analysis and evaluation of the results, report preparation, etc., and have general responsibilities for all work carried out for the test
Person in charge of testing: Naomi Kawazu	to carry out quarantine inspection as well as conditioning and rearing management of animals, test substance preparation, administration, general condition observation, bodyweight measurement, feed intake measurement, etc., and have responsibilities for animal experiment work.
Person in charge of pathological testing: Kazutoshi Shinoda	to carry out work such as dissection, tissue collection, organ weight measurement, histopathological test, etc., and have responsibilities for pathological and morphological work.
Person in charge of clinical testing: Keiji Shiraishi	to carry out work such as hematological tests, hematobiochemical tests, urine tests, etc., and have responsibilities for work related to biochemical analyses of biological samples
Person in charge of analysis: Takaharu Hara	to carry out work such as test substance stability determination, confirmation of stability and uniformity of test substance solutions prepared, etc., and have responsibilities for work related to analyses.

[redacted]

Statement

Chemical Evaluation & Research Institute, Hita Laboratory

Test requestor: DuPont K.K.

Title: 28-Day repeated oral administration toxicity test of [redacted] in rats

[redacted]

This final report (copy) is an accurate transcription of the final report of the above titled test.

December 5, 2003

Operation Manager: Shigeharu Yamasaki

[redacted]

[redacted]

[redacted]

Final Report

28-Day repeated oral administration toxicity test of [redacted] in rats

December 2003

Chemical Evaluation & Research Institute, Hita Laboratory [Seal]

[redacted]

Statement

Chemical Evaluation & Research Institute, Hita Laboratory

Test requestor: DuPont K.K.

Title: 28-Day repeated oral administration toxicity test of [redacted] in rats

[redacted]

The test described above was carried out according to "Testing facilities specified in Ministry Ordinance Article 4 stipulating items, etc., of test related to novel chemical substances and evaluation of toxicity related to designated chemical substance" (GLP) [Environmental Protection Notification 39, Notification No. 229 of Pharmaceutical Affairs Bureau and MITI Basic Industry Bureau Notification No. 85 dated March 31, Showa 59 (1984), amended on March 1, Heisei 12 (2000)] and "OECD Principles of Good Laboratory Practice (November 26, 1997).

In addition, this final report has been confirmed to reflect the raw data accurately, and the test data obtained are confirmed to be effective.

December 5, 2003
Test Manager: Keiji Shiraishi

[redacted]

Quality Assurance Certificate

Chemical Evaluation & Research Institute, Hita Lab.

Test requestor: DuPont K.K.

Title: 28-Day repeated oral administration toxicity test of [redacted] in rats [redacted]

The auditing and inspection of this test were carried out by the QA department of Chemical Evaluation & Research Institute, Hita Lab. The date of auditing or inspection and date of the results reported to the person in charge of study or operation manager are as follows

Auditing or inspection item	Date of auditing or inspection	Date of auditing or inspection result reported
Study protocol	July 18, 2003	July 22, 2003
Study protocol change	July 23, 2003	July 23, 2003
Record of receiving animals	July 28, 2003	July 28, 2003
Test substance preparation	July 29, 2003	July 30, 2003
Study protocol change (No. 2)	July 30, 2003	July 30, 2003
Animal grouping record	July 30, 2003	July 30, 2003
Substance administration	July 31, 2003	July 31, 2003
Study protocol change (No. 3)	August 11, 2003	August 11, 2003
Dissection	August 27, 2003	August 27, 2003
Profile	September 2, 2003	September 2, 2003
Study protocol change (No. 4)	October 31, 2003	November 4, 2003
Study protocol change (No. 5)	October 31, 2003	November 4, 2003
Clinical test results	November 19, 2003	November 19, 2003
Pathological test results	November 25, 2003	November 25, 2003
Animal experiment results	November 27, 2003	November 27, 2003
Physicochemical test report draft	November 27, 2003	November 28, 2003
Clinical test result, 2nd time	November 28, 2003	November 28, 2003
Test substance and rearing conditions records	November 28, 2003	November 28, 2003
Final report draft	November 28, 2003	November 28, 2003
Physicochemical test report draft reevaluation	December 3, 2003	December 3, 2003
Final report draft reevaluation	December 5, 2003	December 5, 2003
Final report	December 5, 2003	December 5, 2003

This report describes the method and procedures used in the test accurately, and the results reported reflect the raw data accurately.

December 5, 2003

Person in charge of quality assurance: Keiji Shiraishi

[redacted]

[redacted]

Test substance code No.: HR5158

[redacted]

Title: 28-Day repeated oral administration toxicity test of [redacted] in rats

Test requestor: DuPont K.K.
1-8-1 Shimomeguro, Meguro-ku, Tokyo, 153-0064

Test facility: Chemical Evaluation & Research Institute, Hita Lab.
3-822 Ishii-cho, Hita City, Ohita Prefecture, 877-0061

Object: the object is to elucidate variety, extent and reversibility of toxic signs developed and to determine no-observed effect level (NOEL) by observing changes in the function and morphology of animal body in the case of 28-day repeated oral administration of the test substance.

Testing method: the method according to "28-day repeated administration toxicity test to use mammals" specified in the "Partial amendment, etc., of "Novel chemical substance testing method" (Environmental Protection Notification No. 700, Notification No. 1039 of Pharmaceutical Affairs Bureau and MITI Basic Industry Bureau Notification No. 1014 dated December 5, 1986" and "407, Repeated dose oral toxicity – rodent: 28-day or 14-day study" specified in "OECD guideline for testing of chemicals" (May 12, 1981) was carried out.

GLP applied: "Testing facilities specified in Ministry Ordinance Article 4 stipulating items, etc., of test related to novel chemical substances and evaluation of toxicity related to designated chemical substance" (GLP) [Environmental Protection Notification 39, Notification No. 229 of Pharmaceutical Affairs Bureau and MITI Basic Industry Bureau Notification No. 85 dated March 31, 1984, amended on March 31, 2000] and "OECD Principles of Good Laboratory Practice (November 26, 1997) was used.

Test schedule

Start of study	July 16, 2003
Experimental animal received	July 22, 2003
Start of experiment (start of substance administration)	July 30, 2003
Dissection at the end of administration term	August 27, 2003

[redacted]

Start of recovery test	August 27, 2003
Dissection at the end of recovery term	September 10, 2003
End of experiment (end of hematological test)	October 31, 2003
End of study	December 5, 2003

Document storage site and storage term

The raw data, study protocol, test request, test substance brochure, final report, QA inspection documents, other records or documents and specimens are to be stored at the document storage room of the Hita Laboratory of the Institution, and the test substance samples by lot were stored in the test substance storage room for 10 years from receiving a notification of the Chemical Substance Control Law, Article 4, Clause 1, No. 1, 2 or 3 being applicable. The date receiving the notification is to be contacted to the Hita Laboratory of the Institution by the test requester. The handling after the storage term requires approval from the test requester. In the case of specimens, test substances, etc., the qualities of which are liable to be changed during the storage, the storage term is for the duration of the qualities being able to be evaluated, and the disposal requires approval from the test requester.

Storage of original documents

The original of the study protocol and amendments is to be stored at the Hita Laboratory of the Institution. Furthermore, its copy is to be stored by the test requester.

The original final report is to be stored at the Hita Laboratory of the Institution. Furthermore, its copy is to be stored by the test requester together with a statement (certificate of the content being not different from the original) issued by the operation manager of Hita Laboratory of the Institution attached.

Study manager and other persons involved in the study and their work assignments

Study manager: Keiji Shiraishi

(Carrying out work such as test planning, test work management, overall analysis and evaluation of the results, report preparation, etc., and having general responsibilities for all works carried out for the test)

Person in charge of testing: Naomi Kawazu

(Carrying out quarantine inspection as well as conditioning and rearing management of animals, test substance preparation, administration, general condition observation, bodyweight measurement, feed intake measurement, etc., and having responsibilities for animal experiment work)

[redacted]

Person in charge of pathological testing: Kazutoshi Shinoda

(Carrying out work such as dissection, tissue collection, organ weight measurement, histopathological test, etc., and having responsibilities for pathological and morphological work)

Person in charge of clinical testing: Keiji Shiraishi

(Carrying out work such as hematological tests, hematobiochemical tests, urine tests, etc., and having responsibilities for work related to biochemical analyses of biological samples)

Person in charge of analysis: Takaharu Hara

(Carrying out work such as test substance stability determination, confirmation of stability and uniformity of test substance solutions prepared, etc., and having responsibilities for work related to analyses)

Approval by final report author

Study manager: December 5, 2003

Keiji Shiraishi [signature]

Affiliation: Hita Laboratory, 2nd Department for Testing

[redacted]

Table of Contents

Page

[redacted]

Figures

Tables

Photos

Addenda

Attached documents

Physicochemical test report

[redacted]

Abstract

For [redacted], 28-day repeated oral administration toxicity test and 14-day recovery test were carried out by using 6 head per group of Crj: CD (SD) IGS male and female rats of 5 weeks old. The doses used were 4 levels from 1,000 mg/kg/day as the maximum dose followed by 200, 40, and 10 mg/kg/day. Incidentally, the 1,000 mg/kg/day group and medium control group were allowed to have recovery groups.

In the present study, there was no fatal case considered to be attributable to the test substance administration. Moreover, there were no toxicological effects of the test substance administration observed during the whole administration term with respect to the results of hematological tests, hematobiochemical tests, urinary tests and dissection carried out after the administration term.

With respect to the general condition, those males and females with a dose of 200 mg/kg or higher showed soft stool, and this finding was considered to be the effect of the test substance administration. In addition, the males in the 1,000 mg/kg group showed body weight increase inhibition from day 12 to day 28.

In the case of organ weight measurements, the relative weight of the liver in the females of the 1,000 mg/kg group was found to be increased.

As a result of histopathological examination, centrilobular hepatic cell hypertrophy and single cell necrosis in the liver were observed in males of the 1,000 mg/kg group.

In the recovery test, all changes observed during the administration term and at the end of the administration terms showed recovery.

The results as described above suggested mainly soft stool, bodyweight increase inhibition and changes in the liver as an effect of the administration of [redacted] and from all of those changes, it was considered to be recoverable. Incidentally, the NOEL of [redacted] under the conditions used in the present study was estimated to be 40 mg/kg/day because of soft stool observed in males and females of groups with a dose of 200 mg/kg/day or more.

[redacted]

Materials and Methods

1. Test substance (information provided by the test requester)

1.1 Name

[redacted]

Another name [redacted]

CAS No. [redacted]

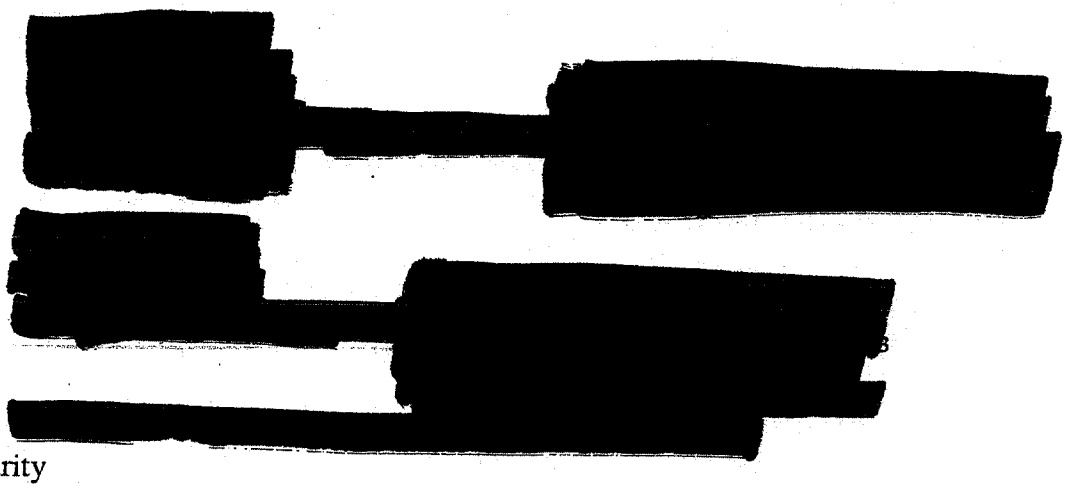
1.2 Lot No.

[redacted]

1.3 Source

DuPont K.K.

1.4 Structural formula



1.5 Purity

[redacted]

1.6 Name and concentration of impurity

[redacted]

1.7 Physicochemical property

State at a room temperature: brown viscous solid

[redacted]

Stability: unknown

Melting point: -

Boiling point: -

Vapor pressure: -

Partition coefficient: -

Hydrolysis: unknown

[redacted]

Dissolution: oil soluble and water soluble

Solubility:

Water	Less than 50 mg/mL (measured at the institution)
DMSO	Less than 50 mg/mL (measured at the institution)
Acetone	-
Other	
Ethanol	Soluble (unknown solubility)

1.8 Storage conditions

The storage was at a room temperature (experimental storage, cabinet 6).

1.9 Handling precaution

Protective gloves, mask, cap and white lab coat were worn.

2. Experimental animals

Crj: CD (SD) IGS rats (SPF) were purchased from Nippon Charles River K.K. (Hino Shiiku Center, 735 Komatuki, Hino-cho, Gamou-gun, Shiga Prefecture 529-1633). After quarantine inspection and conditioning, the random extraction method by weight was used to select animals of normal growth and good general condition, and the animals were grouped so that the mean bodyweight was approximately same in each group. The age of the animals at the time of the start of substance administration was 5 weeks old, the male body weight was in the range of 141.7-159.9 g, and the female bodyweight was in the range of 115.5-132.9 g. The animal identification was with ear tags.

3. Rearing environment

Throughout the whole rearing term including the quarantine inspection and conditioning period, the animals were kept in a barrier system rearing room set at a temperature in the range of 21-25°C, relative humidity in the range of 40-70%, number of ventilation in the range of 10-15 times/hr and light-dark cycle with 12 hr interval (light turned on 7th hour and off on 19th hour of day). The actually measured results of the temperature and relative humidity were 21.9-23.9°C and 54.6-71.8%, respectively.

On the day 2 of the recovery term, the function of the air-conditioner was suspended for 8 min due to being hit by lightning causing the humidity to rise (the maximum humidity of 71.8%). As a result of the subsequent observation of the general condition of the animals, no abnormality was observed, and the incident was considered not to affect the results of the study.

Prior to grouping, the animals were kept 5 head/cage in stainless steel and metal mesh floor cages (260W×380D×180H mm, Tokiwa Kagaku Kikai K.K.), and after grouping the animals were individually kept in stainless steel and metal mesh cages (165W×300D×150H mm,

[redacted]

Tokiwa Kagaku Kikai K.K.). The bottom trays were exchanged once a week before grouping and 2 times a week after grouping. Incidentally, because of soft stool observed in the medium dose group and high dose group as well as high dose recovery group, the trays were exchanged every day from day 2 of the administration term to day 3 of the recovery term for those groups and 2 times a week from day 4 of the recovery term. The feeders, cages and racks were exchanged once each at the time of grouping and end of the administration term (recovery groups only). Incidentally, the racks and cages were tagged for identification.

The feed used was a solid feed (MF, Lot No. 030510, Oriental Yeast Industry K.K.), and the drinking water was tap water of Hita City (chlorine added) allowed to be taken freely from an automated water feeder. The feed and rearing equipment and tools were autoclave-sterilized (121°C for 30 min) before using. For the feed, the analytical data determined by Japan Food Research Laboratories were obtained from the manufacturer, and the items were confirmed to be within the standard values of the US Environmental Protection Agency Regulations. In addition, the miscellaneous inclusions of drinking water were tested twice a year by the Kurume Laboratory of the Institution, in one of those tests, the entire 46 items of water quality described in the Ministry of Welfare and Health Ordinance No. 69 (becoming effective on December 1, 1993 were tested, in the second test, 32 items among them were tested, and the results were confirmed to be within the standard values.

Throughout the whole rearing term including the quarantine inspection and conditioning period, those rearing environmental factors showed no variations considered to affect the results of the study.

4. Group configuration

The group configuration used was as in the following table.

Test group	Dose (mg/kg/day)	Dose volume (mL/kg)	Dose concentration (w/v%)	No. of animal	
				Male (animal No.)	Female (animal No.)
Medium control group	0	10	0	6 (1 – 6)	6 (43 – 48)
Medium control recovery group	0	10	0	6 (7 – 12)	6 (49 – 54)
Low dose group	10	10	0.1	6 (13 – 18)	6 (55 – 60)
Medium dose (1) group	40	10	0.4	6 (19 – 24)	6 (61 – 66)
Medium dose (2) group	200	10	2.0	6 (25 – 30)	6 (67 – 72)
High dose group	1,000	10	10.0	6 (31 – 36)	6 (73 – 78)
High dose recovery group	1,000	10	10.0	6 (37 – 42)	6 (79 – 84)

Reasons for doses used: a 14-day repeated oral administration toxicity test was carried out with 4 doses of 50, 250, 500 and 1,000 mg/kg/day. As a result, there were changes in the general condition observed in the 250 mg/kg group and suspected to be attributable to the test substance. Therefore, in the present study, the high dose was set at 1,000 mg/kg/day followed by 200, 40

[redacted]

and 10 mg/kg/day, that is, the total of 4 doses being used. Incidentally, the recovery groups were set for 1,000 mg/kg/day and medium control.

5. Stability of test substance

The stability of the test substance during the administration term was confirmed at the Hita Laboratory of the Institution.

The stability of the test substance was confirmed by measuring its infrared absorption spectrum before the start and after the end of the administration term.

The infrared absorption spectrum measurements were carried out by using a Fourier transform infrared spectrophotometer (Model FTS 135, Nippon Bio-Rad Laboratories K.K.) in the range of 4,000 cm^{-1} – 400 cm^{-1}.

Before the start of the administration, the identification was carried out by comparing with a spectrum provided by the test requester, and in the measurement carried out after completing the administration term, the spectrum before the administration was used to compare to find any change.

6. Test substance preparation

6.1 Medium

The state of suspension in pure water was found to be good, and thus, the medium selected was pure water (Lot No. A168, Takasugi Seiyaku K.K.).

6.2 Preparation method

The test substance was accurately weighed and suspended in pure water by adding a small amount of pure water at a time into an agate mortar to prepare 0.1, 0.4, 2.0 and 10.0 w/v% solutions. Incidentally, the test substance preparation was carried out once a week.

6.3 Homogeneity test and stability test

For those test substance solutions prepared by the preparation method described above, stability and uniformity tests were carried out at the Hita Laboratory of the Institution. As a result, the 10.0 and 0.05 w/v% solutions prepared were confirmed to be stable in a cool and dark place for 7 days. Furthermore, the homogeneity was found to be good.

For the homogeneity of the test substance solutions prepared, the 10.0 w/v% and 0.05 w/v% solutions immediately after their preparations were sampled at top, middle and bottom layers with n = 3 for each layer, the samples were diluted with methanol, the test substance concentration was measured by using high performance liquid chromatography (HPLC), and the homogeneity was confirmed from the relative standard deviation of the test substance

[redacted]

concentrations at respective sampling sites. For the stability confirmation, the 10.0 w/v% and 0.05 w/v% solutions were stored in a cool and dark place, sampled from the middle layer with n = 3 after 3 days and 7 days, the samples were diluted with methanol, the test substance concentration was measured by using high performance liquid chromatography (HPLC), and the stability was confirmed by finding any change from the concentrations immediately after preparation (results of homogeneity test).

HPLC analysis conditions

(1) Instrument used (HPLC1)

Interface: Model D-7000IF (Hitachi, Ltd.)
Pump: Model L-7100 (Hitachi, Ltd.)
Autosampler: Model L-7200 (Hitachi, Ltd.)
RI detector: Model L-7490 (Hitachi, Ltd.)
Column oven: Model L-5020 (Hitachi, Ltd.)
Date processor: Model D-7000 HPLC System Manager (Hitachi, Ltd.)

(2) Measurement conditions

Column: Shodex Asahipak GF-310HQ 7.6 mm I.D. x 300 mm
Column temperature: 40°C
Mobile phase: methanol
Flow rate: 1 mL/min
Amount injected: 50 μL

7. Administration

A syringe (Terumo Corp.) with a Nelaton catheter (Terumo Corp.) connected was used to carry out forced oral administration everyday in the morning repeatedly for 28 days. Subsequently, a recovery term of 14 days was set.

8. Observations and tests

The day and week calculation system is as follows. The day to start substance administration was set as day 1, the day before the day to start substance administration was set as day −1, and the week when the administration was started was set as week 1. Furthermore, the next day of the final day of substance administration was set as day 1 (recovery), and the week of starting the recovery term was set as week 1 (recovery).

8.1 General condition

[redacted]

The general condition was observed 3 times a day before substance administration (in the morning), during and after substance administration and in the afternoon everyday from day 1 to day 28. During the recovery term, the observation was carried out once a day in the morning every day from day 1 (recovery) to day 14 (recovery).

Incidentally, the symptoms observed were summarized every week, the animal No. of animal showing a symptom was recorded in an individual table (Addendum). Furthermore, the symptoms observed were classified as those observed during the administration term and those in the recovery term, and the number of cases observed in each group was recorded in a group table (Table).

8.2 Bodyweight measurement

The measurement was carried out on day-2 (at the time of grouping) before substance administration, day 1, 3, 8, 12, 17, 21, 26 and 28 during the administration term and day 1 (recovery), 5, 10, and 14 during the recovery term.

Incidentally, to calculate relative weight of organs, the bodyweight measurement was carried out at the end of the administration term and end of the recovery term.

8.3 Feed intake measurement

The measurement was carried out once before substance administration, on day 3, 8, 15, 22, and 28 during the administration term and day 4 (recovery), 8 and 14 during the recovery term.

[redacted]

8.4 Hematological test

The measurements of the following items were carried out on blood or plasma samples collected from the abdominal aorta under ether anesthesia after overnight fasting(16-20 hr) at the end of administration term (excluding the recovery groups) and at the end of the recovery term.

As an anti-coagulant, a 3.2% aqueous solution of sodium citrate was used in the case of measurements of prothrombin time, and activated partial thromboplastin time, and EDTA-2K was used for other measurements.

