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August 18, 1999

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Dear Sir:

On June 23, 1999 we submitted several reports in German on the compound SXX 0665. The English version has just been received and as a follow up, we are submitting these reports. No 8(e) HQ numbers have been assigned as yet.

14497

TRACKING I.D. NUMBER	STUDY NAME	STUDY NUMBER
99-2-46	Study for Acute Oral Toxicity in Rats,	Study # T9034877
99-2-47	Study for Acute Oral Toxicity in Mice	Study # T0034878
99-2-48	Embryotoxicity Study on Postnatal DevelopmentOf Supernumerary Ribs in Rats following Oral Administration	Study # T4039958
99-2-49	Study for Embryotoxic Effects in Rabbits Following Oral Administration	Study # T9037397
99-2-51	Study for Acute Intraperitoneal Toxicity in Rats	Study # T7034875

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Sincerely,

Donald W. Lamb, Ph.D
Vice President, Product Safety & Regulatory Affairs
412-777-7431 Phone

CERTIFIED MAIL: P 917 006924

STUDY TITLE

SXX 0665
Study for Embryotoxic Effects in Rabbits
Following Oral Administration

DATA REQUIREMENT

US EPA-OPPTS Guideline No. 870.3700

AUTHOR

109270

Dr. K. Bartmann

FILE
8866

STUDY COMPLETION DATE

September 6, 1991

PERFORMING LABORATORY

BAYER AG
DEPARTMENT OF TOXICOLOGY
Friedrich-Ebert-Strasse 217-233
D-42096 Wuppertal
Germany

LABORATORY PROJECT ID

Bayer AG Report No. 21091
Bayer AG Study No. T 9037397

STATEMENT OF DATA CONFIDENTIALITY

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is only permitted with the consent of Bayer AG.

The following statement supercedes the above statement of confidentiality that may occur elsewhere in this report:

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C).

BAYER CORPORATION

Dr. J.H. Thyssen: _____
Vice President, Toxicology

Date: Aug. 5, 99

GLP Compliance Statement

This study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP) (Bundesanzeiger No. 42a of March 2, 1983) and Bundesgesetzblatt, Part I of March 22, 1990 and meets the FIFRA Good Laboratory Practice Standards (40 CFR Part 160), with the exception that recognized differences exist between the GLP principles / standards of OECD and FIFRA (for instance, authority granted Agency inspectors and certain record retention requirements).

STUDY DIRECTOR

BAYER AG

for Dr. B. Holzum

12. 3. 1999
Date

SPONSOR

BAYER AG

for Dr. L. Machemer

12. 3. 1999
Date

SUBMITTER

BAYER CORPORATION

Name: Dr. J.H. Thyssen
Vice President, Toxicology

Aug. 5, 99
Date

FLAGGING STATEMENT

I have applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study meets or exceeds the criteria numbered 5.

SUBMITTER

BAYER CORPORATION

Dr. J.H. Thyssen: _____
Vice President, Toxicology

Date: Aug. 5, 99

SPONSOR

AGRICULTURE DIVISION

Dr. J.H. Thyssen: _____
Vice President, Toxicology

Date: Aug. 5, 99

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Tables with clinical and pathologic findings; tables with individual animal data, means and statistics; randomization list; data on active ingredient analysis, diet specification and classification of fetal skeletal deviations; historical control data 31

1. Statement of Quality Assurance Unit

Study no. : T 9037397

Test substance : SXX 0665

This study was monitored by Quality Assurance on the dates given below. The results of the reviews and inspections were communicated in writing to the study director, and if necessary to the head of the institute or further affected persons as well.

Date of review or inspection		Forwarding date of inspection report
October 26, 1990	(study plan)	October 26, 1990
October 02, 1990		October 09, 1990
October 26, 1990		October 26, 1990
November 08, 1990		November 08, 1990
January 10, 1991		January 10, 1991

The study results and methodology are accurately reflected by this report.

Quality Assurance/GLP, Bayer AG

Date: August 29, 1991 Responsible: _____
(Dr. H. Lehn)

SEE PAGE 183 FOR SIGNATURE

2. SIGNATURES

Study director:	(Dr. B. Holzum)	September 06, 1991 (Date)
Report preparation:	(Dr. K. Bartmann)	September 06, 1991 (Date)
Head of Institute:	(Dr. L. Machemer)	February 06, 1992 (Date)

SEE PAGE 184 FOR SIGNATURE

Dr.(USA) Robert Bashe
Translator
May 28, 1999

Bayer

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August 18, 1999

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Office of Toxic Substances
U.S. EPA
401 M Street, SW
Washington, DC 20460

PR25619

Dear Sir:

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99-2-49	Study for Embryotoxic Effects in Rabbits Following Oral Administration	Study # T9037397
99-2-51	Study for Acute Intraperitoneal Toxicity in Rats	Study # T7034875

Please contact us if there are any questions.

Sincerely,

Donald W. Lamb, Ph.D
Vice President, Product Safety &Regulatory Affairs
412-777-7431 Phone

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3. Summary

Groups of 15 female Himalayan rabbits were administered daily SXX 0665 doses of 0, 2, 10 or 50 mg/kg body weight by gavage from p.c.* day 6 - 18. The animals were delivered by cesarian section on p.c. day 29. The general toleration of the active ingredient by the dams and the effect on intrauterine development were examined.

The appearance, behavior, water intakes and excretory products of the dams underwent no treatment-related effect at daily doses up to and including 50 mg/kg body weight.

The food intakes were marginally decreased in the 50 mg/kg group. The body weight gains were adversely affected during gestation in the 50 mg/kg group animals, presumably as a result of the elevated resorption rate.

No treatment-related mortalities occurred.

No significant gross pathologic findings were made at necropsy. The mean liver weights underwent no treatment-related effect at doses up to and including 50 mg/kg body weight. An elevated incidence of cellular scavenging clusters resulting from increased destruction of individual hepatocytes, and low glycogen mobilization, were observed in the histopathology of the livers in the 10 mg/kg and 50 mg/kg groups.

The weights and outward appearance of the placentas, the fetal sex and weight, and the skeletal system development underwent no treatment-related effect at daily doses up to and including 50 mg/kg body weight. Due to an elevated resorption rate, the gestation rate and number of fetuses underwent a decrease in the 50 mg/kg group. The rate of malformations was elevated at daily doses of 10 mg/kg body weight and above. In the 10 mg/kg group, these represented alterations (vertebral body and rib alterations, arthrogryposis, multiple malformations) that can spontaneously arise in the strain of rabbits used in this study. Evidence for a specific teratogenic effect by SXX 0665 (cleft palate) was observed in the 50 mg/kg group.

The no-adverse-effect levels were thus

Dams	: 2 mg/kg body weight per day
Intrauterine development	: 2 mg/kg body weight per day

* Translator: p.c. = post coitum. See page 30 for other abbreviations in text.

4. Introduction

A study for possible maternal and embryonal toxic effects in pregnant rabbits was carried out with SXX 0665, a test substance exhibiting fungicidal properties.

The study was performed during the period from September 25, 1990 to February 14, 1991 at the BAYER AG Fachbereich Toxikologie, Institute of Toxicology - Agrochemicals in D-5600 Wuppertal 1, Friedrich-Ebert-Strasse 217 - 333.

The histopathologic inspections were performed at the BAYER AG Fachbereich Toxikologie, Institute of Pathology.

5. Study Identification and Responsibilities

5.1. Study number

The study number was T 9037397.

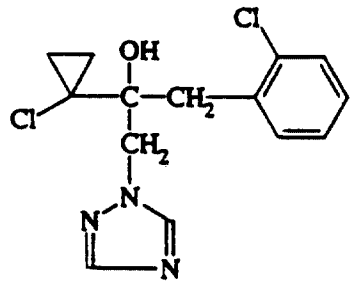
5.2. Responsibilities

Head of Institute	Dr. L. Machemer
Study director	Dr. B. Holzum
Histopathologic inspections	Dr. M. Rinke
Report preparation	Dr. K. Bartmann
Active ingredient analyses	Dr. Tengler
Active ingredient analyses in treatment formulations	Dipl.Ing. K. Riegner
Quality Assurance	Dr. H. Lehn
Filing	Dr. E.A. Löbbecke

6. Material and Method

6.1. Test substance and analysis for active ingredient in treatment formulations

Test substance name	:	SXX 0665 techn.
Manufacturer	:	Bayer AG
Batch no.	:	17005/89
Purity	:	94.7 % and 94.0 % (analyses of June 13 and October 09, 1990 respectively; cf. page 170 in annex)
Approval	:	To December 13, 1990
Physical state	:	Solid
Appearance	:	Beige-brown powder
Test substance storage	:	At ambient temperature
Common name	:	--
Chemical name	:	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol
CAS number	:	--
Structural formula	:	



Molecular mass	:	312.0 g/mole
Empirical formula	:	$C_{14}H_{15}Cl_2N_3O$

Deionized water containing 0.5 % Cremophor® EL (BASF) was used to prepare the treatment formulation suspensions. Cremophor® EL exerts no effect on the test parameters. The treatment formulations were stored at ambient temperature during the period of use. The stability of the active ingredient in the treatment formulations over the period of use (seven days) as well as the homogeneous distribution of the active ingredient throughout the treatment formulations were verified prior to study initiation.

Except for one very minor deviation, analyses for the active ingredient levels in the formulations for all concentrations performed in the second and fifth weeks of treatment afforded no results exceeding the permissible tolerance limits. The sample of 50 mg/kg group treatment formulation taken prior to administration in the fifth week of treatment afforded evidence for minor inhomogeneity. The individual concentration results varied by more than 20 % (in this case 21.8 %) in the dual determination (cf. active ingredient analysis data on pp. 170 - 175 in the annex).

6.2. Experimental animals and maintenance

6.2.1. Experimental animals

The study was conducted with rabbits - an animal species recommended for teratogenicity studies in test guidelines. Rabbits of the strain CHBB:HM supplied by Thomae breeders in Biberach a.d. Riss were used. Animals of this strain have been used for teratogenicity studies at BAYER AG for years. Historical data on the test parameters are available. As demonstrated by historical data on the fertility and gestation rates (cf. page 180 in the annex), animals of this strain have been shown to exhibit a level of fertility sufficiently high for embryotoxicity studies. This strain exhibits adequate sensitivity to embryotoxic substances [1,2].

Following receipt of the animals (on April 11 and July 05, 1990), those scheduled for this study were adapted to the animal room conditions until treatment was initiated (on October 01, 1990), and carefully observed for signs of illness during this period. No vaccinations or treatments with antiinfectives were carried out. Only healthy animals exhibiting no clinical signs were used for the study. The females were nulliparous and nongravid. At the time of mating, the male animals were sexually mature; on p.c. day zero, the sexually mature females exhibited weights of 2018 - 3589 grams.

