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TEST ITEM

**ETHYL TERTIARY BUTYL ETHER (ETBE)
CAS No. 637-92-3**

STUDY TITLE

**TWO-GENERATION STUDY
(REPRODUCTION AND FERTILITY EFFECTS)
BY ORAL ROUTE (GAVAGE) IN RATS**

STUDY DIRECTOR

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STATEMENT OF THE STUDY DIRECTOR

The study was conducted in compliance with the following Good Laboratory Practice regulations:

- . OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17,
- . Commission Directive 1999/11/EC of 8 March 1999 adapting to technical progress the Principles of Good Laboratory Practice as specified in Council Directive 87/18/EEC on the harmonization of laws, regulations and administrative provisions relating to the application of the Principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances (OJ No. L 77 of 23.3.1999),
- . Décret N° 98-1312 du 31 décembre 1998 concernant les Bonnes Pratiques de Laboratoire (Journal Officiel du 1er janvier 1999), Ministère de l'Economie, des Finances et de l'Industrie,
- . US Environmental Protection Agency, Federal Register, 40 CFR Part 792 ; Toxic Substances Control Act; Good Laboratory Practice Standards, August 17, 1989 (and subsequent amendments),
- . Japanese Ministry of International Trade and Industry, Good Laboratory Practice Standards, Basic Industries Bureau, KanHogyo No. 39, March 31, 1984.
- . Japanese Ministry of Health and Welfare, Good Laboratory Practice Standards, Pharmaceutical Affairs Bureau, YakuHatsu No. 229 and Environmental Agency, 59 KiKyoku No. 85, March 31, 1984.

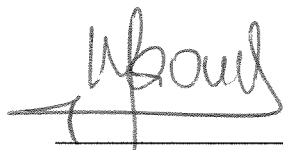
The two exceptions were the measurement of spontaneous locomotor activity and anogenital distance of the pups which were carried out with an equipment which was not GLP-validated. This is not expected to affect the validity of the results obtained or the conclusions drawn from these data.

The study was conducted in compliance with Animal Health regulation, in particular:

- . Council Directive No. 86/609/EEC of 24th November 1986 on the harmonization of laws, regulations or administrative provisions relating to the protection of animals used for experimental or other scientific purposes.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

This study was performed at CIT, BP 563, 27005 Evreux, France.



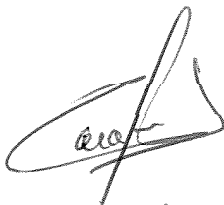
W. Gaoua
Study Director

Doctor of Reproductive Toxicology, Ph.D.

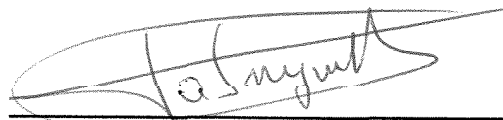
Study completion date: 16 July 2006

OTHER SCIENTISTS INVOLVED IN THE STUDY


Pharmacy


po S. Garapon
X. Manciaux Date: 16 July 2004
Doctor of Pharmacy
Head of Pharmacy

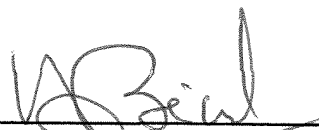
Analytical Chemistry


G. Fabreguettes Date: 15 July 2004
D.E.S.S. (Analytical Chemistry)

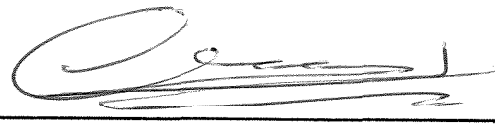
Toxicology


O. Foulon Date: 16 July 2004
Doctor of Pharmacy, Ph.D.
Head of Reproductive Toxicology

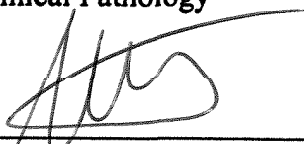
Macroscopic and microscopic examinations


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S. de Jouffrey Date: 16 July 2004
Doctor of Veterinary Medicine
Director of Operations

STATEMENT OF QUALITY ASSURANCE UNIT

| Type of inspection | Dates | | |
|--------------------|------------------|-----------------------------------|-------------------------------|
| | Inspection | Reported to Study Director (*) | Reported to Management (*) |
| Study plan | 13 March 2003 | 20 March 2003 | 07 April 2003 |
| Study inspection | 07 April 2003 | 09 April 2003 | 10 April 2003 |
| Study inspection | 23 April 2003 | 25 April 2003 | 19 May 2003 |
| Study inspection | 12 June 2003 | 23 June 2003 | 24 June 2003 |
| Study inspection | 02 July 2003 | 07 July 2003 | 24 July 2003 |
| Study inspection | 23 July 2003 | 30 July 2003 | 11 August 2003 |
| Study inspection | 25 July 2003 | 30 July 2003 | 08 August 2003 |
| Data audit | 31 July 2003 | 03 August 2003 | 08 August 2003 |
| Study inspection | 02 October 2003 | 07 October 2003 | 09 October 2003 |
| Data audit | 13 October 2003 | 14 October 2003 | 06 April 2004 |
| Study inspection | 09 December 2003 | 10 December 2003 | 12 December 2003 |
| Report | 26 May 2004 | 22 June 2004 | 12 July 2004 |

In addition to the above-mentioned inspections, at about the same time as this study described in the present report, process-based and routine facility inspections of critical procedures relevant to this study were also made by the Quality Assurance Unit.

The findings of these inspections were reported to the Study Director and to CIT Management.

The inspections were performed in compliance with CIT Quality Assurance Unit procedures and Principles of Good Laboratory Practice.

The reported methods and procedures were found to describe those used and the results to constitute an accurate and complete reflection of the study raw data.



C. Galli-Kar Date: 16 July 2004
Ing. Biol.
Head of Quality Assurance Unit

(*) The dates indicated correspond to the dates of signature of audit reports by Study Director and Management.

SUMMARY

The objective of the study was to evaluate the potential effects of the test item, ETHYL TERTIARY BUTYL ETHER (ETBE), CAS No. 637-92-3, on the integrity and functioning of the male and female reproductive systems, including gonadal function, the estrous cycle, mating behaviour, conception, gestation, parturition, lactation and weaning, and on the growth and development of the offspring over two generations.

Methods

Three groups of 25 female and 25 male Sprague-Dawley rats received the test item, ETHYL TERTIARY BUTYL ETHER (ETBE), batch numbers S02-08-159-I3 (S02-08-159-I3 /1, S02-08-159-I3/2) and 308 596, by daily oral administration (gavage) at 250, 500 or 1000 mg/kg/day as follows:

F0 generation

- . 10 weeks before mating, during a 2-week mating period and until sacrifice (after weaning of the pups) for the males,
- . 10 weeks before mating, during mating, pregnancy and lactation periods (until day 21 *post-partum*) for the females.

A group of 25 males and 25 females received the vehicle (corn oil) under the same experimental conditions and acted as a reference control group.

F1 generation

After weaning of the F1 generation, on day 22 *post-partum*, three groups of 25 male and 25 female Sprague-Dawley rats received the test item, ETHYL TERTIARY BUTYL ETHER (ETBE), under the same experimental conditions as described above, during growth, mating, pregnancy and lactation, until weaning of the F2 generation.

A group of 25 males and 25 females received the vehicle alone (corn oil) under the same experimental conditions and acted as a reference control group.

F2 generation

At weaning of the F2 generation, on day 22 *post-partum*, three groups of 25 male and 25 female Sprague-Dawley rats received the test item, ETHYL TERTIARY BUTYL ETHER (ETBE), under the same experimental conditions as described above until sexual maturity.

A group of 25 males and 25 females received the vehicle alone (corn oil) under the same experimental conditions and acted as a reference control group.

Examination of F0 generation

Clinical signs and mortality were checked daily, and food consumption and body weight data recorded at designated intervals. The estrous cycle was monitored 3 weeks before mating and during the mating period.

Males and females were paired for up to 2 weeks or until mating occurred.

The F0 females were allowed to deliver normally, and rear their progeny. Pregnancy and litter parameters were recorded and anogenital distance was measured on day 1 *post-partum*.

During the lactation period, the pups (F1 generation) were observed daily for survival and clinical signs; body weight was recorded at designated intervals; the sex-ratio was recorded.

On day 4 *post-partum*, the size of each litter was adjusted to give eight pups per litter (four males and four females).

Reflex development was assessed at designated time-points.

The F0 parent males and females were sacrificed after weaning of their progeny.

Examination of F1 generation

On day 22 *post-partum*, one or two male and female pups per litter (progeny of F0 females) were selected to constitute the F1 generation, which comprised a total of 25 males and 25 females per dose group.

The F1 animals were observed daily for clinical signs and mortality, and body weight and food consumption data recorded once a week. Time to acquisition of sexual milestones was recorded for both males and females. Neurobehavioural tests were conducted at designated intervals to assess auditory and visual functions. Spontaneous locomotor activity was also evaluated when the animals were between 7 and 8 weeks old.

The estrous cycle was monitored 3 weeks before mating and during the mating period.

F1 males and females were paired for up to 2 weeks or until mating occurred. Brother/sister matings were avoided.

The F1 females were allowed to deliver normally, and rear their progeny. Pregnancy and litter parameters were recorded, including anogenital distance on day 1 *post-partum*.

During the lactation period, the pups (F2 generation) were observed daily for survival and clinical signs; body weight was recorded at designated intervals; the sex-ratio was recorded. On day 4 *post-partum*, the size of each litter was adjusted to give eight pups per litter (four males and four females).

Reflex development was assessed at designated time-points.

Examination of the F2 generation

On day 22 *post-partum*, one or two male and female pups per litter (progeny of F1 females) were selected to constitute the F2 generation, which comprised 25 males and 25 females per group.

The F2 animals were observed daily for clinical signs and mortality. Body weight and food consumption were recorded once a week. Time to acquisition of sexual milestones was recorded for both sexes.

Terminal examination of F0, F1 and F2 animals

After weaning of their respective progeny, F0 and F1 parental males and females were sacrificed.

Selected organs from F0 and F1 parents were weighed together with brain, spleen, thymus and thyroid from one pup per sex per litter from each generation.

Epididymal and testicular sperm parameters were evaluated in F0 and F1 males.

A macroscopic *post-mortem* examination was performed on all F0 and F1 parent animals (both sexes), on F2 animals at sexual maturity and on three weaned (non-selected) pups per sex per litter from each of the F0 and F1 females.

Any pups which died during the lactation period or were otherwise not selected for use in the study were also submitted to macroscopic *post-mortem* examination.

Macroscopic lesions, reproductive organs, adrenal glands, and pituitary glands from all parental animals were sampled and preserved. Any macroscopic lesions present in the pups were also preserved.

A microscopic examination was performed on any macroscopic lesions, the reproductive organs, adrenals and pituitary glands from all F0 and F1 parents from the control and high-dose groups together with testis from intermediate and low-dose males.

Ovaries and testis were subject to a particularly detailed histological examination.

Results

F0 generation

Group 4: 1000 mg/kg/day

- . transient ptyalism (excess salivation) was observed in most animals (similar or decreased incidence in females during pregnancy and lactation),
- . for the males, significantly lower body weight gain was recorded at the end of the treatment period (days 85 to 113, -29%, $p < 0.01$),
- . for the females, higher food consumption was recorded during the lactation period (days 1 to 21, +10%, $p < 0.001$),
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . no gross abnormalities were present in pups born to F0 females,
- . no effects were observed on the progeny from delivery until weaning,
- . absolute and relative liver weights were increased significantly (+17% and +24%, respectively, $p < 0.01$) in males and appeared related to the presence of slight to moderate centrilobular hypertrophy in liver tissue from three parental males that was subjected to histopathological examination,
- . absolute and relative kidneys weights were significantly greater in males (+21% and +28%, respectively, $p < 0.01$) and correlated with the presence of acidophilic globules (slight to moderate severity) in renal tissue from 5 of 6 males selected for histological evaluation,
- . sperm parameters were unaffected by treatment.

Group 3: 500 mg/kg/day

- . transient ptyalism was observed in most males and a few females,
- . for the males, significantly lower body weight gain was noted at the end of the treatment period (days 85 to 113, -22%, $p < 0.001$),
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . no effects were apparent on the progeny from delivery until weaning,
- . absolute and relative kidney weights were increased in males (+15% and +18%, respectively, $p < 0.01$),
- . there were no macroscopic or microscopic findings in parents (male or female) or their progeny (including no gross abnormalities),
- . sperm parameters were unaffected by treatment.

Group 2: 250 mg/kg/day

- . transient ptyalism was observed in a few males and females,
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . no effects were observed on the progeny from birth until weaning,
- . there were no macroscopic and microscopic findings or organ weight effects in parents (male or female) or their progeny (including no gross abnormalities),
- . sperm parameters were unaffected by treatment.

F1 generation

Group 4: 1000 mg/kg/day

- . transient ptyalism was observed in most males and a majority of females (decreased incidence in females during pregnancy and lactation),
- . body weight, body weight gain and food consumption were unaffected in both sexes during the dosing period,
- . there was no effect on sexual development or on neurobehavioural parameters,
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . pup body weight gain was slightly lower during the first 4 days of lactation (-12%, not significant),
- . two pups (born to F1 females) exhibited gross external malformations (absence of tail with anal atresia also present in one pup),
- . no other observations were noted on the progeny from birth until weaning and there were no macroscopic findings or organ weight effects,
- . in parents, absolute and relative kidney weights were increased significantly in males (+58%, $p < 0.01$) and slightly but significantly increased in females (+11% and +10% respectively, $p < 0.01$); the changes in the males correlated with the presence of acidophilic globules (slight to moderate severity) in renal tissue from four animals subject to microscopic evaluation,
- . absolute and relative liver weights were increased in parental males (+27% and +25%, respectively $p < 0.01$) and correlated with liver enlargement recorded during gross necropsy, and the occurrence of slight or moderate centri-lobular hepatocellular hyperthrophy in tissue from two males that were subject to microscopic examination,
- . absolute and relative liver weights were significantly greater in parental females (+10 and +9 %, respectively, $p < 0.05$; no microscopic examination),
- . sperm parameters were unaffected by treatment.

Group 3: 500 mg/kg/day

- . transient ptyalism was observed in most males and a majority of females (only a few females affected during pregnancy and lactation),
- . body weight, body weight gain and food consumption were unaffected in both sexes,
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . no effects were apparent on the progeny from delivery until weaning,
- . absolute and relative liver weights were increased significantly in parental males (+14% $p < 0.05$ and +11% $p < 0.01$, respectively),
- . absolute and relative kidney weights were increased significantly in parental males (+22% and +19%, respectively, $p < 0.01$),
- . there were no macroscopic or microscopic findings in parents (males or female) or their progeny (including no gross abnormalities),
- . sperm parameters were unaffected by treatment.

Group 2: 250 mg/kg/day

- . transient ptyalism was observed in a majority of males and some females (only a few females affected during pregnancy and lactation),
- . no effects were apparent on mating, fertility, gestation, fecundity or delivery,
- . no effects were observed on the progeny from birth until weaning,
- . there were no macroscopic findings or organ weight effects in parents (male or female) or their progeny (including no gross abnormalities),
- . there were no microscopic findings,
- . sperm parameters were unaffected by treatment.

F2 Generation

250, 500 and 1000 mg/kg/day

- . transient ptialism was observed in approximately one half of the high-dose males and females, and a few animal from the lower dose-groups,
- . no effect was noted on body weight, body weight gain or food consumption in either sex during the dosing period,
- . sexual development was unaffected by treatment,
- . there were no macroscopic findings.

Conclusion

The test item, ETHYL TERTIARY BUTYL ETHER (ETBE), CAS No. 637-92-3, was administered daily by oral gavage to male and female Sprague-Dawley rats at 250, 500 and 1000 mg/kg/day, commencing 10 weeks prior to mating and continuing through mating and gestation until the end of lactation in both the F0 and F1 generations. Progeny of the F1 generation (F2 pups) were treated from weaning until sexual maturity.

For all generations, ptyalism (excessive salivation) was observed with a dose-related trend in both males and females.

At 1000 mg/kg/day, F0 males showed significantly lower body weight gain at the end of the dosing period. Liver weight was significantly increased in males only, with slight to moderate centrilobular hepatocellular hypertrophy in tissue from animals subject to microscopic examination. Kidney weights were also significantly increased in F0 parental males, with acidophilic globules detected after microscopic examination. There were no adverse findings for F0 pups. Significantly greater food consumption during the lactation period was the only finding of note in F0 parental females.

Liver and kidney weights were significantly increased in F1 parental males.

Body weight gain of pups born to mothers from the F1 generation was slightly but non-significantly lower than the controls on *post-partum* days 1-4 (no comparable finding in F0 litters). Two pups born to mothers from the F1 generation exhibited gross external malformations (absence of tail with anal atresia also present in one pup), however the incidence of these findings was comparable to laboratory or external historical control data. Neither malformation was present in 566 pups or fetuses from 45 litters from dams treated with ETBE at 1000 mg/kg body weight/day as part of a dose-range finding study and a developmental toxicity study performed at this laboratory. It was concluded that the findings from the present study were therefore most probably unrelated to treatment with the test item.

No effects were noted in the F2 generation at 1000 mg/kg/day.

At 500 mg/kg/day, significantly lower body weight gain was noted at the end of the dosing period in F0 parental males together with significantly increased kidney weights. Liver and kidney weights were statistically significantly increased in F1 parental males, whereas body weight was unaffected. No effects were noted in the F2 generation.

At 250 mg/kg/day, no relevant findings were observed in the F0, F1 and F2 generations.

Based on these observations, the following No Observed Adverse Effect Levels were established from the study:

Systemic toxicity in the adult (parental) F0 and F1 generations: NOAEL = 250 mg/kg body weight/day (based on body weight and organ weight changes at higher treatment levels).

Ptyalism (excess salivation) was noted in all treated animals (LOEL = 250 mg/kg body weight/day but was not considered to represent an adverse effect of treatment).

Fertility, gonadal function, reproductive performance, parturition and lactation in the parental generations, and development of the off-spring to weaning or sexual maturity: NOAEL = 1000 mg/kg body weight/day (the highest dose tested).