Item		Method
1) Red blood cell count (RBC)	($\times 10^4/\mu L$)	Electric resistance method
2) White blood cell count (WBC)	($\times 10^2/\mu L$)	Electric resistance method
3) Hemoglobin concentration (Hb)	(g/dL)	Non-cyanohemoglobin method
4) Hematocrit (Ht)	(%)	$\frac{RBC \times MCV}{10^3}$
5) Mean corpuscular volume (MCV)	(fL)	Electric resistance method
6) Mean corpuscular hemoglobin content (MCH)	(pg)	$\frac{Hb}{RBC} \times 10^3$
7) Mean corpuscular hemoglobin concentration (MCHC)	(g/dL)	$\frac{Hb}{Ht} \times 10^2$
8) Platelet count (Platelet)	($\times 10^4/\mu L$)	Electric resistance method
9) Reticulocyte proportion (Reticulo)	(%)	RNA staining
10) Prothrombin time (PT)	(sec)	Magnetic sensor system
11) Activated partial thromboplastin time (APTT)	(sec)	Magnetic sensor system
12) Leukocyte proportion (Differentiation of leukocyte) Band neutrophils (N-Band) Segmented neutrophils (N-Seg) Eosinophils (Eosino) Basophils (Baso) Lymphocytes (Lymph) Monocyte (Mono)	(%)	Wright staining

Instrument used

1-8) Automated general hematological analyzer (Model CELL-DYN 3500, ABOTT LABORATORIES)

9) General hematological testing device (Model ADVIA 120, Bayer Medical)

10, 11) Automated blood coagulation meter (Model KC-10A, AMELUNG)

12) Microscope (Model VANOX, OLYMPUS)

8.5 Hematobiochemical test

From the blood collected at the same time as in the section 8.4, the serum was isolated, and the measurements of the following items were carried out for serum samples prepared.

[redacted]

Item		Method
1) GOT	(IU/L)	UV method (JSCC-based formula)
2) GPT	(IU/L)	UV method (JSCC-based formula)
3) Alkaline phosphatase (ALP)	(IU/L)	p-Nitrophenyl phosphate method
4) Cholinesterase (ChE)	(IU/L)	Butyrylthiocholine iodide method
5) 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 erasure method
8) Blood glucose (glucose)	(mg/dL)	Hexokinase·G-6-PDH method
9) Total protein (T-Protein)	(g/dL)	Biuret method
10) Albumin (Albumin)	(g/dL)	Bromocresol Green method
11) A/G ratio (A/G ratio)		Albumin/(T-Protein – Albumin) (calculated value)
12) Urea nitrogen (BUN)	(mg/dL)	Urease·GIDH method
13) Creatinine (Creatinine)	(mg/dL)	Creatinase·F-DAOS method
14) Total bilirubin (T-Bil)	(mg/dL)	Azobilirubin 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) Chlorine (Cl)	(mEq/L)	Coulometric titration method

Instrument used

1-3), 6-8), 12), 13), 15), 16)	Automated biochemical analyzer (Hitachi Model 7170 Automatic Analyzer)
4), 5), 9), 10), 14)	Automated biochemical analyzer (Hitachi Model 7150 Automatic Analyzer)
17-19)	Electrolyte analyzer (Model PVA-αIII, A&T)

8.6 Urine test

The measurement was carried out once (day 28) during the administration term (excluding recovery groups) and once (day 14 (recovery)) during the recovery term.

For a urine sample (about 16 hr accumulation) collected in an individual metabolic cage (150W×200D×263H mm), the amount and coloration were measured, and the measurements of pH, protein, ketone body, bilirubin, occult blood, glucose and urobilinogen were carried out by using test paper (N-Multistix® Bayer Medical).

8.7 Pathological test

1) Dissection

All cases were observed in detail.

2) Organ weight measurement

[redacted]

For all cases, the weight measurements of the following organs were carried out. Furthermore, relative weights were calculated based on the bodyweight measured at the end.

Liver, kidney, testicles, ovaries, brain, spleen and adrenal gland

3) Histopathological examination

(1) For all cases, the following organs and tissues were collected.

Classification	Organ or tissue
Respiratory system	Trachea, lung
Digestive system	Incisors, esophagus, stomach, intestines (duodenum, rectum), pancreas, liver
Cardiovascular system	Heart
Urinary system	kidney, bladder
Reproductive system	testicle, epididymis, prostate gland, seminal vesicle (including coagulating gland), ovary, uterus and vagina
Nervous system	Brain (cerebrum and cerebellum)
Hematopoietic system	bone marrow (femur), mesenterium lymphatic nodes, spleen, thymus gland
Endocrine system	pituitary gland, thyroid gland (including parathyroid gland), adrenal gland
Sensory organ	eyeball

The organs and tissues collected were fixed in a 10% neutrally buffered formalin solution. Incidentally, the testicle and epididymis were fixed with Bouin's solution.

(2) For the following organs and tissues, paraffin-embedded section specimens were prepared, stained with hematoxylin-eosin staining and observed under an optical microscope.

Study group	Organ or tissue
Medium control group	Stomach (anterior stomach and glandular stomach), intestine (duodenum, jejunum, ileum, cecum, colon and rectum), liver, heart, kidney, spleen and adrenal gland
Medium control recovery group	Liver (male only)
200 mg/kg group	Liver (male only)
1,000 mg/kg group	Stomach (anterior stomach and glandular stomach), intestine

[redacted]

	(duodenum, jejunum, ileum, cecum, colon and rectum), liver, heart, kidney, spleen and adrenal gland
1,000 mg/kg recovery group	Liver (male only)

(3) Following organs and tissues examined as naked eye-observed morbid portions

Study group (animal no.)	Organ or tissue
40 mg/kg group (No. 22)	Kidney
200 mg/kg group (No. 30)	Spleen
1,000 mg/kg recovery group (No. 42)	Spleen

9. Statistical method

The results on bodyweight (except at the time of body removal), feed intake. Hematological tests, hematobiochemical tests, amount of urine and organ weights were tested for equality of variance by the Bartlett method, and if there was equal variance observed at a 5% significance level, a one-way analysis of variance was carried out. If the results of analysis of variance showed a significant difference, a test by the Dunnett method was carried out between the medium control group and respective administration groups.

If no equal variance was observed, a Kruskal-Wallis test was carried out, and if there was a significant difference observed, a test was carried out between the medium control group and respective administration groups by using the non-parametric Dunnett method.

Factors affecting study

1. Unpredictable incident suspected to affect the reliability of the test results

In the hematobiochemical test of one case (No. 2) in the medium control group, the blood glucose showed an abnormally high value. The result was far higher than the background value of the Laboratory. The result was considered as a reference value because of a risk of affecting statistical processing and excluded from the statistical analysis. Incidentally, this was not[MSOffice1] considered to show any effect on the result of evaluation in the study.

The function of the air-conditioner was temporarily suspended for 8 min due to a lighting strike on day 2 of the recovery term causing the humidity elevation (maximum humidity of 71.8%) in the rearing room. As a result of the observation of the general condition carried out subsequently, no abnormal finding was found, and the incident was considered to have no effect on the results of the study.

2. Violation of the study protocol

[redacted]

According to the study protocol, the bottom tray exchange was to be carried out twice a week, but in the medium and high dose groups as well as high dose recovery group, soft stool was observed, and the tray exchange was carried out every day from day 2 of the administration term to day 3 of the recovery term. This incident was not[MSOffice2] considered to cause any effects on the results of evaluation in the study.

3. No environmental factor considered to affect the reliability of the results of the study was observed

Test results

1. General condition (Table 1, Addendum 1)

1.1 During the administration term

Male: soft stool (6/6) in the 200 mg/kg group and soft stool (12/12) in the 1,000 mg/kg groups

<State of appearance of soft stool>

In the 200 mg/kg group, sporadically or continuously observed from day 15 to day 28.

In the 1,000 mg/kg groups, sporadically or continuously observed from day 2 to day 28.

Female: soft stool (2/6) in the 200 mg/kg group and soft stool (12/12) in the 1,000 mg/kg groups

<State of appearance of soft stool>

In the 200 mg/kg group, sporadically observed from day 16 to day 28.

In the 1,000 mg/kg groups, sporadically or continuously observed from day 2 to day 28.

1.2 During the recovery term

Male: soft stool (6/6) in the 1,000 mg/kg group

<State of appearance of soft stool>

In the 1,000 mg/kg group, observed from day 1 to day 3

Female: soft stool (5/6) in the 1,000 mg/kg group

<State of appearance of soft stool>

In the 1,000 mg/kg group, observed from day 1 to day 3

2. Bodyweight (Figure 1, Table 2, Addendum 2)

2.1 During the administration term

Male: in the 1,000 mg/kg group, low value observed on day 12 and low value tendency observed from day 17 to day 28

Female: no abnormality observed

2.2 During the recovery term

Male: in 1,000 mg/kg, low value observed from day 1 to day 14
Female: no abnormality observed

3. Feed intake (Figure 2, Table 3, Addendum 3)

3.1 During the administration term

Both males and females showed no abnormalities.

3.2 During the recovery terms

Male: no abnormality observed
Female: in the 1,000 mg/kg group, high value observed on day 8

4. Hematological tests (Table 4, Addendum 4)

4.1 At the end of the administration term

Male: in the 200 mg/kg group, shortened activated partial thromboplastin time observed
Female: no abnormality observed

4.2 At the end of the recovery term

Both males and females showed no abnormalities.

5. Hematobiochemical tests (Table 5, Addendum 5)

5.1 At the end of the administration term

Male: in the groups of 200 mg/kg or higher dose, reduced albumin observed. In addition, in the 40 mg/kg group, increased alkaline phosphatase observed.
Female: no abnormality observed.

5.2 At the end of the recovery term

Male: in the 1,000 mg/kg group, reduced blood glucose level observed
Female: no abnormality observed

6. Urine tests (Table 6, Addendum 6)

6.1 At the end of the administration term

Both males and females showed no abnormalities

6.2 At the end of the recovery term

Male: in the 1,000 mg/kg group, increased amount of urine observed
Female: no abnormality observed

[redacted]

7. Organ weight (Tables 7 and 8, Addendums 7 and 8)

7.1 At the end of the administration term

Male: no abnormality observed

Female: in the 1,000 mg/kg group, increased relative weight of the liver observed

7.2 At the end of the recovery term

Male: in the 1,000 mg/kg group, increased relative weights of testicle and brain observed

Female: no abnormality observed

8. Dissection (Table 9, Addendum 9)

8.1 At the end of the administration term

Male: in the medium control group, pyelectasia (1/6) of the kidney; in the 40 mg/kg group, pyelectasia (1/6) of the kidney; and in the 200 mg/kg group, whitened section (1/6) of the spleen observed

Female: no abnormality observed

8.2 At the end of the recovery term

Male: in the 1,000 mg/kg group, node in the spleen (1/6) observed

Female: no abnormality observed

9. Histopathological examination (Table 10, Addendum 9)

9.1 At the end of the administration term

Male: in the 1,000 mg/kg group, centrilobular hepatic cell hypertrophy (+, 3/6) and single cell necrosis (+, 4/6) in the liver observed. In addition, in the medium control group, pyelectasia of the kidney (+, 1/6); in the 40 mg/kg group, pyelectasia of the kidney (+, 1/1); and in 200 mg/kg group, small granuloma (+, 1/6) in the liver and local necrosis (++, 1/1) in the spleen was observed

Female: single-occurrence cyst (+, 1/6) in the medulla of the kidney was observed in the medium control group.

9.2 At the end of the recovery term

Male: in the medium control group, small granuloma (+, 1/6) of the liver and in the 1,000 mg/kg group, follicle hypertrophy (++, 1/1) of the spleen observed

Female: no examination carried out

[redacted]

Discussion

The forced oral administration of [redacted] was carried out to Crj: CD (SD) IGS rats at 4 dose levels of 1,000, 200, 40 and 10 mg/kg/day to carry out 28-day toxicity test and 14-day recovery test.

In the present study, no fatal case considered to be attributable to the test substance administration was observed. Moreover, no effects by the test substance administration were observed on the results of feed intake during the administration term, hematological tests, urinary tests and dissection carried out at the end of the administration term.

In the general condition, both males and females of those groups with a dose of 200 mg/kg or higher showed soft stool considered to be caused by the test substance administration. However, no effects were observed on the results of pathological tests for changes in the digestive tract, etc. Furthermore with respect to body weight, the increases were observed to be inhibited in males of the 1,000 mg/kg group from day 12 to day 28.

As a result of the hematobiochemical tests carried out, the males of the 200 mg/kg or higher groups showed reduced albumin, but the changes were all fluctuations within the background value range of the Laboratory[1], the dose-dependency of the results was found to be poor, and consequently, the changes were not considered as an effect of the test substance administration.

In the measurements of organ weights, the relative weight of the liver was observed to be increased in the females of the 1,000 mg/kg group. Furthermore, as a result of the histopathological examination, centrilobular hepatic cell hypertrophy and single cell necrosis of the liver were observed in the males of the 1,000 mg/kg group. Those changes were considered to be attributable to the effects of the test substance administration on the liver.

In addition, there were changes other than those described above observed at the end of the administration term, but they were observed only sporadically, no dose-dependency was observed, and they were considered to be accidental changes.

In the recovery test, the soft stool in both males and females of the 1,000 mg/kg group was continued during the recovery term, but both males and females showed no soft stool on day 4 showing that it was a recoverable change. In addition, the bodyweight was found to remain low in the males of the 1,000 mg/kg group, but the increases were found to be roughly the same as those observed in the medium control group, and consequently, it was considered to be a recoverable change. In addition, several items showed sporadic changes, but they were not observed at the end of the administration term; furthermore, no related changes were observed, and consequently, they were considered to be accidental changes.

As effects of the administration of [redacted] soft stool, bodyweight increase inhibition and changes in the liver were suggested from those results obtained, and those changes

[redacted]

were considered all recoverable changes. Incidentally, the NOEL of [redacted] in rats under the conditions of the present study was estimated to be 40 mg/kg/day because of soft stool observed in both males and females of the groups with a dose of 200 mg/kg/day or higher.

1) Background value of the Laboratory (at the end of the administration term): medium/pure water (containing gum arabic and CMC)

Item	Sex	n	Mean ± 2 S.D.
Albumin (g/dL)	Male	228	2.7 ± 0.2

[redacted]

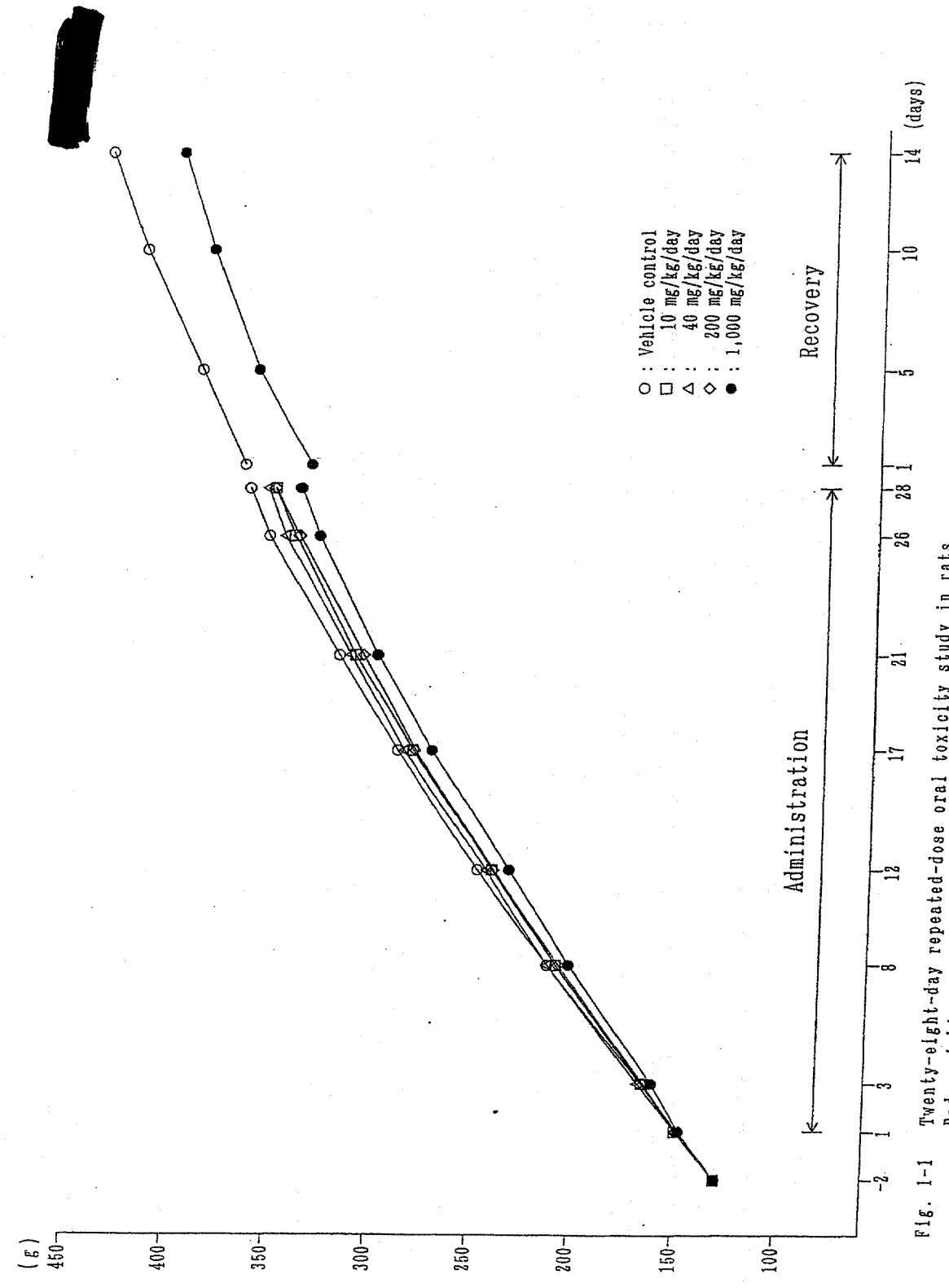


Fig. 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Male

[redacted]

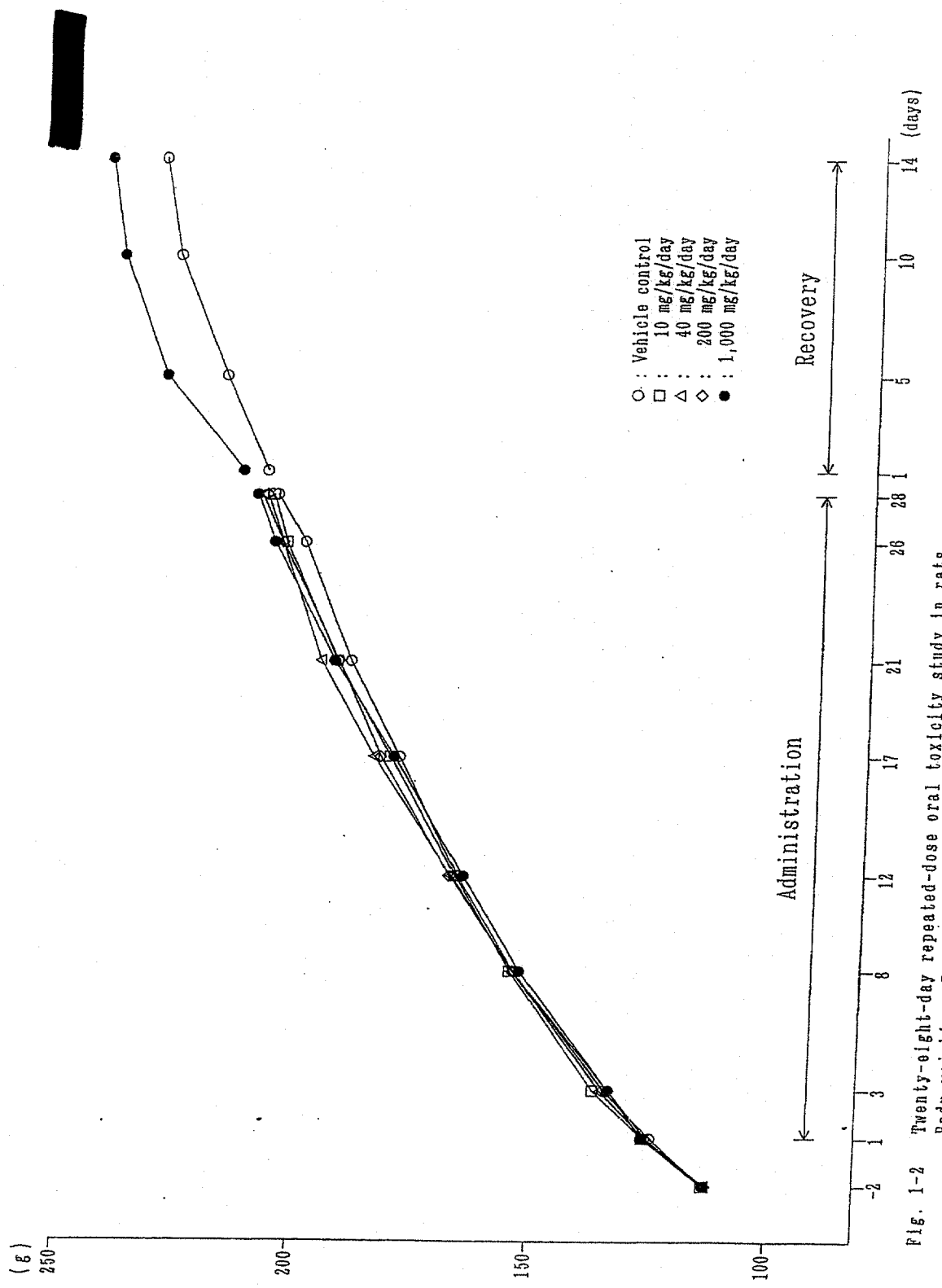


Fig. 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Female

[redacted]