6.2.2. *Animal maintenance*

The animals were individually kept in Cellidor® cages with perforated base plates during the adaptation and study periods.

All animals used in this study were housed in Animal Room 012 of Building 500. No other studies were simultaneously conducted in this animal room.

6.2.3. *Animal room conditions*

The room climate in the animal stalls was standardized as follows.

Room temperature	:	20.5° - 23.5°C (average about 22°C)
Relative humidity	:	33 - 85 % (average about 55 %)
Light/dark cycles	:	Twelve hours; artificial lighting from 6 AM to 6 PM CET
Air exchanges	:	at least 10 times per hour

Occasional deviations from these standards took place, for example due to cleaning of the animal room. They had no apparent effect on animal maintenance.

6.2.4. *Feeding*

The rations during the adaptation and study periods consisted of "Ssniff® K4 Rabbit Food", a standard diet produced by Ssniff Spezialdiäten GmbH in Soest, and tap water; both were provided to the animals for *ad libitum* consumption.

The diet was provided to the animals in racks which were automatically filled from food containers. Polycarbonate bottles with a capacity of 700 mL were used for watering.

The nutritive composition and contaminant levels of the standard diet were routinely spot-checked and determined by analysis (cf. page 176 in the annex for diet specification). The tap water met drinking water standards as specified in the German "Verordnung über Trinkwasser und über Wasser für Lebensmittelbetriebe" (Regulation on Drinking Water and on Water for Food Plants) of May 22, 1986 (**Bundesgesetzblatt** I 760).

Records of the analyses to monitor compliance with the food and water specifications are filed at BAYER AG.

6.2.5. Identification of experimental animals

The animals were identified by cage cards listing the animal number, test substance, dose, study number and test introduction date (gestation day zero); and by marking the inside of the right ear with the randomizing number using a felt pen with water-insoluble ink (Staedtler Co. Marker 352).

6.2.6. Cleaning and disinfection

The animal room was cleaned each day, and disinfected with Rapidosept® or Zephirol® three times each week. The animals were placed in clean cages with cleaned food containers at study initiation. The entire material of the cage was cleaned with hot water. Stool trays and watering bottles were changed at regular intervals.

6.3. Test guidelines

The study conformed to guidelines published by the US EPA ("Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Humans and Domestic Animals", Series 83-3, "Teratogenicity Study", Revised Edition, November 1984) and to the OECD recommendations (Guidelines for Testing of Chemicals, Section 4: Health Effects, No. 414 "Teratogenicity" [adopted May 12, 1981]).

6.4. Mating and onset of gestation

The animals were mated during the period from 8 AM to 10 AM. One male rabbit was mated with one female under observation. Following the first copulation, these animals were remated with one another after a pause of about one hour. In the case of isolated animals, a second buck was used for the second mating. The day copulation was observed was considered gestation day zero.

6.5. Active ingredient dosage, study groups and dose rationale

The male animals were only used for mating and were not treated.

Following copulation, the females were allocated to four study groups according to a computer-generated randomizing plan (HP 3000 system random number generator; cf. pages 168 - 169 in the annex for randomizing list). Each of the four study groups consisted of 15 females.

The animals were treated each day from p.c. day 6 - 18 between 8 AM and 12 AM.

Since oral administration is appropriate and internationally recognized for embryotoxicity studies, the treatment formulation was orally administered to the animals using a stomach tube (Rüsch Co. rubber sonde no. 18).

A uniform volume of 5 mL/kg body weight was administered to the animals of all study groups.

The following doses - corrected for the purity of the test substance and adjusted for the current body weight - were administered.

	Dose, mg/kg b.w	Concentration, mg/mL
Controls	0	0
Group 1	2	0.4
Group 2	10	2
Group 3	50	10

These doses were selected on the basis of results gained in a prior dose-determination study involving daily SXX 0665 doses of 30, 50 and 75 mg/kg body weight.

The daily 30 mg/kg b.w. dose was tolerated by the dams without adverse effects, and had no effect on the resorption rate. The animals exhibited marked body weight losses during the treatment period at daily doses of 50 mg/kg b.w. and above. The resorption rate was elevated in the 50 mg/kg group, and total resorptions occurred in all 75 mg/kg group animals.

6.6. Survey of examinations

6.6.1. General toleration of treatment by dams

The general toleration of the test substance by the pregnant rabbits was assessed on the basis of their appearance and behavior, food and water intakes, the appearance of the excretory products, the body weight gains and mortality of the animals, and on the basis of the gross pathology, liver weights and histopathology of the livers.

6.6.1.1 Appearance, behavior, food and water intakes, excretory products and mortality

All experimental animals were inspected twice daily (once daily on weekends and public holidays) from p.c. day zero - 29, and any observed findings recorded. Note was given to disturbances of the general condition, appearance or behavior; and to alterations in the excretory products. The food intakes of the animals were determined over the gestation period intervals from p.c. day zero to six, six to ten, 10 - 14, 14 - 19, 19 - 24 and 24 - 29 by weighing the amount of food provided and back-weighing the amount that remained unconsumed. The water intakes were assessed during the inspections by visual estimation of the remaining quantities.

6.6.1.2 Body weight gains

The body weights of the animals were determined on p.c. day zero, each day from p.c. day six to 18, and on p.c. day 29. The corrected body weight gain was determined by subtracting the uterine weight from the p.c. day zero - 29 body weight gain.

6.6.1.3 Gross pathology, liver weights and histopathology

The animals were examined for gross pathology in the course of cesarian section on p.c. day 29. The livers of the animals were weighed, then fixed in 10 % aqueous formaldehyde solution and inspected for histopathology. The histopathology methods and pertinent findings are described in the histopathology report on pages 49 - 102 in the annex.

6.6.2. Examinations in connection with cesarian section

The animals were sacrificed for cesarian section on p.c. day 29 by intrapulmonary injection of 3 mL T 61® ad us. vet. (Hoechst AG).

The following data were determined and assessed in connection with cesarian section.

- Number of corpora lutea
- Number of implantations
- Uterine weight
- Individual weights and outward appearance of placentas
- Number of viable and dead fetuses or embryos
- Sex of all viable fetuses
- Individual fetal weights
- Occurrence of outwardly apparent malformations and miscellaneous abnormal findings
- Occurrence of visceral malformations of the fetal skull (examination using the modified Wilson technique [3,4])
- Occurrence of lesions of the abdominal and thoracic organs as well as deviations of the skeletal system (Dawson technique [5]: evisceration, clearance of fetuses with dilute potassium hydroxide solution, staining of skeletal system with alizarin red S and subsequent evaluation)

The fetal examinations using the modified Wilson and the Dawson techniques were carried out using standardized methods [6,7] modified for the study of rabbit fetuses.

6.7. Statistics

The following methods were used for statistical significance testing.

a. The Wilcoxon non-parametric rank sum test (Wilcoxon-Mann- Whitney U-test), and in the case of striking deviations an additional F-test and t-test (weight gains, numbers of fetuses, fetal weights) or Chi^2 test (rates of resorption and malformation) was used for the

   - Mean weight gains
   - Number of corpora lutea per dam
   - Number of implantations per dam
   - Number of fetuses per dam
   - Number of resorptions per dam
   - Mean fetal weight per dam
   - Mean placental weight per dam
   - Mean number of fetuses examined by the Wilson or Dawson technique per dam
   - Mean number of fetuses with minor skeletal deviations per dam
   - Mean number of fetuses exhibiting malformations per dam

The Wilcoxon test calculations were performed on an IBM computer system at the Bayer AG Institute of Biometry using an evaluation program developed for embryotoxicity studies. The F-test, t-test and Chi^2 test calculations were performed using an HP-97 calculator. The stated levels of significance refer to the results of the t-test or Chi^2 test.

b. The F-test and the standard or Welch t-test were used for the

- Corrected body weight gains
- Food intakes

These calculations were performed using an HP-97 calculator. The stated levels of significance refer to the results of the standard or Welch t-test.

c. Fisher's exact test at significance levels of $\alpha = 5$ % and $\alpha = 1$ % (two-tailed) was used for the

- Fertility rate
- Gestation rate
- Number of fetuses exhibiting malformations per group
- Number of litters including malformations per group

These calculations were performed using an HP-3000 system if striking deviations existed relative to the control group.

d. The Nalimov wild result test was used for the

- Liver weight (animal no. 774)

The Nalimov wild result test calculations were performed using an HP-97 calculator.

6.8. Compliance with GLP principles, filing

This study complied with the OECD principles of Good Laboratory Practice (GLP) as published in the **Bundesanzeiger** no. 42a of March 2, 1983 and **BGBl I** of March 22, 1990. Refer to page 3 for the GLP statement. In agreement with these principles, the study records (such as the study plan, report copy, raw data and fetuses) are filed at the BAYER AG Fachbereich Toxikologie in Wuppertal.

7. RESULTS

7.1. General toleration of treatment by dams

7.1.1 Appearance, behavior and mortality

The appearance and behavior of animals administered daily doses up to and including 50 mg/kg body weight did not differ significantly from those of the controls.

No animal died during the study.

A survey of the individual animal clinical findings and the pertinent incidence table are located together with the gross pathologic findings on pages 33 - 37 of the annex.

7.1.2. Food and water intakes, excretory products

The food intakes underwent no treatment-related effect at daily doses up to and including 10 mg/kg body weight, nor did the water intakes at daily doses up to and including 50 mg/kg body weight. The food intake of the 50 mg/kg group animals from p.c. day six - 24 was slightly (not statistically significant) below that of the controls.

The bloody discharges observed in three 50 mg/kg group animals are presumably related to the total (nos. 777, 779) or near-total (no. 782) resorptions in these animals, and are not considered evidence for a specific maternal toxic effect, particularly since this finding was already made on p.c. day five, before treatment was initiated, in one of the animals (no. 777). Similarly, the bloody discharge observed in an isolated 10 mg/kg group animal (no. 772) 11 days after the last treatment (p.c. day 29) is not assessed as a maternal toxic effect.

The food intake data are on pages 38 - 42 in the annex. Data on the water intakes and on the excretory product assessments are located together with the clinical and gross pathologic findings on pages 33 - 37 in the annex.

7.1.3. Body weight gains

The following Table 1 surveys the mean body weight gains of the animals throughout the treatment and gestation periods.

Table 1

Dose, mg/kg b.w. per day	Weight gains (grams)		
	Mean		Corrected
	p.c. days 6-18	p.c. days 0-29	p.c. days 0-29
0	-1.0	98.6	-215.2
2	-1.2	90.8	-253.4
10	12.7	108.8	-203.0
50	-36.0	-23.4*	-263.2

* Statistically significant deviation to control $p < 0.05$

As may be seen in the above table and on pages 103 - 107 in the annex, the body weight gains during gestation did not differ significantly from those in the control animals at daily doses up to and including 10 mg/kg body weight. Presumably due to the elevated resorption rate, the 50 mg/kg group animals exhibited decreased body weight gains during the treatment and gestation periods (statistically significant for the p.c. day 0 - 29 period).