1. INTRODUCTION

1.1 OBJECTIVE

The objective of this study was to provide information on the potential effects of the test item, ETHYL TERTIARY BUTYL ETHER (ETBE; CAS No. 637-92-3), on the integrity and functioning of the reproductive system of male and female Sprague-Dawley rats, including gonadal function, the estrous cycle, mating behavior, conception, gestation, parturition, lactation and weaning, and on the growth and development of the offspring.

The rat was chosen because it is a rodent species commonly accepted by regulatory authorities for this type of study and the Sprague-Dawley strain was selected since background data from previous studies are available at our laboratory.

The oral route was selected since it is acceptable under OECD guidelines for studies of this type and since the uptake of ETBE from the gastrointestinal tract is expected to be rapid and complete.

The dose-levels were selected in agreement with the Sponsor, on the basis of results from a previously conducted study (*CIT/Study No. 24168 RSR*).

1.2 REGULATORY COMPLIANCE

This study was designed to comply with:

- . OECD Guideline No. 416, 22nd January 2001,
- . US EPA Guideline OPPTS 870.3800, August 1998,
- . EC Commission Directive 87/302/EEC of Nov. 18, 1987.

2. MATERIALS AND METHODS

2.1 TEST AND CONTROL ITEMS

2.1.1 Identification

2.1.1.1 Test item

- . Supplier : TOTAL France S.A., Paris-la-Défense, France (purified by SEPAREX, Champagneulles, France)
- . Name : ETHYL TERTIARY BUTYL ETHER
- . Name at receipt : purified ETBE
- . Synonym : Ethyl-tert-Butyl Ether, ETBE, 2-ethoxy-2-methylpropane
- . Batch numbers : **S02-08-159-I3** (subdivided in two aluminum drums referenced as follows:
 - S02-08-159-I3/1 (utilization from 27 March to 30 April 2003)
 - S02-08-159-I3/2 (utilization from 30 April to 6 August 2003))
- . **308 596** (utilization from 13 August 2003)
- . CAS No. : 637-92-3
- . Expiry date : 25 September 2003 (for the first batch)
25 June 2004 (for the second batch)
- . Description : colorless liquid
- . Purity : >98%
- . Container : two aluminium drums (for the first batch)
30 brown glass containers (for the second batch)
- . Intended use : oxygenate additive for automotive fuels
- . Date of receipt : 11 September 2002 (for the first batch)
30 May 2003 (for the second batch)
- . Storage conditions : at room temperature, in well-closed containers (flammable) protected from light.

An analytical certificate, provided by the Sponsor, is presented in Appendix 1.
Confirmation of the correct identity of the test item is the responsibility of the Sponsor.

2.1.1.2 Vehicle

The vehicle was corn oil, batch Nos. 62K0006, 81K2204 and 122K0131, supplied by Sigma (Saint-Quentin-Fallavier, France), batch No. 0007018913, supplied by Cooper (Melun, France).

2.1.2 Dosage form preparation

The test item was administered as a solution in the vehicle.

The test item was mixed with the required quantity of vehicle in order to achieve concentrations of 62.5, 125 and 250 mg/mL and then homogenized using a magnetic stirrer.

The test item dosage forms were prepared once a week and stored at room temperature (in a well closed bottle) prior to use, based on satisfactory stability results obtained in a range finding study (*CIT/Study No. 21468 RSR*) for the first batch (S02-08-159-I3) and in the current study for the second batch (308 596). The dosage form preparations were sub-divided into a suitable number of aliquots so that one bottle per dose per day was opened for dosing. The unused residue remaining in each opened bottle was discarded after use.

2.1.3 Chemical analysis of the dosage forms

Before the start of treatment or during the treatment period (when the batch number altered), the suitability of the proposed preparation procedure was determined by the analysis of homogeneity and stability of dosage forms prepared (according to the procedure) for each batch used in the study (S02-08-159-I3 and 308 596). During the treatment period, the concentration of dosage forms prepared for used in the study was checked.

2.1.3.1 Homogeneity

Two dosage forms were prepared (with each batch of test item), under conditions representative of those of the study, as follows:

- . a dosage form at the lowest concentration (62.5 mg/mL),
- . a dosage form at the highest concentration (250 mg/mL).

Duplicate samples were taken at three different levels within the container (top, middle, bottom) and analyzed for concentration of the test item to evaluate homogeneity.

2.1.3.2 Stability

A previous study performed with the test item batch No. S02-08-159-I3 (*CIT/Study No. 24168 RSR*) demonstrated satisfactory stability of the dosage forms (ETBE concentration in the range 1-333 mg/mL) over a 9-day period at room temperature.

During the current study, the two dosage forms at 62.5 and 250 mg/mL prepared with the second batch of test item (308 596) were sampled just after preparation and again after 4 and 9 days storage at room temperature. Each sample was analyzed as soon as possible after sampling.

2.1.3.3 Concentration

The concentration of ETBE in the dosage forms (including the control) prepared for use in weeks 1 and 2 was confirmed by gas chromatography. These analyses were then performed at four-weekly intervals on subsequent batches of dosing solution. In addition, two samples (2 mL) were taken from all control or test dosage forms prepared during the other weeks of the study and stored frozen (-20°C) for possible future analysis (not performed). These samples are discarded upon finalization of the present report.

The analytical procedure used is presented in Appendix 2.

2.2 TEST SYSTEM

2.2.1 Animals (F0 animals)

Number: 220 rats were received at CIT on 25 March 2003 (110 males and 110 females).

Strain and sanitary status: Sprague-Dawley, CrI CD® (SD) IGS BR, *Caesarian Obtained, Barrier Sustained-Virus Antibody Free*, (COBS-VAF®).

Breeder: Charles River Laboratories France, L'Arbresle, France.

Age/Weight: at the beginning of the treatment period, the animals were 6 weeks old and had a mean body weight of 203 g (range: 181 to 226 g) for the males and 157 g (range: 136 to 201 g) for the females. The females were sexually mature and nulliparous.

Acclimation: a 6-day acclimation period to the conditions of the study preceded the beginning of the treatment period.

Allocation to study: during the acclimation period, the required number of animals (100 males and 100 females) was selected according to body weight and clinical condition and allocated to the groups (by sex), according to a computerized stratification procedure, so that the average body weight of each group was similar. A larger number of animals than necessary was acclimated to permit selection and/or replacement of individuals. Body weight recorded during the acclimation period are not presented in the report but kept in the raw data.

Identification: each animal was individually identified by an ear tattoo and received a unique CIT identity number.

2.2.2 Environmental conditions

From arrival at CIT, the animals were housed in a barriered rodent unit, under specific pathogen free (SPF) standard laboratory conditions.

The animal room conditions are set as follows:

- . temperature : $22 \pm 2^{\circ}\text{C}$
- . relative humidity : $50 \pm 20\%$
- . light/dark cycle : 12h/12h (7:00 - 19:00)
- . ventilation : about 12 cycles/hour of filtered, non-recycled air.

The relevant instrumentation and equipment are checked and calibrated at regular intervals. The temperature and relative humidity were checked regularly and daily records filed.

The animal room was disinfected before the arrival of the animals and cleaned regularly thereafter.

2.2.3 Housing

The F0 animals were housed individually in wire-mesh cages (43.0 x 21.5 x 18.0 cm). A metal tray, containing autoclaved sawdust (SICSA, Alfortville, France), was placed under each cage.

Prior to delivery and during lactation the F0 and F1 females were housed individually in polycarbonate cages (43.0 x 21.5 x 20.0 cm) containing autoclaved sawdust (SICSA, Alfortville, France). Autoclaved wood shavings (SDS, Alfortville, France) were provided as nesting material, a few days before delivery and during the lactation period.

The cages were placed in numerical order on the racks. On a monthly basis, all the racks were moved clockwise around the room, rack by rack. In this way, for each group, identical exposure to environmental conditions was achieved.

2.2.4 Food and water

The animals had free access to A04 C pelleted maintenance diet, batch Nos. 30130, 30227, 30407, 30423, 30227, 30514, 30616, 30905 and 30925 (SAFE, Villemoisson, Epinay-sur-Orge, France) replenished weekly. The diet formula is presented in Appendix 3.
The animals had free access to bottles containing tap water (filtered with a 0.22 µm filter).

2.2.5 Contaminant analyses

The batches of diet, sawdust and wood shavings were analyzed by the suppliers for composition and contaminant levels.

Bacterial and chemical analyses of water are performed regularly by external laboratories. These analyses include the detection of possible contaminants (pesticides, heavy metals and nitrosamines).

No contaminants were present in the diet, drinking water, sawdust or wood shavings at levels which may be expected to interfere with or prejudice the outcome of the study.

2.3 TREATMENT (F0 animals)

2.3.1 Treatment groups

Rationale for dose-level selection

The dose-levels were selected in agreement with the Sponsor on the basis of a previously conducted study (CIT/Study No. 24168 RSR). The results demonstrated a slight but statistically significant decrease in body weight for pregnant female rats given 1000 mg/kg/day, and ptyalism (excess salivation) over the course of the study in both sexes given 1000 mg/kg/day. No effect on mating, pregnancy, lactation or litter data parameters was noted at 50, 250, 500 and 1000 mg/kg/day in this preliminary investigation.

Consequently, dose-levels of 250, 500 and 1000 mg/kg/day were selected for use in the main two-generation study.

It is noted that 1000 mg/kg/day is considered a limit dose for this type of investigation (OECD Guideline 416).

The treatment groups are detailed in the following table:

| Group | Number of animals | Dose-level (mg/kg/day) | Animal numbers |
|-------|-------------------|------------------------|------------------|
| 1 | 25 males | 0 | B29201 to B29225 |
| | 25 females | | B29601 to B29625 |
| 2 | 25 males | 250 | B29226 to B29250 |
| | 25 females | | B29626 to B29650 |
| 3 | 25 males | 500 | B29251 to B29275 |
| | 25 females | | B29651 to B29675 |
| 4 | 25 males | 1000 | B29276 to B29300 |
| | 25 females | | B29676 to B29700 |

2.3.2 Duration

Each animal was dosed once a day, at approximately the same time, 7 days a week, according to the following schedule:

In the males:

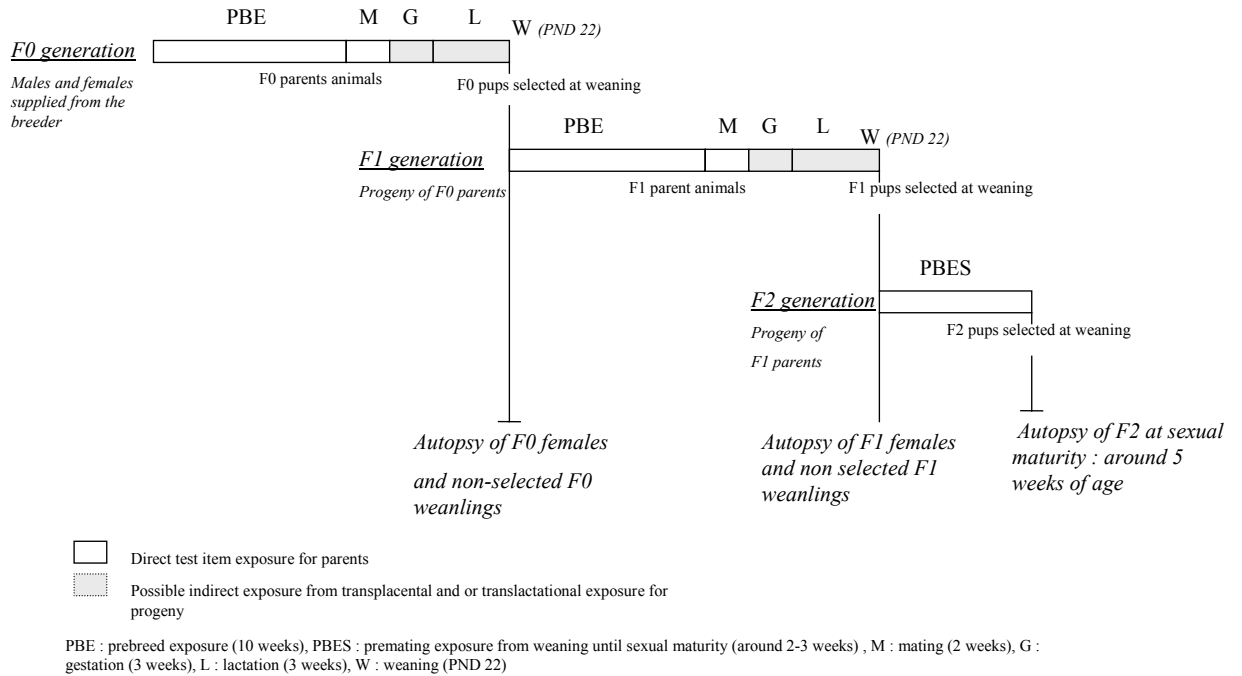
- . 10 weeks before mating,
- . during the mating period (2 weeks),
- . until sacrifice (after weaning of the pups),
- . total duration of treatment: 18 weeks.

In the females:

- . 10 weeks before mating,
- . during the mating period (2 weeks),
- . during pregnancy,
- . during lactation,
- . until sacrifice (after weaning of the pups),
- . total duration of treatment: 18 weeks.

Day 1 correspond to the first day of treatment period.

Study design



2.3.3 Administration

The oral route was selected since it is acceptable under OECD guideline for studies of this type and since uptake of ETBE from the gastrointestinal tract was expected to be rapid and complete. It is also recommended by OECD Guideline 416, and was used in the preliminary range-finding study.

The dosage forms were administered by gavage using a glass syringe fitted a metal gavage tube. The quantity of the dosage form administered to each animal was adjusted according to the most recently recorded body weight.

A constant dosage-volume of 4 mL/kg/day was used.

Control animals (group 1) received the vehicle alone.

The dosage forms were mixed regularly throughout the dosing procedure.

2.4 CLINICAL EXAMINATIONS OF F0 MALES AND FEMALES

2.4.1 Morbidity and mortality

Each animal was checked at least twice a day for mortality and signs of morbidity (once during acclimation period and at least twice a day during the treatment period).

Any animal showing signs of poor clinical condition (especially if death appears imminent), and any female having aborted, was humanely killed.

Any animal killed prematurely was subjected to a macroscopic *post-mortem* examination.

2.4.2 Clinical signs

Each animal was observed two or three times each day, for clinical signs including evidence of physical or behavioural changes together with any signs of overt toxicity (including abortion/resorption for the females).

The details and frequency of these observations are given below:

- study weeks 1 to 4 (pre-mating period): animals were inspected for clinical signs three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week,
- study weeks 5 to 9: since no clinical signs were observed at the end of study week 4, observations 1 hour and 4 hours post-dosing were discontinued,
- study week 10 (one week before mating): the animals were inspected for clinical signs twice daily (immediately post-dosing, 1 hour post-dosing), 7 days per week. Since clinical signs were present one hour post-dosing on days 67 and 68 for group 4, the animals were observed again 4 hours post-dosing,
- gestation days 0 to 14 (pregnancy period): dams were inspected three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week,
- lactation days 1 - 14: dams were inspected three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week.

On the other days, each animal was observed at least once a day, at approximately the same time for recording of clinical signs.

Observations recorded immediately post-dosing were made while the animals were handled. Observations 1 hour and 4 hours post-dosing were performed with the animals in their cages.

2.4.3 Body weight

The body weight of each male was recorded once a week until sacrifice.

The body weight of each female was recorded once a week during the pre-mating and mating periods, then on days 0, 7, 14, 20 *post-coitum* and on days 1, 7, 14 and 21 *post-partum*.

2.4.4 Food consumption

The quantity of food consumed by each male was recorded once a week until sacrifice.

The quantity of food consumed by each female was recorded once a week during the pre-mating period, then over the following intervals:

- days 0-7, 7-14 and 14-20 *post-coitum*,
- days 1-7, 7-14 and 14-21 *post-partum*.

No food consumption was recorded during mating period.

2.5 MATING

2.5.1 Monitoring of estrous cycle

The estrous cycle stage was determined by microscopic examination of a fresh vaginal lavage (stained with methylene blue), each morning as follows:

- . during the last 3 weeks of the pre-mating period,
- . during the mating period, until mating was confirmed.

2.5.2 Mating procedure

Females were paired with males from the same dose-level group: one female was placed with one male in the latter's cage during the night. Confirmation of mating was made in the morning by checking for the presence of sperm in a vaginal lavage.

The day of confirmed mating was designated day 0 *post-coitum* (*p.c.*).

Each female was placed with the same male until mating had occurred or 14 days had elapsed.

The pre-coital time was calculated for each pair.

2.6 PREGNANCY

After mating, each pair was separated.

At the end of pregnancy, the females were individually placed in appropriate cages with nesting material (see § Housing).

Females were checked for any signs of abortion/resorption (bleeding) or premature delivery during clinical monitoring.

2.7 PARTURITION

Females were allowed to litter normally and rear their progeny until weaning. Any evidence of a difficult or prolonged parturition was recorded.

The day of completed parturition was designated day 1 *post-partum*. The length of gestation was calculated.

2.8 OBSERVATION PERFORMED ON PROGENY OF F0 FEMALES DURING THE LACTATION PERIOD

Each pup was identified individually on day 1 *post-partum*, by subcutaneous injection of Indian ink.

2.8.1 Litter size

The total litter size and number of pups of each sex were recorded as soon as possible after birth. The litters were observed daily in order to note the number of live, dead and cannibalized pups. Any gross malformation in the pups was noted.

2.8.2 Litter size adjustment

On day 4 *post-partum*, the size of each litter was adjusted by randomly culling extra pups to obtain, as closely as possible, four males and four females per litter. Whenever necessary partial adjustment (for example five males and three females) was permitted. Standardization of litter size is considered to reduce the litter size-induced variability in the growth and development of pups and thus increase the sensitivity of statistical analysis (according to US EPA Guideline OPPTS 870.3800, August 1998). It also ensures that any adverse effect on pup growth and development is not masked by treatment-related differences in litter size.

