

REPORT

Study of the
Prenatal Toxicity of

UVINUL T 150

in Wistar Rats After Oral Administration
(Gavage)

Project No.: 30R0246/93046

VOLUME I OF III

REPORT SECTION AND SUMMARY TABLES

Testing facility:

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GLP STATEMENT

Title: Report: Study of the Prenatal Toxicity of **UVINUL T**
150 in Wistar Rats After Oral Administration (Gavage)

This study was conducted in accordance with the GLP-provisions of the "Chemikaliengesetz" (Chemicals Act; Bundesgesetzblatt 1990, Teil I, 22.03.90; FR Germany) and with the "OECD Principles of Good Laboratory Practice" (Paris, 1981).

H. W. ... 30. IX 94
.....
(Head of Experimental Toxicology)

... , Sep. 30, 1994
.....
(Study Director)

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STATEMENT
of the Quality Assurance Unit

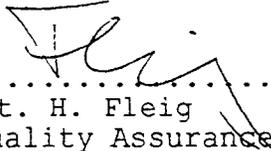
Number of test substance: 93/246
 Name of test substance: UVINUL T 150
 Title: Report: Study of the Prenatal Toxicity of **UVINUL T 150** in Wistar Rats After Oral Administration (Gavage)

The Quality Assurance Unit inspected the study, audited the final report, and reported findings to the Study Director and to Management.

Phase of study/ inspection	Date of inspection	Report to Study Director and to Management
Protocol:	March 10, 1994	April 5, 1994
Conduct of study:	April 5, 1994 April 18, 1994	April 5, 1994 April 18, 1994
Audit of the report:	Sept. 30, 1994	Sept. 30, 1994

Remarks: Analytics were inspected independently by the Quality Assurance Unit of the analytical laboratory.

Ludwigshafen, Sept. 30, 1994



 Dr. rer.nat. H. Fleig
 (Head of Quality Assurance Unit)

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The tables with the individual values/findings are to be found in Volume II. Further information (detailed analytical results and historical control data) is included in Volume III (Supplement).

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A) EXAMINATIONS OF THE DAMS

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- Individual maternal food consumption	A 001 - A 004
- Individual maternal body weights	A 005 - A 008
- Individual maternal body weight change	A 009 - A 012
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- Individual maternal clinical observations	A 017 - A 024
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VOLUME III (Supplement)

1. Analyses of the suspensions of test substance
2. Historical control data

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1. **SUMMARY**

UVINUL T 150 was tested for its prenatal toxicity in Wistar rats. The test substance was administered as an oily suspension to 21 - 24 pregnant female rats/group by stomach tube at dosages of 100; 400 and 1,000 mg/kg body weight on day 6 through day 15 post coitum. A standard dose volume of 5 ml/kg body weight was used. The control group, consisting of 25 dams, was dosed with the vehicle only (olive oil DAB 10).

Food consumption and body weights of the animals were recorded regularly throughout the study period. The state of health of the animals was checked each day.

On day 20 post coitum, all females were sacrificed and assessed by gross pathology (including weight determinations of the liver and the uterus). The fetuses were removed from the uterus, sexed, weighed and further investigated for any external, soft tissue and/or skeletal findings.

There were no substance-related effects on the dams concerning food consumption, body weight, body weight change, absolute and relative liver weights, uterine weights, corrected body weight change, clinical and necropsy observations up to and including a dose of 1,000 mg/kg body weight/day. There were no differences of biological relevance between the control and the substance-treated groups (100, 400 and 1,000 mg/kg body weight/day) in conception rate, mean number of corpora lutea, total implantations, resorptions and live fetuses, fetal sex ratio or in the values calculated for the pre- and the postimplantation losses.

No dose- and/or substance-related differences were recorded for placental and fetal body weights. The external, soft tissue and/or skeletal examination of the fetuses revealed no differences between the control and the substance-treated groups which might be related to the test substance administration. Number and type of the fetal external, soft tissue and skeletal findings, which were classified as malformations, variations and/or retardations, recorded for the 100, 400 and 1,000 mg/kg fetuses were not clearly dose-related and/or substantially similar to concurrent and/or historical control values.

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Thus, under the conditions of this full-scale study, **UVINUL T 150** caused **no signs of maternal toxicity** and **no signs of developmental toxicity** up to and including a dose of 1,000 mg/kg body weight/day; there were **no indications of teratogenic effects** which could be causally related to the test substance administration.

Although no signs of maternal toxicity were found even at the highest dose (1,000 mg/kg body weight/day), no further prenatal toxicity studies in rats with oral administration (gavage) are deemed to be necessary, because this dose is in accordance with the minimum requirement for the **LIMIT TEST**, e.g. in the OECD Guideline for testing of chemicals No. 414 (1981).

For this prenatal toxicity study in Wistar rats, the **no observed adverse effect level (NOAEL)** for the **maternal** and the **fetal organism** is 1,000 mg/kg body weight/day.

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2. INTRODUCTION AND DOSE SELECTION

The purpose of this study was to assess the effects of **UVINUL T 150** on embryonic and fetal development in pregnant Wistar rats. Moreover, information about influences of the test substance on the maternal organism was expected to be obtained.

Since **UVINUL T 150** is absorbed through the gastrointestinal tract, oral administration of **UVINUL T 150** (by gavage) was selected as the route of choice for this prenatal toxicity study.

The selection of doses for the present examination was based on the results of two preceding studies (1a, 1b).

According to the results of the first study (1a), the acute oral toxicity in Sprague-Dawley rats was > 10,000 mg/kg body weight/day.

In a 90-day study (1b) 10 male and 10 female Wistar rats/group received the test substance with the diet in concentrations of 1,000, 4,000 or 16,000 ppm (about 75, 300 or 1,200 mg/kg body weight/day). For comparison 10 untreated animals/sex were used as controls.

Food consumption and body weight were determined each week. The animals' state of health was checked each day. When the animals were weighed they were subjected to an additional comprehensive clinical examination.

At the start of the administration period and towards the end of the study ophthalmological examinations were carried out in the animals of the control and highest dose group.

Clinicochemical and hematological examinations were carried out shortly before the study was terminated.

At the end of the study all animals were subjected to gross-pathological assessment and histopathological examination.

No substance-related findings were obtained in this 90-day study in any of the above mentioned examinations up to and including the highest concentration. Food consumption and body weight development were unaffected. None of the rats showed substance-induced

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clinical findings. The clinicochemical and hematological parameters did not show any relation to treatment and were similar to control values. There were no adverse effects on organ weights, gross pathological or histopathological findings. Thus, no signs of toxicity were found up to a dose level above 1,000 mg/kg body weight/day.

Taking into consideration the results of the two above mentioned studies (1a, 1b), the following doses were fixed for the present full-scale prenatal toxicity study in Wistar rats with **UVINUL T 150**:

100 mg/kg body weight:	as the expected no observed adverse effect level
400 mg/kg body weight:	as the intermediate dose level
1,000 mg/kg body weight:	as the dose level at which 'some overt signs of maternal toxicity' were not expected; testing at higher dose levels (> 1,000 mg/kg body weight/day) were not considered to be necessary due to the recommendations given in the test guidelines mentioned below concerning the limit test.

The study was carried out from March 29, 1994 (beginning of study) to April 20, 1994 (last scheduled sacrifice of the animals) in accordance with the following test guidelines:

- EC Commission Directive 87/302/EEC of Nov. 18, 1987; Part B: Methods for the determination of toxicity: Teratogenicity study (rodent and non-rodent); Official Journal of the European Communities; No. L 133, pp. 24 - 26 (1988)
- OECD Guidelines for Testing of Chemicals; Method No. 414: Teratogenicity (May 1981)

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3. MATERIAL AND METHODS

3.1. TEST SUBSTANCE

Name of
test substance: UVINUL T 150

Test substance No.: 93/246

CAS-No.: 88122-99-0

Batch No.: 08-0083

Date of production: August 3, 1993

Abbreviation
used in the
laboratory: UVIT

Aggregate state/
color: powder/white

Storage conditions: Room temperature; in tightly
sealed container stored in
darkness

Degree of purity: 98.5% (see also 4.1.1.)

Characterization: Further details of the cha-
racterization of the test sub-
stance are included in the raw
data.

Safety precautions: The usual precautions for
handling chemicals.

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3.2. TEST ANIMALS

Sexually mature, virgin Wistar rats (Chbb:THOM (SPF)) supplied by Karl THOMAE, Biberach an der Riss, FRG, which were free from clinical signs of disease, were used for the investigations. This strain was selected since extensive experience is available on Wistar rats and this strain has been proved to be sensitive to substances with a teratogenic potential. The animals were received on March 21, 1994.

After randomization the rats were identified uniquely by ear tattoo. The unit digit of the animal number was tattooed on the outside of a rat's left ear and the ten digit on the inside of the left ear and the hundred digit was tattooed into the right ear.

3.3. HOUSING AND DIET

During the study period, the rats were housed singly in type DK III stainless steel wire mesh cages supplied by BECKER & CO., Castrop-Rauxel, FRG (floor area about 800 cm²).

The cages with the test animals were arranged on the racks in such a way that uniform experimental conditions (ventilation and light) were ensured.

The animals were accommodated in fully air-conditioned rooms in which central air conditioning guaranteed a range of temperature of 20 - 24°C and a range of relative humidity of 30 - 70%. There were no deviations from these limits.

The day/night rhythm was 12 hours (12 hours light from 6.00 to 18.00 hours and 12 hours darkness from 18.00 to 6.00 hours).

Before the study started, the room was completely disinfected using a disinfection apparatus ("AUTEX" fully automatic final disinfecting apparatus using formaldehyde and ammonia). In general, each week the walls and the floor were cleaned with water containing about 0.5% Mikro-Quat (supplied by SCHÜLKE & MAYR GmbH, FRG).

The food used was ground Kliba 343 feed rat/mouse/hamster supplied by KLINGENTALMÜHLE AG, Kaiseraugst, Switzerland, which was available to the animals ad libitum throughout the study (from the day of supply to the day of necropsy), as was drinking water of tap water quality from water bottles.

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3.4. TEST GROUPS AND DOSES

Test group	Dose mg/kg body weight/day	Concen- tration mg/100 ml	Volume ml/kg	Number of ani- mals	Animal No.
0 (white) ²⁾	0	0	5 ³⁾	25	1 - 25
1 (blue) ²⁾	100	2,000	5 ³⁾	25	26 - 50
2 (yellow) ²⁾	400	8,000	5 ³⁾	25	51 - 75
3 (red) ²⁾	1,000	20,000	5 ³⁾	25	76 -100

²⁾ color of cage cards

²⁾ olive oil DAB 10

³⁾ test substance suspensions in olive oil DAB 10

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3.5. ANALYSES

The analytical examinations mentioned below (3.5.1. and 3.5.2.) were carried out at the Analytical Department of BASF Aktiengesellschaft (Dr. P. Schmidt responsible).

3.5.1. Analyses of test substance

Analytical investigations to determine the active ingredient content and the homogeneity of the test substance were carried out before the beginning of the study (methods: e.g. IR spectroscopy, UV spectroscopy and titration (acid value)).

The stability of the test substance over the study period has been proven by reanalysis.

Detailed descriptions of the extent of the analytical investigations and of the analytical methods employed are stored with BASF Aktiengesellschaft.

3.5.2. Analyses of the suspensions of test substance

Analytical verifications of the stability of the test substance suspensions for a period of at least 4 hours at room temperature were carried out before the beginning of this study for a similar batch (No.: 18301/142).

Samples of the test substance suspensions were sent to the analytical laboratory twice during the study period for verification of the concentrations. The samples which were taken for the first concentration control analyses at the beginning of the administration period were also used to verify the homogeneity for the samples of the low and the high concentrations (100 and 1,000 mg/kg body weight/day). 6 samples (2 from the top, middle and bottom in each case) were taken for each of these concentrations from the beaker with a magnetic stirrer running.

The test substance suspensions were analyzed by HPLC.

More details on the methods used for the analytical investigations of the test substance suspensions can be found in Volume III (Supplement: Analyses of the suspensions of the test substance).

