Exponent®

1 December 2025

Office of Environmental Health Hazard Assessment (OEHHA)
1001 I Street
Sacramento, California 95814

Subject: Relevant Information on the Reproductive Toxicity of p,p′-Bisphenols
Exponent Project No. 2501934.UK2

On behalf of Nippon Kayaku Co., Ltd., Exponent is submitting information to address OEHHA's Request for Relevant Information on the Reproductive Toxicity of p,p'-Bisphenol Chemicals. Specifically, Exponent is submitting reliable and relevant studies that evaluated reproductive, developmental, and endocrine potential of the substance 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol] (CASRN 41481-66-7). As detailed further below in **Sections 1** and **2**, these studies showed no evidence of reproductive or developmental toxicity, and no evidence of endocrine effects. Therefore, this evidence supports that 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol] should not be listed under Proposition 65.

Attached to this cover letter are two relevant toxicology reports produced in accordance with Good Laboratory Practice (GLP) that investigated the reproductive and developmental toxicity, and endocrine effects of 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol]. In these study reports, 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol is identified by the abbreviations "TG-SA" or "TG-SH(H)".

- **Attachment 1:** Safepharm Laboratories Limited. 1999. TG-SA: Assessment of Oestrogenic Activity using Recombinant Yeast Screen Assay. Project Number 189/1663. [summary in **Section 1**]
- **Attachment 2:** Chemicals Evaluation and Research Institute (CERI). 2023. Reproduction/Developmental Toxicity Screening Test of TG-SH(H) in Rats. Study Number E16-0045. [summary in **Section 2**]

1. 4,4′-Sulfonylbis[2-(2-propen-1-yl)phenol Does Not Show *In Vitro* Estrogenic Activity

4,4′-Sulfonylbis[2-(2-propen-1-yl)phenol was evaluated for estrogenic (agnostic) activity using a recombinant yeast screening assay conducted under GLP. This is a recognized standardized method for environmental screening of water body estrogenic potential.[1,2]

The study design involved incubating 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol in a dose range from 0.049 to 100 milligrams per liter (mg/l) with a recombinant strain of *Saccharomyces cerevisiae* (yeast) that contained human estrogen receptor (hER) and the reporter gene, lacZ. Furthermore, the study design included incubation of two known hER agonist positive controls, 17β-estradiol and bisphenol A (BPA). Agonistic activity was measured through color absorbance (spectrophotometer), with activation of the lacZ-controlled β-galactosidase enzyme and administration of cholorphenol red-β-D-galactopyranoside (CPRG) causing a color change from yellow to red, i.e., an increase in absorbance at 540 nm wavelength. Compounds that are not hER agonists will either show no increase in absorbance or, if cytotoxicity and/or enzyme interference occurs, a potential decrease in absorbance at 540 nm.[3]

17β-estradiol and BPA demonstrated a clear dose-response increase in absorbance at 540 nm, with BPA's dose response indicating a potency approximately 2100-fold less than 17β-estradiol. Overall, these results indicate the validity of the assay to detect relatively strong and weak estrogenic activity as indicated by the 17β-estradiol and BPA results, respectively.

There was no increase in absorbance for 4,4′-evaluate sulfonylbis[2-(2-propen-1-yl)phenol at any tested dose level, which demonstrates the compound is not an estrogen agonist.

[1] ISO 19040-1:2018. Water quality — Determination of the estrogenic potential of water and waste water. Part 1: Yeast estrogen screen (Saccharomyces cerevisiae). https://www.iso.org/standard/64450.html.

[2] Routledge, E.J. and Sumpter, J.P., 1996. Estrogenic activity of surfactants and some of their degradation products assessed using a recombinant yeast screen. Environmental toxicology and chemistry, 15(3), pp.241-248.

[3] Ibid.

2. 4,4′-Sulfonylbis[2-(2-propen-1-yl)phenol Does Not Show *In Vivo* Reproductive, Developmental, or Endocrine Effects.

4,4′-Sulfonylbis[2-(2-propen-1-yl)phenol was evaluated for multiple female reproductive, male reproductive and developmental toxicity, and endocrine endpoints using an Organization for Economic and Cooperative Development (OECD) Test Guideline 421 reproductive/developmental toxicity screening test conducted under GLP. This is an internationally recognized test guideline validated for evaluating male and female reproductive performance and also includes endocrine disruptor endpoints.

The study design involved groups of ten male and female young adult rats administered 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol via oral gavage at 0 (vehicle control), 20, 100, 300 or 1000 mg/kg bw/day for 14 days prior to mating through to 29 days total for males and until lactation day 13 for females. The female reproductive, male reproductive, developmental, and endocrine effects endpoints are listed below:

Female reproductive	**Male reproductive**	**Developmental**	**Endocrine effects**
Vaginal smears (estrous cyclicity)	Copulation index	Live birth index	Parental thyroid weights
Copulation index	Fertility index	Number of offspring	Parental male and offspring serum thyroxine (T4)
Fertility index	Testes, epididymides, prostate, and seminal vesicle weights	Sex ratio	
Gestation index		Litter size	Offspring anogenital distance (AGD)
Implantation count	Testes and epididymides and ovary histopathology	Offspring bodyweights	
Ovary histopathology		External examinations	Offspring nipple retention
		Clinical observations	

There were no treatment-related effects across any of the measured female reproductive, male reproductive, developmental, and endocrine effects endpoints up to 1000 mg/kg bw/day (highest dose tested). Note that 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol did elicit systemic toxicity in males as evidenced by degeneration, necrosis, and dilatation and regeneration of the tubule of the kidney at 1000 mg/kg bw/day. Further, there was evidence that the compound induced local irritation in the stomach of the females including mucosal hyperplasia of the duodenum, cecum and colon. Therefore, even in the presence of dosages that elicited evidence of systemic toxicity or local toxicity in the stomach, there was no evidence of reproductive, developmental or endocrine effects.

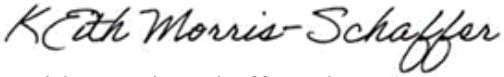
In summary, the study supports that 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol is not a female reproductive, male reproductive or developmental toxicant.

Overall Summary

The attached study reports for 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol] are responsive to OEHHA's Request for Relevant Information on the Reproductive Toxicity of p,p'-Bisphenol Chemicals. These studies showed no evidence of reproductive or developmental toxicity, and no evidence of endocrine effects. Therefore, this evidence supports that 4,4′-sulfonylbis[2-(2-propen-1-yl)phenol] should not be listed under Proposition 65.

If you have any questions or require additional information, please do not hesitate to contact me at (212) 895-8151 or kmorrischaffer@exponent.com.

Sincerely,



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Enclosures 2

Attachment 1: Assessment of Oestrogenic Activity Using a Recombinant Yeast Screen Assay

This study report is provided in response to the OEHHA's Request for Relevant Information, and submission of this study report is not a waiver of Nippon Kayaku Co., Ltd's ownership rights. No third-party is granted consent to use this study report for any purpose, in any jurisdiction.

TG-SA (Lot No. 710427):

ASSESSMENT OF OESTROGENIC ACTIVITY

USING A RECOMBINANT YEAST SCREEN ASSAY

SPL PROJECT NUMBER: 189/1663

AUTHOR: C MEAD

STUDY SPONSOR:

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ECCMR00412

SPL PROJECT NUMBER: 189/1663

QUALITY ASSURANCE REPORT

The routine inspection of short term studies at Safepharm is carried out as a continuous process designed to encompass all major phases of each study type once per month. Inspection findings are reported to Management/Study Directors on the day of inspection in each case. Dates of relevant monthly inspections are as follows:

01, 03, 18 March 1999

This report has been audited by Safepharm Quality Assurance Unit. It is considered to be an accurate account of the data generated and of the procedures followed.

Date of Report Audit:

21 April 1999

..... DATE: 24 MAY 1999

For Safepharm Quality Assurance Unit*

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*Authorised QA Signatures:

Head of Department: JR Pateman CBiol MIBiol DipRQA
Deputy Head of Department: JM Crowther MIScT
Senior Audit Staff: JV Johnson BSc; G Wren ONC; AJ Cooper HNC; RJ Gilbert BSc

GLP COMPLIANCE STATEMENT

I, the undersigned, hereby declare that the objectives laid down in the protocol were achieved and as nothing occurred to adversely affect the quality or integrity of the study, I consider the data generated to be valid. This report fully and accurately reflects the procedures used and data generated.

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1997 (SI 1997/654)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC and 88/320/EEC.

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended); and to the Japanese Ministry of Agriculture, Forestry and Fisheries (59 NohSan, Notification No. 3850, Agricultural Production Bureau) - confirmed by an Arrangement between the Ministry and UK Department of Health; the Japanese Ministry of Health and Welfare (Notification No. 313, Pharmaceutical Affairs Bureau - as amended, and Kanpogyo No. 39 Environmental Agency, Yakuhatsu No. 229); and the Japanese Ministry of International Trade and Industry (Chemical Substances Control Law, Kanpogyo No. 39 Environmental Agency, Kikyoku No. 85).

..... Date: 21 MAY 1999

C Mead BSc
Study Director

CONTENTS

SPL PROJECT NUMBER: 189/1663

SUMMARY

STUDY SPONSOR : NIPPON KAYAKU CO., LTD.

STUDY TITLE : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

TEST MATERIAL : TG-SA (Lot No. 710427)

Methods

A study was performed to assess the oestrogenic activity of the test material using a recombinant yeast screen assay. The method was based on a proven recombinant yeast assay for the determination of environmental endocrine disruption (Routledge and Sumpter, 1996).

Procedure

A recombinant strain of *Saccharomyces cerevisiae* was exposed to an aqueous dispersion of the test material at concentrations of 0.049, 0.098, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 mg/l (four replicate wells per concentration) for approximately 2 days at a temperature of 25 ± 1 °C.

The response of the recombinant yeast screen assay to known oestrogenic compounds was confirmed using 17β-estradiol and Bisphenol A as positive control materials.

The absorbance values of the yeast populations were determined for each control and treatment group after approximately 2 days.

Results

The test material showed no significant oestrogenic activity at all concentrations tested.

TG-SA (Lot No. 710427):
ASSESSMENT OF OESTROGENIC ACTIVITY
USING A RECOMBINANT YEAST SCREEN ASSAY

1. INTRODUCTION

This report contains a description of the methods used and results obtained during a study to investigate the oestrogenic activity of TG-SA (Lot No. 710427) using a recombinant yeast screen assay. The method was based on a proven recombinant yeast assay for the determination of environmental endocrine disruption (Routledge and Sumpter, 1996).

Range-finding was not performed due to data obtained from previous studies from the same test material with different lot numbers.

The definitive study was conducted between 6 April 1999 and 8 April 1999.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's Identification	:	TG-SA (Lot No. 710427)
Description	:	white solid
Batch Number	:	710427
Date Received	:	16 March 1999
Storage Conditions	:	room temperature in darkness

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Experimental Preparation

For the purpose of the definitive study the test material was prepared using a preliminary solution in ethanol.

An amount of test material (20 mg) was dissolved in ethanol with the aid of ultrasonics and the volume adjusted to 10 ml to give a 20 mg/10 ml solvent stock solution from which serial dilutions were made in a 96-well, optically flat microtitre plate, to give 10, 5.0, 2.5, 1.25, 0.63, 0.31, 0.16, 0.078, 0.039, 0.020 and 0.0098 mg/10 ml solvent stock solutions.

An aliquot (10 μl) of each relevant solvent stock solution was transferred to a 96-well, optically flat microtitre plate, and the solvent allowed to evaporate to dryness prior to addition of 200 μl of assay medium (Appendix II) to each well on the microtitre plate to give the test concentrations of 0.049, 0.098, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 mg/l.

Analysis of the concentration, homogeneity and stability of the test material in the test solutions were not appropriate to the Test Method.

2.3 Positive Controls

2.3.1 17β-estradiol

A positive control, 17β-estradiol (Sigma Lot No. 28H0818) was included in the definitive study. An initial stock solution was prepared by dissolving an amount of positive control material (54.5 mg) in ethanol with the aid of ultrasonics and adjusting the volume to 10 ml to give a 54.5 mg/10 ml solvent stock solution from which dilutions were made to give 5.45×10^{-4}, 2.73×10^{-4}, 1.36×10^{-4}, 6.81×10^{-5}, 3.41×10^{-5}, 1.70×10^{-5}, 8.52×10^{-6}, 4.26×10^{-6}, 2.13×10^{-6}, 1.06×10^{-6}, 5.32×10^{-7} and 2.66×10^{-7} ml/10 ml solvent stock solutions.

An aliquot (10 μl) of each relevant solvent stock solution was transferred to a 96-well, optically flat microtitre plate, and the solvent allowed to evaporate to dryness prior to addition of 200 μl assay medium (Appendix II) to each well on the microtitre plate to give the test concentrations of 1.33×10^{-6}, 2.66×10^{-6}, 5.32×10^{-6}, 1.06×10^{-5}, 2.13×10^{-5}, 4.26×10^{-5}, 8.52×10^{-5} , 1.70×10^{-4}, 3.41×10^{-4}, 6.81×10^{-4}, 1.36×10^{-3} and 2.73×10^{-3} mg/l.

2.3.2 Bisphenol A

A second positive control, Bisphenol A (Sigma Lot No. 68H3448) was included in the definitive study. An initial stock solution was prepared by dissolving an amount of positive control material (20 mg) in ethanol with the aid of ultrasonication and adjusting the volume to 10 ml to give a 20 mg/10 ml solvent stock solution from which dilutions were made to give 10, 5.0, 2.5, 1.25, 0.63, 0.31, 0.16, 0.078, 0.039, 0.020 and 0.0098 mg/10 ml solvent stock solutions.

An aliquot (10 μl) of each solvent stock solution was transferred to a 96-well, optically flat microtitre plate, and the solvent allowed to evaporate to dryness prior to addition of 200 μl assay medium (Appendix II) to each well on the microtitre plate to give the test concentrations of 0.049, 0.098, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 mg/l.

3. METHODS

3.1 Test Species

3.1.1 Stock culture

The test was carried out using a recombinant strain of *Saccharomyces cerevisiae*, containing the human oestrogen receptor (hER) and the reporter gene *lac-Z* (encoding for the enzyme β-galactosidase), obtained from Brunel University, Uxbridge, Middlesex.

Stock cultures of the yeast strain were stored in the laboratory at -20°C as a 10x concentrated stock culture in sterile cryogenic vials.

3.1.2 Preparation of inoculum

Approximately 24 hours prior to commencing the test, an aqueous suspension of *Saccharomyces cerevisiae* was produced by inoculating 50 ml of growth medium (Appendix II) with an aliquot (125 µl) of a 10x concentrated stock culture in a sterile conical flask. The flask was plugged with sterile cotton wool and incubated at 28 ± 1 °C for approximately 24 hours on an orbital shaker at approximately 100 rpm.

After approximately 24 hours incubation the yeast suspension had an absorbance value of 0.468 at 620 nm (equivalent to a cell density of approximately 4.0×10^7 cells/ml). An aliquot (3.2 ml) of the 24-hour yeast suspension was used to inoculate 158 ml of assay medium in order to give an initial cell density of approximately 8×10^5 cells/ml.

3.2 Test Media

Stock solutions required for the preparation of test media are defined in Appendix I. The growth medium and assay medium used for the preparation of inoculum and the test solution preparation is defined in Appendix II.

3.3 Procedure

3.3.1 Definitive study

For the purpose of the definitive study the following test concentrations were assigned to the definitive study 0.049, 0.098, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 mg/l.

3.3.1.1 Preparation of the test material

For the purpose of the definitive study the required amount of test material was added to each test well using the method described in Section 2.2.

3.3.1.2 Exposure conditions

The study was conducted in 96-well, optically flat microtitre plates, each well containing 200 µl of test solution. Two replicate plates were prepared for the

test material each containing two rows of test solution wells and six rows of control wells. Two replicate plates were prepared for the positive control materials each plate containing two rows of each positive control test solution wells, two rows of solvent control wells and two rows of control wells.

The control and solvent control groups were maintained under identical conditions but not exposed to the test material. The solvent control group was exposed to 10 μl ethanol per 200 μl of assay medium.

The microtitre plates were sealed with autoclave tape and incubated at 25 ± 1 °C in darkness (LMS cooled incubator) for a period of approximately 2 days. Each day the plates were shaken (Titramax 100) vigorously for approximately 2 minutes.

After incubation for 2 days, the absorbance values of the control and test cultures were determined at 540 nm (for colour) and 620 nm (for turbidity) using a Multiskan RC plate reader.

3.3.2 Evaluation of data

The corrected absorbance at 540 nm was calculated for each test material and positive control concentration using the following equation:

$$CA_{540} = Tm_{540} - [Tm_{620} - Sc_{620}]$$

where: CA_{540} = Corrected Absorbance at 540 nm
Tm_{540} = Absorbance of test culture at 540 nm
Tm_{620} = Absorbance of test culture at 620 nm
Sc_{620} = Mean absorbance of solvent control culture at 620 nm

Dose-Response curves were constructed by plotting mean corrected absorbance at 540 nm against concentration (Figure 1).

The absorbance values of the solvent control cultures were measured and plotted on the same axes as the 17β-estradiol curve.

The relative potency of the test material and Bisphenol A with respect to 17β-estradiol was calculated using the following equation:

$$\text{relative potency} = \frac{\text{concentration of test material or Bisphenol A required to produce 50\% of maximum response}}{\text{concentration of 17}\beta\text{-estradiol required to produce 50\% of maximum response}}$$

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 Definitive Study

Mean corrected absorbance values for the positive control materials, test material and associated solvent control cultures are given in Tables 1 to 3. Dose-response curves for the test and positive control materials and the associated solvent control cultures are presented in Figure 1.

Bisphenol A was determined to be 2100 times less potent than 17β-estradiol.

The response of the recombinant yeast screen assay to both of the positive control materials was comparable to published results thereby confirming the suitability of the inoculum and culture conditions.

The test material showed no significant oestrogenic activity at all concentrations tested.

Care should be taken in the interpretation of this result as the dose-response curve for the test material shows a concentration dependent decrease in the absorbance values obtained for the 3.13 mg/l to 50 mg/l test cultures. This decrease is considered to be due to inhibition of the β-D-galactosidase enzyme responsible for the metabolism of chlorophenol red-β-D-galactopyranoside (CPRG) from its normal yellow colour to the red product that is monitored at 540 nm as a measure of oestrogenic activity. At the test concentration of 100 mg/l, the response of the yeast overcomes this inhibition and results in an increase in the measured absorbance at 540 nm.

Overall the results of the study show that the test material does not bind to the oestrogen receptor site in the recombinant yeast and produces an oestrogenic response. However, the response to the test material is approximately 4 orders of magnitude less than that of 17β-estradiol and approximately 1 order of magnitude less than Bisphenol A. Based on these results the test material can be said to be significantly less oestrogenic than the natural steroid 17β-estradiol, however without additional information as to likely environmental concentrations and a knowledge

of the test materials life cycle, the oestrogenic activity of the test material in the environment cannot be predicted.

In accordance with current regulatory guidelines for the environmental classification of chemicals, it was considered unnecessary and unrealistic to test at concentrations in excess of 100 mg/l in order to obtain a significant response in the yeast screen assay.

6. CONCLUSION

The test material showed no significant oestrogenic activity at all concentrations tested.

7. REFERENCE

Routledge E J and Sumpter J P, 1996, "Estrogenic activity of surfactants and some of their degradation products assessed using a recombinant yeast screen", *Environmental Toxicology and Chemistry* **15**: 241-248.

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

TABLE 1

CORRECTED MEAN ABSORBANCE VALUES FOR 17β-ESTRADIOL AND ASSOCIATED SOLVENT CONTROL CULTURES IN THE DEFINITIVE STUDY

Concentration (mg/l)	17β-estradiol	Solvent Control *
1.33×10^{-6}	1.685	1.717
2.66×10^{-6}	1.732	1.753
5.32×10^{-6}	1.720	1.759
1.06×10^{-5}	1.724	1.711
2.13×10^{-5}	1.747	1.727
4.26×10^{-5}	1.758	1.699
8.52×10^{-5}	1.725	1.717
1.70×10^{-4}	1.880	1.723
3.41×10^{-4}	1.957	1.698
6.81×10^{-4}	2.155	1.676
1.36×10^{-3}	2.394	1.617
2.73×10^{-3}	2.559	1.622

* Solvent control absorbance values represent the mean absorbance values of solvent control wells in the same row on the microtitre plate as the stated 17β-estradiol concentration

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

TABLE 2

CORRECTED MEAN ABSORBANCE VALUES FOR BISPHENOL A AND ASSOCIATED SOLVENT CONTROL CULTURES IN THE DEFINITIVE STUDY

Concentration (mg/l)	Bisphenol A	Solvent Control*
0.049	1.640	1.717
0.098	1.634	1.753
0.20	1.688	1.759
0.39	1.735	1.711
0.78	1.889	1.727
1.56	2.007	1.699
3.13	2.150	1.717
6.25	2.264	1.723
12.5	2.251	1.698
25	2.282	1.676
50	2.110	1.617
100	2.040	1.622

* Solvent control absorbance values represent the mean absorbance values of pairs of solvent control wells in the same row on the microtitre plate as the stated Bisphenol A concentration

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

TABLE 3

CORRECTED MEAN ABSORBANCE VALUES FOR TG-SA (Lot No. 710427) AND ASSOCIATED SOLVENT CONTROL CULTURES IN THE DEFINITIVE STUDY

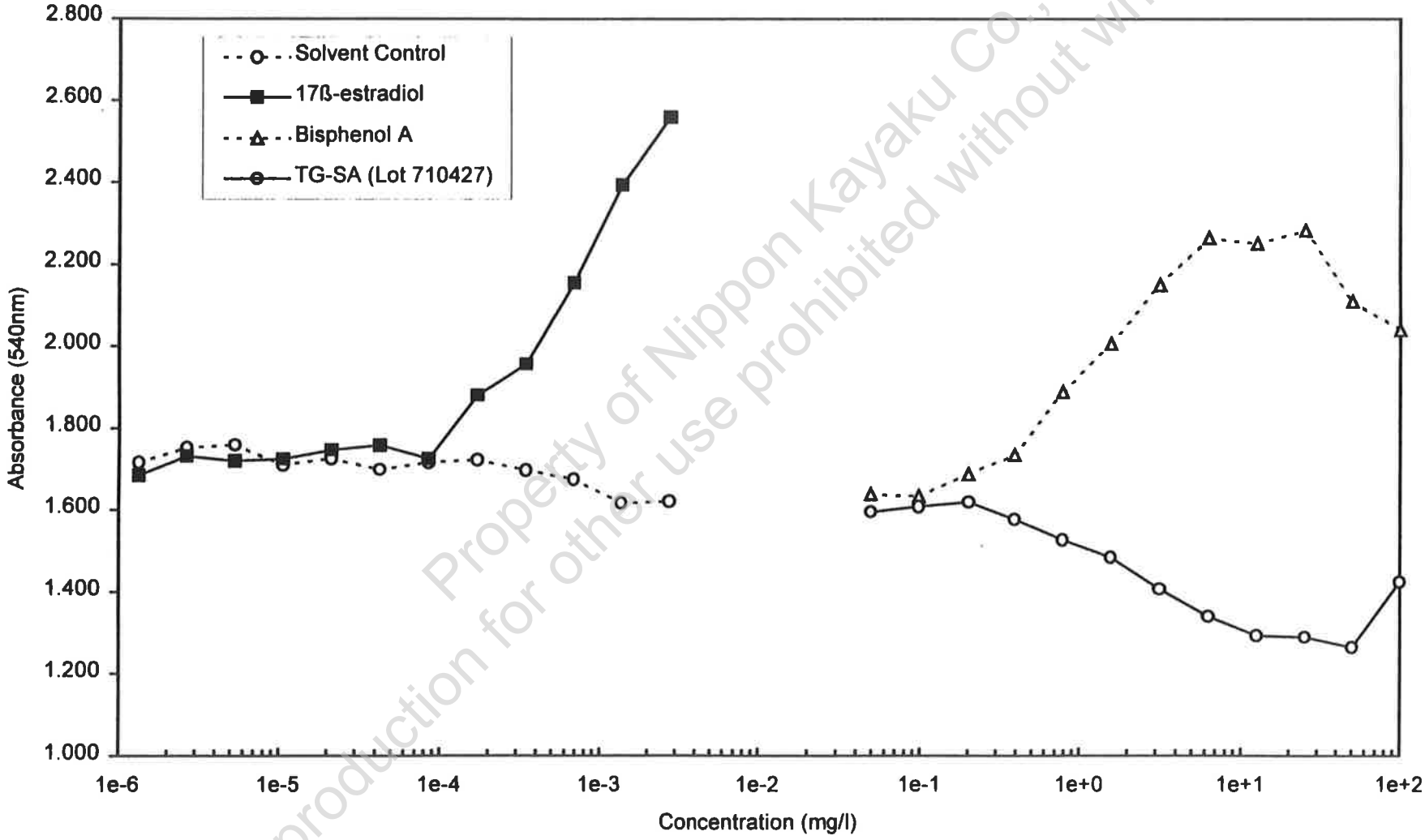
Concentration (mg/l)	TG-SA (Lot No. 710427)	Solvent Control*
0.049	1.595	1.717
0.098	1.609	1.753
0.20	1.619	1.759
0.39	1.577	1.711
0.78	1.527	1.727
1.56	1.485	1.699
3.13	1.407	1.717
6.25	1.340	1.723
12.5	1.294	1.698
25	1.290	1.676
50	1.265	1.617
100	1.424	1.622

* Solvent control absorbance values represent the mean absorbance values of solvent control wells in the same row on the microtitre plate as the 17β-estradiol and Bisphenol A concentrations given in Tables 2 and 3

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

FIGURE 1

DOSE-RESPONSE CURVES FOR 17β-ESTRADIOL, BISPHENOL A, TG-SA (Lot No. 710427) AND ASSOCIATED SOLVENT CONTROLS



APPENDICES

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

APPENDIX I

TEST MEDIA STOCK SOLUTIONS

The following stock solutions are prepared in double distilled water.

a) Minimal Medium

KH_2PO_4	13.61	g/l
$(NH_4)_2SO_4$	1.98	g/l
KOH	4.2	g/l
$MgSO_4$	200	mg/l
$Fe_2(SO_4)$	0.8	mg/l
L-leucine	50	mg/l
L-histidine	50	mg/l
Adenine	50	mg/l
L-arginine-HCl	20	mg/l
L-methionine	20	mg/l
L-tyrosine	30	mg/l
L-isoleucine	30	mg/l
L-lysine-HCl	30	mg/l
L-phenylalanine	25	mg/l
L-glutamic acid	100	mg/l
L-valine	150	mg/l
L-serine	375	mg/l

Place on heated stirrer to dissolve. Dispense 45 ml aliquots into glass bottles. Sterilise at 121°C for 10 minutes and store at room temperature.

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

APPENDIX I (continued)

TEST MEDIA STOCK SOLUTIONS

b) Vitamin Solution

Thiamine	8.0 mg/200 ml
Pyridoxine	8.0 mg/200 ml
Pantothenic acid	8.0 mg/200 ml
Inositol	40 mg/200 ml
Biotin solution (2 mg/100ml)	20 ml/200 ml

Sterilise by 0.22 μm filtration. Dispense 10 ml aliquots into sterile glass bottles and store at +4°C.

c) D-(+)-glucose

D-(+)-glucose	20% w/v

Sterilise in 20 ml aliquots at 121°C for 10 minutes and store at room temperature.

d) L-Aspartic Acid

L-aspartic acid	400 mg/100 ml

Sterilise in 20 ml aliquots at 121°C for 10 minutes and store at room temperature.

e) L-Threonine

L-threonine	2.4 g/100 ml

Sterilise in 5 ml aliquots at 121°C for 10 minutes and store at +4°C.

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

APPENDIX I (continued)

TEST MEDIA STOCK SOLUTIONS

f) Copper (II) Sulphate

$CuSO_4$	3.192 g/l

Sterilise by 0.22 μm filtration. Dispense 5 ml aliquots into sterile glass bottles and store at +4°C.

g) Chlorophenol red-β-D-galactopyranoside (CPRG)

Chlorophenol red-β-D-galactopyranoside 500 mg/50 ml

Sterilise by 0.22 μm filtration. Dispense 5 ml aliquots into sterile glass bottles and store at +4°C.