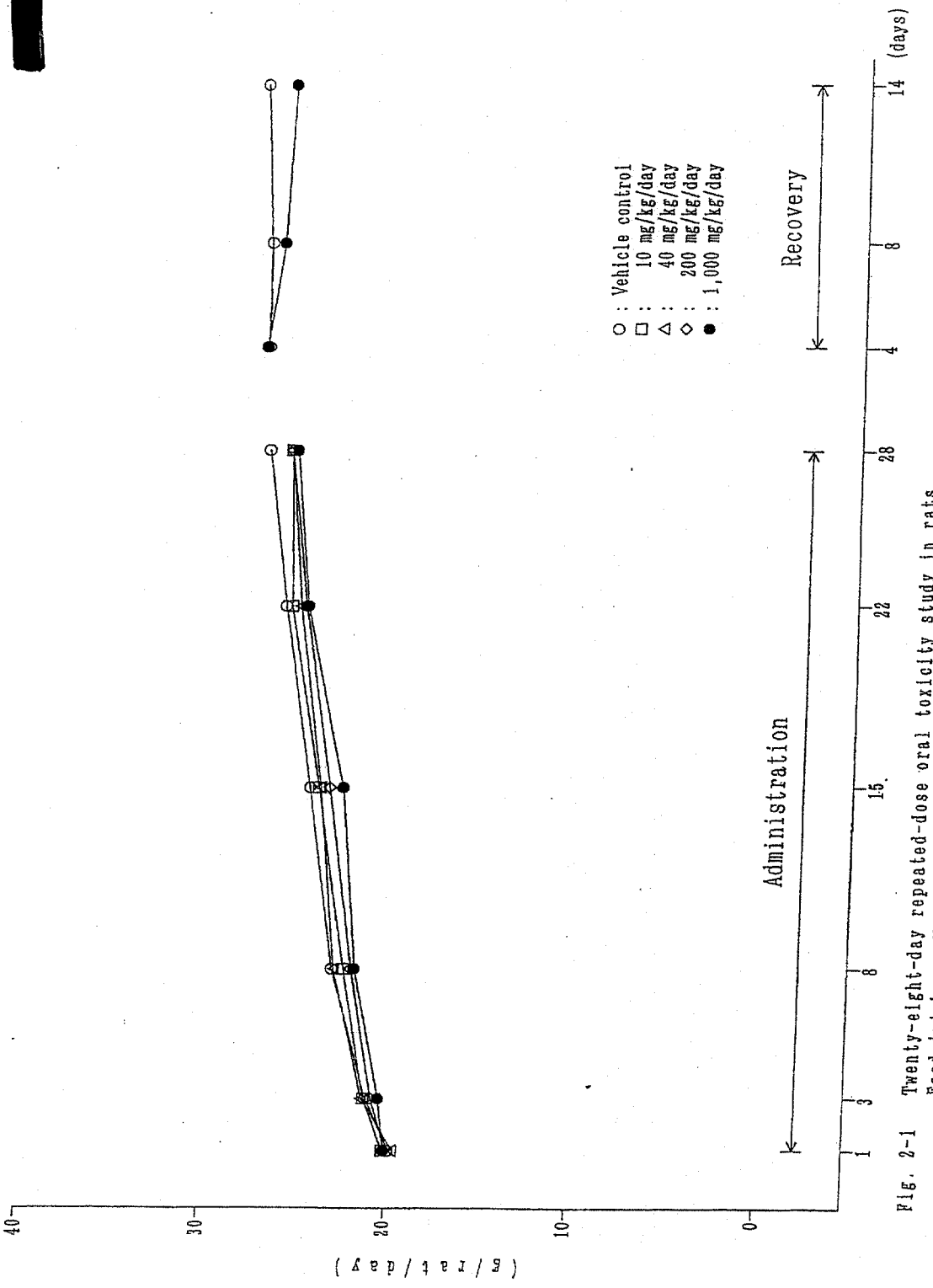


Fig. 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food Intakes : Male

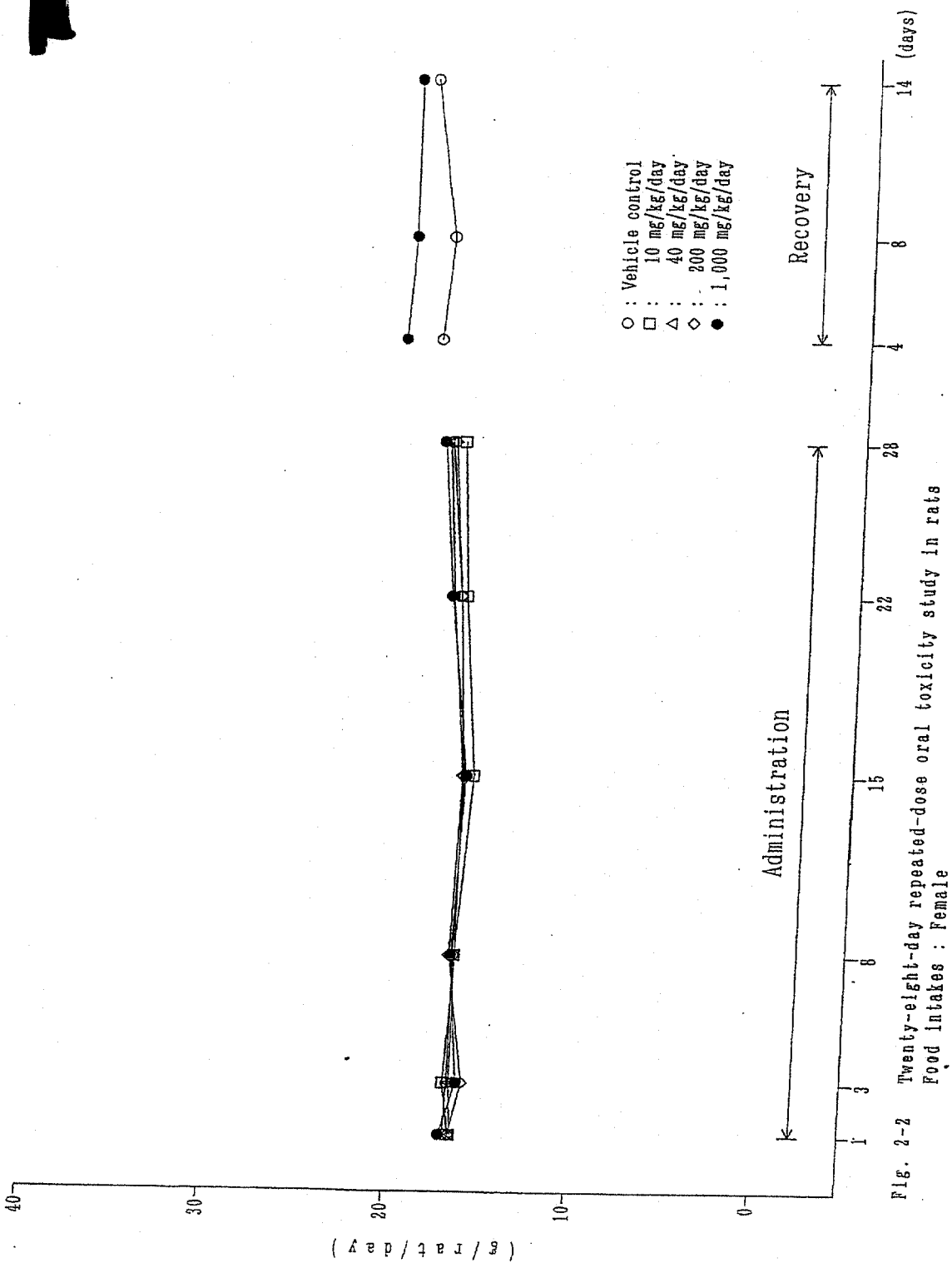


Fig. 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Food Intakes : Female

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)	10	40	200	1,000	1,000 (R)	VC	1,000
Male		ta 6[a)]	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6
	No abnormalities detected	6	6	6	6				6	
	Soft stool					6	6	6		6
Female		ta 6[a)]	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6	ta 6
	No abnormalities detected	6	6	6	6	4			6	1
	Soft stool					2	6	6		5

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

[redacted]

Table 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period								
			-2	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	12	129.4 ± 4.1	148.4 ± 5.9	166.4 ± 6.8	214.0 ± 9.8	249.9 ± 12.3	291.4 ± 13.8	321.5 ± 14.6	357.4 ± 17.2	367.7 ± 16.6
	10	6	129.8 ± 4.1	149.3 ± 4.5	166.1 ± 4.9	209.8 ± 10.0	242.2 ± 11.1	283.5 ± 12.6	313.5 ± 16.8	344.6 ± 19.2	355.0 ± 20.5
	40	6	129.8 ± 2.6	149.1 ± 4.6	168.3 ± 5.2	214.0 ± 8.3	245.4 ± 8.6	288.1 ± 8.4	315.8 ± 12.1	349.4 ± 13.7	358.6 ± 15.1
	200	6	129.3 ± 4.1	149.2 ± 5.0	165.3 ± 7.0	208.5 ± 12.4	241.5 ± 17.5	282.3 ± 23.6	309.4 ± 29.2	342.6 ± 34.2	354.8 ± 36.8
	1,000	12	129.5 ± 4.2	147.5 ± 4.3	161.5 ± 4.6	203.4 ± 7.1	233.6** ± 10.6	273.9 ± 14.9	302.5 ± 19.1	332.8 ± 23.0	342.3 ± 24.6
Female	Vehicle control	12	112.6 ± 3.8	124.1 ± 6.3	134.2 ± 5.7	154.5 ± 8.0	166.8 ± 8.1	179.9 ± 10.2	190.8 ± 11.8	201.1 ± 11.9	207.2 ± 13.6
	10	6	112.9 ± 4.2	125.7 ± 4.7	136.6 ± 5.4	155.3 ± 12.2	167.2 ± 17.3	181.8 ± 20.5	193.6 ± 24.2	205.0 ± 24.1	208.0 ± 26.6
	40	6	112.4 ± 4.4	125.2 ± 6.2	135.1 ± 6.3	154.7 ± 9.0	168.1 ± 11.4	185.3 ± 13.3	197.0 ± 16.3	205.9 ± 14.3	210.5 ± 18.3
	200	6	112.2 ± 3.7	125.0 ± 4.2	133.2 ± 4.7	154.7 ± 5.6	168.4 ± 7.8	183.8 ± 11.1	193.3 ± 10.6	205.8 ± 14.0	209.3 ± 10.7
	1,000	12	112.4 ± 3.9	125.9 ± 4.6	133.2 ± 4.5	153.2 ± 6.9	165.6 ± 9.1	181.0 ± 9.6	194.2 ± 10.6	207.5 ± 13.1	211.4 ± 13.8

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

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

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period			
			1	5	10	14 (days)
Male	Vehicle control	6	370.5 ± 13.4	392.8 ± 15.1	421.2 ± 13.7	440.0 ± 14.9
	1,000	6	337.9** ± 20.8	365.0* ± 19.7	388.4* ± 23.9	404.1** ± 22.6
Female	Vehicle control	6	209.4 ± 15.9	218.6 ± 16.9	229.0 ± 14.2	232.7 ± 14.9
	1,000	6	214.5 ± 16.6	231.1 ± 17.1	241.2 ± 22.8	244.6 ± 25.7

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

Table 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats
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	12	19.8 ± 1.8	21.2 ± 1.8	23.2 ± 1.8	24.7 ± 2.1	26.3 ± 1.8	27.4 ± 1.7
	10	6	20.2 ± 1.1	21.3 ± 1.1	22.6 ± 1.6	24.2 ± 1.7	26.0 ± 2.3	26.2 ± 2.7
	40	6	19.6 ± 1.4	21.4 ± 1.2	23.1 ± 1.2	24.1 ± 1.1	25.5 ± 1.2	26.2 ± 1.8
	200	6	20.0 ± 1.0	20.9 ± 1.4	22.2 ± 1.9	23.6 ± 2.6	25.2 ± 3.4	26.2 ± 3.8
	1,000	12	20.1 ± 1.3	20.5 ± 0.8	22.0 ± 0.8	22.9 ± 1.0	25.1 ± 1.6	25.9 ± 2.2
Female	Vehicle control	12	16.7 ± 1.3	16.6 ± 1.1	16.6 ± 1.0	16.4 ± 1.0	17.0 ± 1.1	17.8 ± 1.3
	10	6	16.4 ± 1.0	16.8 ± 1.0	16.5 ± 1.0	15.9 ± 1.4	16.7 ± 1.7	17.1 ± 1.4
	40	6	16.3 ± 1.2	16.5 ± 1.5	16.5 ± 1.4	16.5 ± 1.5	17.4 ± 1.7	17.9 ± 2.3
	200	6	16.4 ± 0.4	15.8 ± 0.7	16.8 ± 1.0	16.5 ± 1.2	17.0 ± 1.3	17.6 ± 1.2
	1,000	12	16.9 ± 1.3	16.1 ± 1.2	16.7 ± 1.3	16.3 ± 1.5	17.5 ± 1.8	18.2 ± 1.9

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

Table 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats
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	6	27.6 ± 1.5	27.6 ± 1.4	28.0 ± 1.8
	1,000	6	27.7 ± 2.1	26.9 ± 1.7	26.5 ± 1.4
Female	Vehicle control	6	18.6 ± 1.1	18.1 ± 1.1	19.3 ± 1.7
	1,000	6	20.6 ± 2.1	20.2* ± 2.0	20.2 ± 1.9

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

Table 4-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

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	6	757 ± 15	90 ± 21	14.8 ± 0.4	46.1 ± 0.9	60.9 ± 1.0	19.6 ± 0.4	32.2 ± 0.4	114.3 ± 6.9	2.6 ±0.4	21.1 ± 2.9	36.4 ± 3.0
	10	6	778 ± 37	89 ± 14	15.0 ± 0.4	46.9 ± 1.6	60.3 ± 2.0	19.3 ± 0.8	32.1 ± 0.4	110.5 ± 3.8	2.6 ±0.3	20.9 ± 6.3	34.5 ± 3.9
	40	6	769 ± 26	92 ± 13	15.1 ± 0.4	46.1 ± 1.5	60.0 ± 1.4	19.6 ± 0.4	32.6 ± 0.4	112.9 ± 7.5	2.6 ±0.2	18.3 ± 3.3	33.2 ± 2.7
	200	6	753 ± 13	97 ± 20	14.7 ± 0.4	45.0 ± 0.9	59.8 ± 1.7	19.5 ± 0.7	32.6 ± 0.3	105.2 ± 12.4	2.7 ±0.3	17.4 ± 3.9	28.9** ± 6.1
	1,000	6	757 ± 29	96 ± 18	15.1 ± 0.3	46.5 ± 0.9	61.5 ± 1.6	19.9 ± 0.5	32.4 ± 0.3	105.7 ± 9.9	2.7 ±0.4	16.3 ± 1.8	32.8 ± 2.2
	Recovery												
	Vehicle control	6	796 ± 30	113 ± 22	14.9 ± 0.5	45.9 ± 2.3	57.6 ± 1.6	18.8 ± 0.5	32.6 ± 0.7	113.1 ± 4.8	2.4 ±0.4	17.3 ± 3.5	31.2 ± 3.1
	1,000	6	803 ± 31	105 ± 21	15.1 ± 0.3	46.2 ± 1.7	57.5 ± 1.0	18.8 ± 0.5	32.7 ± 0.7	115.8 ± 9.0	2.4 ±0.3	18.6 ± 4.5	36.9 ± 6.1
Female	Vehicle control	6	793 ± 34	82 ± 12	15.3 ± 0.3	46.3 ± 1.1	58.4 ± 1.6	19.3 ± 0.6	33.0 ± 0.2	109.2 ± 5.7	2.1 ±0.4	13.6 ± 0.7	23.8 ± 0.7
	10	6	785 ± 32	95 ± 21	15.4 ± 0.5	46.9 ± 1.3	59.8 ± 1.1	19.6 ± 0.4	32.8 ± 0.2	113.7 ± 16.0	1.8 ±0.2	13.7 ± 1.0	25.4 ± 1.3
	40	6	784 ± 17	88 ± 15	15.5 ± 0.3	46.8 ± 1.0	59.8 ± 1.3	19.8 ± 0.4	33.1 ± 0.2	110.1 ± 10.6	2.0 ±0.2	13.4 ± 1.0	24.7 ± 2.3
	200	6	802 ± 43	85 ± 29	15.3 ± 0.6	46.4 ± 2.1	57.9 ± 1.0	19.1 ± 0.5	33.0 ± 0.3	114.2 ± 2.9	2.0 ±0.2	13.4 ± 1.2	25.5 ± 2.0
	1,000	6	783 ± 22	93 ± 31	15.1 ± 0.4	45.8 ± 1.5	58.5 ± 1.0	19.3 ± 0.2	32.9 ± 0.4	110.1 ± 9.2	1.9 ±0.3	14.0 ± 0.8	24.4 ± 1.6
	Recovery												
	Vehicle control	6	808 ± 35	81 ± 14	15.1 ± 0.7	45.1 ± 1.9	55.8 ± 1.3	18.7 ± 0.4	33.5 ± 0.4	124.6 ± 8.5	2.1 ±0.2	13.3 ± 0.4	24.8 ± 2.1
	1,000	6	789 ± 30	81 ± 20	14.8 ± 0.6	44.1 ± 2.0	55.8 ± 1.0	18.8 ± 0.4	33.6 ± 0.3	127.1 ± 11.7	2.4 ±0.6	13.0 ± 0.3	24.9 ± 3.1

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

Table 4-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

Sex	Exp.group (mg/kg/day)	Number of animals	Differentiation of leukocyte (%)					
			N-Band	N-Seg	Eosino	Baso	Lymph	Mono
Male	Vehicle control	6	2.0 ±0.8	9.0 ± 3.4	0.6 ±0.4	0.0 ±0.0	88.0 ± 4.0	0.4 ±0.7
	10	6	2.2 ±1.7	10.3 ± 4.3	0.9 ±0.4	0.0 ±0.0	86.3 ± 5.4	0.4 ±0.5
	40	6	3.1 ±0.9	10.1 ± 5.1	1.0 ±0.6	0.1 ±0.2	85.3 ± 5.7	0.4 ±0.6
	200	6	3.1 ±1.7	10.3 ± 2.9	0.9 ±0.9	0.0 ±0.0	85.4 ± 3.9	0.3 ±0.3
	1,000	6	2.2 ±1.1	12.4 ± 5.2	1.1 ±0.5	0.0 ±0.0	84.2 ± 5.8	0.2 ±0.3
	Recovery							
	Vehicle control	6	1.2 ±0.6	10.0 ± 2.0	0.7 ±0.5	0.0 ±0.0	87.6 ± 2.4	0.6 ±0.6
	1,000	6	1.9 ±0.9	7.8 ± 2.8	0.7 ±0.6	0.0 ±0.0	88.8 ± 3.8	0.8 ±0.5
Female	Vehicle control	6	1.7 ±1.5	8.7 ± 3.5	0.5 ±0.4	0.0 ±0.0	88.8 ± 4.0	0.4 ±0.4
	10	6	1.3 ±0.4	9.1 ± 2.2	0.8 ±0.4	0.0 ±0.0	88.5 ± 2.5	0.3 ±0.4
	40	6	1.3 ±1.1	10.2 ± 5.1	0.3 ±0.4	0.0 ±0.0	87.9 ± 5.0	0.3 ±0.3
	200	6	1.8 ±1.4	8.8 ± 4.9	0.9 ±0.7	0.1 ±0.2	88.5 ± 6.3	0.0 ±0.0
	1,000	6	1.9 ±0.9	10.5 ± 2.1	0.8 ±0.5	0.0 ±0.0	86.4 ± 2.8	0.4 ±0.2
	Recovery							
	Vehicle control	6	2.0 ±0.9	11.1 ± 2.9	0.8 ±0.8	0.0 ±0.0	85.3 ± 4.5	0.8 ±0.7
	1,000	6	1.8 ±0.6	8.9 ± 2.7	1.3 ±0.8	0.0 ±0.0	87.9 ± 3.4	0.3 ±0.5

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

Table 5-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

Sex	Exp.group (mg/kg/day)	Number of animals	GOT (IU/L)	GPT (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	6	74 ± 9	26 ± 3	422 ± 53	50 ± 15	0.9 ±0.5	56 ± 7	65 ±14	128 ± 10(5)	5.4 ±0.1	2.9 ±0.1	1.15 ±0.07
	10	6	79 ± 8	27 ± 5	470 ± 80	45 ± 8	1.1 ±0.5	51 ±15	58 ±24	131 ± 13	5.4 ±0.2	2.8 ±0.1	1.10 ±0.08
	40	6	71 ± 8	27 ± 2	518* ± 49	50 ± 9	0.8 ±0.6	47 ± 8	50 ±12	132 ± 24	5.3 ±0.2	2.8 ±0.1	1.10 ±0.04
	200	6	80 ±13	30 ± 5	459 ± 65	45 ± 10	0.6 ±0.3	46 ± 7	76 ±32	129 ± 9	5.3 ±0.2	2.6** ±0.1	1.02 ±0.12
	1,000	6	74 ± 6	25 ± 3	386 ± 52	49 ± 17	0.6 ±0.2	39 ± 6	65 ±29	118 ± 9	5.2 ±0.1	2.7* ±0.1	1.10 ±0.06
	Recovery												
	Vehicle control	6	79 ± 9	24 ± 2	321 ± 40	49 ± 8	0.7 ±0.3	55 ±13	71 ±16	138 ± 15	5.4 ±0.2	2.7 ±0.1	0.95 ±0.04
	1,000	6	84 ±15	27 ± 3	379 ± 63	49 ± 14	0.9 ±0.2	42 ±11	68 ±18	120* ± 12	5.3 ±0.3	2.7 ±0.1	1.00 ±0.06
Female	Vehicle control	6	70 ± 4	20 ± 1	240 ± 59	283 ± 35	1.0 ±0.4	74 ± 8	22 ± 6	121 ± 20	5.5 ±0.2	2.9 ±0.1	1.15 ±0.05
	10	6	81 ±11	25 ±10	313 ± 58	321 ±147	0.9 ±0.3	60 ± 8	25 ± 4	128 ± 14	5.6 ±0.4	3.0 ±0.2	1.14 ±0.07
	40	6	81 ±11	23 ± 4	274 ± 44	287 ±107	0.9 ±0.3	72 ± 7	21 ±11	121 ± 13	5.6 ±0.4	3.0 ±0.2	1.19 ±0.10
	200	6	70 ± 6	18 ± 2	227 ± 40	225 ± 72	0.9 ±0.4	80 ±22	28 ±14	120 ± 9	5.7 ±0.3	3.1 ±0.2	1.20 ±0.05
	1,000	6	72 ±16	19 ± 3	251 ± 61	262 ± 30	1.2 ±0.4	68 ±11	30 ±12	120 ± 23	5.5 ±0.1	3.0 ±0.1	1.22 ±0.12
	Recovery												
	Vehicle control	6	86 ±18	22 ± 4	214 ± 5	369 ±158	0.9 ±0.3	66 ±11	23 ± 4	125 ± 10	5.7 ±0.3	2.9 ±0.2	1.05 ±0.06
	1,000	6	82 ±16	24 ± 6	192 ± 23	315 ± 64	0.8 ±0.5	61 ±10	19 ± 7	128 ± 7	5.7 ±0.2	2.9 ±0.2	1.05 ±0.11

Mean ±S.D.
Figure(s) in parentheses indicate number of animals used for mean calculation.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 5-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