7.1.4. Gross pathologic findings, liver weights and histopathology findings

No toxicologically significant findings were made at necropsy of the animals during cesarian section on p.c. day 29 at daily doses up to and including 50 mg/kg body weight.

The mean liver weights underwent no treatment-related effect in the three dose groups.

An elevated incidence of cellular scavenging clusters resulting from increased destruction of individual hepatocytes, and slight glycogen mobilization, were observed in the histopathology of the livers in the groups treated at daily 10 mg/kg b.w. and 50 mg/kg b.w. doses.

The findings made at necropsy are presented together with the clinical findings on pages 33 - 36 in the annex. A pertinent incidence table is located on page 37 in the annex. The liver weights are located on page 48 in the annex, and the histopathology results on pages 49 - 102.

7.2. General reproduction data

As shown in the following Table 3, the percentage of inseminated animals with implantations (fertility rate) did not differ significantly from the control figure at daily doses up to and including 50 mg/kg body weight.

Table 3

Dose, mg/kg b.w. per day	Inseminated animals	Animals with implantations	
		Total	In % of inseminated
0	15	15	100.0
2	15	15	100.0
10	14	14	100.0
50	12	12	100.0

Similarly, the mean numbers of corpora lutea and implantations per animal did not differ significantly among the individual groups (cf. page 107 in the annex).

Evidence for inhomogeneous distribution of the animal material among the different study groups with respect to the mentioned parameters is thus lacking.

7.3. Test substance effect on intrauterine development

A table of means with statistical test results for the intrauterine development parameters listed in Sections 7.3.2 to 7.3.7 is located on page 107 in the annex.

7.3.1. Gestation rate

As shown by the following Table 4 on page 23, the gestation rates in the 2 mg/kg and 10 mg/kg groups did not differ from control to a statistically significant extent, and were situated within the usual range of variation for this laboratory (cf. historical data on page 180 in the annex). A treatment-related effect cannot be excluded in the 50 mg/kg group, in which the gestation rate was lower than control and marginally below the usual range of variation for this laboratory.

Table 4

Dose, mg/kg b.w. per day	Animals with viable fetuses	
	Total	In % of animals with implantations
0	15	100.0
2	14	93.3
10	13	92.9
50	10	83.3

7.3.2. Weights and outward appearance of placentas

No abnormal macroscopic findings were made in the placentas of any study group.

7.3.3. Resorption rate and number of fetuses

The mean number of resorptions was elevated to a statistically significant extent in all dose groups. Since no dose relationship was evident at daily doses up to and including 10 mg/kg body weight and the resorption rates in the 2 mg/kg and 10 mg/kg groups were situated within the usual range of variation for this laboratory (cf. historical data on page 181 in the annex), the elevated resorption rates relative to control in these groups are not assessed as a treatment-related effect. The mean number of resorptions was markedly elevated in the 50 mg/kg group.

The observed resorptions are differentiated into early and late resorptions on page 165 in the annex.

The mean number of fetuses underwent no treatment-related effect at daily doses up to and including 10 mg/kg body weight. In the 50 mg/kg group, the mean number of fetuses exhibited a statistically significant decline due to the high resorption rate.

7.3.4. Sex of fetuses

The ratio of male to female fetuses underwent no toxicologically significant effect at daily doses up to and including 50 mg/kg body weight (cf. page 108 in the annex).

7.3.5. Weight of fetuses

The mean fetal weight underwent no treatment-related adverse effect at daily doses up to and including 50 mg/kg body weight.

7.3.6. Malformations

The following Table 5 on page 25 surveys the malformations that occurred in viable fetuses. A summary of the malformations observed in individual fetuses is located on page 167 in the annex.

Table 5 shows that no toxicologically significant effects with regard to the number or type of malformations occurred at a daily dose of 2 mg/kg body weight. The rate of fetuses exhibiting malformations was elevated at daily doses of 10 mg/kg body weight and above (at 50 mg/kg body weight per day to a statistically significant extent).

The malformations observed in the 10 mg/kg group (vertebral body and rib alterations, arthrogryposis, multiple malformations) represented changes that - except for the vertebral body alterations - had already been observed as spontaneous malformations in the same strain of rabbits (cf. historical data on page 182 in the annex).

The cleft palates observed in the 50 mg/kg group argue in favor of a specific teratogenic effect by SXX 0665.

Table 5

Malformation	Dose (mg/kg b.w. per day)			
	0	2	10	50
Cleft palate				5
Forked rib		1		
Floating rib	1			
Vertebral body and rib alterations			1	
Arthrogryposis		1	5	1
Shortening of tail				1
Multiple malformations			2	
Occlusion of nostrils	1			
Number of fetuses per group	77	78	66	37
Number of fetuses with malformations				
- Per group	2	2	7	7*
- Per dam (mean)	0.13	0.14	0.54	0.70**
Fetuses with malformations, per group (%)	2.6	2.5	10.6	18.9
Number of litters per group	15	14	13	10
Number of litters with malformations	2	2	5	3
Litters with malformations, per group (%)	13.3	14.2	38.4	30.0

* Statistically significant, $p < 0.05$

** Statistically significant, $p < 0.01$

7.3.7. Deviations in skeletal system

No toxicologically significant, minor skeletal deviations resulting from retarded ossification occurred at daily doses up to and including 50 mg/kg body weight (cf. page 166 in the annex).

The scheme for classifying observed skeletal system deviations as variations, retardations or malformations is shown in the list on pages 177 - 179 in the annex.

8. Assessment

Groups of 15 female Himalayan rabbits were administered daily SXX 0665 doses of 0, 2, 10 or 50 mg/kg body weight by gavage from p.c. day six to 18. The animals were delivered by cesarian section on p.c. day 29. The general toleration of the active ingredient by the dams and the effect on intrauterine development were examined.

The appearance, behavior, water intakes (visual assessment) and excretory products of the dams underwent no treatment-related effect at daily doses up to and including 50 mg/kg body weight. The food intake was marginally depressed in the 50 mg/kg group; it was not adversely affected in the other study groups treated with SXX 0665. The body weight gains of the animals were comparable to those in the controls at daily doses up to and including 10 mg/kg body weight. Presumably due to the elevated resorption rate, decreased body weight gains were observed in the 50 mg/kg group during the gestation period.

No treatment-related mortalities occurred.

No significant gross pathologic findings were made at necropsy of the animals. The mean liver weights underwent no treatment-related effect at daily doses up to and including 50 mg/kg body weight.

An elevated incidence of cellular scavenging clusters resulting from increased destruction of individual hepatocytes, and low glycogen mobilization, were observed in the histopathology of the livers in the 10 mg/kg and 50 mg/kg groups.

The weights and outward appearance of the placentas, the fetal sex and weight, and the skeletal system development underwent no treatment-related effect at daily doses up to and including 50 mg/kg body weight. No toxicologically significant findings with respect to the gestation rate, the resorption rate or the number of fetuses were made at daily doses up to and including 10 mg/kg body weight. Due to an elevated resorption rate, the gestation rate and number of fetuses underwent a decrease in the 50 mg/kg group. No toxicologically significant findings with regard to the number or type of malformations were made in the 2 mg/kg group. The rate of malformations was elevated at daily doses of 10 mg/kg body weight and above. In the 10 mg/kg group, these represented alterations (vertebral body and rib alterations, arthrogryposis, multiple malformations) that can spontaneously arise in the strain of rabbits used in this study. Evidence for a specific teratogenic effect by SXX 0665 (cleft palate) was observed in the 50 mg/kg group.

The embryotoxicity observed at daily doses of 10 mg/kg body weight and above correlated with maternal toxic effects.

The no-adverse-effect levels were thus

Dams	:	2 mg/kg body weight per day
Intrauterine development	:	2 mg/kg body weight per day

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10. Key to Abbreviations*

ABSOL.	absolute
Anim.	animal
ANZ., N.	number
B.w.	body weight
B.w.g.	body weight gain
CONTR.	control
CORP.	Corpora
DEV.	deviation
EINGES.	used, introduced to study
E/L	early / late
Extrem.	extremities, legs
FEM, F	female
G	gross
g, G.	gram
GES.	total
GRP., GR.	group
IMPL., impl.	implantations
KGW	body weight
KNOCHENVERAENDER.	skeletal deviation(s)
LEB.	viable
LFD-Nr.	running number
LIV.	living, viable
M	male
MEZ	Central European Time (CET)
Mißb.	malformations
MITTELW., $\bar{x}$	mean
MNL.,MAENNL.	male
NO., no., n, Nr.	number
o.b.	no pathologic findings, n.o.e.
p.	page
Pathol.-Nr.	pathology number
P.C., p.c.	post coitum
PLACENT.	placentas
p.o.	oral
RAND-NO (NR)	random number
RESO.	resorptions
Retard.	retardation
S	skeletal
S.D., s	standard deviation
SPEZ.	special
STANDARD-ABW.	standard deviation
THEOR.	theoretical
TOT.	total
V	visceral
waes., waess.	aqueous
WBL., WEIBL.	female

* Translator's note: Following German usage, a comma is used instead of a decimal point in the original tables. The sign "'" (geographical minute, apostrophe) is sometimes used to indicate minutes of time. Days are abbreviated "d" and hours "h" in the original tables. The dates are specified in European order (dd.mm.yyyy, for example 28.10.1992 for October 28, 1992). In keeping with American usage and to avoid confusion with the numeral "1", the unit "liter" was abbreviated "L" in the translated text.