TG-SA (Lot No. 710427) : ASSESSMENT OF OESTROGENIC ACTIVITY USING A RECOMBINANT YEAST SCREEN ASSAY

APPENDIX II

TEST MEDIA

Growth Medium

To each 45 ml of minimal medium was added the following:

D-(+)-glucose solution	5 ml
L-aspartic acid solution	1.25 ml
Vitamin solution	0.5 ml
L-threonine solution	0.4 ml
Copper (II) sulphate solution	0.125 ml

Assay Medium

To each 50 ml of fresh growth medium was added the following :

CPRG solution	0.5 ml

Sufficient yeast pre-culture to give a cell density of approximately 8×10^5 cells/ml

SPL PROJECT NUMBER: 189/1663

APPENDIX III

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY	TEST TYPE
SafePharm Laboratories Ltd. Shardlow Business Park London Road Shardlow Derbyshire DE72 2GD	Analytical Chemistry Environmental Fate Environmental Toxicity Mutagenicity Phys/Chem Tests Toxicology

DATE OF INSPECTION

23rd March 1998

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

21st July 1998

UK GLP Monitoring Authority

Attachment 2: Reproductive/Developmental Toxicity Screening Test of TG-SH(H) in Rats

This study report is provided in response to the OEHHA's Request for Relevant Information, and submission of this study report is not a waiver of Nippon Kayaku Co., Ltd's ownership rights. No third-party is granted consent to use this study report for any purpose, in any jurisdiction.

CERI

Receipt No.	822-22-D-5148
Study No.	E16-0045

FINAL REPORT

REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST OF
TG-SH(H)
IN RATS

November, 2023

Chemicals Evaluation and Research Institute, Japan, Hita

This document is exact copy of the original.
Date: November 29, 2023
Study director: Kahori Ryota

GLP STATEMENT

Chemicals Evaluation and Research Institute, Japan, Hita

Sponsor Nippon Kayaku Co., Ltd.

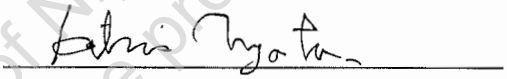
Title Reproduction/developmental toxicity screening test of TG-SH(H) in rats

Study Number E16-0045

This study was conducted in compliance with the following GLP principle.

OECD Principles of Good Laboratory Practice, November 26, 1997, ENV/MC/CHEM (98)17

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

Study Director  Date November 23, 2023

Katsumi Miyata

QUALITY ASSURANCE STATEMENT

Chemicals Evaluation and Research Institute, Japan, Hita

Sponsor: Nippon Kayaku Co., Ltd.

Title: Reproduction/developmental toxicity screening test of TG-SH(H) in rats

Study Number: E16-0045

I assure that the final report accurately describes the test methods and procedures, and that the reported results accurately reflect the raw data of this study. The inspections of the study were carried out and the results were reported to the Study Director and the Test Facility Management by Quality Assurance Unit as follows.

Item of inspection	Date of inspection	Date of report
Study plan	December 5, 2022	December 5, 2022
Preparation of test item formulations	December 20, 2022	December 20, 2022
Administration and clinical observations	December 22, 2022	December 22, 2022
Record of accident or deviation from the study plan	December 28, 2022	December 28, 2022
Copulation	January 5, 2023	January 5, 2023
Study plan amendment No. 1	January 6, 2023	January 6, 2023
Confirmation of mating	January 6, 2023	January 6, 2023
Assessment of response (study plan amendment No. 1)	January 10, 2023	January 10, 2023
Blood sampling	January 20, 2023	January 20, 2023
Dissection, necropsy and organ weight measurements	January 20, 2023	January 20, 2023
Confirmation of delivery	January 31, 2023	January 31, 2023
Blood sampling (offspring)	February 1, 2023	February 2, 2023
Anogenital distance (AGD)	February 2, 2023	February 2, 2023
Number of nipples/areolae	February 10, 2023	February 10, 2023
Dissection (offspring)	February 10, 2023	February 10, 2023
Number of implantation site	February 13, 2023	February 13, 2023
Blood chemical examinations: T4 measurement	April 4, 2023	April 4, 2023
Clinical chemistry data	May 9, 2023	May 9, 2023
Record of accident or deviation from the study plan	May 12, 2023	May 12, 2023
Re-inspection of clinical chemistry data	May 12, 2023	May 12, 2023
Animal data	May 23, 2023	May 23, 2023
Pathological data	May 29, 2023	May 30, 2023
Record of accident or deviation from the study plan	June 1, 2023	June 2, 2023
Re-inspection of animal data	June 1, 2023	June 2, 2023
Test item and housing condition data	June 1, 2023	June 2, 2023
Re-inspection of test item and housing condition data	June 5, 2023	June 5, 2023

Item of inspection	Date of inspection	Date of report
Record of accident or deviation from the study plan	June 8, 2023	June 9, 2023
Re-inspection of pathological data	June 8, 2023	June 9, 2023
Draft final report	November 8, 2023	November 11, 2023
Re-inspection of draft final report	November 16, 2023	November 17, 2023
Draft final report (second)	November 24, 2023	November 24, 2023
Re-inspection of draft final report (second)	November 28, 2023	November 28, 2023
Final report	November 28, 2023	November 28, 2023

The facility-based inspection and/or process-based inspection result of following item was reported to the Test Facility Management immediately after the inspection. The date reported to the Study Director and the Test Facility Management to adduce this inspection result into this quality assurance statement was described below.

Item of inspection	Date of inspection	Date of report
Animal receipt	October 25, 2022	November 28, 2023
Quarantine and acclimatization	October 25, 2022	November 28, 2023
Animal management	September 15, 2022	November 28, 2023
Allocation	December 13, 2022	November 28, 2023
Body weight measurement	September 15, 2022	November 28, 2023
Food consumption measurements	October 5, 2022	November 28, 2023
Estrous cycle examinations	November 29, 2022	November 28, 2023
Preparation of histopathological specimen	January 24, 26 and 31, 2023	November 28, 2023
Microscopic examinations	February 15, 2023	November 28, 2023

Quality Assurance Manager : Ryuichiro Mizuguchi — November 28, 2023

Ryuichiro Mizuguchi — Date

TABLE OF CONTENTS

1. TITLE

Reproduction/developmental toxicity screening test of TG-SH(H) in rats

2. SPONSOR

Name Nippon Kayaku Co., Ltd.

Address 1-1 Marunouchi, 2-chome, Chiyoda-ku, Tokyo 100-0005, Japan

3. TESTING FACILITY

Name Chemicals Evaluation and Research Institute, Japan, Hita (CERI Hita)

Address 3-822 Ishii-machi, Hita-shi, Oita 877-0061, Japan

4. PURPOSE OF STUDY

The purpose of this study was to assess the toxic effect of TG-SH(H) for gonadal function, mating behavior and implantation, development of conceptus and delivery when administered to rats from before mating until after delivery.

5. TESTING METHOD

OECD Guidelines for the Testing of Chemicals, No. 421, adopted July 29, 2016, "Reproduction/Developmental Toxicity Screening Test".

6. GLP COMPLIANCE

OECD Principles of Good Laboratory Practice, November 26, 1997, ENV/MC/CHEM (98)17

7. ANIMAL WELFARE

This study complied with the guideline for the animal experiment at CERI Hita which refers to the following act and guidelines.

a) Act on Welfare and Management of Animals (Japanese Low No. 105, 1973)

b) Standards relating to the Care and Keeping and Reducing Pain of Laboratory Animals (Ministry of the Environment, Japan, 2006)

c) Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Research Institutions under the Jurisdiction of the Ministry of Health, Labour and Welfare (Ministry of Health, Labour and Welfare, Japan, 2006)

d) Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions under the Jurisdiction of the Ministry of Agriculture, Forestry, and Fisheries (Ministry of Agriculture, Forestry, and Fisheries, Japan, 2006)

e) Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions (Ministry of Education, Culture, Sports, Science and Technology, Japan, 2006)

f) Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan, 2006)

8. PERIOD OF STUDY

Commencement of Study	December 1, 2022
Animal Receipt	December 6, 2022
Initiation of Dosing (start of experiment)	December 22, 2022
Initiation of Mating	January 5, 2023
Necropsy of Males	January 20, 2023
Initiation of Delivery	January 28, 2023
Initiation of Collection of Blood of Offspring (postnatal day 4)	February 1, 2023
Initiation of Necropsy of Offspring (postnatal day 13)	February 10, 2023
Initiation of Necropsy of Parturient Females	February 11, 2023
Completion of Histopathological Examinations (completion of experiment)	April 5, 2023
Completion of Study	November 28, 2023

9. STUDY DIRECTOR

Katsumi Miyata Section 2, CERI Hita

10. PERSONNEL CONCERNED WITH THE STUDY

Study Staff Kosuke Goto and Kimika Yamamoto
(Quarantine, acclimation, care and management of animals, preparation and administration of dose formulations, clinical observations, body weights and food consumption measurements, examination of reproduction/development, and responsible for the animal examinations)

Person in Charge of Pathological Examination
Yutaka Oshima
(Necropsy, collection of tissues, organ weight measurements, histopathological examinations, and responsible for the pathological examinations)

Person in Charge of Clinical Laboratory Investigations
Takako Muroi
(Blood chemistry, and responsible for the clinical laboratory investigations)

Other Staffs

Chiune Hirano, Masafumi Horiuchi, Yasuhiro Kajiwara, Ayari Kinjyo, Takayuki Koga, Shinichi Kudo, Katsumi Miyata, Hisako Morioka, Takako Muroi and Yutaka Oshima
(Animal examinations)

Aya Fukushima, Satsuki Hoshuyama, Toshio Kobayashi, Yuka Kohiyama, Takako Muroi and Kimika Yamamoto
(Pathological examinations)

Natsuyo Kajiwara and Kimika Yamamoto
(Clinical laboratory investigations)

11. RETENTION OF RAW DATA AND SPECIMENS

The original study plan, amendment of study plan, original final report, paper raw data, study contract documents, test item information, other record documents and specimens will be retained in the archive of the testing facility. Samples of the test item will be retained in the test item storage room of the testing facility. Electronic raw data will be retained in the server room of the testing facility. The retention period will be 10 years after completion of the study. Stability of the test item during the retention period will not be confirmed. At the end of the retention period, any measures (continued storage, disposal or return) will be done with the approval of the sponsor.

12. AUTHOR APPROVAL

Study Director _____ Date: November 28, 2023
Katsumi Miyata

13. SUMMARY

"A reproduction/developmental toxicity screening test" was performed to assess the reproductive and developmental toxicity of TG-SH(H) in accordance with OECD Guideline for the Testing of Chemicals No. 421.

Male and female Crl:CD(SD) rats at 9 weeks of age were treated with the test item for 14 days prior to mating and during the mating period for maximum of 14 days. Males were dosed for total of 29 days. Mated females were dosed during gestation and lactation, until lactation day 13. The dose levels were set at 0, 20, 100, 300 and 1000 mg/kg bw/day. Control animals were similarly dosed with olive oil.

Salivation was observed in males and females of the 300 and 1000 mg/kg bw/day dose groups. Soft stool, staining around the external genitalia, staining around the anus and staining on the lower abdomen were observed in males and females of the 1000 mg/kg bw/day dose group. Diarrhea was observed in males of the 1000 mg/kg bw/day dose group. Staining around the nose and mouth was observed in females of the 1000 mg/kg bw/day dose group. One female died during delivery in the 100 mg/kg bw/day dose group. Whole litter death was observed in one female of the 100 mg/kg bw/day dose group and in one female of the 300 mg/kg bw/day dose group.

There were no significant changes in body weights or food consumption at any dose level.

Serum T4 levels were not affected in parental males or offspring on lactation day 13.

No abnormal organ weights were noted in males or females.

In macroscopic examinations, bilateral discolored region and enlargement of the kidneys were observed in males of the 1000 mg/kg bw/day dose group. Enlargement of the cecum and thickening of the wall of the intestine were observed in females of the 1000 mg/kg bw/day dose group.

In histopathological examinations, degeneration, necrosis, dilatation and regeneration of the tubule of the kidney were observed in males of the 1000 mg/kg bw/day dose group. Mucosa hyperplasia of the duodenum, cecum and colon was observed in females of the 1000 mg/kg bw/day dose group.

No treatment-related or toxicologically significant changes were noted in any of the reproductive parameters of estrous cycles, mating, fertility and conception indices, precoital time, and histopathological examinations of the reproductive organs.

No treatment-related or toxicologically significant changes were noted in any of the developmental parameters of gestation, parturition, maternal care, clinical signs, external observations, body weights, anogenital distance (AGD) or nipple retention in offspring.

The No Observed Adverse Effect Level (NOAEL) for reproduction and developmental toxicity under the conditions tested was considered to be 1000 mg/kg/day.

14. MATERIALS

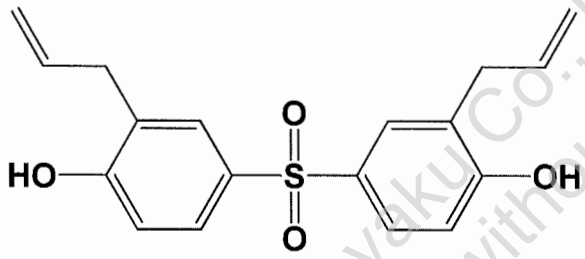
14.1 TEST ITEM

a) Name, etc. (Information provided by the sponsor)

Chemical name	2,2'-diallyl-4,4'-sulfonyldiphenol
Other name	TG-SH(H)
CAS number	41481-66-7

b) Structural Formula, etc. (Information provided by the sponsor)

Structural formula



Molecular formula	$C_{18}H_{18}O_4S$
Molecular weight	330.40

c) Purity, etc. (Information provided by the sponsor)

Purity	97.52%	
Impurities	Unknown organic constituent	2.48%
Supplier	Nippon Kayaku Co., Ltd.	
Lot No.	204195	

The test item was treated as 100% of purity.

d) Physicochemical Properties (Information provided by the sponsor)

Appearance at ordinary temperature	White powder
Melting point	151-156°C
Density	1.3076 g/cm^3 (21.5±2°C)
Partition coefficient	LogPow = 3.22 (23±0.5°C)
Solubility	
Water	4.79 mg/L
Dimethyl sulfoxide	Soluble
Acetone	Soluble

e) Storage

The test item was stored in an airtight container at room temperature (tolerance temperature: 10-30°C) in the test item storage room.

f) Identity and Stability under Storage Condition

Identity and stability of the test item under the storage condition during the dosing period was confirmed in 'Identity and stability analyses of TG-SH(H), homogeneity, stability and concentration analyses of TG-SH(H) formulation' in the testing facility (study number X02-0338).

Identity of the test item was confirmed by comparing IR spectra between measured before the dosing period in the testing facility and provided by the sponsor. The IR spectrum measured before the dosing period was identical with that provided by the sponsor.

Stability of the test item under the storage condition was confirmed by comparing IR spectra measured before and after the dosing period. The test item was confirmed to be stable during the dosing period.

g) Test Item Handling

In order to avoid inhalation and contact with the skin or eyes, chemically resistant gloves, a mask, a head cap, safety glasses and a lab coat were worn.

14.2 VEHICLE

a) Name

Olive oil Lot no. 205017 and 105025, Japanese Pharmacopoeia, TAISEI Pharmaceutical Industries

b) Reason of Selection

Preparation method of the test item formulation was investigated using olive oil since the test item was oil soluble. The test item did not dissolve in olive oil at a concentration of 10 w/v%; however, state of the suspension was good. After approximately 26 hours at a cold place, the state of the formulation was good. Olive oil has been commonly used in general toxicity studies and there are historical control data of this vehicle in the Test Facility.

14.3 ANIMALS

Crl:CD(SD) rats (SPF) were obtained from Jackson Laboratory Japan Hino Breeding Center. This strain has been established as a laboratory animal, and there are historical data for this strain at the Test Facility.

a) Numbers, Age and Body Weights

Fifty five males and fifty five females were obtained at 7 weeks old with body weights ranging from 190 g to 270 g for males and 140 g to 210 g for females at the time of order. At the start of dosing fifty males and fifty females that were 9 weeks old were used. The body weights at start of dosing were 308.9 g - 360.7 g for males and 210.8 g - 278.0 g for females.

b) Quarantine and Acclimatization

The animals were observed once or more a day during the quarantine and acclimatization periods until the beginning of dosing. Body weights were measured at receipt and after day 6. Estrous cycle was observed in females from the next day of receipt until the day before group allocation for 14 days prior to initiation of dosing. During the quarantine and acclimatization period two females showed abnormal estrous cycles and one female showed increased white blood cells in the estrous cycle examination.

c) Allocation to Treatment Groups

The animals that showed no abnormalities in clinical observations, body weights and estrous cycle examination were allocated to groups using a body weight-stratified randomization on the day before the initiation of dosing. Body weights of each animal were confirmed to be in the range of ±20% of the mean body weights for each sex at group allocation. The animals not allocated were excluded from the study.

d) Identification

The animals were identified by a marker on the tail before group allocation and ear-tags (KN-295-A, NATSUME SEISAKUSHO) after group allocation. Before group allocation, cages were identified by a cage card which had details including study number, cage number, animal number (discrimination number), study director, study staff, animal information of species, strain, age and sex, and receipt date. After group allocation, cages were identified by a cage card which had details including study number, cage number, animal number, study director, study staff, animal information of species, strain and sex, breeding period, color sticker showing dose level and dose group or dose level. Racks were identified by indications described study number, sex and dose levels.

14.4 HOUSING CONDITIONS

a) Environmental Control

Animal room	Quarantine room no. 1 and animal room no. 6
Temperature	Target range 21-25°C (actual range 21.8-24.4°C)
Relative humidity	Target range 40-70% (actual range 46.7-69.4%)
Air supply	10-15 air changes per hour
Lighting	12 hours light (07:00-19:00) : 12 hours dark (19:00-07:00)

b) Animal Accommodation

During quarantine and acclimation all animals were group housed, 3 to 4 of the same sex, in hanging stainless steel cages with wire-mesh floor (260 W × 380 D × 180 H mm). After group allocation males and females were housed individually in hanging stainless steel cages with wire-mesh floor (260 W × 380 D × 180 H mm and 165 W × 300 D × 150 H mm), respectively. Enrichment of irradiated hemp mats with gamma-ray (Happi-mats, lot no. 221115, Marshall Bio Resources) was used after group allocation.

During the mating period, each female was housed in a male's cage in each dose group. Copulated females were housed in polycarbonate cages (PC cage, 265 W×426 D×150 H mm) with wooden bedding (Sunflake, lot no. 220927 and 230124, Jackson Laboratory Japan), and enrichments of autoclaved gnawing wood (Woodbite, lot no. 221025, Jackson Laboratory Japan) and hemp mats from gestation day 14. Offspring were housed with a dam after delivery.

Undertrays were changed twice during the acclimation period including at the end of quarantine, and at the group allocation, before necropsy and twice a week after group allocation. When the abnormal excretions were observed the undertrays were also changed. Feeders, hanging cages and racks were changed at group allocation. PC cages and wooden bedding were changed on gestation day 20, and lactation days 4 and 8. All housing materials were autoclaved prior to use.

c) Diet and Water Supply

The animals had free access to a pelleted diet (MF, lot no. 220711, 220809 and 221108, Oriental Yeast) autoclaved prior to use. The diet was supplied from a stainless feeder. Chlorinated Hita City supply was maintained at 3-5 ppm of chloric level by adding sodium hypochlorite (Purelox) and provided via an automatic watering system for hanging cages and polycarbonate water bottles for PC cages.

d) Contaminants Assay

The analytical data of contaminants in the diets, wooden bedding and enrichments were provided by the manufacturer or supplier. The tested parameters were confirmed to meet the requirements

of CERI Hita according to the "Contaminant analysis of feeds and vehicles in EPA Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules" (1979). Contaminants in drinking water were analyzed twice a year according to the water regulations of the "Ordinance on drinking water quality standards" [Ordinance number 101 of Ministry of Health, Labour and Welfare, Japan]. The analytical data of contaminants in the water were confirmed to be in the stated ranges of CERI Hita.

15. METHODS

15.1 DOSE SETTING

"A 14-day repeated-dose oral toxicity study (study no. X20-0251)" was performed at dose levels of 0, 100, 300, 600 and 1000 mg/kg bw/day consisting of three males and three females in each group. The 14-day dose range finding study identified no severe toxicity up to the OECD guideline limit dose of 1000 mg/kg bw/day. Only increased salivation was apparent in both sexes and a slightly enlarged cecum was apparent at low incidence in females from 600 mg/kg bw/day. Therefore, 1000 mg/kg bw/day was considered to be appropriate as a high dose level for the main OECD 421 study. Lower dose levels of 300, 100 and 20 mg/kg bw/day were selected for the main reproduction/developmental toxicity screening test in order to establish a no-observed-adverse effect level (NOAEL).

15.2 GROUP ALLOCATION

Test groups are shown in tabular form below.

Groups		Dose levels (mg/kg/day)	Dose volume (mL/kg/day)	Dose concentrations (w/v%)	Number of Animals (Animal No.)	
					Male	Female
Vehicle control		0	4	0	10 (1101-1110)	10 (5101-5110)
Test item	Low dose	20	4	0.500	10 (1201-1210)	10 (5201-5210)
	Intermediate Dose-1	100	4	2.50	10 (1301-1310)	10 (5301-5310)
	Intermediate Dose-2	300	4	7.50	10 (1401-1410)	10 (5401-5410)
	High dose	1000	4	25.0	10 (1501-1510)	10 (5501-5510)

15.3 DOSE FORMULATIONS

a) Preparation and Storage of Formulations

The test item was weighed, and olive oil was added and mixed with the test item. The mixture was filled up with olive oil to prepare the 25.0 w/v% formulation. A part of the 25.0 w/v% formulation was taken while being stirred with a magnetic stirrer and diluted with olive oil to prepare the 0.500, 2.50 and 7.50 w/v% formulations.

The formulations and vehicle were subdivided into plastic containers and stored at the cold place (target range: 1 to 10 °C). On each dosing day formulations and vehicle were taken out from the storage place and dosed to the animals. The test item formulations were used within a stable period of 12 days after preparation based on the results of the stability analysis.

b) Homogeneity and Stability Analyses of Formulations

Homogeneity and stability of the 25.0 and 0.100 w/v% formulations were confirmed with a high-performance liquid chromatography (HPLC) before the initiation of dosing in the testing facility (study number X02-0338).

In the homogeneity, concentrations of the upper, middle and lower layers of the formulations were taken and measured. The concentrations of these layers were within the acceptable range of CERI Hita, therefore the formulations were regarded to be homogenous.

Stability of the test item formulations at 25.0 and 0.100 w/v% were confirmed with HPLC (study no. X02-0338). Actual concentrations measured after storage period were confirmed to be within the acceptable range of CERI Hita compared to those measured immediately after preparation. These formulations were confirmed to be stable for 12 days at the cold place.

c) Concentration Analysis

Concentrations of the test item formulations were confirmed with HPLC in the first and last preparations (study no. X02-0338). Actual concentrations of 0.500, 2.50, 7.50 and 25.0 w/v% formulations at first preparation were 0.500, 2.43, 7.27 and 24.3 w/v%, respectively. Actual concentrations of 0.500, 2.50, 7.50 and 25.0 w/v% formulations at last preparation were 0.487, 2.44, 7.19 and 25.2 w/v%, respectively. These formulations were within the acceptable range of CERI Hita.

15.4 ADMINISTRATION

Treatment was conducted according to the relevant test method by oral (gavage) once a day using a syringe (Terumo) connected to a nelaton catheter (Terumo) at a dose volume of 4 mL/kg based on the latest body weights between 09:20-12:38. The oral route was considered to be the relevant route of exposure and it is the preferred route according to the OECD 421 test guideline.

Males and females were administrated for 14 days before mating. Males were treated for 29 days including the mating period. Females were administrated the test item during maximum 14 days of mating, gestation and throughout lactation period, until lactation day 13. When administration coincided with delivery, the female in delivery was not dosed on this occasion.

15.5 DAILY CLINICAL OBSERVATIONS

All animals were observed for clinical signs before dosing and from just after dosing to after approximately 1 hour of dosing. Mortality or death were also recorded. Females were observed during delivery and their nursing conditions.

15.6 BODY WEIGHT

Body weights were measured using an electric balance (SARTORIUS) on the following days:

- males on day 1, 3, 8, 15, 22, 29 of dosing
- females on day 1, 3, 8, 15 of dosing, on gestation day 0, 7, 14, 20, on lactation day 0, 4, 13
- in addition, all animals were weighed on each necropsy day.

15.7 FOOD CONSUMPTION

Food weights were measured using an electric balance (SARTORIUS) on the following days:

- males on day 1, 3, 8, 15, 22, 29 of dosing
- females on day 1, 3, 8, 15 of dosing, on gestation day 0, 7, 14, 20 and on lactation day 0, 4, 7, 10, 13.

Feeding weights were measured on dosing day 1, gestation day 0 and lactation day 0. From dosing day 8, feeding weights were measured after remainder weights were measured and replenished with food. On dosing day 15, remainder weights were measured in both sexes because the mating period was started on this day. On each final measurement day remainder weights were measured.

Mean food consumption per day was calculated from their feeding and remainder weights.

15.8 CLINICAL LABORATORY INVESTIGATIONS

a) Blood Sampling and Preparation

Blood was collected from the abdominal aorta under isoflurane anesthesia between 09:13-13:12 from the following animals. Parental animals were fasted for 16-20 hours:

- survived males and dams
- two offspring per litter on lactation day 4
- two offspring per litter at termination on lactation day 13.

Serum was collected in a glass tube and micro tube for parental animals and offspring, respectively. The serum was centrifuged at 3000 r.p.m. for 10 min and stored at -20°C or below until measurements.

b) Blood Chemistry

T4 levels were measured with ELISA method using Rodent thyroxin T4 ELISA test kit, Endocrine technologies for parental males and offspring on lactation day 13.

15.9 PATHOLOGICAL EXAMINATIONS

a) Gross Necropsy

Survived parental animals were subjected to a detailed gross necropsy including external surface of the body, all orifices, subcutis, cranial, thoracic, abdominal and pelvic cavities, and their contents after bleeding from the ventral aorta under isoflurane anesthesia on the day following completion of dosing.

Dams (animal no. 5302, 5401) which had total litter loss were subjected to necropsy. Dead female (animal no. 5305) during delivery was subjected to necropsy. Non-delivered females (animal no. 5110, 5402, 5407, 5502) were subjected to necropsy on the day that corresponds to day 25 of the gestation period.

Vaginal smears were collected before gross necropsy in surviving females, and stages of the estrous cycle were determined with a light microscope after Giemsa staining. The number of implantation site of the uterus after incision were counted. When the implantation sites were observed in the uterus the females were regarded to be pregnant.

b) Tissue Collecting and Organ Weight Measurements

The testes, epididymides, prostate, seminal vesicles (including coagulating gland), ovaries, uterus (including cervix), thyroids and macroscopic lesions were taken from all parental animals.

The testes, epididymides, prostate, seminal vesicles and thyroids of parental animals were weighed using an electric balance (SARTORIUS), and their relative weights were calculated based on the body weight at the time of necropsy. Bilateral organs were weighed right and left together. The prostate, seminal vesicles and coagulating gland were measured with a part of the urethra. The thyroid adhered to the trachea including the parathyroid were fixed in 10% neutralized buffered formalin, and the right and left lobes were removed from the trachea and weighed on the day following necropsy for parental animals.

c) Histopathological Examinations

All organs/tissues were preserved in 10% neutralized buffered formalin. Testes were fixed in modified Davidson's fixative.

Light microscopic examinations were performed after embedding the tissues in paraffin wax, sectioning and hematoxylin and eosin (HE) staining. The testes, epididymides and ovaries were examined. The cecum, colon, rectum and kidneys the macroscopic lesions were observed were examined as some findings in these tissues were expected.

15.10 ESTROUS CYCLE EXAMINATIONS

Vaginal smears of all females were collected from day 1 to 14 of dosing. The stages of estrous cycle were determined with a light microscope following Giemsa staining. The days from estrus to the next estrus were regarded as an estrous cycle length and the mean estrous cycle length was calculated. When the estrus was successive the first day was regarded as an estrus.

15.11 REPRODUCTIVE CAPABILITY EXAMINATIONS

Each female was cohabited in the cage of a male in the same dose level, as a pair on the night of dosing day 15, and the females were returned to the original cage the following morning. Cohabitation was continued until there was evidence of copulation or a maximum of 14 days had elapsed. When a vaginal plug or sperm was detected in the vaginal smear, it was considered to be evidence of mating (day 0 of gestation).

When the dams delivered spontaneously, built a nest or nursed their offspring by 10:00, those were regarded as evidence of delivery and the day was designated as delivery day (day 0 of lactation, postnatal day 0). If the delivery finished after 10:00, the delivery day was regarded as a next day.

Number of days from copulation to the day before delivery was regarded as a gestation period. The number of pairing (number of paired animals), number of cohabited animals (number of mated animals), number of animals confirmed to be pregnant (number of pregnant females), number of animals which had surviving offspring on postpartum day 0 and 4 (number of females with live offspring) were calculated from the results of copulation, delivery and gestation.

The days from the first pairing to the copulation (pairing days until copulation, day of conceiving), days from confirmation day of mating to the day before delivery (gestation length) and number of implantation sites were examined, and the mean values and standard deviations were calculated for each dose group.

In the following indices, the value of each litter, and the mean values and standard deviations were calculated for each dose group:

- Copulation index (number of mated animals / numbers of paired animals) × 100
- Fertility index (number of pregnant females / numbers of copulated pairs) × 100
- Gestation index (number of females with live offspring / number of pregnant females) × 100.