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	6	13.8 ± 1.1	0.22 ±0.02	0.09 ±0.02	10.0 ± 0.2	8.2 ±0.4	142 ± 1	4.3 ±0.1	105.4 ± 1.3
	10	6	12.8 ± 0.9	0.18 ±0.03	0.09 ±0.01	10.1 ± 0.2	8.2 ±0.4	142 ± 1	4.3 ±0.3	106.2 ± 1.9
	40	6	13.7 ± 1.2	0.20 ±0.03	0.08 ±0.02	10.1 ± 0.1	7.9 ±0.4	141 ± 1	4.3 ±0.4	105.7 ± 1.1
	200	6	14.4 ± 1.8	0.19 ±0.01	0.08 ±0.01	10.0 ± 0.3	7.8 ±0.5	143 ± 1	4.3 ±0.3	106.8 ± 1.9
	1,000	6	14.5 ± 1.9	0.22 ±0.02	0.08 ±0.01	9.9 ± 0.1	8.0 ±0.4	142 ± 1	4.2 ±0.3	106.1 ± 1.5
	Recovery									
	Vehicle control	6	15.9 ± 1.2	0.25 ±0.03	0.11 ±0.02	9.9 ± 0.3	7.2 ±0.5	141 ± 1	4.3 ±0.3	105.1 ± 2.0
	1,000	6	14.7 ± 1.6	0.23 ±0.03	0.09 ±0.01	9.9 ± 0.2	7.1 ±0.5	141 ± 1	4.4 ±0.4	105.4 ± 1.1
Female	Vehicle control	6	14.7 ± 1.9	0.21 ±0.02	0.09 ±0.01	9.8 ± 0.3	7.2 ±0.4	142 ± 1	3.9 ±0.4	108.4 ± 1.2
	10	6	16.1 ± 1.5	0.22 ±0.02	0.11 ±0.03	9.9 ± 0.1	7.8 ±0.8	141 ± 1	4.0 ±0.4	107.8 ± 0.7
	40	6	13.6 ± 1.9	0.22 ±0.02	0.11 ±0.01	10.0 ± 0.2	7.4 ±0.6	141 ± 1	4.1 ±0.4	107.8 ± 0.3
	200	6	15.6 ± 1.2	0.23 ±0.02	0.09 ±0.02	10.0 ± 0.2	7.3 ±0.6	142 ± 1	3.9 ±0.2	108.9 ± 1.3
	1,000	6	15.9 ± 2.6	0.22 ±0.03	0.08 ±0.02	9.9 ± 0.2	7.7 ±0.8	142 ± 1	4.1 ±0.3	107.9 ± 1.3
	Recovery									
	Vehicle control	6	17.2 ± 2.4	0.26 ±0.03	0.12 ±0.02	9.8 ± 0.3	7.1 ±0.7	140 ± 1	4.3 ±0.2	107.1 ± 1.2
	1,000	6	17.2 ± 2.7	0.28 ±0.04	0.12 ±0.02	9.8 ± 0.3	6.8 ±0.4	140 ± 1	4.1 ±0.4	108.1 ± 1.8

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

Table 6 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses

Sex	Exp.group (mg/kg/day)	Number of animals	Volume[a] (mL)	Color SY	Color Y	Color B	pH 6.0	pH 6.5	pH 7.0	Protein −	Protein ±	Protein +	Protein ++	Ketones −	Ketones ±	Ketones +	Bilirubin −	Occult Blood −	Occult Blood ±	Occult Blood +	Occult Blood ++	Glucose −	Urobilinogen (EU/dL) 0.1
Male	Vehicle control	6	13 ± 8	3	3	0	0	4	2	0	2	4	0	1	4	1	6	5	1	0	0	6	6
	10	6	16 ± 8	4	2	0	0	5	1	0	3	3	0	1	5	0	6	6	0	0	0	6	6
	40	6	18 ± 6	4	2	0	0	5	1	0	4	2	0	2	4	0	6	5	1	0	0	6	6
	200	6	19 ± 5	4	2	0	0	2	4	0	4	2	0	0	5	1	6	5	1	0	0	6	6
	1,000	6	18 ± 6	5	1	0	0	5	1	0	4	2	0	1	5	0	6	5	1	0	0	6	6
	Recovery																						
	Vehicle control	6	9 ± 2	0	6	0	2	4	0	0	2	4	0	0	5	1	6	6	0	0	0	6	6
	1,000	6	18 * ± 8	2	4	0	1	3	2	0	3	3	0	1	3	2	6	4	1	1	0	6	6
Female	Vehicle control	6	10 ± 2	3	3	0	0	5	1	0	6	0	0	6	0	0	6	6	0	0	0	6	6
	10	6	5 ± 3	1	5	0	0	5	1	0	1	4	1	6	0	0	6	6	0	0	0	6	6
	40	6	11 ± 6	4	2	0	0	5	1	1	4	1	0	6	0	0	6	6	0	0	0	6	6
	200	6	7 ± 4	1	4	1	0	5	1	0	2	4	0	6	0	0	6	5	0	0	1	6	6
	1,000	6	8 ± 4	2	4	0	0	5	1	0	5	1	0	6	0	0	6	6	0	0	0	6	6
	Recovery																						
	Vehicle control	6	6 ± 2	0	6	0	3	2	1	1	3	2	0	6	0	0	6	6	0	0	0	6	6
	1,000	6	7 ± 3	0	6	0	3	3	0	1	4	0	1	6	0	0	6	5	0	0	1	6	6

a) Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.
SY, Slightly yellow.
Y, Yellow.
B, Brown.

Table 7 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of absolute organ weights

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g)	Kidney (g)	Testis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Adrenal (mg)	Body weight a) (g)
Male	Vehicle control	6	10.29 ± 0.90	2.73 ± 0.16	2.84 ± 0.28	– –	1.98 ± 0.06	0.65 ± 0.07	52.5 ± 7.6	340.5 ± 19.8
	10	6	9.78 ± 1.00	2.71 ± 0.23	2.92 ± 0.14	– –	1.92 ± 0.06	0.65 ± 0.10	51.8 ± 8.8	326.6 ± 19.7
	40	6	10.12 ± 0.87	2.80 ± 0.31	2.99 ± 0.28	– –	2.05 ± 0.04	0.62 ± 0.08	52.2 ± 8.5	334.0 ± 13.1
	200	6	10.46 ± 1.91	2.80 ± 0.33	2.79 ± 0.23	– –	1.93 ± 0.04	0.68 ± 0.17	47.9 ± 4.5	327.0 ± 32.3
	1,000	6	10.37 ± 1.00	2.62 ± 0.23	2.74 ± 0.11	– –	1.98 ± 0.08	0.53 ± 0.08	51.5 ± 4.4	324.3 ± 27.9
	Recovery									
	Vehicle control	6	11.90 ± 1.18	2.91 ± 0.32	3.05 ± 0.19	– –	2.00 ± 0.08	0.72 ± 0.12	53.7 ± 7.9	412.4 ± 17.1
	1,000	6	10.52 ± 1.12	2.91 ± 0.27	3.11 ± 0.41	– –	2.01 ± 0.04	0.75 ± 0.24	52.8 ± 4.8	379.6 ± 23.1
Female	Vehicle control	6	5.76 ± 0.45	1.64 ± 0.07	– –	74.0 ± 8.9	1.79 ± 0.07	0.42 ± 0.07	60.5 ± 10.0	193.9 ± 12.6
	10	6	5.64 ± 0.56	1.57 ± 0.08	– –	72.2 ± 9.3	1.85 ± 0.06	0.42 ± 0.11	65.0 ± 6.9	193.0 ± 22.3
	40	6	5.76 ± 0.66	1.66 ± 0.19	– –	74.8 ± 10.4	1.76 ± 0.09	0.41 ± 0.06	61.3 ± 7.4	197.5 ± 16.2
	200	6	5.95 ± 0.62	1.57 ± 0.09	– –	75.1 ± 10.1	1.83 ± 0.06	0.40 ± 0.04	62.4 ± 7.2	195.2 ± 8.5
	1,000	6	6.44 ± 0.55	1.62 ± 0.13	– –	70.0 ± 9.9	1.78 ± 0.04	0.36 ± 0.02	62.7 ± 7.6	197.8 ± 8.7
	Recovery									
	Vehicle control	6	6.13 ± 0.44	1.59 ± 0.10	– –	84.4 ± 16.6	1.83 ± 0.07	0.43 ± 0.04	71.9 ± 8.6	218.5 ± 12.4
	1,000	6	6.33 ± 0.60	1.67 ± 0.20	– –	88.5 ± 14.9	1.83 ± 0.04	0.45 ± 0.05	76.6 ± 6.6	231.2 ± 22.2

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

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g/100g)	Kidney (g/100g)	Testis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Adrenal (mg/100g)	Body weight a) (g)
Male	Vehicle control	6	3.02 ±0.20	0.80 ±0.06	0.84 ±0.07	–	0.58 ±0.05	0.19 ±0.02	15.4 ± 1.9	340.5 ± 19.8
	10	6	2.99 ±0.13	0.83 ±0.05	0.90 ±0.06	–	0.59 ±0.05	0.20 ±0.03	15.9 ± 2.7	326.6 ± 19.7
	40	6	3.03 ±0.22	0.84 ±0.07	0.89 ±0.09	–	0.61 ±0.03	0.19 ±0.02	15.6 ± 2.4	334.0 ± 13.1
	200	6	3.18 ±0.27	0.86 ±0.06	0.86 ±0.11	–	0.60 ±0.05	0.21 ±0.03	14.7 ± 1.7	327.0 ± 32.3
	1,000	6	3.20 ±0.10	0.81 ±0.03	0.85 ±0.08	–	0.62 ±0.07	0.16 ±0.02	16.0 ± 1.6	324.3 ± 27.9
	Recovery									
	Vehicle control	6	2.88 ±0.20	0.71 ±0.06	0.74 ±0.04	–	0.49 ±0.03	0.17 ±0.02	13.0 ± 1.9	412.4 ± 17.1
	1,000	6	2.77 ±0.22	0.77 ±0.08	0.82* ±0.08	–	0.53* ±0.04	0.20 ±0.07	13.9 ± 1.1	379.6 ± 23.1
Female	Vehicle control	6	2.97 ±0.11	0.85 ±0.05	–	38.2 ± 3.9	0.92 ±0.06	0.22 ±0.04	31.1 ± 4.0	193.9 ± 12.6
	10	6	2.93 ±0.13	0.82 ±0.08	–	37.4 ± 1.3	0.97 ±0.10	0.21 ±0.04	33.9 ± 3.6	193.0 ± 22.3
	40	6	2.91 ±0.14	0.84 ±0.05	–	37.8 ± 3.5	0.90 ±0.06	0.21 ±0.02	31.1 ± 3.0	197.5 ± 16.2
	200	6	3.04 ±0.19	0.80 ±0.05	–	38.5 ± 5.4	0.94 ±0.05	0.20 ±0.02	32.1 ± 4.7	195.2 ± 8.5
	1,000	6	3.26* ±0.20	0.82 ±0.04	–	35.4 ± 4.4	0.90 ±0.04	0.18 ±0.00	31.7 ± 3.1	197.8 ± 8.7
	Recovery									
	Vehicle control	6	2.80 ±0.14	0.73 ±0.04	–	38.5 ± 6.3	0.84 ±0.04	0.20 ±0.02	32.8 ± 2.5	218.5 ± 12.4
	1,000	6	2.74 ±0.21	0.72 ±0.03	–	38.2 ± 3.9	0.80 ±0.07	0.20 ±0.02	33.4 ± 4.0	231.2 ± 22.2

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

Findings	Male							Female							
	Vehicle control	Vehicle control (Recovery)	10	40	200	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	10	40	200	1,000	1,000 (Recovery)	(mg/kg/day)
	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
	6[a)]	6	6	6	6	6	6	6	6	6	6	6	6	6	
No abnormalities detected	5	6	6	5	5	6	5	6	6	6	6	6	6	6	
Kidney															
Pelvic dilatation	1	0	0	1	0	0	0	0	0	0	0	0	0	0	
Spleen															
Nodule	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
Whitish region	0	0	0	0	1	0	0	0	0	0	0	0	0	0	

ta, terminal autopsy.
a) Number of animals examined.

Table 10-1 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)	10	40	200	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	10	40	200	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		6[a)]	6	6	6	6	6	6	6	6	6	6	6	6	6	
Forestomach																
No abnormalities detected		6/6[b)]	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Glandular stomach																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Duodenum																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Jejunum																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Ileum																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Cecum																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Colon																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Rectum																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Liver																
No abnormalities detected		6/6	5/6	—	—	5/6	1/6	6/6	6/6	—	—	—	—	6/6	—	
Centrilobular hypertrophy of hepatocytes	+	0/6	0/6	—	—	0/6	3/6	0/6	0/6	—	—	—	—	0/6	—	
Microgranuloma	+	0/6	1/6	—	—	1/6	0/6	0/6	0/6	—	—	—	—	0/6	—	
Single cell necrosis of hepatocytes	+	0/6	0/6	—	—	0/6	4/6	0/6	0/6	—	—	—	—	0/6	—	

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

Table 10-2 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)	10	40	200	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	10	40	200	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		6[a)]	6	6	6	6	6	6	6	6	6	6	6	6	6	
Heart																
No abnormalities detected		6/6[b)]	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	
Kidney																
No abnormalities detected		5/6	—	—	0/1	—	6/6	—	5/6	—	—	—	—	6/6	—	
Pelvic dilatation	+	1/6	—	—	1/1	—	0/6	—	0/6	—	—	—	—	0/6	—	
Solitary cyst in medulla	+	0/6	—	—	0/1	—	0/6	—	1/6	—	—	—	—	0/6	—	
Spleen																
No abnormalities detected		6/6	—	—	—	0/1	6/6	0/1	6/6	—	—	—	—	6/6	—	
Focal necrosis	++	0/6	—	—	—	1/1	0/6	0/1	0/6	—	—	—	—	0/6	—	
Follicular hypertrophy	++	0/6	—	—	—	0/1	0/6	1/1	0/6	—	—	—	—	0/6	—	
Adrenal																
No abnormalities detected		6/6	—	—	—	—	6/6	—	6/6	—	—	—	—	6/6	—	

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

Attached document

Physicochemical test report

December 5, 2003, Person in charge of analysis: Yoshiharu Hara

[redacted]

Study object

A stability test is to be carried out for the test substance used in "Rat 28-day repeated oral administration toxicity test of [redacted] in rats" [redacted] during the administration term. Furthermore, the homogeneity and stability are to be tested for the test substance in its preparation solutions.

Test item

Stability test for test substance

Homogeneity and stability test of test substance in its preparation solution

Measurement date

Test substance stability test	June 4, 2003 (before the start of administration)
	August 27, 2003 (after the end of administration)
Stability test of test substance in preparation solution	July 1, 2003
	- July 8, 2003
Homogeneity test of test substance in preparation solution	July 1, 2003

Test results

The test substance used in "Rat 28-day repeated oral administration toxicity test of [redacted] in rats" [redacted] was found to be stable during the administration term.

The test substance in the preparation solution was found to be stable for 7 days after preparation. Furthermore, the relative standard deviation of the test substance concentrations at various sampling positions was less than 5% confirming the solution has good homogeneity.

[redacted]

1. Test materials

1.1 Test substance

1) Name

[redacted]

2) Lot no.

[redacted]

3) Source

DuPont K.K.

4) Storage condition

It was stored at a room temperature (in the test substance storage room, cabinet No. 6).

1.2 Test substance preparation solution

1) Concentration

[redacted]

2) Medium

Pure water

3) Storage condition

Stored at a cool and dark place (Biotron Building (7), Test room 3, refrigerator).

2. Testing method

2.1 Stability test for test substance

The stability of the test substance was confirmed by measuring the infrared absorption spectrum before and after the administration term.

The infrared absorption spectrum measurements were carried out using a Fourier transform infrared spectrophotometer (Model FTS 135, Nippon Bio-Rad Laboratories K.K.) in the range of 4,000 cm^{-1} – 400 cm^{-1}. Before the start of the administration, the identification was carried out by comparing with a spectrum provided by the test requester, and in the measurement carried out after completing the administration term, the spectrum before the administration was used to compare to find any change.

2.2 Homogeneity and stability test for test substance in preparation solution

For the homogeneity of the test substance solutions prepared, the 10.0 w/v% and 0.05 w/v% solutions immediately after their preparations were sampled at top, middle, and bottom layers with n=3 for each layer, the samples were diluted with methanol, the test substance concentration was measured using high performance liquid chromatography (HPLC), and the homogeneity was confirmed from the relative standard deviation of the test substance concentrations at respective sampling sites. For the stability confirmation, the 10.0 w/v% and

[redacted]

0.05 w/v% solutions were stored in a cool and dark place, sampled from the middle layer with n=3 after 3 days and 7 days, the samples were diluted with methanol, the test substance concentration was measured by using HPLC, and the stability was confirmed by finding any change from the concentrations immediately after preparation (results of homogeneity test).

2.3 Standard solution preparation

In methanol, 0.1029 g of the accurately weighed test substance was dissolved, and it was made up to exactly 100 mL to obtain a 1.029 μg/mL standard stock solution. It was diluted with methanol to prepare standard solutions.

Standard solution concentrations: 103, 206, and 309 μg/mL

A suitable amount of the standard stock solution was diluted 500 times with pure water and then methanol to obtain a medium-added standard solution for test substance concentration measurement in the 10 w/v% preparation solution.

Standard solution concentrations: 103, 206, and 309 μg/mL

A suitable amount of the standard stock solution was diluted 2.5 times with pure water and then methanol to obtain a medium-added standard solution for test substance concentration measurement in the 0.05 w/v% preparation solution.

Standard solution concentrations: 103, 206, and 309 μg/mL

2.4 Pretreatment

1) Test substance stability test

The KBr solution film method was used.

2) Homogeneity and stability of test substance in preparation solution

The preparation solution was stirred thoroughly with a magnetic stirrer, and the following pretreatment procedures were carried out.

(1) 10 w/v% Preparation solution

To 0.5 mL of the preparation solution, methanol was added to accurately make up to 25 mL. From the solution prepared, 1 mL was taken, and methanol was added to accurately make up to 10 mL. The solution prepared was used as an HPLC sample (dilution proportion of 500).

(2) 0.05 w/v% Preparation solution

To 4 mL of the preparation solution, methanol was added to accurately make up to 10 mL. The solution prepared was used as an HPLC sample (dilution proportion of 2.5).

2.5 Measurement condition

1) Infrared absorption spectrum measurement condition

(1) Instrument used

[redacted]

Infrared spectrophotometer: Model FTS 135 (Nippon BioRad Laboratories K.K.)

(2) Measurement condition

Wave number: 4,000 cm^{-1} – 400 cm^{-1}

2) HPLC analysis condition

(1) Instrument used (HPLC1)

Interface: Model D-7000IF (Hitachi, Ltd.)

Pump: Model L-7100 (Hitachi, Ltd.)

Auto-sampler: Model L-7200 (Hitachi, Ltd.)

RI detector: Model L-7490 (Hitachi, Ltd.)

Column oven: Model L-5020 (Hitachi, Ltd.)

Date processor: Model D-7000 HPLC System Manager (Hitachi, Ltd.)

(2) Measurement condition

Column: Shodex Asahipak GF-310HQ 7.6 mm I.D. × 300 mm

Column temperature: 40°C

Moving phase: methanol

Flow rate: 1 mL/min

Amount injected: 50 μL

3. Data processing in homogeneity and stability test for standard substance in preparation solution

3.1 Detected value

The peak area was used as a detected value.

3.2 Working curve preparation

Standard solutions were prepared according to procedures in 2.5 and section 2), and from the detected values on the chromatograms obtained and known concentrations, a working curve was prepared. The working curve prepared passed the origin and showed good linearity, but the detected values and chromatograms of the test substance were different depending on the content of the medium used in the preparation solutions, and thus, for the quantitative determination of the test substance in the 10 w/v% preparation solution and 0.05 w/v% preparation solution, medium-added standard solutions were used. The standard solutions of the 10 w/v% preparation solution and 0.05 w/v% preparation solution were prepared according to procedures in 2.5 and section 2), and from the detected values on the chromatograms obtained and known concentrations, working curves were prepared. The working curves prepared passed the origin and showed good linearity. Therefore, the quantitative determination of analytical samples was

[redacted]

carried out using a standard solution of a medium concentration with one-point weight determination.

3.3 Computation of test substance concentration in analytical samples

The following formula was used to calculate the concentration (C: w/v%) of the test substance, and the results of the computation were round up to 3 digits.

$C = Cs \times A \times D / As \times 10{,}000$

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

As: peak area of test substance in standard solution

A: peak area of test substance in each HPLC sample

D: dilution proportion of each HPLC sample

4. Test result

4.1 Test substance stability test

The infrared absorption spectrum (Figure 1) provided by the study requester was found to coincide with an infrared absorption spectrum (Figure 2) of the test substance measured prior to the start of test substance administration at the Hita Laboratory of the Institution. Furthermore, an infrared absorption spectrum (Figure 3) measured after completion of the administration showed no change.

4.2 Quantitative determination

Figure 4 and Figure 5 show working curves, and Figure 6 and Figure 7 show typical chromatograms. The working curves showed good linearity with correlation coefficient R=0.999.

4.3 Stability test in test substance in preparation solution

Table 1 shows the results of the stability test for the test substance in preparation solutions.

For the 10 and 0.05 w/v% preparation solutions, the means of the test substance concentration immediately after preparation were in the range of 100 ± 10% of the prescribed values. In addition, the test substance concentrations after 3 days and 7 days were within 100 ± 10% of the results on the test substance concentration immediately after preparation.

[redacted]

Table 1 Chemical stability of the test substance in dose formulations

Nominal conc.(w/v%)	Mean conc.(w/v%)			R.P. (%)
	Immediately*	3 days*	7 days*	
10	10.8	10.8	10.7	99.1
0.05	0.0538	0.0539	0.0538	100

*: after preparation

R.P.(%): Rate of the final concentration to the concentration measured immediately after preparation

4.4 Homogeneity test of test substance in preparation

Table 2 shows the results of the homogeneity test carried out for the test substance in the preparation solutions.

The results on the relative standard deviation of the test substance concentrations sampled at respective layers was less than 5% for all concentrations of 10 and 0.05 w/v%.