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3.5.3. Food analyses

The food used in the study was assayed for chemical as well as for microbiological contaminants.

3.5.4. Drinking water analyses

The drinking water is regularly assayed for chemical contaminants by the municipal authorities of Frankenthal and the Technical Services of BASF Aktiengesellschaft as well as for the presence of microorganisms by a contract laboratory.

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3.6. EXPERIMENTAL PROCEDURE

The female rats were 59 or 70 days old when supplied. After an acclimatization period of at least 5 days, 1-4 untreated female rats were mated with one untreated fertile male animal of the same breed.

Mating took place from about 16.00 hours to about 7.30 hours on the following day. If sperm were detected microscopically in the vaginal smear in the morning, the animals were considered to be fertilized. This day was designated "day 0" (beginning of the study) and the following day "day 1" post coitum (p.c.).

At the beginning of the study (day 0, detection of sperm), the rats were 69 to 80 days old. Their mean weight was approx. 248 g.

On day 0, the animals were assigned to the different test groups according to a randomization plan (2).

The test substance was administered to the animals orally (by gavage) once a day during the period of major organogenesis (day 6 to day 15 p.c.) always at approx. the same time of day (in the morning). The animals of the control group were treated in the same way with the vehicle (olive oil DAB 10). The volume administered each day was 5 ml/kg body weight. The calculation of the volume administered was based on the individual body weight determined at the beginning of the administration period (day 6 p.c.).

On day 20 p.c., all females were sacrificed in a randomized order and the liver and the unopened uterus of each rat were weighed. Subsequently, the animals were examined macroscopically. The fetuses were removed from the uterus and further investigated with different methods (for details see 3.8.).

Each day the test substance suspensions were freshly prepared shortly before the test substance was administered. For the preparation of the suspensions, an appropriate amount of the test substance was weighed and subsequently suspended in olive oil DAB 10 using a high speed sonicator (Ultra Turrax, JANKE & KUNKEL KG, FRG). A magnetic stirrer was used to keep the suspensions homogeneous during treatment of the animals.

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Due to technical reasons, the study was carried out in 2 sections. Each dose group was represented in each section. A treatment interval of 2 days elapsed before the next section. For further details, see Fig. 3.6.1.

Fig. 3.6.1.: Time schedule

	Acclima- tization period	Beginning of study (day 0 p.c.)	Beginning of treat- ment (day 6 p.c.)	End of treatment (day 15 p.c.)	Sacrifice (day 20 p.c.)
1st section	by March 28, 1994	March 29, 1994	April 04, 1994	April 13, 1994	April 18, 1994
2nd section	by March 30, 1994	March 31, 1994	April 06, 1994	April 15, 1994	April 20, 1994

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3.7. EXAMINATIONS OF THE DAMS

3.7.1. Clinical examinations

3.7.1.1. Food consumption

With the exception of day 0, the consumption of food was determined on the same days as was body weight.

3.7.1.2. Body weight data

All animals were weighed on days 0, 1, 3, 6, 8, 10, 13, 15, 17 and 20 p.c. The body weight change of the animals was calculated from these results.

3.7.1.3. Corrected body weight gain (net maternal body weight change)

Furthermore, the corrected body weight gain was calculated after terminal sacrifice (terminal body weight on day 20 p.c. minus weight of the uterus before it was opened minus body weight on day 6 p.c.).

3.7.1.4. Clinical symptoms

The animals were examined for clinical symptoms at least once a day, or more often when clinical signs of toxicity were elicited (days 0 - 20 p.c.).

3.7.1.5. Mortality

A check was made twice a day on working days or once a day (Saturday, Sunday or on public holidays) (days 0 - 20 p.c.).

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3.7.2. Examinations of the dams at termination

On day 20 p.c., the dams were sacrificed in randomized order by cervical dislocation and the fetuses dissected from the uterus.

After the dams had been sacrificed, they were necropsied and assessed by gross pathology. The uterus and the ovaries were removed and the following data were recorded:

- Weight of liver
- Weight of uterus before it was opened
- Number of corpora lutea
- Number and distribution of implantation sites classified as:
 - live fetuses
 - dead implantations:
 - a) early resorptions (only decidual or placental tissues visible or according to SALEWSKI (3) from uteri from apparently non-pregnant animals and the empty uterus horn in the case of single-horn pregnancy)
 - b) late resorptions (embryonic or fetal tissue in addition to placental tissue visible)
 - c) dead fetuses (hypoxemic fetuses which did not breathe spontaneously after the uterus had been opened)

Furthermore, calculations of conception rate and pre- and postimplantation losses were carried out:

- The **conception rate** (in %) was calculated according to the following formula:

$$\frac{\text{number of pregnant animals}}{\text{number of fertilized animals}} \times 100$$

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- The **preimplantation loss** (in %) was calculated* according to the following formula:

$$\frac{\text{number of corpora lutea} - \text{number of implantations}}{\text{number of corpora lutea}} \times 100$$

- The **postimplantation loss** (in %) was calculated* from the following formula:

$$\frac{\text{number of implantations} - \text{number of live fetuses}}{\text{number of implantations}} \times 100$$

* Calculation on the basis of each individual pregnant animal with scheduled sacrifice

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3.8. EXAMINATIONS OF THE FETUSES

3.8.1. Examination of the fetuses after dissection from the uterus

At necropsy each fetus was weighed, sexed and examined macroscopically for any external findings. The sex was determined by observing the distance between the anus and the base of the genital tubercle and was later confirmed in all fetuses fixed in BOUIN'S solution by internal examination. If there were discrepancies between the "external" and the "internal" sex of a fetus, the fetus was finally sexed according to the appearance of its gonads.

Furthermore, the viability of the fetuses and the condition of the placentae, the umbilical cords, the fetal membranes and fluids were examined. Individual placental weights were recorded.

After these examinations, approximately one half of the fetuses of each litter was placed in ethyl alcohol and the other half was placed in BOUIN'S solution for fixation and further evaluation.

3.8.2. Soft tissue examination of the fetuses

After fixation in BOUIN'S solution, approximately one half of the fetuses of each litter was examined for any findings in the organs according to the method of BARROW and TAYLOR (4). After these examinations the relevant fetuses were discarded.

3.8.3. Skeletal examination of the fetuses

After fixation in ethyl alcohol, the skeletons of the remaining fetuses were stained according to a modified method of DAWSON (5). Thereafter, the skeletons of these fetuses were examined under a stereomicroscope. After these examinations the relevant fetuses were retained by litter.

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3.8.4. Evaluation criteria for assessing the fetuses

There are differing opinions on the classification and assessment of changes in fetuses. MÜNTEFERING (6) differentiates between malformations, which he defines as "severe morphological defects outside the range of variation of the species", and macroscopic/microscopic anomalies, which he defines as "slighter morphological deviations from normal". If these changes occur, they are regarded by MÜNTEFERING (6) as a teratogenic effect. However, transition from variation to malformation is fluid, and the term "slighter morphological deviation" is not defined. NEUBERT (7), on the other hand, tends to describe a change as a morphological abnormality, anomaly or functional anomaly instead of malformation since malformation refers primarily to gross-pathological changes.

In the present investigations the following terms (definitions) were used for describing a change:

- **Malformations** (concerning external, soft tissue and skeletal observations)

Rare and/or probably lethal changes were classified as malformations (e.g. exencephaly, atresia ani, hernia umbilicalis).

- **Variations** (concerning external, soft tissue and skeletal observations)

Changes which occur regularly also in control groups and have generally no adverse effect on survival were regarded as variations (e.g. dilated renal pelvis).

- **Retardations** (concerning skeletal observations only)

Delays in skeletal development compared with the norm at the time of the examination were considered to be retardations (e.g. sternebra(e) not ossified).

- **Unclassified observations** (concerning external and soft tissue observations only)

External or soft tissue observations, which could not be classified as malformations or variations (e.g. blood coagulum around placenta).

According to the definitions specified before, the findings obtained in fetuses were classified and listed in the tables accordingly.

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3.9. STATISTICAL EVALUATION

The data were evaluated statistically using the computer systems of the Department of Toxicology of BASF Aktiengesellschaft (laboratory data processing, responsible Dr. H.D. Hoffmann).

3.9.1. Examinations of dams and fetuses

The DUNNETT-Test (8, 9) was used for a simultaneous comparison of several dose groups with the control. The hypothesis of equal means was tested. This test was performed two-sided and was used for the statistical evaluation of the following parameters:

Food consumption*, body weight, body weight change, corrected body weight gain (net maternal body weight change), liver weights (absolute and relative), weight of the uterus before it was opened, number of corpora lutea, number of implantations, number of resorptions and number of live fetuses; proportion of preimplantation loss, postimplantation loss, resorptions and live fetuses in each litter; litter mean fetal body weight and litter mean placental weight.

FISHER's Exact Test (10) was used for a pairwise comparison of each dose group with the control for the hypothesis of equal proportions. This test was performed one-sided and was used for female mortality, females pregnant at terminal sacrifice and the number of litters with fetal findings.

The WILCOXON-Test (11, 12) was used for a comparison of each dose group with the control for the hypothesis of equal medians. This test was performed one-sided and was used for the proportion of fetuses with malformations, variations, retardations and/or unclassified observations in each litter.

If the results of these tests were significant, labels (* for $p < 0.05$, ** for $p \leq 0.01$) were printed in the Summary Tables.

* Note: For the parameter food consumption the "mean of means" was calculated and can be found in the relevant Summary Tables. The "mean of means" values allow a rough estimation of the total food consumption during the different time intervals (pretreatment, treatment and posttreatment period); they are not exactly precise values, because the size of the intervals taken for calculation differs. For the "mean of means" values no statistical analysis was performed.

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3.10. RETENTION OF RECORDS

The study protocol, the raw data, the reserve sample and the specimens, as well as the original of this report, are stored in the archives of BASF Aktiengesellschaft at least for the period of time specified in the GLP regulations. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data. The specimens will be retained as long as the quality of the material allows evaluation.

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4. RESULTS AND ASSESSMENT OF FINDINGS

4.1. ANALYSES

4.1.1. Analyses of test substance

The homogeneity of the test substance was proven. The content of active ingredient was 98.5% before the beginning of the study (analytical report from Dec. 14, 1993). The stability of the test substance over the study period was proven by reanalysis. The relevant results and more details on the analytical methods used are included in the raw data.

4.1.2. Analyses of the suspensions of test substance

The stability of the test substance suspensions over a period of up to 4 hours at room temperature and the homogeneous distribution of the test substance in the vehicle could be demonstrated. The results of the analyses of the suspensions of test substance confirmed the correctness of the prepared concentrations (the maximum deviation was about 6% from the target value).

The relevant analytical reports are included in Volume III (Supplement).

4.1.3. Food analyses

On the basis of the duration of use and the analytical findings with respect to chemical and microbiological contaminants the food was found to be suitable. Fed. Reg. Vol. 44, No. 91 of May 9, 1979, p. 27354 (EPA), served as a guideline for maximum tolerable chemical contaminants. The amount of microorganisms did not exceed 10^5 /g feed.

The individual results are to be found in the archives of the Department of Toxicology.

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4.1.4. Drinking water analyses

On the basis of the analytical findings, the drinking water was found to be suitable. German Drinking Water Regulation (Trinkwasserverordnung, Bundesgesetzblatt December 05, 1990) served as a guideline for maximum tolerable contaminants.

The individual results are to be found in the archives of the Department of Toxicology.

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4.2. EXAMINATIONS OF THE DAMS

The results of this part of the study can be found in the following Summary Tables in the Appendix:

	Tables
Key to the abbreviations, page 37	
Mean maternal food consumption	001 - 002
Mean maternal body weights	003
Mean maternal body weight change	004 - 005
Mean gravid uterine weights and net maternal body weight change	006
Summary of maternal clinical observations	007
Mean absolute maternal organ weights	008
Mean relative maternal organ weights	009
Summary of maternal necropsy observations	010
Summary of reproduction data	011 - 013

The relevant individual values are to be found in Volume II (Tables A 001 - A 040).