11. Annex

Tables with clinical and pathologic findings; tables with individual animal data, means and statistics; randomization list; data on active ingredient analysis, diet specification and classification of fetal skeletal deviations; historical control data

Page		
33 - 102	**Data on tolerance by dams**	
33 - 37	-	Clinical observations and gross pathologic findings (individual animal data and incidence table)
38 - 42	-	Food intakes (individual animal data for dams with group means)
43 - 46	-	Body weights (individual animal data for dams with group means)
47	-	Corrected body weight gains (individual animal data for dams with group means)
48	-	Liver weights (individual animal data for dams with group means)
49 - 102	-	Histopathology report
103 - 167	**Data on cesarian section and fetal assessment**	
103 - 107	-	Weight gains during gestation and during the treatment period, corpora lutea, implantations, number of fetuses, losses, fetal weights, placental weights, skeletal deviations and malformations (individual animal data for dams and group means with statistical test results)
108	-	Sex ratio (group means)
109 - 164	-	Resorptions, fetal sex, fetal weight, placental weight and number of fetuses exhibiting malformations (individual fetal data with mean figures for litters)
165	-	Differentiation of resorptions (comprehensive survey of individual data for dams)
166	-	Retardations of skeletal system (individual fetal results)
167	-	Malformations (individual fetal results)

Page

168 - 169 **Randomizing list**

170 - 175 **Active ingredient analysis results**

170 - Approval certificate

171 - Stability

172 - 173 - Homogeneity

174 - 175 - Control analyses

176 **Diet specification**

177 - 179 **Classification of fetal skeletal deviations**

180 - 182 **Historical control data**

180 - Fertility and gestation rates

181 - Cesarian section and fetal assessment

182 - Spontaneous malformations

Clinical signs and observations in dams

Group	Animal no.	Signs and observations	Observed on p.c. day(s)
Control	751	Low water intake	10-12,14-16,18-20
		Few feces	12,13,15-20
		Whitish discharge	19
	752	Soft feces/diarrhea	12,27
	754	Low water intake	10-12,24
		Soft feces	22
	757	Soft feces	2,5
	758	Small fecal pellets	11
		Soft feces	14
		Few feces	17
		Whitish discharge	16,19
	760	Few feces	6-21,23,24
		Small fecal pellets	19-21
		Low water intake	6-14,16-21,23,24,27
	762	Soft feces	8,9
	773	Low water intake	7,15,17,29
		Whitish discharge	8
		Few feces	15,17-20,22,23
		Small fecal pellets	16,17
	780	Low water intake	5
		Cyst on left oviduct, marked lobulation of liver	29 (necropsy)
	783	Few feces	1
	793	Few feces	15-17
		Low water intake	17
	794	Cyst on right oviduct	29 (necropsy)
	797	Few feces	15-22
		Cyst on left oviduct	29 (necropsy)

Clinical signs and observations in dams

Group	Animal no.	Signs and observations	Observed on p.c. day(s)
2 mg/kg	753	Low water intake	14,17
		Whitish discharge	15,27
		Few feces	17,18
		Large cyst on left ovary	29 (necropsy)
	764	Soft feces	4,22
		Few feces	15,19
		Low water intake	15,19
		Marked lobulation of liver	29 (necropsy)
	766	Low water intake	11,14-24,29
		Few feces	15-23
		Small fecal pellets	29
		Pale feces	22,23
		Diarrhea	16
	771	Few feces	6,11-20
		Low water intake	7,11,12
	775	Few feces	14-26
		Small fecal pellets	15,22-25,29
		Pale feces	26
		Low water intake	14-25,29
		Cysts on both oviducts	29 (necropsy)
	786	Stomach and small intestine nearly empty	29 (necropsy)
	798	Cysts on both oviducts	29 (necropsy)
	801	Diarrhea	18
	802	Few feces	11,15-18
		Whitish discharge	14
		Low water intake	16
	809	Low water intake	7
		Few feces	15
		Whitish discharge	22
	810	Few feces, small fecal pellets	16-18
		Low water intake	16,18

Clinical signs and observations in dams

Group	Animal no.	Signs and observations	Observed on p.c. day(s)
10 mg/kg	765	Low water intake	12,19,22,23,26
		Whitish discharge	4,12
		Few feces	9
		Marked lobulation of liver, cyst on left oviduct	29 (necropsy)
	768	Few feces	3-14,16-27,29
		Small fecal pellets	8,9,14,29
		Pale feces	21,23-25
		Low water intake	8-10,14,16,18-20,22-27
	772	Soft feces	6,14
		Few feces	14,18,20,22-24
		Small fecal pellets	14,15,17
		Low water intake	7,23
		Bloody discharge	29
	778	Soft feces	4
		Few feces	18
		Marked lobulation of liver, cyst on left oviduct	29 (necropsy)
	788	Few feces	9,10
		Low water intake	9
	789	Soft feces	7,9,26,27,29
		Diarrhea	15,16
		Marked lobulation of liver, pale liver, stomach nearly empty	29 (necropsy)
	796	Few feces	15-18
		Cyst on right oviduct	29 (necropsy)
	799	Soft feces	13,14,18,28
		Few feces	27
		Small intestine nearly empty	29 (necropsy)
	800	Few feces	8,20,22,29
		Small fecal pellets	8,20,27-29
		White tears	8
		Cyst on right oviduct	29 (necropsy)
	803	Stomach empty, cyst on right oviduct	29 (necropsy)
	804	Few feces	15,16
	807	Few feces	2,3,10-19

Clinical signs and observations in dams

Group	Animal no.	Signs and observations	Observed on p.c. day(s)
50 mg/kg	755	Soft feces	11
		Few feces	15,17
	756	Low water intake	15
		Few feces	16,17
	759	Few feces	10,11,15-17
		Soft feces	10,11
		Low water intake	15-17
	763	Cyst on left oviduct	29 (necropsy)
	767	Low water intake	8
	774	Soft feces	3,5,14
		Few or no feces	8-13,15-27
		Small fecal pellets	17
		Low water intake	7-26
		Marked lobulation of liver, cysts on both oviducts	29 (necropsy)
	776	Low water intake	6-11,13,15-23,28
		Small fecal pellets	8,14-22
		Few feces	18-22,29
		Cyst on left oviduct, marked lobulation of liver, cyst in liver tissue	29 (necropsy)
	777	Soft feces	3,12,14,17-21,29
		Small fecal pellets	15,16
		Low water intake	5-9,11-19,21-23,28
		Bloody discharge	5
	779	Low water intake	4,5,16
		Few feces	6,8
		Bloody discharge	18-23
		Bloody vagina	18
		Cyst on right oviduct, cyst in liver tissue	29 (necropsy)
	781	Few feces	4,5,22
		Cyst on left oviduct	29 (necropsy)
	782	Bloody discharge	16-18
		Few feces	16
		Soft feces	17
	787	Few feces	14,15

Incidence table of clinical signs and observations

Signs and observations	Dose, mg/kg body weight per day 0	2	10	50
Changes in feces				
Few/no feces	7	8	10	9
Soft feces/diarrhea	5	3	4	5
Small fecal pellets	3	3	3	3
Pale feces	0	2	1	0
Discharges				
Whitish	3	3	1	0
Bloody	0	0	1	3
Bloody vagina	0	0	0	1
White tears	0	0	1	0
Low water intake	6	8	4	7
At necropsy				
Cyst(s) on oviduct or ovary	3	3	5	5
Lobulation of liver	1	1	3	2
Liver tissue pale	0	0	1	0
Cyst in liver tissue	0	0	0	2
Stomach/small intestine (nearly) empty	0	1	3	0

FOOD CONSUMPTION (G)

Group: Control (0 mg/kg) SXX 0665 Study No.: T9037397

Animal No.	Day p.c. 0-6	6-10	10-14	14-19	19-24	24-29	0-29
751	408	178	59	24	186	403	1258
752	513	361	320	238	374	291	2097
754	399	217	194	265	287	257	1619
757	339	196	230	346	338	387	1836
758	440	206	185	166	277	403	1677
760	353	66	43	38	210	369	1079
762	413	288	316	337	391	450	2195
773	363	199	173	66	178	235	1214
780	440	272	251	379	349	310	2001
783	381	262	271	326	335	408	1983
785	409	293	272	282	369	502	2127
790	350	273	288	343	396	470	2120
793	586	317	178	216	415	397	2109
794	393	249	207	285	436	388	1958
797	502	228	231	100	251	447	1759
sum	6289	3605	3218	3411	4792	5717	27032
g/animal	419	240	214	227	319	381	1802
g/animal/day	70	60	54	45	64	76	62

FOOD CONSUMPTION (G)

Group: 2 mg/kg | SXX 0665 | Study No.: T9037397

Animal No.	Day p.c. 0-6	6-10	10-14	14-19	19-24	24-29	0-29
753 *	372	230	263	186	375	392	1818
761	418	279	311	372	373	384	2137
764	367	246	170	167	334	388	1672
766	355	174	134	35	149	310	1157
770	514	314	274	373	354	401	2230
771	291	148	88	189	335	411	1462
775	397	216	133	49	43	194	1032
786	505	288	269	365	400	375	2202
795	379	226	259	321	313	353	1851
798	415	259	254	336	355	507	2126
801	463	353	258	416	484	519	2493
802	341	165	125	152	310	295	1388
808	405	283	257	353	412	468	2178
809	525	313	278	304	344	287	2051
810	358	240	199	191	300	346	1634
sum	5733	3504	3009	3623	4506	5238	25613
g/animal	410	250	215	259	322	374	1830
g/animal/day	68	63	54	52	64	75	63

* not used for calculations, not pregnant

FOOD CONSUMPTION (G)

Group: 10 mg/kg SXX 0665 Study No.: T 9037397

Animal No.	Day p.c. 0-6	6-10	10-14	14-19	19-24	24-29	0-29
765	387	276	226	276	395	385	1945
768	215	46	30	80	141	212	724
772	392	206	145	190	102	198	1233
778	417	192	193	234	375	423	1834
788	467	201	280	413	379	315	2055
789	421	309	258	208	218	352	1766
791	426	243	244	360	407	477	2157
796	515	282	258	154	360	450	2019
799	517	232	281	339	386	270	2025
800	283	139	230	177	165	212	1206
803	424	251	307	374	421	400	2177
804	437	187	166	199	343	341	1673
805	372	245	244	319	340	332	1852
807*	333	200	151	209	277	296	1466
sum	5273	2809	2862	3323	4032	4367	22666
g/animal	406	216	220	256	310	336	1744
g/animal/day	68	54	55	51	62	67	60

*not used for calculation - not pregnant

FOOD CONSUMPTION (G)

Group: 50 mg/kg SXX 0665 Study No.: T9037397

Animal No.	Day p.c. 0-6	6-10	10-14	14-19	19-24	24-29	0-29
755	393	268	210	257	342	463	1933
756	409	247	224	145	282	341	1648
759	332	151	156	118	211	334	1302
763	408	217	227	275	349	409	1885
767	553	370	327	397	437	406	2510
774	453	48	72	5	12	189	779
776	421	116	117	74	188	192	1108
777*	432	205	239	264	219	313	1672
779*	333	155	213	252	281	315	1549
781	381	271	188	241	288	386	1755
782	337	261	198	200	309	376	1681
787	372	212	161	308	281	418	1752
sum	4059	2161	1880	2020	2699	3514	16353
g/animal	406	216	188	202	270	351	1635
g/animal/day	68	54	47	40	54	70	56

* not used for calculation - not pregnant

Food Consumption during Pregnancy

Mean Values (g/animal/day)