15.12 EXAMINATION OF OFFSPRING

After completion of delivery (postnatal day 0), number of males and females including number of dead or live offspring and their total number were counted. Body weight measurements and observations of the external surface were performed.

Clinical observations were carried out once a day until postnatal day 13. Males and females were counted for sex ratio following delivery, on postnatal days 4 and 13. Total number of offspring was counted following delivery, on postnatal days 4 and day 13. Body weights of live offspring were measured on the same days. Anogenital distance (AGD) of each offspring was measured by a digital vernier calipers on postnatal day 4. Each AGD was collected with the cube root of the body weight on the same day. The number of nipples of males was counted for nipple retention examination on postnatal day 13. External surface was observed in males and females on postnatal day 13. Blood samples for T4 analysis were taken from the ventral aorta under isoflurane anesthesia from two offspring per litter on lactation day 4 and 13 prior to sacrifice. The thyroids of offspring were taken after blood sampling on lactation day 4 and 13. Histopathological examinations of the thyroid was not performed.

From these results, the mean values and standard deviations of each dose group were calculated as follows:

- Delivery index	(number of offspring delivered / number of implantations) × 100
- Viability index on postnatal day 0 (Live birth index)	(number of live offspring delivered / number of offspring delivered) × 100
- Sex ratio of live offspring on postnatal day 0	number of live males delivered / number of live offspring delivered.
- Sex ratio of offspring on postnatal day 0	number of males delivered / number of offspring delivered.
- Viability index on postnatal day 4	(number of live offspring on postnatal day 4 / number of live offspring delivered) × 100
- Sex ratio of live offspring on postnatal day 4	number of live males on postnatal day 4 / number of live offspring on postnatal day 4.

15.13 CLASSIFICATION OF RAW DATA

For the items described as electronic raw data in the table below, the data was collected using the safety study system (MiTOX, Mitsui E&S Systems Research) and the electronic data was defined as raw data. For the items described as paper raw data, the data was collected using recording paper, etc., and paper materials were defined as raw data.

Data of number of offspring, body weights, external examinations and nipple retention were collected using recording paper in one litter (animal no. 5501) on lactation day 13, since input of these data could not be performed using MiTOX.

Electronic raw data	Collection of vaginal smears, estrous cycle examination, mating, copulation, group allocation, administration, body weights, food consumption, organ weights, pregnant, delivery, and number, sex, body weights, AGD, nipple retention and external examinations of offspring
Paper raw data	Clinical observations, clinical investigation, necropsy, implantations, histopathological examinations, collection of vaginal smears and estrous cycle examinations at necropsy, and other records

The electric low data was defined as follows.

a) Males

From day 1 of dosing to the first mating on day 15 of dosing	Period before mating of F0
From first pairing to scheduled necropsy	Mating period of F0

b) Females

From day 1 of dosing to the first mating on day 15 of dosing	Period before mating of F0
From first mating to confirm of copulation (Including non-copulated females)	Mating period of F0
From copulation confirmation to delivery	Gestation period of F0
After delivery	Lactation period of F0

15.14 STATISTICAL ANALYSIS

Data regarding body weights of parental animals, food consumption, T4 level, organ weights, mean estrous cycle length, pairing days until copulation, gestation length, number of implantations, number of offspring born, number of live offspring, body weights and T4 level of offspring, AGD and number of nipples were analyzed by the Bartlett's test for homogeneity of variance. When significant difference ($p<0.05$) was not noted, the Dunnett's test was performed. When significant difference ($p<0.05$) was noted, the Steel's test was performed. Body weights of offspring were calculated on each sex as sample unit for each litter.

Abnormal estrous cyclicity, copulation index, fertility index and gestation index were analyzed by the Fisher's exact test between the control group and each test item group.

Delivery index, viability index and sex ratio of offspring were examined by the Bartlett's test. When significant difference ($p<0.05$) was not noted, the Dunnet's test were performed. When significant difference ($p<0.05$) was noted, the Steel's test was performed.

The following data were excluded from the statistical analysis:

- body weights and food consumption during the gestation period and organ weights in non-pregnant females
- body weights on necropsy day and organ weights of dams which all offspring dead
- body weights on necropsy day and organ weights in dead female.

16. DEVIATIONS FROM THE STUDY PLAN

The following deviations were noted which did not affect the test results.

Although number of animals were 54 males and 54 females at ordering in the study plan, one male and one female were added at receipt. Number of animals became 55 males and 55 females. Added animals were excluded from study after group allocation.

Observation of the animals was for 1 hour after dosing in the study plan. However, observation after dosing was performed from 1 min to 5 min earlier than scheduled in some days. These deviations were small and the effects of the test item disappeared within 30 minutes after dosing.

The time of blood sampling was 13:12 for two litters (animal no. 5505, 5508) on lactation day 13 (February 11, 2023). There were no significant differences in T4 levels in these litters compared to those of other litters.

Organ weights of the thyroids were not measured in non-delivered animals (no. 5110, 5402, 5407 and 5502), dams whole litter loss (no. 5302 and 5401) and dead female during delivery (no. 5305). However, no abnormal changes were noted in the thyroids of any survived animals at any dose levels.

17. RESULTS

17.1 DAILY CLINICAL OBSERVATIONS

See Table 1 and Appendix 1.

In males, salivation was observed after dosing in the 300 mg/kg bw/day group from day 7, and the salivation disappeared within 15 min after dosing. In the 1000 mg/kg bw/day group the following signs were observed: staining around the anus from day 3, soft stool and salivation from day 7, staining on the lower abdomen from day 8, staining around the external genitalia from day 16, diarrhea on days 22 and 24. The salivation disappeared within 15 min or 30 min after dosing in

the 1000 mg/kg bw/day group. No abnormal signs were observed in the 20 or 100 mg/kg bw/day groups.

In females that delivered, salivation was observed after dosing in the 300 mg/kg bw/day group from day 11, and the salivation disappeared within 15 min after dosing. In the 1000 mg/kg bw/day dose group the following signs were observed: staining around the anus from day 3, soft stool and salivation from day 7, staining on the lower abdomen from day 8, staining around the nose and mouth from days 9 and 10, staining around the external genitalia from day 11. Salivation which disappeared within 15 min or 30 min after dosing was also observed in the 1000 mg/kg bw/day group. One female in the control group showed swelling of the left hindlimb from day 26 to day 29. No abnormal signs were observed in the 20 mg/kg bw/day group.

In females that did not deliver, one animal of the 1000 mg/kg bw/day group (animal no. 5502) showed salivation from day 8, soft stool from day 11 and staining on the lower abdomen from day 17. No abnormal signs were observed in one animal of the control group (animal no. 5110) and two animals of the 300 mg/kg bw/day group (animal no. 5402, 5407) which did not deliver.

One female died during delivery in the 100 mg/kg bw/day group (animal no. 5305). This animal showed no abnormal signs.

Total litter loss was observed in the 100 mg/kg bw/day (animal no. 5302) and 300 mg/kg bw/day (animal no. 5401) dose groups. In the animal from 100 mg/kg bw/day group (animal no. 5302) staining around the nose and mouth and staining around the anus were observed. In the animal from 300 mg/kg bw/day group (animal no. 5401) staining around the external genitalia was observed. These changes were observed after delivery or the next day of delivery. The other animals in these dose levels did not show the same signs. Therefore, they were not considered toxicologically significant.

17.2 BODY WEIGHTS

See Fig. 1, Table 2 and Appendix 2.

In males, no significant changes were noted at any dose levels.

In females, mean body weights in the 1000 mg/kg bw/day group were increased on lactation day 13 (7% with statistical significance). No abnormal changes were noted in the 20, 100 or 300 mg/kg bw/day groups.

17.3 FOOD CONSUMPTION

See Fig. 2, Table 3 and Appendix 3.

In males, mean food consumption was decreased in the 300 and 1000 mg/kg bw/day groups on day 3 (13% and 15% respectively with statistical significance). Mean food consumption was increased in the 1000 mg/kg bw/day group on days 15 and 29 (11% and 12% respectively with statistically significance). There were no changes in the 20 or 100 mg/kg bw/day groups.

In females, mean food consumption was decreased in the 300 and 1000 mg/kg bw/day groups on day 3 (17% and 18% respectively with statistical significance). Mean food consumption was increased in the 300 mg/kg bw/day group on lactation days 7, 10 and 13 (13%, 13% and 16% respectively) and in the 1000 mg/kg bw/day group on lactation days 7, 10 and 13 (13%, 14% and 24% respectively) with statistical significance. Although food consumption was decreased in the 100 mg/kg bw/day group, dose-relationship was not noted and considered to be single occurrence. No abnormalities were noted in the 20 mg/kg bw/day group.

17.4 CLINICAL LABORATORY INVESTIGATIONS

a) Blood Chemistry

See Table 4 and Appendix 4.

T4 levels were not affected in parental males.

T4 levels were not affected in offspring on day 13 of lactation. Blood samples from day 4 offspring were therefore not analyzed for T4 levels.

17.5 PATHOLOGICAL EXAMINATIONS

a) Organ Weights

See Table 5 and Appendix 5.

Organ weights were not affected in males or females at any dose levels.

b) Gross Necropsy

See Table 6 and Appendix 6.

In males, enlargement of the cecum (five animals), bilateral discolored region (three animals) and enlargement (one animal) of the kidneys were observed in the 1000 mg/kg bw/day group. No abnormal changes were observed in the 20, 100 or 300 mg/kg bw/day groups.

In one dam with total litter loss at 300 mg/kg bw/day (animal no. 5401), bilateral enlargement of the kidneys, small thymus, bilateral enlargement of the adrenals and atrophy of the mammary gland were observed. No macroscopic lesions were observed in the dam with total litter loss at 100 mg/kg bw/day group (animal no. 5302).

In the female that died during delivery in the 100 mg/kg bw/day group (animal no. 5305), edematous change of the lung was observed and was considered to be not treatment related but incidental finding.

In one female that did not deliver in the 1000 mg/kg bw/day group (animal no. 5502), enlargement of the cecum was observed. No macroscopic lesions were observed in the animals from the control (animal no 5110) or 300 mg/kg bw/day groups (animal nos.5402, 5407) that did not deliver.

In females that delivered, thickening of the wall of the duodenum, jejunum, ileum, cecum, colon and rectum, and enlargement of the cecum were observed in the 1000 mg/kg bw/day group. Black patch/spot in the mucosa of the glandular stomach was observed in the control, 20, 100, 300 and 1000 mg/kg bw/day groups, which was a spontaneous lesion and not treatment related.

c) Histopathological Examinations

See Table 7 and Appendix 7.

In males, degeneration and necrosis (four animals), dilatation (three animals) and regeneration (four animals) of the tubule of the kidney were observed in the 1000 mg/kg bw/day group. Unilateral focal atrophy of the seminiferous tubule of the testis in one control group male was considered to be a spontaneous lesion.

In the female that died during delivery in the 100 mg/kg bw/day group (animal no. 5305), focal hemorrhage and perivascular edema in the lung were observed and were considered to be incidental and non-treatment related since these changes were limited to this animal.

In one dam with total litter loss in the 300 mg/kg bw/day group (animal no. 5401), tubular vacuolation of the kidney, atrophy of the thymus, diffuse cortical hypertrophy of the adrenal were observed and were likely incidental and non-treatment related since the same changes were not observed in other animals. No abnormal changes were observed in the one animal (animal no. 5302) with total litter loss at100 mg/kg bw/day group.

In females that did not deliver (non-pregnant females), mucosa hyperplasia of the colon was observed in the 1000 mg/kg bw/day group (animal no. 5502). This change was considered to be test item related. No abnormal changes were observed in the remaining non-pregnant females from

the control (animal no. 5110) or 300 mg/kg bw/day dose groups (animal nos.5402, 5407).

In dams that delivered, mucosa hyperplasia of the duodenum and cecum was observed in the 1000 mg/kg bw/day group. Focal erosion in the glandular stomach was observed as a spontaneous lesion in the control, 20, 100, 300 or 1000 mg/kg bw/day groups.

d) Estrous Cycle Stages at Necropsy

See Table 8 and Appendix 8.

No test item related effects on estrous cycle stage were observed at any dose levels.
The 100 and 300 mg/kg bw/day group females (animal no. 5302, 5401) with total litter loss were in proestrus.

Non-pregnant females showed proestrus in one control group animal (no. 5110), proestrus in one female (animal no. 5407) and estrus in another female (animal no. 5402) of the 300 mg/kg bw/day group, and proestrus in one female (animal no. 5502) of the 1000 mg/kg bw/day group.

Delivered females showed metestrus in eight (animal no. 5101, 5102, 5103, 5104, 5105, 5107, 5108, 5109) and diestrus in one (animal no. 5106) of the control group, metestrus in nine (animal no. 5201, 5202, 5203, 5204, 5206, 5207, 5208, 5209, 5210) and diestrus in one (animal no. 5205) of the 20 mg/kg bw/day group, metestrus in six (animal no. 5301, 5303, 5304, 5307, 5308, 5309) and diestrus in two (animal no. 5306, 5310) of the 100 mg/kg bw/day group, metestrus in five (animal no. 5403, 5404, 5408, 5409, 5410) and diestrus in two (animal no. 5405, 5406) of the 300 mg/kg bw/day group, and metestrus in five (animal no. 5504, 5506, 5507, 5509, 5510) and diestrus in four (animal no. 5501, 5503, 5505, 5508) of the 1000 mg/kg bw/day group.

17.6 REPRODUCTIVE CAPABILITY

See Tables 9, 10 and 11, Appendices 9, 10 and 11.

No effects were seen in estrous cycle in any test groups. No abnormal changes were noted in copulation index, fertility index, gestation period or gestation index at any dose levels.

The number of implantation was decreased in the 300 mg/kg bw/day (mean 12.50) and 1000 mg/kg bw/day (mean 12.80) dose groups when compared to the control (mean 14.10). This was due to the increased number of non-pregnant animals seen in these dose groups (8 pregnant out of 10 at 300 mg/kg bw/day, 9 pregnant out of 10 at 1000 mg/kg bw/day). However, dose relationship or statistical significance were not observed. Furthermore, the number of implantation in the mid and high dose group were within the Test Facility historical control data (number of implantations: 10-19) and the number of pregnant animals in the high dose group was also within the Test Facility

historical control data (number of pregnant: 9-11). Therefore, this change was not considered to be toxicologically significant.

17.7 EXAMINATION OF OFFSPRING

See Tables 11, 12, 13, 14, 15, 16 and 17 Appendices 11, 12, 13, 14, 15, 16 and 17.

No abnormal changes were noted in delivery index, live birth index, number of offspring, number of live newborns, sex ratio, litter size, viability index, body weights, AGD or nipple retention examination.

In the external examinations and clinical signs of offspring including nursing state, following changes were observed: unclearance of placenta, no retrieving, no crouching, no milk band, subnormal temperature, no tail, loss of tip tail in the 100 mg/kg bw/day group; no retrieving, no crouching, no milk band, subnormal temperature in the 300 mg/kg bw/day group; no milk band, subnormal temperature, no tail in the 1000 mg/kg bw/day group. The no tail was a single incidence each at 100 (1 pup out of 93 examined) and 1000 mg/kg bw/day (1 pup out of 101 examined) lacking dose relationship. Therefore, these changes were not treatment related.

18. DISCUSSION

Parental systemic toxicity:

Parental animals in the 1000 mg/kg bw/day group showed salivation, soft stool, diarrhea, staining around the nose and mouth, lower abdomen, anus and external genitalia. Salivation was also observed in the 300 mg/kg bw/day group.

Body weights were increased in females of the 1000 mg/kg bw/day group on lactation day 13. This change was considered to be related to the increased food consumption on lactation days 7, 10 and 13 and not toxicologically significant. Although food consumption was increased in males of the 1000 mg/kg bw/day group, body weights were not affected in males. The increases in body weights and food consumption were not considered to be toxicologically significant since there were no related changes in other parameters. Decreased food consumption in males and females of the 300 and 1000 mg/kg bw/day groups on day 3 of dosing was considered to be not toxicologically significant since the same changes were not noted after day 3.

Macroscopic examination of males revealed bilateral discolored region and enlargement of the kidneys at 1000 mg/kg bw/day. At histopathology, degeneration, necrosis, dilatation and regeneration of the tubule of the kidney were observed in males of the 1000 mg/kg bw/day dose group. These findings were likely related to the test item since they were observed in the highest

dose group.

Macroscopic examination of females revealed enlargement of the cecum and thickening of the wall of the intestine at 1000 mg/kg bw/day. At histopathology, mucosa hyperplasia of the duodenum, cecum and colon was observed in females of the 1000 mg/kg bw/day dose group. These findings were likely due to local irritation caused by the test item.

Reproduction toxicity:

No treatment-related or toxicologically significant changes were noted in any of the reproductive parameters of estrous cycles, mating, fertility and conception indices, precoital time, and histopathological examinations of the reproductive organs.

Developmental toxicity:

No treatment-related or toxicologically significant changes were noted in any of the developmental parameters of gestation, parturition, maternal care, clinical signs, external observations, body weights, AGD or nipple retention.

The No Observed Adverse Effect Levels (NOAEL) for reproduction and developmental toxicity was 1000 mg/kg/day under the conditions tested since no abnormal reproductive or developmental parameters were noted.

19. HISTORICAL CONTROL DATA

1) Historical range of reproductive parameters in control SD rats (Period: 2018-2022)

	Parameter	Number of studies	Mean	Min – Max	Mean±2S.D.
Dam	Number of implantations	8	15	4 - 20	10 - 19
	Number of pregnant	8	10	9 – 10	9 - 11

2) Historical range of developmental parameters in control SD rats (Period: 2018-2022)

	Parameter	Number of studies	Mean	Min – Max	Mean±2S.D.
Offspring	No tail	8	0	0 - 0	0 - 0

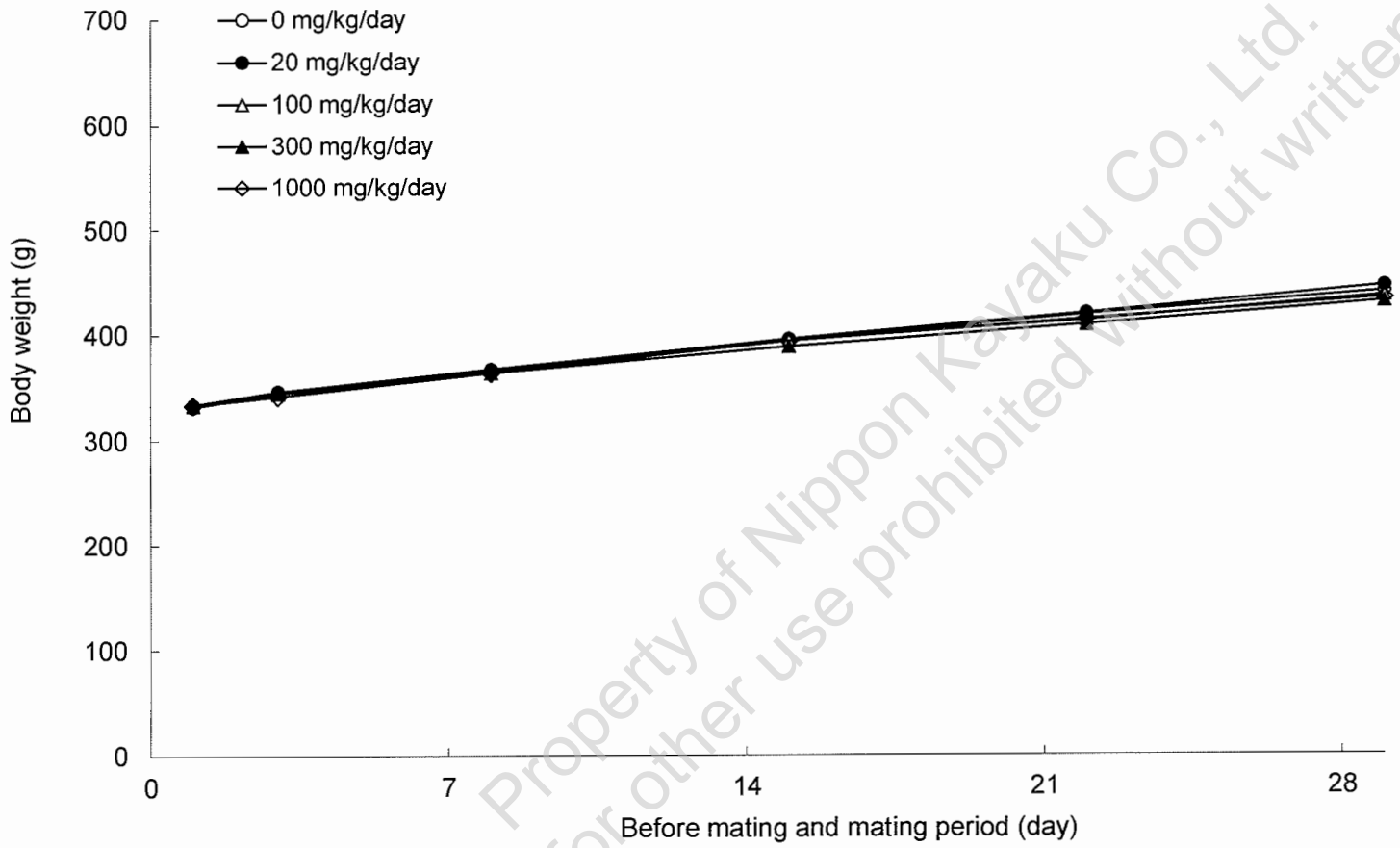


Fig. 1-1 Reproduction/developmental toxicity screening test in rats
Body weights: Male

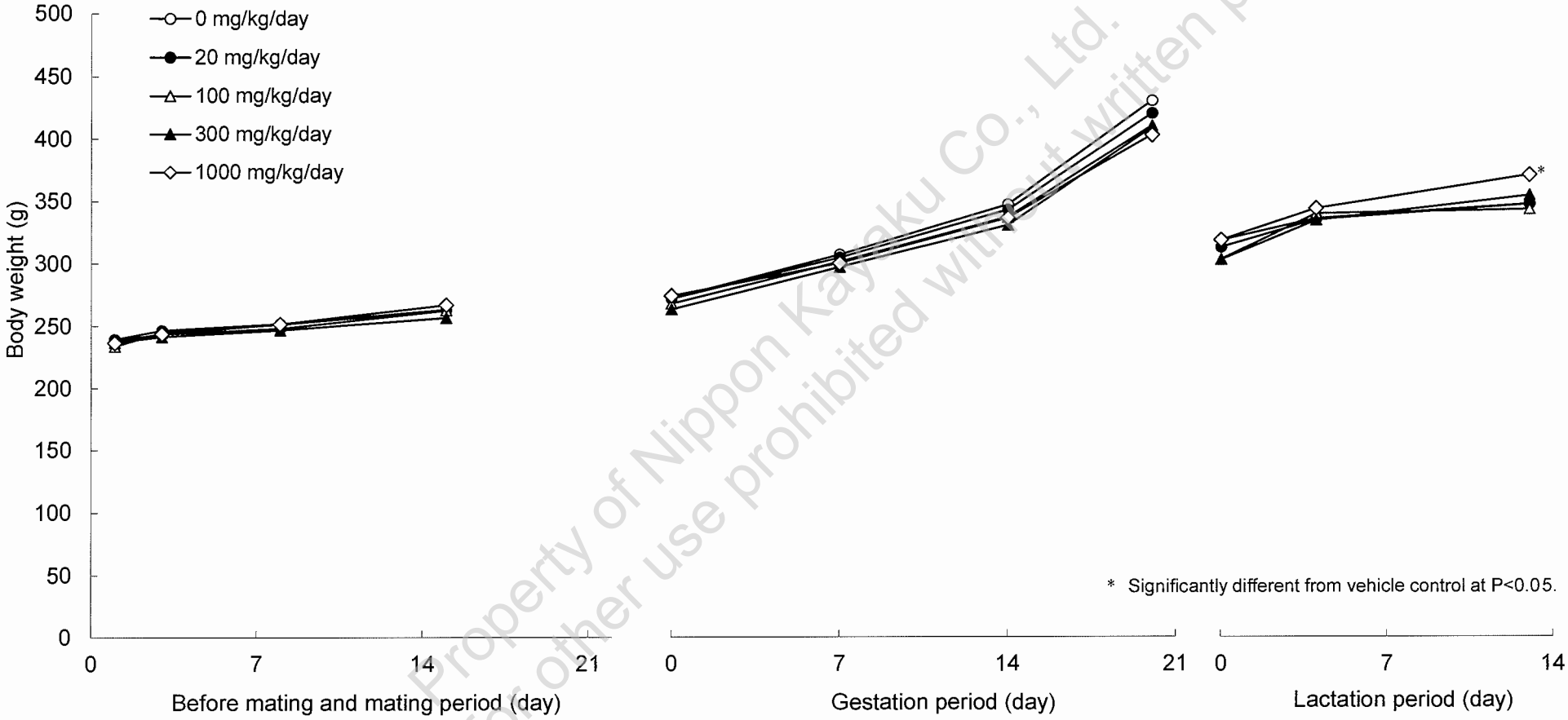


Fig. 1-2 Reproduction/developmental toxicity screening test in rats
Body weights: Female

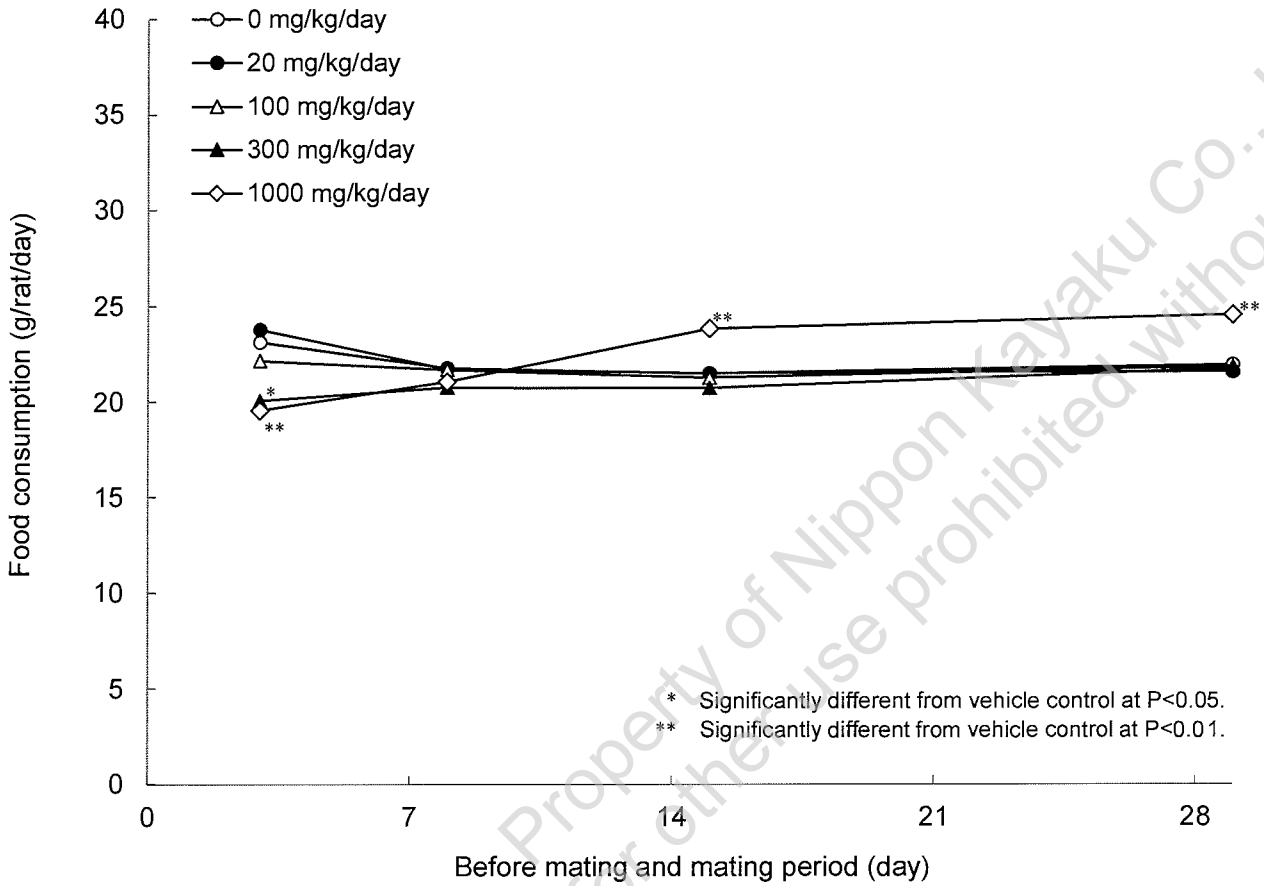


Fig. 2-1 Reproduction/developmental toxicity screening test in rats
Food consumption: Male