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4.2.1. Clinical examinations

Only **pregnant dams** were used for the calculations of mean maternal food consumption, body weight and body weight change. Only **pregnant dams with scheduled sacrifice** (day 20 p.c.) were taken for the calculation of mean absolute and relative liver weights, mean gravid uterine weights, mean net maternal body weight change (corrected body weight gain) and summary of reproduction data.

In this study the following females were partially or totally excluded from the above mentioned calculations:

Test group 0 (Control):
- none

Test group 1 (100 mg/kg body weight/day):
- females Nos. 38, 41, 42 and 50 - not pregnant

Test group 2 (400 mg/kg body weight/day):
- females Nos. 53, 63, 68 and 75 - not pregnant

Test group 3 (1,000 mg/kg body weight/day):
- female No. 97

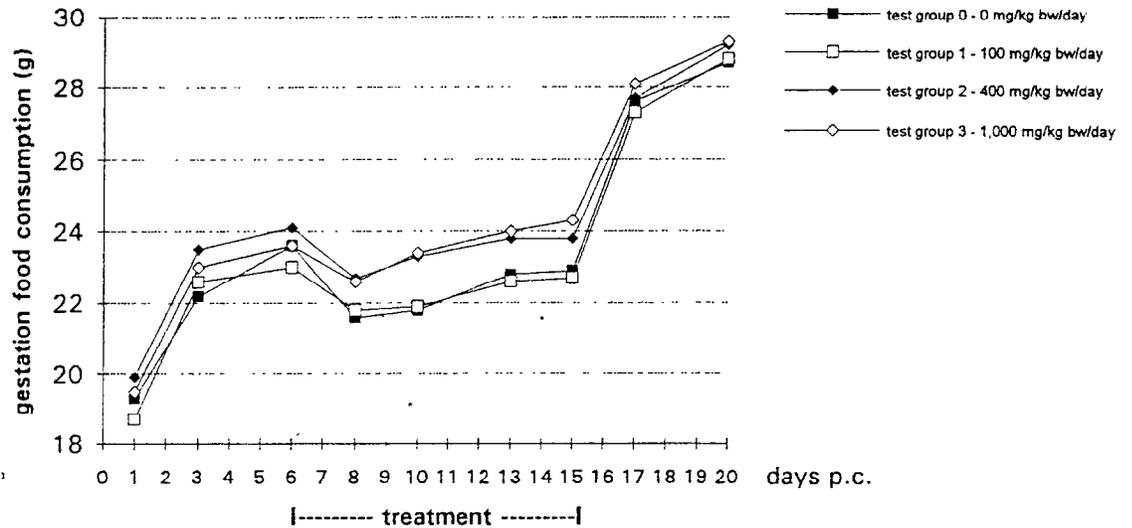
4.2.1.1. Food consumption (Tabs. 001 - 002)

The food consumption of the female rats of test groups 1, 2 and 3 (100, 400 or 1,000 mg/kg body weight/day) did not show any differences of biological relevance if compared to the controls. All food consumption values calculated are within the range of biological variation.

(See also Fig. 4.2.1.1.1.: Mean food consumption (g/animal/day)).

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Fig. 4.2.1.1.1.: Mean food consumption (g/animal/day)



4.2.1.2. Body weight data (Tabs. 003 - 005)

Body weights and body weight gains of the dams of test groups 1, 2 and 3 (100, 400 or 1,000 mg/kg body weight/day) were similar to those of the controls. All observable differences between these groups and the control group are without any biological relevance.

(See also Figs. 4.2.1.2.1. and 4.2.1.2.2.)

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Fig. 4.2.1.2.1.: Mean body weight of pregnant animals

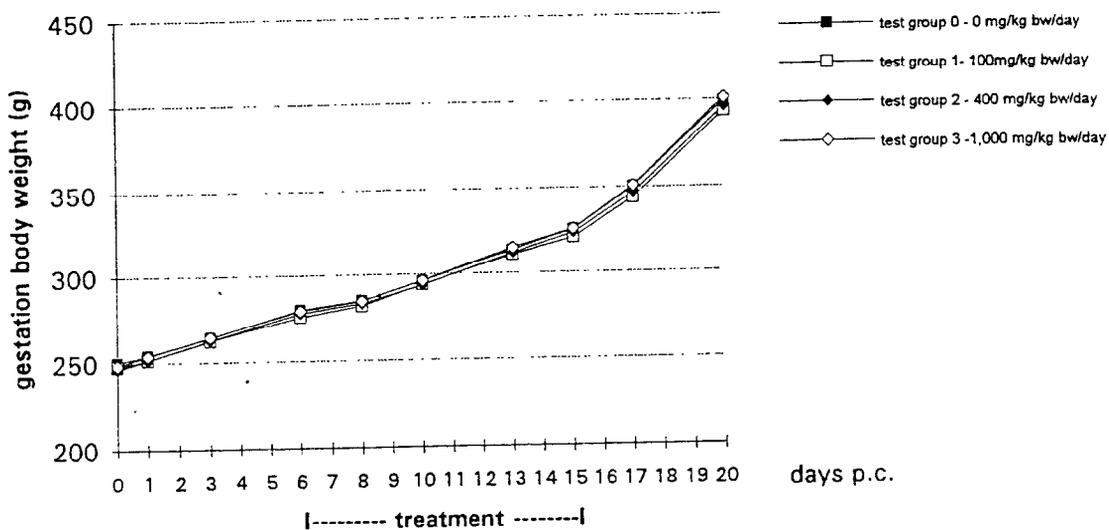
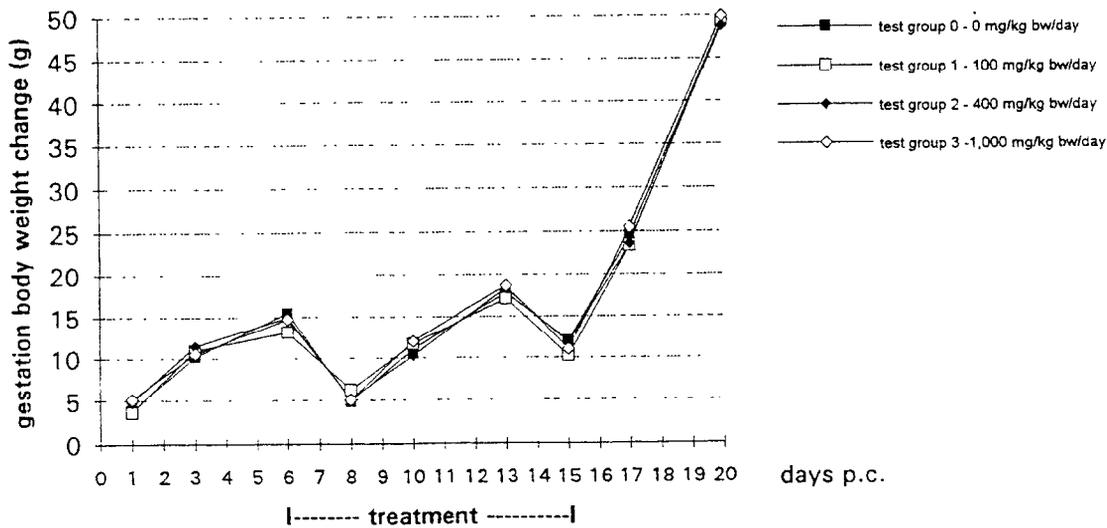


Fig. 4.2.1.2.2.: Mean body weight change of pregnant animals



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4.2.1.3. Corrected body weight gain (net maternal body weight change) (Tab. 006)

The results of the corrected body weight gain (terminal body weight on day 20 p.c. minus weight of the uterus before it was opened minus body weight on day 6 p.c.) of all substance-treated groups (100, 400 or 1,000 mg/kg body weight/day) did not show any differences of biological relevance if compared to the controls.

4.2.1.4. Clinical symptoms (Tab. 007)

There were no abnormal clinical findings in any dam of anyone group.

4.2.1.5. Mortality

There were no mortalities in any of the groups.

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4.2.2. Examinations of the dams at termination

4.2.2.1. Organ weights

4.2.2.1.1. Uterus weight (Tab. 006)

The uterus weights of the animals of test groups 1-3 (100, 400 or 1,000 mg/kg body weight/day) were not influenced by the administration of the test substance. The differences between these groups and the control group are without biological relevance and do not show a clear relation to dosing.

4.2.2.1.2. Weight of liver (Tabs. 008 - 009)

Absolute and relative liver weights were not influenced by the administration of the test substance. The differences between the groups are without biological relevance and do not show a clear relation to dosing.

4.2.2.2. Necropsy findings (Tab. 010)

At necropsy, two spontaneous findings were observed. One animal from the 400 mg/kg group (No. 53), which did not become pregnant, had a hydrometra and one high dose dam (No. 90) showed a hernia diaphragmatica, which, however, did not lead to any disturbances of the general health or the gestational parameters of this rat.

Moreover, single animals of all groups including the controls showed lungs with edema; this finding, which showed no relation to dosing, has to be related to the sacrifice of the animals.

4.2.2.3. Reproduction data of dams (Tabs. 011 - 013)

The conception rate reached 100% in the control group, 84% in test groups 1 and 2 (100 or 400 mg/kg body weight/day) and 96% in the 1,000 mg/kg group.

There were no substance-related and/or biologically relevant differences between the groups in conception rate, in the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and the postimplantation losses, the number of resorptions and viable fetuses. The differences evident are considered to be incidental and within the normal range of deviations for animals of this strain and age [see Volume III (Supplement) for historical control data].

One fetus from the intermediate dose (No. 10 from dam No. 61) was already dead when the uterus was opened. The isolated and disparate nature of this finding does not suggest any treatment-related aetiology.

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4.3. EXAMINATIONS OF THE FETUSES

The results of this part of the study can be found in the following Summary Tables in the Appendix.

	Tables
Key to the abbreviations, page 37	
Mean placental and fetal body weights	014
Summary of all classified fetal external observations	015 - 018
Summary of fetal external unclassified observations	019
Summary of all classified fetal soft tissue observations	020 - 022
Summary of fetal soft tissue unclassified observations	023
Summary of all classified fetal skeletal observations	024 - 039
Summary of all classified fetal external, soft tissue, and skeletal observations	040

The relevant individual values or findings are to be found in Volume II (Tables B 001 - B 113).

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4.3.1. Examination of the fetuses after dissection from the uterus

4.3.1.1. Sex distribution of fetuses (Tab. 013)

The sex distribution of the fetuses in test groups 1 - 3 (100, 400 and 1,000 mg/kg body weight/day) was comparable with the control fetuses. The differences observed in comparison to the control are without any biological relevance.

4.3.1.2. Weight of placentae (Tab. 014)

The mean placental weights in test groups 1, 2 and 3 (100, 400 and 1,000 mg/kg body weight/day) were not influenced by the test substance administration and were similar to the control values.

4.3.1.3. Weight of fetuses (Tab. 014)

The mean fetal body weights in test groups 1, 2 and 3 (100, 400 or 1,000 mg/kg body weight/day) were not influenced by the test substance administration and were similar to the control values.

4.3.1.4. External examination of the fetuses (Tabs. 015 - 019)

The external examination revealed three fetuses with external **malformations**. For one low dose fetus (No. 2 from dam No. 35) anophthalmia was recorded, another fetus of this group (No. 17 of dam No. 44) showed brachygnathia. A cleft palate occurred in one intermediate dose fetus (No. 16 from dam No. 66). No external malformations were observed in any of the control and the high dose fetuses.

The aforementioned external malformations are also present at a low incidence in the historical control data [see Volume III (Supplement)] and do not show a clear dose-response relationship; therefore, these findings are considered to be spontaneous in nature.

The external examination of the fetuses revealed no **variations** in any group.

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Two so-called **unclassified observations** were recorded. Fused placentae were found in 2 control fetuses (fetus No. 4 from dam No. 3 and fetus No. 2 from dam No. 17) and one low dose fetus (No. 2 from dam No. 34), while blood coagulum around the placenta was recorded for the one high dose fetus (No. 7 from dam No. 78).