Table 2 Physical stability of the test substance in dose formulations

Nominal conc. (w/v%)	Layer of measurement	Actual conc. (w/v%)	Mean conc. (w/v%)	R.S.D. (%)
10	top	10.8	10.8	0.5
	middle	10.9		
	bottom	10.8		
0.05	top	0.0540	0.0538	0.4
	middle	0.0536		
	bottom	0.0537		

R.S.D.(%): Relative standard deviation

[redacted]

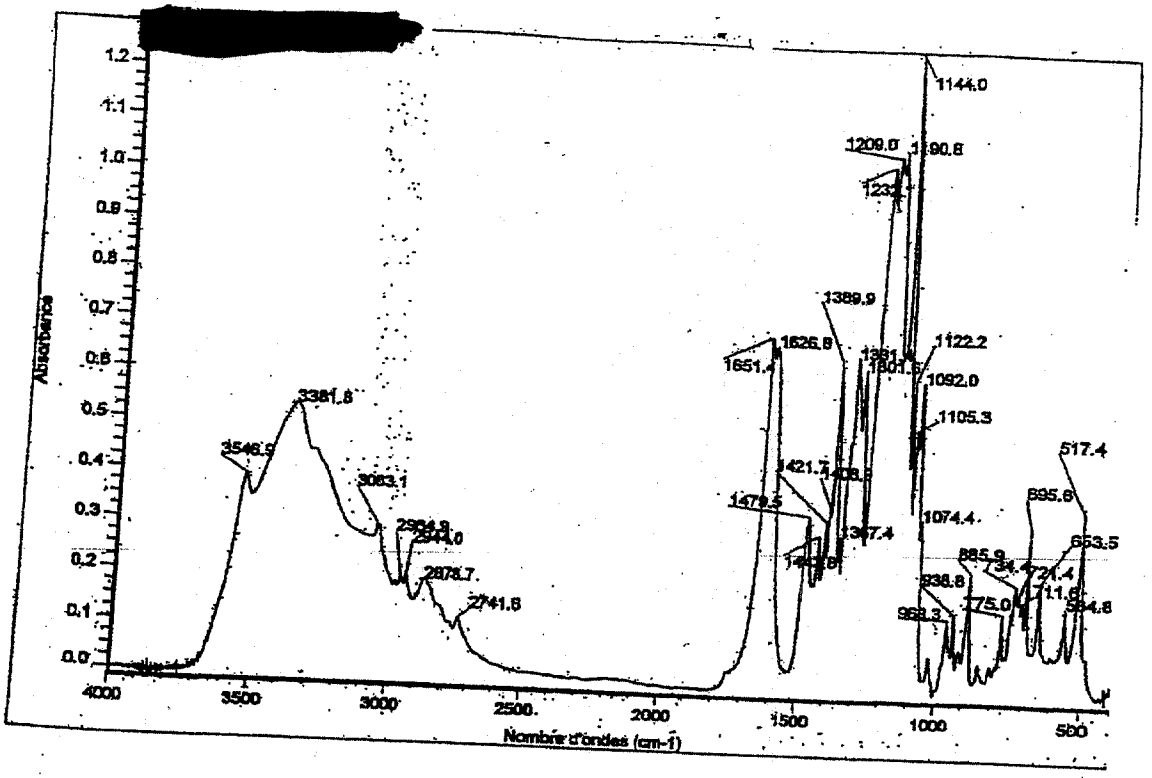


Fig.1 IR spectrum provided by the sponsor

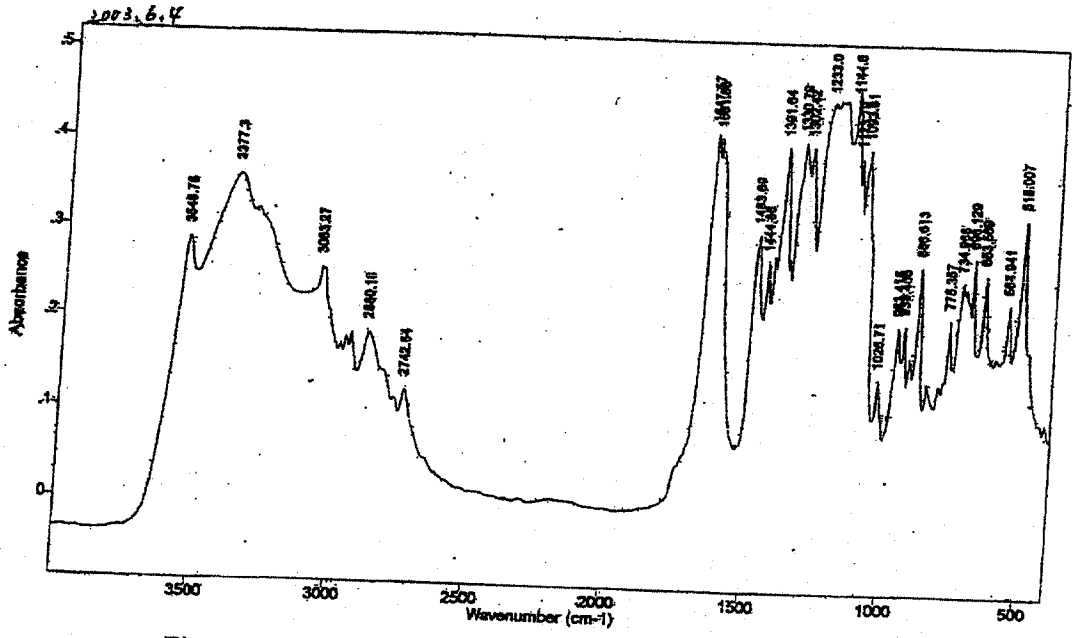


Fig.2 IR spectrum measured prior to the administration period

[redacted]

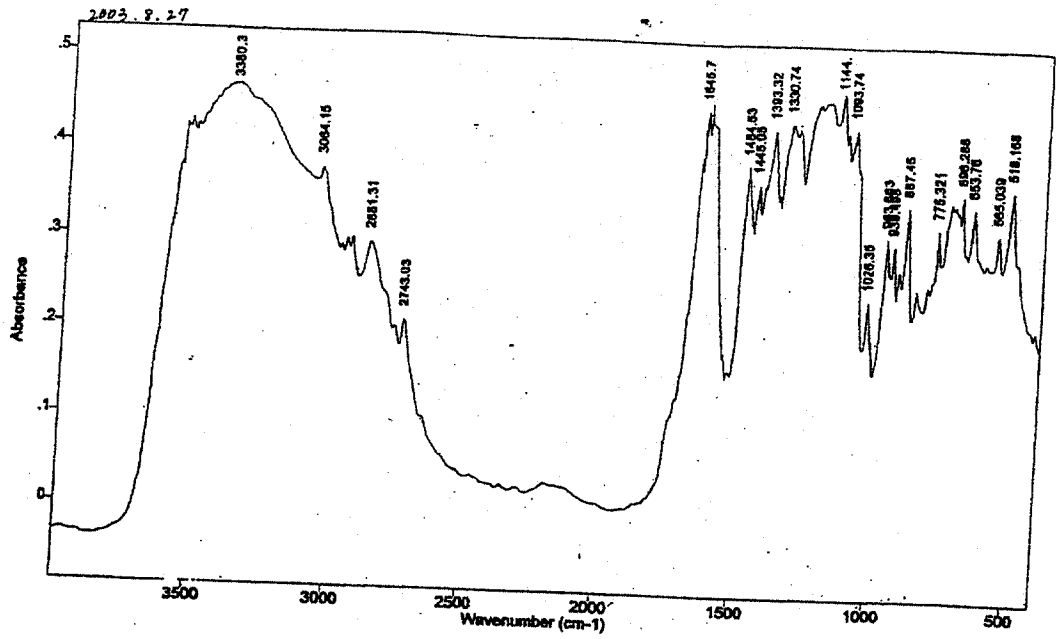


Fig.3 IR spectrum measured after the end of the administration period

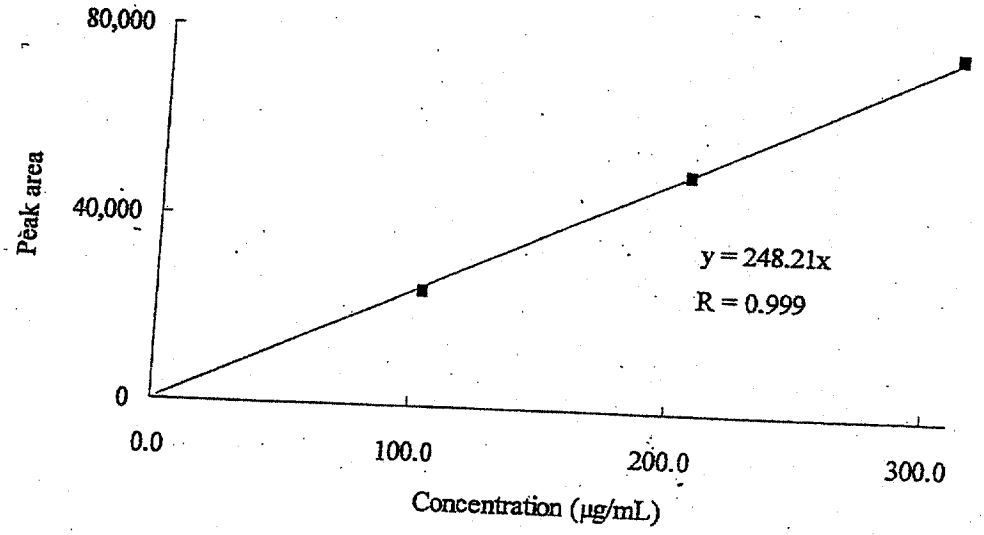


Fig.4 Calibration curve for 10 w/v% dose formulation analysis

Concentration (μg/mL)	Peak Area
103	24,647
206	50,615
309	77,345

[redacted]

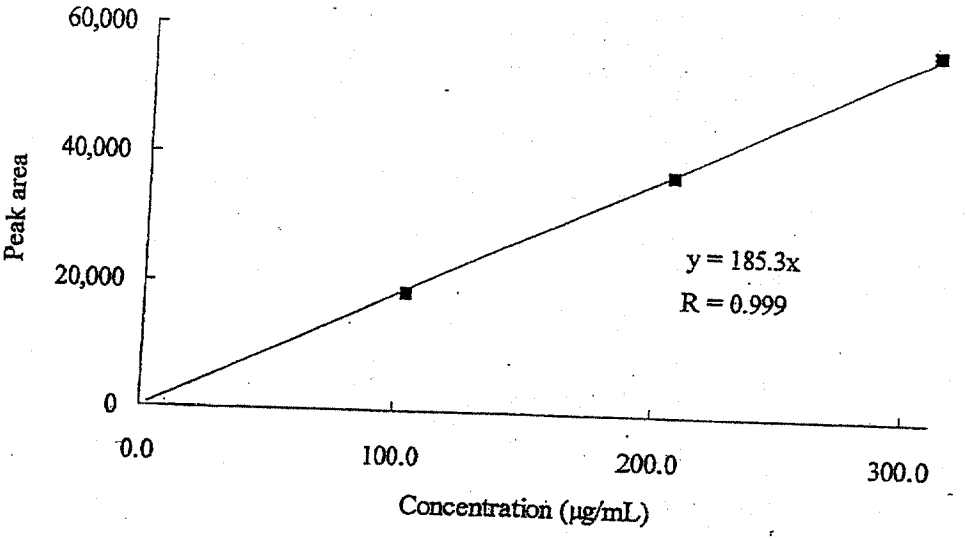


Fig.5 Calibration curve for 0.05 w/v% dose formulation analysis

Concentration (µg/mL)	Peak Area
103	18,334
206	37,778
309	57,769

Signal density (mV)

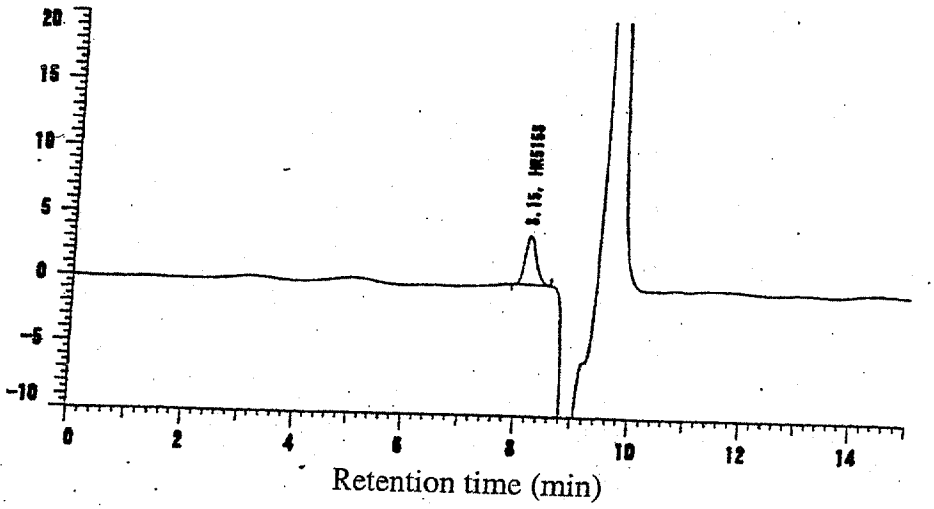


Fig.6 Typical chromatogram for 10 w/v% dose formulation analysis

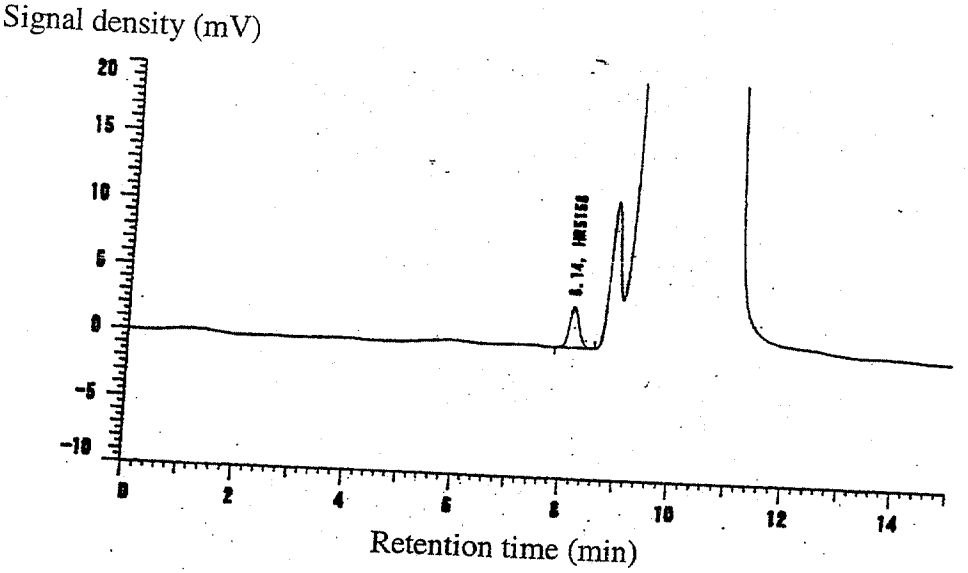


Fig.7 Typical chromatogram for 0.05 w/v% dose formulation analysis

[redacted]

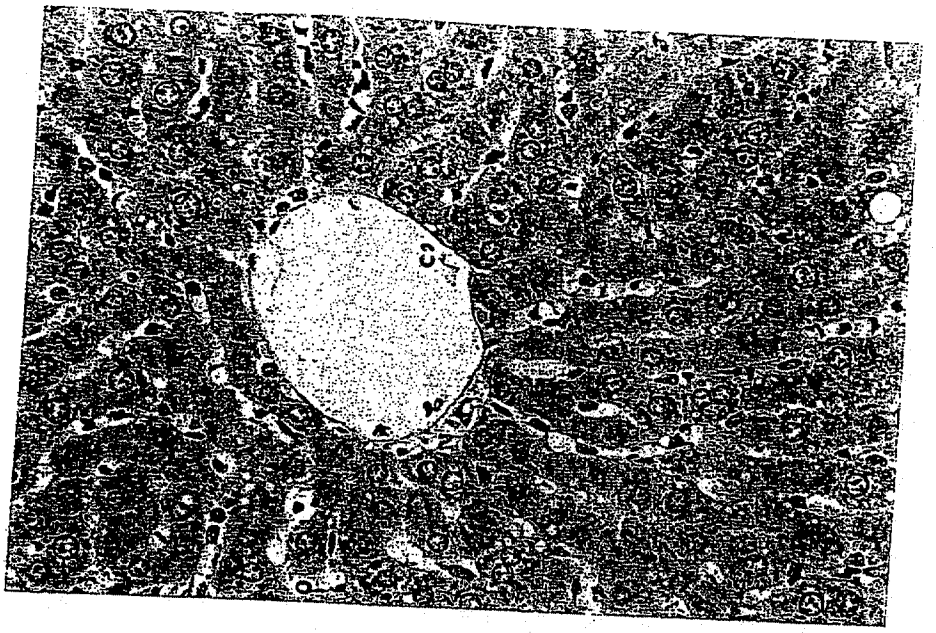


Photo. 1 Liver of a male rat from vehicle control group.
Normal.
No. 1 animal. HE. ×360.

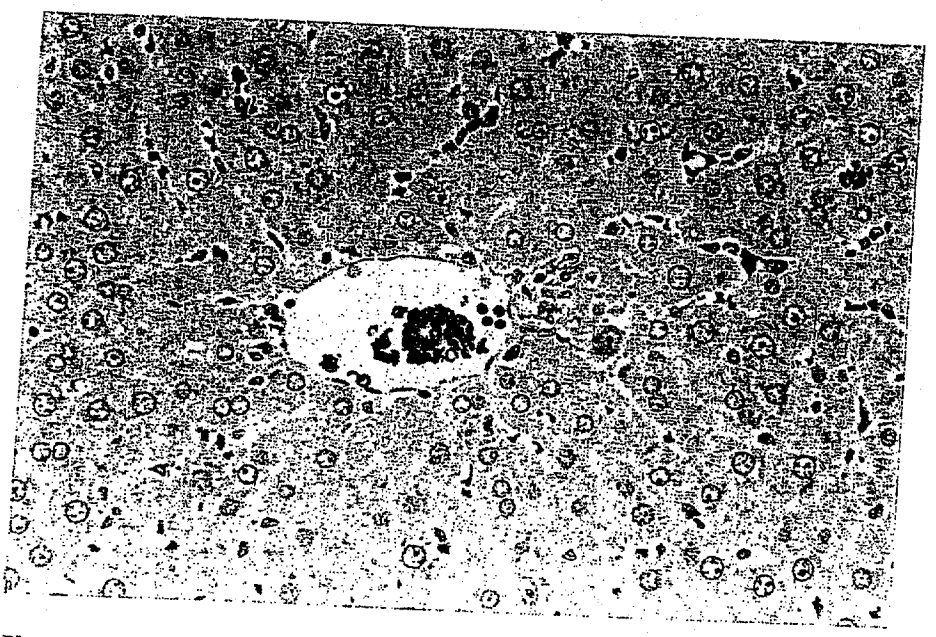


Photo. 2 Liver of a male rat from 1,000 mg/kg/day group.
Centrilobular hypertrophy and single cell necrosis of hepatocytes.
No. 35 animal. HE. ×360.

[redacted]

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

Signs	Sex	Administration 1	2	3	4	Recovery 1	2	(week)
No abnormalities detected	Male	1,2,3,4,[a] 5,6,7,8, 9,10,11, 12	1,2,3,4, 5,6,7,8, 9,10,11, 12	1,2,3,4, 5,6,7,8, 9,10,11, 12	1,2,3,4, 5,6,7,8, 9,10,11, 12	7,8,9,10, 11,12	7,8,9,10, 11,12	
	Female	43,44,45, 46,47,48, 49,50,51, 52,53,54	43,44,45, 46,47,48, 49,50,51, 52,53,54	43,44,45, 46,47,48, 49,50,51, 52,53,54	43,44,45, 46,47,48, 49,50,51, 52,53,54	49,50,51, 52,53,54	49,50,51, 52,53,54	

a) Animal number.

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

Signs	Sex	Administration 1	2	3	4	Recovery 1	2	(week)
No abnormalities detected	Male	13,14,15,[a] 16,17,18	13,14,15, 16,17,18	13,14,15, 16,17,18	13,14,15, 16,17,18			
	Female	55,56,57, 58,59,60	55,56,57, 58,59,60	55,56,57, 58,59,60	55,56,57, 58,59,60			

a) Animal number.

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

Signs	Sex	Administration 1	2	3	4	Recovery 1	2	(week)
No abnormalities detected	Male	19,20,21,[a] 22,23,24	19,20,21, 22,23,24	19,20,21, 22,23,24	19,20,21, 22,23,24			
	Female	61,62,63, 64,65,66	61,62,63, 64,65,66	61,62,63, 64,65,66	61,62,63, 64,65,66			

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 1	2	3	4	Recovery 1	2	(week)
No abnormalities detected	Male	25,26,27,[a] 28,29,30	25,26,27, 28,29,30	27	28			
	Female	67,68,69, 70,71,72	67,68,69, 70,71,72	67,70,71, 72	67,68,70, 71,72			
Soft stool	Male			25,26,28, 29,30	25,26,27, 29,30			
	Female			68,69	69			

a) Animal number.

Addendum 1-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
1,000 mg/kg/day

Signs	Sex	Administration				Recovery		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	32,36,37,[a] 41,42	36,38,42	38,42			37,38,39, 40,41,42	
	Female	73,74,75, 76,78,80, 81,83	75,78,80, 83	75,79	78,79	80	79,80,81, 82,83,84	
Soft stool	Male	31,33,34, 35,38,39, 40	31,32,33, 34,35,37, 39,40,41	31,32,33, 34,35,36, 37,39,40, 41	31,32,33, 34,35,36, 37,38,39, 40,41,42	37,38,39, 40,41,42		
	Female	77,79,82, 84	73,74,76, 77,79,81, 82,84	73,74,76, 77,78,80, 81,82,83, 84	73,74,75, 76,77,80, 81,82,83, 84	79,81,82, 83,84		

a) Animal number.