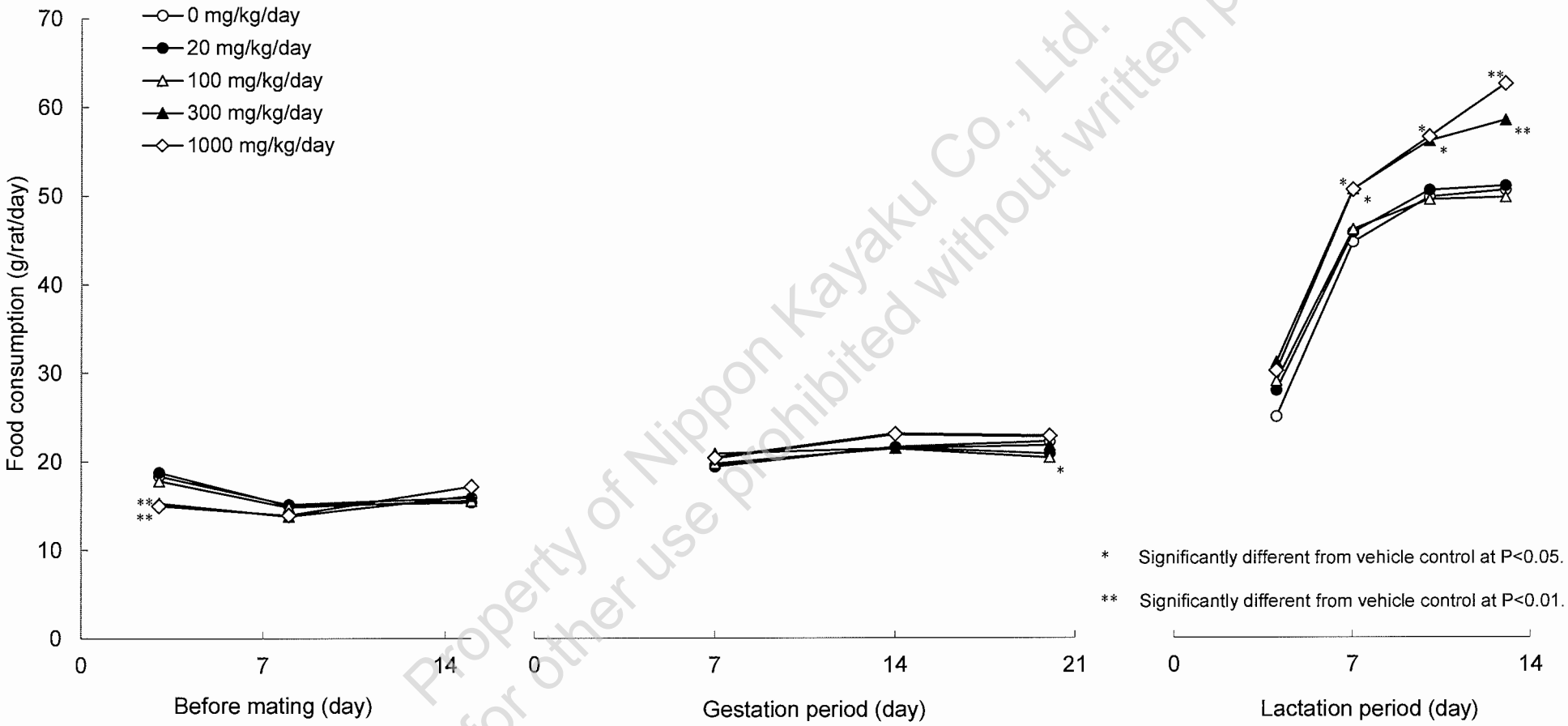


Fig. 2-2 Reproduction/developmental toxicity screening test in rats
Food consumption: Female

Table 1-1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Clinical sign

Sex : Male

Dose (mg/kg/day)	Administration period				
	0	20	100	300	1000
	ta	ta	ta	ta	ta
Signs Number of animals examined	10	10	10	10	10
No abnormalities detected	10	10	10	2	
Salivation				8	10
Soft stool					10
Staining around external genitaria					9
Staining around anus					4
Staining lower abdomen					4
Diarrhea					2

ta : Terminal autopsy

Table 1-2 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female

Dose (mg/kg/day)		Administration period										
		0		20	100			300			1000	
		ta	nd	ta	ta	wd	dd	ta	wd	nd	ta	nd
Signs	Number of animals examined	9	1	10	8	1	1	7	1	2	9	1
No abnormalities detected		8	1	10	8		1	3		2		
Swelling of left hindlimb		1										
Salivation								4			9	1
Soft stool											9	1
Staining around nose and mouth						1					1	
Staining lower abdomen											6	1
Staining around external genitaria									1		4	
Staining around anus						1					6	

ta : Terminal autopsy
nd : No delivery
wd : Whole litter death
dd : Death during delivery

Table 2 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Unit : g Species : Rat

Test item / Dose		/Day 1	3	8	15	22	29
TG-SH(H)	n	10	10	10	10	10	10
0 mg/kg/day	Mean	332.10	345.03	365.56	393.22	418.19	439.38
	S.D.	13.06	14.62	18.87	20.41	16.77	18.58
TG-SH(H)	n	10	10	10	10	10	10
20 mg/kg/day	Mean	334.18	346.58	367.06	395.10	419.27	444.67
	S.D.	12.54	13.73	17.33	19.68	22.70	29.95
TG-SH(H)	n	10	10	10	10	10	10
100 mg/kg/day	Mean	334.02	345.08	367.24	393.71	412.49	435.17
	S.D.	13.92	14.69	16.99	20.56	18.06	19.80
TG-SH(H)	n	10	10	10	10	10	10
300 mg/kg/day	Mean	333.39	344.85	363.88	388.10	408.30	430.03
	S.D.	13.51	11.90	16.78	19.99	22.14	24.06
TG-SH(H)	n	10	10	10	10	10	10
1000 mg/kg/day	Mean	333.63	342.11	363.91	393.34	413.69	433.10
	S.D.	14.43	14.75	17.25	18.63	20.74	23.58

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 2 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Unit : g Species : Rat

Test item		/Day										
Dose		1	3	8	15	0	7	14	20	0	4	13
TG-SH(H)	n	10	10	10	10	9	9	9	9	9	9	9
0 mg/kg/day	Mean	238.71	243.39	247.94	262.19	272.01	306.72	346.68	430.17	311.13	327.90	339.31
	S.D.	14.44	16.11	17.38	19.40	17.25	19.28	21.17	25.02	24.34	28.20	23.98
TG-SH(H)	n	10	10	10	10	10	10	10	10	10	10	10
20 mg/kg/day	Mean	239.35	246.49	251.59	262.96	271.63	304.23	342.50	419.83	305.57	327.18	338.97
	S.D.	19.29	18.03	19.38	23.55	23.74	24.78	24.17	27.25	15.27	18.34	18.55
TG-SH(H)	n	10	10	10	10	10	10	10	10	9	8	8
100 mg/kg/day	Mean	233.83	244.61	251.14	262.53	267.66	300.84	336.71	409.95	295.90	331.69	335.03
	S.D.	14.24	13.43	14.31	16.42	14.55	17.21	17.21	23.42	22.14	19.94	13.04
TG-SH(H)	n	10	10	10	10	8	8	8	8	8	7	7
300 mg/kg/day	Mean	236.82	241.35	246.72	256.36	263.05	296.69	330.26	408.59	295.78	326.53	346.03
	S.D.	12.78	13.45	13.30	12.01	12.55	14.84	14.65	15.97	13.32	12.02	12.10
TG-SH(H)	n	10	10	10	10	9	9	9	9	9	9	9
1000 mg/kg/day	Mean	236.51	243.78	251.47	266.64	273.98	299.91	336.06	402.63	311.19	335.87	361.86
	S.D.	13.08	12.51	14.19	18.32	12.97	16.38	17.51	22.51	18.97	26.71	16.84
												DT *

Significantly different from TG-SH(H) 0 mg/kg/day : * P<0.05

DT : Dunnett test (two-side)

Table 3 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Unit : g Species : Rat

Test item		/Day			
Dose		3	8	15	29
TG-SH(H)	n	10	10	10	10
0 mg/kg/day	Mean	23.15	21.80	21.52	21.97
	S.D.	1.81	1.29	1.59	1.66
TG-SH(H)	n	10	10	10	10
20 mg/kg/day	Mean	23.80	21.75	21.53	21.61
	S.D.	2.62	1.59	1.26	0.83
TG-SH(H)	n	10	10	10	10
100 mg/kg/day	Mean	22.19	21.72	21.29	21.88
	S.D.	1.99	2.15	1.57	2.18
TG-SH(H)	n	10	10	10	10
300 mg/kg/day	Mean	20.08	20.78	20.75	21.79
	S.D.	1.92	1.98	1.85	1.77
		DT *			
TG-SH(H)	n	10	10	10	10
1000 mg/kg/day	Mean	19.57	21.08	23.85	24.58
	S.D.	2.58	1.99	1.85	1.99
		DT **		DT **	DT **

Significantly different from TG-SH(H) 0 mg/kg/day : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 3 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Unit : g Species : Rat

Test item		/Day									
Dose		3	8	15	7	14	20	4	7	10	13
TG-SH(H)	n	10	10	10	9	9	9	9	9	9	9
0 mg/kg/day	Mean	18.41	15.15	15.90	19.40	21.61	22.22	24.89	44.57	49.67	50.44
	S.D.	2.13	1.25	1.71	1.90	1.85	1.77	6.65	4.42	4.10	7.03
TG-SH(H)	n	10	10	10	10	10	10	10	10	10	10
20 mg/kg/day	Mean	18.81	15.06	15.39	19.53	21.60	20.85	27.85	45.68	50.41	50.92
	S.D.	1.68	1.60	1.94	1.65	1.23	1.43	3.02	4.02	4.30	4.43
TG-SH(H)	n	10	10	10	10	10	10	8	8	8	8
100 mg/kg/day	Mean	17.86	14.87	15.58	19.74	21.45	20.41	28.90	45.99	49.35	49.63
	S.D.	1.55	1.21	1.39	1.03	1.30	1.60	5.57	6.37	5.37	4.92
							DT *				
TG-SH(H)	n	10	10	10	8	8	8	7	7	7	7
300 mg/kg/day	Mean	15.31	13.82	16.12	20.86	21.46	21.80	31.04	50.56	55.96	58.30
	S.D.	2.17	1.28	1.84	1.29	1.31	1.01	7.56	2.26	3.41	3.44
		DT **							DT *	DT *	DT **
TG-SH(H)	n	10	10	10	9	9	9	9	9	9	9
1000 mg/kg/day	Mean	15.02	13.95	17.19	20.39	23.07	22.86	30.06	50.49	56.44	62.42
	S.D.	1.72	1.14	1.58	0.76	1.23	1.18	5.80	4.18	5.52	2.84
		DT **							DT *	DT *	DT **

Significantly different from TG-SH(H) 0 mg/kg/day : * P<0.05, ** P<0.01

DT : Dunnett test (two-side)

Table 4 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Species : Rat

Test item Dose		T4 ng/mL
TG-SH(H) 0 mg/kg/day	n Mean S.D.	10 13.373 6.104
TG-SH(H) 20 mg/kg/day	n Mean S.D.	10 16.572 5.822
TG-SH(H) 100 mg/kg/day	n Mean S.D.	10 11.204 4.231
TG-SH(H) 300 mg/kg/day	n Mean S.D.	10 12.144 6.378
TG-SH(H) 1000 mg/kg/day	n Mean S.D.	10 9.577 5.595

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 4 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Blood chemical finding

Stage : Postnatal day 13

Species : Rat

Test item Dose		T4 (F1, Day 13) ng/mL
TG-SH(H)	n	9
0 mg/kg/day	Mean	10.858
	S.D.	2.971
TG-SH(H)	n	10
20 mg/kg/day	Mean	10.454
	S.D.	2.467
TG-SH(H)	n	8
100 mg/kg/day	Mean	12.309
	S.D.	4.323
TG-SH(H)	n	7
300 mg/kg/day	Mean	11.806
	S.D.	3.161
TG-SH(H)	n	9
1000 mg/kg/day	Mean	9.512
	S.D.	3.174

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 5 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Species : Rat

Test item / Dose		Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
			AB	RE	AB	RE	AB	RE	AB	RE
		g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
TG-SH(H)	n	10	10	10	10	10	10	10	10	10
0 mg/kg/day	Mean	420.89	3.167	0.754	1.231	0.292	2.902	0.689	19.75	4.69
	S.D.	14.45	0.352	0.092	0.145	0.035	0.288	0.068	2.03	0.49
TG-SH(H)	n	10	10	10	10	10	10	10	10	10
20 mg/kg/day	Mean	422.39	3.119	0.738	1.224	0.290	2.980	0.706	20.05	4.75
	S.D.	25.97	0.259	0.055	0.099	0.016	0.381	0.073	2.01	0.52
TG-SH(H)	n	10	10	10	10	10	10	10	10	10
100 mg/kg/day	Mean	414.02	3.029	0.733	1.213	0.293	2.850	0.691	20.92	5.08
	S.D.	19.42	0.215	0.064	0.111	0.029	0.365	0.090	4.93	1.27
TG-SH(H)	n	10	10	10	10	10	10	10	10	10
300 mg/kg/day	Mean	408.99	3.288	0.805	1.248	0.305	2.805	0.686	18.33	4.51
	S.D.	23.74	0.353	0.083	0.090	0.026	0.318	0.080	3.32	0.89
TG-SH(H)	n	10	10	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	403.52	3.061	0.760	1.171	0.293	2.543	0.631	18.25	4.55
	S.D.	21.96	0.296	0.069	0.143	0.035	0.359	0.089	3.18	0.88

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 5 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Species : Rat

Test item / Dose		Body weight	Thyroid	
			AB	RE
		g	mg	mg/100g
TG-SH(H)	n	9	9	9
0 mg/kg/day	Mean	320.77	19.27	5.98
	S.D.	20.68	4.14	1.12
TG-SH(H)	n	10	10	10
20 mg/kg/day	Mean	314.30	19.03	6.07
	S.D.	20.74	3.81	1.20
TG-SH(H)	n	8	8	8
100 mg/kg/day	Mean	314.18	19.43	6.18
	S.D.	14.71	3.11	0.91
TG-SH(H)	n	7	7	7
300 mg/kg/day	Mean	313.27	18.73	6.00
	S.D.	12.96	3.08	1.10
TG-SH(H)	n	9	9	9
1000 mg/kg/day	Mean	318.84	19.52	6.17
	S.D.	12.73	3.03	0.93

AB : Absolute weight, RE : Relative weight by body weight

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 6 - 1 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Sex : Male

Stage : Main group
Species : Rat

Organ / Findings		Test item	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)
		Dose	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
		Number of Animals	10	10	10	10	10
Cecum			<10/10>	<10/10>	<10/10>	<10/10>	<5/10>
Enlargement	P		0	0	0	0	5
Kidney			<10/10>	<10/10>	<10/10>	<10/10>	<6/10>
Discolored region, bilateral	P		0	0	0	0	3
Enlargement, bilateral	P		0	0	0	0	1
Other organs and tissues			<10/10>	<10/10>	<10/10>	<10/10>	<10/10>

<> : Not remarkable/Number of animals examined
P : Non-graded change

Table 6 - 2 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Sex : Female
Stage : Whole litter death
Species : Rat

Organ / Findings	Test item / Dose / Number of Animals		TG-SH(H) 100 mg/kg/day 1	TG-SH(H) 300 mg/kg/day 1
Kidney			<1/1>	<0/1>
Enlargement, bilateral		P	0	1
Thymus			<1/1>	<0/1>
Small		P	0	1
Adrenal			<1/1>	<0/1>
Enlargement, bilateral		P	0	1
Mammary gland			<1/1>	<0/1>
Atrophy		P	0	1
Other organs and tissues			<1/1>	<1/1>

<> : Not remarkable/Number of animals examined
P : Non-graded change

Table 6 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Macroscopic findings

Sex : Female Stage : Mortality

Species : Rat

	Test item		TG-SH(H)
	Dose		100 mg/kg/day
Organ Findings	Number of Animals		1
Lung			<0/1>
Edematous change		P	1
Other organs and tissues			<1/1>

<> : Not remarkable/Number of animals examined

P : Non-graded change

Table 6 - 4 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Sex : Female

Stage : Non delivery (F0)
Species : Rat

	Test item		TG-SH(H)	TG-SH(H)	TG-SH(H)
	Dose		0 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Organ Findings	Number of Animals		1	2	1
Cecum			<1/1>	<2/2>	<0/1>
Enlargement		P	0	0	1
Other organs and tissues			<1/1>	<2/2>	<1/1>

<> : Not remarkable/Number of animals examined
P : Non-graded change

Table 6 - 5 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Sex : Female

Stage : After delivery (F0)
Species : Rat

Organ / Findings		Test item	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)
		Dose	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
		Number of Animals	9	10	8	7	9
Glandular stomach			<4/9>	<9/10>	<5/8>	<2/7>	<5/9>
Black patch/spot, mucosa	P		5	1	3	5	4
Duodenum			<9/9>	<10/10>	<8/8>	<7/7>	<7/9>
Thickening, wall	P		0	0	0	0	2
Jejunum			<9/9>	<10/10>	<8/8>	<7/7>	<7/9>
Thickening, wall	P		0	0	0	0	2
Ileum			<9/9>	<10/10>	<8/8>	<7/7>	<7/9>
Thickening, wall	P		0	0	0	0	2
Cecum			<9/9>	<10/10>	<8/8>	<7/7>	<5/9>
Enlargement	P		0	0	0	0	2
Thickening, wall	P		0	0	0	0	2
Colon			<9/9>	<10/10>	<8/8>	<7/7>	<8/9>
Thickening, wall	P		0	0	0	0	1
Rectum			<9/9>	<10/10>	<8/8>	<7/7>	<8/9>
Thickening, wall	P		0	0	0	0	1
Other organs and tissues			<9/9>	<10/10>	<8/8>	<7/7>	<9/9>

<> : Not remarkable/Number of animals examined
P : Non-graded change

Table 7 - 1 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Sex : Male
Stage : Main group
Species : Rat

Organ / Findings		Test item	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)
		Dose	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
		Number of Animals	10	10	10	10	10
Cecum			<0/0>	<0/0>	<0/0>	<0/0>	<5/5>
Colon			<0/0>	<0/0>	<0/0>	<0/0>	<5/5>
Rectum			<0/0>	<0/0>	<0/0>	<0/0>	<5/5>
Kidney			<0/0>	<0/0>	<0/0>	<0/0>	<0/4>
Degeneration and necrosis, tubule	±		0	0	0	0	0
	1+		0	0	0	0	2
	2+		0	0	0	0	2
	3+		0	0	0	0	0
Dilatation, tubule	±		0	0	0	0	0
	1+		0	0	0	0	1
	2+		0	0	0	0	2
	3+		0	0	0	0	0
Regeneration, tubule	±		0	0	0	0	0
	1+		0	0	0	0	2
	2+		0	0	0	0	2
	3+		0	0	0	0	0
Testis			<9/10>	<0/0>	<0/0>	<0/0>	<10/10>
Atrophy, seminiferous tubule, focal, unilateral	±		0	0	0	0	0
	1+		1	0	0	0	0
	2+		0	0	0	0	0
	3+		0	0	0	0	0
Epididymis			<10/10>	<0/0>	<0/0>	<0/0>	<10/10>

<> : Not remarkable/Number of animals examined
± : Very slight, 1+ : Slight, 2+ : Moderate, 3+ : Severe

Table 7 - 2 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Sex : Female

Stage : Mortality
Species : Rat

Test item		TG-SH(H)
Dose		100 mg/kg/day
Organ / Findings	Number of Animals	1
Lung		<0/1>
Hemorrhage, focal	±	0
	1+	1
	2+	0
	3+	0
Perivascular edema	±	0
	1+	1
	2+	0
	3+	0

<> : Not remarkable/Number of animals examined
± : Very slight, 1+ : Slight, 2+ : Moderate, 3+ : Severe

Table 7 - 3 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Sex : Female
Stage : Whole litter death
Species : Rat

Organ / Findings	Test item / Dose / Number of Animals		TG-SH(H) 100 mg/kg/day 1	TG-SH(H) 300 mg/kg/day 1
Kidney			<0/0>	<0/1>
Vacuolation, tubular		±	0	0
		1+	0	0
		2+	0	1
		3+	0	0
Thymus			<0/0>	<0/1>
Atrophy		±	0	0
		1+	0	0
		2+	0	1
		3+	0	0
Adrenal			<0/0>	<0/1>
Hypertrophy, cortical, diffuse		±	0	0
		1+	0	1
		2+	0	0
		3+	0	0
Mammary gland			<0/0>	<1/1>

<> : Not remarkable/Number of animals examined
± : Very slight, 1+ : Slight, 2+ : Moderate, 3+ : Severe

Table 7 - 4 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Sex : Female
Stage : Non delivery (F0)
Species : Rat

Organ / Findings	Test item / Dose / Number of Animals		TG-SH(H) 0 mg/kg/day 1	TG-SH(H) 300 mg/kg/day 2	TG-SH(H) 1000 mg/kg/day 1
Cecum			<0/0>	<0/0>	<1/1>
Colon			<0/0>	<0/0>	<0/1>
Hyperplasia, mucosa		±	0	0	0
		1+	0	0	1
		2+	0	0	0
		3+	0	0	0
Rectum			<0/0>	<0/0>	<1/1>
Ovary			<1/1>	<0/0>	<1/1>

<> : Not remarkable/Number of animals examined
± : Very slight, 1+ : Slight, 2+ : Moderate, 3+ : Severe

Table 7 - 5 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Sex : Female

Stage : After delivery (F0)
Species : Rat

Organ / Findings	Test item / Dose / Number of Animals		TG-SH(H) 0 mg/kg/day 9	TG-SH(H) 20 mg/kg/day 10	TG-SH(H) 100 mg/kg/day 8	TG-SH(H) 300 mg/kg/day 7	TG-SH(H) 1000 mg/kg/day 9
Glandular stomach			<0/5>	<0/1>	<0/3>	<0/5>	<0/4>
Erosion, focal		±	0	0	0	0	0
		1+	5	1	2	4	4
		2+	0	0	1	1	0
		3+	0	0	0	0	0
Duodenum			<0/0>	<0/0>	<0/0>	<0/0>	<1/2>
Hyperplasia, mucosa		±	0	0	0	0	0
		1+	0	0	0	0	1
		2+	0	0	0	0	0
		3+	0	0	0	0	0
Jejunum			<0/0>	<0/0>	<0/0>	<0/0>	<2/2>
Ileum			<0/0>	<0/0>	<0/0>	<0/0>	<2/2>
Cecum			<0/0>	<0/0>	<0/0>	<0/0>	<3/4>
Hyperplasia, mucosa		±	0	0	0	0	0
		1+	0	0	0	0	1
		2+	0	0	0	0	0
		3+	0	0	0	0	0
Colon			<0/0>	<0/0>	<0/0>	<0/0>	<4/4>
Rectum			<0/0>	<0/0>	<0/0>	<0/0>	<4/4>
Ovary			<9/9>	<0/0>	<0/0>	<0/0>	<9/9>

<> : Not remarkable/Number of animals examined
± : Very slight, 1+ : Slight, 2+ : Moderate, 3+ : Severe

Table 8 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : Whole litter death

Sex : Female Species : Rat

Test item / Dose		Estrous cycle P	E	M	D
TG-SH(H) 100 mg/kg/day	n	1	0	0	0
TG-SH(H) 300 mg/kg/day	n	1	0	0	0

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Table 8 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : Non delivery (F0)

Sex : Female Species : Rat

Test item / Dose		Estrous cycle P	E	M	D
TG-SH(H) 0 mg/kg/day	n	1	0	0	0
TG-SH(H) 300 mg/kg/day	n	1	1	0	0
TG-SH(H) 1000 mg/kg/day	n	1	0	0	0

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Table 8 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : After delivery (F0)

Sex : Female Species : Rat

Test item / Dose		Estrous cycle P	E	M	D
TG-SH(H) 0 mg/kg/day	n	0	0	8	1
TG-SH(H) 20 mg/kg/day	n	0	0	9	1
TG-SH(H) 100 mg/kg/day	n	0	0	6	2
TG-SH(H) 300 mg/kg/day	n	0	0	5	2
TG-SH(H) 1000 mg/kg/day	n	0	0	5	4

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Table 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Estrus cycles

Generation : F0 Species : Rat

Test item / Dose		/Before mating Mean length of estrous cycle (Days)	Number of estrus	Number of animals with acyclic or irregular cycle	Abnormal estrous cycle index (%)
TG-SH(H)	n	10	10	10	
0 mg/kg/day				(0)	0.00
	Mean	4.05	3.2		
	S.D.	0.16	0.4		
TG-SH(H)	n	10	10	10	
20 mg/kg/day				(0)	0.00
	Mean	4.33	3.2		
	S.D.	0.62	0.6		
TG-SH(H)	n	10	10	10	
100 mg/kg/day				(0)	0.00
	Mean	4.00	3.4		
	S.D.	0.00	0.7		
TG-SH(H)	n	10	10	10	
300 mg/kg/day				(0)	0.00
	Mean	4.25	3.3		
	S.D.	0.42	0.5		
TG-SH(H)	n	10	10	10	
1000 mg/kg/day				(0)	0.00
	Mean	4.23	3.4		
	S.D.	0.34	0.5		

() : Values in brackets represent number of animals with acyclic or irregular cycle.
Abnormal estrous cycle index = (No. of animals with abnormal estrous cycle / No. of animals examined)×100
Not significantly different from TG-SH(H) 0 mg/kg/day

Table 10 Reproduction/developmental toxicity screening test in rats
Reproductive performance

Study No. : E16-0045

Generation : F0 Sex : Female Species : Rat

Test item / Dose		Number of pairs	Day of conceiving	1st mating Copulation index (%)	1st mating Fertility index (%)	Total Copulation index (%)	Total Fertility index (%)
TG-SH(H)	n	10	10	(10/10)	(9/10)	(10/10)	(9/10)
0 mg/kg/day	Mean		1.8	100.0	90.0	100.0	90.0
	S.D.		1.1				
TG-SH(H)	n	10	10	(10/10)	(10/10)	(10/10)	(10/10)
20 mg/kg/day	Mean		2.1	100.0	100.0	100.0	100.0
	S.D.		1.1				
TG-SH(H)	n	10	10	(10/10)	(10/10)	(10/10)	(10/10)
100 mg/kg/day	Mean		2.0	100.0	100.0	100.0	100.0
	S.D.		0.9				
TG-SH(H)	n	10	10	(10/10)	(8/10)	(10/10)	(8/10)
300 mg/kg/day	Mean		1.9	100.0	80.0	100.0	80.0
	S.D.		1.1				
TG-SH(H)	n	10	10	(10/10)	(9/10)	(10/10)	(9/10)
1000 mg/kg/day	Mean		2.0	100.0	90.0	100.0	90.0
	S.D.		1.2				

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 11 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Delivery data

Generation : F0 Species : Rat

Test item / Dose		Gestation period (day)	Gestation index (%)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Sex ratio (%)		Number of dead newborns
								M	F	Total	live-borns	delivered pups	
TG-SH(H)	n	9	9/10	10	9	9	9	9	9	9	71/131	71/134	9
0 mg/kg/day	Mean	22.11	90.0	14.10	95.02	97.91	14.89	7.89	6.67	14.56	54.2	53.0	0.33
	S.D.	0.33		5.09	4.38	3.14	1.36	1.90	1.80	1.13			0.50
TG-SH(H)	n	10	10/10	10	10	10	10	10	10	10	74/138	74/142	10
20 mg/kg/day	Mean	22.20	100.0	15.10	94.07	97.42	14.20	7.40	6.40	13.80	53.6	52.1	0.40
	S.D.	0.42		1.29	4.96	5.44	1.40	1.35	1.65	1.23			0.84
TG-SH(H)	n	9	9/10	10	10	9	9	9	9	9	62/122	64/124	9
100 mg/kg/day	Mean	22.33	90.0	14.50	87.06	98.52	13.78	6.89	6.67	13.56	50.8	51.6	0.22
	S.D.	0.50		2.92	31.22	2.94	2.68	2.47	2.55	2.60			0.44
TG-SH(H)	n	8	8/10	10	8	8	8	8	8	8	58/115	58/118	8
300 mg/kg/day	Mean	22.13	80.0	12.50	94.28	97.73	14.75	7.25	7.13	14.38	50.4	49.2	0.38
	S.D.	0.35		6.74	4.08	4.28	1.91	1.16	1.73	1.51			0.74
TG-SH(H)	n	9	9/10	10	9	9	9	9	9	9	66/121	66/121	9
1000 mg/kg/day	Mean	22.22	90.0	12.80	94.63	100.00	13.44	7.33	6.11	13.44	54.5	54.5	0.00
	S.D.	0.44		4.71	10.97	0.00	2.07	1.73	1.36	2.07			0.00

M : Male, F : Female
Not significantly different from TG-SH(H) 0 mg/kg/day

Table 12 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Litter size and viability index of offspring