Both placental findings are not associated with treatment.

For overall assessment of the external findings of the fetuses, see 4.3.4.

4.3.2. Soft tissue examination of the fetuses
(Tabs. 020 - 023)

The examination of the organs of the fetuses revealed no **soft tissue malformations** in any of the groups.

Soft tissue variations (dilated renal pelvis and/or hydroureter) were detected in all groups without any statistically significant and/or biologically relevant differences between the groups. Both findings are very common ones in the rat strain used and all respective values are fully in the range of biological variation.

One so-called **unclassified observation** (bloody imbibition of kidney(s)) was recorded for low dose fetus No. 19 (from dam No. 46). This finding is regarded to be spontaneous in nature.

For overall assessment of the soft tissue findings of the fetuses, see 4.3.4.

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4.3.3. Skeletal examination of the fetuses (Tabs. 024 - 039)

Various malformations of the skull (mandible shortened), the vertebral column (thoracic vertebral body/bodies dumbbell-shaped or bipartite (asymmetrical); lumbar vertebra absent), the scapula (deformed) and/or the sternum (cleft sternum; sternebra(e) bipartite, ossification centers dislocated) were seen in 11 out of 173 (= 6.4%) fetuses (in 9 out of 25 litters (= 36%)) of the control, in 8 out of 143 (= 5.6%) fetuses (in 7 out of 21 litters (= 33%)) of the 100 mg/kg group, in 8 out of 143 (= 5.6%) fetuses (in 8 out of 21 litters (= 38%)) of the 400 mg/kg group and in 11 out of 169 (= 6.5%) fetuses (in 9 out of 24 litters (= 38%)) of the 1,000 mg/kg group.

All skeletal malformations occurred without any statistically significant differences between the substance-treated groups and the concurrent control group and did not show a clear dose-response relationship. Furthermore, most of the aforementioned skeletal malformations or very similar ones can be found at a comparable fetal/litter incidence in the historical control data [see Volume III (Supplement)].

The **skeletal variations** elicited were related to the vertebral column (accessory thoracic or lumbar vertebra), the clavícula (deformed), the sternum (sternebra(e) of irregular shape or bipartite; accessory/fused sternebra(e)) and/or the ribs (shortened or absent 13th, accessory 14th, rudimentary cervical or wavy rib(s)).

All except one of the skeletal variations recorded appeared without any statistically significant differences between the substance-treated groups and the concurrent control group and/or without a clear dose-response relationship.

One skeletal variation, however, irregular-shaped sternebra(e), affected most frequently the high dose fetuses (Tab. 029). It appeared also quite often in the concurrent control and the intermediate dose fetuses, but was found at the lowest rate at 100 mg/kg; thus, a clear dose-response relationship concerning the finding 'irregular-shaped sternebra(e)' is not given. Moreover, if the historical control data is taken into account [see Volume III (Supplement)], it becomes obvious, that this skeletal variation is a very common finding in the rat strain used.

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Therefore, the isolated, but statistically significantly increased occurrence of high dose fetuses/litter with this finding and the consequently statistically significantly increased rate of 1,000 mg/kg fetuses with total skeletal variations are not assessed as a treatment-related effect, but are considered to be spontaneous in nature and without biological relevance.

In all groups signs of **skeletal retardation** occurred substantiated by incomplete or missing ossification of skull (incl. hyoid) bones, vertebral column, sternebra(e), metacarpal and metatarsal bones and os pubis.

The only statistically significant difference between the substance-treated groups and the concurrent control group concerning skeletal retardations was an increased occurrence of incompletely ossified thoracic vertebral body/bodies in the 100 mg/kg group. If, however, the respective fetal (14%) and litter (48%) incidences and the mean percentage of affected fetuses/litter (16.7%) are compared with the historical control data it becomes obvious, that these values are fully within the historical control range (fetal incidence: 8.0% (0 - 49.1%); litter incidence: 22.8% (0 - 100%); mean percentage of affected fetuses/litter: 7.7% (0 - 50%)).

Therefore and due to a missing dose-response relationship, the statistically significantly increased occurrence of incompletely ossified thoracic vertebral body/bodies at 100 mg/kg is finally considered to be spontaneous in nature.

All other differences between the groups in respect to skeletal retardations appeared without statistical significance and/or again without a clear relation to dosing.

For overall assessment of the skeletal findings of the fetuses, see 4.3.4.

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4.3.4. Abstract of fetal external, soft tissue and skeletal observations and their assessment

As can be seen from Tabs. 015, 020, 024 and 040 there were no statistically significant differences between the control and the substance-treated groups with respect to **external, soft tissue, skeletal or total malformations**.

The overall **malformation rate** (Tab. 040) was not increased in a dose-related manner; fetal and litter incidences for external (Tab. 015), soft tissue (Tab. 020) or skeletal malformations (Tab. 024) and the mean percentage of malformed fetuses/litter were within the range of biological variation [see Volume III (Supplement)].

Fetal and litter incidences for **soft tissue** (Tab. 020), **skeletal** (Tab. 024) and **overall variations** (Tab. 040) and **skeletal** (Tab. 024) and **overall retardations** (Tab. 040) and the mean percentage of fetuses/litter with these findings were generally also within the historical control range [see Volume III (Supplement)].

The only statistically significant differences

- **an increased rate of high dose fetuses with one skeletal variation** (irregular-shaped sternebra(e)) (Tab. 029), which led as a consequence also to an increased percentage of total skeletal (Tab. 032) and overall variations (Tab. 040)

and

- **an increased rate of low dose fetuses with one skeletal retardation** (incompletely ossified thoracic vertebral body/bodies (Tab. 034)

were already discussed before (see 4.3.3.).

Both findings are not clearly dose-related, are very common ones in the rat strain taken for this prenatal toxicity study and/or can be found at similar or even higher incidences in the historical control data [see Volume III (Supplement)].

Therefore, the increased percentage of 1,000 mg/kg fetuses/litter with irregular-shaped sternebra(e) and of 100 mg/kg fetuses/litter with incompletely ossified thoracic vertebral body/bodies are finally considered random and not assessed as substance-induced effects.

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5. DISCUSSION AND CONCLUSION

It can be said in conclusion of this prenatal toxicity study that the daily oral administration of **UVINUL T 150** to pregnant Wistar rats by stomach tube in dosages of 100, 400 and 1,000 mg/kg body weight on day 6 through day 15 p.c. caused no substance-related adverse effects on the dams.

There were no indications of embryo-/fetotoxicity and especially no substance-induced signs of teratogenicity in the present full-scale prenatal toxicity study up to and including the limit dose of 1,000 mg/kg body weight/day.

The differences observed between the control and the substance-treated groups appeared either without a clear dose-response relationship and/or were assessed to be without biological relevance, because the relevant values/findings are to be found in similar or even higher range/incidences within the historical control data.

Based on these results, the **no observed adverse effect level (NOAEL)** on the **maternal and fetal organism** is **1,000 mg/kg body weight/day**.

According to the test guidelines which were taken into consideration (see 2. Introduction and Dose Selection) no further embryotoxicity studies at higher dose levels are considered necessary for substances of low toxicity (i.e. "if a dose level of at least 1,000 mg/kg body weight/day produces no evidence of embryotoxicity or teratogenicity").

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6. LITERATURE

- 1a) Report:
Über die akute Toxizität von BE 3767 bei
peroraler Verabreichung an Ratten
[About the acute toxicity of BE 3767 after
peroral administration to rats]
Laboratorium für Pharmakologie und Toxikologie;
Prof. Dr. F. Leuschner; Hamburg (July 3, 1973)
- 1b) Report:
Prüfung der oralen Toxizität von 2,4,6-
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Next k-subset of a n-set.
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Statistical inference based on ranks.
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APPENDIX
SUMMARY TABLES

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KEY TO THE ABBREVIATIONS

Tables 001 - 040 (EXAMINATION OF THE DAMS AND THE FETUSES)

MEAN	= mean value
MG/KG BW/D	= milligram per kilogram body weight per day
N/#/NO.	= number
S.D.	= standard deviation
%	= per cent

All other abbreviations used are explained in the tables.

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TABLE : 001

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAYS 0 TO 1	MEAN	19.3 D	18.7	19.9	19.5
	S.D.	2.17	1.71	2.39	2.52
	N	25	21	21	24
DAYS 1 TO 3	MEAN	22.2 D	22.6	23.5	23.0
	S.D.	2.46	1.72	1.48	2.15
	N	25	21	21	24
DAYS 3 TO 6	MEAN	23.6 D	23.0	24.1	23.6
	S.D.	2.34	1.55	1.34	2.56
	N	25	21	21	24
DAYS 6 TO 8	MEAN	21.6 D	21.8	22.7	22.6
	S.D.	2.43	1.89	1.59	2.80
	N	25	21	21	24
DAYS 8 TO 10	MEAN	21.8 D	21.9	23.3	23.4
	S.D.	3.73	2.55	2.17	2.18
	N	25	21	21	24
DAYS 10 TO 13	MEAN	22.8 D	22.6	23.8	24.0
	S.D.	2.10	2.00	1.26	2.35
	N	25	21	21	24
DAYS 13 TO 15	MEAN	22.9 D	22.7	23.8	24.3
	S.D.	2.25	2.49	1.99	3.92
	N	25	21	21	24
DAYS 15 TO 17	MEAN	27.6 D	27.3	27.7	28.1
	S.D.	2.51	2.38	2.18	2.47
	N	25	21	21	24
DAYS 17 TO 20	MEAN	28.7 D	28.8	29.2	29.3
	S.D.	2.19	1.77	2.05	2.43
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 002

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAYS 0 TO 6	MEAN OF MEANS	21.7	21.4	22.5	22.1
	S.D.	2.17	2.38	2.28	2.20
	N	3	3	3	3
DAYS 6 TO 15	MEAN OF MEANS	22.3	22.3	23.4	23.6
	S.D.	0.65	0.43	0.51	0.74
	N	4	4	4	4
DAYS 15 TO 20	MEAN OF MEANS	28.1	28.0	28.4	28.7
	S.D.	0.77	1.10	1.08	0.85
	N	2	2	2	2
DAYS 0 TO 20	MEAN OF MEANS	23.4	23.3	24.2	24.2
	S.D.	2.94	3.02	2.72	2.90
	N	9	9	9	9

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TABLE : 003

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAY 0	MEAN	250.4 D	247.9	246.5	248.7
	S.D.	11.74	8.66	11.99	10.13
	N	25	21	21	24
DAY 1	MEAN	254.2 D	251.5	251.3	253.9
	S.D.	11.72	9.04	12.11	12.42
	N	25	21	21	24
DAY 3	MEAN	264.4 D	262.5	262.8	264.5
	S.D.	12.39	9.60	13.84	12.72
	N	25	21	21	24
DAY 6	MEAN	279.9 D	275.6	277.7	279.2
	S.D.	14.29	10.68	13.68	15.30
	N	25	21	21	24
DAY 8	MEAN	284.7 D	281.8	282.9	284.3
	S.D.	13.99	11.07	15.22	16.20
	N	25	21	21	24
DAY 10	MEAN	295.9 D	293.5	293.3	296.3
	S.D.	16.15	13.85	16.32	16.20
	N	25	21	21	24
DAY 13	MEAN	313.7 D	310.6	311.7	314.9
	S.D.	18.06	16.54	15.89	18.82
	N	25	21	21	24
DAY 15	MEAN	325.8 D	320.8	323.4	325.9
	S.D.	19.55	19.32	16.68	19.61
	N	25	21	21	24
DAY 17	MEAN	350.4 D	344.1	347.1	351.4
	S.D.	20.60	20.75	19.51	21.47
	N	25	21	21	24
DAY 20	MEAN	399.5 D	393.4	395.8	401.2
	S.D.	27.17	20.05	21.60	25.09
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)