Dose mg/kg	n		p.c. Day 0-6	6-10	10-14	14-19	19-24	24-29	0-29
0	15	$\bar{x}$	70	60	54	45	64	76	62
		SD	11.44	17.41	20.40	24.11	16.73	15.46	12.59
2	14	$\bar{x}$	68	63	54	52	64	75	63
		SD	11.66	15.09	17.87	25.18	21.80	17.67	15.32
10	13	$\bar{x}$	68	54	55	51	62	67	60
		SD	13.88	17.11	18.32	19.89	22.32	18.42	14.98
50	10	$\bar{x}$	68	54	47	40	54	70	56
		SD	10.58	22.81	17.27	23.54	22.92	18.52	16.54

BODY WEIGHT (G)

Group: Control SXX 0665 T9037397

Animal No.	Gestation day 0	6	7	8	9	10	11	12	13	14	15	16	17	18	29
751	3404	3294	3291	3270	3249	3245	3224	3204	3204	3188	3197	3147	3117	3130	3327
752	2546	2693	2678	2670	2708	2747	2724	2759	2727	2733	2717	2740	2747	2738	2785
754	2782	2780	2764	2757	2748	2733	2723	2715	2715	2736	2718	2731	2735	2726	2706
757	2508	2456	2480	2457	2470	2465	2443	2477	2472	2469	2466	2468	2515	2517	2615
758	2841	2809	2797	2778	2785	2772	2771	2777	2788	2772	2776	2779	2779	2770	2905
760	2942	2869	2840	2796	2798	2778	2777	2739	2746	2740	2723	2713	2687	2675	2799
762	2634	2743	2738	2732	2730	2748	2731	2758	2777	2800	2806	2841	2850	2890	3092
773	3029	2994	2986	2999	2969	2982	2988	2985	2982	3006	2983	2997	2973	2973	2960
780	2852	2811	2781	2797	2779	2769	2769	2756	2761	2778	2770	2760	2774	2801	2734
783	2462	2476	2481	2480	2443	2501	2467	2469	2484	2503	2541	2561	2546	2562	2742
785	2549	2494	2542	2505	2501	2505	2518	2538	2537	2549	2556	2551	2569	2558	2704
790	2282	2287	2317	2321	2331	2330	2338	2334	2351	2380	2399	2415	2418	2428	2531
793	3095	3089	3105	3084	3085	3106	3046	3027	3012	2991	2971	2972	2979	2989	3119
794	2561	2566	2566	2577	2553	2532	2511	2545	2548	2538	2580	2627	2633	2640	2836
797	2824	2847	2848	2807	2839	2815	2773	2775	2793	2782	2833	2783	2817	2796	2936
N :	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mean :	2754.1	2747.2	2747.6	2735.3	2732.5	2735.2	2720.2	2723.9	2726.5	2731.0	2735.7	2739.0	2742.6	2746.2	2852.7
SD :	290.1	264.6	255.0	251.9	249.0	247.2	241.2	230.6	226.7	220.0	211.8	200.1	190.8	193.5	209.1

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BODY WEIGHT (G)

Group: 2 mg/kg

SXX 0665

T9037397

Animal No.	Gestation day 0	6	7	8	9	10	11	12	13	14	15	16	17	18	29
753*	2837	2790	2759	2777	2755	2766	2744	2723	2711	2707	2703	2646	2594	2564	2666
761	2826	2799	2800	2813	2790	2791	2792	2782	2807	2828	2846	2839	2833	2842	2716
764	2911	2855	2840	2835	2838	2838	2823	2829	2844	2844	2827	2821	2796	2822	2990
766	3105	3071	3067	3067	3066	3052	3050	3036	3040	3032	3039	3011	2990	2990	3091
770	3183	3233	3208	3258	3200	3183	3202	3175	3186	3216	3233	3229	3266	3240	3300
771	2904	2795	2756	2766	2752	2773	2748	2738	2747	2757	2760	2754	2727	2733	2916
775	3212	3176	3176	3181	3176	3170	3165	3164	3158	3143	3147	3133	3101	3100	3056
786	2685	2668	2663	2676	2667	2667	2654	2660	2676	2679	2698	2712	2699	2703	2775
795	2759	2638	2621	2619	2642	2621	2607	2597	2596	2613	2608	2609	2595	2598	2597
798	2454	2465	2485	2470	2481	2473	2462	2514	2498	2515	2537	2571	2542	2530	2721
801	2388	2513	2516	2489	2497	2500	2502	2547	2552	2594	2641	2656	2694	2659	2948
802	2733	2668	2653	2639	2620	2610	2616	2609	2599	2616	2612	2606	2609	2613	2807
808	2155	2164	2158	2171	2196	2184	2212	2208	2201	2228	2237	2291	2260	2251	2558
809	2880	2845	2831	2831	2815	2823	2833	2788	2802	2839	2843	2837	2838	2864	2906
810	2749	2733	2684	2685	2675	2680	2698	2676	2683	2683	2689	2685	2677	2661	2834
N :	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean :	2781.7	2758.8	2747.0	2750.0	2743.9	2740.4	2740.3	2737.4	2742.1	2756.2	2765.5	2768.1	2759.1	2757.6	2872.5
SD :	299.0	284.0	280.4	288.7	274.7	274.1	272.2	261.4	265.3	259.0	257.4	241.5	248.3	248.7	200.8

* not used for calculation - not pregnant

BODY WEIGHT (G)

Group: 10 mg/kg

SXX 0665

T9037397

Animal No.	Gestation day 0	6	7	8	9	10	11	12	13	14	15	16	17	18	29
765	2760	2753	2752	2762	2770	2755	2754	2769	2770	2783	2828	2819	2826	2870	2951
768	2986	2890	2857	2823	2819	2828	2836	2810	2820	2839	2800	2785	2797	2785	2742
772	2836	2838	2821	2816	2796	2784	2785	2770	2777	2779	2783	2793	2795	2790	2732
778	2527	2556	2546	2539	2543	2546	2531	2531	2560	2580	2609	2636	2634	2639	2804
788	2224	2245	2253	2263	2168	2167	2172	2184	2218	2239	2255	2305	2330	2293	2321
789	2695	2697	2688	2686	2707	2702	2710	2703	2723	2742	2725	2721	2716	2724	2892
791	2241	2314	2305	2293	2295	2280	2292	2289	2301	2322	2355	2372	2347	2357	2561
796	2574	2613	2601	2614	2615	2604	2593	2604	2605	2626	2607	2595	2635	2593	2847
799	3024	2986	2979	2958	2944	2930	2928	2935	2928	2940	2940	2921	2947	2952	2969
800	2705	2639	2633	2625	2602	2591	2604	2609	2615	2623	2638	2642	2655	2634	2649
803	2699	2787	2729	2751	2721	2754	2746	2761	2805	2791	2847	2850	2865	2888	3092
804	2535	2551	2533	2514	2494	2517	2512	2536	2539	2535	2537	2585	2548	2562	2713
805	2480	2465	2472	2448	2401	2418	2415	2416	2406	2401	2417	2413	2408	2412	2428
806##	2018	2132	2098	2062	2043	2073	2077	2068	2098	2077	2085	2079	2094	2089	2268
807*	2671	2667	2663	2662	2651	2570	2581	2540	2523	2526	2531	2519	2540	2513	2443
N :	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean :	2637.4	2641.1	2628.4	2622.5	2605.8	2605.8	2606.0	2609.0	2620.5	2630.8	2641.6	2649.0	2654.1	2653.8	2746.2
SD :	244.4	217.5	209.7	207.6	222.3	220.9	219.7	216.4	213.4	211.3	206.8	192.7	199.1	208.3	218.5

* not used for calculation - not pregnant
\## - uterusanomaly

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BODY WEIGHT (G)

Group: 50 mg/kg SXX 0665 T9037397

Animal No.	Gestation day 0	6	7	8	9	10	11	12	13	14	15	16	17	18	29
755	2620	2628	2635	2649	2644	2623	2631	2648	2650	2686	2679	2693	2703	2754	2939
756	2703	2685	2681	2662	2687	2674	2671	2697	2690	2669	2634	2597	2630	2635	2754
759	2857	2828	2845	2823	2789	2766	2808	2784	2780	2797	2806	2781	2774	2772	2855
763	2875	2860	2843	2831	2812	2807	2804	2799	2820	2815	2805	2820	2814	2825	2872
767	2986	3058	3059	3046	3024	3017	3008	3003	3000	3000	3004	3007	3003	3018	3004
769##	2596	2640	2623	2609	2590	2569	2588	2568	2567	2579	2597	2584	2597	2593	2686
774	3589	3522	3494	3468	3454	3462	3429	3421	3408	3409	3438	3403	3357	3350	3261
776	3307	3268	3261	3228	3209	3206	3191	3194	3182	3181	3181	3158	3161	3126	3038
777*	3339	3269	3252	3260	3244	3259	3253	3241	3222	3202	3172	3171	3172	3175	3185
779*	2926	2896	2884	2878	2854	2860	2870	2858	2840	2852	2833	2812	2804	2787	2759
781	2811	2733	2742	2703	2696	2669	2675	2676	2667	2685	2687	2694	2703	2688	2702
782	2799	2717	2712	2697	2713	2721	2713	2704	2695	2729	2720	2755	2725	2735	2714
784##	2543	2536	2467	2531	2396	2415	2388	2421	2394	2405	2398	2419	2436	2436	2516
787	2417	2383	2360	2332	2371	2348	2375	2352	2365	2386	2380	2410	2406	2411	2591
792##	2509	2457	2453	2443	2417	2430	2383	2373	2370	2355	2347	2355	2336	2327	2324
N :	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean :	2896.4	2867.4	2863.2	2843.9	2839.9	2829.3	2830.5	2827.8	2825.7	2835.7	2833.4	2831.8	2827.6	2831.4	2873.0
SD :	336.4	332.8	328.5	325.4	310.7	319.3	304.0	304.3	298.6	291.2	301.9	287.4	275.6	267.8	196.6

* not used for calculation - not pregnant
\## - uterusanomaly

Body Weight Gain (corrected) during Pregnancy (Day 0 - 29 p.c.)