Generation : F0 Species : Rat

Test item / Dose		/Days after birth 0	4 Pre-culled	4 Sex rate (%)	4 Viability index (%)	4 Culled	13		
TG-SH(H)	Total	131	127	68/127		109	109		
0 mg/kg/day	n	9	9	9	9	9	9		
	Mean			54	97.13				
	S.D.				6.38				
TG-SH(H)	Total	138	137	73/137		117	117		
20 mg/kg/day	n	10	10	10	10	10	10		
	Mean			53	99.33				
	S.D.				2.12				
TG-SH(H)	Total	122	107	55/107		93	93		
100 mg/kg/day	n	9	8	8	8	8	8		
	Mean			51	100.00				
	S.D.				0.00				
TG-SH(H)	Total	115	97	51/97		83	83		
300 mg/kg/day	n	8	7	7	7	7	7		
	Mean			53	99.04				
	S.D.				2.53				
TG-SH(H)	Total	121	119	65/119		101	101		
1000 mg/kg/day	n	9	9	9	9	9	9		
	Mean			55	98.51				
	S.D.				2.95				

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 13 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Body weight of offspring

Generation : F0 Unit : g Species : Rat

Test item / Dose			/Days after birth 0	4	13
TG-SH(H) 0 mg/kg/day	Male	n	9	9	9
		Mean	6.68	10.42	28.23
		S.D.	0.27	1.20	1.76
	Female	n	9	9	9
		Mean	6.40	10.08	27.62
		S.D.	0.44	0.95	1.91
TG-SH(H) 20 mg/kg/day	Male	n	10	10	10
		Mean	6.86	11.30	29.53
		S.D.	0.46	1.04	2.19
	Female	n	10	10	10
		Mean	6.56	10.87	28.87
		S.D.	0.40	0.74	2.09
TG-SH(H) 100 mg/kg/day	Male	n	9	8	8
		Mean	6.79	11.46	29.84
		S.D.	0.84	1.62	3.27
	Female	n	9	8	8
		Mean	6.54	10.91	29.10
		S.D.	0.71	1.56	3.47
TG-SH(H) 300 mg/kg/day	Male	n	8	7	7
		Mean	6.53	10.57	29.30
		S.D.	0.61	1.05	2.71
	Female	n	8	7	7
		Mean	6.26	10.21	28.53
		S.D.	0.60	1.19	2.51
TG-SH(H) 1000 mg/kg/day	Male	n	9	9	9
		Mean	7.14	11.42	30.67
		S.D.	0.75	1.91	4.56
	Female	n	9	9	9
		Mean	6.79	10.88	29.36
		S.D.	0.74	1.77	3.94

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 14 Reproduction/developmental toxicity screening test in rats
Anogenital distance of offspring

Study No. : E16-0045

Generation : F0

Unit : mm Species : Rat

Dose / Test item	Sex		/Days after birth 4 AGD	AGD/3√BW
TG-SH(H) 0 mg/kg/day	Male	n	9	9
		Mean	5.909	2.713
		S.D.	0.309	0.085
	Female	n	9	9
		Mean	3.301	1.534
		S.D.	0.189	0.077
TG-SH(H) 20 mg/kg/day	Male	n	10	10
		Mean	5.689	2.538
		S.D.	0.520	0.208
	Female	n	10	10
		Mean	3.023	1.367
		S.D.	0.411	0.176
TG-SH(H) 100 mg/kg/day	Male	n	8	8
		Mean	5.829	2.590
		S.D.	0.601	0.240
	Female	n	8	8
		Mean	3.195	1.444
		S.D.	0.455	0.197
TG-SH(H) 300 mg/kg/day	Male	n	7	7
		Mean	5.540	2.529
		S.D.	0.435	0.206
	Female	n	7	7
		Mean	2.947	1.364
		S.D.	0.433	0.210
TG-SH(H) 1000 mg/kg/day	Male	n	9	9
		Mean	5.806	2.584
		S.D.	0.733	0.295
	Female	n	9	9
		Mean	3.124	1.414
		S.D.	0.515	0.227

AGD : Anogenital Distance
AGD/3√body weight
Not significantly different from TG-SH(H) 0 mg/kg/day

Table 15 - 1 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Days after birth : 0

Generation : F0

Species : Rat

Test item		TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)
Dose		0	20	100	300	1000
Dose unit		mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of dams		9	10	9	8	9
Number of offspring		131	138	122	115	121
Number of dams with anomalous offspring (incidence%)		0(0.0)	0(0.0)	1(11.11)	0(0.0)	1(11.11)
Number of offspring with any anomaly (incidence%)		0(0.0)	0(0.0)	1(0.86)	0(0.0)	1(1.01)
Others	n	0(0)	0(0)	1(1)	0(0)	1(1)
	Mean			0.86		1.01
	S.D.			2.57		3.03

n : Number of anomalous offspring (number of dams with anomalous offspring)
Mean : Number of anomalous offspring / Number of offspring examined x 100(%), on litter basis

Table 15 - 2 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Generation : F0

Study No. : E16-0045

Days after birth : 13
Species : Rat

Test item		TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)	TG-SH(H)
Dose		0	20	100	300	1000
Dose unit		mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of dams		9	10	8	7	9
Number of offspring		109	117	93	83	101
Number of dams with anomalous offspring (incidence%)		0(0.0)	0(0.0)	2(25.00)	0(0.0)	1(11.11)
Number of offspring with any anomaly (incidence%)		0(0.0)	0(0.0)	2(2.10)	0(0.0)	1(1.23)
Others	n	0(0)	0(0)	2(2)	0(0)	1(1)
	Mean			2.10		1.23
	S.D.			3.91		3.70

n : Number of anomalous offspring (number of dams with anomalous offspring)
Mean : Number of anomalous offspring / Number of offspring examined x 100(%), on litter basis

Table 16 Reproduction/developmental toxicity screening test in rats
Nipple retention of offspring

Study No. : E16-0045

Generation : F0

Species : Rat

Test item			/Days after birth
Dose			13
TG-SH(H)	Male	n	9
0 mg/kg/day		Mean	0.0
		S.D.	0.0
TG-SH(H)	Male	n	10
20 mg/kg/day		Mean	0.0
		S.D.	0.0
TG-SH(H)	Male	n	8
100 mg/kg/day		Mean	0.0
		S.D.	0.0
TG-SH(H)	Male	n	7
300 mg/kg/day		Mean	0.0
		S.D.	0.0
TG-SH(H)	Male	n	9
1000 mg/kg/day		Mean	0.0
		S.D.	0.0

Not significantly different from TG-SH(H) 0 mg/kg/day

Table 17 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

		Lactation period				
Dose (mg/kg/day)		0	20	100	300	1000
Signs	Number of dams examined	9	10	9	8	9
No abnormalities detected		9	10	5	7	7
Unclearance of placenta				1		
No retrieving				1	1	
No crouching				1	1	
No milk band				2	1	1
Subnormal temperature				2	1	1
No tail				1		1
Loss of tip tail				1		
Whole litter death				1	1	

Appendix 1-1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Clinical sign

Sex : Male Dose : 0 mg/kg/day

Animal No.	Signs	Administration period (day) 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	
1101	No abnormalities detected	. . . . .	S
1102	No abnormalities detected	. . . . .	S
1103	No abnormalities detected	. . . . .	S
1104	No abnormalities detected	. . . . .	S
1105	No abnormalities detected	. . . . .	S
1106	No abnormalities detected	. . . . .	S
1107	No abnormalities detected	. . . . .	S
1108	No abnormalities detected	. . . . .	S
1109	No abnormalities detected	. . . . .	S
1110	No abnormalities detected	. . . . .	S

. : No abnormalities detected

S : Sacrificed

Appendix 1-2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Clinical sign

Sex : Male Dose : 20 mg/kg/day

Animal No.	Signs	Administration period (day) 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	
1201	No abnormalities detected	. . . . .	S
1202	No abnormalities detected	. . . . .	S
1204	No abnormalities detected	. . . . .	S
1205	No abnormalities detected	. . . . .	S
1206	No abnormalities detected	. . . . .	S
1207	No abnormalities detected	. . . . .	S
1208	No abnormalities detected	. . . . .	S
1209	No abnormalities detected	. . . . .	S
1210	No abnormalities detected	. . . . .	S

. : No abnormalities detected
S : Sacrificed

Appendix 1-3 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Male Dose : 100 mg/kg/day

Animal No.	Signs	Administration period (day) 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	
1301	No abnormalities detected	. . . . .	S
1302	No abnormalities detected	. . . . .	S
1303	No abnormalities detected	. . . . .	S
1304	No abnormalities detected	. . . . .	S
1305	No abnormalities detected	. . . . .	S
1306	No abnormalities detected	. . . . .	S
1307	No abnormalities detected	. . . . .	S
1308	No abnormalities detected	. . . . .	S
1309	No abnormalities detected	. . . . .	S
1310	No abnormalities detected	. . . . .	S

. : No abnormalities detected
S : Sacrificed

Appendix 1-4 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Male Dose : 300 mg/kg/day

Animal No.	Signs	Administration period (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
1401	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation											1																1	1	
1402	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
1403	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
1404	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation																										1				
1405	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation																					1									
1406	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation											1	1	1						1				1	1	1	1	1			
1407	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation							1									1					1									
1408	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation											1	1	1	1									1			1	1			
1409	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation																												1		
1410	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S
	Salivation																								1				1		

. : No abnormalities detected
S : Sacrificed
Salivation: 1, Disappeared within 15 min after dosing

Appendix 1-5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Clinical sign

Sex : Male Dose : 1000 mg/kg/day

Animal No.	Signs	Administration period (day)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
1501	No abnormalities detected	.	.	.	.	.	.	.																							S
	Soft stool							2	2	2	2	2	2	2	2	2				2		2	2	2	2	2	2	2			
	Salivation							1	1	1	1	1	1	2	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Staining around anus									1	1																				
	Staining around external genitalia																2	2	2	2	1										
1502	No abnormalities detected	.	.	.	.	.	.	.																							S
	Soft stool							2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	1	2	
	Salivation							1	1	2	2	2	2	2	1	1	2	1	1	1	1	2	2	1	2	2	2	1	1	1	
	Staining around external genitalia																1														
1503	No abnormalities detected	.	.	.	.	.	.	.																							S
	Soft stool							2	2	2	2	2	2	2	2	2		2	2		2	2	2	2	2	2	2	2		2	
	Salivation										1	1	1	1	1			1	1	1	1	1	1	2	1	1	1	1		1	
	Staining around external genitalia																1	1	1	1	1										
1504	No abnormalities detected	.	.	.	.	.	.	.	.																						S
	Salivation									1	1	1	1	1	1	1	1		1	1	1	1	1	1	2	1	1	1	1	2	
	Soft stool											2	2	2	2	2						2		2	2	2	2	2	1	2	
	Staining around external genitalia																2	2	2	2	1	1		1							
	Staining lower abdomen																					1									
	Diarrhea																						2								
1505	No abnormalities detected	.	.	.	.	.	.	.																							S
	Soft stool							2	2	2	2	2	2	2	2	2				2	2	2	2	2	2	2	2	2	2	2	
	Salivation							1	1	1		1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	2	1	
	Staining around external genitalia																1					1		1							
1506	No abnormalities detected	.	.																												S
	Staining around anus			1	1	1	1	1	1		1																				
	Soft stool							2	2	2	2	2	2	2	2	2				2	2	2	2	2	2	2	2	2	1	2	
	Salivation												1	1	1			1	1	1	1	1	1	1	1	1	1	1	2	1	
	Staining around external genitalia																2	2	2	2	2	1		2		1					
	Staining lower abdomen																					1									
1507	No abnormalities detected	.	.	.	.	.	.	.	.																						S
	Soft stool									2	2	2	2	2	2	2				2		2		2	2	2	2	2	1	2	
	Salivation										1	1	1	1	1	1	1			1	1	2	2	1	1	1	1			1	
	Staining around external genitalia																2	2	2	2	2	2		2		2					
	Staining lower abdomen																					1		1	1	1		1	1		
1508	No abnormalities detected	.	.	.	.	.	.																								S
	Staining around anus						1	1	1																			1			
	Soft stool							2	2	2	2	2	2	2	2	2		2	2	2		2	2		2	2	2	2	1	2	
	Salivation							1		1	1	1	1	1	1	1	1			1	1	1	2	1	2	2	2	2	1	2	
	Staining lower abdomen								1	1	1	1	1	1	1	2								2		2					
	Staining around external genitalia																2	2	2	2	2	1		2	1		1				
	Diarrhea																								2						

. : No abnormalities detected

S : Sacrificed

Salivation: 1, Disappeared within 15 min after dosing; 2, Disappeared within 30 min after dosing

Signs other than salivation: 1, Slight; 2, Severe

Appendix 1-6 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Clinical sign

Sex : Male Dose : 1000 mg/kg/day

Animal No.	Signs	Administration period (day)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
1509	No abnormalities detected	.	.	.	.	.	.	.	.																						S
	Soft stool							2		2	2	2	2	2	2	2		2	2		2	2	2	2	2	2	2	2	1	2	
	Salivation							1		2	2	1	1	1	1	1	2	1	1	1	1	2	1	1	2	1	2	2	2		
	Staining around external genitalia																2	1	1	1	2	2		2		2					
	Staining around anus																								2						
1510	No abnormalities detected	.	.	.	.	.	.										.														S
	Soft stool							2	2	2	2	2	2	2	2	2		2	2		2	2	2	2	2	2	2	2	2	2	
	Salivation								1			1	1	1	1	1		1	1	1	1	2	1	1	1	2		1	2	1	

. : No abnormalities detected

S : Sacrificed

Salivation: 1, Disappeared within 15 min after dosing; 2, Disappeared within 30 min after dosing

Signs other than salivation: 1, Slight; 2, Severe

Appendix 1-7 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female   Dose : 0 mg/kg/day

Administration period (day)

Animal No.	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
5101																			P0																							L0														S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
5102																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5103																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5104																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
5105																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	Swelling of left hindlimb																										2	2	2	1																										
5106																				P0																						L0														S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
5107																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5108																			P0																						L0														S	
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
5109																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5110																	P0																									S (No delivery)														
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.															

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed
1 : Slight, 2 : Severe
No. 5110 : No delivery

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Appendix 1-8 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female Dose : 20 mg/kg/day

Administration period (day)

Animal No.	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
5201																			P0																							L0														S	
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
5202																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5203																	P0																							L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
5204																			P0																								L0														S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
5205																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5206																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
5207																				P0																							L0														S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
5208																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
5209																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
5210																			P0																							L0														S	
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed

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Appendix 1-9 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female Dose : 100 mg/kg/day

Animal No.	Signs	Administration period (day) 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55
5301		P0 L0 S
	No abnormalities detected	. . . . .
5302		P0 L0 S (Whole litter death)
	No abnormalities detected	. . . . .
	Staining around nose and mouth	2 1
	Staining around anus	1
5303		P0 L0 S
	No abnormalities detected	. . . . .
5304		P0 L0 S
	No abnormalities detected	. . . . .
5305		P0 S (Death)
	No abnormalities detected	. . . . .
5306		P0 L0 S
	No abnormalities detected	. . . . .
5307		P0 L0 S
	No abnormalities detected	. . . . .
5308		P0 L0 S
	No abnormalities detected	. . . . .
5309		P0 L0 S
	No abnormalities detected	. . . . .
5310		P0 L0 S
	No abnormalities detected	. . . . .

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed
1 : Slight, 2 : Severe
No. 5302 : Whole litter death
No. 5305 : Death during delivery (gestation day 22)

Appendix 1-10 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female   Dose : 300 mg/kg/day

Administration period (day)

Animal No.	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
5401																				P0																						L0		S (Whole litter death)												
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.														
	Staining around external genitalia																																										2													
5402																	P0																									S (No delivery)														
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.															
5403																			P0																						L0														S	
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
5404																			P0																						L0														S	
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
	Salivation																																																					1		
5405																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.			.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	Salivation											1	1																																											
5406																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
	Salivation											1												1																																
5407																	P0																									S (No delivery)														
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.															
5408																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
5409																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.				.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	Salivation											1	1	1																																								
5410																	P0																							L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed
Salivation: 1, Disappeared within 15 min after dosing
Signs other than salivation: 2, Severe
No. 5401 : Whole litter death
No. 5402, 5407: No delivery

Appendix 1-11 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female   Dose : 1000 mg/kg/day

Administration period (day)

Animal No.	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
5501																			P0																							L0														S
	No abnormalities detected	.	.	.	.	.	.																						.		.			.	.		.	.		.	.		.		.	.	.	.	.			.	.	.	.	
	Salivation							1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1		1	1			1			1					1						1	1					
	Staining around anus									1	1											1	1																																	
	Soft stool											2	2	2	2						2	2	2	2	2	2	2	2		2																										
	Staining lower abdomen																	1	1	1																																				
5502																	P0																									S (No delivery)														
	No abnormalities detected	.	.	.	.	.	.	.																									.	.			.	.	.	.																
	Salivation								1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1			1	1					1															
	Soft stool											2	2	2	2	2		2	2	2	2								1																											
	Staining lower abdomen																	2	1	1	1	1	1	1		1	1	1	1																											
5503																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.	.	.																											.			.		.	.			.	.					.						
	Soft stool								2			2	2	2	2	2		1			2			2																																
	Salivation									1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1		1	1		1			1	1			1	1	1	1		1	1				
5504																			P0																						L0														S	
	No abnormalities detected	.	.	.	.	.	.	.																.	.								.	.	.	.	.	.	.		.	.	.	.	.	.	.	.	.	.		.	.	.		
	Staining lower abdomen								1	1	1	2	2	2	2	2	2	2	2	2	2	2	2				1	1	2	1																										
	Salivation									1	1	1	1	1	1				2	2		1	1			1		1	2			1								1											1					
	Soft stool											2	2	2	2	2		1		2		1	2			2	2	2	1	2	1																									
	Staining around anus																														2	2																								
5505																		P0																						L0														S		
	No abnormalities detected	.	.	.	.	.	.	.	.						.																								.	.	.	.	.			.		.	.							
	Soft stool									2	2		2	2		2			2		2				2	2				2																										
	Salivation									1	1	1	1	1		1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1			1	1								1	1		1			1	1	1	1			
	Staining around anus										1														2	2							2	2	2		1	1																		
	Staining around external genitalia											2	2																																											
	Staining lower abdomen																2	1	2	2	1	2	2	1			2	2	2	2	2	2				1																				
5506																			P0																						L0														S	
	No abnormalities detected	.	.				.	.	.																											.	.	.				.		.				.	.		.					
	Staining around anus			1	1	1																											2	1	1																					
	Salivation									1	1	1	1	1	1	1	1	1	2	2	1	1	1		1	1	1	1	2	1	1	1	1	1	1				1	1	1		1		1	1	1			1		1	1	1		
	Soft stool										2	2	2	2	2	2					2		2	2	2	2	2	2				2	2																							
	Staining around external genitaria											2	2																																											
	Staining lower abdomen															2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2																								
5507																				P0																						L0														S
	No abnormalities detected	.	.	.	.	.	.	.	.					.			.												.	.				.	.		.	.	.	.	.		.		.	.	.			.	.		.	.	.	
	Soft stool									2	2	2	2		2	2		1	2	2	2	1	2	2	2	2	2				1	2																								
	Salivation									1	1												1			1		1					1			1						1		1				1	1			1				

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed
Salivation: 1, Disappeared within 15 min after dosing; 2, Disappeared within 30 min after dosing
Signs other than salivation: 1, Slight; 2, Severe
No. 5502 : No delivery

Appendix 1-12 Reproduction/developmental toxicity screening test in rats
Clinical sign

Study No. : E16-0045

Sex : Female
Dose : 1000 mg/kg/day

Administration period (day)

Animal No.	Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
5508																	P0																							L0														S		
	No abnormalities detected	.	.	.	.	.	.		.																													.	.		.	.														
	Salivation							1		1	1	2	1	1	2		1	1	2	2	1	1	2	1	1	2	1	2	1	2		2	1	1	2	1	1			1			1	1	1	1	1	1	1	1	1	1	1			
	Soft stool											2		2	2	2			2	2	2								2																											
	Staining lower abdomen																												2		2	2																								
5509																	P0																						L0														S			
	No abnormalities detected	.	.		.	.	.		.	.																			.		.					.	.		.				.					.								
	Staining around anus			1																		1	1																																	
	Salivation							2			1	2	1	2	2	1	2		2	1	2	2	2	1	1	1	2	1				1	1	1	1			1		1	1	1		1	1	1	1		1	1	1	1				
	Soft stool															2		2		2		1	2	2	2	2				2																										
	Staining around external genitaria																		2	2																																				
5510																	P0																						L0														S			
	No abnormalities detected	.	.	.	.	.																																			.			.												
	Staining around anus						1			1	1	2	2	2	1	2	2										1	1					1																							
	Soft stool							2			2	2	2	2	2	2		2	2	2	2	2	2	2		2			1	2																										
	Salivation							1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1		1	1		1	1	1	1	1	1	1	1				
	Staining nose and mouth									1	1																																													
	Staining around external genitaria											2	2	2	1				2	2																																				
	Staning lower abdomen																	1				2	2	1		1	1	1	2	1	2	2																								

. : No abnormalities detected
P0 : Pregnant day 0, L0 : Lactation day 0
S : Sacrificed
Salivation: 1, Disappeared within 15 min after dosing; 2, Disappeared within 30 min after dosing
Signs other than salivation: 1, Slight; 2, Severe

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Appendix 2 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 0 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	22	29
1101	323.0	332.4	348.3	362.9	390.6	412.5
1102	345.9	354.1	383.9	412.5	443.0	471.4
1103	327.2	337.7	354.0	384.0	406.2	430.1
1104	331.3	344.4	367.6	395.9	417.9	413.6
1105	308.9	321.0	332.5	360.2	396.8	431.2
1106	345.2	360.7	386.0	419.7	430.1	451.5
1107	340.4	351.8	375.5	397.6	419.8	441.0
1108	348.3	363.7	385.3	410.9	431.6	447.8
1109	332.7	356.3	375.3	405.2	432.5	457.2
1110	318.1	328.2	347.2	383.3	413.4	437.5
n	10	10	10	10	10	10
Mean	332.10	345.03	365.56	393.22	418.19	439.38
S.D.	13.06	14.62	18.87	20.41	16.77	18.58

Appendix 2 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 20 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	22	29
1201	328.2	343.4	359.3	387.7	413.0	435.3
1202	349.9	365.3	391.1	431.0	461.2	495.5
1203	336.0	343.7	356.6	387.8	417.0	445.5
1204	330.9	342.7	362.5	392.2	412.1	434.8
1205	322.4	330.0	348.4	371.9	400.6	415.8
1206	318.5	328.0	346.6	369.2	387.2	405.1
1207	344.5	360.3	377.0	402.9	426.6	487.5
1208	326.0	340.4	365.0	398.5	431.3	455.1
1209	328.3	344.0	364.5	387.5	397.4	415.9
1210	357.1	368.0	399.6	422.3	446.3	456.2
n	10	10	10	10	10	10
Mean	334.18	346.58	367.06	395.10	419.27	444.67
S.D.	12.54	13.73	17.33	19.68	22.70	29.95

Appendix 2 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 100 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	22	29
1301	337.0	351.9	379.2	400.7	413.8	435.5
1302	316.7	327.6	344.4	370.8	394.0	418.0
1303	343.8	348.8	371.6	409.4	428.6	450.4
1304	346.6	351.4	373.8	391.2	410.9	432.0
1305	328.9	337.6	350.1	372.3	392.5	414.9
1306	331.7	345.0	369.5	389.2	410.0	439.9
1307	333.7	343.1	368.6	411.1	425.8	453.2
1308	360.7	377.9	399.8	429.7	440.2	463.8
1309	314.4	325.3	344.9	364.1	383.9	398.9
1310	326.7	342.2	370.5	398.6	425.2	445.1
n	10	10	10	10	10	10
Mean	334.02	345.08	367.24	393.71	412.49	435.17
S.D.	13.92	14.69	16.99	20.56	18.06	19.80

Appendix 2 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 300 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	22	29
1401	332.5	342.9	351.7	379.0	392.9	410.0
1402	340.0	348.6	368.5	387.3	399.2	420.2
1403	337.6	346.0	366.6	383.0	403.1	425.9
1404	312.9	327.6	335.3	359.9	375.5	402.1
1405	347.4	361.8	380.5	418.9	440.3	459.2
1406	324.8	335.8	352.3	366.1	388.3	408.0
1407	351.0	364.3	391.1	416.9	438.8	469.9
1408	326.2	341.7	361.5	385.7	403.1	414.3
1409	314.7	331.2	351.9	378.1	408.9	433.7
1410	346.8	348.6	379.4	406.1	432.9	457.0
n	10	10	10	10	10	10
Mean	333.39	344.85	363.88	388.10	408.30	430.03
S.D.	13.51	11.90	16.78	19.99	22.14	24.06

Appendix 2 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 1000 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	22	29
1501	315.5	327.0	358.6	394.6	410.3	434.4
1502	327.5	331.4	360.6	390.2	404.3	424.8
1503	312.1	319.3	343.7	376.1	399.7	425.1
1504	343.0	346.2	363.0	398.3	415.5	436.2
1505	331.7	343.4	368.0	400.2	426.2	452.7
1506	352.3	361.0	376.9	409.2	431.8	452.6
1507	327.3	334.6	352.9	377.0	394.6	402.8
1508	335.5	355.6	380.4	401.8	423.0	429.2
1509	357.3	363.8	396.0	425.8	452.0	476.2
1510	334.1	338.8	339.0	360.2	379.5	397.0
n	10	10	10	10	10	10
Mean	333.63	342.11	363.91	393.34	413.69	433.10
S.D.	14.43	14.75	17.25	18.63	20.74	23.58

Appendix 2 - 6 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 0 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	0	7	14	20	0	4	13
5101	233.6	231.8	242.3	253.1	264.2	292.5	340.2	427.3	277.8	300.5	338.5
5102	246.8	256.9	261.7	278.3	285.6	327.1	369.8	447.1	331.2	356.6	361.2
5103	233.8	241.5	243.3	266.5	266.2	300.5	349.9	427.7	322.3	342.3	332.4
5104	235.3	239.4	243.1	246.4	255.0	294.5	332.2	413.6	304.8	316.8	335.3
5105	270.7	279.5	283.5	303.5	309.3	339.5	373.7	464.3	320.5	373.5	365.8
5106	249.8	247.1	258.8	267.0	276.0	312.7	354.7	444.4	311.5	294.7	355.4
5107	228.0	233.3	233.1	245.8	252.2	278.0	309.4	380.5	274.2	301.2	283.7
5108	237.8	240.7	250.3	261.1	270.9	297.1	327.8	416.3	306.9	316.7	341.2
5109	234.2	244.2	244.2	265.7	268.7	318.6	362.4	450.3	351.0	348.8	340.3
5110	217.1	219.5	219.1	234.5	238.6 #	272.2 #	289.1 #	274.0 #			
n	10	10	10	10	9	9	9	9	9	9	9
Mean	238.71	243.39	247.94	262.19	272.01	306.72	346.68	430.17	311.13	327.90	339.31
S.D.	14.44	16.11	17.38	19.40	17.25	19.28	21.17	25.02	24.34	28.20	23.98

: Excepted data from calculation

Appendix 2 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 20 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	0	7	14	20	0	4	13
5201	249.3	253.6	262.7	270.7	278.2	305.5	346.7	428.3	331.1	343.6	349.5
5202	224.3	233.1	227.6	231.2	232.7	275.4	312.2	374.7	284.0	295.5	304.4
5203	278.0	285.6	291.4	310.8	316.2	352.9	388.2	457.2	317.9	353.1	367.0
5204	241.8	250.0	259.8	274.1	285.9	322.7	362.6	451.8	298.5	324.2	359.2
5205	234.3	242.8	242.4	255.1	264.1	291.3	330.2	416.3	293.1	308.7	328.2
5206	225.5	233.9	242.9	256.1	259.1	292.1	331.8	400.0	293.2	325.0	340.0
5207	232.6	236.0	238.9	246.4	259.6	293.3	332.4	404.3	305.0	326.3	328.0
5208	210.8	222.8	230.6	236.7	251.4	274.5	314.7	396.6	295.1	318.8	322.6
5209	260.3	263.8	267.9	283.8	295.1	330.0	368.3	450.9	320.7	352.6	347.5
5210	236.6	243.3	251.7	264.7	274.0	304.6	337.9	418.2	317.1	324.0	343.3
n	10	10	10	10	10	10	10	10	10	10	10
Mean	239.35	246.49	251.59	262.96	271.63	304.23	342.50	419.83	305.57	327.18	338.97
S.D.	19.29	18.03	19.38	23.55	23.74	24.78	24.17	27.25	15.27	18.34	18.55