* : p<=0.05 ** : p<=0.01

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TABLE : 004

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAYS 0 TO 1	MEAN	3.8 D	3.6	4.8	5.2
	S.D.	3.54	3.11	3.52	3.48
	N	25	21	21	24
DAYS 1 TO 3	MEAN	10.2 D	11.0	11.5	10.6
	S.D.	5.56	3.32	4.33	4.24
	N	25	21	21	24
DAYS 3 TO 6	MEAN	15.5 D	13.1	14.9	14.7
	S.D.	7.34	5.17	4.34	5.07
	N	25	21	21	24
DAYS 6 TO 8	MEAN	4.9 D	6.2	5.2	5.1
	S.D.	3.72	4.44	2.99	6.16
	N	25	21	21	24
DAYS 8 TO 10	MEAN	11.1 D	11.7	10.3	12.0
	S.D.	6.15	4.73	4.07	4.40
	N	25	21	21	24
DAYS 10 TO 13	MEAN	17.8 D	17.1	18.4	18.7
	S.D.	4.91	4.36	3.16	3.52
	N	25	21	21	24
DAYS 13 TO 15	MEAN	12.1 D	10.2	11.8	11.0
	S.D.	3.48	5.46	3.22	3.62
	N	25	21	21	24
DAYS 15 TO 17	MEAN	24.5 D	23.4	23.6	25.5
	S.D.	4.80	4.20	5.62	4.54
	N	25	21	21	24
DAYS 17 TO 20	MEAN	49.2 D	49.3	48.8	49.9
	S.D.	9.47	10.18	6.06	8.42
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 005

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAYS 0 TO 6	MEAN	29.5 D	27.7	31.2	30.4
	S.D.	7.04	5.75	3.88	7.13
	N	25	21	21	24
DAYS 6 TO 15	MEAN	46.0 D	45.2	45.7	46.7
	S.D.	9.67	10.74	6.76	6.18
	N	25	21	21	24
DAYS 15 TO 20	MEAN	73.7 D	72.6	72.4	75.4
	S.D.	11.28	11.21	10.01	9.86
	N	25	21	21	24
DAYS 0 TO 20	MEAN	149.2 D	145.6	149.3	152.5
	S.D.	21.51	22.33	15.56	18.56
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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TABLE : 006

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN GRAVID UTERINE WEIGHTS AND NET MATERNAL BODY WEIGHT CHANGE -- GRAMS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
GRAVID UTERUS	MEAN	77.2 D	74.4	75.5	78.5
	S.D.	16.92	18.95	16.22	12.82
	N	25	21	21	24
CARCASS	MEAN	322.3 D	319.0	320.3	322.7
	S.D.	16.82	14.80	18.93	19.22
	N	25	21	21	24
NET WEIGHT CHANGE FROM DAY 6	MEAN	42.5 D	43.4	42.6	43.5
	S.D.	8.52	8.59	8.83	6.94
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

CARCASS WEIGHT = TERMINAL BODY WEIGHT MINUS UTERINE WEIGHT
 NET WEIGHT CHANGE FROM DAY 6 = CARCASS WEIGHT MINUS DAY 6 BODY WEIGHT

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TABLE : 008

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN ABSOLUTE MATERNAL ORGAN WEIGHTS -- GRAMS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
FINAL BODY WEIGHT	MEAN	399.5 D	393.4	395.8	401.2
	S.D.	27.17	28.05	21.60	25.09
	N	25	21	21	24
LIVER	MEAN	17.39 D	17.25	17.52	17.50
	S.D.	1.606	1.662	1.604	1.468
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
* : p<-0.05 ** : p<-0.01

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TABLE : 009

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
MEAN RELATIVE MATERNAL ORGAN WEIGHTS -- %

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
LIVER	MEAN	4.351 D	4.384	4.423	4.362
	S.D.	0.2385	0.2564	0.2959	0.2680
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL NECROPSY OBSERVATIONS

TABLE : 010

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
DAMS EXAMINED	N	25	25	25	25
NOTHING ABNORMAL DETECTED	N	23	23	23	22
	%	92	92	92	88
LUNGS: EDEMA	N	2	2	1	2
	%	8.0	8.0	4.0	8.0
HERNIA DIAPHRAGMATICA	N	0	0	0	1
	%	0.0	0.0	0.0	4.0
HYDROMETRA	N	0	0	1	0
	%	0.0	0.0	4.0	0.0

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TABLE : 011

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Females Mated	N	25	25	25	25
Pregnant	N	25	21	21	24
Conception Rate	%	100	84	84	96
Aborted	N	0	0	0	0
Premature Births	N	0	0	0	0
Dams with Viable Fetuses	N	25	21	21	24
Dams with all Resorptions	N	0	0	0	0
Female Mortality	N	0 ^{Fi}	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at Terminal Sacrifice	N	25 ^{Fi}	21	21	24
	%	100	84	84	96
Corpora Lutea	MEAN	16.4 D	15.9	16.1	15.5
	S.D.	2.38	2.21	1.22	1.67
	TOTAL	411	334	338	373
Implantation Sites	MEAN	14.3 D	14.1	14.5	14.9
	S.D.	3.22	3.65	2.64	1.89
	TOTAL	358	297	305	358
Preimplantation Loss	MEAN%	13.1 D	11.9	9.8	4.0
	S.D.	15.13	18.04	14.77	6.37
Postimplantation Loss	MEAN%	6.6 D	7.6	10.3	9.3
	S.D.	7.98	6.22	11.03	8.24

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 012

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Pregnant at Terminal Sacrifice	N	25	21	21	24
Resorptions: Total	MEAN	1.0 D	1.1	1.5	1.4
	S.D.	1.22	0.89	1.63	1.28
	TOTAL	25	23	31	33
	MEAN%	6.6 D	7.6	10.0	9.3
	S.D.	7.98	6.22	11.22	8.24
Early	MEAN	0.6 D	0.9	1.3	1.1
	S.D.	0.86	0.94	1.59	1.26
	TOTAL	16	19	28	27
	MEAN%	4.2 D	6.4	9.2	7.5
	S.D.	5.63	6.62	11.12	8.04
Late	MEAN	0.4 D	0.2	0.1	0.3
	S.D.	0.76	0.40	0.36	0.68
	TOTAL	9	4	3	6
	MEAN%	2.5 D	1.3	0.8	1.7
	S.D.	5.15	2.74	2.12	4.76
Dead Fetuses	N	0	0	1	0

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 013

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Dams with Viable Fetuses	N	25	21	21	24
Live Fetuses	MEAN	13.3 D	13.0	13.0	13.5
	S.D.	3.09	3.47	2.83	2.21
	TOTAL	333	274	273	325
	MEAN% S.D.	93.4 D 7.98	92.4 6.21	89.7 11.03	90.7 8.24
Females	MEAN	6.3 D	6.3	6.4	6.3
	S.D.	2.39	2.70	2.38	2.17
	TOTAL	157	132	135	150
	MEAN% S.D.	45.6 D 17.47	42.8 13.89	43.8 13.50	42.3 14.73
Males	MEAN	7.0 D	6.8	6.6	7.3
	S.D.	3.02	2.32	1.91	2.76
	TOTAL	176	142	138	175
	MEAN% S.D.	47.8 D 16.59	49.6 15.24	45.9 11.92	48.4 15.73
PER CENT LIVE FEMALES		47.1	48.2	49.5	46.2
PER CENT LIVE MALES		52.9	51.8	50.5	53.8

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 014

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 MEAN PLACENTAL AND FETAL BODY WEIGHTS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
PLACENTAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	0.46 D	0.44	0.45	0.44
	S.D.	0.047	0.042	0.030	0.031
	N	25	21	21	24
of Male Fetuses	MEAN	0.46 D	0.45	0.45	0.44
	S.D.	0.047	0.044	0.031	0.034
	N	25	21	21	24
of Female Fetuses	MEAN	0.45 D	0.44	0.44	0.44
	S.D.	0.052	0.044	0.035	0.057
	N	25	21	21	24
FETAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	3.9 D	3.9	3.9	3.9
	S.D.	0.22	0.17	0.22	0.20
	N	25	21	21	24
of Male Fetuses	MEAN	4.0 D	3.9	4.0	4.0
	S.D.	0.24	0.20	0.20	0.19
	N	25	21	21	24
of Female Fetuses	MEAN	3.8 D	3.8	3.8	3.8
	S.D.	0.22	0.18	0.24	0.21
	N	25	21	21	24

Statistics: D=Dunnett-test (two-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 015

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL OBSERVATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	333	274	274	325
Live	N	333	274	273	325
Dead	N	0	0	1	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	0	2	1	0
	%	0.0	0.7	0.4	0.0
Litter Incidence	N	0/1	2	1	0
	%	0.0	9.5	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0/1	0.6	0.3	0.0
	S.D.	0.00	1.97	1.56	0.00
TOTAL VARIATIONS					
Fetal Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Litter Incidence	N	0/1	0	0	0
	%	0.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0/1	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 016

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL EXTERNAL MALFORMATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Animals Evaluated	N	25	21	21	24
Fetuses Evaluated	N	333	274	274	325
Live	N	333	274	273	325
Dead	N	0	0	1	0
ACHYGNATHIA					
Fetal Incidence	N	0	1	0	0
	%	0.0	0.4	0.0	0.0
Litter Incidence	N	0 Fi	1	0	0
	%	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.3	0.0	0.0
	S.D.	0.00	1.28	0.00	0.00
EFT PALATE					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.4	0.0
Litter Incidence	N	0 Fi	0	1	0
	%	0.0	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.0	0.3	0.0
	S.D.	0.00	0.00	1.56	0.00
OPHTHALMIA					
Fetal Incidence	N	0	1	0	0
	%	0.0	0.4	0.0	0.0
Litter Incidence	N	0 Fi	1	0	0
	%	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.3	0.0	0.0
	S.D.	0.00	1.56	0.00	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 017

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL MALFORMATIONS

		TEST GROUP 0	TEST GROUP 1	TEST GROUP 2	TEST GROUP 3
		0 MG/KG BW/D	100 MG/KG BW/D	400 MG/KG BW/D	1,000 MG/KG BW/D
TAL FETAL EXTERNAL MALFORMATIONS					
Fetal Incidence	N	0	2	1	0
	%	0.0	0.7	0.4	0.0
Litter Incidence	N	0	2	1	0
	%	0.0	9.5	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0	0.6	0.3	0.0
	S.D.	0.00	1.97	1.56	0.00

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL EXTERNAL VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Animals Evaluated	N	25	21	21	24
Litters Evaluated	N	333	274	274	325
Alive	N	333	274	273	325
Dead	N	0	0	1	0
FETAL FETAL EXTERNAL VARIATIONS					
Fetal Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Litter Incidence	N	0/1	0	0	0
	%	0.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL EXTERNAL UNCLASSIFIED FINDINGS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D
Litters Evaluated	N	25	21	21
Fetuses Evaluated	N	333	274	274
Live	N	333	274	273
Dead	N	0	0	1
PLACENTAE FUSED				
Fetal Incidence	N	2	1	0
	%	0.6	0.4	0.0
Litter Incidence	N	2Fi	1	0
	%	8.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.5Wi	0.4	0.0
	S.D.	1.71	1.68	0.00
BLOOD COAGULUM AROUND PLACENTA				
Fetal Incidence	N	0	0	0
	%	0.0	0.0	0.0
Litter Incidence	N	0Fi	0	0
	%	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0
	S.D.	0.00	0.00	0.00
TOTAL FETAL EXTERNAL UNCLASSIFIED FINDINGS				
Fetal Incidence	N	2	1	0
	%	0.6	0.4	0.0
Litter Incidence	N	2Fi	1	0
	%	8.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.5Wi	0.4	0.0
	S.D.	1.71	1.68	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL SOFT TISSUE OBSERVATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D
Litters Evaluated	N	25	21	21
Fetuses Evaluated	N	160	131	131
Live	N	160	131	130
Dead	N	0	0	1
TOTAL MALFORMATIONS				
Fetal Incidence	N	0	0	0
	%	0.0	0.0	0.0
Litter Incidence	N	0Fi	0	0
	%	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0
	S.D.	0.00	0.00	0.00
TOTAL VARIATIONS				
Fetal Incidence	N	33	24	21
	%	21	18	16
Litter Incidence	N	15Fi	14	11
	%	60	67	52
Affected Fetuses/Litter	MEAN%	19.7Wi	21.8	15.0
	S.D.	22.38	25.60	18.00