Individual Values and Means

0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg	
Animal no.	B.w.g. g	Animal no.	B.w.g. g	Animal no.	B.w.g. g	Animal no.	B.w.g. g
751	-609	753*	-191	765	-166	755	-110
752	+ 11	761	-390	768	-406	756	-280
754	-172	764	-329	772	-299	759	-324
757	-197	766	-282	778	- 93	763	-141
758	-285	770	- 99	788	- 92	767	- 70
760	-371	771	-387	789	-256	769**	----
762	+ 59	775	-479	791	- 3	774	-572
773	-395	786	-136	796	-140	776	-372
780	-201	795	-312	799	-310	777*	-189
783	-187	798	-135	800	-344	779*	-193
785	-146	801	+ 53	803	-175	781	-302
790	- 13	802	-415	804	-219	782	-241
793	-326	808	- 22	805	-136	784**	----
794	- 81	809	-320	806**	----	787	-220
797	-315	810	-294	807*	-247	792**	----
n	15		14		13		10
$\bar{x}$	-215.2		-253.4		-203.0		-263.2
SD	175.67		159.00		115.42		145.59

* not used for calculation - not pregnant (no viable fetuses)

** not used for calculation - uterusanomaly

Liver Weights

Individual Values and Means

0 mg/kg Anim. no.	0 mg/kg L.w. g	2 mg/kg Anim. no.	2 mg/kg L.w. g	10 mg/kg Anim. no.	10 mg/kg L.w. g	50 mg/kg Anim. no.	50 mg/kg L.w. g
751	69.05	753	61.46	765	48.96	755	57.16
752	57.37	761	55.41	768	47.84	756	51.39
754	58.68	764	59.27	772	46.23	759	58.67
757	57.37	766	46.11	778	54.36	763	61.07
758	51.11	770	67.80	788	45.48	767	69.42
760	61.96	771	66.65	789	51.42	774	108.41+
762	59.11	775	52.67	791	52.23	776	63.71
773	49.68	786	78.13	796	55.66	777	51.89
780	52.05	795	59.41	799	63.77	779	44.72
783	44.88	798	47.83	800	45.02	781	63.07
785	64.17	801	67.29	803	60.92	782	53.23
790	52.47	802	47.62	804	44.98	787	49.36
793	71.99	808	45.20	805	49.78		
794	56.57	809	53.34	807	51.68		
797	58.77	810	48.73				
n	15		15		14		11
$\bar{x}$	57.68		57.13		51.31*		56.70
SD	7.22		9.73		5.79		7.31

\+ not used for calculation

* significant difference to Control

TEST ARTICLE	: SXX 0665	PATHOL. NO.	: 03507 RIN
TEST SYSTEM	: RABBIT, EMBRYOTOX., P.O.	DATE	: 06 AUG 91
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Prepared by : Dr. M. Rinke, Pathologist

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AUTHENTICATION

I certify that I am the author of this report.

Dr. M. Rinke
Pathologist

Data reviewed by:

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SEE PAGE 185 FOR SIGNATURE

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SUMMARY

Oral administration of SXX 0665 to female rabbits at doses of 0, 2, 10 or 50 mg/kg in a study for embryotoxic effects led to morphologically evident alterations in the histologically inspected livers of animals in the mid and high dose groups. These were manifested by slight glycogen mobilization and an elevated incidence of cellular scavenging clusters that are interpreted as an expression of the fact that increased destruction of individual hepatocytes took place.

All other findings listed in this report are considered spontaneous in nature. From the viewpoint of the pathology, the 2 mg/kg dose of SXX 0665 was tolerated without adverse effects on the liver.

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METHODS

The experimental animals for the present histologic investigation were 60 female rabbits of the strain CHBB : HM from Dr. Karl Thomae GmbH breeders in Biberach; these had received SXX 0665 at doses of 0, 2, 10 or 50 mg/kg in a study for embryotoxic effects following oral administration. Group definitions 01 - 04 were assigned to the four dose groups for the histopathologic investigation.

All animals were sacrificed on the 11th day after the final treatment (p.c. day 29), and examined for gross pathology in connection with cesarian section. Four animals (no. 806 in group 03 and nos. 769, 784 and 792 in group 04) were eliminated from the study due to uterine anomalies.

Only the liver of all 56 dams was fixed in 10 % aqueous formaldehyde and subsequently embedded in Paraplast. Sections approx. 5 µm thick were prepared from these, and stained with hemalum-eosin (HE).

The communicated macroscopic findings were entered off-line, and the results of the histologic investigation on-line into the PATHDATA computer program.

The specimens are registered at the BAYER AG Institute of Toxicologic Pathology under the running pathology number 3507.

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RESULTS

1. MACROSCOPIC FINDINGS

Cysts on the oviducts were observed at necropsy of multiple animals from all groups (animal nos. 780, 794 and 797 in group 01; nos. 775 and 798 in group 02; nos. 765, 778, 796, 800 and 803 in group 03; and nos. 763, 774, 776, 779 and 781 in group 04), and a cyst on the left ovary in one animal (no. 753, group 02). The stomach and small intestine were nearly empty at necropsy of animal no. 786 (group 02), only the stomach of animal nos. 789 and 803 from group 03, and only the small intestine of animal no. 799 from the same group. These organs were not subjected to histologic inspection.

Implantation sites in the uterus, but no viable fetuses were present in one animal each in groups 02 and 03, and in two group 04 animals (animal nos. 753, 807, 777 and 779).

Marked lobulation of the liver was seen in one animal in group 01 (no. 780), 02 (no. 764) and 04 (no. 774), as well as in three group 03 animals (nos. 765, 778 and 789). In the latter animal no. 789, the liver was also strikingly pale. Cysts in the liver tissue were observed at necropsy of two group 04 animals (nos. 776 and 779).

2. HISTOLOGIC FINDINGS

Histologic inspection showed a range of liver findings that are partly attributable to the treatment, but probably developed spontaneously in most cases. Thus, an optically denser cytoplasm of the hepatocytes manifested by enhanced stainability of the liver cells was found in the animals treated with SXX 0665 at 10 mg/kg and 50 mg/kg (groups 03 and 04) relative to the controls and the group 02 (2 mg/kg) animals. This relatively commonly affected the periportal cells that otherwise exhibited a rather honeycombed appearance. Two high-dose animals (nos. 763 and 777) also exhibited low-grade centrilobular hepatocellular hypertrophy. A higher incidence and greater intensity of focal round-cell infiltrations, most of which represented nodular Kupffer's cell proliferations (cellular scavenging clusters), were similarly observed in the mid and upper dose group animals (9/14 animals in group 03 and 8/12 in group 04) than in the animals of groups 01 and 02.

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RESULTS

Partly diffuse, partly limited to the lobular periphery, mainly large-droplet vacuolization of liver cells was found distributed relatively homogeneously throughout all the groups. It is highly probable that this represented fatty inclusions. In two animals, this finding was of high (animal 775, group 02) or extreme (animal 774, group 04) intensity. Focal accumulations of large, optically void cells located in the parenchyma were found in isolated animals, and were termed fatty cell foci. In addition to the group 04 (50 mg/kg) animals 776 and 779 already found macroscopically exceptional because of cysts, a further animal from group 02 (no. 753, 2 mg/kg) exhibited a medium-grade cyst. These cysts were lined with endothelial tissue and filled with a honeycombed-cloudy fluid. Their location was nearly exclusively subcapsular.

Periportal, in some cases very marked round-cell infiltrations were found in multiple animals, and were similarly distributed nearly homogeneously throughout all groups. Isolated focal necroses were found in two control group animals, and in one animal from each of the dose groups. In some cases, these focal necroses were accompanied by giant cells and/or (pseudo) eosinophilic granulocytes and hemorrhages. One animal in each of the groups 01, 02 and 03 exhibited dirty yellow perivascular pigments, and one dose group 02 animal (no. 795) displayed high-intensity deposits of a brown-yellow pigment occurring in both the lobular periphery (portal fields and interstices) and the liver cells themselves. It was striking that this pigmentation occurred immediately next to completely unexceptional tissues within a lobe of the liver.

Finally, three animals stood out as a result of the reduced stainability of the hepatocytes and their plant cell-like structure (nos. 793, group 01; 786, group 02; and 799, group 03); bile duct proliferation of very low intensity was found in one animal (no. 791, group 03).

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CONCLUSIONS

Histologic inspections of the livers from 56 female rabbits that had been treated with SXX 0665 at doses of 0, 2, 10 or 50 mg/kg in a study for possible embryotoxic effects showed morphologic alterations attributable to the substance in the animals of the mid and upper dose groups.

On the one hand, these represented an optically denser cytoplasm of the hepatocytes that most likely resulted from a reduced intracellular glycogen level and occurred in 7/14 animals of group 03 (10 mg/kg) and 9/12 animals of group 04 (50 mg/kg). This finding was also made in non-pregnant animals of both groups, whereas the liver of a non-pregnant group 02 animal was unexceptional with respect to the stainability. As an expression of enhanced liver function, two high-dose group animals exhibited slight hepatocellular hypertrophy.

On the other, focal infiltration with round cells was similarly observed in the animals of groups 03 and 04 (in 9/14 and 8/12 animals respectively) at a higher incidence than in the control group and group 02 (in 4/15 and 5/15 animals respectively). This primarily represented nodular Kupffer's cell proliferation, and is considered evidence for scavenging activity due to increased cell destruction. In contrast, fresh single-cell necroses were not observed. However, these would not be expected either, since eleven days had elapsed between the time treatment was concluded and sacrifice of the dams.

The vacuolation of liver cells homogeneously distributed throughout all groups is an expression of substance-independent, pregnancy-determined steatosis; this finding was not observed in the four non-pregnant animals. The liver steatosis of high/extreme intensity in one animal in each of the groups 02 (2 mg/kg) and 04 (50 mg/kg) is an expression of the condition termed gestation hepatosis or gestation toxosis, and is a familiar spontaneous alteration in rabbits.

As in the case of the cysts observed macroscopically in two animals and histologically in one further animal, that presumably represent extended lymph passages in the superficial lymph network of the organic capsule, the fatty cell foci are considered treatment-independent spontaneous alterations. The periportal round cell infiltrations, in some cases of quite high intensity, are familiar from other studies, and are attributable to the encaphalitozoonosis that is widespread in rabbit populations.

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CONCLUSIONS

The focal necroses and pigmentations observed in isolated cases, and the enhanced glycogen storage manifested by decreased stainability of the hepatocytes seen in three animals, are similarly considered alterations within the normal range, and are familiar from studies with animals of the same age and origin.

From the viewpoint of the pathology, the 2 mg/kg dose of SXX 0665 was tolerated by pregnant rabbits without adverse effects on the liver.