Appendix 2 - 8 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 100 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	0	7	14	20	0	4	13
5301	251.6	253.2	264.8	272.7	283.8	311.4	348.0	433.9	302.2	353.7	348.3
5302	219.8	237.8	246.1	261.2	262.3	295.7	327.3	396.6	261.7	...	...
5303	243.2	256.1	259.3	279.9	282.5	321.0	355.5	421.1	296.3	341.5	352.5
5304	213.1	223.2	228.9	239.3	251.6	265.2	305.0	372.7	269.7	287.8	319.8
5305	254.2	270.5	280.8	292.6	294.2	325.7	366.5	454.7			
5306	240.3	244.0	246.2	264.5	267.1	305.0	333.4	388.3	327.6	343.1	339.0
5307	215.8	231.7	244.8	243.0	258.1	298.0	330.5	401.7	310.2	335.4	346.0
5308	233.2	241.5	247.8	258.7	261.2	297.7	336.0	414.1	315.4	339.8	329.3
5309	236.1	249.8	252.2	264.0	265.3	301.9	340.1	415.6	276.5	327.5	322.0
5310	231.0	238.3	240.5	249.4	250.5	286.8	324.8	400.8	303.5	324.7	323.3
n	10	10	10	10	10	10	10	10	9	8	8
Mean	233.83	244.61	251.14	262.53	267.66	300.84	336.71	409.95	295.90	331.69	335.03
S.D.	14.24	13.43	14.31	16.42	14.55	17.21	17.21	23.42	22.14	19.94	13.04

... : Mortality data

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Appendix 2 - 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 300 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	0	7	14	20	0	4	13
5401	250.5	257.2	270.6	276.6	285.0	320.3	356.5	440.5	287.9	...	...
5402	232.0	243.5	248.4	260.6	263.4 #	281.4 #	285.5 #	293.0 #			
5403	233.7	245.7	248.9	259.7	261.2	298.7	328.6	417.1	288.6	311.3	354.9
5404	215.4	221.5	230.5	232.6	245.0	278.4	326.0	404.6	291.0	326.8	345.2
5405	257.2	259.9	256.2	267.8	274.5	307.6	337.4	404.9	315.9	326.8	349.6
5406	249.9	253.0	255.9	260.4	261.6	293.5	334.0	406.4	290.4	342.3	343.5
5407	241.7	242.4	254.7	253.9	265.7 #	270.1 #	285.4 #	289.2 #			
5408	228.7	222.5	229.8	245.3	250.5	277.1	304.0	385.4	279.4	316.6	320.8
5409	227.5	231.5	236.6	253.0	262.9	306.8	331.4	411.8	315.8	319.8	356.7
5410	231.6	236.3	235.6	253.7	263.7	291.1	324.2	398.0	297.2	342.1	351.5
n	10	10	10	10	8	8	8	8	8	7	7
Mean	236.82	241.35	246.72	256.36	263.05	296.69	330.26	408.59	295.78	326.53	346.03
S.D.	12.78	13.45	13.30	12.01	12.55	14.84	14.65	15.97	13.32	12.02	12.10

: Excepted data from calculation

... : Mortality data

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Appendix 2 - 10 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weights

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 1000 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 1	3	8	15	0	7	14	20	0	4	13
5501	235.4	248.5	257.3	268.1	277.3	300.6	332.3	370.3	315.1	344.4	360.7
5502	230.8	236.5	242.2	247.6	255.2 #	259.8 #	258.9 #	264.2 #			
5503	261.1	261.8	269.7	288.1	278.1	309.4	353.5	428.6	310.5	317.8	369.8
5504	235.8	246.0	264.4	287.6	287.8	318.3	360.0	431.0	319.8	375.8	385.0
5505	221.1	228.8	232.8	249.6	257.2	274.3	310.8	387.0	265.7	295.3	331.2
5506	234.7	240.6	255.7	266.6	278.3	292.4	327.3	397.3	298.8	309.6	347.1
5507	217.9	224.8	229.5	237.5	251.9	279.3	322.0	394.6	318.5	333.9	367.9
5508	237.5	247.1	251.7	273.6	279.6	306.2	337.7	396.5	321.6	332.1	355.9
5509	254.2	263.4	268.1	289.1	289.6	322.8	357.9	432.3	326.4	372.3	382.2
5510	236.6	240.3	243.3	258.6	266.0	295.9	323.0	386.1	324.3	341.6	356.9
n	10	10	10	10	9	9	9	9	9	9	9
Mean	236.51	243.78	251.47	266.64	273.98	299.91	336.06	402.63	311.19	335.87	361.86
S.D.	13.08	12.51	14.19	18.32	12.97	16.38	17.51	22.51	18.97	26.71	16.84

: Excepted data from calculation

Appendix 3 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 0 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	29
1101	21.4	20.0	18.7	19.5
1102	21.8	22.4	21.5	21.6
1103	22.5	20.4	20.6	22.4
1104	23.5	21.0	21.2	22.2
1105	21.7	21.5	22.4	23.2
1106	24.6	21.9	21.3	20.3
1107	22.2	21.6	20.3	21.4
1108	22.9	21.5	21.4	20.4
1109	27.5	23.7	24.2	24.5
1110	23.4	24.0	23.6	24.2
n	10	10	10	10
Mean	23.15	21.80	21.52	21.97
S.D.	1.81	1.29	1.59	1.66

Appendix 3 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 20 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	29
1201	23.1	21.6	21.9	22.2
1202	25.9	24.0	24.0	23.4
1203	22.3	20.0	21.0	21.3
1204	20.5	20.3	20.5	21.7
1205	23.3	20.9	20.9	21.9
1206	20.8	21.3	20.1	20.8
1207	27.1	23.6	22.3	22.1
1208	21.4	20.1	20.2	21.0
1209	26.7	21.6	21.5	20.7
1210	26.9	24.1	22.9	21.0
n	10	10	10	10
Mean	23.80	21.75	21.53	21.61
S.D.	2.62	1.59	1.26	0.83

Appendix 3 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 100 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	29
1301	22.1	21.1	20.5	19.4
1302	18.4	18.1	18.2	18.8
1303	22.1	21.7	21.7	20.6
1304	22.0	22.2	21.0	21.7
1305	22.6	18.8	19.7	21.9
1306	22.2	23.9	22.2	25.2
1307	21.3	20.8	21.8	22.9
1308	26.7	23.8	22.8	24.6
1309	22.2	22.0	21.3	20.1
1310	22.3	24.8	23.7	23.6
n	10	10	10	10
Mean	22.19	21.72	21.29	21.88
S.D.	1.99	2.15	1.57	2.18

Appendix 3 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 300 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	29
1401	18.8	19.7	20.6	20.6
1402	19.0	21.7	19.8	22.1
1403	17.3	19.5	17.2	19.7
1404	19.2	18.5	20.5	21.4
1405	23.7	24.7	23.9	22.6
1406	19.9	19.2	19.6	20.0
1407	22.8	23.1	22.8	24.1
1408	19.6	19.2	20.1	20.4
1409	21.0	20.6	21.1	21.9
1410	19.5	21.6	21.9	25.1
n	10	10	10	10
Mean	20.08	20.78	20.75	21.79
S.D.	1.92	1.98	1.85	1.77

Appendix 3 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 mating Day 15-29

Sex : Male Dose : TG-SH(H) 1000 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	29
1501	19.4	20.3	24.2	24.8
1502	16.7	22.6	25.2	24.2
1503	20.2	19.8	22.8	24.0
1504	18.5	19.1	22.5	22.1
1505	23.7	24.5	27.2	28.5
1506	21.2	21.2	23.9	25.6
1507	17.0	17.9	20.3	21.3
1508	23.6	23.3	24.7	24.5
1509	17.3	21.4	24.7	24.9
1510	18.1	20.7	23.0	25.9
n	10	10	10	10
Mean	19.57	21.08	23.85	24.58
S.D.	2.58	1.99	1.85	1.99

Appendix 3 - 6 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 0 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	7	14	20	4	7	10	13
5101	15.8	14.4	14.3	18.3	20.8	21.5	20.2	44.9	47.9	51.6
5102	20.2	16.4	17.0	21.0	23.3	22.0	29.8	49.1	52.7	56.6
5103	19.5	15.4	15.8	19.4	22.3	20.3	29.7	41.5	48.8	44.8
5104	16.6	14.0	14.6	19.4	21.7	21.2	25.2	45.7	49.6	52.5
5105	22.7	18.0	19.5	20.3	21.0	24.1	33.7	49.0	54.6	50.8
5106	16.1	14.7	13.9	17.2	20.4	22.5	11.6	45.5	53.9	58.3
5107	17.9	13.8	15.0	17.1	19.2	19.7	26.1	36.9	42.2	38.3
5108	17.6	15.1	15.1	18.8	20.4	23.8	27.5	49.0	51.9	58.0
5109	19.7	15.2	17.3	23.1	25.4	24.9	20.2	39.5	45.4	43.1
5110	18.0	14.5	16.5	18.6 #	18.1 #	13.5 #				
n	10	10	10	9	9	9	9	9	9	9
Mean	18.41	15.15	15.90	19.40	21.61	22.22	24.89	44.57	49.67	50.44
S.D.	2.13	1.25	1.71	1.90	1.85	1.77	6.65	4.42	4.10	7.03

: Excepted data from calculation

Appendix 3 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 20 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	7	14	20	4	7	10	13
5201	20.8	16.3	15.2	20.6	23.9	22.7	30.1	44.9	50.6	50.7
5202	17.8	12.6	11.5	18.9	21.2	18.0	32.2	40.7	53.0	53.4
5203	19.8	16.9	17.8	20.1	21.0	20.3	32.1	54.5	59.3	60.0
5204	17.4	15.2	16.0	20.3	21.6	22.8	26.5	48.4	51.5	50.5
5205	20.2	14.8	16.0	19.3	20.7	21.1	23.7	46.0	47.7	48.7
5206	16.2	13.6	14.8	18.2	22.1	19.9	28.7	44.6	51.4	53.8
5207	18.2	14.8	14.7	19.9	21.8	20.1	26.8	42.1	42.2	44.0
5208	18.2	13.0	13.6	16.1	19.6	20.5	28.7	41.7	48.8	47.6
5209	21.5	17.0	18.1	22.4	23.1	21.7	25.4	46.0	49.6	47.5
5210	18.0	16.4	16.2	19.5	21.0	21.4	24.3	47.9	50.0	53.0
n	10	10	10	10	10	10	10	10	10	10
Mean	18.81	15.06	15.39	19.53	21.60	20.85	27.85	45.68	50.41	50.92
S.D.	1.68	1.60	1.94	1.65	1.23	1.43	3.02	4.02	4.30	4.43

Appendix 3 - 8 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 100 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	7	14	20	4	7	10	13
5301	15.0	15.1	15.2	18.4	20.8	21.0	33.1	45.1	46.6	50.2
5302	17.3	15.2	15.8	21.0	21.0	19.7	...	...	...	...
5303	19.8	16.2	18.3	20.2	22.0	20.9	33.6	51.4	51.8	53.7
5304	18.0	13.2	15.1	18.5	22.3	19.8	18.7	48.3	51.5	51.5
5305	19.1	16.6	16.7	21.4	23.7	23.6				
5306	16.5	13.4	15.2	19.7	20.1	21.1	22.3	33.2	38.2	39.8
5307	17.9	13.8	13.6	19.9	20.1	17.2	32.6	40.2	46.7	52.1
5308	16.5	13.9	13.7	18.6	21.6	20.5	31.6	50.3	55.1	53.1
5309	19.5	15.7	16.3	19.5	19.9	20.7	27.7	51.4	52.0	52.2
5310	19.0	15.6	15.9	20.2	23.0	19.6	31.6	48.0	52.9	44.4
n	10	10	10	10	10	10	8	8	8	8
Mean	17.86	14.87	15.58	19.74	21.45	20.41	28.90	45.99	49.35	49.63
S.D.	1.55	1.21	1.39	1.03	1.30	1.60	5.57	6.37	5.37	4.92

... : Mortality data

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Appendix 3 - 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 300 mg/kg/day Unit : g Species : Rat

	/Day									
Animal No.	3	8	15	7	14	20	4	7	10	13
5401	17.3	15.4	17.4	22.0	22.3	23.9	...	...	...	...
5402	15.8	13.1	15.1	16.1 #	16.3 #	15.2 #				
5403	14.0	12.0	13.9	20.5	20.3	22.2	22.8	51.0	58.2	62.9
5404	13.9	13.2	14.4	20.0	22.0	21.9	33.2	49.6	52.7	57.4
5405	19.4	15.4	19.6	22.4	23.0	21.8	34.3	50.6	55.6	57.6
5406	15.4	15.5	16.5	21.3	23.1	21.1	34.1	55.2	56.2	57.3
5407	15.7	14.1	15.0	17.0 #	17.0 #	15.9 #				
5408	11.3	12.5	14.6	18.4	19.9	20.4	34.3	49.0	51.4	52.8
5409	14.3	14.1	16.6	21.7	20.0	21.6	18.5	50.3	55.9	57.7
5410	16.0	12.9	18.1	20.6	21.1	21.5	40.1	48.2	61.7	62.4
n	10	10	10	8	8	8	7	7	7	7
Mean	15.31	13.82	16.12	20.86	21.46	21.80	31.04	50.56	55.96	58.30
S.D.	2.17	1.28	1.84	1.29	1.31	1.01	7.56	2.26	3.41	3.44

: Excepted data from calculation

... : Mortality data

Appendix 3 - 10 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Food consumption

Period : F0 before mating Day 1-15, F0 gestation Day 0-20, F0 lactation Day 0-13

Sex : Female Dose : TG-SH(H) 1000 mg/kg/day Unit : g Species : Rat

Animal No.	/Day 3	8	15	7	14	20	4	7	10	13
5501	17.0	13.5	15.8	20.9	23.2	23.4	34.2	48.4	56.0	62.3
5502	16.0	12.4	14.6	15.4 #	15.8 #	15.3 #				
5503	13.0	14.5	18.1	20.2	23.5	22.8	19.9	50.5	61.2	64.4
5504	15.0	14.3	18.1	21.1	24.3	24.5	34.4	57.1	58.7	67.6
5505	15.1	13.1	16.6	19.2	20.9	21.2	24.3	48.7	60.5	62.2
5506	12.2	14.0	17.2	19.5	23.8	21.0	25.0	47.6	53.4	60.3
5507	14.6	12.7	15.8	20.2	21.8	23.0	31.4	54.9	63.4	65.4
5508	15.4	15.1	19.3	20.6	24.3	22.5	30.6	43.1	50.6	59.7
5509	17.9	16.2	19.5	21.6	23.9	24.2	32.8	52.8	58.0	59.4
5510	14.0	13.7	16.9	20.2	21.9	23.1	37.9	51.3	46.2	60.5
n	10	10	10	9	9	9	9	9	9	9
Mean	15.02	13.95	17.19	20.39	23.07	22.86	30.06	50.49	56.44	62.42
S.D.	1.72	1.14	1.58	0.76	1.23	1.18	5.80	4.18	5.52	2.84

: Excepted data from calculation

Appendix 4 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Animal No.	T4 ng/mL
1101	22.04
1102	4.27
1103	21.88
1104	10.67
1105	12.45
1106	4.27
1107	13.34
1108	13.40
1109	14.47
1110	16.94
n	10
Mean	13.373
S.D.	6.104

Appendix 4 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Animal No.	T4 ng/mL
1201	21.47
1202	12.31
1203	15.55
1204	11.88
1205	30.42
1206	18.59
1207	11.29
1208	15.00
1209	12.89
1210	16.32
n	10
Mean	16.572
S.D.	5.822

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Appendix 4 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Animal No.	T4 ng/mL
1301	10.86
1302	15.58
1303	10.61
1304	3.44
1305	4.92
1306	10.00
1307	13.30
1308	13.07
1309	14.24
1310	16.02
n	10
Mean	11.204
S.D.	4.231

Appendix 4 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Dose : TG-SH(H) 300 mg/kg/day Species : Rat

	T4
Animal No.	ng/mL
1401	23.86
1402	6.49
1403	5.35
1404	4.80
1405	15.78
1406	19.63
1407	11.58
1408	7.26
1409	13.81
1410	12.88
n	10
Mean	12.144
S.D.	6.378

Appendix 4 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Main group

Sex : Male Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

	T4
Animal No.	ng/mL
1501	4.40
1502	3.68
1503	15.45
1504	3.65
1505	19.86
1506	5.28
1507	10.56
1508	7.36
1509	13.00
1510	12.53
n	10
Mean	9.577
S.D.	5.595

Appendix 4 - 6 Reproduction/developmental toxicity screening test in rats
Blood chemical finding

Study No. : E16-0045

Stage : Postnatal day 13
Dose : TG-SH(H) 0 mg/kg/day
Species : Rat

Animal No.	T4 (F1, Day 13) ng/mL
5101	10.63
5102	11.46
5103	8.54
5104	11.02
5105	6.58
5106	9.08
5107	11.15
5108	11.91
5109	17.35
n	9
Mean	10.858
S.D.	2.971

Appendix 4 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Postnatal day 13

Dose : TG-SH(H) 20 mg/kg/day Species : Rat

	T4 (F1, Day 13)
Animal No.	ng/mL
5201	8.20
5202	13.15
5203	8.76
5204	9.85
5205	6.83
5206	15.18
5207	9.67
5208	9.72
5209	11.60
5210	11.58
n	10
Mean	10.454
S.D.	2.467

Appendix 4 - 8 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Blood chemical finding

Stage : Postnatal day 13
Dose : TG-SH(H) 100 mg/kg/day Species : Rat

	T4 (F1, Day 13)
Animal No.	ng/mL
5301	11.20
5303	12.34
5304	6.23
5306	10.12
5307	18.78
5308	11.34
5309	18.57
5310	9.89
n	8
Mean	12.309
S.D.	4.323

Appendix 4 - 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Blood chemical finding

Stage : Postnatal day 13

Dose : TG-SH(H) 300 mg/kg/day Species : Rat

	T4 (F1, Day 13)
Animal No.	ng/mL
5403	8.15
5404	10.16
5405	12.66
5406	11.37
5408	11.22
5409	10.82
5410	18.26
n	7
Mean	11.806
S.D.	3.161

Appendix 4 - 10 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Blood chemical finding

Stage : Postnatal day 13
Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

	T4 (F1, Day 13)
Animal No.	ng/mL
5501	9.96
5503	6.96
5504	7.77
5505	7.83
5506	5.00
5507	12.66
5508	15.63
5509	10.02
5510	9.78
n	9
Mean	9.512
S.D.	3.174

Appendix 5 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Dose : TG-SH(H) 0 mg/kg/day Species : Rat

	Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
		AB	RE	AB	RE	AB	RE	AB	RE
Animal No.	g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1101	394.1	3.49	0.89	1.26	0.32	2.66	0.67	19.8	5.0
1102	445.6	3.23	0.72	1.35	0.30	3.13	0.70	17.4	3.9
1103	411.3	3.20	0.78	1.25	0.30	3.14	0.76	16.2	3.9
1104	422.0	2.98	0.71	1.23	0.29	3.17	0.75	19.4	4.6
1105	408.0	3.20	0.78	1.26	0.31	2.99	0.73	20.3	5.0
1106	428.7	3.73	0.87	1.32	0.31	2.73	0.64	22.9	5.3
1107	418.8	2.94	0.70	1.18	0.28	2.32	0.55	19.2	4.6
1108	426.4	3.52	0.83	1.36	0.32	3.14	0.74	19.0	4.5
1109	434.8	2.79	0.64	1.25	0.29	2.68	0.62	22.2	5.1
1110	419.2	2.59	0.62	0.85	0.20	3.06	0.73	21.1	5.0
n	10	10	10	10	10	10	10	10	10
Mean	420.89	3.167	0.754	1.231	0.292	2.902	0.689	19.75	4.69
S.D.	14.45	0.352	0.092	0.145	0.035	0.288	0.068	2.03	0.49

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Dose : TG-SH(H) 20 mg/kg/day Species : Rat

	Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
		AB	RE	AB	RE	AB	RE	AB	RE
Animal No.	g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1201	418.0	2.86	0.68	1.12	0.27	2.51	0.60	21.0	5.0
1202	475.1	3.44	0.72	1.45	0.31	3.36	0.71	24.1	5.1
1203	430.6	3.06	0.71	1.15	0.27	2.53	0.59	16.7	3.9
1204	415.6	2.91	0.70	1.21	0.29	2.97	0.71	18.9	4.5
1205	399.8	2.64	0.66	1.10	0.28	2.82	0.71	20.4	5.1
1206	381.9	3.17	0.83	1.24	0.32	2.65	0.69	21.1	5.5
1207	433.0	3.17	0.73	1.27	0.29	2.97	0.69	18.6	4.3
1208	433.6	3.33	0.77	1.22	0.28	3.46	0.80	19.6	4.5
1209	399.0	3.17	0.79	1.21	0.30	2.94	0.74	21.3	5.3
1210	437.3	3.44	0.79	1.27	0.29	3.59	0.82	18.8	4.3
n	10	10	10	10	10	10	10	10	10
Mean	422.39	3.119	0.738	1.224	0.290	2.980	0.706	20.05	4.75
S.D.	25.97	0.259	0.055	0.099	0.016	0.381	0.073	2.01	0.52

AB : Absolute weight, RE : Relative weight by body weight

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Appendix 5 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Dose : TG-SH(H) 100 mg/kg/day Species : Rat

	Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
		AB	RE	AB	RE	AB	RE	AB	RE
Animal No.	g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1301	415.5	3.10	0.75	1.14	0.27	2.36	0.57	18.4	4.4
1302	396.8	3.04	0.77	1.11	0.28	2.75	0.69	19.5	4.9
1303	422.4	2.93	0.69	1.01	0.24	2.81	0.67	21.0	5.0
1304	411.3	2.70	0.66	1.24	0.30	3.49	0.85	29.2	7.1
1305	392.8	3.46	0.88	1.26	0.32	3.02	0.77	20.2	5.1
1306	412.5	2.82	0.68	1.15	0.28	2.47	0.60	27.6	6.7
1307	440.0	3.25	0.74	1.40	0.32	3.07	0.70	21.6	4.9
1308	442.2	3.07	0.69	1.24	0.28	2.60	0.59	12.7	2.9
1309	382.5	2.91	0.76	1.30	0.34	2.63	0.69	23.0	6.0
1310	424.2	3.01	0.71	1.28	0.30	3.30	0.78	16.0	3.8
n	10	10	10	10	10	10	10	10	10
Mean	414.02	3.029	0.733	1.213	0.293	2.850	0.691	20.92	5.08
S.D.	19.42	0.215	0.064	0.111	0.029	0.365	0.090	4.93	1.27

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Dose : TG-SH(H) 300 mg/kg/day Species : Rat

	Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
		AB	RE	AB	RE	AB	RE	AB	RE
Animal No.	g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1401	394.7	3.31	0.84	1.23	0.31	3.05	0.77	19.9	5.0
1402	403.3	3.62	0.90	1.34	0.33	2.68	0.66	25.8	6.4
1403	405.2	3.28	0.81	1.14	0.28	3.34	0.82	18.9	4.7
1404	376.0	3.27	0.87	1.23	0.33	2.33	0.62	17.4	4.6
1405	437.1	2.74	0.63	1.11	0.25	2.61	0.60	14.5	3.3
1406	383.8	2.89	0.75	1.25	0.33	2.89	0.75	16.4	4.3
1407	450.1	3.78	0.84	1.36	0.30	2.85	0.63	19.2	4.3
1408	400.6	3.46	0.86	1.24	0.31	2.83	0.71	20.3	5.1
1409	406.8	2.89	0.71	1.20	0.29	2.37	0.58	15.8	3.9
1410	432.3	3.64	0.84	1.38	0.32	3.10	0.72	15.1	3.5
n	10	10	10	10	10	10	10	10	10
Mean	408.99	3.288	0.805	1.248	0.305	2.805	0.686	18.33	4.51
S.D.	23.74	0.353	0.083	0.090	0.026	0.318	0.080	3.32	0.89

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : Main group

Sex : Male Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

	Body weight	Testis		Epididymis		Prostate and seminal vesicle		Thyroid	
		AB	RE	AB	RE	AB	RE	AB	RE
Animal No.	g	g	g/100g	g	g/100g	g	g/100g	mg	mg/100g
1501	406.1	2.46	0.61	0.80	0.20	2.01	0.49	18.5	4.6
1502	396.4	3.31	0.84	1.25	0.32	2.85	0.72	13.0	3.3
1503	396.5	3.12	0.79	1.14	0.29	2.61	0.66	19.4	4.9
1504	411.5	2.93	0.71	1.22	0.30	2.72	0.66	14.4	3.5
1505	419.1	3.50	0.84	1.24	0.30	2.80	0.67	22.9	5.5
1506	427.0	3.20	0.75	1.24	0.29	2.22	0.52	19.1	4.5
1507	371.4	2.80	0.75	1.13	0.30	1.92	0.52	17.8	4.8
1508	399.2	3.24	0.81	1.30	0.33	2.63	0.66	17.2	4.3
1509	438.1	3.15	0.72	1.26	0.29	2.89	0.66	17.2	3.9
1510	369.9	2.90	0.78	1.13	0.31	2.78	0.75	23.0	6.2
n	10	10	10	10	10	10	10	10	10
Mean	403.52	3.061	0.760	1.171	0.293	2.543	0.631	18.25	4.55
S.D.	21.96	0.296	0.069	0.143	0.035	0.359	0.089	3.18	0.88

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 6 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 0 mg/kg/day Species : Rat

	Body weight	Thyroid	
		AB	RE
Animal No.	g	mg	mg/100g
5101	306.3	19.3	6.3
5102	335.8	26.8	8.0
5103	322.5	20.8	6.4
5104	313.8	19.7	6.3
5105	354.2	24.1	6.8
5106	326.1	14.8	4.5
5107	283.1	15.7	5.5
5108	309.1	17.1	5.5
5109	336.0	15.1	4.5
n	9	9	9
Mean	320.77	19.27	5.98
S.D.	20.68	4.14	1.12

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Animal No.	Body weight	Thyroid	
		AB	RE
	g	mg	mg/100g
5201	323.3	16.5	5.1
5202	274.7	19.7	7.2
5203	348.8	22.8	6.5
5204	323.1	17.3	5.4
5205	303.1	23.7	7.8
5206	309.4	22.2	7.2
5207	308.4	14.7	4.8
5208	303.7	16.8	5.5
5209	339.4	23.3	6.9
5210	309.1	13.3	4.3
n	10	10	10
Mean	314.30	19.03	6.07
S.D.	20.74	3.81	1.20

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 8 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Animal No.	Body weight	Thyroid	
		AB	RE
	g	mg	mg/100g
5301	325.9	21.3	6.5
5303	323.2	20.4	6.3
5304	293.8	17.3	5.9
5306	338.0	22.9	6.8
5307	316.5	17.1	5.4
5308	300.8	22.7	7.5
5309	312.2	13.9	4.5
5310	303.0	19.8	6.5
n	8	8	8
Mean	314.18	19.43	6.18
S.D.	14.71	3.11	0.91

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Animal No.	Body weight	Thyroid	
		AB	RE
	g	mg	mg/100g
5403	316.3	14.1	4.5
5404	315.3	17.7	5.6
5405	322.0	21.9	6.8
5406	325.0	16.7	5.1
5408	285.6	21.1	7.4
5409	311.9	22.3	7.1
5410	316.8	17.3	5.5
n	7	7	7
Mean	313.27	18.73	6.00
S.D.	12.96	3.08	1.10

AB : Absolute weight, RE : Relative weight by body weight

Appendix 5 - 10 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Organ weights

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

	Body weight	Thyroid	
		AB	RE
Animal No.	g	mg	mg/100g
5501	321.6	16.6	5.2
5503	338.7	20.9	6.2
5504	329.1	14.0	4.3
5505	307.2	18.3	6.0
5506	307.8	20.5	6.7
5507	310.7	21.3	6.9
5508	314.2	19.4	6.2
5509	335.0	24.7	7.4
5510	305.3	20.0	6.6
n	9	9	9
Mean	318.84	19.52	6.17
S.D.	12.73	3.03	0.93

AB : Absolute weight, RE : Relative weight by body weight

Appendix 6 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Macroscopic findings

Stage : Main group

Sex : Male Species : Rat

Test item	TG-SH(H)										TG-SH(H)										TG-SH(H)										TG-SH(H)									
Dose	0 mg/kg/day										20 mg/kg/day										100 mg/kg/day										300 mg/kg/day									
Animal No.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4
	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Organ	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0
Findings																																								
Cecum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Enlargement																																								
Kidney	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Discolored region, bilateral (mottled)																																								
Enlargement, bilateral																																								
Other organs and tissues	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

N : Finding absent

Appendix 6 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Macroscopic findings

Stage : Main group

Sex : Male Species : Rat

Test item	TG-SH(H)									
Dose	1000 mg/kg/day									
Animal No.	15001	15002	15003	15004	15005	15006	15007	15008	15009	15010
Organ / Findings										
Cecum	N	N	N	Y	N	Y	Y	Y	Y	N
Enlargement				P		P	P	P	P	
Kidney	N	N	N	Y	N	N	Y	N	Y	Y
Discolored region, bilateral (mottled)							P		P	P
Enlargement, bilateral				P						
Other organs and tissues	N	N	N	N	N	N	N	N	N	N