2.8.3 Clinical signs

The pups were observed daily for clinical signs.

2.8.4 Body weight

The weight of each pup was recorded on days 1, 4, 7, 14 and 21 of *post-partum*.

2.8.5 Anogenital distance

Anogenital distance (AGD) was measured on day 1 *post-partum* for all pups. AGD corresponds to the distance (in millimeters) between the middle of the genital tubercle and the centrum of the anus.

The anogenital index was calculated:

$$\frac{\text{AGD}}{\text{body weight}}$$

The ratio of AGD to the cube root of body weight was also calculated.

2.8.6 Reflex development

The number of pups in each litter exhibiting the required characteristics of reflex development was recorded at designated time-points:

- . surface righting reflex (ability to re-right from a position of lateral recumbency) on day 5 *post-partum*,
- . cliff avoidance (ability to avoid falling into an empty space) on day 11 *post-partum*,
- . air-righting reflex (ability to right after falling from a short height) on day 17 *post-partum*.

2.9 TERMINAL SACRIFICE OF THE F0 GENERATION

Details of the terminal examinations performed at sacrifice of the F0 animals and their pups not selected for the F1 generation are given in § Terminal examinations and pathology.

2.10 CONSTITUTION AND TREATMENT OF THE F1 GENERATION

On day 22 *post-partum*, one or two males and one or two females per litter (from as many litters as possible) were selected to obtain 25 animals/sex/group and used to constitute the F1 generation. Day 22 *post-partum* was designated day 1 of the F1 generation.

Selected F1 animals were treated from day 1 (following the same procedure as for the F0 animals) throughout pre-mating, mating, pregnancy and until sacrifice (after weaning of their F2 progeny).

The experimental groups were as follows:

| Group | Number of animals | Dose-level (mg/kg/day) | Animal numbers |
|-------|-------------------|------------------------|------------------|
| 1 | 25 males | 0 | B29301 to B29325 |
| | 25 females | | B29701 to B29725 |
| 2 | 25 males | 250 | B29326 to B29350 |
| | 25 females | | B29726 to B29750 |
| 3 | 25 males | 500 | B29351 to B29375 |
| | 25 females | | B29751 to B29775 |
| 4 | 25 males | 1000 | B29376 to B29400 |
| | 25 females | | B29776 to B29800 |

2.11 CLINICAL EXAMINATIONS OF THE F1 GENERATION AFTER WEANING

2.11.1 Morbidity and mortality

Each animal was checked at least twice a day for mortality and signs of morbidity.

Any animal showing signs of poor clinical condition (especially if death appeared imminent), or any female having aborted, was humanely killed.

Any animal found dead or killed prematurely was subjected to a macroscopic *post-mortem* examination.

2.11.2 Clinical signs

Each animal was observed at least three times each day for the recording of clinical signs, including evidence of physical or behavioural changes together with any overt signs of toxicity (including abortion/resorption for the females).

The details and frequency of these clinical observations are given below:

- . study weeks 1 and 2 (pre-mating period): animals were inspected for clinical signs three times per day (immediately post-dosing, 1 hour post-dosing, 4 hour post-dosing), 7 days per week,
- . study weeks 3 and 4 (pre-mating period): the frequency of observations was reduced to twice daily (immediately post-dosing, 1 hour post-dosing), 5 days per week (Monday to Friday),
- . study weeks 5 to 9: routine observations ceased,
- . study week 10 (one week before mating): the animals were inspected for clinical signs twice daily (immediately post-dosing, 1 hour post-dosing), 7 days per week,
- . gestation days 0 to 14 (pregnancy period): dams were inspected three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week,
- . lactation days 1 - 14: dams were inspected three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week.

On the other days, each animal was observed at least once a day at approximately the same time for the recording of clinical signs.

Observations recorded immediately post-dosing were made while the animals were being handled. Observations 1 hour and 4 hours post-dosing were performed with the animals in their cages.

2.11.3 Body weight

The body weight of each male was recorded once a week until sacrifice.

The body weight of each female was recorded once a week during the pre-mating and mating periods, then on days 0, 7, 14, 20 *post-coitum* and on days 1, 7, 14, and 21 *post-partum*.

2.11.4 Food consumption

The quantity of food consumed by each male was recorded once a week until sacrifice.

The quantity of food consumed by each female was recorded once a week during the pre-mating periods, then over the following intervals:

- . days 0-7, 7-14 and 14-20 *post-coitum*,
- . days 1-7, 7-14 and 14-21 *post-partum*.

No food consumption was recorded during the mating period.

2.11.5 Sexual development

All male animals were observed daily between 32 and 47 days of age (i.e. day 11 to day 26 of the F1 generation), until cleavage of the balanopreputial groove (preputial separation) was observed. Individual body weight was recorded at that time.

All females were observed daily between 28 and 40 days of age (i.e. day 7 to day 19 of the F1 generation), until vaginal opening was observed. Individual body weight was recorded at that time.

2.12 NEUROBEHAVIOURAL TESTS IN THE F1 GENERATION

2.12.1 Auditory function

Acoustic startle response was assessed when the animals were 4 weeks old. This is an evaluation of the animal's automatic reaction to a specific sound (small sudden movement).

2.12.2 Pupil constriction

Pupil constriction reflex was assessed when the animals were 4 weeks old. This test evaluates the animal's automatic reaction to light (blinking the eyes).

2.12.3 Spontaneous locomotor activity

Spontaneous locomotor activity was evaluated when the animals are between 7 and 8 weeks old, using equipment fitted with an automated infra-red sensor. Each animal was tested twice at an interval of approximately 1 week. Activity was recorded over a 10-minute interval for each trial. The following parameters were recorded:

- . movements within the front of the cage,
- . movements within the back of the cage,
- . back and forth movements,
- . vertical movements.

2.13 MATING OF THE F1 GENERATION

2.13.1 Monitoring of estrous cycle

The estrous cycle stage was determined each morning by microscopic examination of a fresh vaginal lavage (stained with methylene blue), as follows:

- . during the last 3 weeks of the pre-mating period,
- . during the mating period, until mating was confirmed.

2.13.2 Mating procedure

When the animals were between 12 and 14 weeks old, females were paired overnight with males from the same dose-level group. One female was placed with one male from another litter of the same dose-level group, in order to avoid brother-sister matings from the same litter.

Confirmation of mating was made the following morning by checking for the presence of a vaginal plug or of sperm in a vaginal lavage.

The day of confirmed mating was designated day 0 *post-coitum* (*p.c.*).

Each female was placed with the same male until mating had occurred or 14 days had elapsed, whichever occurred first.

The pre-coital time was calculated for each pair.

2.14 PREGNANCY

After mating, each pair was separated.

At the end of pregnancy, the females were individually placed in appropriate cages with nesting material (see § Housing).

Females were checked for any signs of abortion/resorption (bleeding) or premature delivery during clinical monitoring.

2.15 PARTURITION

Females were allowed to litter normally and rear their progeny until weaning. Any evidence of a difficult or prolonged parturition was recorded.

The day of completed parturition was designated day 1 *post-partum*. The length of gestation was calculated.

2.16 OBSERVATIONS PERFORMED ON PROGENY OF THE F1 FEMALES DURING THE LACTATION PERIOD

Each pup was identified individually on day 1 *post-partum*, by subcutaneous injection of Indian ink.

2.16.1 Litter size

The total litter size and numbers of pups of each sex were recorded as soon as possible after birth.

The litters were observed daily in order to note the number of live, dead and cannibalized pups. Any gross malformation of the pups was noted.

2.16.2 Litter size adjustment

On day 4 *post-partum*, the size of each litter was adjusted by randomly culling extra pups to obtain as closely as possible four males and four females per litter. Whenever necessary, partial adjustment (for example five males and three females) was permitted.

Standardization of litter size was considered to reduce the litter size-induced variability in the growth and development of the pups and thus increase the sensitivity of statistical analysis (according to US EPA guideline OPPTS 870.3800, August 1998). It was also ensure that any adverse effects on pup growth and development are not masked by a treatment-related differences in litter size.

2.16.3 Clinical signs

The pups were observed daily for clinical signs.

2.16.4 Body weight

The weight of each pup was recorded on days 1, 4, 7, 14 and 21 of *post-partum*.

2.16.5 Anogenital distance

Anogenital distance (AGD) was measured on day 1 *post-partum* for all pups. AGD corresponds to the distance (in millimeters) between the middle of the genital tubercle and the centrum of the anus.

The anogenital index was calculated:
$$\frac{\text{AGD}}{\text{body weight}}$$

The ratio of AGD to the cube root of body weight was also calculated.

2.16.6 Reflex development

The number of pups in each litter exhibiting the required characteristics of reflex development was recorded at designated time-points:

- . surface righting reflex (ability to re-right from a position of lateral recumbency) on day 5 *post-partum*,
- . cliff avoidance (ability to avoid falling into an empty space) on day 11 *post-partum*,
- . air-righting reflex (ability to right after falling from a short height) on day 17 *post-partum*.

2.17 TERMINAL SACRIFICE OF THE F1 GENERATION

Details of the terminal examinations performed at sacrifice of the F1 animals and their pups not selected for the F2 generation are given in § Terminal examination and pathology.

2.18 CONSTITUTION AND TREATMENT OF THE F2 GENERATION

On day 22 *post-partum*, one or two males and one or two females per litter (from as many litters as possible) were selected to obtain 25 animals/sex/group and therefore constitute the F2 generation. Day 22 *post-partum* was designated day 1 of the F2 generation.

F2 selected animals were treated from day 1 until sexual maturity following the same procedure as for F0 and F1 animals.

The experimental groups were as follows:

| Group | Number of animals | Dose-level (mg/kg/day) | Concentration (mg/mL) |
|-------|-------------------|------------------------|-----------------------|
| 1 | 25 males | 0 | B29401 to B29425 |
| | 25 females | | B29801 to B29825 |
| 2 | 25 males | 250 | B29426 to B29450 |
| | 25 females | | B29826 to B29850 |
| 3 | 25 males | 500 | B29451 to B29475 |
| | 25 females | | B29851 to B29875 |
| 4 | 25 males | 1000 | B29476 to B29500 |
| | 25 females | | B29876 to B29900 |

2.19 CLINICAL EXAMINATIONS OF THE F2 GENERATION AFTER WEANING

2.19.1 Morbidity and mortality

Each animal was checked at least twice a day for mortality and signs of morbidity.

Any animal showing signs of poor clinical condition, (especially if death appeared imminent) was humanely killed.

Any animal found dead or killed prematurely was subjected to a macroscopic *post-mortem* examination.

2.19.2 Clinical signs

Each animal was observed at least three times each day for the recording of clinical signs, including evidence of physical or behavioural changes together with any overt signs of toxicity (including abortion/resorption for the females).

The details and frequency of these clinical observations are given below:

- . from weaning until sexual maturity: animals were inspected three times per day (immediately post-dosing, 1 hour post-dosing, 4 hours post-dosing), 7 days per week.

2.19.3 Body weight

The body weight of each animal was recorded once a week until sacrifice.

2.19.4 Food consumption

The quantity of food consumed by each animal was recorded once a week until sacrifice.

2.19.5 Sexual development

All males were observed daily between 32 and 47 days of age (i.e. day 11 to day 26 of the F2 generation), until cleavage of the balanopreputial groove (preputial separation) was observed. Individual body weight was recorded at that time.

All females were observed daily between 28 and 40 days of age (i.e. day 7 to day 19 of the F2 generation), until vaginal opening was observed. Individual body weight was recorded at that time.

2.20 TERMINAL EXAMINATIONS AND PATHOLOGY

2.20.1 Sacrifice

F0 animals and their progeny

All animals were humanely sacrificed by asphyxiation using carbon dioxide and exsanguinated:

- . F0 surviving males and females: after the weaning of F1 litters (between day 22 and day 25 *post-partum*),
- . F0 females which had not delivered: after day 25 *post-coitum*,
- . F0 females which did not mate: at least one week after the end of the mating period (14 days at maximum after the beginning of mating),
- . pups not selected for use in the study on day 4 or 22 *post-partum*,
- . any mother with an entirely dead litter.

F1 animals and their progeny

All animals were humanely sacrificed by asphyxiation using carbon dioxide and exsanguinated:

- . F1 surviving males and females: after the weaning of each F2 litter (between day 22 and day 25 *post-partum*),
- . F1 females which had not delivered: after day 25 *post-coitum*,
- . F1 females which did not mate: at least one week after the end of the mating period,
- . pups not selected for use in the study on day 4 or 22 *post-partum*,
- . any mother with an entirely dead litter.

2.20.2 F2 animals

All animals were humanely sacrificed at sexual maturity by asphyxiation using carbon dioxide and exsanguination.

2.20.3 Organ weights

The body weight of all F0 and F1 animals was determined at terminal sacrifice and the following organs weighed (wet) as soon as possible at the start of necropsy:

- . in all F0 and F1 males: testes (separately), epididymides (separately), prostate, seminal vesicles together with coagulating glands, brain, liver, kidneys, spleen, pituitary gland, thyroids with parathyroids, adrenals,
- . in all F0 and F1 females: uterus, ovaries, brain, liver, kidneys, spleen, pituitary gland, thyroid with parathyroids, adrenals,
- . in one F1 pup/sex/litter and one F2 pup/sex/litter: body weight, brain, spleen and thymus.

2.20.4 Seminology (F0 and F1 animals)

These investigations were performed for all F0 and F1 males of all groups.

2.20.4.1 Epididymal sperm

Before sacrifice, each male was anaesthetised by isoflurane, the left epididymis removed and weighed (see § Organ weights) and sperm collected for quantitative investigations.

The animals were then asphyxiated with carbon dioxide and exsanguinated.

The following investigations were performed in all males.

2.20.4.1.1 Epididymal sperm motility

Sperm motility was evaluated by microscopic examination (40 fold magnification) immediately after sampling from the left epididymis following appropriate dilution in Ham's nutrient liquid medium.

Results are expressed as a proportion of motile and non-motile spermatozoa.

2.20.4.1.2 Epididymal sperm count (cauda sperm reserve)

Cauda sperm reserve was obtained by mincing the cauda tissue.

The sperm was sampled from the left epididymis diluted one thousand fold in 0.9% NaCl solution and the number of spermatozoa counted in a Malassez cell.

Results are expressed as the number of spermatozoa per mm³ of sperm.

2.20.4.1.3 Epididymal sperm morphology

The presence of abnormal spermatozoa was evaluated by microscopic examination (40 fold magnification) after eosin staining of an aliquot (5 µL) sampled from the left epididymis.

Results for 100 spermatozoa per slide were expressed as the proportion of spermatozoa in each of the following categories:

- . normal,
- . normally shaped head separated from flagellum,
- . mis-shapen head separated from flagellum,
- . mis-shapen head with normal flagellum,
- . mis-shapen head with abnormal flagellum,
- . degenerative flagellar defect(s) with normal head,
- . other flagellar defect(s) with normal head.

2.20.4.2 Testicular sperm

These investigations were performed in all males.

The left testis was weighed and ground with a blender for 2 minutes in 50 mL of Saline-Triton-Merthiolate solution, and sperm heads resistant to homogenization (i.e. elongated spermatids and mature spermatozoa) were counted in a Neubauer cell.

Results are expressed as the number of sperm heads per gram of testis and the daily sperm production rate was calculated using a time divisor of 6.10 (Robb and *al.*, 1978).

2.20.5 Macroscopic *post-mortem* examination

2.20.5.1 F0 and F1 animals

A macroscopic *post-mortem* examination of the principal thoracic and abdominal organs was performed on all parent animals (F0 and F1 males and females) including any that died during the study or were sacrificed prematurely. In all F0 and F1 females, the number of implantation sites was recorded and classified as appropriate as scars, late resorptions, live or dead fetuses.

In apparently non-pregnant or un-mated females, the presence of implantation scars on the uterus was checked using ammonium sulphide staining technique (Salewski and *al.*, 1964).

Pups from females for which mating was not detected were discarded.

2.20.5.2 F2 animals

A macroscopic *post-mortem* examination of the principal thoracic and abdominal organs was performed on all animals including any that died during the study.

2.20.5.3 Pups

A macroscopic *post-mortem* examination of the principal thoracic and abdominal organs was performed at weaning on three pups/sex/litter from F0 and F1 females; brain, spleen and thymus were removed and weighed (see § organ weight). Any pups that died during lactation, or sacrificed prematurely were subjected to a macroscopic *post-mortem* examination of the principal thoracic and abdominal organs.

Other pups (e.g. those not selected on day 4 or 21 *post-partum*) were not examined.

2.20.6 Preservation of tissues

2.20.6.1 F0 and F1 animals

The following organs from all F0 and F1 animals were preserved in 10% buffered formalin (except for testes and epididymides which were fixed in Bouin's fluid):

- . any macroscopic abnormalities,
- . ovaries and oviducts,
- . uterus (with cervix and horns),
- . vagina,
- . testis (right),
- . epididymis (right),
- . seminal vesicles,
- . prostate,
- . coagulating glands,
- . pituitary glands,
- . adrenal glands.

In addition, a vaginal smear was taken from all F0 and F1 females and stained (using Harris Schorr's technique).

In addition, the following organs were preserved in 10% buffered formalin:

- . liver and kidneys in five males from the F0 and F1 generations,
- . thyroid gland and spleen in five males from the F1 generation,
- . thymus in five females from the F0 generation.

2.20.6.2 Pups

Any macroscopic abnormalities present in the F0 and F1 pups were preserved in 10% buffered formalin (except for testes and epididymides which were fixed in Bouin's fluid).

2.20.7 Preparation of slides

All tissues selected for microscopic examination were embedded in paraffin wax, sectioned at a thickness of approximately 4 microns and stained with hematoxylin-eosin (except testes and epididymides which were stained with hematoxylin/PAS).

2.20.8 Microscopic examination

Microscopic examination of tissues was performed at CIT as follows:

F0 and F1 animals

The following organs from F0 and F1 control and high-dose groups were examined:

- . any macroscopic abnormalities,
- . ovaries and oviducts,
- . uterus (with cervix and horns),
- . vagina,
- . testis* (a),
- . epididymis,
- . seminal vesicles,
- . prostate,
- . coagulating glands,
- . pituitary glands,
- . adrenal glands.