Addendum 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-2	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	1	129.8	145.5	158.3	204.7	242.6	284.1	314.6	350.4	355.9
		2	134.1	156.4	172.2	229.3	266.8	308.3	333.4	373.5	377.7
		3	125.5	141.9	162.3	207.5	240.9	284.2	314.9	350.8	361.6
		4	127.4	143.8	160.1	199.2	227.0	267.0	294.5	326.2	337.0
		5	128.3	146.1	164.5	213.1	253.2	292.5	325.2	364.1	372.1
		6	132.2	152.6	175.2	229.0	268.6	316.2	347.1	389.4	397.0
		7	129.0	145.4	164.8	208.7	247.9	286.3	313.6	344.5	356.6
		8	129.7	151.4	171.4	219.1	257.5	297.8	331.8	367.4	377.5
		9	128.0	144.6	161.8	211.2	244.5	287.2	317.6	357.0	368.3
		10	136.1	159.9	179.6	225.7	263.0	307.0	340.3	374.2	390.9
		11	120.7	141.7	159.6	206.5	242.9	285.4	316.0	349.5	361.8
		12	132.3	151.7	167.3	213.9	243.5	280.2	309.4	341.8	355.9
	10	13	125.5	143.1	158.8	198.3	233.1	275.2	299.9	329.5	335.9
		14	137.2	155.6	173.7	221.9	255.0	294.9	322.3	350.0	359.0
		15	129.9	151.1	167.5	220.9	253.5	297.1	337.2	372.3	388.0
		16	130.3	150.9	166.2	199.9	226.5	263.9	292.7	318.8	332.5
		17	128.8	149.6	166.9	208.9	242.3	281.7	305.6	340.4	349.9
		18	126.9	145.4	163.6	208.7	242.9	288.1	323.2	356.5	364.7
	40	19	129.5	144.3	161.6	205.0	234.0	280.1	303.5	334.3	338.8
		20	133.3	155.2	174.0	224.4	258.1	301.6	337.1	372.0	380.5
		21	127.9	150.4	169.0	216.9	245.2	282.4	309.9	340.9	348.2
		22	129.0	150.0	171.1	221.0	252.5	294.9	322.2	358.8	370.8
		23	126.5	143.1	162.4	204.0	241.8	285.5	312.2	346.9	358.1
		24	132.3	151.7	171.8	212.6	241.0	283.8	309.9	343.5	354.9
	200	25	126.5	146.0	158.4	199.5	226.0	257.3	276.0	303.0	312.5
		26	131.1	150.5	167.9	220.2	258.1	301.6	331.0	367.7	375.5
		27	124.2	142.9	158.8	193.1	220.3	258.1	279.5	306.8	314.8
		28	129.9	146.5	160.2	199.7	232.2	273.1	300.6	337.4	351.7
		29	128.0	153.2	172.9	217.7	250.7	288.6	319.7	350.3	366.5
		30	136.1	156.3	173.5	221.0	261.5	315.1	349.3	390.5	407.7
	1,000	31	136.5	156.4	167.3	215.0	250.4	297.6	325.8	360.3	366.3
		32	132.2	150.6	165.3	206.1	238.3	280.2	312.3	343.9	358.1
		33	128.9	145.5	160.4	200.9	229.5	271.2	297.6	327.9	336.2
		34	126.8	146.5	163.5	211.1	242.8	285.6	321.5	358.2	370.6
		35	122.9	141.8	153.1	190.7	212.2	244.9	263.8	283.9	294.4
		36	129.7	146.6	162.7	205.9	239.6	284.5	318.1	353.1	368.2
		37	129.6	144.7	156.8	196.2	223.4	258.8	282.9	309.8	316.8
		38	128.7	151.8	166.3	212.0	243.5	285.3	312.8	335.5	343.3
		39	130.8	148.3	161.7	201.3	227.7	268.2	296.6	331.7	339.3
		40	125.0	143.4	156.1	199.3	229.1	265.6	291.3	326.2	331.5
		41	136.7	150.9	165.9	204.3	240.0	284.7	320.6	352.5	366.2
		42	126.7	142.9	158.3	198.1	227.1	260.9	286.6	310.1	316.6

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

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-2	1	3	8	12	17	21	26	28 (days)
Female	Vehicle control	43	117.0	130.6	137.4	158.6	173.4	190.4	200.4	216.0	227.2
		44	108.0	119.5	128.4	144.6	156.6	166.1	172.6	183.3	183.9
		45	108.5	119.1	127.7	147.1	162.5	171.8	186.0	203.3	212.8
		46	116.2	132.4	138.5	162.8	172.0	180.7	190.0	193.9	206.8
		47	113.2	123.3	133.7	155.6	166.1	183.6	194.5	197.9	203.5
		48	112.3	128.9	137.5	155.6	167.7	182.8	197.8	206.9	213.4
		49	108.3	115.6	131.3	154.8	169.0	181.2	192.0	200.3	210.0
		50	113.9	128.6	141.3	160.8	171.4	187.2	196.9	214.0	211.6
		51	118.3	132.1	141.9	162.8	176.2	191.5	202.7	212.3	216.5
		52	112.2	115.5	125.3	137.9	149.2	158.0	165.7	178.3	181.2
		53	115.4	124.6	138.3	162.7	176.0	188.9	204.5	210.1	220.1
		54	107.4	119.4	129.0	150.6	162.0	176.9	186.7	197.2	199.6
	10	55	107.5	122.5	135.9	161.8	172.8	188.1	202.3	211.3	212.5
		56	110.6	121.7	130.2	139.9	144.1	156.8	164.8	176.1	177.9
		57	115.5	130.1	144.7	171.5	188.9	205.7	218.5	232.3	238.3
		58	113.0	124.7	135.3	156.3	168.3	185.1	197.5	205.2	212.3
		59	111.2	122.4	132.6	142.2	149.8	157.1	163.3	177.4	174.8
		60	119.5	132.9	141.0	160.2	179.5	197.7	215.0	227.6	232.0
	40	61	106.8	119.6	127.6	143.8	154.3	169.8	178.3	192.0	187.2
		62	114.1	129.4	137.8	157.2	173.7	191.7	208.0	209.3	220.4
		63	118.0	132.6	141.6	161.5	178.2	196.6	208.9	218.3	224.9
		64	111.6	122.6	133.0	151.8	166.8	187.7	198.4	212.0	213.1
		65	108.0	117.2	128.7	146.4	154.9	167.7	175.5	184.6	188.4
		66	115.9	129.5	142.1	167.2	180.5	198.1	212.9	219.0	228.8
	200	67	111.6	126.3	134.7	162.0	176.5	187.8	196.9	207.7	212.4
		68	108.5	121.4	128.0	152.1	172.8	194.9	204.3	224.3	220.5
		69	112.7	124.0	131.6	155.8	167.8	187.1	198.1	212.3	213.9
		70	117.1	129.8	141.0	160.0	173.8	192.0	199.2	208.9	216.0
		71	108.0	119.2	129.3	147.3	155.2	165.6	175.5	182.7	191.9
		72	115.5	129.0	134.6	151.1	164.1	175.3	185.9	199.1	200.9
	1,000	73	114.0	128.4	132.2	150.5	165.1	188.9	201.5	216.3	209.2
		74	110.6	124.2	132.3	153.6	165.5	182.5	198.3	215.2	218.4
		75	114.7	130.0	136.9	147.3	153.3	167.5	182.2	190.6	189.7
		76	112.5	124.0	131.8	158.2	169.2	181.3	192.6	210.9	213.4
		77	107.3	121.3	130.5	156.1	169.7	179.9	189.3	207.5	213.0
		78	116.8	132.4	136.9	159.8	177.2	189.1	200.4	204.7	216.9
		79	109.8	124.8	133.2	152.5	164.6	173.6	184.1	195.3	197.4
		80	115.6	128.7	139.7	161.9	177.3	192.6	208.7	230.4	232.9
		81	104.4	116.0	123.1	139.6	146.5	160.3	171.7	181.4	187.5
		82	113.7	126.9	131.5	151.1	164.2	186.0	198.5	210.1	211.6
		83	111.6	123.4	131.4	145.8	160.9	182.0	199.6	216.2	221.0
		84	117.9	130.6	138.7	162.0	173.9	188.5	203.6	211.8	225.7

Addendum 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 1	5	10	14 (days)
Male	Vehicle control	7	362.3	385.1	412.9	431.9
		8	380.3	400.6	430.2	448.7
		9	369.4	390.8	414.6	430.3
		10	392.2	418.6	444.0	466.3
		11	362.3	386.8	419.6	435.0
		12	356.7	375.1	406.1	427.5
	1,000	37	315.0	339.7	359.2	373.5
		38	348.6	376.4	397.1	415.1
		39	336.5	367.0	391.3	406.2
		40	335.0	362.9	393.7	410.3
		41	372.5	395.0	424.6	436.1
		42	319.9	349.1	364.2	383.6
Female	Vehicle control	49	208.7	213.6	218.4	226.2
		50	219.0	229.1	242.3	248.3
		51	220.7	234.5	241.5	248.8
		52	180.4	188.8	207.3	209.9
		53	222.7	230.6	238.5	236.3
		54	204.9	215.0	226.2	226.5
	1,000	79	201.4	218.3	227.6	225.5
		80	229.7	249.0	266.5	275.9
		81	187.8	204.6	203.0	205.8
		82	217.0	229.9	243.8	241.4
		83	222.8	238.8	250.8	257.3
		84	228.0	245.8	255.7	261.5

Addendum 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats
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	18.7	19.8	21.5	24.2	25.0	26.7
		2	20.8	22.6	25.9	27.8	28.6	29.1
		3	17.6	20.7	22.2	22.9	25.4	26.7
		4	18.4	19.7	20.7	22.2	24.7	25.9
		5	19.2	20.9	23.0	25.3	25.9	27.6
		6	22.2	24.7	26.6	28.6	30.2	31.2
		7	18.2	20.0	21.8	22.7	24.1	24.7
		8	21.3	22.5	24.3	26.0	26.9	27.5
		9	18.1	19.3	22.4	22.6	25.1	26.1
		10	23.2	23.9	24.3	25.3	27.2	28.9
		11	19.7	21.2	23.2	25.4	27.5	27.6
		12	19.6	19.6	22.0	23.1	24.6	26.3
	10	13	18.4	19.4	20.1	22.4	23.1	22.2
		14	20.2	22.1	23.7	25.8	26.7	27.1
		15	21.9	21.8	24.4	25.8	29.0	30.1
		16	20.1	20.3	21.1	21.8	23.6	24.6
		17	20.5	22.3	23.2	24.4	26.2	26.5
		18	19.9	21.6	23.0	25.1	27.6	26.9
	40	19	17.7	20.6	21.9	22.7	24.1	24.0
		20	21.3	21.8	24.4	25.5	27.8	29.0
		21	18.8	20.1	22.2	23.0	25.0	25.1
		22	19.8	22.7	24.5	24.7	26.8	27.7
		23	18.9	20.2	22.1	24.5	25.1	25.6
		24	21.2	22.7	23.4	24.3	25.4	25.8
	200	25	20.4	19.4	21.1	21.8	22.3	22.0
		26	19.1	21.4	23.2	24.9	26.2	26.3
		27	19.8	20.0	19.5	20.9	21.3	22.9
		28	18.7	19.7	21.0	22.2	24.9	26.5
		29	21.2	22.7	23.8	23.7	25.7	26.9
		30	20.9	22.4	24.3	28.0	30.9	32.7
	1,000	31	21.1	20.3	22.1	24.0	26.1	25.6
		32	20.3	21.1	22.8	23.0	25.8	27.2
		33	18.8	20.8	21.3	22.7	24.2	26.0
		34	19.5	20.7	23.0	24.1	27.3	28.4
		35	19.3	19.1	21.5	22.2	22.1	22.0
		36	19.4	20.4	21.5	23.6	26.6	28.5
		37	19.6	19.6	21.6	21.8	23.5	23.0
		38	23.4	21.1	23.3	23.6	25.3	25.1
		39	19.6	20.4	20.9	21.5	24.4	25.9
		40	19.4	21.5	22.6	23.1	24.6	25.1
		41	21.4	21.7	21.9	24.3	27.5	29.4
		42	19.9	19.5	21.2	21.3	23.6	24.1

Addendum 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats
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	43	18.7	16.3	16.4	16.9	17.7	18.8
		44	14.5	15.8	16.0	15.6	14.8	15.4
		45	15.7	15.6	15.8	17.0	17.4	18.4
		46	18.0	17.2	17.9	16.2	16.3	17.7
		47	16.7	16.0	16.0	15.8	16.8	16.4
		48	17.3	17.2	16.6	16.5	17.3	18.6
		49	15.7	15.8	16.4	15.6	16.5	17.3
		50	17.3	17.2	17.1	16.4	17.1	18.0
		51	18.0	17.7	17.2	17.8	18.5	19.1
		52	15.3	15.8	14.9	15.1	15.7	16.4
		53	17.1	19.0	18.5	18.3	18.8	19.9
		54	15.8	15.1	16.3	15.5	16.8	17.0
	10	55	16.3	17.3	16.7	15.4	16.4	16.7
		56	15.2	15.6	15.3	14.4	14.8	15.6
		57	17.3	18.4	18.2	17.4	17.9	17.9
		58	15.3	16.0	16.3	16.2	16.8	17.4
		59	17.0	17.3	15.9	14.4	15.0	15.8
		60	17.3	16.2	16.8	17.4	19.1	19.4
	40	61	15.5	14.6	15.1	14.8	15.0	15.3
		62	17.2	16.2	16.1	16.2	17.3	18.0
		63	18.0	17.8	17.4	17.8	18.8	19.5
		64	14.9	15.8	15.9	17.2	17.8	17.4
		65	15.4	15.8	15.5	14.9	16.9	15.8
		66	17.0	18.7	18.9	18.3	19.6	21.4
	200	67	17.0	16.4	17.7	17.5	17.1	17.3
		68	16.0	14.7	16.3	16.7	17.5	18.2
		69	16.1	16.3	18.2	18.0	18.9	19.4
		70	16.5	16.1	16.4	16.7	17.6	18.0
		71	15.9	15.9	16.2	15.1	15.6	16.2
		72	16.7	15.3	15.8	15.0	15.4	16.2
	1,000	73	16.7	16.1	15.7	16.4	17.8	18.2
		74	15.9	15.8	16.4	15.5	17.2	18.1
		75	17.1	15.8	15.1	14.3	15.3	15.7
		76	15.0	15.1	16.6	15.2	15.8	16.9
		77	16.7	15.2	16.8	16.1	17.3	18.5
		78	18.0	15.9	16.8	17.0	17.9	18.9
		79	16.6	17.0	16.8	14.8	15.3	15.2
		80	17.7	18.1	18.4	18.2	19.7	20.6
		81	15.5	14.2	14.5	14.4	14.9	16.5
		82	16.9	16.0	17.3	18.0	19.2	18.6
		83	16.7	16.0	16.0	16.9	19.3	19.6
		84	20.0	18.5	19.4	18.7	20.0	21.8

[redacted]

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

[redacted]

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 4	8	14 (days)
Male	Vehicle control	7	26.7	26.0	26.7
		8	28.7	28.8	29.5
		9	26.2	26.2	25.0
		10	30.2	28.5	29.6
		11	26.7	29.2	28.2
		12	27.1	27.0	28.7
	1,000	37	24.0	24.2	24.1
		38	27.1	26.9	26.7
		39	27.4	26.9	26.0
		40	29.5	28.2	28.2
		41	29.8	29.2	27.7
		42	28.2	26.2	26.5
Female	Vehicle control	49	17.6	17.6	17.2
		50	20.2	18.2	20.0
		51	19.5	19.8	21.8
		52	17.6	16.7	17.7
		53	18.4	18.8	20.1
		54	18.1	17.2	18.9
	1,000	79	18.3	18.0	18.3
		80	23.0	21.7	22.4
		81	18.3	17.4	18.0
		82	19.9	20.6	19.7
		83	21.3	21.2	20.6
		84	22.7	22.4	22.1

Addendum 4-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	RBC (x10⁴/μL)	WBC (x10²/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet (x10⁴/μL)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	1	772	108	15.2	46.5	60.3	19.7	32.6	119.5	2.8	21.4	33.8
		2	740	69	14.9	46.3	62.6	20.2	32.2	123.7	2.0	23.7	33.6
		3	753	118	14.4	45.5	60.5	19.1	31.5	115.2	3.1	17.8	39.3
		4	778	67	15.1	46.8	60.3	19.4	32.2	112.0	2.4	24.9	40.9
		5	759	97	15.0	46.8	61.7	19.8	32.0	104.0	2.9	17.9	34.8
		6	743	80	14.4	44.5	59.9	19.4	32.4	111.3	2.5	20.8	35.7
		Recovery											
		7	761	106	14.2	42.6	55.9	18.6	33.2	112.2	2.1	22.0	33.1
		8	767	96	15.0	45.3	59.0	19.5	33.1	113.1	2.7	14.3	25.6
		9	819	93	15.3	48.7	59.4	18.7	31.5	116.4	1.8	14.6	31.1
		10	832	152	15.5	48.5	58.2	18.7	32.0	119.7	2.9	14.3	31.8
		11	780	110	14.8	44.9	57.5	19.0	33.0	105.4	2.6	21.0	34.7
		12	815	123	14.8	45.4	55.7	18.1	32.6	111.8	2.3	17.3	31.1
	10	13	776	81	15.7	48.7	62.8	20.3	32.3	114.4	2.8	18.6	32.7
		14	825	100	14.9	47.4	57.4	18.1	31.5	115.9	2.0	19.9	32.2
		15	772	86	14.8	46.0	59.6	19.2	32.2	109.5	2.8	15.0	31.8
		16	741	93	14.8	46.1	62.3	19.9	32.0	106.3	2.8	33.3	42.2
		17	738	108	14.6	44.6	60.5	19.7	32.6	108.2	2.4	18.6	33.4
		18	816	68	15.4	48.4	59.3	18.8	31.7	108.8	2.6	19.7	34.7
	40	19	735	92	14.8	45.0	61.2	20.1	32.8	115.8	2.3	15.9	32.7
		20	763	99	15.1	46.5	60.9	19.8	32.4	103.8	2.6	19.3	30.6
		21	775	79	15.0	45.5	58.7	19.4	33.1	118.2	2.4	17.6	33.7
		22	814	109	15.8	48.4	59.5	19.1	32.1	123.5	2.7	18.0	33.7
		23	758	97	14.6	44.2	58.3	19.2	33.0	108.4	2.6	14.8	30.4
		24	766	75	15.3	47.1	61.6	20.0	32.4	107.8	2.8	24.1	37.8
	200	25	775	86	14.7	45.1	58.2	19.0	32.6	118.8	2.3	14.7	27.8
		26	754	105	15.2	46.1	61.1	20.2	33.0	105.0	3.0	23.5	33.8
		27	763	63	14.5	44.5	59.0	19.2	32.6	90.7	2.7	16.1	33.7
		28	755	102	14.2	44.2	58.6	18.8	32.2	121.3	2.3	21.0	32.5
		29	736	103	15.0	46.0	62.6	20.4	32.6	96.7	2.6	15.3	27.5
		30	745	122	14.4	44.2	59.3	19.3	32.5	98.7	3.1	13.7	17.9
	1,000	31	734	124	15.1	46.8	63.8	20.6	32.3	104.6	3.0	14.6	30.8
		32	737	84	14.8	45.9	62.3	20.1	32.2	122.5	2.5	17.8	31.3
		33	764	97	15.0	47.0	61.5	19.6	31.9	107.9	3.2	14.7	30.7
		34	744	85	14.9	45.6	61.3	20.1	32.7	91.6	2.7	17.9	33.4
		35	813	76	15.6	48.0	59.1	19.2	32.5	103.3	2.0	14.6	33.9
		36	752	111	14.9	45.8	60.9	19.8	32.5	104.4	2.7	18.0	36.4
		Recovery											
		37	773	146	14.7	43.9	56.8	19.0	33.5	128.5	2.9	21.1	41.2
		38	828	86	15.3	48.5	58.6	18.4	31.4	102.7	2.0	20.2	42.7
		39	853	95	15.5	47.7	55.9	18.1	32.4	120.2	2.2	15.2	34.2
		40	792	98	15.1	46.0	58.0	19.1	32.9	109.4	2.6	15.7	30.5
		41	793	95	15.2	45.9	57.8	19.1	33.1	115.1	2.2	25.7	43.0
		42	779	108	14.9	45.3	58.1	19.2	33.0	119.1	2.5	13.9	29.8

Addendum 4-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	RBC (x10⁴/μL)	WBC (x10²/μL)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet (x10⁴/μL)	Reticulo (%)	P T (sec)	APTT (sec)
Female	Vehicle control	43	764	63	14.9	44.8	58.7	19.5	33.2	105.9	2.3	14.8	24.1
		44	848	88	15.6	47.5	56.1	18.4	32.7	115.1	1.6	13.9	24.9
		45	756	73	15.1	45.8	60.6	20.0	33.1	112.0	2.4	13.5	23.5
		46	776	95	15.2	45.5	58.6	19.5	33.3	99.5	2.3	13.4	23.6
		47	801	83	15.6	47.6	59.5	19.5	32.8	110.3	1.6	13.2	22.7
		48	812	88	15.2	46.3	57.0	18.7	32.8	112.5	2.5	12.9	23.9
		Recovery											
		49	785	87	15.3	45.2	57.6	19.5	33.9	135.9	2.1	12.7	23.4
		50	784	73	14.3	42.4	54.0	18.2	33.6	127.1	1.9	13.3	21.5
		51	800	79	14.9	44.4	55.5	18.6	33.5	124.7	2.5	13.0	20.8
		52	777	60	14.5	44.1	56.8	18.7	32.9	109.6	1.9	13.9	24.4
		53	835	87	15.4	46.3	55.5	18.4	33.2	125.6	2.0	13.0	26.5
		54	866	102	16.1	48.0	55.4	18.6	33.6	124.9	2.3	13.6	26.4
	10	55	828	103	16.2	49.0	59.2	19.6	33.1	119.7	1.5	12.8	26.5
		56	772	58	15.3	46.6	60.4	19.8	32.8	98.0	1.9	12.9	23.9
		57	756	110	15.1	46.0	60.9	19.9	32.7	108.7	1.5	15.5	24.1
		58	808	116	15.1	46.8	57.9	18.8	32.4	112.1	2.0	14.3	26.5
		59	801	93	15.7	47.8	59.7	19.6	32.9	101.4	1.7	13.5	24.7
		60	745	91	14.8	45.2	60.7	19.9	32.7	142.3	1.9	13.2	26.4
	40	61	814	77	15.7	47.5	58.3	19.3	33.1	120.4	1.7	13.1	22.0
		62	771	69	15.0	45.5	59.0	19.5	33.1	92.2	1.9	12.4	27.2
		63	783	87	15.6	46.8	59.8	20.0	33.4	111.6	2.2	12.8	25.0
		64	790	107	15.9	48.3	61.2	20.1	32.9	106.7	2.0	12.9	22.8
		65	778	83	15.2	45.8	58.9	19.5	33.1	121.1	2.1	15.1	27.6
		66	766	105	15.4	46.9	61.3	20.1	32.8	108.5	1.9	13.8	23.8
	200	67	747	70	14.4	43.4	58.0	19.3	33.2	110.6	2.3	16.4	26.2
		68	755	69	15.0	45.0	59.7	19.9	33.4	119.2	1.7	13.2	24.0
		69	827	93	15.8	47.8	57.8	19.1	33.0	113.8	2.0	13.3	27.0
		70	799	60	15.3	46.0	57.5	19.1	33.2	113.4	2.3	13.5	23.7
		71	834	78	15.5	47.1	56.5	18.5	32.8	115.5	2.0	13.3	28.4
		72	851	139	16.0	49.3	57.9	18.8	32.5	112.6	1.8	11.8	23.8
	1,000	73	791	122	15.1	46.7	59.0	19.1	32.3	108.1	1.6	14.1	26.0
		74	779	77	15.0	45.6	58.6	19.3	33.0	110.1	2.3	15.5	24.6
		75	804	70	15.3	45.8	56.9	19.0	33.3	118.2	1.5	14.1	24.0
		76	799	81	15.7	47.9	59.9	19.6	32.8	102.2	1.9	13.4	26.1
		77	744	141	14.4	43.4	58.3	19.4	33.2	123.1	1.9	13.4	21.8
		78	778	64	14.9	45.5	58.5	19.1	32.7	99.1	2.3	13.6	23.6
		Recovery											
		79	807	59	14.9	44.8	55.5	18.5	33.3	125.2	2.2	13.1	26.5
		80	768	67	14.8	43.4	56.5	19.2	34.1	110.5	1.7	12.9	19.0
		81	738	93	13.6	40.3	54.6	18.4	33.6	125.9	3.4	12.9	26.3
		82	818	113	15.1	45.0	55.0	18.5	33.8	146.2	2.5	13.6	24.0
		83	802	78	15.2	45.1	56.3	19.0	33.7	131.9	2.1	12.8	27.3
		84	800	74	15.3	45.7	57.1	19.1	33.5	123.0	2.3	12.9	26.0