Y : Finding present, N : Finding absent

P : Non-graded change

Appendix 6 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Macroscopic findings

Sex : Female Stage : Whole litter death
Species : Rat

Test item	TG-SH(H)	TG-SH(H)
Dose	100 mg/kg/day	300 mg/kg/day
Animal No.	5	5
	3	4
	0	0
Organ	2	1
Findings		
Kidney	N	Y
Enlargement, bilateral		P
Thymus	N	Y
Small		P
Adrenal	N	Y
Enlargement, bilateral		P
Mammary gland	N	Y
Atrophy		P
Other organs and tissues	N	N

Y : Finding present, N : Finding absent
P : Non-graded change

Appendix 6 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Macroscopic findings

Stage : Mortality

Sex : Female Species : Rat

Test item	TG-SH(H)
Dose	100 mg/kg/day
Animal No.	5
	3
	0
Organ	5
Findings	
Lung	Y
Edematous change	P
Other organs and tissues	N

Y : Finding present, N : Finding absent

P : Non-graded change

Appendix 6 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Macroscopic findings

Stage : Non delivery (F0)

Sex : Female Species : Rat

Test item	TG-SH(H)	TG-SH(H)		TG-SH(H)
Dose	0 mg/kg/day	300 mg/kg/day		1000 mg/kg/day
Animal No.	5	5	5	5
	1	4	4	5
	1	0	0	0
Organ	0	2	7	2
Findings				
Cecum	N	N	N	Y
Enlargement				P
Other organs and tissues	N	N	N	N

N : Finding absent

Appendix 6 - 6 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Stage : After delivery (F0)
Sex : Female Species : Rat

Test item	TG-SH(H)									TG-SH(H)										TG-SH(H)										TG-SH(H)						
Dose	0 mg/kg/day									20 mg/kg/day										100 mg/kg/day										300 mg/kg/day						
Animal No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1
Organ	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	0	1	3	4	6	7	8	9	0	3	4	5	6	8	9	0	1	2
Findings																																				
Glandular stomach	N	Y	N	Y	Y	Y	N	N	Y	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	Y		N	Y	Y	N	Y	Y	Y		
Black patch/spot, mucosa																																				
(1×1.5 mm)											P																									
(1×2 mm)																													P							
(1×4 mm)																																	P			
(1×5 mm)				P																																
(2 regions, spotty, 1×5 mm)																				P																
(2 regions, 1×5 mm, 1×6 mm)									P																											
(2 regions, 1×5 mm, 1×7 mm)																													P							
(3 regions, φ1 mm - 1×4 mm)																																P				
(multiple, spotty - 1×2 mm)																																		P		
(multiple, spotty - 1×5 mm)						P																														
(multiple, spotty - 1×6 mm)																									P											
(multiple, spotty - 1×8 mm)					P																															
(multiple, spotty - 2×3 mm)		P																																		
(multiple, spotty - 3×8 mm)																										P										
Duodenum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Thickening, wall																																				
Jejunum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Thickening, wall																																				
Ileum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Thickening, wall																																				
Cecum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Enlargement																																				
Thickening, wall																																				
Colon	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Thickening, wall																																				
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Thickening, wall																																				
Other organs and tissues	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Y : Finding present, N : Finding absent
P : Non-graded change

Appendix 6 - 7 Reproduction/developmental toxicity screening test in rats
Macroscopic findings

Study No. : E16-0045

Stage : After delivery (F0)
Sex : Female Species : Rat

Test item	TG-SH(H)								
Dose	1000 mg/kg/day								
Animal No.	50101	50103	50104	50105	50106	50107	50108	50109	50110
Organ / Findings									
Glandular stomach	N	N	N	Y	N	Y	N	Y	Y
Black patch/spot, mucosa									
(1×6 mm)				P					
(φ1.5 mm)						P			
(3 regions, 1×2 mm - 1×5 mm)									P
(4 regions, spotty - φ1 mm)								P	
Duodenum	N	N	N	N	N	N	N	Y	Y
Thickening, wall								P	P
Jejunum	N	N	N	N	N	N	N	Y	Y
Thickening, wall								P	P
Ileum	N	N	N	N	N	N	N	Y	Y
Thickening, wall								P	P
Cecum	Y	N	N	N	N	N	Y	Y	Y
Enlargement	P						P		
Thickening, wall								P	P
Colon	N	N	N	N	N	N	N	Y	N
Thickening, wall								P	
Rectum	N	N	N	N	N	N	N	Y	N
Thickening, wall								P	
Other organs and tissues	N	N	N	N	N	N	N	N	N

Y : Finding present, N : Finding absent
P : Non-graded change

Appendix 7 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Histopathological findings

Sex : Male Stage : Main group
Species : Rat

Test item	TG-SH(H)										TG-SH(H)										TG-SH(H)										TG-SH(H)									
Dose	0 mg/kg/day										20 mg/kg/day										100 mg/kg/day										300 mg/kg/day									
Animal No.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4
	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0
Organ / Findings																																								
Cecum																																								
Colon																																								
Rectum																																								
Kidney																																								
Degeneration and necrosis, tubule																																								
Dilatation, tubule																																								
Regeneration, tubule																																								
Testis	N	N	N	N	N	N	N	Y	N	N																														
Atrophy, seminiferous tubule, focal, unilateral								1+																																
Epididymis	N	N	N	N	N	N	N	N	N	N																														

Y : Finding present, N : Finding absent
1+ : Slight

Appendix 7 - 2 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Stage : Main group
Sex : Male Species : Rat

Test item	TG-SH(H)									
Dose	1000 mg/kg/day									
Animal No.	15001	15002	15003	15004	15005	15006	15007	15008	15009	15010
Organ / Findings										
Cecum				N		N	N	N	N	
Colon				N		N	N	N	N	
Rectum				N		N	N	N	N	
Kidney				Y			Y		Y	Y
Degeneration and necrosis, tubule				2+			2+		1+	1+
Dilatation, tubule				2+			2+		1+	
Regeneration, tubule				2+			2+		1+	1+
Testis	N	N	N	N	N	N	N	N	N	N
Atrophy, seminiferous tubule, focal, unilateral										
Epididymis	N	N	N	N	N	N	N	N	N	N

Y : Finding present, N : Finding absent
1+ : Slight, 2+ : Moderate

Appendix 7 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Histopathological findings

Stage : Mortality

Sex : Female Species : Rat

Test item	TG-SH(H)
Dose	100 mg/kg/day
Animal No.	5
	3
	0
	5
Organ	
Findings	
Lung	
Hemorrhage, focal	1+
Perivascular edema	1+

Y : Finding present, N : Finding absent

1+ : Slight

Appendix 7 - 4 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Stage : Whole litter death
Sex : Female Species : Rat

Test item	TG-SH(H)	TG-SH(H)
Dose	100 mg/kg/day	300 mg/kg/day
Animal No.	5	5
	3	4
	0	0
	2	1
Organ Findings		
Kidney		Y
Vacuolation, tubular		2+
Thymus		Y
Atrophy		2+
Adrenal		Y
Hypertrophy, cortical, diffuse		1+
Mammary gland		N

Y : Finding present, N : Finding absent
1+ : Slight, 2+ : Moderate

Appendix 7 - 5 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Stage : Non delivery (F0)
Sex : Female Species : Rat

Test item	TG-SH(H)	TG-SH(H)	TG-SH(H)
Dose	0 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Animal No.	5	5 5	5
	1	4 4	5
	1	0 0	0
	0	2 7	2
Organ Findings			
Cecum			N
Colon			Y
Hyperplasia, mucosa			1+
Rectum			N
Ovary	N		N

Y : Finding present, N : Finding absent
1+ : Slight

Appendix 7 - 6 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Stage : After delivery (F0)
Sex : Female Species : Rat

Test item	TG-SH(H)									TG-SH(H)										TG-SH(H)										TG-SH(H)									
Dose	0 mg/kg/day									20 mg/kg/day										100 mg/kg/day										300 mg/kg/day									
Animal No.	5 1 0 1	5 1 0 2	5 1 0 3	5 1 0 4	5 1 0 5	5 1 0 6	5 1 0 7	5 1 0 8	5 1 0 9	5 2 0 1	5 2 0 2	5 2 0 3	5 2 0 4	5 2 0 5	5 2 0 6	5 2 0 7	5 2 0 8	5 2 0 9	5 2 1 0	5 3 0 1	5 3 0 3	5 3 0 4	5 3 0 6	5 3 0 7	5 3 0 8	5 3 0 9	5 3 1 0	5 4 0 1	5 4 0 3	5 4 0 4	5 4 0 5	5 4 0 6	5 4 0 8	5 4 0 9	5 4 1 0
Organ Findings																																							
Glandular stomach		Y		Y	Y	Y			Y		Y										Y									Y	Y		Y	Y	Y			
Erosion, focal		1+		1+	1+	1+			1+		1+										1+									1+	1+		2+	1+	1+			
Duodenum																																							
Hyperplasia, mucosa																																							
Jejunum																																							
Ileum																																							
Cecum																																							
Hyperplasia, mucosa																																							
Colon																																							
Rectum																																							
Ovary	N	N	N	N	N	N	N	N	N																														

Y : Finding present, N : Finding absent
1+ : Slight, 2+ : Moderate

Appendix 7 - 7 Reproduction/developmental toxicity screening test in rats
Histopathological findings

Study No. : E16-0045

Stage : After delivery (F0)
Sex : Female Species : Rat

Test item	TG-SH(H)								
Dose	1000 mg/kg/day								
Animal No.	5 5 0 1	5 5 0 3	5 5 0 4	5 5 0 5	5 5 0 6	5 5 0 7	5 5 0 8	5 5 0 9	5 5 1 0
Organ / Findings									
Glandular stomach				Y		Y		Y	Y
Erosion, focal				1+		1+		1+	1+
Duodenum								Y	N
Hyperplasia, mucosa								1+	
Jejunum								N	N
Ileum								N	N
Cecum	N						N	N	Y
Hyperplasia, mucosa									1+
Colon	N						N	N	N
Rectum	N						N	N	N
Ovary	N	N	N	N	N	N	N	N	N

Y : Finding present, N : Finding absent
1+ : Slight

Appendix 8 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : Whole litter death

Sex : Female Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Estrous cycle

Animal No.	
5302	P
n	1

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : Whole litter death

Sex : Female Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Estrous cycle

Animal No.	
5401	P
n	1

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : Non delivery (F0)

Sex : Female Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Estrous cycle

Animal No.	
5110	P
n	1

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Sex : Female Stage : Non delivery (F0) Species : Rat

Dose : TG-SH(H) 300 mg/kg/day

Estrous cycle

Animal No.	
5402	E
5407	P
n	2

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Sex : Female Stage : Non delivery (F0) Species : Rat

Dose : TG-SH(H) 1000 mg/kg/day

Estrous cycle

Animal No.	
5502	P
n	1

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 6 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Sex : Female Stage : After delivery (F0) Species : Rat

Dose : TG-SH(H) 0 mg/kg/day

Estrous cycle

Animal No.	
5101	M
5102	M
5103	M
5104	M
5105	M
5106	D
5107	M
5108	M
5109	M
n	9

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Animal No.	Estrous cycle
5201	M
5202	M
5203	M
5204	M
5205	D
5206	M
5207	M
5208	M
5209	M
5210	M
n	10

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 8 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Animal No.	Estrous cycle
5301	M
5303	M
5304	M
5306	D
5307	M
5308	M
5309	M
5310	D
n	8

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 9 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Animal No.	Estrous cycle
5403	M
5404	M
5405	D
5406	D
5408	M
5409	M
5410	M
n	7

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 8 - 10 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrous cycle stage

Stage : After delivery (F0)

Sex : Female Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

Animal No.	Estrous cycle
5501	D
5503	D
5504	M
5505	D
5506	M
5507	M
5508	D
5509	M
5510	M
n	9

P:Proestrus, E:Estrus, M:Metestrus, D:Diestrus

Appendix 9 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrus cycles

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Animal No.	/Before mating (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Length of estrous cycle (days)			Mean	Number of estrus	Animal with acyclic or irregular cycle
5101	D	E	M	D	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5102	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5103	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5104	D	E	M	D	D	E	E	M	D	D	E	E	M	D	4	5		4.5	3	-
5105	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5106	D	D	E	M	D	D	E	M	D	D	E	M	D	D	4	4		4.0	3	-
5107	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5108	D	E	M	D	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5109	M	D	D	E	M	D	D	E	M	D	P	E	M	D	4	4		4.0	3	-
5110	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with acyclic or irregular cycle, - : Animal with normal and regular cycle

Appendix 9 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Estrus cycles

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Animal No.	/Before mating (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Length of estrous cycle (days)			Mean	Number of estrus	Animal with acyclic or irregular cycle
5201	M	D	D	P	E	M	D	D	E	M	D	D	D	E	4	5		4.5	3	-
5202	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5203	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5204	D	E	M	D	D	E	M	D	D	E	M	D	P	E	4	4	4	4.0	4	-
5205	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5206	D	E	M	D	D	P	E	M	D	D	E	E	D	D	5	4		4.5	3	-
5207	D	D	P	E	E	D	D	D	P	E	M	D	D	P	6			6.0	2	-
5208	E	M	D	D	E	M	D	D	E	M	D	D	E	M	4	4	4	4.0	4	-
5209	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5210	E	M	D	D	D	E	M	D	D	E	M	D	D	E	5	4	4	4.3	4	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus
+ : Animal with acyclic or irregular cycle, - : Animal with normal and regular cycle

Appendix 9 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrus cycles

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Animal No.	/Before mating (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Length of estrous cycle (days)			Mean	Number of estrus	Animal with acyclic or irregular cycle
5301	P	E	M	D	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5302	E	M	D	D	E	M	D	D	E	M	D	D	E	M	4	4	4	4.0	4	-
5303	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5304	E	M	D	P	E	M	D	D	E	M	D	D	E	M	4	4	4	4.0	4	-
5305	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4	4	4.0	4	-
5306	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5307	M	D	D	D	E	M	D	D	E	M	D	D	D	P	4			4.0	2	-
5308	E	M	D	D	E	M	D	D	E	M	D	D	E	M	4	4	4	4.0	4	-
5309	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5310	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with acyclic or irregular cycle, - : Animal with normal and regular cycle

Appendix 9 - 4 Reproduction/developmental toxicity screening test in rats
Estrus cycles

Study No. : E16-0045

Generation : F0 Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Animal No.	/Before mating (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Length of estrous cycle (days)			Mean	Number of estrus	Animal with acyclic or irregular cycle
5401	E	M	D	P	E	M	D	D	P	E	M	D	D	M	4	5		4.5	3	-
5402	E	M	D	D	E	M	D	D	E	M	D	D	E	M	4	4	4	4.0	4	-
5403	D	E	M	D	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5404	D	E	M	M	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5405	M	D	D	E	M	D	P	E	M	M	D	E	M	M	4	4		4.0	3	-
5406	D	E	M	D	D	P	E	M	D	D	P	E	M	D	5	5		5.0	3	-
5407	D	D	E	M	D	D	E	M	D	P	E	M	D	D	4	4		4.0	3	-
5408	D	E	E	M	D	D	E	E	M	D	P	E	E	M	5	5		5.0	3	-
5409	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4		4.0	3	-
5410	D	D	P	E	M	D	D	E	M	D	P	E	D	D	4	4		4.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus
+ : Animal with acyclic or irregular cycle, - : Animal with normal and regular cycle

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Appendix 9 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Estrus cycles

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

Animal No.	/Before mating (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Length of estrous cycle (days)			Mean	Number of estrus	Animal with acyclic or irregular cycle
5501	E	M	D	D	E	E	D	D	E	E	M	D	D	E	4	4	5	4.3	4	-
5502	M	D	D	E	M	D	D	E	E	M	D	D	E	E	4	5		4.5	3	-
5503	D	E	M	D	D	E	E	M	D	D	E	E	D	D	4	5		4.5	3	-
5504	D	E	M	D	D	E	M	D	P	E	M	D	D	E	4	4	4	4.0	4	-
5505	E	M	D	D	E	M	D	P	E	M	D	D	E	M	4	4	4	4.0	4	-
5506	D	E	M	D	D	E	M	D	D	E	M	D	D	E	4	4	4	4.0	4	-
5507	M	D	P	E	E	M	D	D	E	M	M	D	D	E	5	5		5.0	3	-
5508	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5509	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-
5510	M	D	D	E	M	D	D	E	M	D	D	E	M	D	4	4		4.0	3	-

P : Proestrus, E : Estrus, M : Metestrus, D : Diestrus

+ : Animal with acyclic or irregular cycle, - : Animal with normal and regular cycle

Appendix 10 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Reproductive performance

Generation : F0 Sex : Female Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Animal No.	Day of conceiving	1st mating			Total	
		Paired animal	Copulation	Fertility	Copulation	Fertility
5101	3	1101	+	+	+	+
5102	1	1102	+	+	+	+
5103	1	1103	+	+	+	+
5104	2	1104	+	+	+	+
5105	1	1105	+	+	+	+
5106	4	1106	+	+	+	+
5107	1	1107	+	+	+	+
5108	3	1108	+	+	+	+
5109	1	1109	+	+	+	+
5110	1	1110	+	-	+	-
n	10		10	10	10	10
Mean	1.8					
S.D.	1.1					
No. of positives			10	9	10	9
%			100.0	90.0	100.0	90.0

+: present, -: absent

Appendix 10 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Reproductive performance

Generation : F0 Sex : Female Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Animal No.	Day of conceiving	1st mating			Total	
		Paired animal	Copulation	Fertility	Copulation	Fertility
5201	3	1201	+	+	+	+
5202	1	1202	+	+	+	+
5203	1	1203	+	+	+	+
5204	3	1204	+	+	+	+
5205	1	1205	+	+	+	+
5206	2	1206	+	+	+	+
5207	4	1207	+	+	+	+
5208	2	1208	+	+	+	+
5209	1	1209	+	+	+	+
5210	3	1210	+	+	+	+
n	10		10	10	10	10
Mean	2.1					
S.D.	1.1					
No. of positives			10	10	10	10
%			100.0	100.0	100.0	100.0

+: present, -: absent

Appendix 10 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Reproductive performance

Generation : F0 Sex : Female Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Animal No.	Day of conceiving	1st mating			Total	
		Paired animal	Copulation	Fertility	Copulation	Fertility
5301	3	1301	+	+	+	+
5302	2	1302	+	+	+	+
5303	1	1303	+	+	+	+
5304	2	1304	+	+	+	+
5305	2	1305	+	+	+	+
5306	2	1306	+	+	+	+
5307	4	1307	+	+	+	+
5308	2	1308	+	+	+	+
5309	1	1309	+	+	+	+
5310	1	1310	+	+	+	+
n	10		10	10	10	10
Mean	2.0					
S.D.	0.9					
No. of positives			10	10	10	10
%			100.0	100.0	100.0	100.0

+: present, -: absent

Appendix 10 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Reproductive performance

Generation : F0 Sex : Female Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Animal No.	Day of conceiving	1st mating			Total	
		Paired animal	Copulation	Fertility	Copulation	Fertility
5401	4	1401	+	+	+	+
5402	1	1402	+	-	+	-
5403	3	1403	+	+	+	+
5404	3	1404	+	+	+	+
5405	1	1405	+	+	+	+
5406	2	1406	+	+	+	+
5407	1	1407	+	-	+	-
5408	2	1408	+	+	+	+
5409	1	1409	+	+	+	+
5410	1	1410	+	+	+	+
n	10		10	10	10	10
Mean	1.9					
S.D.	1.1					
No. of positives			10	8	10	8
%			100.0	80.0	100.0	80.0

+: present, -: absent

Appendix 10 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Reproductive performance

Generation : F0 Sex : Female Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

Animal No.	Day of conceiving	1st mating			Total	
		Paired animal	Copulation	Fertility	Copulation	Fertility
5501	3	1501	+	+	+	+
5502	1	1502	+	-	+	-
5503	1	1503	+	+	+	+
5504	3	1504	+	+	+	+
5505	2	1505	+	+	+	+
5506	3	1506	+	+	+	+
5507	4	1507	+	+	+	+
5508	1	1508	+	+	+	+
5509	1	1509	+	+	+	+
5510	1	1510	+	+	+	+
n	10		10	10	10	10
Mean	2.0					
S.D.	1.2					
No. of positives			10	9	10	9
%			100.0	90.0	100.0	90.0

+: present, -: absent

Appendix 11 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Delivery data

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Dam No.	Gestation period (day)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
5101	23	16(9/7)	100.0	100.0	16	12	4	16	0	0	0	0
5102	22	17(7/10)	94.1	93.8	16	7	8	15	0	1	0	1
5103	22	16(5/11)	93.8	100.0	15	7	8	15	0	0	0	0
5104	22	15(8/7)	86.7	100.0	13	9	4	13	0	0	0	0
5105	22	18(9/9)	94.4	94.1	17	8	8	16	0	1	0	1
5106	22	15(7/8)	100.0	93.3	15	6	8	14	0	1	0	1
5107	22	15(9/6)	93.3	100.0	14	9	5	14	0	0	0	0
5108	22	15(4/11)	100.0	100.0	15	7	8	15	0	0	0	0
5109	22	14(4/10)	92.9	100.0	13	6	7	13	0	0	0	0
5110	-	0(0/0)	:::	:::	-	-	-	-	-	-	-	-
n	9	10	9	9	9	9	9	9	9	9	9	9
Mean	22.11	14.10	95.02	97.91	14.89	7.89	6.67	14.56	0.00	0.33	0.00	0.33
S.D.	0.33	5.09	4.38	3.14	1.36	1.90	1.80	1.13	0.00	0.50	0.00	0.50

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

::: : Impossible to calculate

Delivery data

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Dam No.	Gestation period (day)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
5201	22	16(9/7)	93.8	100.0	15	6	9	15	0	0	0	0
5202	22	14(7/7)	85.7	100.0	12	8	4	12	0	0	0	0
5203	23	17(9/8)	94.1	100.0	16	10	6	16	0	0	0	0
5204	23	16(8/8)	87.5	100.0	14	7	7	14	0	0	0	0
5205	22	16(9/7)	100.0	87.5	16	7	7	14	0	2	0	2
5206	22	14(8/6)	92.9	100.0	13	6	7	13	0	0	0	0
5207	22	13(8/5)	100.0	100.0	13	8	5	13	0	0	0	0
5208	22	14(6/8)	92.9	100.0	13	6	7	13	0	0	0	0
5209	22	15(8/7)	100.0	86.7	15	9	4	13	0	2	0	2
5210	22	16(9/7)	93.8	100.0	15	7	8	15	0	0	0	0
n	10	10	10	10	10	10	10	10	10	10	10	10
Mean	22.20	15.10	94.07	97.42	14.20	7.40	6.40	13.80	0.00	0.40	0.00	0.40
S.D.	0.42	1.29	4.96	5.44	1.40	1.35	1.65	1.23	0.00	0.84	0.00	0.84

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

Appendix 11 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Delivery data

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Dam No.	Gestation period (day)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
5301	23	17(5/12)	88.2	100.0	15	8	7	15	0	0	0	0
5302	22	16(7/9)	100.0	93.8	16	7	8	15	1	0	0	1
5303	23	14(8/6)	100.0	100.0	14	8	6	14	0	0	0	0
5304	22	13(6/7)	100.0	100.0	13	2	11	13	0	0	0	0
5305	-	16(7/9)	0.0	:::	-	-	-	-	-	-	-	-
5306	22	7(3/4)	100.0	100.0	7	5	2	7	0	0	0	0
5307	22	17(6/11)	82.4	92.9	14	6	7	13	1	0	0	1
5308	22	15(6/9)	100.0	100.0	15	8	7	15	0	0	0	0
5309	23	15(8/7)	100.0	100.0	15	11	4	15	0	0	0	0
5310	22	15(4/11)	100.0	100.0	15	7	8	15	0	0	0	0
n	9	10	10	9	9	9	9	9	9	9	9	9
Mean	22.33	14.50	87.06	98.52	13.78	6.89	6.67	13.56	0.22	0.00	0.00	0.22
S.D.	0.50	2.92	31.22	2.94	2.68	2.47	2.55	2.60	0.44	0.00	0.00	0.44

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

::: : Impossible to calculate

Appendix 11 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Delivery data

Generation : F0 Dose : TG-SH(H) 300 mg/kg/day Species : Rat

Dam No.	Gestation period (day)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
5401	22	19(10/9)	100.0	89.5	19	7	10	17	0	2	0	2
5402	-	0(0/0)	:::	:::	-	-	-	-	-	-	-	-
5403	22	15(8/7)	100.0	100.0	15	6	9	15	0	0	0	0
5404	22	16(8/8)	93.8	100.0	15	7	8	15	0	0	0	0
5405	22	14(6/8)	92.9	92.3	13	6	6	12	0	1	0	1
5406	22	16(7/9)	87.5	100.0	14	9	5	14	0	0	0	0
5407	-	0(0/0)	:::	:::	-	-	-	-	-	-	-	-
5408	22	15(7/8)	93.3	100.0	14	7	7	14	0	0	0	0
5409	22	14(9/5)	92.9	100.0	13	7	6	13	0	0	0	0
5410	23	16(6/10)	93.8	100.0	15	9	6	15	0	0	0	0
n	8	10	8	8	8	8	8	8	8	8	8	8
Mean	22.13	12.50	94.28	97.73	14.75	7.25	7.13	14.38	0.00	0.38	0.00	0.38
S.D.	0.35	6.74	4.08	4.28	1.91	1.16	1.73	1.51	0.00	0.74	0.00	0.74

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed

::: : Impossible to calculate

Delivery data

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

Dam No.	Gestation period (day)	Number of implan-tation	Delivery index (%)	Live birth index (%)	Number of offspring	Number of live newborns			Number of dead newborns			
						M	F	Total	M	F	U	Total
5501	23	12(7/5)	100.0	100.0	12	7	5	12	0	0	0	0
5502	-	0(0/0)	:::	:::	-	-	-	-	-	-	-	-
5503	22	15(5/10)	100.0	100.0	15	8	7	15	0	0	0	0
5504	22	16(7/9)	100.0	100.0	16	10	6	16	0	0	0	0
5505	22	15(8/7)	100.0	100.0	15	8	7	15	0	0	0	0
5506	22	13(6/7)	100.0	100.0	13	8	5	13	0	0	0	0
5507	22	15(9/6)	93.3	100.0	14	9	5	14	0	0	0	0
5508	23	12(8/4)	91.7	100.0	11	5	6	11	0	0	0	0
5509	22	15(6/9)	100.0	100.0	15	6	9	15	0	0	0	0
5510	22	15(9/6)	66.7	100.0	10	5	5	10	0	0	0	0
n	9	10	9	9	9	9	9	9	9	9	9	9
Mean	22.22	12.80	94.63	100.00	13.44	7.33	6.11	13.44	0.00	0.00	0.00	0.00
S.D.	0.44	4.71	10.97	0.00	2.07	1.73	1.36	2.07	0.00	0.00	0.00	0.00

(/) : Right/Left, M : Male, F : Female, U : Unable to be sexed
::: : Impossible to calculate

Appendix 12 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Litter size and viability index of offspring

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Species : Rat

	/Days after birth	0	4	4	4	13			
Dam No.	Sex	Male/Female	Pre-culled Male/Female	Viability index (%)	Culled Male/Female	Male/Female			
5101	Total	16	13	81.3	11	11			
		(12/4)	(10/3)		(8/3)	(8/3)			
5102	Total	15	15	100.0	13	13			
		(7/8)	(7/8)		(6/7)	(6/7)			
5103	Total	15	15	100.0	13	13			
		(7/8)	(7/8)		(6/7)	(6/7)			
5104	Total	13	13	100.0	11	11			
		(9/4)	(9/4)		(7/4)	(7/4)			
5105	Total	16	16	100.0	14	14			
		(8/8)	(8/8)		(7/7)	(7/7)			
5106	Total	14	14	100.0	12	12			
		(6/8)	(6/8)		(5/7)	(5/7)			
5107	Total	14	13	92.9	11	11			
		(9/5)	(8/5)		(7/4)	(7/4)			
5108	Total	15	15	100.0	13	13			
		(7/8)	(7/8)		(6/7)	(6/7)			
5109	Total	13	13	100.0	11	11			
		(6/7)	(6/7)		(5/6)	(5/6)			
Total		131	127		109	109			
Male/Female		71/60	68/59		57/52	57/52			
n		9	9	9	9	9			
Mean				97.13					
S.D.				6.38					

Appendix 12 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Litter size and viability index of offspring