(a): testis sections from all F1 males (including intermediate and low dose groups) were examined, at the request of the Sponsor.

The following organs were also examined from F1 low- and intermediate-dose animals suspected to be non-fertile (b):

- . ovaries*,
- . uterus (with cervix and oviducts),
- . vagina,
- . testis*,
- . epididymis,
- . seminal vesicles,
- . prostate,
- . coagulating glands.

In addition, the vaginal smear taken from the F0 and F1 females at terminal sacrifice was also examined.

* In addition, a detailed histopathological examination was conducted in order to evaluate:

- . retained spermatids, missing germ cell layers or types, multinucleated giant cells or sloughing of spermatogenic cells into the lumen, in F0 and F1 males,
- . qualitative depletion of the primordial follicle population in F0 and F1 females,
- . quantitatively the primordial and small growing follicles in F0 and F1 females (for comparison of control and treated ovaries, the evaluation of growing and primordial follicles was done separately).

(b): there were no F0 animals suspected to be infertile.

2.21 ASSESSMENT OF DATA

Data are expressed as group mean values \pm standard deviation (body weight, food consumption, implantations, resorptions, pups, gestation length) or as proportions (mating index, fertility index, gestation index live birth index, viability and lactation indices). Whenever necessary, the experimental unit of comparison was the litter.

Data from non pregnant females were not included in the group mean calculations.

The calculations were performed for each group as follows:

Mating index:

$$\frac{\text{Number of mated animals}}{\text{Number of paired animals}} \times 100$$

Fertility index:

$$\frac{\text{Number of pregnant female partners}}{\text{Number of mated pairs}} \times 100$$

Gestation index:

$$\frac{\text{Number of females with live born pups}}{\text{Number of pregnant females}} \times 100$$

Live birth index:

$$\frac{\text{Number of live born pups}}{\text{Number of delivered pups}} \times 100$$

Viability index on day 4 *post-partum*:

$$\frac{\text{Number of surviving pups on day 4 } \textit{post-partum}}{\text{Number of live born pups}} \times 100$$

Lactation index:

$$\frac{\text{Number of surviving pups on day 21 } \textit{post-partum}}{\text{Number of surviving pups on day 4 } \textit{post-partum}} \times 100$$

2.22 STATISTICAL ANALYSIS

2.22.1 Data other than organ weights

Mean values were compared by one-way analysis of variance and Dunett's test (mean values being considered as normally distributed and variances being considered homogeneous).

Percentage values were compared by the Fisher exact probability test. All the above statistics were performed with a dedicated and validated computer system (Reprotox, version B1).

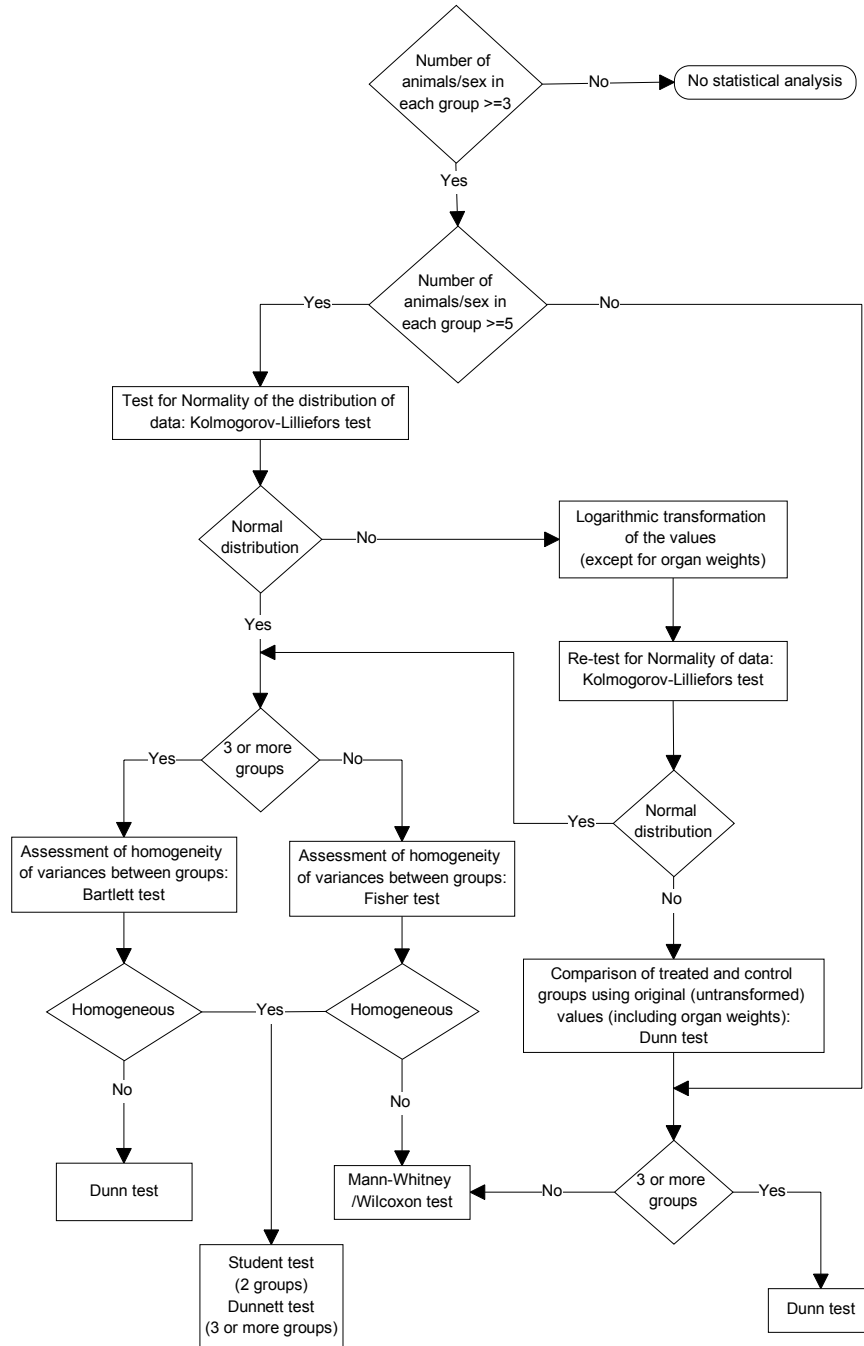
Mean percentages of motility and morphology sperm parameters were Arcsine transformed and then compared by analysis variance.

Mean values for anogenital distance, ratio of anogenital distance to pup body weight and anogenital distance normalized to the cube root of pups body weight were compared by analysis of variance.

These analyses were performed using a dedicated commercial software package (Statview, version 5.0.1 SAS Institute Inc).

2.22.2 Organ weights

The following sequence was used for organ weight data:



2.23 ARCHIVING

The following study materials are retained in the archives of CIT (BP 563, 27005 Evreux, France) for 10 years after the end of the *in vivo* phase of the study:

- . Study plan and amendments,
- . raw data,
- . correspondence,
- . final report and possible amendments,
- . sample of the test item,
- . photographs.

On completion of this period, the archived study materials will be returned to the Sponsor, or may be archived at CIT for a further period.

The total duration of archiving (depending on regulations) is the responsibility of the Sponsor.

In addition, raw data not specific to the study, including but not limited to certificates of analyses for food, water, sawdust and wood shavings and records of environmental data and equipment calibration are also archived at CIT for at least 30 years.

At the end of the study, all remaining test item (excluding the archive sample(s)) will be returned to the Sponsor unless otherwise stated by the Sponsor.

Unless otherwise requested by the study Sponsor, deep frozen specimens will be retained until acceptance of the final report by the Sponsor. Samples will then be disposed of unless prior instructions have been received from the Sponsor, requesting shipment of the samples or continued storage.

2.24 CHRONOLOGY OF THE STUDY

The chronology of the study is summarized as follows:

| Procedure | Date |
|--|---------------|
| Study plan approved by: | |
| . Study Director | 28 March 2003 |
| . Study Monitor | 28 March 2003 |
| ----- | |
| F0 GENERATION | |
| Experimental starting date | |
| (first day of acclimation period) | 25 March 2003 |
| . Pre-identification and weighing | 27 March 2003 |
| . Randomization and identification | 28 March 2003 |
| First day of treatment | 31 March 2003 |
| Mating (day 0 <i>post-coitum</i>) | |
| . first female | 10 June 2003 |
| . last female | 23 June 2003 |
| Delivery | |
| . first female | 1 July 2003 |
| . last female | 15 July 2003 |
| Day of necropsy of F0 males | |
| . first male | 25 July 2003 |
| . last male | 29 July 2003 |
| Day of necropsy of F0 females and pups (at weaning) | |
| . first female/litter | 23 July 2003 |
| . last female/litter | 6 August 2003 |

| Procedure | Date |
|--|-------------------|
| F1 GENERATION | |
| First day of treatment | |
| . first animal | 23 July 2003 |
| . last animal | 27 July 2003 |
| Mating (day 0 <i>post-coitum</i>) | |
| . first female | 30 September 2003 |
| . last female | 12 October 2003 |
| Delivery | |
| . first female | 21 October 2003 |
| . last female | 3 November 2003 |
| Day of necropsy of F1 males | |
| . first male | 24 November 2003 |
| . last male | 26 November 2003 |
| Day of necropsy of F1 females and pups (at weaning) | |
| . first female/litter | 12 November 2003 |
| . last female/litter | 25 November 2003 |
| ----- | |
| F2 GENERATION | |
| First day of treatment | |
| . first animal | 12 November 2003 |
| . last animal | 16 November 2003 |
| Day of necropsy | |
| . first animal | 8 December 2003 |
| . last animal (experimental completion date) | 12 December 2003 |

2.25 STUDY PLAN ADHERENCE

The study was performed in accordance with Study Plan No. 24859 RSR and subsequent amendments, with the following deviations from the agreed Study plan:

F0 generation:

- . on days 6 and 7, clinical signs were performed approximately 3 hours after dosing instead of 4,
- . on day 9, clinical signs were performed 6 hours after dosing instead of 4,
- . on weeks 3, 4 and 10 the recording of clinical signs for some animals in groups 1 to 3 was carried out more than 4 hours after dosing,
- . on week 5, the recording of clinical signs was performed more than one hour after dosing,
- . the food hopper of female B29660 was not filled on day 14 *post-partum*,
- . pup No. 8 from dam B29605 was missing from day 1 *post-partum*,
- . for female B29672, no information on the estrous cycle is available on day 67 because the slide bearing the vaginal lavage was broken,
- . by error, the estrous cycle was not recorded on day 68 of the pre-mating period (missing data),
- . on week 64, the food consumption of males from the low dose-group was recorded over a 6-day instead of a 7-day period,
- . by error, the clinical signs of all animals were recorded after 4 hours of dosing during 2 days of the pre-mating period,
- . the liver from one male of the control group with a macroscopic lesion was not sampled,
- . by error, one pup (No. 15 dam B29700) was culled on day 6 instead of day 4.

F1 generation:

- . on day 25, animals B29394 and B29395 were reversed in the cages,
- . recording of clinical signs immediately post-dosing, was not performed for the males and females of group 4 one day during weeks 9 and 10 but were recorded one hour after dosing,
- . on day 69, monitoring of the estrous cycle was not performed for female B29705 from group 1,
- . for the F1 generation, the vertical movements for evaluation of spontaneous locomotor activity were recorded (typing error in the Study plan),
- . in all F0 and F1 females, thyroids and parathyroids were weighed together instead of thyroid alone (typing error in the Study plan),
- . macroscopic *post-mortem* examination was performed by excess in few pups of the F1 generation,
- . clinical signs were not recorded one day during week 12 for animals of the intermediate and high dose-groups.

F2 generation:

- . on days 21 and 25, recording of clinical signs was performed 6 hours after dosing instead of 4,
- . females B29804 and B29854 were observed for vaginal opening when 44 and 46 days of age, respectively,
- . for logistical reasons, all animals (F0, F1 and F2 generation) were observed one hour and four hours after the end of dosing of each group (and not of each animal).

These deviations were not considered to have compromised the validity or integrity of the study.

3. RESULTS

3.1 CHEMICAL ANALYSIS OF THE DOSAGE FORMS (Appendix 2)

3.1.1 Homogeneity

The results of the analyses demonstrated a satisfactory homogeneity of the dosage forms (62.5 and 250 mg/mL) prepared with each batch (S02-08-159-I3 and 308 596) of test item used in the study.

3.1.2 Stability

The results of the analyses demonstrated a satisfactory stability of the two dosage forms investigated (62.5 and 250 mg/mL) prepared using batch No. 308 596 over a 9-day period at room temperature. The stability of batch S02-08-159-I3 was evaluated in the preliminary study (CIT/Study No. 24168 RSR) and demonstrated to be satisfactory over 9 days at room temperature.

3.1.3 Concentration

Analytical results demonstrated a satisfactory agreement between the nominal and actual concentration of the test item in the administered dosage forms when analyzed before treatment (deviation from nominal concentration $\pm 10\%$). The values obtained are presented in the following tables:

| Group | Nominal concentration (mg/mL) | Actual concentration (generation F0) (mg/mL) | | | | | |
|-------|---------------------------------------|--|-----------|--------------|-----------|-----------|------------|
| | | Week 1 | Week 2 | Week 6 | Week 10 | Week 14 | Week 18 |
| 1 | 0 | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ |
| | <i>Deviation from nominal value :</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> |
| | | [66.5-59.4]* | | [57.7-58.0]* | | | |
| 2 | 62.5 | 63.0 | 64.6 | 57.9 | 66.5 | 58.0 | 63.6 |
| | <i>Deviation from nominal value :</i> | 1% | 3% | -7% | 6% | -7% | 2% |
| | | [127-139]* | | | | | |
| 3 | 125 | 133 | 124 | 113 | 130 | 128 | 133 |
| | <i>Deviation from nominal value :</i> | 6% | -1% | -10% | 4% | 2% | 6% |
| | | [235-274]* | | [232-252]* | | | [258-264]* |
| 4 | 250 | 255 | 226 | 242 | 226 | 227 | 261 |
| | <i>Deviation from nominal value :</i> | 2% | -10% | -3% | -10% | -9% | 4% |

*: individual values of replicate determinations used to calculate the mean value (written below)

BLQ: Below Limit of Quantification (< 0.1 mg/mL)

nc: not calculated

| Group | Nominal concentration (mg/mL) | Actual concentration (F1 generation) (mg/mL) | | | | |
|-------|---------------------------------------|--|-----------|-----------|-----------|-----------|
| | | Week 1 | Week 6 | Week 9 | Week 13 | Week 17 |
| 1 | 0 | BLQ | BLQ | BLQ | BLQ | BLQ |
| | <i>Deviation from nominal value :</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> |
| 2 | 62.5 | 63.6 | 64.9 | 57.7 | 59.6 | 65.3 |
| | <i>Deviation from nominal value :</i> | 2% | 4% | -8% | -5% | 4% |
| 3 | 125 | 133 | 135 | 119 | 125 | 132 |
| | <i>Deviation from nominal value :</i> | 6% | 8% | -5% | 0% | 6% |
| 4 | 250 | 261 | 237 | 265 | 234 | 233 |
| | <i>Deviation from nominal value :</i> | 4% | -5% | 6% | -6% | -7% |

*: individual values of replicate determinations used to calculate the mean value (written below)

BLQ: Below Limit of Quantification (< 0.1 mg/mL)

nc: not calculated

3.2 F0 GENERATION*

3.2.1 Clinical examinations of parent males and females

3.2.1.1 Mortality (Tables 1 to 4, Appendices 4 to 7)

Males

No deaths occurred during the study.

Females

There were no deaths noted during the pre-mating, mating and gestation periods.

One female given 250 mg/kg/day and three females given 500 mg/kg/day were prematurely sacrificed during the first week of lactation because their entire litters died or were in poor clinical condition. Since no similar findings were noted in pups from dams given 1000 mg/kg/day, these deaths/poor clinical conditions were not attributed to treatment.

*Note: off-spring born to F0 dams (parental females supplied by the breeder) are described as "F0 pups" until weaning, after which those that receive further treatment are the new generation called "F1 animals".

3.2.1.2 Clinical signs (Tables 1 to 4, Appendices 4 to 7)

Males

Transient ptyalism (excess salivation) was observed immediately after dosing in 2, 7, 19 or 23/25 males from the control, 250, 500 or 1000 mg/kg/day dose groups, respectively, at various times during the study.

Females

During the pre-mating period, transient ptyalism was recorded immediately after dosing in 2, 6, 3 or 13/25 females from the control, 250, 500 or 1000 mg/kg/day dose groups, respectively and in 2/23, 7/21, 11/22 and 19/25 females from these same groups during the pregnancy period. It was also recorded immediately after dosing in 0/23, 1/20, 2/19 or 11/25 females from the control, 250, 500 or 1000 mg/kg/day dose groups during the lactation period.

In general, symptoms of ptyalism resolved in most animals (a single exception) one hour after dosing. It is commonly noted following gavage administration of unpalatable test items, and is therefore not considered an adverse effect.

Areas of hair loss, chromodacryorrhea and regurgitation were observed sporadically in a few animals randomly distributed among the groups including the control group and therefore were considered not to be related to treatment.

3.2.1.3 Body weight (Figures 1, 2, 4, 5, 7, 8 and 10, Tables 5 to 12, Appendices 8 to 15)

For males, significantly lower body weight gain was noted in the 500 mg/kg/day (-29%, $p < 0.01$) and 1000 mg/kg/day (-22%, $p < 0.001$) treatment groups on days 85-113 of the study (i.e the final 28 days of treatment, following mating). This finding was considered to be related to treatment. Although some variations in female body weight gain were apparent during the pre-mating and lactation periods, these were considered unrelated to the treatment since they were minor and/or not dose-related.