Addendum 4-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%)					
			N-Band	N-Seg	Eosino	Baso	Lymph	Mono
Male	Vehicle control	1	2.0	8.5	0.5	0.0	89.0	0.0
		2	1.0	3.5	1.0	0.0	94.5	0.0
		3	1.0	12.5	0.5	0.0	86.0	0.0
		4	2.5	10.5	0.5	0.0	86.5	0.0
		5	2.5	7.0	0.0	0.0	89.5	1.0
		6	3.0	12.0	1.0	0.0	82.5	1.5
		Recovery						
		7	1.5	8.5	1.5	0.0	87.5	1.0
		8	1.0	9.0	0.0	0.0	89.5	0.5
		9	0.5	13.0	0.5	0.0	86.0	0.0
		10	1.5	11.0	0.5	0.0	87.0	0.0
		11	0.5	7.5	0.5	0.0	91.0	0.5
		12	2.0	11.0	1.0	0.0	84.5	1.5
	10	13	5.5	13.0	1.0	0.0	80.5	0.0
		14	1.5	9.5	1.0	0.0	87.0	1.0
		15	1.0	4.5	1.5	0.0	92.5	0.5
		16	2.0	7.5	0.5	0.0	90.0	0.0
		17	2.0	17.0	1.0	0.0	79.0	1.0
		18	1.0	10.0	0.5	0.0	88.5	0.0
	40	19	3.5	7.5	1.0	0.0	87.5	0.5
		20	2.5	4.5	0.5	0.0	92.5	0.0
		21	2.0	18.0	2.0	0.0	76.5	1.5
		22	4.0	14.5	0.5	0.0	81.0	0.0
		23	4.0	8.0	0.5	0.0	87.5	0.0
		24	2.5	8.0	1.5	0.5	87.0	0.5
	200	25	1.5	9.5	2.0	0.0	87.0	0.0
		26	3.5	8.0	0.0	0.0	88.0	0.5
		27	4.5	15.0	0.5	0.0	79.5	0.5
		28	2.5	11.0	0.0	0.0	86.0	0.5
		29	1.0	7.0	2.0	0.0	90.0	0.0
		30	5.5	11.5	1.0	0.0	82.0	0.0
	1,000	31	1.0	5.0	1.5	0.0	92.5	0.0
		32	2.5	11.0	1.0	0.0	85.5	0.0
		33	0.5	9.5	1.5	0.0	88.0	0.5
		34	3.0	13.5	1.5	0.0	82.0	0.0
		35	3.0	20.0	0.5	0.0	76.0	0.5
		36	3.0	15.5	0.5	0.0	81.0	0.0
		Recovery						
		37	1.5	8.5	0.0	0.0	90.0	0.0
		38	2.0	6.5	1.5	0.0	90.5	0.5
		39	2.5	9.5	0.5	0.0	86.0	1.5
		40	2.0	7.0	1.0	0.0	89.5	0.5
		41	0.5	4.5	0.0	0.0	94.0	1.0
		42	3.0	12.0	1.0	0.0	83.0	1.0

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

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%)					
			N-Band	N-Seg	Eosino	Baso	Lymph	Mono
Female	Vehicle control	43	0.5	9.5	1.0	0.0	89.0	0.0
		44	3.0	10.5	0.5	0.0	85.0	1.0
		45	4.0	7.0	1.0	0.0	87.5	0.5
		46	0.5	4.0	0.0	0.0	95.5	0.0
		47	1.5	7.0	0.5	0.0	90.5	0.5
		48	0.5	14.0	0.0	0.0	85.0	0.5
		Recovery						
		49	3.0	14.0	2.0	0.0	79.0	2.0
		50	2.5	9.0	1.5	0.0	86.5	0.5
		51	1.5	12.5	0.0	0.0	86.0	0.0
		52	1.0	8.5	0.5	0.0	89.5	0.5
		53	1.0	8.0	0.5	0.0	90.0	0.5
		54	3.0	14.5	0.5	0.0	81.0	1.0
	10	55	1.5	10.0	0.0	0.0	88.0	0.5
		56	1.5	8.5	1.0	0.0	88.5	0.5
		57	2.0	11.5	1.0	0.0	85.5	0.0
		58	1.0	8.0	1.0	0.0	90.0	0.0
		59	1.0	11.0	0.5	0.0	86.5	1.0
		60	1.0	5.5	1.0	0.0	92.5	0.0
	40	61	0.5	8.5	0.0	0.0	91.0	0.0
		62	1.0	6.0	0.0	0.0	92.5	0.5
		63	0.5	19.5	0.5	0.0	79.0	0.5
		64	0.5	12.5	1.0	0.0	85.5	0.5
		65	3.0	8.0	0.0	0.0	88.5	0.5
		66	2.5	6.5	0.0	0.0	91.0	0.0
	200	67	0.5	6.0	0.0	0.0	93.5	0.0
		68	1.5	16.5	2.0	0.0	80.0	0.0
		69	3.5	8.5	1.5	0.5	86.0	0.0
		70	3.0	12.5	1.0	0.0	83.5	0.0
		71	0.0	3.5	0.5	0.0	96.0	0.0
		72	2.0	5.5	0.5	0.0	92.0	0.0
	1,000	73	2.0	10.5	0.5	0.0	86.5	0.5
		74	1.5	8.0	0.5	0.0	89.5	0.5
		75	3.5	11.0	1.5	0.0	83.5	0.5
		76	2.0	11.0	0.0	0.0	86.5	0.5
		77	1.5	14.0	1.0	0.0	83.0	0.5
		78	1.0	8.5	1.0	0.0	89.5	0.0
		Recovery						
		79	2.0	8.0	2.0	0.0	88.0	0.0
		80	1.0	14.0	2.0	0.0	82.0	1.0
		81	2.5	8.5	0.5	0.0	87.5	1.0
		82	1.5	7.5	0.5	0.0	90.5	0.0
		83	1.5	6.0	0.5	0.0	92.0	0.0
		84	1.0	9.5	2.0	0.0	87.5	0.0

Addendum 5-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	GOT (IU/L)	GPT (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	75	25	340	42	1.6	67	57	130	5.5	3.0	1.20
		2	78	25	422	67	1.2	53	77	202 a)	5.3	2.7	1.04
		3	89	25	490	70	0.4	59	66	119	5.5	3.0	1.20
		4	71	31	431	41	0.4	47	45	124	5.3	2.8	1.12
		5	66	22	387	32	1.0	54	83	143	5.3	2.9	1.21
		6	65	26	460	49	0.7	53	63	122	5.5	2.9	1.12
		Recovery											
		7	90	22	331	55	0.7	37	66	140	5.2	2.6	1.00
		8	70	26	286	46	0.8	61	86	131	5.8	2.8	0.93
		9	83	27	398	34	1.0	53	76	136	5.4	2.6	0.93
		10	69	25	300	49	1.0	74	89	161	5.6	2.8	1.00
		11	87	24	313	55	0.5	58	60	144	5.4	2.6	0.93
		12	72	22	300	56	0.4	47	47	115	5.2	2.5	0.93
	10	13	65	22	513	38	0.5	67	72	127	5.4	2.8	1.08
		14	86	26	377	36	0.8	39	63	123	5.4	2.8	1.08
		15	83	36	419	51	1.7	62	94	156	5.6	2.9	1.07
		16	75	24	598	44	0.8	29	25	123	5.4	2.7	1.00
		17	85	28	489	56	0.8	48	52	130	5.1	2.8	1.22
		18	80	25	426	43	1.8	60	41	124	5.4	2.9	1.16
	40	19	62	26	498	53	0.4	38	44	170	5.1	2.7	1.12
		20	67	28	446	53	0.4	60	52	130	5.1	2.7	1.12
		21	81	29	552	38	1.2	41	68	115	5.4	2.9	1.16
		22	73	28	514	64	1.7	43	61	145	5.5	2.8	1.04
		23	78	27	589	47	0.3	50	40	101	5.4	2.8	1.08
		24	64	24	511	47	0.5	47	37	128	5.2	2.7	1.08
	200	25	75	27	385	33	0.5	52	60	125	5.3	2.7	1.04
		26	61	23	371	39	0.6	53	126	125	5.4	2.8	1.08
		27	91	36	519	61	0.2	43	56	118	5.0	2.7	1.17
		28	76	26	518	50	0.8	37	85	128	5.4	2.6	0.93
		29	99	34	488	45	0.9	41	34	130	4.9	2.5	1.04
		30	75	34	472	42	0.3	52	92	145	5.5	2.5	0.83
	1,000	31	77	23	356	40	0.8	36	53	113	5.2	2.8	1.17
		32	70	24	413	48	0.8	40	91	116	5.2	2.7	1.08
		33	73	26	438	32	0.6	37	38	103	5.3	2.8	1.12
		34	64	21	397	64	0.4	49	108	120	5.3	2.8	1.12
		35	82	31	295	35	0.2	31	36	125	5.1	2.7	1.12
		36	75	26	415	74	0.5	41	64	130	5.0	2.5	1.00
		Recovery											
		37	77	22	371	42	1.2	25	57	109	5.2	2.6	1.00
		38	72	25	314	34	0.9	40	72	130	5.1	2.5	0.96
		39	89	32	350	70	0.9	49	42	131	5.0	2.6	1.08
		40	67	28	352	56	1.1	55	85	132	5.5	2.8	1.04
		41	92	28	390	35	0.6	35	61	112	5.4	2.6	0.93
		42	106	28	496	54	0.8	48	89	108	5.7	2.8	0.97

a) This value(s) was excluded from the statistical analysis because the abnormality not related to treatment was detected.

Addendum 5-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	GOT (IU/L)	GPT (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	43	66	18	226	244	0.6	66	28	114	5.6	3.0	1.15
		44	63	19	150	217	1.3	66	11	102	5.5	2.9	1.12
		45	72	20	275	269	1.3	73	28	153	5.6	3.1	1.24
		46	72	21	265	321	0.5	71	23	136	5.1	2.7	1.12
		47	70	19	207	275	1.2	84	19	106	5.7	3.0	1.11
		48	74	21	318	250	0.9	85	20	116	5.4	2.9	1.16
		Recovery											
		49	77	24	221	379	0.6	75	28	118	5.7	2.8	0.97
		50	99	26	207	642	0.6	47	26	119	5.7	3.0	1.11
		51	110	24	215	203	1.0	62	20	125	5.5	2.8	1.04
		52	96	22	209	431	1.2	69	19	113	5.3	2.8	1.12
		53	64	14	212	315	1.2	63	21	138	6.2	3.2	1.07
		54	69	19	217	241	0.5	78	21	135	5.8	2.9	1.00
	10	55	75	16	365	591	0.6	60	21	114	5.8	3.1	1.15
		56	102	45	237	350	0.9	60	24	124	5.9	3.2	1.19
		57	78	24	386	158	1.3	49	24	141	5.0	2.7	1.17
		58	79	23	307	303	1.1	70	29	149	5.9	3.0	1.03
		59	83	23	323	245	0.8	68	31	120	5.5	3.0	1.20
		60	70	19	259	279	0.6	54	22	119	5.4	2.8	1.08
	40	61	81	29	285	478	0.7	72	10	115	6.2	3.4	1.21
		62	78	17	264	300	1.4	74	11	110	5.4	3.1	1.35
		63	78	22	214	303	0.5	84	36	146	5.8	3.1	1.15
		64	70	22	335	219	0.7	64	24	121	5.2	2.8	1.17
		65	102	25	240	168	1.0	69	14	112	5.3	2.9	1.21
		66	79	24	305	253	1.1	70	31	120	5.5	2.8	1.04
	200	67	65	18	200	202	1.1	80	27	119	5.6	3.0	1.15
		68	77	17	195	353	1.5	107	40	129	6.1	3.4	1.26
		69	75	21	200	183	0.8	89	21	118	5.5	3.0	1.20
		70	66	16	225	167	0.8	75	45	131	5.4	3.0	1.25
		71	71	19	299	179	0.4	41	7	108	6.0	3.2	1.14
		72	64	17	245	263	0.5	90	28	114	5.5	3.0	1.20
	1,000	73	100	19	356	294	1.8	55	24	107	5.3	3.1	1.41
		74	70	18	209	222	1.4	81	40	100	5.6	3.0	1.15
		75	77	23	196	266	0.6	63	16	99	5.6	3.0	1.15
		76	68	18	282	232	1.0	60	38	129	5.4	3.0	1.25
		77	53	15	209	294	1.0	69	45	158	5.5	3.1	1.29
		78	62	20	253	264	1.1	80	19	129	5.4	2.8	1.08
		Recovery											
		79	73	19	198	240	0.6	58	19	131	5.5	3.0	1.20
		80	94	20	227	293	0.4	77	28	119	5.8	2.9	1.00
		81	106	30	194	290	1.3	60	10	127	5.3	2.6	0.96
		82	76	20	191	349	0.3	58	21	131	5.7	2.9	1.04
		83	82	33	186	426	0.8	46	23	123	5.8	2.8	0.93
		84	62	21	155	294	1.4	67	13	139	5.8	3.1	1.16

Addendum 5-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

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	12.7	0.20	0.06	9.8	8.5	144	4.3	105.9
		2	13.1	0.25	0.10	10.0	8.4	142	4.1	105.1
		3	15.0	0.22	0.10	9.9	7.8	141	4.3	102.9
		4	12.7	0.19	0.07	9.9	7.9	142	4.4	106.5
		5	14.0	0.22	0.12	10.2	8.0	142	4.3	106.3
		6	15.2	0.23	0.09	10.3	8.7	143	4.4	105.7
		Recovery								
		7	17.1	0.27	0.09	9.8	7.5	141	4.0	104.9
		8	14.5	0.24	0.11	10.0	7.4	140	4.6	102.9
		9	15.8	0.30	0.09	10.1	7.1	142	4.7	105.8
		10	15.8	0.23	0.11	10.2	7.0	141	4.0	104.7
		11	17.3	0.24	0.11	9.7	7.7	141	4.5	103.7
		12	14.6	0.23	0.15	9.5	6.2	142	4.2	108.5
	10	13	13.2	0.24	0.07	9.9	7.5	142	4.7	108.2
		14	13.7	0.18	0.10	10.0	8.0	142	4.0	106.7
		15	13.8	0.20	0.09	10.3	8.5	143	4.0	102.6
		16	12.6	0.17	0.09	9.9	8.4	143	4.0	106.9
		17	11.9	0.16	0.07	9.9	8.0	142	4.3	106.4
		18	11.5	0.14	0.10	10.4	8.7	141	4.5	106.6
	40	19	15.3	0.25	0.09	10.1	7.6	140	4.2	106.7
		20	12.4	0.20	0.06	10.0	7.6	141	4.0	106.6
		21	13.4	0.21	0.06	10.0	7.4	141	4.9	105.9
		22	14.8	0.19	0.10	10.0	8.3	143	3.9	106.1
		23	14.0	0.19	0.09	10.1	7.9	141	4.4	104.0
		24	12.3	0.16	0.10	10.1	8.5	140	4.3	104.9
	200	25	12.7	0.20	0.08	9.7	7.2	142	4.2	107.1
		26	11.7	0.20	0.07	10.2	7.4	144	3.8	106.4
		27	14.8	0.17	0.09	9.6	7.4	142	4.2	109.4
		28	15.2	0.20	0.08	10.0	8.4	143	4.4	108.1
		29	15.3	0.19	0.08	10.0	8.3	142	4.6	106.1
		30	16.4	0.20	0.08	10.4	8.1	142	4.5	103.9
	1,000	31	16.5	0.23	0.07	10.0	8.0	142	4.5	107.6
		32	13.3	0.20	0.08	10.0	7.7	142	3.9	104.0
		33	17.0	0.23	0.08	9.8	8.1	141	4.5	107.4
		34	14.7	0.23	0.08	10.0	7.9	141	4.3	104.7
		35	12.9	0.22	0.09	9.9	7.4	142	4.0	107.0
		36	12.6	0.19	0.07	9.7	8.7	143	3.7	105.6
		Recovery								
		37	11.8	0.18	0.09	9.5	7.0	140	4.4	106.1
		38	16.6	0.26	0.07	9.8	7.1	141	4.4	105.1
		39	15.5	0.27	0.10	9.8	6.4	143	4.0	107.1
		40	15.3	0.25	0.10	10.2	8.1	142	4.3	103.9
		41	14.0	0.22	0.10	9.9	7.1	142	4.3	105.5
		42	14.9	0.21	0.08	10.0	7.0	140	5.1	104.9

Addendum 5-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

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	43	14.5	0.23	0.09	10.0	6.8	141	4.2	109.5
		44	15.0	0.20	0.09	9.6	6.8	140	3.9	109.3
		45	11.9	0.18	0.08	10.0	6.8	143	3.4	106.6
		46	16.9	0.23	0.11	9.4	7.3	142	3.6	107.4
		47	16.5	0.19	0.08	9.9	7.6	141	4.6	109.3
		48	13.2	0.20	0.10	10.1	7.7	142	3.8	108.5
		Recovery								
		49	17.8	0.27	0.11	9.9	6.7	139	4.5	107.5
		50	20.6	0.30	0.14	9.8	6.4	139	4.3	107.9
		51	19.0	0.28	0.10	9.5	6.9	139	4.5	106.9
		52	15.7	0.23	0.14	9.5	6.6	140	4.3	108.5
		53	16.2	0.22	0.12	10.0	8.3	140	4.1	104.9
		54	14.0	0.25	0.12	10.1	7.6	141	4.1	106.7
	10	55	15.3	0.22	0.09	9.9	7.3	142	3.7	108.5
		56	15.5	0.21	0.11	9.7	6.9	140	3.8	107.3
		57	17.8	0.23	0.08	10.0	8.5	141	4.2	108.4
		58	15.7	0.22	0.15	10.0	8.4	142	3.6	106.8
		59	14.4	0.20	0.09	9.8	7.0	140	4.2	107.7
		60	18.1	0.25	0.11	10.1	8.4	141	4.6	108.3
	40	61	15.3	0.24	0.11	9.8	6.6	141	4.0	108.3
		62	11.5	0.22	0.11	9.9	7.4	141	3.7	107.6
		63	14.6	0.21	0.09	10.0	7.0	142	3.9	107.4
		64	13.5	0.19	0.11	10.0	8.3	140	3.9	107.8
		65	15.5	0.23	0.12	9.8	7.8	142	4.5	107.8
		66	11.2	0.20	0.09	10.3	7.5	141	4.6	107.7
	200	67	14.7	0.25	0.08	10.1	6.9	141	4.2	108.2
		68	15.0	0.23	0.07	10.1	6.8	142	4.0	108.7
		69	17.4	0.24	0.08	9.7	7.9	143	3.7	110.7
		70	14.3	0.20	0.07	9.9	7.8	141	3.8	107.9
		71	15.2	0.22	0.13	9.7	6.5	142	3.8	110.4
		72	16.7	0.22	0.09	10.2	7.6	140	4.1	107.5
	1,000	73	17.7	0.26	0.08	10.0	8.3	141	4.6	107.5
		74	16.7	0.24	0.09	10.0	6.8	142	4.0	107.9
		75	19.1	0.23	0.09	9.6	6.6	141	4.4	109.9
		76	16.3	0.22	0.08	9.9	8.2	141	4.1	108.5
		77	12.9	0.18	0.05	9.6	8.2	141	3.9	105.9
		78	12.8	0.20	0.09	10.2	8.2	144	3.7	107.5
		Recovery								
		79	17.2	0.25	0.08	9.7	6.5	139	4.0	108.8
		80	21.3	0.26	0.13	9.8	7.4	139	4.6	108.4
		81	18.9	0.32	0.13	9.1	6.5	140	3.4	106.6
		82	14.2	0.21	0.13	9.9	7.2	140	4.3	105.4
		83	17.2	0.26	0.15	9.9	7.0	140	4.1	109.1
		84	14.4	0.25	0.11	10.1	6.3	142	4.3	110.5

Addendum 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Volume (mL)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dL)
Male	Vehicle control	1	6	Y	6.5	+	±	−	−	−	0.1
		2	13	SY	6.5	+	±	−	−	−	0.1
		3	11	Y	6.5	+	±	−	−	−	0.1
		4	25	SY	7.0	±	−	−	±	−	0.1
		5	20	SY	7.0	±	±	−	−	−	0.1
		6	6	Y	6.5	+	+	−	−	−	0.1
		Recovery									
		7	8	Y	6.5	+	±	−	−	−	0.1
		8	11	Y	6.5	±	±	−	−	−	0.1
		9	8	Y	6.5	+	±	−	−	−	0.1
		10	9	Y	6.0	+	±	−	−	−	0.1
		11	6	Y	6.5	+	+	−	−	−	0.1
		12	12	Y	6.0	±	±	−	−	−	0.1
	10	13	12	SY	7.0	+	±	−	−	−	0.1
		14	7	Y	6.5	+	±	−	−	−	0.1
		15	22	SY	6.5	±	±	−	−	−	0.1
		16	16	SY	6.5	±	±	−	−	−	0.1
		17	29	SY	6.5	±	−	−	−	−	0.1
		18	10	Y	6.5	+	±	−	−	−	0.1
	40	19	21	SY	7.0	±	−	−	±	−	0.1
		20	18	SY	6.5	±	±	−	−	−	0.1
		21	9	Y	6.5	+	±	−	−	−	0.1
		22	19	SY	6.5	±	±	−	−	−	0.1
		23	27	SY	6.5	±	−	−	−	−	0.1
		24	12	Y	6.5	+	±	−	−	−	0.1
	200	25	19	SY	7.0	±	±	−	−	−	0.1
		26	19	SY	6.5	±	+	−	−	−	0.1
		27	10	Y	6.5	+	±	−	−	−	0.1
		28	23	SY	7.0	±	±	−	−	−	0.1
		29	23	SY	7.0	±	±	−	±	−	0.1
		30	17	Y	7.0	+	±	−	−	−	0.1
	1,000	31	20	SY	6.5	±	±	−	−	−	0.1
		32	30	SY	7.0	±	−	−	−	−	0.1
		33	16	SY	6.5	±	±	−	−	−	0.1
		34	15	SY	6.5	+	±	−	−	−	0.1
		35	14	Y	6.5	±	±	−	−	−	0.1
		36	14	SY	6.5	+	±	−	±	−	0.1
		Recovery									
		37	24	SY	6.5	±	±	−	+	−	0.1
		38	14	Y	7.0	+	+	−	−	−	0.1
		39	28	SY	6.5	±	±	−	−	−	0.1
		40	18	Y	7.0	+	+	−	−	−	0.1
		41	15	Y	6.5	±	±	−	±	−	0.1
		42	7	Y	6.0	+	−	−	−	−	0.1

SY, Slightly yellow.
Y, Yellow.