END OF REPORT SECTION

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KEY TO ABBREVIATIONS

Key to Abbreviations - **Animal related**

F = Female animal
K0 = Sacrifice at study termination
n<10 = Base smaller than 10, no percentage calculated

Key to Abbreviations - **Organ related**

G = Macroscopic finding histologically examined
! = Macroscopic finding not histologically examined
' = Histological examination unnecessary
+ = Organ examined, findings present
- = Organ examined, no pathological findings

Key to Abbreviations - **Findings related**

Grade 1 = Minimal / very few / very small
Grade 2 = Slight / few / small
Grade 3 = Moderate / moderate number / medium size
Grade 4 = Severe / many / large
Grade 5 = Extremely severe / extremely many / extremely large
* = Comment in individual animal sheet

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INCIDENCE AND INTENSITIES OF NON-NEOPLASTIC ALTERATIONS BY ORGAN/GROUP/SEX
NECROPSY STATUS: K0

Organ/Finding	Sex	:					Female
	Dose group	:	01	02	03	04	
	Number of animals	:	15	15	14	12	
Liver	Examined	:	15	15	14	12	
- Enhanced stainability		:	3	4	7	9	
	Percent affected	:	20	27	50	75	
	Average grade	:	1.3	1.3	1.6	1.9	
- Liver cell hypertrophy		:				2	
	Percent affected	:				17	
	Average grade	:				1.5	
- Focal round-cell infiltration		:	4	5	9	8	
	Percent affected	:	27	33	64	67	
	Average grade	:	1.3	1.0	1.4	1.5	
- Hepatocellular vacuolation		:	7	5	7	5	
	Percent affected	:	47	33	50	42	
	Average grade	:	1.6	2.0	1.9	2.2	
- Fatty cell focus		:	1	5	1	2	
	Percent affected	:	7	33	7	17	
	Average grade	:	1.0	1.0	1.0	1.0	
- Cyst(s)		:		1		2	
	Percent affected	:		7		17	
	Average grade	:		3.0		1.5	
- Periportal round-cell infiltration		:	6	7	8	7	
	Percent affected	:	40	47	57	58	
	Average grade	:	1.5	1.7	2.0	1.3	
- Focal necrosis(es)		:	2	1	1	1	
	Percent affected	:	13	7	7	8	
	Average grade	:	1.0	1.0	2.0	2.0	
- Focal bile duct proliferation		:			1		
	Percent affected	:			7		
	Average grade	:			1.0		

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INCIDENCE AND INTENSITIES OF NON-NEOPLASTIC ALTERATIONS BY ORGAN/GROUP/SEX
NECROPSY STATUS: K0

Organ/Finding	Sex	:					Female
	Dose group	:	01	02	03	04	
	Number of animals	:	15	15	14	12	
- Perivascular pigments		:	1	1	1		
	Percent affected	:	7	7	7		
	Average grade	:	1.0	1.0	2.0		
- Pigmentation		:		1			
	Percent affected	:		7			
	Average grade	:		4.0			
- Reduced stainability		:	1	1	1		
	Percent affected	:	7	7	7		
	Average grade	:	1.0	3.0	3.0		

END OF REPORT SECTION

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

Animal number :

	751 FK0	752 FK0	754 FK0	757 FK0	758 FK0	760 FK0	762 FK0	773 FK0	780 FK0	783 FK0
Liver	+	+	+	+	-	+	+	+	+G	+
- Enhanced stainability	.	1.	.	.	.	.	.	.	2*	.
- Focal round-cell infiltration	1.	.	1.	1.	.	.	.	.	2.	.
- Hepatocellular vacuolation	3.	.	1.	.	.	1.	.	2.	.	2.
- Periportal round-cell infiltration	.	1.	.	3.	.	.	1.	1.	1.	.
- Focal necrosis(es)	.	.	1*	1.	.	.	.	.	.	.
- Perivascular pigments	.	.	.	1.	.	.	.	.	.	.
Oviducts	'	'	'	'	'	'	'	'	'	'
Ovaries	'	'	'	'	'	'	'	'	'	'
Stomach	'	'	'	'	'	'	'	'	'	'
Small intestine	'	'	'	'	'	'	'	'	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

Animal number :	785 FK0	790 FK0	793 FK0	794 FK0	797 FK0
Liver	+	+	+	+	+
- Enhanced stainability	1.	.	.	.	.
- Hepatocellular vacuolation	.	.	1.	.	1.
- Fatty cell focus	.	1.	.	.	.
- Periportal round-cell infiltration	.	.	.	2.	.
- Reduced stainability	.	.	1.	.	.
Oviducts	'	'	'	'!	'!
Ovaries	'	'	'	'	'
Stomach	'	'	'	'	'
Small intestine	'	'	'	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

Animal number :

	753 FK0	761 FK0	764 FK0	766 FK0	770 FK0	771 FK0	775 FK0	786 FK0	795 FK0	798 FK0
Liver	+	+	+G	+	+	+	+	+	+	+
- Enhanced stainability	.	1.	.	.	.	.	.	.	.	.
- Focal round-cell infiltration	.	.	1.	.	.	1.	.	.	.	1.
- Hepatocellular vacuolation	.	1.	.	2.	.	.	4.	.	.	.
- Fatty cell focus	1.	.	.	.	.	1.	.	1.	.	1.
- Cyst(s)	3.	.	.	.	.	.	.	.	.	.
- Periportal round-cell infiltration	.	1.	.	2.	1.	2.	1.	.	2.	.
- Pigmentation	.	.	.	.	.	.	.	.	4*	.
- Reduced stainability	.	.	.	.	.	.	.	3.	.	.
Oviducts	'	'	'	'	'	'	'!	'	'	'!
Ovaries	'!	'	'	'	'	'	'	'	'	'
Stomach	'	'	'	'	'	'	'	'!	'	'
Small intestine	'	'	'	'	'	'	'	'!	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

Animal number :

	801 FK0	802 FK0	808 FK0	809 FK0	810 FK0
Liver	-	+	+	+	+
- Enhanced stainability	.	1.	2.	.	1.
- Focal round-cell infiltration	.	.	1.	1.	.
- Hepatocellular vacuolation	.	2.	.	1.	.
- Fatty cell focus	.	.	.	1.	.
- Periportal round-cell infiltration	.	.	3.	.	.
- Focal necrosis(es)	.	.	1.	.	.
- Perivascular pigments	.	.	.	.	1.
Oviducts	,	,	,	,	,
Ovaries	,	,	,	,	,
Stomach	,	,	,	,	,
Small intestine	,	,	,	,	,

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

Animal number :

	765 FK0	768 FK0	772 FK0	778 FK0	788 FK0	789 FK0	791 FK0	796 FK0	799 FK0	800 FK0
Liver	+G	+	+	+G	+	+G	+	+	+	+
- Enhanced stainability	2*	1.	1.	.	3.	.	1.	.	.	.
- Focal round-cell infiltration	1.	.	1.	2.	2.	.	3.	1.	.	1.
- Hepatocellular vacuolation	2.	2.	2.	.	.	3.	.	.	1.	2.
- Fatty cell focus	.	.	.	.	.	.	.	.	1.	.
- Periportal round-cell infiltration	.	.	.	2.	3.	.	3.	2.	.	3.
- Focal necrosis(es)	.	.	.	.	.	.	2*	.	.	.
- Focal bile duct proliferation	.	.	.	.	.	.	1.	.	.	.
- Perivascular pigments	.	2.	.	.	.	.	.	.	.	.
- Reduced stainability	.	.	.	.	.	.	.	.	3.	.
Oviducts	'	'	'	'	'	'	'	'	'	'
Ovaries	'	'	'	'	'	'	'	'	'	'
Stomach	'	'	'	'	'	'	'	'	'	'
Small intestine	'	'	'	'	'	'	'	'	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

Animal number :

	803 FK0	804 FK0	805 FK0	807 FK0
Liver	+	+	+	+
- Enhanced stainability	.	.	1*	2.
- Focal round-cell infiltration	.	.	1.	1.
- Hepatocellular vacuolation	1.	.	.	.
- Periportal round-cell infiltration	.	1.	1.	1.
Oviducts	'!	'	'	'
Ovaries	'	'	'	'
Stomach	'!	'	'	'
Small intestine	'	'	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg

Animal number :

	755 FK0	756 FK0	759 FK0	763 FK0	767 FK0	774 FK0	776 FK0	777 FK0	779 FK0	781 FK0
Liver	+	+	+	+	+	+G	+G	+	+G	+
- Enhanced stainability	2.	1.	2*	2.	.	.	2.	2.	2.	.
- Liver cell hypertrophy	.	.	.	2*	.	.	.	1.	.	.
- Focal round-cell infiltration	2.	.	.	2.	2.	1.	.	2.	1.	1.
- Hepatocellular vacuolation	2.	.	2.	.	.	5.	1.	.	.	1.
- Fatty cell focus	.	.	.	.	.	.	.	.	1.	1.
- Cyst(s)	.	.	.	.	.	.	1.	.	2.	.
- Periportal round-cell infiltration	2.	.	.	2.	.	1.	1.	1.	.	.
- Focal necrosis(es)	.	.	.	2.	.	.	.	.	.	.
Oviducts	'	'	'	'!	'	'!	'!	'	'!	'!
Ovaries	'	'	'	'	'	'	'	'	'	'
Stomach	'	'	'	'	'	'	'	'	'	'
Small intestine	'	'	'	'	'	'	'	'	'	'

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg

Animal number :	782 FKO	787 FKO
Liver	+	+
- Enhanced stainability	1.	3.
- Focal round-cell infiltration	.	1.
- Periportal round-cell infiltration	1.	1.
Oviducts	'	'
Ovaries	'	'
Stomach	'	'
Small intestine	'	'

END OF REPORT SECTION

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

ANIMAL DATA
DOSE GROUP : 01, 0 mg/kg

Animal number	Sex M/F	Sacrifice status Scheduled	Sacrifice status Actual	Test days	First and last day in study		Date of necropsy
751	F	K0	K0	30	25-Sep-90	24-Oct-90	24-Oct-90
752	F	K0	K0	30	25-Sep-90	24-Oct-90	24-Oct-90
754	F	K0	K0	30	25-Sep-90	24-Oct-90	24-Oct-90
757	F	K0	K0	30	26-Sep-90	25-Oct-90	25-Oct-90
758	F	K0	K0	30	26-Sep-90	25-Oct-90	25-Oct-90
760	F	K0	K0	30	26-Sep-90	25-Oct-90	25-Oct-90
762	F	K0	K0	30	27-Sep-90	26-Oct-90	26-Oct-90
773	F	K0	K0	30	02-Oct-90	31-Oct-90	31-Oct-90
780	F	K0	K0	30	04-Oct-90	02-Nov-90	02-Nov-90
783	F	K0	K0	30	08-Oct-90	06-Nov-90	06-Nov-90
785	F	K0	K0	30	08-Oct-90	06-Nov-90	06-Nov-90
790	F	K0	K0	30	09-Oct-90	07-Nov-90	07-Nov-90
793	F	K0	K0	30	10-Oct-90	08-Nov-90	08-Nov-90
794	F	K0	K0	30	10-Oct-90	08-Nov-90	08-Nov-90
797	F	K0	K0	30	11-Oct-90	09-Nov-90	09-Nov-90

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 751

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 3

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 752

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 754

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 1
- Focal necrosis(es), Grade 1
  With giant cell participation, infiltration with eosinophilic granulocytes, hemorrhages and pigment-containing macrophages