3.2.1.4 Food consumption (Figures 3, 6, 9 and 11, Tables 13 to 16, Appendices 16 to 19)

Food consumption during pre-mating was unaffected by treatment in both males and females. During pregnancy, food consumption for all treated females was comparable to controls but increased significantly (+10%, $p < 0.001$) in the 1000 mg/kg/day group during lactation when compared to controls. This effect was not considered to represent an adverse effect.

3.2.2 Reproductive data for the F0 generation

3.2.2.1 Mating data (Tables 17 and 18, Appendix 20)

Data obtained after the F0 mating trial are summarized as follows:

Summary of mating data

| Dose-level (mg/kg/day) | 0 | 250 | 100 | 300 |
|---|-------|-------|-------|-------|
| Paired males + females | 25+25 | 25+25 | 25+25 | 25+25 |
| Males able to mate with at least one female | 25 | 25 | 25 | 25 |
| Male mating index (%) | 100 | 100 | 100 | 100 |
| Females able to mate | 25 | 25 | 25 | 25 |
| Female mating index (%) | 100 | 100 | 100 | 100 |
| Pre-coital time (days) | | | | |
| . mean | 3.28 | 2.76 | 2.52 | 2.72 |

The F0 male and female mating indices were comparable among the groups and unaffected by treatment.

3.2.2.2 Fertility data (Tables 17 and 18, Appendices 21 to 23)

Male and female fertility data are summarized as follows:

Summary of fertility data

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------------------------------------|----|-----|-----|------|
| <i>- Males</i> | | | | |
| . which mated at least once | 25 | 25 | 25 | 25 |
| . with at least one pregnant partner | 23 | 21 | 22 | 25 |
| . male fertility index (%) | 92 | 84 | 88 | 100 |
| <i>- Females</i> | | | | |
| . mated females | 25 | 25 | 25 | 25 |
| . pregnant females | 23 | 21 | 22 | 25 |
| . female fertility index (%) | 92 | 84 | 88 | 100 |

The male and female fertility indices were comparable among the groups and unaffected by treatment.

The estrous cycle was unaffected at all dose-levels.

3.2.3 Pregnancy and parturition data (Table 18, Appendices 22 and 23)

The data obtained during pregnancy and delivery are summarized as follows:

Summary of pregnancy and parturition data

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|------|------|------|------|
| Pregnant females | 23 | 21 | 22 | 25 |
| . died during pregnancy | 0 | 0 | 0 | 0 |
| . females with live born pups | 23 | 21 | 22 | 25 |
| Pregnancy index (%) | 100 | 100 | 100 | 100 |
| Duration of gestation (days) | 21.7 | 21.5 | 21.5 | 21.8 |
| Litter size at birth | 14.3 | 14.1 | 14.9 | 14.2 |
| Post-implantation loss (%) | 4.3 | 5.7 | 4.9 | 6.5 |
| Pup weight/litter on day 1 <i>pp</i> (g) | 6.6 | 6.5 | 6.3 | 6.8 |
| male pups (%) | 52.4 | 47.6 | 48.0 | 54.8 |

pp.: post-partum.

All of the parameters listed above were similar for the control and treated females, and any fluctuations present were generally considered to reflect normal variability. The exception was a slightly higher post-implantation loss recorded at 250 and 500 mg/kg/day (due to litters found dead or sacrificed prematurely due to poor clinical condition). This finding was considered unrelated to treatment since it was not present in the high-dose group.

In conclusion, treatment with the test item had no influence on implantation, fecundity, post-implantation and neo-natal losses, gestation and delivery parameters.

3.2.4 Examination of the pups during the lactation period (Table 18, Appendices 24 to 30)

3.2.4.1 Survival (Table 18, Appendices 24 and 25)

The survival of the pups during the lactation period is summarized as follows:

| Survival of the pups | | | | |
|---|------------|-------------|------------|-----------|
| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
| Litters obtained | 23 | 21 | 22 | 25 |
| Pups delivered/dam | 14.3 | 14.1 | 14.9 | 14.2 |
| Females with total litter losses (number of pups dead or sacrificed) | 0 | 1 (6) | 3 (35) | 0 |
| Pups which died between days 1 and 4 <i>pp</i> | 8 | 21** | 58*** | 8 |
| Number of litters with pups lost ^(a) between days 1 and 4 <i>pp</i> | 1 | 8 | 9 | 2 |
| Total number of litters with pups lost during lactation ^(a) | 5 | 13 | 11 | 4 |
| Viability index on day 4 <i>pp</i> (before culling) | 97.6% | 92.9% | 82.3% | 97.7% |
| Pups which died during the 2 nd week | 2 | 2 | 1 | 2 |
| Pups which died during the 3 rd week | 0 | 0 | 0 | 0 |
| Total of decedent pups | 18 (5.48%) | 35 (11.82%) | 64 (19.6%) | 10 (2.8%) |
| Lactation index (%) | 94.6 | 91.7 | 96.1 | 99.0 |

pp: *post-partum*

** : $p < 0.01$

*** : $p < 0.01$

(a): including females with total litter loss.

At 250 and 500 mg/kg/day, the number of pups which died during the lactation period was slightly higher during the first 4 days after birth than in controls, but was within normal limits for the high-dose group. Since no dose/response relationship was apparent, pup survival was therefore considered to be unaffected by the treatment.

Viability and lactation indices were unaffected by the treatment at all dose-levels.

3.2.4.2 Clinical signs and gross external abnormalities (Appendix 26)

The following relevant clinical signs were noted during the lactation period:

Number of pups and [litters] with clinical signs

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|-------|--------|--------|-------|
| Emaciated appearance and/or cold to the touch and/or dehydration | 1 [1] | 10 [4] | 20 [4] | 6 [4] |

Clinical signs observed (emaciated appearance, coldness to the touch, dehydration) were present in one (B29626) and three litters (B29661, B29668 and B29675) from the 250 and 500 mg/kg/day, respectively. Pups from these litters were found dead or were prematurely sacrificed for ethical reasons (6 pups from the low-dose group and 17 pups from the intermediate dose group).

Similar findings were also observed in four pups from three litters at 250 mg/kg/day, three pups from one litter at 500 mg/kg/day and six pups from four different litters at 1000 mg/kg/day.

Most of these pups displayed lower body weight. However, since the incidence of these clinical signs was not dose related and did not correlate with lower mean group body weight gain, they were consequently considered fortuitous and unrelated to treatment.

There were no gross external abnormalities in the pups.

3.2.4.3 Body weight (Figures 12 and 13, Tables 18 and 19, Appendix 27)

Body weight and body weight gain of pups during the lactation period are summarized as follows:

Mean body weight and body weight gain of the pups (g)

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|------|------------|------------|------------|
| Body weight on day 1 <i>pp</i> | 6.6 | 6.5 (-2%) | 6.3 (-5%) | 6.8 (+3%) |
| Body weight gain day 1-day 4 <i>pp</i> | 2.2 | 2.2 (0%) | 2.0 (-9%) | 2.4 (+9%) |
| Body weight gain day 4-day 21 <i>pp</i> | 40.2 | 41.5 (+3%) | 41.0 (+2%) | 42.3 (+5%) |
| Body weight on day 21 <i>pp</i> | 49.1 | 50.4 (+3%) | 49.4 (+1%) | 51.5 (+5%) |

pp: post-partum.

Body weight and body weight gain were not affected by the treatment at any dose-level.

3.2.4.4 Anogenital distance (Table 20, Appendix 28)

In all treated groups, anogenital distance, the ratio of anogenital distance to pup body weight and anogenital distance normalized with the cube root of the pup's body weight, were not significantly affected by treatment.

F0 generation
Mean values of anogenital distance

| Dose-level (mg/kg/day) | F0 generation Mean values of anogenital distance | | | | | | | | |
|-------------------------------------|---|------|------|------|--------|------|------|------|------|
| | Male | | | | Female | | | | |
| | 0 | 250 | 500 | 1000 | 0 | 250 | 500 | 1000 | |
| AGD (mean/female) | Mean | 4.71 | 4.62 | 4.47 | 4.64 | 2.84 | 2.77 | 2.63 | 2.68 |
| | SD | 0.43 | 0.33 | 0.39 | 0.30 | 0.36 | 0.24 | 0.26 | 0.37 |
| PW (mean/female) | Mean | 6.80 | 6.70 | 6.50 | 7.00 | 6.40 | 6.40 | 6.00 | 6.50 |
| | SD | 0.70 | 0.60 | 0.70 | 0.70 | 0.60 | 0.60 | 0.60 | 0.60 |
| AGD/PW (mean/female) | Mean | 0.69 | 0.69 | 0.70 | 0.67 | 0.44 | 0.44 | 0.44 | 0.42 |
| | SD | 0.06 | 0.07 | 0.09 | 0.07 | 0.06 | 0.06 | 0.05 | 0.07 |
| AGD/Cube root of body weight (a) | Mean | 2.48 | 2.45 | 2.40 | 2.43 | 1.53 | 1.50 | 1.45 | 1.44 |
| | SD | 0.18 | 0.17 | 0.21 | 0.15 | 0.18 | 0.14 | 0.14 | 0.20 |

AGD: anogenital distance (mm)

PW: pup weight (grams)

GD/PW: corrected anogenital distance

(a): the anogenital distance is normalized to the cube root of pup body weight

The slightly lower anogenital distance observed in females given 1000 mg/kg/day was minor (-6% compared to controls), not indicative of masculinization (no lengthening of anogenital distance) and did not correlate with any delay in sexual development (see § sexual development of F1 generation) and was consequently not considered to be of biological significance.

3.2.4.5 Assessment of reflex development (Table 21, Appendix 29)

There was no evidence of any adverse treatment-related changes in surface righting, cliff avoidance and air righting (95 to 100% positive response). Although the proportion of pups exhibiting a positive righting response in the low and intermediate treatment groups was significantly lower than in the controls ($p < 0.05$), the magnitude of this difference was very small (3-4%) suggesting it was a chance finding of no biological relevance.

3.3 F1 GENERATION*

3.3.1 Clinical examinations of F1 parent males and females

3.3.1.1 Mortality (Tables 32 to 35, Appendices 36 to 39)

Males

No deaths occurred during the study in males given 250 and 1000 mg/kg/day.

In the control group, one male in poor clinical condition on day 36 (round back, emaciated appearance, piloerection, cold to the touch, hypokinesia, dyspnea) with marked body weight loss (days 29 to 36, -44 g) was prematurely sacrificed on day 37.

At 500 mg/kg/day, one male was found dead after dosing on day 93. No clinical signs were noted prior to death except ptialism, which was transiently observed immediately after dosing. The necropsy revealed dilatation of the lungs and foamy contents within the lungs suggesting difficulties during gavage dosing of this animal. This death was not considered to be related to the toxicity of the test item since no deaths were recorded at the highest dose-level.

Females

There were no deaths during the gestation period at any dose-level.

During the pre-mating period, one female given 1000 mg/kg/day was found dead on day 47. This death was considered to be incidental since there were no remarkable clinical signs, no change in body weight or food consumption and no findings at necropsy.

During the lactation period, two females given 250 and 1000 mg/kg/day, were prematurely sacrificed because their whole litters were found dead a few days after birth. The death of these litters is discussed in § 3.3.5.1).

3.3.1.2 Clinical signs (Tables 32 to 35, Appendices 36 to 39)

Males

In the treated groups, transient ptialism (excess of salivation) was observed immediately after dosing in 11, 21, 24 or 25/25 males from the control, 250, 500 or 1000 mg/kg/day dose groups, respectively, at various times during the study and was still present one hour after dosing in 5, 6 and 9/25 males at 250, 500 and 1000 mg/kg/day.

Females

During the pre-mating period, transient ptialism was recorded immediately after dosing in 2, 10, 17 or 22/25 females from the control, 250, 500 or 1000 mg/kg/day dose groups, respectively. During the pregnancy period, transient ptialism was observed immediately after dosing in 2/21, 4/22 or 10/20 females from the 250, 500 or 1000 mg/kg/day dose groups. During the lactation period, ptialism was also recorded immediately after dosing in 2/20, 4/22 or 9/19 females from the 250, 500 or 1000 mg/kg/day dose groups.

In general, symptoms of ptialism resolved in all females and in most males one hour after dosing.

Ptialism is commonly noted following gavage administration of unpalatable test items, and is therefore not considered an adverse effect.

Areas of hair loss, chromodacryorrhea, mass on mammary gland, necrosis of the tail, soft feces, loud breathing, dyspnea, abdominal breathing and regurgitation were observed sporadically in a few animals randomly distributed among the groups, including the control group, and therefore were not considered to be treatment related.

*Note: off-spring born to F1 dams are described as "F1 pups" until weaning, after which those that receive further treatment are called "F2 animals".

3.3.1.3 Body weight (Figures 14, 15, 17, 18, 20, 21 and 23, Tables 36 to 43, Appendices 40 to 47)

No differences in body weight or body weight gain were observed in males or females throughout the dosing period.

Although some variations in female body weight gain were apparent during the pre-mating, pregnancy and lactation periods, these were considered unrelated to the treatment since they were minor and/or not dose-related and were not correlated with any change in food consumption.

3.3.1.4 Food consumption (Figures 16, 19, 22 and 24, Tables 44 to 47, Appendices 48 to 51)

No difference was recorded in food consumption for females throughout the dosing period.

For males, although the food consumption was slightly increased during few periods reaching significance (days 50 to 57, +8%, $p < 0.05$, days 57 to 64, +12%, $p < 0.01$, days 106 to 113, +8%, $p < 0.05$), this change was not considered to represent an adverse effect.

3.3.1.5 Sexual development of the F1 generation (Tables 48 and 49, Appendix 52)

Males

The mean age at preputial separation (cleavage of the balanopreputial gland) was unaffected by the treatment (i.e. occurred on day 35, 34, 35 or 35 for pups from the control, 250, 500 and 1000 mg/kg/day groups, respectively).

Females

The mean age for vaginal opening was unaffected by the treatment (i.e. occurred on day 34, 34, 35 or 33 for pups from the control, 250, 500 and 1000 mg/kg/day, respectively).

3.3.2 Neurobehavioral tests of the F1 generation

3.3.2.1 Auditory function (Table 50, Appendix 53.1.)

Auditory function (as assessed by acoustic startle reflex) was not affected in any of the treated groups when the animals were tested at 4 weeks old.

3.3.2.2 Visual function (Table 51, Appendix 53.2.)

Visual function (as assessed by pupil constriction reflex) was not affected in any of the treated groups when the animals were tested at 4 weeks old.

3.3.2.3 Spontaneous locomotor activity (Tables 52 to 55, Appendix 53.3.)

The fluctuations recorded for spontaneous locomotor activity (measured twice using an automated infra-red sensor equipment when the animals were 7 and 8 weeks old) were slight, not consistent between the two trials and unrelated to dose, and were therefore considered not to reflect any treatment-related effect.

3.3.3 Reproductive data for the F1 generation

3.3.3.1 Mating data (Tables 56 and 57, Appendix 54)

Data obtained after the F1 mating trial are summarized below:

Summary of mating data

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---------------------------|-------|-------|-------|--------|
| Paired males + females | 24+25 | 25+25 | 25+25 | 25+24* |
| Male mating index (%) | 96 | 96 | 100 | 96 |
| Females able to mate ** | 24 | 24 | 25 | 23 |
| Female mating index **(%) | 100 | 96 | 100 | 96 |
| Pre-coital time (days) | | | | |
| . mean | 3.0 | 3.5 | 2.6 | 2.4 |

*: one female dead before mating

** : including pregnant females with no detection of sperm at vaginal lavage

The F1 male and female mating indices were similar among the groups and unaffected by treatment.

3.3.3.2 Fertility data (Tables 56 and 57, Appendices 55 to 57)

Male and female fertility data are summarized below:

Summary of fertility data

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------------------------------------|----|-----|-----|------|
| <i>- Males</i> | | | | |
| . which mated at least once | 24 | 24 | 25 | 23* |
| . with at least one pregnant partner | 22 | 22 | 22 | 22 |
| . male fertility index (%) | 92 | 92 | 88 | 96 |
| <i>- Females</i> | | | | |
| . mated females ** | 25 | 24 | 25 | 23* |
| . pregnant females ** | 22 | 22 | 22 | 22 |
| . non pregnant females | 3 | 3 | 3 | 2 |
| . female fertility index (%) | 88 | 92 | 88 | 96 |

*: one female dead before mating

** : including pregnant females with no detection of sperm at vaginal lavage

The male and female fertility indices were similar among the groups and unaffected by treatment. As confirmed by histopathological examination of reproductive organs from non pregnant females, no abnormalities indicative of lower fertility were noted (see § Pathology). The estrous cycle was unaffected at all dose-levels.

3.3.4 Pregnancy and parturition data (Table 57, Appendices 56 and 57)

Data obtained during pregnancy and delivery are summarized below:

Summary of pregnancy and parturition data

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|------|------|-------|------|
| Pregnant females* | 21 | 22 | 22 | 20 |
| Pregnant females** | 22 | 22 | 22 | 22 |
| . died during pregnancy | 0 | 0 | 0 | 0 |
| . with no delivery | 0 | 1 | 0 | 0 |
| . females with live born pups | 21 | 21 | 22 | 20 |
| Pregnancy index* (%) | 95.5 | 95.5 | 100.0 | 91.0 |
| Duration of gestation (days) | 21.5 | 21.6 | 21.6 | 21.6 |
| Litter size at birth | 13.7 | 13.7 | 13.7 | 14.0 |
| Pup weight/litter on day 1 <i>pp</i> (g) | 6.7 | 6.5 | 6.5 | 6.6 |
| Male pups (%) | 50.5 | 51.0 | 51.5 | 52.1 |

pp.: *post-partum*

*: all pregnant females with detection of sperm at vaginal lavage

** : including pregnant females with no detection of sperm at vaginal lavage

All of the parameters listed above were similar for the control and treated females, and any fluctuations present were generally considered to reflect normal variability.

Absence of delivery was observed in one pregnant female from the 250 mg/kg/day group. At necropsy of this female a single implantation site was recorded; this finding was considered to have occurred by chance since it was only present in one animal from the low dose-level.

In conclusion, treatment with the test item had no influence on mating, implantation, fecundity, gestation and delivery parameters.