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

	/Days after birth	0	4	4	4	13			
Dam No.	Sex	Male/Female	Pre-culled Male/Female	Viability index (%)	Culled Male/Female	Male/Female			
5201	Total	15	15	100.0	13	13			
		(6/9)	(6/9)		(5/8)	(5/8)			
5202	Total	12	12	100.0	10	10			
		(8/4)	(8/4)		(6/4)	(6/4)			
5203	Total	16	16	100.0	14	14			
		(10/6)	(10/6)		(9/5)	(9/5)			
5204	Total	14	14	100.0	12	12			
		(7/7)	(7/7)		(6/6)	(6/6)			
5205	Total	14	14	100.0	12	12			
		(7/7)	(7/7)		(6/6)	(6/6)			
5206	Total	13	13	100.0	11	11			
		(6/7)	(6/7)		(5/6)	(5/6)			
5207	Total	13	13	100.0	11	11			
		(8/5)	(8/5)		(7/4)	(7/4)			
5208	Total	13	13	100.0	11	11			
		(6/7)	(6/7)		(5/6)	(5/6)			
5209	Total	13	13	100.0	11	11			
		(9/4)	(9/4)		(7/4)	(7/4)			
5210	Total	15	14	93.3	12	12			
		(7/8)	(6/8)		(5/7)	(5/7)			
Total		138	137		117	117			
Male/Female		74/64	73/64		61/56	61/56			
n		10	10	10	10	10			
Mean				99.33					
S.D.				2.12					

Appendix 12 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Litter size and viability index of offspring

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Species : Rat

	/Days after birth	0	4	4	4	13
Dam No.	Sex	Male/Female	Pre-culled Male/Female	Viability index (%)	Culled Male/Female	Male/Female
5301	Total	15	15	100.0	13	13
		(8/7)	(8/7)		(7/6)	(7/6)
5302	Total	15	...	:::	###	...
		(7/8)				
5303	Total	14	14	100.0	12	12
		(8/6)	(8/6)		(7/5)	(7/5)
5304	Total	13	13	100.0	11	11
		(2/11)	(2/11)		(2/9)	(2/9)
5306	Total	7	7	100.0	7	7
		(5/2)	(5/2)		(5/2)	(5/2)
5307	Total	13	13	100.0	11	11
		(6/7)	(6/7)		(5/6)	(5/6)
5308	Total	15	15	100.0	13	13
		(8/7)	(8/7)		(7/6)	(7/6)
5309	Total	15	15	100.0	13	13
		(11/4)	(11/4)		(9/4)	(9/4)
5310	Total	15	15	100.0	13	13
		(7/8)	(7/8)		(6/7)	(6/7)
Total		122	107		93	93
Male/Female		62/60	55/52		48/45	48/45
n		9	8	8	8	8
Mean				100.00		
S.D.				0.00		

: Input/measure omission, ... : Mortality data, ::: : Impossible to calculate

Appendix 12 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Litter size and viability index of offspring

Generation : F0 Dose : TG-SH(H) 300 mg/kg/day Species : Rat

	/Days after birth	0	4	4	4	13
Dam No.	Sex	Male/Female	Pre-culled Male/Female	Viability index (%)	Culled Male/Female	Male/Female
5401	Total	17 (7/10)	...	:::	###	...
5403	Total	15 (6/9)	15 (6/9)	100.0	13 (5/8)	13 (5/8)
5404	Total	15 (7/8)	14 (7/7)	93.3	12 (6/6)	12 (6/6)
5405	Total	12 (6/6)	12 (6/6)	100.0	10 (5/5)	10 (5/5)
5406	Total	14 (9/5)	14 (9/5)	100.0	12 (8/4)	12 (8/4)
5408	Total	14 (7/7)	14 (7/7)	100.0	12 (6/6)	12 (6/6)
5409	Total	13 (7/6)	13 (7/6)	100.0	11 (6/5)	11 (6/5)
5410	Total	15 (9/6)	15 (9/6)	100.0	13 (8/5)	13 (8/5)
Total		115	97		83	83
Male/Female		58/57	51/46		44/39	44/39
n		8	7	7	7	7
Mean				99.04		
S.D.				2.53		

: Input/measure omission, ... : Mortality data, ::: : Impossible to calculate

Appendix 12 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Litter size and viability index of offspring

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Species : Rat

	/Days after birth	0	4	4	4	13
Dam No.	Sex	Male/Female	Pre-culled Male/Female	Viability index (%)	Culled Male/Female	Male/Female
5501	Total	12	12	100.0	10	10
		(7/5)	(7/5)		(6/4)	(6/4)
5503	Total	15	15	100.0	13	13
		(8/7)	(8/7)		(7/6)	(7/6)
5504	Total	16	16	100.0	14	14
		(10/6)	(10/6)		(9/5)	(9/5)
5505	Total	15	14	93.3	12	12
		(8/7)	(8/6)		(7/5)	(7/5)
5506	Total	13	13	100.0	11	11
		(8/5)	(8/5)		(7/4)	(7/4)
5507	Total	14	14	100.0	12	12
		(9/5)	(9/5)		(8/4)	(8/4)
5508	Total	11	11	100.0	9	9
		(5/6)	(5/6)		(4/5)	(4/5)
5509	Total	15	14	93.3	12	12
		(6/9)	(5/9)		(4/8)	(4/8)
5510	Total	10	10	100.0	8	8
		(5/5)	(5/5)		(4/4)	(4/4)
Total		121	119		101	101
Male/Female		66/55	65/54		56/45	56/45
n		9	9	9	9	9
Mean				98.51		
S.D.				2.95		

Appendix 13 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weight of offspring

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Unit : g Species : Rat

		/Days after birth 0		4		13	
Dam No.	Sex	n	B.W.	n	B.W.	n	B.W.
5101	Male	12	6.3	10	10.3	8	29.6
	Female	4	5.7	3	9.6	3	28.8
5102	Male	7	6.3	7	10.5	6	28.1
	Female	8	6.2	8	10.3	7	26.8
5103	Male	7	6.7	7	11.2	6	27.8
	Female	8	6.0	8	9.9	7	26.1
5104	Male	9	6.9	9	11.6	7	31.2
	Female	4	7.0	4	11.3	4	31.4
5105	Male	8	6.6	8	9.8	7	25.7
	Female	8	6.6	8	10.2	7	25.8
5106	Male	6	6.7	6	7.6	5	25.8
	Female	8	6.6	8	7.9	7	25.3
5107	Male	9	6.9	8	11.3	7	27.8
	Female	5	6.4	5	10.8	4	27.8
5108	Male	7	6.6	7	11.1	6	29.3
	Female	8	6.1	8	10.3	7	27.6
5109	Male	6	7.1	6	10.4	5	28.8
	Female	7	7.0	7	10.4	6	29.0
n	Male	71		68		57	
	Female	60		59		52	
Mean	Male		6.68		10.42		28.23
	Female		6.40		10.08		27.62
S.D.	Male		0.27		1.20		1.76
	Female		0.44		0.95		1.91

Appendix 13 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Body weight of offspring

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Unit : g Species : Rat

		/Days after birth 0		4		13	
Dam No.	Sex	n	B.W.	n	B.W.	n	B.W.
5201	Male	6	6.8	6	10.7	5	27.6
	Female	9	6.2	9	10.3	8	26.8
5202	Male	8	7.4	8	13.6	6	33.7
	Female	4	6.9	4	12.7	4	33.0
5203	Male	10	6.6	10	9.9	9	26.0
	Female	6	6.9	6	10.7	5	26.4
5204	Male	7	7.1	7	11.9	6	31.1
	Female	7	6.8	7	11.1	6	29.2
5205	Male	7	6.3	7	10.6	6	28.2
	Female	7	6.0	7	10.2	6	27.2
5206	Male	6	7.6	6	11.6	5	31.1
	Female	7	7.1	7	11.0	6	30.2
5207	Male	8	6.6	8	11.2	7	28.9
	Female	5	6.3	5	10.1	4	26.7
5208	Male	6	7.3	6	12.0	5	30.8
	Female	7	6.9	7	11.1	6	29.6
5209	Male	9	6.6	9	10.8	7	28.6
	Female	4	6.4	4	10.9	4	30.1
5210	Male	7	6.3	6	10.7	5	29.3
	Female	8	6.1	8	10.6	7	29.5
n	Male	74		73		61	
	Female	64		64		56	
Mean	Male		6.86		11.30		29.53
	Female		6.56		10.87		28.87
S.D.	Male		0.46		1.04		2.19
	Female		0.40		0.74		2.09

Appendix 13 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Body weight of offspring

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Unit : g Species : Rat

		/Days after birth 0		4		13	
Dam No.	Sex	n	B.W.	n	B.W.	n	B.W.
5301	Male	8	7.2	8	11.3	7	27.3
	Female	7	6.7	7	11.0	6	27.6
5302	Male	7	5.2				
	Female	8	5.4				
5303	Male	8	7.8	8	12.5	7	30.7
	Female	6	7.5	6	11.7	5	28.6
5304	Male	2	6.6	2	9.9	2	29.5
	Female	11	6.4	11	9.1	9	27.5
5306	Male	5	8.0	5	14.8	5	37.1
	Female	2	7.7	2	14.1	2	36.9
5307	Male	6	6.7	6	11.7	5	30.4
	Female	7	6.4	7	11.3	6	30.0
5308	Male	8	6.8	8	11.2	7	29.4
	Female	7	6.3	7	10.5	6	29.7
5309	Male	11	6.7	11	10.0	9	27.2
	Female	4	6.5	4	9.5	4	25.6
5310	Male	7	6.1	7	10.3	6	27.1
	Female	8	6.0	8	10.1	7	26.9
n	Male	62		55		48	
	Female	60		52		45	
Mean	Male		6.79		11.46		29.84
	Female		6.54		10.91		29.10
S.D.	Male		0.84		1.62		3.27
	Female		0.71		1.56		3.47

Appendix 13 - 4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weight of offspring

Generation : F0 Dose : TG-SH(H) 300 mg/kg/day Unit : g Species : Rat

		/Days after birth 0		4		13	
Dam No.	Sex	n	B.W.	n	B.W.	n	B.W.
5401	Male	7	5.1				
	Female	10	4.9				
5403	Male	6	6.5	6	9.4	5	25.8
	Female	9	6.5	9	9.0	8	26.4
5404	Male	7	6.8	7	10.3	6	27.0
	Female	8	6.2	7	9.9	6	25.9
5405	Male	6	6.9	6	12.4	5	33.7
	Female	6	6.6	6	12.2	5	33.3
5406	Male	9	6.8	9	10.5	8	29.3
	Female	5	6.4	5	9.8	4	28.8
5408	Male	7	6.4	7	10.2	6	28.1
	Female	7	6.1	7	9.9	6	27.2
5409	Male	7	7.0	7	9.7	6	29.5
	Female	6	6.8	6	9.2	5	28.3
5410	Male	9	6.7	9	11.5	8	31.7
	Female	6	6.6	6	11.5	5	29.8
n	Male	58		51		44	
	Female	57		46		39	
Mean	Male		6.53		10.57		29.30
	Female		6.26		10.21		28.53
S.D.	Male		0.61		1.05		2.71
	Female		0.60		1.19		2.51

Appendix 13 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Body weight of offspring

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Unit : g Species : Rat

		/Days after birth 0		4		13	
Dam No.	Sex	n	B.W.	n	B.W.	n	B.W.
5501	Male	7	8.3	7	13.6	6	33.4
	Female	5	7.7	5	12.9	4	32.0
5503	Male	8	6.8	8	9.4	7	25.0
	Female	7	6.5	7	9.0	6	24.6
5504	Male	10	7.0	10	10.6	9	28.0
	Female	6	6.4	6	9.7	5	25.9
5505	Male	8	6.3	8	9.1	7	26.7
	Female	7	5.7	6	9.0	5	26.0
5506	Male	8	6.7	8	11.2	7	30.8
	Female	5	6.5	5	10.6	4	29.6
5507	Male	9	6.4	9	10.6	8	29.2
	Female	5	6.2	5	10.4	4	28.8
5508	Male	5	8.0	5	13.1	4	33.3
	Female	6	7.6	6	12.2	5	31.3
5509	Male	6	6.8	5	10.6	4	29.3
	Female	9	6.7	9	10.1	8	28.5
5510	Male	5	8.0	5	14.6	4	40.3
	Female	5	7.8	5	14.0	4	37.5
n	Male	66		65		56	
	Female	55		54		45	
Mean	Male		7.14		11.42		30.67
	Female		6.79		10.88		29.36
S.D.	Male		0.75		1.91		4.56
	Female		0.74		1.77		3.94

Appendix 14 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Anogenital distance of offspring

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Unit : mm Species : Rat

Dam No.	Sex	/Days after birth 4 n	AGD	AGD/3√BW
5101	Male	10	6.08	2.79
	Female	3	3.07	1.45
5102	Male	7	5.91	2.71
	Female	8	3.31	1.53
5103	Male	7	6.03	2.70
	Female	8	3.45	1.61
5104	Male	9	6.18	2.73
	Female	4	3.23	1.44
5105	Male	8	6.06	2.84
	Female	8	3.47	1.60
5106	Male	6	5.16	2.64
	Female	8	3.06	1.54
5107	Male	8	5.96	2.65
	Female	5	3.35	1.52
5108	Male	7	5.73	2.57
	Female	8	3.16	1.46
5109	Male	6	6.07	2.79
	Female	7	3.61	1.66
n	Male	68		
	Female	59		
Mean	Male		5.909	2.713
	Female		3.301	1.534
S.D.	Male		0.309	0.085
	Female		0.189	0.077

AGD : Anogenital Distance

AGD/3√ body weight

Appendix 14 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Anogenital distance of offspring

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Unit : mm Species : Rat

Dam No.	Sex	/Days after birth 4 n	AGD	AGD/3√BW
5201	Male	6	5.88	2.67
	Female	9	3.10	1.42
5202	Male	8	6.35	2.66
	Female	4	3.47	1.49
5203	Male	10	5.92	2.76
	Female	6	3.39	1.55
5204	Male	7	6.32	2.77
	Female	7	3.46	1.55
5205	Male	7	4.73	2.15
	Female	7	2.24	1.03
5206	Male	6	5.70	2.52
	Female	7	2.87	1.29
5207	Male	8	5.97	2.67
	Female	5	2.99	1.40
5208	Male	6	5.51	2.40
	Female	7	3.00	1.34
5209	Male	9	5.03	2.28
	Female	4	2.47	1.12
5210	Male	6	5.48	2.50
	Female	8	3.24	1.48
n	Male	73		
	Female	64		
Mean	Male		5.689	2.538
	Female		3.023	1.367
S.D.	Male		0.520	0.208
	Female		0.411	0.176

AGD : Anogenital Distance

AGD/3√body weight

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Appendix 14 - 3

Reproduction/developmental toxicity screening test in rats
Anogenital distance of offspring

Study No. : E16-0045

Generation : F0 | Dose : TG-SH(H) 100 mg/kg/day | Unit : mm | Species : Rat

Dam No.	Sex	/Days after birth 4 n	AGD	AGD/3√BW
5301	Male	8	6.18	2.76
	Female	7	3.38	1.52
5303	Male	8	6.19	2.67
	Female	6	2.76	1.22
5304	Male	2	5.83	2.71
	Female	11	3.36	1.61
5306	Male	5	6.29	2.56
	Female	2	3.72	1.54
5307	Male	6	5.90	2.60
	Female	7	3.37	1.50
5308	Male	8	5.95	2.66
	Female	7	3.50	1.60
5309	Male	11	5.89	2.74
	Female	4	3.17	1.50
5310	Male	7	4.40	2.02
	Female	8	2.30	1.06
n	Male	55		
	Female	52		
Mean	Male		5.829	2.590
	Female		3.195	1.444
S.D.	Male		0.601	0.240
	Female		0.455	0.197

AGD : Anogenital Distance
AGD/3√body weight

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Appendix 14 - 4

Reproduction/developmental toxicity screening test in rats
Anogenital distance of offspring

Study No. : E16-0045

Generation : F0 | Dose : TG-SH(H) 300 mg/kg/day | Unit : mm | Species : Rat

Dam No.	Sex	/Days after birth 4 n	AGD	AGD/3√BW
5403	Male	6	5.57	2.64
	Female	9	3.09	1.49
5404	Male	7	5.95	2.73
	Female	7	3.27	1.52
5405	Male	6	5.25	2.27
	Female	6	2.51	1.09
5406	Male	9	5.99	2.74
	Female	5	3.16	1.48
5408	Male	7	5.54	2.55
	Female	7	3.30	1.54
5409	Male	7	4.74	2.23
	Female	6	2.17	1.04
5410	Male	9	5.74	2.54
	Female	6	3.13	1.39
n	Male	51		
	Female	46		
Mean	Male		5.540	2.529
	Female		2.947	1.364
S.D.	Male		0.435	0.206
	Female		0.433	0.210

AGD : Anogenital Distance
AGD/3√body weight

Appendix 14 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Anogenital distance of offspring

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Unit : mm Species : Rat

Dam No.	Sex	/Days after birth 4 n	AGD	AGD/3√BW
5501	Male	7	6.77	2.83
	Female	5	3.76	1.60
5503	Male	8	4.66	2.21
	Female	7	2.43	1.17
5504	Male	10	6.13	2.79
	Female	6	3.10	1.46
5505	Male	8	5.70	2.73
	Female	6	3.47	1.67
5506	Male	8	6.07	2.71
	Female	5	3.18	1.45
5507	Male	9	6.38	2.91
	Female	5	3.59	1.64
5508	Male	5	6.32	2.68
	Female	6	3.49	1.52
5509	Male	5	4.72	2.15
	Female	9	2.32	1.07
5510	Male	5	5.50	2.25
	Female	5	2.78	1.15
n	Male	65		
	Female	54		
Mean	Male		5.806	2.584
	Female		3.124	1.414
S.D.	Male		0.733	0.295
	Female		0.515	0.227

AGD : Anogenital Distance
AGD/3√body weight

Appendix 15 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

External examination of offspring

Unit : Number of anomalous offspring (incidence %) Days after birth : 0

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Dam No.	Number of offspring examined	/Findings
5101	16	No anomaly
5102	15	No anomaly
5103	15	No anomaly
5104	13	No anomaly
5105	16	No anomaly
5106	14	No anomaly
5107	14	No anomaly
5108	15	No anomaly
5109	13	No anomaly
Total	131	
n	9	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

External examination of offspring

Unit : Number of anomalous offspring (incidence %) Days after birth : 0

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Dam No.	Number of offspring examined	/Findings
5201	15	No anomaly
5202	12	No anomaly
5203	16	No anomaly
5204	14	No anomaly
5205	14	No anomaly
5206	13	No anomaly
5207	13	No anomaly
5208	13	No anomaly
5209	13	No anomaly
5210	15	No anomaly
Total	138	
n	10	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

External examination of offspring

Unit : Number of anomalous offspring (incidence %) Days after birth : 0

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Species : Rat

Dam No.	Number of offspring examined	/Findings Others
5301	15	No anomaly
5302	15	No anomaly
5303	14	No anomaly
5304	13	No anomaly
5306	7	No anomaly
5307	13	1(7.7)
5308	15	No anomaly
5309	15	No anomaly
5310	15	No anomaly
Total	122	1
n	9	
Mean		0.86
S.D.		2.57

Mean : Average of incidence (%)

Others : No tail

Appendix 15 - 4 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Unit : Number of anomalous offspring (incidence %)
Generation : F0
Dose : TG-SH(H) 300 mg/kg/day

Days after birth : 0
Species : Rat

Dam No.	Number of offspring examined	/Findings
5401	17	No anomaly
5403	15	No anomaly
5404	15	No anomaly
5405	12	No anomaly
5406	14	No anomaly
5408	14	No anomaly
5409	13	No anomaly
5410	15	No anomaly
Total	115	
n	8	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 5 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Unit : Number of anomalous offspring (incidence %)
Generation : F0
Dose : TG-SH(H) 1000 mg/kg/day

Days after birth : 0
Species : Rat

Dam No.	Number of offspring examined	/Findings Others
5501	12	No anomaly
5503	15	No anomaly
5504	16	No anomaly
5505	15	No anomaly
5506	13	No anomaly
5507	14	No anomaly
5508	11	1(9.1)
5509	15	No anomaly
5510	10	No anomaly
Total	121	1
n	9	
Mean		1.01
S.D.		3.03

Mean : Average of incidence (%)
Others : No tail

Appendix 15 - 6 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Generation : F0
Unit : Number of anomalous offspring (incidence %)
Dose : TG-SH(H) 0 mg/kg/day

Days after birth : 13
Species : Rat

Dam No.	Number of offspring examined	/Findings
5101	11	No anomaly
5102	13	No anomaly
5103	13	No anomaly
5104	11	No anomaly
5105	14	No anomaly
5106	12	No anomaly
5107	11	No anomaly
5108	13	No anomaly
5109	11	No anomaly
Total	109	
n	9	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 7 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

External examination of offspring

Unit : Number of anomalous offspring (incidence %) Days after birth : 13

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Dam No.	Number of offspring examined	/Findings
5201	13	No anomaly
5202	10	No anomaly
5203	14	No anomaly
5204	12	No anomaly
5205	12	No anomaly
5206	11	No anomaly
5207	11	No anomaly
5208	11	No anomaly
5209	11	No anomaly
5210	12	No anomaly
Total	117	
n	10	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 8 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Unit : Number of anomalous offspring (incidence %)
Generation : F0
Dose : TG-SH(H) 100 mg/kg/day

Days after birth : 13
Species : Rat

Dam No.	Number of offspring examined	/Findings Others
5301	13	No anomaly
5303	12	No anomaly
5304	11	No anomaly
5306	7	No anomaly
5307	11	1(9.1)
5308	13	1(7.7)
5309	13	No anomaly
5310	13	No anomaly
Total	93	2
n	8	
Mean		2.10
S.D.		3.91

Mean : Average of incidence (%)
Others : No tail (No. 5307), Loss of tail tip (No. 5308)

Appendix 15 - 9 Reproduction/developmental toxicity screening test in rats
External examination of offspring

Study No. : E16-0045

Generation : F0
Unit : Number of anomalous offspring (incidence %)
Dose : TG-SH(H) 300 mg/kg/day

Days after birth : 13
Species : Rat

Dam No.	Number of offspring examined	/Findings
5403	13	No anomaly
5404	12	No anomaly
5405	10	No anomaly
5406	12	No anomaly
5408	12	No anomaly
5409	11	No anomaly
5410	13	No anomaly
Total	83	
n	7	
Mean		
S.D.		

Mean : Average of incidence (%)

Appendix 15 - 10 Reproduction/developmental toxicity screening test in rats
External examination of offspring
Study No. : E16-0045

Generation : F0
Unit : Number of anomalous offspring (incidence %)
Dose : TG-SH(H) 1000 mg/kg/day
Days after birth : 13
Species : Rat

Dam No.	Number of offspring examined	/Findings Others
5501	10	No anomaly
5503	13	No anomaly
5504	14	No anomaly
5505	12	No anomaly
5506	11	No anomaly
5507	12	No anomaly
5508	9	1(11.1)
5509	12	No anomaly
5510	8	No anomaly
Total	101	1
n	9	
Mean		1.23
S.D.		3.70

Mean : Average of incidence (%)
Others : No tail

Appendix 16 - 1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Nipple retention of offspring

Days after birth : 13

Generation : F0 Dose : TG-SH(H) 0 mg/kg/day Species : Rat

Dam No.	Sex	Nipple retention								Mean	S.D.	n
5101	Male	0	0	0	0	0	0	0	0	0	0	8
5102	Male	0	0	0	0	0	0			0	0	6
5103	Male	0	0	1	0	0	0			0	0	6
5104	Male	0	0	0	0	0	0	0		0	0	7
5105	Male	0	0	0	0	0	0	0		0	0	7
5106	Male	0	0	0	0	0				0	0	5
5107	Male	0	0	0	0	0	0	0		0	0	7
5108	Male	0	0	0	0	0	0			0	0	6
5109	Male	0	0	0	0	0				0	0	5

Appendix 16 - 2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Nipple retention of offspring

Days after birth : 13

Generation : F0 Dose : TG-SH(H) 20 mg/kg/day Species : Rat

Dam No.	Sex	Nipple retention									Mean	S.D.	n
5201	Male	0	0	0	0	0					0	0	5
5202	Male	0	0	0	0	0	0				0	0	6
5203	Male	0	0	0	0	0	0	0	0	0	0	0	9
5204	Male	0	0	0	0	0	0				0	0	6
5205	Male	0	0	0	0	0	0				0	0	6
5206	Male	0	0	0	0	0					0	0	5
5207	Male	0	0	0	0	0	0	0			0	0	7
5208	Male	0	0	0	0	0					0	0	5
5209	Male	0	0	0	0	0	0	0			0	0	7
5210	Male	0	0	0	0	0					0	0	5

Appendix 16 - 3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Nipple retention of offspring

Generation : F0 Dose : TG-SH(H) 100 mg/kg/day Days after birth : 13

Species : Rat

Dam No.	Sex	Nipple retention									Mean	S.D.	n
5301	Male	0	0	0	0	0	0	0			0	0	7
5303	Male	0	0	0	0	0	0	0			0	0	7
5304	Male	0	0								0	0	2
5306	Male	0	0	0	0	0					0	0	5
5307	Male	0	0	0	0	0					0	0	5
5308	Male	0	0	0	0	0	0	0			0	0	7
5309	Male	0	0	0	0	0	0	0	0	0	0	0	9
5310	Male	0	0	0	0	0	0				0	0	6

Appendix 16 - 4 Reproduction/developmental toxicity screening test in rats
Nipple retention of offspring

Study No. : E16-0045

Days after birth : 13
Species : Rat

Generation : F0 Dose : TG-SH(H) 300 mg/kg/day

Dam No.	Sex	Nipple retention								Mean	S.D.	n
5403	Male	0	0	0	0	0				0	0	5
5404	Male	0	0	0	0	0	0			0	0	6
5405	Male	0	0	0	0	0				0	0	5
5406	Male	0	0	0	0	0	0	0	0	0	0	8
5408	Male	0	0	0	0	0	0			0	0	6
5409	Male	0	0	0	0	0	0			0	0	6
5410	Male	0	0	0	0	0	0	0	0	0	0	8

Appendix 16 - 5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045

Nipple retention of offspring

Generation : F0 Dose : TG-SH(H) 1000 mg/kg/day Days after birth : 13

Species : Rat

Dam No.	Sex	Nipple retention									Mean	S.D.	n
5501	Male	0	0	0	0	0	0				0	0	6
5503	Male	0	0	0	0	0	0	0			0	0	7
5504	Male	0	0	0	0	0	0	0	0	0	0	0	9
5505	Male	0	0	0	0	0	0	0			0	0	7
5506	Male	0	0	0	0	0	0	0			0	0	7
5507	Male	0	0	0	0	0	0	0	0		0	0	8
5508	Male	0	0	0	0						0	0	4
5509	Male	0	0	0	0						0	0	4
5510	Male	0	0	0	0						0	0	4

Appendix 17-1 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

Dose : 0 mg/kg/day

Animal No.	Signs	Lactation period (day) 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5101															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5102															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5103															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5104															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5105															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5106															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5107															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5108															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5109															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5110	---														

. : No abnormalities detected
S : Sacrificed
No. 5110 : No delivery

Appendix 17-2 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

Dose : 20 mg/kg/day

Animal No.	Signs	Lactation period (day) 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5201															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5202															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5203															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5204															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5205															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5206															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5207															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5208															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5209															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5210															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.

. : No abnormalities detected
S : Sacrificed

Appendix 17-3 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

Dose : 100 mg/kg/day

Animal No.	Signs	Lactation period (day) 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5301															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5302															
	Unclearance of placenta	1													
	No retrieving	1	1												
	No crouching		1												
	No milk band	1	1												
	Subnormal temperature	1	1												
	Whole litter death			1											
5303															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5304															S
	No abnormalities detected		.	.	.	.	.	.	.	.	.	.	.	.	.
	No milk band	1													
	Subnormal temperature	1													
5305	---														
5306															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5307															S
	No tail (one female)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5308															S
	No abnormalities detected	.	.	.	.										
	Loss of tip tail (one female)					1	1	1	1	1	1	1	1	1	1
5309															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5310															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.

. : No abnormalities detected
1 : Present
S : Sacrificed
No. 5302 : Whole litter death
No. 5305 : Death during delivery

Appendix 17-4 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

Dose : 300 mg/kg/day

Animal No.	Signs	Lactation period (day) 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5401															
	No abnormalities detected	.													
	No retrieving		1												
	No crouching		1												
	No milk band		1												
	Subnormal temperature		1												
	Whole litter death			1											
5402	---														
5403															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5404															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5405															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5406															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5407	---														
5408															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5409															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5410															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.

. : No abnormalities detected
1 : Present
S : Sacrificed
No. 5401 : Whole litter death
No. 5402, 5407 : No delivery

Appendix 17-5 Reproduction/developmental toxicity screening test in rats Study No. : E16-0045
Clinical sign of offspring

Dose : 1000 mg/kg/day

Animal No.	Signs	Lactation period (day) 0	1	2	3	4	5	6	7	8	9	10	11	12	13
5501															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5502	---														
5503															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5504															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5505															S
	No abnormalities detected		.	.	.	.	.	.	.	.	.	.	.	.	.
	No milk band (one female)	1													
	Subnormal temperature (one female)	1													
5506															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5507															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5508															S
	No tail (one female)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5509															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5510															S
	No abnormalities detected	.	.	.	.	.	.	.	.	.	.	.	.	.	.

. : No abnormalities detected
1 : Present
S : Sacrificed
No. 5502 : No delivery