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 757

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Periportal round-cell infiltration, Grade 3
- Focal necrosis(es), Grade 1
- Perivascular pigment-containing macrophages, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

* Necropsy Status : K0
Days in Study : 30 * Animal no. : 758

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Organ examined, no pathologic findings

* Necropsy Status : K0
Days in Study : 30 * Animal no. : 760

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

* Necropsy Status : K0
Days in Study : 30
* Animal no. : 762

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : K0
Days in Study : 30
* Animal no. : 773

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 2
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 780

* Macroscopic Finding

Liver:
- Marked lobulation
Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
  Particularly periportal
- Focal round-cell infiltration, Grade 2
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 783

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 785

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 790

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Fatty cell focus, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 793

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 1
- Reduced stainability of cytoplasm, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 794

* Macroscopic Finding

Oviduct:
- Cyst on right oviduct

* Microscopic Finding

Liver:
- Periportal round-cell infiltration, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 797

* Macroscopic Finding

Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

ANIMAL DATA
DOSE GROUP : 02, 2 mg/kg

Animal number	Sex M/F	Sacrifice status Scheduled	Sacrifice status Actual	Test days	First and last day in study		Date of necropsy
753	F	K0	K0	30	25-Sep-90	24-Oct-90	24-Oct-90
761	F	K0	K0	30	27-Sep-90	26-Oct-90	26-Oct-90
764	F	K0	K0	30	27-Sep-90	26-Oct-90	26-Oct-90
766	F	K0	K0	30	01-Oct-90	30-Oct-90	30-Oct-90
770	F	K0	K0	30	01-Oct-90	30-Oct-90	30-Oct-90
771	F	K0	K0	30	02-Oct-90	31-Oct-90	31-Oct-90
775	F	K0	K0	30	02-Oct-90	31-Oct-90	31-Oct-90
786	F	K0	K0	30	09-Oct-90	07-Nov-90	07-Nov-90
795	F	K0	K0	30	10-Oct-90	08-Nov-90	08-Nov-90
798	F	K0	K0	30	11-Oct-90	09-Nov-90	09-Nov-90
801	F	K0	K0	30	15-Oct-90	13-Nov-90	13-Nov-90
802	F	K0	K0	30	15-Oct-90	13-Nov-90	13-Nov-90
808	F	K0	K0	30	16-Oct-90	14-Nov-90	14-Nov-90
809	F	K0	K0	30	16-Oct-90	14-Nov-90	14-Nov-90
810	F	K0	K0	30	16-Oct-90	14-Nov-90	14-Nov-90

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 753

* Macroscopic Finding

Ovaries:
- Large cyst on left ovary

* Microscopic Finding

Liver:
- Fatty cell focus, Grade 1
- Fluid-filled cysts with endothelial tissue lining, Grade 3

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 761

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Hepatocellular vacuolation, Grade 1
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 764

* Macroscopic Finding

Liver:
- Marked lobulation

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 766

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 2
- Periportal round-cell infiltration, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 770

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 771

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Fatty cell focus, Grade 1
- Periportal round-cell infiltration, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 775

* Macroscopic Finding

Oviduct:
- Cysts on both oviducts

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 4
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 786

* Macroscopic Finding

Stomach:
- Nearly empty
Small intestine:
- Nearly empty

* Microscopic Finding

Liver:
- Fatty cell focus, Grade 1
- Reduced stainability of cytoplasm, Grade 3

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 795

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Periportal round-cell infiltration, Grade 2
- Pigmentation of liver cells and lobular periphery, Grade 4
  Yellow-brown, extensive with abrupt transition from otherwise unexceptional tissue within a lobe of the liver

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 798

* Macroscopic Finding

Oviduct:
- Cysts on both oviducts

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Fatty cell focus, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 801

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Organ examined, no pathologic findings

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 802

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Hepatocellular vacuolation, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 808

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Focal round-cell infiltration, Grade 1
- Periportal round-cell infiltration, Grade 3
- Focal necrosis(es), Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 809

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 1
- Fatty cell focus, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 2 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 810

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Perivascular pigment-containing macrophages, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

ANIMAL DATA
DOSE GROUP : 03, 10 mg/kg

Animal number	Sex M/F	Sacrifice status Scheduled	Sacrifice status Actual	Test days	First and last day in study		Date of necropsy
765	F	K0	K0	30	27-Sep-90	26-Oct-90	26-Oct-90
768	F	K0	K0	30	01-Oct-90	30-Oct-90	30-Oct-90
772	F	K0	K0	30	02-Oct-90	31-Oct-90	31-Oct-90
778	F	K0	K0	30	04-Oct-90	02-Nov-90	02-Nov-90
788	F	K0	K0	30	09-Oct-90	07-Nov-90	07-Nov-90
789	F	K0	K0	30	09-Oct-90	07-Nov-90	07-Nov-90
791	F	K0	K0	30	10-Oct-90	08-Nov-90	08-Nov-90
796	F	K0	K0	30	11-Oct-90	09-Nov-90	09-Nov-90
799	F	K0	K0	30	11-Oct-90	09-Nov-90	09-Nov-90
800	F	K0	K0	30	11-Oct-90	09-Nov-90	09-Nov-90
803	F	K0	K0	30	15-Oct-90	13-Nov-90	13-Nov-90
804	F	K0	K0	30	15-Oct-90	13-Nov-90	13-Nov-90
805	F	K0	K0	30	15-Oct-90	13-Nov-90	13-Nov-90
807	F	K0	K0	30	16-Oct-90	14-Nov-90	14-Nov-90

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 765

* Macroscopic Finding

Liver:
- Marked lobulation
Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
  Particularly centrilobular
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 2

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 768

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Hepatocellular vacuolation, Grade 2
- Perivascular pigment-containing macrophages, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 772

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 2

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 778

* Macroscopic Finding

Liver:
- Marked lobulation

Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 2
- Periportal round-cell infiltration, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 788

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 3
- Focal round-cell infiltration, Grade 2
- Periportal round-cell infiltration, Grade 3

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 789

* Macroscopic Finding

Liver:
- Marked lobulation, liver pale
Stomach:
- Nearly empty

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 3

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 791

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
- Focal round-cell infiltration, Grade 3
- Periportal round-cell infiltration, Grade 3
- Focal necrosis(es), Grade 2
  Mainly periportal, in some cases with giant cell participation
- Focal bile duct proliferation, Grade 1

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 796

* Macroscopic Finding

Oviduct:
- Cyst on right oviduct

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Periportal round-cell infiltration, Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg FEMALE

* Necropsy Status : KO
Days in Study : 30 * Animal no. : 799

* Macroscopic Finding

Small intestine:
- Nearly empty

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 1
- Fatty cell focus, Grade 1
- Reduced stainability of cytoplasm, Grade 3

* Necropsy Status : KO
Days in Study : 30 * Animal no. : 800

* Macroscopic Finding

Oviduct:
- Cyst on right oviduct

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 2
- Periportal round-cell infiltration, Grade 3

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 803

* Macroscopic Finding

Oviduct:
- Cyst on right oviduct
Stomach:
- Nearly empty

* Microscopic Finding

Liver:
- Hepatocellular vacuolation, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 804

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 10 mg/kg

FEMALE

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 805

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1
  Particularly periportal
- Focal round-cell infiltration, Grade 1
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : K0
Days in Study : 30

* Animal no. : 807

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Focal round-cell infiltration, Grade 1
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

ANIMAL DATA
DOSE GROUP : 04, 50 mg/kg

Animal number	Sex M/F	Sacrifice status Scheduled/Actual		Test days	First and last day in study		Date of necropsy
755	F	K0	K0	30	25-Sep-90	24-Oct-90	24-Oct-90
756	F	K0	K0	30	26-Sep-90	25-Oct-90	25-Oct-90
759	F	K0	K0	30	26-Sep-90	25-Oct-90	25-Oct-90
763	F	K0	K0	30	27-Sep-90	26-Oct-90	26-Oct-90
767	F	K0	K0	30	01-Oct-90	30-Oct-90	30-Oct-90
774	F	K0	K0	30	02-Oct-90	31-Oct-90	31-Oct-90
776	F	K0	K0	30	04-Oct-90	02-Nov-90	02-Nov-90
777	F	K0	K0	30	04-Oct-90	02-Nov-90	02-Nov-90
779	F	K0	K0	30	04-Oct-90	02-Nov-90	02-Nov-90
781	F	K0	K0	30	08-Oct-90	06-Nov-90	06-Nov-90
782	F	K0	K0	30	08-Oct-90	06-Nov-90	06-Nov-90
787	F	K0	K0	30	09-Oct-90	07-Nov-90	07-Nov-90

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg FEMALE

* Necropsy Status : K0
Days in Study : 30 * Animal no. : 755

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Focal round-cell infiltration, Grade 2
- Hepatocellular vacuolation, Grade 2
- Periportal round-cell infiltration, Grade 2

* Necropsy Status : K0
Days in Study : 30 * Animal no. : 756

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg FEMALE

* Necropsy Status : KO
Days in Study : 30 * Animal no. : 759

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
  Particularly periportal
- Hepatocellular vacuolation, Grade 2

* Necropsy Status : KO
Days in Study : 30 * Animal no. : 763

* Macroscopic Finding

Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Liver cell hypertrophy; Grade 2
  With increasing basophilia toward liver cell border
- Focal round-cell infiltration, Grade 2
- Periportal round-cell infiltration, Grade 2
- Focal necrosis(es), Grade 2

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 767

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 2

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 774

* Macroscopic Finding

Liver:
- Marked lobulation
Oviduct:
- Cysts on both oviducts

* Microscopic Finding

Liver:
- Focal round-cell infiltration, Grade 1
- Hepatocellular vacuolation, Grade 5
- Periportal round-cell infiltration, Grade 1

TEST ARTICLE : SXX 0665
TEST SYSTEM : RABBIT, EMBRYOTOX., P.O.
SPONSOR : BAYER AG

PATHOL. NO. : 03507 RIN
DATE : 06 AUG 91
PDS PATHDATA SYSTEM TM

DESCRIPTIONS OF MACROSCOPIC AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 50 mg/kg

FEMALE

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 776

* Macroscopic Finding

Liver:
- Cysts, marked lobulation
Oviduct:
- Cyst on left oviduct

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Hepatocellular vacuolation, Grade 1
- Fluid-filled cysts with endothelial tissue lining, Grade 1
- Periportal round-cell infiltration, Grade 1

* Necropsy Status : KO
Days in Study : 30

* Animal no. : 777

* Macroscopic Finding

All organs without anomalies.

* Microscopic Finding

Liver:
- Enhanced stainability of cytoplasm, Grade 2
- Liver cell hypertrophy, Grade 1
- Focal round-cell infiltration, Grade 2
- Periportal round-cell infiltration, Grade 1