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
* : p<=0.05 ** : p<=0.01

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TABLE : 021

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE MALFORMATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Animals Evaluated	N	25	21	21	24
Fetuses Evaluated	N	160	131	131	156
Live	N	160	131	130	156
Dead	N	0	0	1	0
TOTAL FETAL SOFT TISSUE MALFORMATIONS					
Fetal Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Litter Incidence	N	0Fi	0	0	0
	%	0.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
* : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D
Litters Evaluated	N	25	21	21
Fetuses Evaluated	N	160	131	131
Live	N	160	131	130
Dead	N	0	0	1
DILATED RENAL PELVIS				
Fetal Incidence	N	33	24	21
	%	21	18	16
Litter Incidence	N	15Fi	14	11
	%	60	67	52
Affected Fetuses/Litter	MEAN%	19.7Wi	21.8	15.0
	S.D.	22.38	25.60	18.00
HYDROURETER				
Fetal Incidence	N	8	2	3
	%	5.0	1.5	2.3
Litter Incidence	N	6Fi	2	2
	%	24	9.5	9.5
Affected Fetuses/Litter	MEAN%	4.9Wi	1.3	2.0
	S.D.	11.12	4.27	6.40
TOTAL FETAL SOFT TISSUE VARIATIONS				
Fetal Incidence	N	33	24	21
	%	21	18	16
Litter Incidence	N	15Fi	14	11
	%	60	67	52
Affected Fetuses/Litter	MEAN%	19.7Wi	21.8	15.0
	S.D.	22.38	25.60	18.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SOFT TISSUE UNCLASSIFIED FINDINGS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D
Litters Evaluated	N	25	21	21
Fetuses Evaluated	N	160	131	131
Live	N	160	131	130
Dead	N	0	0	1
BLOODY IMBIBITION OF KIDNEY(S)				
Fetal Incidence	N	0	1	0
	%	0.0	0.8	0.0
Litter Incidence	N	0/1	1	0
	%	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0/1	0.5	0.0
	S.D.	0.00	2.42	0.00
TOTAL FETAL SOFT TISSUE UNCLASSIFIED FINDINGS				
Fetal Incidence	N	0	1	0
	%	0.0	0.8	0.0
Litter Incidence	N	0/1	1	0
	%	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0/1	0.5	0.0
	S.D.	0.00	2.42	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF ALL CLASSIFIED FETAL SKELETAL OBSERVATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D
Litters Evaluated	N	25	21	21
Fetuses Evaluated	N	173	143	143
Live	N	173	143	143
Dead	N	0	0	0
TOTAL MALFORMATIONS				
Fetal Incidence	N %	11 6.4	8 5.6	8 5.6
Litter Incidence	N %	9Fi 36	7 33	8 38
Affected Fetuses/Litter	MEAN% S.D.	6.2Wi 8.82	4.8 7.33	6.0 8.30
TOTAL VARIATIONS				
Fetal Incidence	N %	81 47	63 44	70 49
Litter Incidence	N %	25Fi 100	19 90	21 100
Affected Fetuses/Litter	MEAN% S.D.	47.4Wi 19.59	44.4 21.79	49.2 19.09
TOTAL RETARDATIONS				
Fetal Incidence	N %	79 46	80 56	70 49
Litter Incidence	N %	24Fi 96	21 100	20 95
Affected Fetuses/Litter	MEAN% S.D.	44.8Wi 25.30	56.9 26.72	51.6 24.24

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 025

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL MALFORMATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
MANDIBLE SHORTENED					
Fetal Incidence	N	0	1	0	0
	%	0.0	0.7	0.0	0.0
Litter Incidence	N	0Fi	1	0	0
	%	0.0	4.8	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.5	0.0	0.0
	S.D.	0.00	2.42	0.00	0.00
THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (ASYMMETR.)					
Fetal Incidence	N	9	5	5	6
	%	5.2	3.5	3.5	3.6
Litter Incidence	N	8Fi	5	5	6
	%	32	24	24	25
Affected Fetuses/Litter	MEAN%	5.1Wi	3.2	4.2	3.9
	S.D.	8.11	5.93	8.03	7.07
THORACIC VERTEBRAL BODY/BODIES BIPARTITE (ASYMMETRICAL)					
Fetal Incidence	N	0	1	0	2
	%	0.0	0.7	0.0	1.2
Litter Incidence	N	0Fi	1	0	2
	%	0.0	4.8	0.0	8.3
Affected Fetuses/Litter	MEAN%	0.0Wi	0.5	0.0	1.4
	S.D.	0.00	2.42	0.00	4.71

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 026

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL MALFORMATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
LUMBAR VERTEBRA ABSENT					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0Fi	0	1	0
	%	0.0	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.6	0.0
	S.D.	0.00	0.00	2.73	0.00
SCAPULA(E) DEFORMED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.7
	S.D.	0.00	0.00	0.00	3.40
STERNEBRA(E) BIPARTITE, OSSIFICATION CENTERS DISLOCATED					
Fetal Incidence	N	3	1	3	2
	%	1.7	0.7	2.1	1.2
Litter Incidence	N	2Fi	1	3	2
	%	8.0	4.8	14	8.3
Affected Fetuses/Litter	MEAN%	1.5Wi	0.6	1.9	1.1
	S.D.	5.18	2.73	4.71	3.79

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

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TABLE : 027

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL MALFORMATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
CLEFT STERNUM					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.7
	S.D.	0.00	0.00	0.00	3.40
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	11	8	8	11
	%	6.4	5.6	5.6	6.5
Litter Incidence	N	9Fi	7	8	9
	%	36	33	38	38
Affected Fetuses/Litter	MEAN%	6.2Wi	4.8	6.0	7.1
	S.D.	8.82	7.33	8.30	10.33

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 028

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
ACCESSORY THORACIC VERTEBRA					
Fetal Incidence	N	1	0	0	0
	%	0.6	0.0	0.0	0.0
Litter Incidence	N	1Fi	0	0	0
	%	4.0	0.0	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.4Wi	0.0	0.0	0.0
	S.D.	2.22	0.00	0.00	0.00
ACCESSORY LUMBAR VERTEBRA					
Fetal Incidence	N	0	0	1	1
	%	0.0	0.0	0.7	0.6
Litter Incidence	N	0Fi	0	1	1
	%	0.0	0.0	4.8	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.6	0.7
	S.D.	0.00	0.00	2.73	3.40
CLAVICULA DEFORMED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.7
	S.D.	0.00	0.00	0.00	3.40

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 029

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
STERNEBRA(E) OF IRREGULAR SHAPE					
Fetal Incidence	N	70	51	57	96
	%	40	36	40	57
Litter Incidence	N	24Fi	18	21	24
	%	96	86	100	100
Affected Fetuses/Litter	MEAN%	40.8Wi	34.4	40.1	56.6**
	S.D.	19.97	20.13	21.03	19.81
STERNEBRA(E) BIPARTITE					
Fetal Incidence	N	3	1	1	6
	%	1.7	0.7	0.7	3.6
Litter Incidence	N	3Fi	1	1	5
	%	12	4.8	4.8	21
Affected Fetuses/Litter	MEAN%	1.5Wi	0.7	0.6	3.1
	S.D.	4.11	3.12	2.73	6.69
ACCESSORY STERNEBRA					
Fetal Incidence	N	0	0	0	2
	%	0.0	0.0	0.0	1.2
Litter Incidence	N	0Fi	0	0	2
	%	0.0	0.0	0.0	8.3
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	1.4
	S.D.	0.00	0.00	0.00	4.71

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 030

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
STERNEBRAE FUSED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.7
	S.D.	0.00	0.00	0.00	3.40
13TH RIB(S) SHORTENED					
Fetal Incidence	N	21	11	11	27
	%	12	7.7	7.7	16
Litter Incidence	N	12Fi	8	8	13
	%	48	38	38	54
Affected Fetuses/Litter	MEAN%	12.0Wi	7.3	6.8	16.1
	S.D.	14.93	11.37	9.92	21.41
RUDIMENTARY CERVICAL RIB(S)					
Fetal Incidence	N	6	3	4	4
	%	3.5	2.1	2.8	2.4
Litter Incidence	N	4Fi	3	2	4
	%	16	14	9.5	17
Affected Fetuses/Litter	MEAN%	3.0Wi	2.1	3.5	2.3
	S.D.	7.53	5.41	13.31	5.35

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 031

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
ACCESSORY 14TH RIB(S)					
Fetal Incidence	N	1	2	1	0
	%	0.6	1.4	0.7	0.0
Litter Incidence	N	1F1	2	1	0
	%	4.0	9.5	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.4Wi	2.9	1.0	0.0
	S.D.	2.22	11.06	4.36	0.00
WAVY RIB(S)					
Fetal Incidence	N	0	0	1	2
	%	0.0	0.0	0.7	1.2
Litter Incidence	N	0F1	0	1	2
	%	0.0	0.0	4.8	8.3
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.6	1.3
	S.D.	0.00	0.00	2.73	4.38
13TH RIB(S) ABSENT					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0F1	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.5
	S.D.	0.00	0.00	0.00	2.55

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 032

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0	TEST GROUP 1	TEST GROUP 2	TEST GROUP 3
		0 MG/KG BW/D	100 MG/KG BW/D	400 MG/KG BW/D	1,000 MG/KG BW/D

TOTAL FETAL SKELETAL VARIATIONS					
Fetal Incidence	N	81	63	70	110
	%	47	44	49	65
Litter Incidence	N	25Fi	19	21	24
	%	100	90	100	100
Affected Fetuses/Litter	MEAN%	47.4Wi	44.4	49.2	65.0**
	S.D.	19.59	21.79	19.09	20.75

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

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TABLE : 033

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
SKULL INCOMPLETELY OSSIFIED					
Fetal Incidence	N	4	2	3	3
	%	2.3	1.4	2.1	1.8
Litter Incidence	N	4Fi	1	3	3
	%	16	4.8	14	13
Affected Fetuses/Litter	MEAN%	2.0Wi	1.2	1.9	2.0
	S.D.	4.83	5.46	4.71	5.38
HYOID BONE INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	1	2	0
	%	0.0	0.7	1.4	0.0
Litter Incidence	N	0Fi	1	2	0
	%	0.0	4.8	9.5	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.5	1.2	0.0
	S.D.	0.00	2.42	3.76	0.00
TYMPANIC ANNULUS INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0Fi	0	1	0
	%	0.0	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.6	0.0
	S.D.	0.00	0.00	2.73	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 034

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
VERTEBRAL COLUMN INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	2
	%	0.0	0.0	0.0	1.2
Litter Incidence	N	0Fi	0	0	2
	%	0.0	0.0	0.0	8.3
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	1.3
	S.D.	0.00	0.00	0.00	4.38
THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (SYMMETR.)					
Fetal Incidence	N	28	22	24	22
	%	16	15	17	13
Litter Incidence	N	19Fi	14	14	17
	%	76	67	67	71
Affected Fetuses/Litter	MEAN%	16.5Wi	15.5	18.9	13.8
	S.D.	13.03	17.08	20.12	12.89
THORACIC VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	8	20	13	9
	%	4.6	14	9.1	5.3
Litter Incidence	N	6Fi	10	7	5
	%	24	48	33	21
Affected Fetuses/Litter	MEAN%	5.1Wi	16.7*	8.7	5.3
	S.D.	11.66	26.58	13.95	12.23

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 035

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
THORACIC VERTEBRAL BODY/BODIES BIPARTITE (SYMMETRICAL)					
Fetal Incidence	N	1	0	1	0
	%	0.6	0.0	0.7	0.0
Litter Incidence	N	1Fi	0	1	0
	%	4.0	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.6Wi	0.0	0.7	0.0
	S.D.	2.86	0.00	3.12	0.00
THORACIC VERTEBR. BODY/BODIES-ONLY ONE OSSIFICATION CENTER					
Fetal Incidence	N	0	1	1	2
	%	0.0	0.7	0.7	1.2
Litter Incidence	N	0Fi	1	1	2
	%	0.0	4.8	4.8	8.3
Affected Fetuses/Litter	MEAN%	0.0Wi	0.5	0.7	1.3
	S.D.	0.00	2.42	3.12	4.38
LUMBAR VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.92