Addendum 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Volume (mL)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dL)
Female	Vehicle control	43	13	SY	6.5	±	–	–	–	–	0.1
		44	11	SY	6.5	±	–	–	–	–	0.1
		45	10	Y	7.0	±	–	–	–	–	0.1
		46	9	Y	6.5	±	–	–	–	–	0.1
		47	12	SY	6.5	±	–	–	–	–	0.1
		48	7	Y	6.5	±	–	–	–	–	0.1
		Recovery									
		49	9	Y	6.5	–	–	–	–	–	0.1
		50	8	Y	6.0	±	–	–	–	–	0.1
		51	6	Y	6.5	±	–	–	–	–	0.1
		52	4	Y	6.0	+	–	–	–	–	0.1
		53	5	Y	7.0	±	–	–	–	–	0.1
		54	4	Y	6.0	+	–	–	–	–	0.1
	10	55	4	Y	6.5	+	–	–	–	–	0.1
		56	5	Y	6.5	+	–	–	–	–	0.1
		57	11	SY	7.0	±	–	–	–	–	0.1
		58	3	Y	6.5	++	–	–	–	–	0.1
		59	2	Y	6.5	+	–	–	–	–	0.1
		60	6	Y	6.5	+	–	–	–	–	0.1
	40	61	9	SY	6.5	±	–	–	–	–	0.1
		62	13	SY	7.0	±	–	–	–	–	0.1
		63	7	Y	6.5	±	–	–	–	–	0.1
		64	21	SY	6.5	–	–	–	–	–	0.1
		65	12	SY	6.5	±	–	–	–	–	0.1
		66	4	Y	6.5	+	–	–	–	–	0.1
	200	67	14	SY	6.5	±	–	–	–	–	0.1
		68	4	Y	6.5	+	–	–	–	–	0.1
		69	3	Y	6.5	+	–	–	–	–	0.1
		70	8	Y	6.5	±	–	–	–	–	0.1
		71	6	Y	6,5	+	–	–	–	–	0.1
		72	5	B	7.0	+	–	–	–	–	0.1
	1,000	73	7	Y	6.5	±	–	–	++	–	0.1
		74	15	SY	7.0	±	–	–	–	–	0.1
		75	7	Y	6.5	±	–	–	–	–	0.1
		76	5	Y	6.5	+	–	–	–	–	0.1
		77	9	SY	6.5	±	–	–	–	–	0.1
		78	7	Y	6.5	±	–	–	–	–	0.1
		Recovery									
		79	5	Y	6.5	±	–	–	–	–	0.1
		80	9	Y	6.5	±	–	–	–	–	0.1
		81	5	Y	6.0	±	–	–	–	–	0.1
		82	3	Y	6.0	++	–	–	++	–	0.1
		83	10	Y	6.5	–	–	–	–	–	0.1
		84	8	Y	6.0	±	–	–	–	–	0.1

SY, Slightly yellow.
Y, Yellow.
B, Brown.

Addendum 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Kidney (g)	Testis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Adrenal (mg)	Body weight (g)
Male	Vehicle control	1	9.29	2.78	3.09	–	1.98	0.59	46.3	326.8
		2	11.53	2.74	2.79	–	2.02	0.64	62.2	345.1
		3	9.70	2.41	2.88	–	2.05	0.71	54.5	334.3
		4	9.90	2.77	2.31	–	2.00	0.59	46.7	313.8
		5	10.04	2.79	3.04	–	1.90	0.61	44.9	354.0
		6	11.28	2.87	2.93	–	1.90	0.77	60.4	369.0
		Recovery								
		7	10.93	2.68	3.15	–	1.96	0.74	50.2	402.3
		8	13.08	3.17	3.25	–	1.93	0.79	53.7	421.6
		9	10.85	2.46	2.76	–	1.90	0.53	53.4	404.2
		10	13.22	3.26	3.23	–	2.04	0.85	53.7	442.8
		11	12.59	3.12	2.95	–	2.07	0.64	67.8	406.9
		12	10.75	2.78	2.94	–	2.08	0.76	43.5	396.7
	10	13	9.13	2.37	2.68	–	1.95	0.53	48.8	309.3
		14	9.56	2.96	3.04	–	1.87	0.72	62.3	330.9
		15	11.68	2.85	2.96	–	1.89	0.67	49.5	360.6
		16	8.90	2.59	3.03	–	2.00	0.59	40.7	306.1
		17	9.47	2.60	2.84	–	1.84	0.79	62.5	321.3
		18	9.96	2.89	2.94	–	1.96	0.59	47.2	331.5
	40	19	9.70	2.28	3.08	–	2.03	0.56	43.4	317.1
		20	10.23	3.03	3.21	–	2.06	0.72	55.7	355.0
		21	9.15	2.58	3.22	–	2.01	0.68	55.5	324.6
		22	11.72	3.06	2.63	–	1.99	0.52	54.6	340.3
		23	9.88	2.94	3.16	–	2.11	0.66	63.2	335.1
		24	10.06	2.92	2.62	–	2.07	0.59	40.7	332.1
	200	25	8.91	2.46	2.71	–	1.86	0.53	45.8	289.1
		26	11.38	2.74	3.08	–	1.96	0.67	45.2	345.0
		27	8.77	2.69	2.99	–	1.97	0.61	47.9	295.3
		28	9.52	2.53	2.50	–	1.93	0.59	43.5	321.6
		29	10.37	3.05	2.84	–	1.94	0.66	56.2	335.3
		30	13.82	3.32	2.59	–	1.94	1.01	48.9	375.6
	1,000	31	10.60	2.53	2.82	–	2.11	0.61	48.3	341.2
		32	10.66	2.76	2.84	–	2.03	0.57	54.4	334.5
		33	10.36	2.57	2.78	–	1.95	0.80	52.9	311.1
		34	11.34	2.83	2.55	–	1.86	0.49	58.3	342.2
		35	8.44	2.21	2.67	–	1.98	0.39	48.1	273.1
		36	10.81	2.79	2.75	–	1.97	0.54	47.2	343.6
		Recovery								
		37	9.33	2.95	2.60	–	2.02	0.75	45.6	345.3
		38	11.10	2.60	2.87	–	1.96	0.66	54.6	390.0
		39	9.07	2.63	3.08	–	2.07	0.47	59.6	377.3
		40	10.50	2.88	2.98	–	1.98	0.56	49.5	385.6
		41	11.94	3.31	3.77	–	2.01	0.90	54.7	413.7
		42	11.15	3.11	3.34	–	2.00	1.13	52.9	365.9

Addendum 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Kidney (g)	Testis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Adrenal (mg)	Body weight (g)
Female	Vehicle control	43	6.32	1.69	–	80.5	1.86	0.48	73.3	212.4
		44	5.17	1.57	–	61.0	1.78	0.40	48.4	174.5
		45	6.05	1.59	–	73.2	1.67	0.39	50.4	194.2
		46	5.62	1.75	–	86.7	1.83	0.53	69.4	189.4
		47	5.35	1.63	–	69.1	1.77	0.39	59.4	191.5
		48	6.04	1.63	–	73.4	1.80	0.33	62.3	201.2
		Recovery								
		49	6.16	1.65	–	63.9	1.78	0.48	65.1	210.6
		50	6.10	1.63	–	93.7	1.79	0.40	74.0	231.6
		51	6.40	1.54	–	82.8	1.92	0.44	86.7	230.2
		52	5.35	1.47	–	73.5	1.82	0.37	62.6	201.5
		53	6.67	1.73	–	111.6	1.91	0.45	73.7	225.8
		54	6.07	1.52	–	80.7	1.78	0.46	69.1	211.1
	10	55	5.86	1.58	–	73.0	1.92	0.44	58.4	194.8
		56	5.15	1.58	–	63.3	1.76	0.26	62.8	169.1
		57	5.88	1.68	–	78.2	1.91	0.45	66.2	217.5
		58	5.65	1.47	–	72.0	1.86	0.42	61.6	195.7
		59	4.88	1.47	–	60.7	1.82	0.33	62.6	165.0
		60	6.43	1.62	–	85.9	1.81	0.59	78.2	215.6
	40	61	5.16	1.62	–	68.4	1.73	0.38	57.6	179.9
		62	5.80	1.73	–	74.8	1.76	0.48	65.8	208.8
		63	6.43	1.92	–	73.1	1.68	0.36	53.9	211.0
		64	5.54	1.55	–	80.0	1.83	0.39	67.3	197.1
		65	4.99	1.37	–	60.8	1.66	0.35	53.1	175.9
		66	6.61	1.75	–	91.4	1.91	0.48	70.3	212.3
	200	67	6.38	1.48	–	82.1	1.76	0.41	67.1	200.8
		68	6.67	1.72	–	77.5	1.91	0.34	51.9	204.6
		69	6.19	1.50	–	58.8	1.85	0.39	55.6	198.0
		70	6.01	1.56	–	85.0	1.81	0.43	67.8	197.3
		71	4.99	1.54	–	80.1	1.87	0.37	69.8	181.2
		72	5.46	1.60	–	67.0	1.76	0.44	62.3	189.4
	1,000	73	6.39	1.62	–	78.4	1.75	0.36	74.3	201.1
		74	6.56	1.73	–	68.8	1.81	0.37	57.0	202.4
		75	5.59	1.46	–	63.9	1.74	0.32	54.2	180.7
		76	6.23	1.47	–	58.4	1.84	0.35	58.8	198.3
		77	7.26	1.71	–	65.3	1.75	0.38	63.1	199.4
		78	6.63	1.75	–	85.1	1.80	0.36	68.6	204.7
		Recovery								
		79	6.54	1.55	–	74.2	1.84	0.46	73.1	212.6
		80	6.58	1.84	–	96.5	1.85	0.48	68.7	259.6
		81	5.14	1.31	–	74.1	1.76	0.37	74.6	199.2
		82	6.57	1.71	–	77.6	1.86	0.50	81.9	229.5
		83	6.34	1.80	–	102.0	1.84	0.39	74.6	242.5
		84	6.80	1.78	–	106.7	1.85	0.48	86.8	244.0

Addendum 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Kidney (g/100g)	Testis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Adrenal (mg/100g)	Body weight (g)
Male	Vehicle control	1	2.84	0.85	0.95	–	0.61	0.18	14.2	326.8
		2	3.34	0.79	0.81	–	0.59	0.19	18.0	345.1
		3	2.90	0.72	0.86	–	0.61	0.21	16.3	334.3
		4	3.15	0.88	0.74	–	0.64	0.19	14.9	313.8
		5	2.84	0.79	0.86	–	0.54	0.17	12.7	354.0
		6	3.06	0.78	0.79	–	0.51	0.21	16.4	369.0
		Recovery								
		7	2.72	0.67	0.78	–	0.49	0.18	12.5	402.3
		8	3.10	0.75	0.77	–	0.46	0.19	12.7	421.6
		9	2.68	0.61	0.68	–	0.47	0.13	13.2	404.2
		10	2.99	0.74	0.73	–	0.46	0.19	12.1	442.8
		11	3.09	0.77	0.72	–	0.51	0.16	16.7	406.9
		12	2.71	0.70	0.74	–	0.52	0.19	11.0	396.7
	10	13	2.95	0.77	0.87	–	0.63	0.17	15.8	309.3
		14	2.89	0.89	0.92	–	0.57	0.22	18.8	330.9
		15	3.24	0.79	0.82	–	0.52	0.19	13.7	360.6
		16	2.91	0.85	0.99	–	0.65	0.19	13.3	306.1
		17	2.95	0.81	0.88	–	0.57	0.25	19.5	321.3
		18	3.00	0.87	0.89	–	0.59	0.18	14.2	331.5
	40	19	3.06	0.72	0.97	–	0.64	0.18	13.7	317.1
		20	2.88	0.85	0.90	–	0.58	0.20	15.7	355.0
		21	2.82	0.79	0.99	–	0.62	0.21	17.1	324.6
		22	3.44	0.90	0.77	–	0.58	0.15	16.0	340.3
		23	2.95	0.88	0.94	–	0.63	0.20	18.9	335.1
		24	3.03	0.88	0.79	–	0.62	0.18	12.3	332.1
	200	25	3.08	0.85	0.94	–	0.64	0.18	15.8	289.1
		26	3.30	0.79	0.89	–	0.57	0.19	13.1	345.0
		27	2.97	0.91	1.01	–	0.67	0.21	16.2	295.3
		28	2.96	0.79	0.78	–	0.60	0.18	13.5	321.6
		29	3.09	0.91	0.85	–	0.58	0.20	16.8	335.3
		30	3.68	0.88	0.69	–	0.52	0.27	13.0	375.6
	1,000	31	3.11	0.74	0.83	–	0.62	0.18	14.2	341.2
		32	3.19	0.83	0.86	–	0.61	0.17	16.3	334.5
		33	3.33	0.83	0.89	–	0.63	0.19	17.0	311.1
		34	3.31	0.83	0.75	–	0.54	0.14	17.0	342.2
		35	3.09	0.81	0.98	–	0.73	0.14	17.8	273.1
		36	3.15	0.81	0.80	–	0.57	0.16	13.7	343.6
		Recovery								
		37	2.70	0.85	0.75	–	0.58	0.22	13.2	345.3
		38	2.85	0.67	0.74	–	0.50	0.17	14.0	390.0
		39	2.40	0.70	0.82	–	0.55	0.12	15.8	377.3
		40	2.72	0.75	0.77	–	0.51	0.15	12.8	385.6
		41	2.89	0.80	0.91	–	0.49	0.22	13.2	413.7
		42	3.05	0.85	0.91	–	0.55	0.31	14.5	365.9

Addendum 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Kidney (g/100g)	Testis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Adrenal (mg/100g)	Body weight (g)
Female	Vehicle control	43	2.98	0.80	-	37.9	0.88	0.23	34.5	212.4
		44	2.96	0.90	-	35.0	1.02	0.23	27.7	174.5
		45	3.12	0.82	-	37.7	0.86	0.20	26.0	194.2
		46	2.97	0.92	-	45.8	0.97	0.28	36.6	189.4
		47	2.79	0.85	-	36.1	0.92	0.20	31.0	191.5
		48	3.00	0.81	-	36.5	0.89	0.16	31.0	201.2
		Recovery								
		49	2.92	0.78	-	30.3	0.85	0.23	30.9	210.6
		50	2.63	0.70	-	40.5	0.77	0.17	32.0	231.6
		51	2.78	0.67	-	36.0	0.83	0.19	37.7	230.2
		52	2.66	0.73	-	36.5	0.90	0.18	31.1	201.5
		53	2.95	0.77	-	49.4	0.85	0.20	32.6	225.8
		54	2.88	0.72	-	38.2	0.84	0.22	32.7	211.1
	10	55	3.01	0.81	-	37.5	0.89	0.23	30.0	194.8
		56	3.05	0.93	-	37.4	1.04	0.15	37.1	169.1
		57	2.70	0.77	-	36.0	0.88	0.21	30.4	217.5
		58	2.89	0.75	-	36.8	0.95	0.21	31.5	195.7
		59	2.96	0.89	-	36.8	1.10	0.20	37.9	165.0
		60	2.98	0.75	-	39.8	0.84	0.27	36.3	215.6
	40	61	2.87	0.90	-	38.0	0.96	0.21	32.0	179.9
		62	2.78	0.83	-	35.8	0.84	0.23	31.5	208.8
		63	3.05	0.91	-	34.6	0.80	0.17	25.5	211.0
		64	2.81	0.79	-	40.6	0.93	0.20	34.1	197.1
		65	2.84	0.78	-	34.6	0.94	0.20	30.2	175.9
		66	3.11	0.82	-	43.1	0.80	0.23	33.1	212.3
	200	67	3.18	0.74	-	40.9	0.88	0.20	33.4	200.8
		68	3.26	0.84	-	37.8	0.93	0.17	25.4	204.6
		69	3.13	0.76	-	29.7	0.93	0.20	28.1	198.0
		70	3.05	0.79	-	43.1	0.92	0.22	34.4	197.3
		71	2.75	0.85	-	44.2	1.03	0.20	38.5	181.2
		72	2.88	0.84	-	35.4	0.93	0.23	32.9	189.4
	1,000	73	3.18	0.81	-	39.0	0.87	0.18	36.9	201.1
		74	3.24	0.85	-	34.0	0.89	0.18	28.2	202.4
		75	3.09	0.81	-	35.4	0.96	0.18	30.0	180.7
		76	3.14	0.74	-	29.5	0.93	0.18	29.7	198.3
		77	3.64	0.86	-	32.7	0.88	0.19	31.6	199.4
		78	3.24	0.85	-	41.6	0.88	0.18	33.5	204.7
		Recovery								
		79	3.08	0.73	-	34.9	0.87	0.22	34.4	212.6
		80	2.53	0.71	-	37.2	0.71	0.18	26.5	259.6
		81	2.58	0.66	-	37.2	0.88	0.19	37.4	199.2
		82	2.86	0.75	-	33.8	0.81	0.22	35.7	229.5
		83	2.61	0.74	-	42.1	0.76	0.16	30.8	242.5
		84	2.79	0.73	-	43.7	0.76	0.20	35.6	244.0

Addendum 9-1 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	Kidney Pelvic dilatation (right)	Kidney Pelvic dilatation +
		3	ta	No abnormalities detected	No abnormalities detected
		4	ta	No abnormalities detected	No abnormalities detected
		5	ta	No abnormalities detected	No abnormalities detected
		6	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, spleen and adrenals.
ta, terminal autopsy.
+, slight.

Addendum 9-2 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)	7	ta	No abnormalities detected	No abnormalities detected
		8	ta	No abnormalities detected	No abnormalities detected
		9	ta	No abnormalities detected	Liver Microgranuloma +
		10	ta	No abnormalities detected	No abnormalities detected
		11	ta	No abnormalities detected	No abnormalities detected
		12	ta	No abnormalities detected	No abnormalities detected

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

Addendum 9-3 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
Male	10	13	ta	No abnormalities detected	Not examined
		14	ta	No abnormalities detected	Not examined
		15	ta	No abnormalities detected	Not examined
		16	ta	No abnormalities detected	Not examined
		17	ta	No abnormalities detected	Not examined
		18	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

[redacted]

Addendum 9-4 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	40	19	ta	No abnormalities detected	Not examined
		20	ta	No abnormalities detected	Not examined
		21	ta	No abnormalities detected	Not examined
		22	ta	Kidney Pelvic dilatation (right)	Kidney Pelvic dilatation +
		23	ta	No abnormalities detected	Not examined
		24	ta	No abnormalities detected	Not examined

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

Addendum 9-5 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	25	ta	No abnormalities detected	No abnormalities detected
		26	ta	No abnormalities detected	Liver Microgranuloma +
		27	ta	No abnormalities detected	No abnormalities detected
		28	ta	No abnormalities detected	No abnormalities detected
		29	ta	No abnormalities detected	No abnormalities detected
		30	ta	Spleen Whitish region (ϕ 3 mm)	Spleen Focal necrosis ++

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

[redacted]

Addendum 9-6 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	1,000	31	ta	No abnormalities detected	Liver Centrilobular hypertrophy of hepatocytes + Single cell necrosis of hepatocytes +
		32	ta	No abnormalities detected	Liver Single cell necrosis of hepatocytes +
		33	ta	No abnormalities detected	Liver Single cell necrosis of hepatocytes +
		34	ta	No abnormalities detected	Liver Centrilobular hypertrophy of hepatocytes +
		35	ta	No abnormalities detected	Liver Centrilobular hypertrophy of hepatocytes + Single cell necrosis of hepatocytes +
		36	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, spleen and adrenals.
ta, terminal autopsy.
+, slight.

Addendum 9-7 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	1,000 (Recovery)	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	No abnormalities detected
		41	ta	No abnormalities detected	No abnormalities detected
		42	ta	Spleen Nodule (ϕ 7 mm)	Spleen Follicular hypertrophy ++

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

[redacted]

Addendum 9-8 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	43	ta	No abnormalities detected	No abnormalities detected
		44	ta	No abnormalities detected	No abnormalities detected
		45	ta	No abnormalities detected	No abnormalities detected
		46	ta	No abnormalities detected	Kidney Solitary cyst in medulla +
		47	ta	No abnormalities detected	No abnormalities detected
		48	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, spleen and adrenals.
ta, terminal autopsy.
+, slight.

Addendum 9-9 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
Female	Vehicle control (Recovery)	49	ta	No abnormalities detected	Not examined
		50	ta	No abnormalities detected	Not examined
		51	ta	No abnormalities detected	Not examined
		52	ta	No abnormalities detected	Not examined
		53	ta	No abnormalities detected	Not examined
		54	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

Addendum 9-10 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
Female	10	55	ta	No abnormalities detected	Not examined
		56	ta	No abnormalities detected	Not examined
		57	ta	No abnormalities detected	Not examined
		58	ta	No abnormalities detected	Not examined
		59	ta	No abnormalities detected	Not examined
		60	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

Addendum 9-11 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
Female	40	61	ta	No abnormalities detected	Not examined
		62	ta	No abnormalities detected	Not examined
		63	ta	No abnormalities detected	Not examined
		64	ta	No abnormalities detected	Not examined
		65	ta	No abnormalities detected	Not examined
		66	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

[redacted]

Addendum 9-12 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
Female	200	67	ta	No abnormalities detected	Not examined
		68	ta	No abnormalities detected	Not examined
		69	ta	No abnormalities detected	Not examined
		70	ta	No abnormalities detected	Not examined
		71	ta	No abnormalities detected	Not examined
		72	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

Addendum 9-13 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	1,000	73	ta	No abnormalities detected	No abnormalities detected
		74	ta	No abnormalities detected	No abnormalities detected
		75	ta	No abnormalities detected	No abnormalities detected
		76	ta	No abnormalities detected	No abnormalities detected
		77	ta	No abnormalities detected	No abnormalities detected
		78	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, spleen and adrenals.
ta, terminal autopsy.

Addendum 9-14 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
Female	1,000 (Recovery)	79	ta	No abnormalities detected	Not examined
		80	ta	No abnormalities detected	Not examined
		81	ta	No abnormalities detected	Not examined
		82	ta	No abnormalities detected	Not examined
		83	ta	No abnormalities detected	Not examined
		84	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

[redacted]

[MSOffice1]Check with translator; I think there should be a 'not' in this sentence.
[MSOffice2]Same as above; check with translator; I think there should be a 'not' in this sentence.