3.3.5 Examination of the pups during the lactation period

3.3.5.1 Survival (Table 58, Appendices 59 and 60)

Survival of pups during the lactation period is summarized as follows:

Survival of the pups

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|---------|---------|--------|---------|
| Litters obtained | 21 | 21 | 22 | 20 |
| Pups delivered/dam | 13.7 | 13.7 | 13.7 | 14.0 |
| Females with total litter loss *(N) (No. of pups lost in bracket) | 0 | 1 (12) | 0 | 1 (16) |
| Pups which died between days 1 and 4 <i>pp</i> (N) | 7 | 15 | 9 | 20** |
| Total of decedent pups (%) (between days 1 to 21 <i>pp</i>) | 11 (4%) | 17 (5%) | 9 (3%) | 21 (8%) |
| Viability index on day 4 <i>pp</i> (%) (before culling) | 97.6 | 94.8 | 97.0 | 92.9 |
| Lactation index (%) | 97.6 | 98.8 | 100.0 | 99.3 |

pp: post-partum

*: dead or cannibalized pups

** : p<0.01

At 250 and 1000 mg/kg/day, the number of pups which died during the lactation period was slightly higher than controls during the first 4 days of lactation. Because this change was not dose-related (concerned only one litter in each of these two groups with particularly high litter size (B29739 and B29799), it was considered to be spontaneous and therefore not related to treatment. Furthermore, lactation index (survival of animals during the whole lactation period) was not affected by treatment at any dose-level.

3.3.5.2 Clinical signs and gross external abnormalities (Appendix 60)

At 1000 mg/kg/day, absence of tail (acaudia) was observed at birth in two female pups from two different litters (dam B29776 pup 13; dam B29796 pup 13), with anal atresia also present in one of these pups (dam B29776, pup 13). Body weight of these pups was lower than controls on days 1 and 4 *post-partum*. Since the incidence of the absence of tail (2/280 pups; 0.7%) was not within the range of CIT reference control data (minimum = 0.0%; maximum = 0.05% (data obtained from 16 studies ranging between October 2000 and December 2003)) but close to MARTA (2004) historical control database (mean percent affected fetuses per litter per group: 0.31% for a total of 22147 fetuses from 1575 control litters during the period 1990 to present), a relationship to treatment could not be clearly established.

No historical control data are available from CIT for the incidence of anal atresia in SD rats, however the incidence observed in this study (1/280 pups; 0.35%) was close than that recorded in the MARTA (2004) historical control database (mean percent affected fetuses per litter per group: 0.32%) for a total of 22147 fetuses from 1575 control litters during the period 1990 to present.

It is also noted that no instance of acaudia or anal atresia was found in off-spring from dams treated with ETBE at a dose of 1000 mg/kg/day during a preliminary dose-range finding study (zero incidence in 164 fetuses from 12 litters and 144 pups from 11 litters; *CIT/Study No. 24168 RSR*, October 2003) or a developmental toxicity study (zero incidence in 258 fetuses from 22 litters; *CIT/Study No. 24860 RSR*, January 2004). Overall, therefore, it is concluded that the occurrence of acaudia and anal atresia in the present study was most probably spontaneous in origin and not clearly related to treatment with the test item.

Tremors and ataxia were present from day 15 *post-partum* in one pup from the 250 mg/kg/day group which was sacrificed prematurely for humane reasons.

The other clinical signs observed in the pups (necrosis of the tail or of the limbs, cold to the touch, emaciated appearance) were low in incidence, not dose-related and randomly distributed between the litters and treatment groups.

3.3.5.3 Body weight (Figures 25 and 26, Table 58, Appendix 61)

Body weight and body weight gain of pups during the lactation period are summarized as follows:

Mean body weight and body weight gain of the pups (g) and percentage compared to controls (%)

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|------|------------|------------|--------------|
| Body weight on day 1 <i>pp</i> | 6.7 | 6.5 (-3%) | 6.5 (-3%) | 6.6 (-1%) |
| Body weight gain day 1-day 4 <i>pp</i> | 2.6 | 2.5 (-4%) | 2.5 (-4%) | 2.3 (-11.5%) |
| Body weight gain day 4-day 21 <i>pp</i> | 41.4 | 42.0 (+1%) | 40.5 (-2%) | 41.2 (-0.5%) |
| Body weight on day 21 <i>pp</i> | 50.6 | 51.0 (+1%) | 49.6 (-2%) | 50.2 (-1%) |

pp: post-partum

No effect on body weight or body weight gain was noted at 250 and 500 mg/kg/day while a transient, non-significant reduction in body weight gain was observed at 1000 mg/kg/day during the first 4 days after birth which returned to normal thereafter. Although this difference in body weight gain was slight (-11.5%), transient and non-significant it was considered possibly related to the treatment.

However no comparable effect was present in F0 pups or in pups from a preliminary range-finding study (CIT/Study No. 24168 RSR, October 2003), hence its biological significance is unclear.

3.3.5.4 Anogenital distance (Table 59, Appendix 62)

The anogenital distance measured on day 1 *post-partum* is summarized in the table below:

F1 generation
Mean values of anogenital distance

| Dose-level (mg/kg/day) | | Male | | | | Female | | | |
|-------------------------------------|------|------|------|------|------|--------|------|------|------|
| | | 0 | 250 | 500 | 1000 | 0 | 250 | 500 | 1000 |
| AGD (mean/female) | Mean | 4.57 | 4.56 | 4.54 | 4.63 | 2.80 | 2.72 | 2.81 | 2.90 |
| | SD | 0.39 | 0.42 | 0.42 | 0.38 | 0.35 | 0.29 | 0.29 | 0.33 |
| PW (mean/female) | Mean | 6.9 | 6.7 | 6.6 | 6.8 | 6.5 | 6.3 | 6.4 | 6.3 |
| | SD | 0.6 | 0.6 | 0.5 | 0.6 | 0.6 | 0.6 | 0.5 | 0.6 |
| AGD/PW | Mean | 0.67 | 0.69 | 0.69 | 0.69 | 0.44 | 0.44 | 0.45 | 0.47 |
| | SD | 0.06 | 0.10 | 0.08 | 0.09 | 0.06 | 0.07 | 0.06 | 0.09 |
| AGD/Cube root of body weight (a) | Mean | 2.41 | 2.42 | 2.42 | 2.45 | 1.51 | 1.47 | 1.51 | 1.57 |
| | SD | 0.18 | 0.25 | 0.23 | 0.21 | 0.21 | 0.18 | 0.16 | 0.22 |

AGD: anogenital distance (mm)

PW: pup weight (grams)

AGD/PW: corrected anogenital distance

(a): the anogenital distance is normalized to the cube root of pup body weight

In all treated groups, anogenital distance, ratio of anogenital distance to pup body weight and anogenital distance normalized to the cube root of the pup's body weight, were not affected by treatment. The minimal non significant increase in mean anogenital distance when normalized to the cube root of body weight for females given 1000 mg/kg/day (+4%) was mainly due to the influence of several pups from one litter (B29799) which were found dead on day 2 or 3 *post-partum*. When compared with values from other litters, this litter exhibited higher mean anogenital distance (3.46 mm) and lower mean pup weight (4.1 g). Furthermore, although pups No. 13 from dams B29776 and B29796 given 1000 mg/kg/day group displayed anouria and anal atrasia, normal anogenital distance was measured.

This change in mean anogenital distance did not correlate with any change in sexual maturation or in sex ratio, consequently these variations were considered to be spontaneous in origin.

3.3.5.5 Assessment of reflex development (Table 60, Appendix 63)

There was no evidence that any reflex or response was disturbed at any dose-level in any pup as assessed by surface righting, cliff avoidance and air righting (between 96.0 and 99.4% positive response).

3.3.5.6 Macroscopic *post-mortem* examination of dead pups and non selected pups sacrificed at weaning (Table 61, Appendix 64)

No macroscopic findings were noted in any non-selected pups sacrificed after weaning or in dead pups.

3.4 F2 GENERATION

3.4.1 Clinical examinations of F2 parent males and females from weaning until sexual maturation

3.4.1.1 Mortality (Tables 72 and 73, Appendices 70 and 71)

Males

No deaths occurred during the study in any group.

Females

One female from the control group was found dead on day 25 of the dosing period. No clinical sign was recorded prior to death. The necropsy revealed foamy contents in the trachea and the lungs and reddish color of the lungs, which are indicative of a difficulties during gavage dosing. No other death was observed in the treated groups.

3.4.1.2 Clinical signs (Tables 72 and 73, Appendices 70 and 71)

Males

Transient ptyalism was observed immediately after dosing in 2, 8, 4 and 13/25 males from the control, 250, 500 or 1000 mg/kg/day dose groups, respectively, at various times during the study. This sign was considered to be related to treatment with the test item but was not considered to represent an adverse effect.

One male from the 1000 mg/kg/day group exhibited piloerection and a rounded back from days 4 to 6 of the dosing period; these signs were considered most probably related to abnormal tooth growth observed from days 4 to 23 of dosing.

Females

Transient ptyalism was recorded immediately after dosing in 2, 3 and 11/25 females from the 250, 500 or 1000 mg/kg/day dose groups, respectively.

Ptyalism resolved in all males and females one hour after dosing.

As indicated when discussing findings for the F0 and F1 generations, ptyalism is commonly noted following gavage administration of unpalatable test items and is therefore not considered an adverse effect.

3.4.1.3 Body weight (Figures 27, 28, 30 and 31, Tables 74 to 77, Appendices 72 to 75)

Except for a minimal non significant decrease in body weight gain in females given 1000 mg/kg/day over the whole dosing period (days 1 to 22, -5%), no differences in body weight or body weight gain were observed for either sex in the other groups.

This change in females body weight gain, recorded at 1000 mg/kg/day, was minor, not statistically significant and did not correlate with any alteration in food consumption. It was therefore considered unrelated to treatment.

3.4.1.4 Food consumption (Figures 29 and 32, Tables 78 and 79, Appendices 76 and 77)

No difference was recorded in food consumption for both males and females throughout the dosing period.

3.4.1.5 Sexual development (Tables 80 and 81, Appendix 78)

Males

The mean age at preputial separation (cleavage of the balanopreputial gland) was similar in the control and the treated groups (i.e. occurred on day 36, 35, 35 or 36 for pups from the control, 250, 500, 500 and 1000 mg/kg/day, respectively).

Females

The mean age for vaginal opening was similar in the control and the treated groups (i.e. occurred on day 35, 34, 34 or 33 for pups from the control, 250, 500 and 1000 mg/kg/day, respectively).

3.5 SEMINOLOGY OF F0 AND F1 PARENT MALES (Tables 23, 24, 62 and 63, Appendices 31 and 65)

The seminology parameters of males of the F1 generation sacrificed after weaning of the pups is summarized in the table below:

Summary of sperm parameters (F0 and F1 generations)

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|-------|------|-------|-------|
| F0 males | | | | |
| <i>Epididymal sperm count</i> | | | | |
| Spermatozoa ($10^3/\text{mm}^3$) | 923 | 938 | 935 | 918 |
| Motility (% motile) | 99.7 | 100 | 98.6 | 97.6 |
| Normal morphology (%) | 93 | 93 | 97 | 96 |
| <i>Testicular sperm</i> | | | | |
| Sperm heads ($10^6/\text{g}$ of testis) | 114.8 | 109 | 108 | 109.8 |
| Daily sperm production ($10^6/\text{g}$ of testis/day) | 18.8 | 17.9 | 17.7 | 18.0 |
| F1 males | | | | |
| <i>Epididymal sperm count</i> | | | | |
| Spermatozoa ($10^3/\text{mm}^3$) | 725 | 673 | 701 | 688 |
| Motility (% motile) | 84.6 | 87.1 | 93.3 | 88.3 |
| Normal morphology (%) | 84 | 86 | 86 | 88 |
| <i>Testicular sperm</i> | | | | |
| Sperm heads ($10^6/\text{g}$ of testis) | 100.6 | 97.8 | 105.3 | 99.8 |
| Daily sperm production ($10^6/\text{g}$ of testis/day) | 16.5 | 16.0 | 17.3 | 16.4 |

The fluctuations noted in seminology parameters from F0 and F1 males were minor in magnitude, not statistically significant and not dose-related.

The slightly lower testicular sperm head count noted in treated males from the F0 generation appeared to be the consequence of a high control value.

The decrease and/or occasional absence of spermatozoa in the testis or epididymis (oligospermia, aspermia) of few individuals randomly distributed within the groups was confirmed by histopathological examination but considered to be spontaneous in nature (no dose/response relationship).

It was concluded that seminology parameters were unaffected by treatment at all dose-levels.

3.6 PATHOLOGY F0, F1 AND F2 GENERATIONS

3.6.1 F0 generation

3.6.1.1 Organ weights

3.6.1.1.1 Parents (Table 25, Appendix 32)

The principal differences (expressed in %) noted between treated and control animals in the absolute and relative organ weights are given in the table below:

| Group | Males | | | Females | | |
|------------------------|-------|-------|-------|---------|-----|------|
| | 2 | 3 | 4 | 2 | 3 | 4 |
| Dose-level (mg/kg/day) | 250 | 500 | 1000 | 250 | 500 | 1000 |
| - Liver | | | | | | |
| . absolute | +2 | +2* | +17** | -1 | +4 | +6 |
| . relative | +3 | +6 | +24** | +10 | +8 | +4 |
| - Kidneys | | | | | | |
| . absolute | +11 | +15** | +21** | -1 | +2 | +5 |
| . relative | +11 | +18** | +28** | +9 | +5 | +3 |

** : p<0.01, * : p<0.05

The higher absolute and relative liver weights in males given 1000 mg/kg/day were considered to be treatment-related and correlated with liver enlargement noted during necropsy and hepatocellular hypertrophy detected in livers from three animals subject to histopathological examination. Liver weights from females given 1000 mg/kg/day were slightly (increased 4-6%) but non-significantly increased.

The higher kidney weights in male rats from the 1000 mg/kg/day group were also considered to be treatment-related, and correlated with the presence of acidophilic globules detected microscopically in the cortical tubular epithelium from five animals subjected to histopathological examination. Kidney weights were also significantly increased in male rats given 500 mg/kg/day (no microscopic examination performed).

There were sporadic, occasionally significant, differences in other absolute and/or relative organ weights between treated and control animals, however the changes were generally minimal, not dose-related, inconsistently expressed within the sexes or did not correlate with any histopathological abnormalities upon microscopic examination. They were therefore considered to be of no toxicological importance.

3.6.1.1.2 Pups sacrificed at weaning (Table 26, Appendix 32)

Some differences were noted in absolute and relative brain, spleen and thymus weights between groups, however these were minor and not statistically significant and were therefore considered to be of no toxicological importance.

3.6.1.2 Macroscopic *post-mortem* examination

3.6.1.2.1 Parents (Table 27, Appendix 33)

Liver enlargement was noted in three males given 1000 mg/kg/day, and tissue was therefore sampled for histopathological evaluation. This was considered to be treatment-related and correlated with the hepatocellular hypertrophy noted in these animals.

Kidneys from six males given 1000 mg/kg/day exhibited an unusual coloration (grey/green color or pale), and were sampled for histological assessment.

All other necropsy findings were consistent with commonly observed changes in rats of this strain and age and none were considered to be of toxicological importance.

3.6.1.2.2 Dead pups and non selected pups sacrificed at weaning (Table 22, Appendix 30)

No relevant macroscopic findings were noted in any non-selected pups sacrificed after weaning. No obvious gross findings were recorded for pups found dead. Blackish intestinal contents were the only findings of note in moribund pups subject to premature sacrifice.

3.6.1.3 Microscopic examination (Tables 28 to 31, Appendix 33)

All microscopic findings noted for individuals from the F0 generation are given in detail in the Appendix 33. The following comments are made to summarize.

Liver

Slight to moderate centrilobular hepatocellular hypertrophy was noted in three males from the high-dose group that were considered to show signs of liver enlargement at necropsy. However, there was no evidence of nuclear/cytoplasmic changes indicative of degenerative/ necrotic abnormalities. Consequently, this hepatocellular hypertrophy was considered an adaptive response reflecting an increased metabolic demand following treatment with high doses of ETBE.

Kidneys

Slight to moderate accumulation of acidophilic globules in cortical tubular epithelium was noted in five of six male rats given 1000 mg/kg/day, which were selected for histopathological evaluation due to necropsy abnormalities. The intracellular accumulation of acidophilic globules is commonly encountered in the cortical tubular epithelium of male rat kidneys following exposure to a variety of substances, and is considered due to impaired lysosomal degradation of alpha 2 µglobulin in the cortical tubular cells. This is a species and sex-linked phenomenon considered of no toxicological relevance for human beings (Alden C.L. (1985); Borghoff S.J. *et al* (1990); Hard G.C. and *al* (1993)).

Female genital organs

Microscopic examination of the ovaries, uterus and vagina from control and high-dose females revealed morphological changes consistent with a regular estrous cycle. There was no histopathological evidence that the estrous cycle was disturbed by treatment with the test item. Quantitative analysis of the primordial and growing follicles in the ovaries showed considerable variation between individuals within the same group and between the control and high-dose groups (see summary tables 30 and 31 and Appendix 34). From the values obtained in the individual and summary tables, it can be concluded that no perceptible differences were noted in the number of primordial and growing follicles between control and treated animals.

Male genital organs

Minimal degeneration of seminiferous tubules was noted in two animals from control and two from the high dose group. In addition, desquamated spermatocytes were present in both control (8/25 animals) and treated animals (1/25 animals).

These findings are commonly recorded in rats of this strain and age and were considered to be of no toxicological importance.

Microscopic findings noted in the prostate (interstitial mononuclear cell aggregation, subacute prostatitis) and epididymides (spermatic granuloma) are commonly observed in rats of this strain and age and occurred with equal incidence and severity in both control and treated animals. None were considered to be of toxicological importance.

Other organs and tissue

All other microscopic findings are commonly recorded in rats of this strain, sex and age and were considered to be of no toxicological importance.