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 036

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
SACRAL VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0 Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.92
SACRAL VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0 Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.92
SACRAL VERTEBRAL ARCH(ES) NOT OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0 Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0 Wi	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.92

Statistics: Fi -Fisher's exact test (one-sided) Wi -Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 037

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
STERNEBRA(E) NOT OSSIFIED					
Fetal Incidence	N	9	15	7	19
	%	5.2	10	4.9	11
Litter Incidence	N	6Fi	7	6	11
	%	24	33	29	46
Affected Fetuses/Litter	MEAN%	4.6Wi	10.0	4.5	10.9
	S.D.	8.80	16.45	7.72	14.31
STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE					
Fetal Incidence	N	40	38	43	45
	%	23	27	30	27
Litter Incidence	N	16Fi	17	16	17
	%	64	81	76	71
Affected Fetuses/Litter	MEAN%	21.4Wi	26.2	31.6	26.0
	S.D.	22.56	18.28	27.56	22.41
STERNEBRA(E)-ONLY ONE OSSIFICATION CENTER					
Fetal Incidence	N	16	20	11	11
	%	9.2	14	7.7	6.5
Litter Incidence	N	11Fi	12	9	8
	%	44	57	43	33
Affected Fetuses/Litter	MEAN%	9.1Wi	12.9	8.0	6.2
	S.D.	11.39	14.68	10.44	11.63

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 038

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	173	143	143	169
Live	N	173	143	143	169
Dead	N	0	0	0	0
METACARPAL BONES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.92
METATARSAL BONES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	0	1
	%	0.0	0.0	0.0	0.6
Litter Incidence	N	0Fi	0	0	1
	%	0.0	0.0	0.0	4.2
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.0	0.7
	S.D.	0.00	0.00	0.00	3.40
OS PUBIS INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.7	0.0
Litter Incidence	N	0Fi	0	1	0
	%	0.0	0.0	4.8	0.0
Affected Fetuses/Litter	MEAN%	0.0Wi	0.0	0.6	0.0
	S.D.	0.00	0.00	2.73	0.00

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

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TABLE : 039

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
TOTAL FETAL SKELETAL RETARDATIONS					
Fetal Incidence	N	79	80	70	76
	%	46	56	49	45
Litter Incidence	N	24	21	20	23
	%	96	100	95	96
Affected Fetuses/Litter	MEAN%	44.8	56.9	51.6	44.6
	S.D.	25.30	26.72	24.24	24.11

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

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TABLE : 040

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL, SOFT TISSUE, AND SKELETAL OBSERVATIONS

		TEST GROUP 0 0 MG/KG BW/D	TEST GROUP 1 100 MG/KG BW/D	TEST GROUP 2 400 MG/KG BW/D	TEST GROUP 3 1,000 MG/KG BW/D
Litters Evaluated	N	25	21	21	24
Fetuses Evaluated	N	333	274	274	325
Live	N	333	274	273	325
Dead	N	0	0	1	0
TOTAL MALFORMATIONS					
Fetal Incidence	N %	11 3.3	9 3.3	8 2.9	11 3.4
Litter Incidence	N %	9Fi 36	8 38	8 38	9 38
Affected Fetuses/Litter	MEAN% S.D.	3.2Wi 4.71	2.9 3.94	3.1 4.25	3.7 5.39
TOTAL VARIATIONS					
Fetal Incidence	N %	114 34	87 32	91 33	143 44
Litter Incidence	N %	25Fi 100	21 100	21 100	24 100
Affected Fetuses/Litter	MEAN% S.D.	34.2Wi 14.45	33.1 14.99	32.8 14.95	43.8** 14.09
TOTAL RETARDATIONS					
Fetal Incidence	N %	79 24	80 29	70 26	76 23
Litter Incidence	N %	24Fi 96	21 100	20 95	23 96
Affected Fetuses/Litter	MEAN% S.D.	23.3Wi 13.25	29.7 13.81	27.0 13.12	23.2 12.75

Statistics: Fi = Fisher's exact test (one-sided) Wi = Wilcoxon-test (one-sided)
 * : p<=0.05 ** : p<=0.01

BASE

BASF

Abteilung Toxikologie
Department of Toxicology
OCT 04 1994
D-67056 Ludwigshafen, FRG

he0033

REPORT

Study of the
Prenatal Toxicity of

UVINUL T 150

in Wistar Rats After Oral Administration
(Gavage)

Project No.: 30R0246/93046

VOLUME II OF III

TABLES SECTION, INDIVIDUAL VALUES
AND OBSERVATIONS

Testing facility:

BASF Aktiengesellschaft
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Report; Project No.: 30R0246/93046

A) EXAMINATIONS OF THE DAMS

Key to the abbreviations, page A1

Tables

- Individual maternal food consumption	A 001 - A 004
- Individual maternal body weights	A 005 - A 008
- Individual maternal body weight change	A 009 - A 012
- Individual uterine weights and net maternal body weight change	A 013 - A 016
- Individual maternal clinical observations	A 017 - A 024
- Individual absolute and relative maternal organ weights	A 025 - A 028
- Individual maternal necropsy observations	A 029 - A 036
- Individual reproduction data	A 037 - A 040

B) EXAMINATIONS OF THE FETUSES

Key to the abbreviations, page B1

Tables

- Individual fetal status and uterine location	B 001 - B 004
- Individual placental weights	B 005 - B 008
- Individual fetal body weights	B 009 - B 012
- Individual fetal external observations	B 013 - B 047
- Individual fetal soft tissue observations	B 048 - B 065
- Individual fetal skeletal observations	B 066 - B 113

Report; Project No.: 30R0246/93046

KEY TO THE ABBREVIATIONS USED IN PART A OF THE TABLES

MEAN	= mean value
MG/KG BW/D	= milligram per kilogram body weight per day
N/#/NO.	= number
S.D.	= standard deviation
%	= per cent

All other abbreviations used are explained in the tables.

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TABLE : A 002

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

TEST GROUP 1 (100 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0 - 1	1 - 3	3 - 6	6 - 8	8 - 10	10 - 13	13 - 15	15 - 17	17 - 20	
26	17.4	19.3	20.1	19.3	18.0	21.1	20.1	26.8	25.5	
27	20.7	22.4	24.1	21.8	21.6	23.3	18.4	23.8	29.8	
28	17.4	23.4	24.0	26.1	21.4	23.1	25.5	24.2	31.3	
29	18.2	21.3	22.8	22.2	20.8	23.6	23.8	27.6	28.8	
30	22.3	22.0	24.3	20.7	25.1	25.0	26.1	30.3	31.3	
31	19.4	22.9	23.2	22.0	24.3	23.7	24.4	28.5	30.4	
32	18.9	23.4	23.6	20.5	16.4	17.3	17.3	22.9	26.5	
33	19.2	24.9	25.1	22.1	25.8	25.3	24.6	29.4	29.7	
34	18.7	22.5	24.6	21.9	23.3	22.2	21.5	27.1	27.4	
35	18.9	24.1	24.0	24.3	24.6	23.5	23.1	29.1	29.4	
36	20.4	22.9	24.1	21.7	23.5	23.4	23.1	28.4	29.9	
37	15.3	21.0	19.5	18.4	18.6	18.5	19.6	25.1	26.6	
38x NP	18.5	25.7	23.4	21.3	23.0	20.6	10.1	16.9	15.6	
39	17.5	21.8	22.3	21.5	19.6	21.9	22.4	28.0	28.1	
40	15.6	19.3	20.7	20.9	20.6	20.9	21.9	24.6	27.2	
41x NP	18.3	23.0	22.1	20.5	21.4	20.1	12.6	18.4	19.2	
42x NP	17.6	20.3	21.4	20.0	19.5	18.8	13.1	18.1	19.1	
43	20.0	24.2	24.2	23.5	22.2	23.3	24.0	29.8	29.6	
44	20.7	23.0	21.8	20.2	21.0	23.5	23.6	28.3	31.1	
45	16.4	20.6	20.9	18.5	19.7	20.9	20.9	24.1	27.7	
46	18.5	22.9	23.8	23.6	25.5	24.6	25.9	31.9	30.5	
47	19.1	25.5	22.6	22.8	23.7	24.2	26.0	27.2	29.8	
48	19.4	25.3	22.9	23.4	22.4	22.7	22.9	27.5	26.4	
49	18.5	22.5	24.0	22.9	22.7	22.3	20.9	28.1	28.1	
50x NP	18.5	20.8	19.7	18.8	17.8	16.0	16.0	19.5	20.1	
MEAN	18.7	22.6	23.0	21.8	21.9	22.6	22.7	27.3	28.8	
S.D.	1.71	1.72	1.55	1.89	2.55	2.00	2.49	2.38	1.77	
N	21	21	21	21	21	21	21	21	21	

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

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TABLE : A 003

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

TEST GROUP 2 (400 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0 - 1	1 - 3	3 - 6	6 - 8	8 - 10	10 - 13	13 - 15	15 - 17	17 - 20	
51	21.7	24.9	25.1	25.8	25.1	25.3	24.9	29.4	31.0	
52	20.4	21.8	23.5	20.8	19.6	23.4	22.0	26.1	25.9	
53x NP	18.2	21.8	21.5	18.1	19.5	16.0	15.1	14.3	20.1	
54	22.3	21.5	26.3	22.4	25.4	23.0	23.4	28.9	29.8	
55	21.6	22.3	25.3	23.3	22.1	24.5	23.1	25.5	28.9	
56	17.8	21.5	21.7	21.1	19.0	21.6	20.3	25.4	27.3	
57	18.4	21.6	23.0	21.8	23.0	23.6	24.1	29.0	28.5	
58	21.1	25.3	26.1	23.2	23.7	24.5	23.6	26.0	30.1	
59	23.2	21.7	23.2	22.1	23.2	22.9	20.1	23.3	25.0	
60	23.1	23.8	25.2	21.6	22.5	21.8	20.6	24.0	27.3	
61	20.8	26.0	26.1	22.5	26.9	25.4	23.6	29.6	27.2	
62	13.9	21.6	22.9	20.2	25.0	23.3	24.0	27.5	29.0	
63x NP	21.1	25.3	23.5	22.4	21.5	19.7	14.0	21.0	19.3	
64	19.3	25.1	25.1	24.1	23.0	24.7	25.1	27.3	28.0	
65	22.1	23.8	24.3	23.6	24.0	25.0	27.1	31.0	30.1	
66	18.1	24.1	23.6	21.6	22.1	23.3	24.4	27.0	31.3	
67	18.1	25.1	24.7	26.2	26.5	26.2	27.2	30.7	31.3	
68x NP	21.1	21.9	22.2	21.9	22.7	17.2	17.8	16.8	22.1	
69	22.2	23.7	25.4	24.4	26.1	25.4	26.2	30.9	31.6	
70	18.1	22.8	23.0	21.4	20.5	23.2	22.5	26.9	30.6	
71	16.7	25.2	23.3	23.3	25.4	23.7	23.8	28.4	30.7	
72	17.8	23.2	22.3	21.9	22.1	22.5	22.8	27.0	26.5	
73	20.1	24.4	23.5	24.5	22.6	24.9	26.0	29.7	32.5	
74	20.9	23.5	23.3	22.1	21.8	22.7	24.3	27.1	30.0	
75x NP	18.4	23.1	18.3	19.4	15.7	17.7	14.2	19.6	19.8	
MEAN	19.9	23.5	24.1	22.7	23.3	23.8	23.8	27.7	29.2	
S.D.	2.39	1.48	1.34	1.59	2.17	1.26	1.99	2.18	2.05	
N	21	21	21	21	21	21	21	21	21	

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

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TABLE : A 004

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
ORAL ADMINISTRATION (GAVAGE)