3.6.2 F1 Generation

3.6.2.1 Organ weights

3.6.2.1.1 Parents (Table 64, Appendix 66)

The principal differences (expressed in %) noted between treated and control animals in the absolute and relative organ weights are given in the table below:

| Group | Males | | | Females | | |
|------------------------|-------|-------|-------|---------|-----|-------|
| | 2 | 3 | 4 | 2 | 3 | 4 |
| Dose-level (mg/kg/day) | 250 | 500 | 1000 | 250 | 500 | 1000 |
| Body weight | 0 | +3 | +1 | -2 | -3 | +2 |
| - Kidneys | | | | | | |
| . absolute | +10 | +22** | +58** | +4 | +3 | +11** |
| . relative | +10** | +19** | +58** | +6 | +6 | +10** |
| - Liver | | | | | | |
| . absolute | 0 | +14* | +27** | +1 | +3 | +10* |
| . relative | 0 | +11** | +25** | +3 | +6 | +9* |
| - Pituitary | | | | | | |
| . absolute | +8 | +9 | +14* | -2 | -8 | +0 |
| . relative | +9 | +8 | +13* | -0 | -4 | -1 |
| - Uterus | | | | | | |
| . absolute | | | | -2 | -12 | +46 |
| . relative | | | | -1 | -10 | +30 |

*: statistically significant (p<0.05)

** : statistically significant (p<0.01)

When compared to controls, the statistically significant increase in absolute and relative kidney weights observed in males given 1000 or 500 mg/kg/day was considered to be due to treatment with the test item and possibly related to the intracellular accumulation of sex-linked alpha 2 µglobulin in the cortical tubular epithelium of the kidneys among these animals, some of which were subject to microscopic examination due to necropsy abnormalities.

The statistically significantly higher absolute and relative liver weights observed in males given 1000 mg/kg/day were also considered to be treatment-related and correlated with liver enlargement and hepatocellular hypertrophy noted among some of these animals.

In the absence of microscopic examination, no conclusion could be drawn with respect to the underlying cause of the slight, statistically significant increase in liver and kidney weights from female rats given 1000 mg/kg/day, or the slight significant increase in liver weights from males given 500 mg/kg/day.

As all the individual pituitary values were within the range of the controls from this study, the slightly higher pituitary weights for males given 1000 mg/kg/day were considered to be of no toxicological importance. Moreover, no relevant microscopic finding was observed.

As other differences in absolute and relative organ weights noted between treated and control animals were minimal, they were considered to be of no toxicological importance.

3.6.2.1.2 Pups sacrificed at weaning (Table 65, Appendix 66)

Due to some higher individual values in the control females, there were lower mean absolute and relative spleen weights in the treated females. However, these differences from controls were minor (-6%, -2%, -13%; -5%, -1%, -11%, respectively for absolute and relative weights) not statistically significant and not dose-related. In addition, the differences from controls in spleen weights in the male F2 pups were of lower magnitude (-5%, -6%, -7%; -3%, -3%, -5% respectively for absolute and relative weights) and no similar trend was observed in the male and female F1 pups. Consequently the differences from control in spleen weights were considered to be of no toxicological importance. Some differences from controls were observed in the other organs (brain, thymus). However, they were minor and not dose-related and consequently considered to be of no toxicological importance.

3.6.2.2 Macroscopic *post-mortem* examination

3.6.2.2.1 Parents (Table 66, Appendix 67)

The liver showed an accentuated lobular pattern and/or was enlarged in 2/25 (B29390 and B29399) males given 1000mg/kg/day. This correlated with higher absolute and relative liver weights at necropsy and slight or moderate centri-lobular hepatocellular hypertrophy.

In occasional treated animals (at all dose-levels), grey/green or irregular coloration of the kidneys was observed. This correlated, for the two males (B29391 and B29399) given 1000 mg/kg/day, with moderate or marked acidophilic globules in the cortico-tubular epithelium. Enlargement of the left kidney was observed in 1/25 (B29387) males given 1000 mg/kg/day which had a mass in each kidney. This finding correlated with a microscopic diagnosis of bilateral nephroblastoma, and was considered to be without relationship to the treatment (see Microscopic examination).

All other macroscopic findings were of a type commonly encountered spontaneously in untreated laboratory rat of this strain and age and were thus considered to be of no toxicological significance.

3.6.2.2.2 Pups (Tables 82 and 83, Appendix 79)

Necropsy of the F2 pups after sexual maturation did not reveal any obvious treatment-related effects.

The few findings present (dilated pelvis or intestines, brownish nodule on the liver, serous contents in uterine horns) were recorded sporadically in only a few animals and were randomly distributed between the groups.

3.6.2.3 Microscopic examination (Tables 67 to 71, Appendix 67)

Individual microscopic findings for the F1 generation are given in detail in Appendix 67, however only those found in male liver and kidney were considered to be related to treatment with the test material.

The following comments are made in summary:

Liver

Slight or moderate centrilobular hepatocellular hypertrophy was observed in the liver of two males given 1000 mg/kg/day, the livers of which were examined microscopically. This correlated with enlargement and/or an accentuated lobular pattern and higher liver weight in these animals at necropsy. This was considered to be treatment-related. However, there was no evidence of nuclear/cytoplasmic changes indicative of degenerative/necrotic abnormalities. Consequently, the observed hepatocellular hypertrophy may represent a demand for increased liver function following exposure to high doses of the test item.

Kidneys

Microscopic examination of kidneys from one male given 500 mg/kg/day and four males given 1000 mg/kg/day revealed the presence of acidophilic globules of slight to marked severity. This correlated in 2/4 animals with irregular or grey/green kidney color and was considered to be due to the accumulation of alpha 2 μ globulin in the cortical tubular epithelium of the male rat kidney. In one male given 500 mg/kg/day (B29357), this finding was associated with the presence of sloughed degenerated/necrotic cells (moderate severity) in the tubular lumen.

The intracellular accumulation of acidophilic globules is commonly encountered in the cortical tubular epithelium of male rat kidneys following exposure to a variety of substances, and is considered due to impaired lysosomal degradation of alpha 2 μ globulin in these cells. This is a species and sex-linked phenomenon considered of no toxicological relevance for human beings (Alden C.L. (1985); Borghoff S.J. and *al* (1990); Hard G.C. and *al* (1993)).

Nephroblastoma was found in one male given 1000 mg/kg/day, and correlated with the presence of grossly detected masses in both kidneys and enlargement of the left kidney reported at necropsy. This was considered to be without relationship to treatment with the test item, as it can occur spontaneously, although not commonly in the rat (Hard Gordon C. *et al*, 1995). In addition, such tumors have previously been recorded in our historical control data.

Female genital organs

Microscopic examination of the ovaries, uterus and vagina showed morphological changes indicative of a regular estrous cycle in both control and treated animals, as shown in the table below:

| Dose-level (mg/kg/day) | 0 | 1000 |
|---|-------|-------|
| Presence of estrous cycle | 22/25 | 20/24 |
| Mucification of vaginal epithelium | 2/25 | 4/24 |
| Epithelial cell hyperplasia of the vaginal epithelium | 1/25 | 0/24 |
| Total number of females examined microscopically | 25 | 24 |

It was concluded that the estrous cycle was not disturbed by treatment with the test item at doses up to 1000 mg/kg/day.

Quantitative analysis of the primordial and growing follicles in the ovaries showed considerable variation between individuals within the same group and between the control and high-dose groups (see summary tables 69 and 70 and Appendix 68). From the values obtained in the individual and summary tables, it can be concluded that no perceptible differences were noted in the number of primordial and growing follicles between control and treated animals.

Male genital organs

Histopathological examination of testis was conducted in the F1 controls and all F1 treated males.

A reduced number of tailed and round spermatids, spermatocytes, and spermatogonia was observed in 3/25 males given 250 mg/kg/day, 1/24 males given 500 mg/kg/day and 3/25 males given 1000 mg/kg/day *versus* none in the control group. In the three males given 250 mg/kg/day, the male given 500 mg/kg/day and 2/3 males given 1000 mg/kg/day, the marked or severe grading of these findings correlated with disturbance of the different stages of spermatogenic cycle: for these animals, the seminiferous tubules were lined with Sertoli cells only (marked or severe and sometimes vacuolated) and marked oligospermia or aspermia was observed in the epididymides of the males receiving 1000 mg/kg/day (epididymides not examined in the low and intermediate dose-level groups). Nevertheless seminiferous tubules lined by Sertoli cells only were observed with minimal severity and similar incidence in all groups of F1 males including the control. Minimal focal degeneration of germinal epithelium was observed in 1/24, 1/25 or 1/25 males from the control, low- or high-dose groups, respectively. Minimally or slightly degenerated/necrotic cells were observed sloughed in the testicular lumen of 9/24 control males, 4/25 males given 250 mg/kg/day, 8/24 males given 500 mg/kg/day and in 6/25 males given 1000 mg/kg/day. Minimal or moderate vacuolation of the seminiferous tubules or Sertoli cells was observed with similar incidence in treated and control animals, whereas minimal multinucleated giant cells were observed in the testis of 1/25 males given 250 mg/kg/day and 1/25 males given 1000 mg/kg/day. Retained spermatids were found in one male from the intermediate dose group.

In the prostate, apart from minimal or slight hypersecretion, atrophy of the tubulo alveolar units, and acute prostatitis recorded in 1/25 treated males given 1000 mg/kg/day *versus* none in the controls, other findings were recorded at a similar incidence and severity in both high-dose and control males. No relevant microscopic findings were noted in the seminal vesicles.

Although some of the observations detailed above were not present in the controls used in this study, there was no evidence of any dose-response relationship in their incidence and/or severity, and similar findings can arise spontaneously with an equivalent incidence and severity in the untreated rats of this strain and age.

Consequently, all these findings were considered to be without relationship to the treatment.

Other organs and tissues

Vacuolated cortical cells (slight severity) were recorded in the adrenals of 5/25 males given 1000 mg/kg/day vs. none in the control group. Altered cell foci, cystic degeneration and lipomatosis were recorded, each, at minimal severity, in the adrenals of 1/25 males given 1000 mg/kg/day.

Adrenal cortical cell hypertrophy (slight), minimal cystic degeneration and minimal interstitial mononuclear cell aggregation were noted in the adrenals of 1/24, 1/24 or 5/24 treated females, respectively, vs. none in the control group.

Altered cell foci, acidophilic or clear, were recorded in the liver of 1/2 males given 1000 mg/kg/day which were selected for histopathological examination, due to macroscopic abnormalities seen at necropsy.

Fibroadenoma of the mammary gland, correlating with a palpable mass observed at external examination, was observed in one female receiving 1000 mg/kg/day.

As all these findings can occur spontaneously in untreated rats of this strain and age, their low incidence/severity in the top dose group was considered to bear no relationship to treatment with the test item.

4. CONCLUSION

The test item, ETHYL TERTIARY BUTYL ETHER (ETBE), CAS No. 637-92-3, was administered daily by oral gavage to male and female Sprague-Dawley rats at 250, 500 and 1000 mg/kg/day, commencing 10 weeks prior to mating and continuing through mating and gestation until the end of lactation in both the F0 and F1 generations. Progeny of the F1 generation (F2 pups) were treated from weaning until sexual maturity.

For all generations, ptyalism (excessive salivation) was observed with a dose-related trend in both males and females.

At 1000 mg/kg/day, F0 males showed significantly lower body weight gain at the end of the dosing period. Liver weight was significantly increased in males only, with slight to moderate centrilobular hepatocellular hypertrophy in tissue from animals subject to microscopic examination. Kidney weights were also significantly increased in F0 parental males, with acidophilic globules detected after microscopic examination. There were no adverse findings for F0 pups. Significantly greater food consumption during the lactation period was the only finding of note in F0 parental females.

Liver and kidney weights were significantly increased in F1 parental males.

Body weight gain of pups born to mothers from the F1 generation was slightly but non-significantly lower than the controls on *post-partum* days 1-4 (no comparable finding in F0 litters). Two pups born to mothers from the F1 generation exhibited gross external malformations (absence of tail with anal atresia also present in one pup), however the incidence of these findings was comparable to laboratory or external historical control data. Neither malformation was present in 566 pups or fetuses from 45 litters from dams treated with ETBE at 1000 mg/kg body weight/day as part of a dose-range finding study and a developmental toxicity study performed at this laboratory. It was concluded that the findings from the present study were therefore most probably unrelated to treatment with the test item.

No effects were noted in the F2 generation at 1000 mg/kg/day.

At 500 mg/kg/day, significantly lower body weight gain was noted at the end of the dosing period in F0 parental males together with significantly increased kidney weights. Liver and kidney weights were statistically significantly increased in F1 parental males, whereas body weight was unaffected. No effects were noted in the F2 generation.

At 250 mg/kg/day, no relevant findings were observed in the F0, F1 and F2 generations.

Based on these observations, the following No Observed Adverse Effect Levels were established from the study:

Systemic toxicity in the adult (parental) F0 and F1 generations: NOAEL = 250 mg/kg body weight/day (based on body weight and organ weight changes at higher treatment levels).

Ptyalism (excess salivation) was noted in all treated animals (LOEL = 250 mg/kg body weight/day but was not considered to represent an adverse effect of treatment).

Fertility, gonadal function, reproductive performance, parturition and lactation in the parental generations, and development of the off-spring to weaning or sexual maturity: NOAEL = 1000 mg/kg body weight/day (the highest dose tested).