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

TEST GROUP 3 (1,000 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0 - 1	1 - 3	3 - 6	6 - 8	8 - 10	10 - 13	13 - 15	15 - 17	17 - 20	
76	15.9	20.3	20.4	20.3	21.9	21.9	22.4	28.8	29.8	
77	23.7	21.3	26.3	14.6	23.5	24.6	25.1	26.8	27.2	
78	19.0	22.3	24.8	23.6	23.6	25.1	23.4	28.2	31.7	
79	18.6	21.6	23.0	20.0	22.9	21.8	22.9	25.1	28.1	
80	20.0	23.8	24.7	23.3	24.3	25.8	23.6	27.8	28.7	
81	20.9	24.5	24.2	22.9	24.8	25.0	23.1	27.6	26.8	
82	15.9	20.4	20.8	20.1	21.9	23.6	22.3	27.6	30.6	
83	22.0	23.5	24.5	25.1	25.0	27.6	26.1	28.3	30.0	
84	21.6	22.6	26.1	25.1	26.3	25.7	24.1	28.7	28.2	
85	22.6	21.8	24.8	24.8	24.7	24.5	24.4	29.3	31.8	
86	18.6	19.5	20.7	20.0	21.5	21.8	21.0	26.1	26.5	
87	21.6	24.6	26.8	25.5	27.3	27.5	26.1	32.2	32.4	
88	18.1	22.3	23.1	23.7	22.3	24.1	23.9	28.3	30.2	
89	21.9	24.9	25.6	24.6	23.1	25.1	25.9	30.6	30.8	
90	24.4	29.3	29.5	28.6	29.1	30.1	40.4	35.1	35.5	
91	17.4	23.8	22.8	21.5	23.1	22.7	24.7	27.2	30.5	
92	18.3	23.5	23.2	23.1	23.0	23.3	23.5	25.6	27.2	
93	18.4	23.6	21.9	20.8	20.8	22.3	20.6	26.4	26.6	
94	16.5	20.0	18.1	20.6	19.3	19.7	19.6	25.3	27.4	
95	19.1	22.6	22.6	22.5	22.9	23.5	23.1	28.5	27.7	
96	17.4	24.4	23.1	21.6	22.6	23.0	23.4	27.5	28.6	
97 x NP	18.8	22.9	22.5	22.4	21.8	17.9	13.0	14.5	20.5	
98	22.8	26.3	27.0	25.8	23.5	25.0	26.0	31.5	32.3	
99	17.1	22.8	22.2	23.2	24.1	22.5	26.3	27.1	28.8	
100	17.2	22.3	20.8	21.5	20.2	20.5	20.4	23.8	24.9	
MEAN	19.5	23.0	23.6	22.6	23.4	24.0	24.3	28.1	29.3	
S.D.	2.52	2.15	2.56	2.80	2.18	2.35	3.92	2.47	2.43	
N	24	24	24	24	24	24	24	24	24	

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

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TABLE : A 006

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

TEST GROUP 1 (100 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0	1	3	6	8	10	13	15	17	20
26	240.6	239.7	246.0	261.3	262.1	269.2	285.7	289.4	307.6	330.3
27	249.8	257.3	264.3	283.1	286.6	300.5	321.0	316.9	337.8	388.5
28	243.8	244.7	257.7	275.0	282.3	288.2	308.2	324.1	336.1	394.8
29	250.0	258.2	264.9	279.0	283.3	294.5	313.4	327.5	348.4	409.9
30	250.1	262.3	268.6	290.6	291.0	313.3	334.5	350.4	372.2	432.9
31	250.1	254.4	266.9	284.1	285.3	298.9	320.1	331.0	354.7	413.5
32	238.9	244.7	254.2	268.8	269.4	277.0	284.3	290.1	313.0	370.4
33	259.2	261.4	269.7	285.1	289.6	309.9	328.1	342.1	367.4	423.8
34	247.3	248.8	258.7	273.0	275.9	287.3	306.2	316.5	343.6	391.9
35	258.8	260.4	269.2	285.6	294.9	307.1	320.3	330.5	353.8	404.5
36	252.7	254.7	265.4	282.4	284.9	301.1	320.6	331.0	354.3	403.2
37	239.4	241.9	255.4	259.2	265.5	273.9	285.8	287.4	312.6	340.7
38x NP	268.9	266.5	285.4	296.2	305.2	311.4	311.8	298.9	300.1	294.7
39	237.7	242.4	254.6	265.2	277.2	281.5	295.8	308.9	338.4	387.3
40	243.3	243.1	251.2	261.2	269.6	281.8	294.6	304.4	322.0	366.6
41x NP	260.6	259.0	271.4	279.8	284.0	291.3	295.0	286.6	287.0	282.0
42x NP	243.8	245.6	254.8	264.0	269.3	272.4	271.5	268.6	273.8	273.2
43	241.6	247.8	264.7	268.6	286.8	297.0	308.5	324.4	349.1	388.4
44	265.3	267.8	280.2	285.1	292.4	304.0	331.0	342.5	372.2	433.2
45	234.1	235.8	246.4	254.9	259.6	269.7	283.4	293.3	314.8	361.8
46	254.1	256.8	269.5	285.3	293.1	312.5	329.0	347.4	376.5	430.5
47	259.8	262.2	279.6	287.8	298.2	307.9	326.7	338.0	360.7	409.0
48	252.1	254.8	270.6	279.6	288.7	295.3	312.6	325.2	349.6	394.9
49	236.4	242.5	254.2	272.2	281.9	293.1	312.0	315.6	342.2	385.6
50x NP	224.4	225.5	236.6	243.3	242.4	252.2	255.2	254.2	261.1	263.6
MEAN	247.9	251.5	262.5	275.6	281.8	293.5	310.6	320.8	344.1	393.4
S.D.	8.66	9.04	9.60	10.68	11.07	13.85	16.54	19.32	20.75	28.05
N	21	21	21	21	21	21	21	21	21	21

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

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TABLE : A 007

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

TEST GROUP 2 (400 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0	1	3	6	8	10	13	15	17	20
51	251.6	256.9	269.1	291.1	300.9	311.2	331.5	346.5	371.3	428.0
52	232.4	238.1	246.7	263.0	265.4	268.9	293.8	305.0	329.0	375.4
53x NP	244.0	247.3	255.3	271.9	269.2	277.6	279.4	282.4	268.9	277.5
54	245.5	252.9	254.7	276.9	276.0	289.6	301.9	308.7	325.6	360.3
55	234.7	246.6	249.2	268.0	271.8	278.4	299.2	314.6	328.1	373.6
56	228.0	231.6	239.8	254.1	256.1	259.8	278.0	290.7	310.6	358.9
57	242.3	243.2	253.8	273.4	280.5	294.8	314.4	327.9	351.8	408.6
58	245.5	250.5	261.3	279.5	283.3	295.0	311.9	319.2	331.6	370.8
59	231.7	243.1	248.7	261.7	266.9	274.6	296.5	301.8	322.6	374.0
60	252.2	261.1	272.4	290.9	293.2	303.3	320.5	329.0	342.8	387.5
61	242.0	242.3	256.2	275.2	275.7	292.5	308.8	323.9	348.4	400.9
62	246.5	245.0	262.2	277.3	281.0	301.2	314.7	324.2	349.7	390.8
63x NP	245.0	248.9	266.5	277.2	286.3	290.4	292.7	283.0	285.9	279.2
64	267.0	271.8	285.8	302.7	310.5	317.1	339.7	353.6	379.0	426.2
65	254.7	257.9	272.1	287.8	294.5	307.4	327.8	342.5	376.7	426.4
66	248.1	250.7	263.6	273.7	277.0	284.9	302.2	314.4	340.9	396.5
67	252.9	255.4	272.9	280.8	290.6	301.8	321.2	334.3	361.1	408.6
68x NP	239.1	246.9	256.8	265.8	272.8	282.3	270.4	268.3	263.5	269.9
69	275.8	284.3	295.5	306.2	314.3	321.9	336.3	346.2	372.8	416.1
70	249.2	251.4	266.0	274.3	280.5	288.4	310.3	317.2	345.1	394.9
71	249.7	251.9	269.1	279.0	287.8	301.1	316.3	328.8	355.5	406.7
72	240.3	247.9	260.8	272.3	278.4	287.4	304.2	317.5	348.5	398.7
73	257.5	260.0	274.7	288.9	296.4	307.8	326.6	341.8	368.4	422.8
74	228.9	233.8	244.0	255.2	260.9	271.4	289.6	304.5	328.7	386.5
75x NP	228.4	229.2	240.2	236.0	242.7	244.4	247.9	242.4	253.0	248.2
MEAN	246.5	251.3	262.8	277.7	282.9	293.3	311.7	323.4	347.1	395.8
S.D.	11.99	12.11	13.84	13.68	15.22	16.32	15.89	16.68	19.51	21.60
N	21	21	21	21	21	21	21	21	21	21

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

15-AUG-94

93046

PROJECT NO. 30R0246/93046: PRENATAL TOXICITY STUDY IN RATS
 ORAL ADMINISTRATION (GAVAGE)
 INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

TABLE : A 008

TEST GROUP 3 (1,000 MG/KG BW/D)

FEMALE#	DAY OF GESTATION									
	0	1	3	6	8	10	13	15	17	20
76	237.8	239.9	250.0	262.9	267.8	279.1	296.3	313.8	343.1	404.0
77	257.7	267.4	268.2	291.6	272.7	302.2	320.9	340.0	363.9	419.2
78	255.6	256.3	265.0	284.6	289.1	301.2	320.9	332.2	354.1	416.9
79	240.7	246.1	254.4	266.9	267.1	280.5	295.0	307.2	326.5	371.6
80	258.1	261.8	269.0	284.9	290.0	299.5	322.2	332.1	354.7	403.2
81	257.5	267.3	277.9	292.6	295.8	308.8	328.3	339.4	364.9	419.1
82	241.0	240.0	247.2	265.1	265.5	276.5	294.0	303.6	327.6	384.7
83	253.7	258.7	267.9	284.7	293.4	304.7	331.3	344.2	364.4	422.5
84	255.5	262.6	272.2	291.9	293.1	306.1	326.1	334.5	355.1	398.0
85	252.8	258.5	267.7	290.0	301.1	308.5	331.2	341.2	360.9	423.0
86	238.3	245.0	244.5	261.6	263.4	277.2	295.8	303.8	324.9	368.4
87	259.8	269.3	281.8	298.5	309.8	321.0	346.7	352.0	381.9	428.7
88	248.1	250.1	264.8	279.3	289.9	298.9	315.5	325.6	354.1	402.4
89	256.1	265.3	277.2	293.1	299.1	308.1	329.0	341.8	373.6	428.8
90	263.3	273.5	289.3	308.6	312.4	329.8	350.0	367.5	404.2	462.5
91	235.9	238.1	254.0	265.9	270.8	283.2	297.1	308.3	333.2	378.8
92	240.8	248.7	259.6	269.4	274.8	287.0	304.9	312.5	333.6	367.0
93	241.9	247.9	261.0	269.2	274.1	284.2	301.1	306.3	337.2	384.3
94	251.3	254.0	264.7	266.4	275.1	283.5	296.6	305.4	333.7	386.1
95	258.8	266.4	276.2	289.9	298.7	309.7	327.0	334.2	362.6	393.6
96	250.8	251.4	265.7	274.5	285.2	293.7	311.0	319.2	345.0	383.5
97 x NP	238.2	244.2	259.1	265.1	270.9	278.1	275.4	272.7	266.2	270.9
98	256.3	264.4	279.0	297.8	306.5	315.5	336.9	351.0	380.8	430.5
99	229.9	233.2	250.3	264.0	274.3	289.1	304.5	318.3	340.2	392.4
100	227.7	227.6	239.2	246.4	253.3	262.5	276.2	287.2	312.9	360.7
MEAN	248.7	253.9	264.5	279.2	284.3	296.3	314.9	325.9	351.4	401.2
S.D.	10.13	12.42	12.72	15.30	16.20	16.20	18.82	19.61	21.47	25.09
N	24	24	24	24	24	24	24	24	24	24

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