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Figure 1

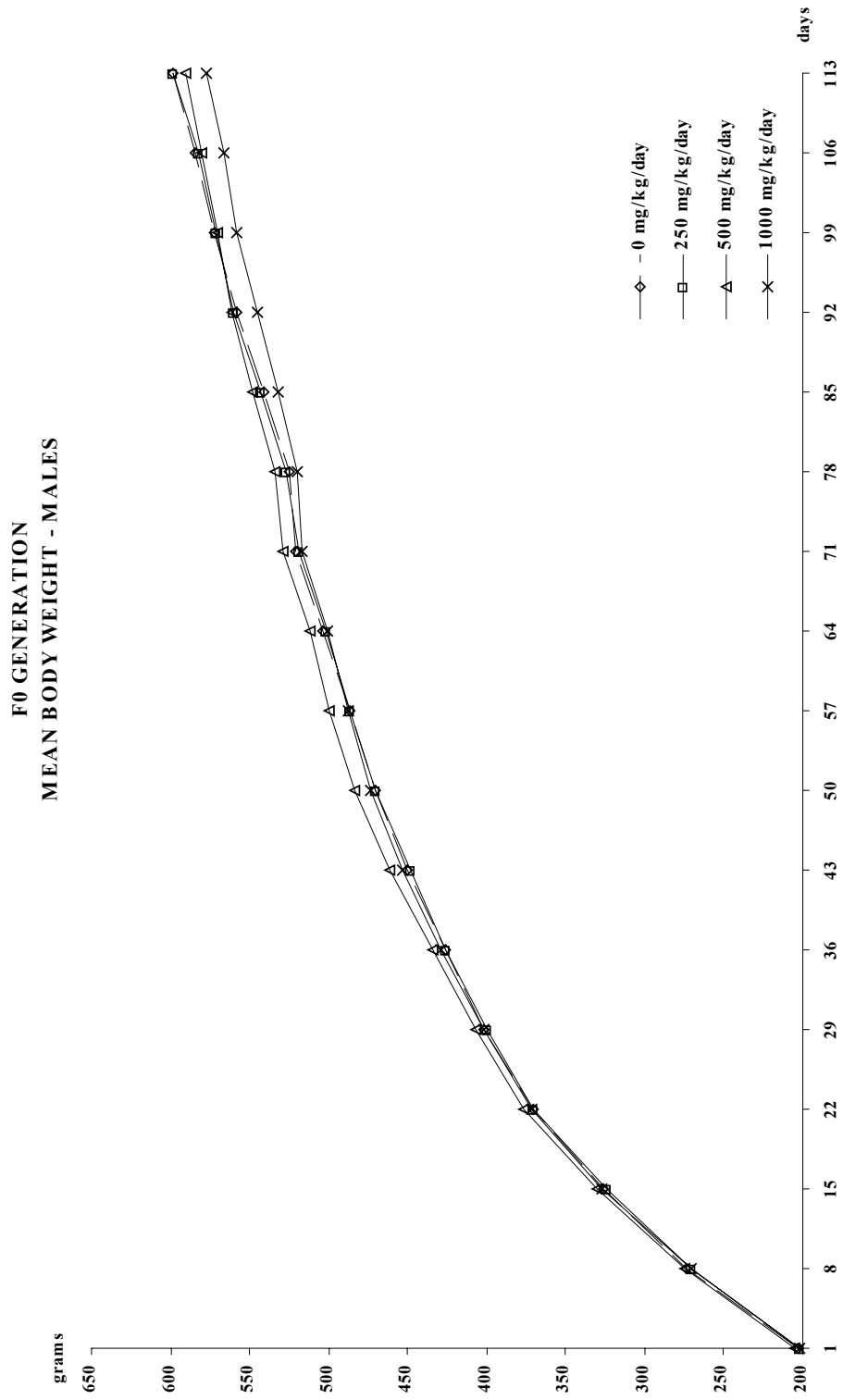


Figure 2

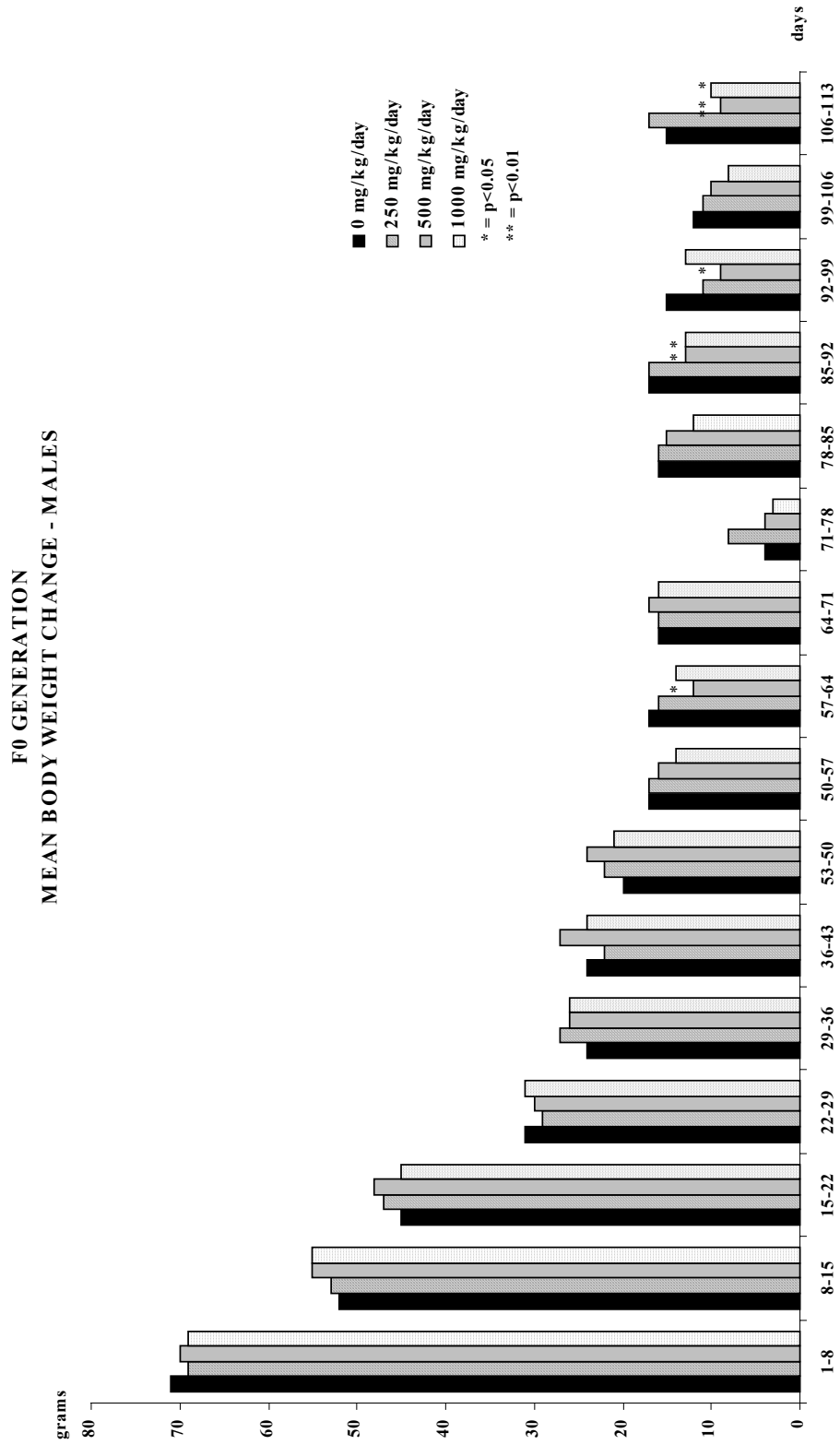


Figure 3

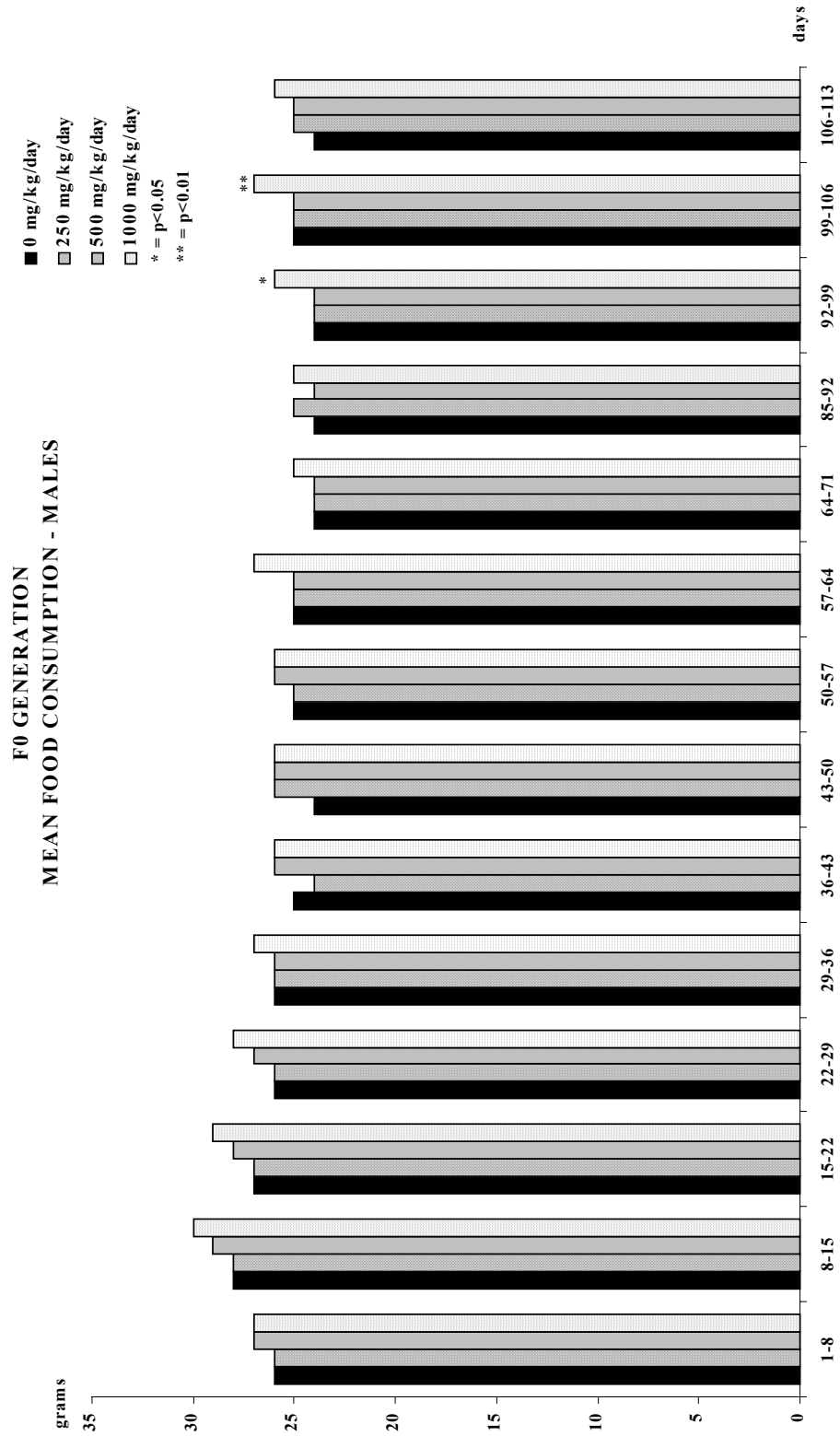


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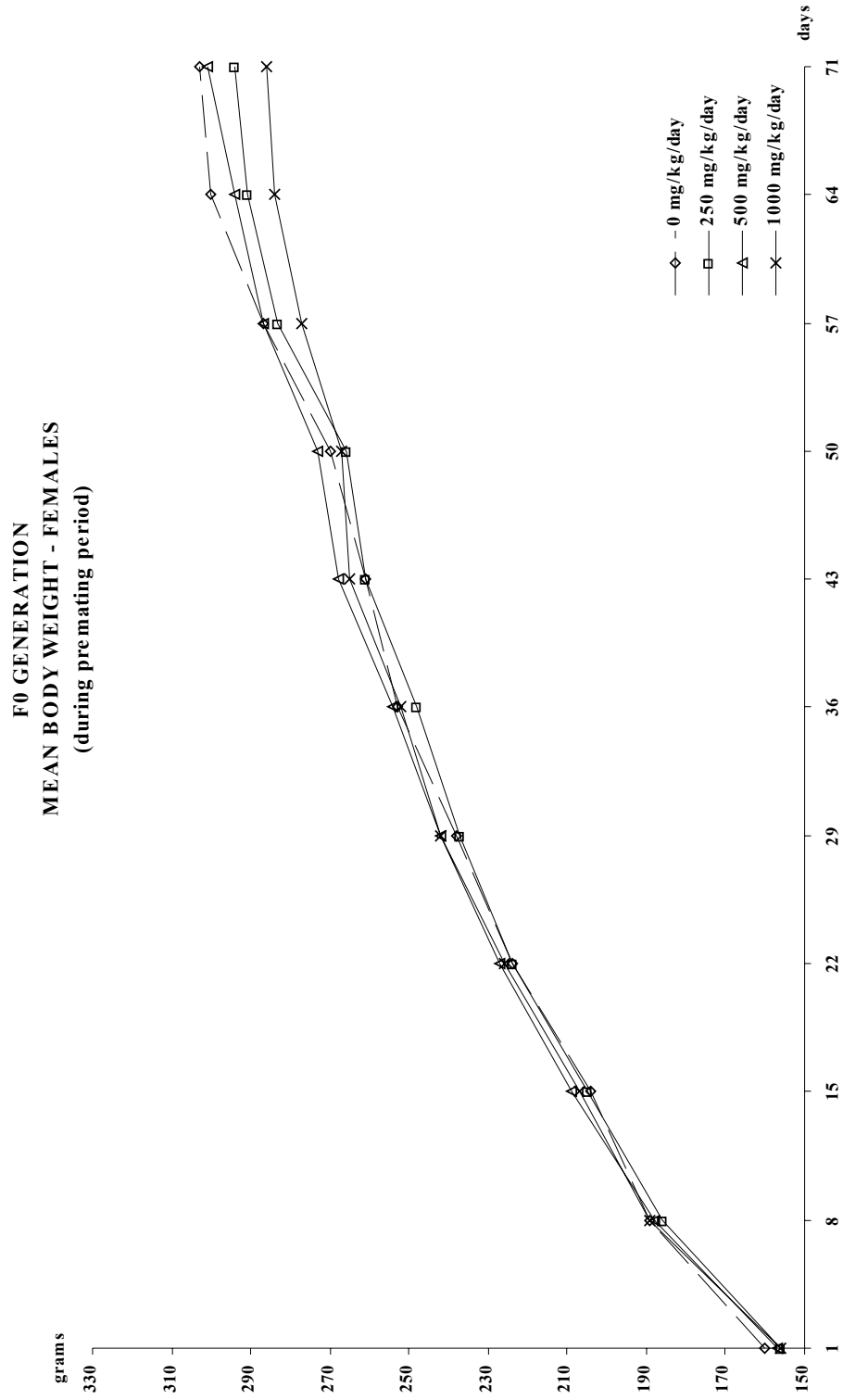


Figure 5

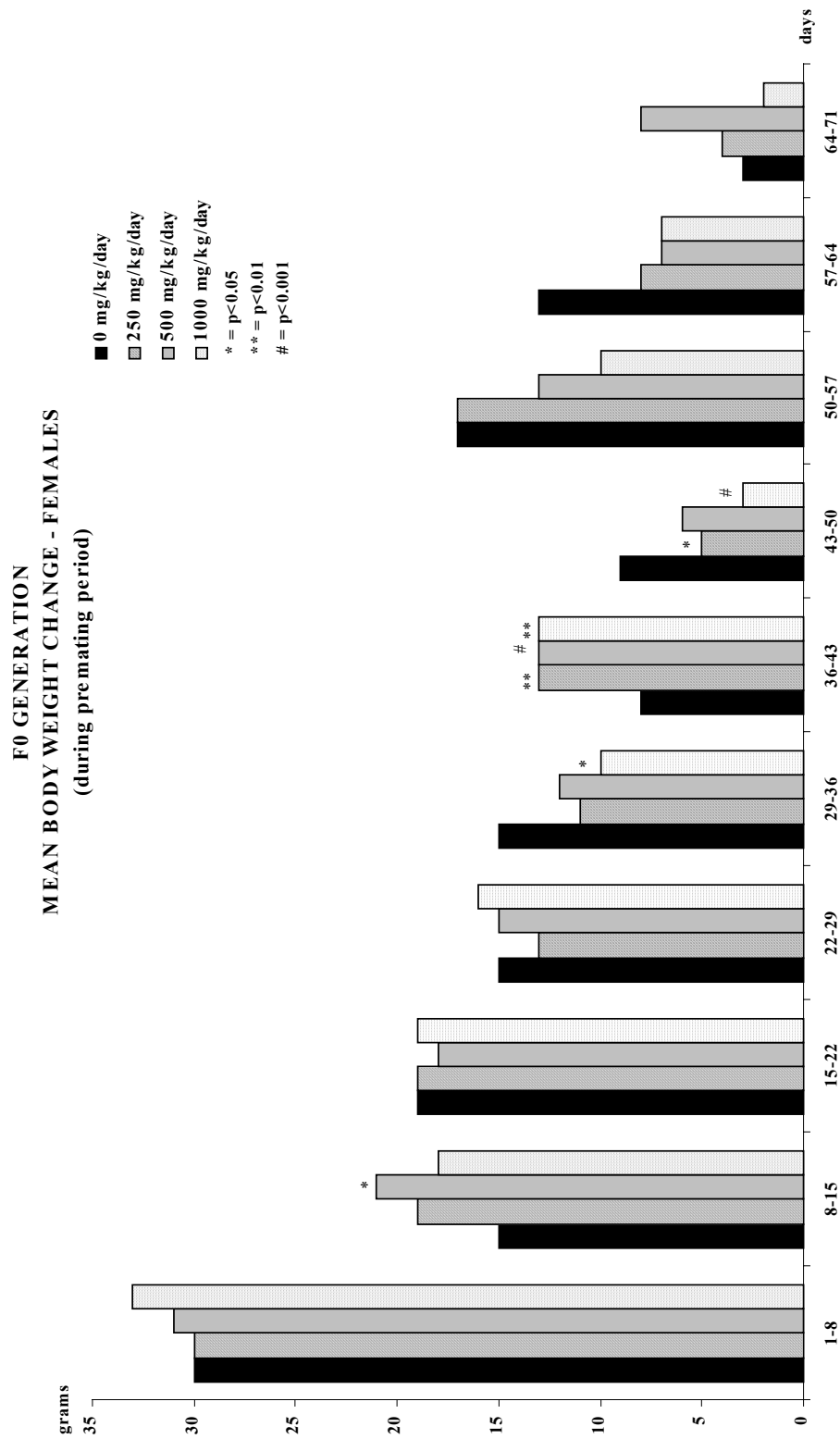


Figure 6

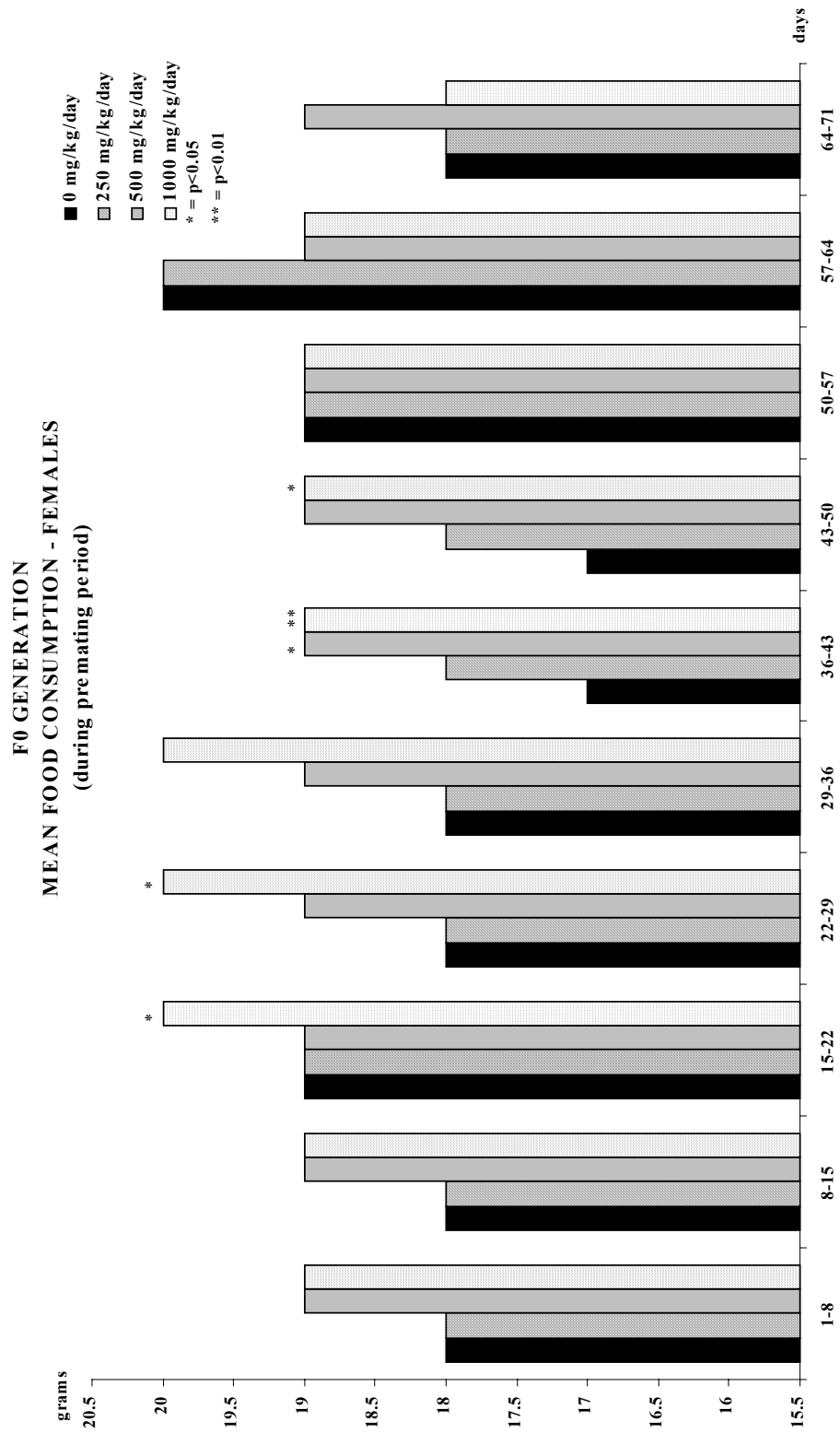


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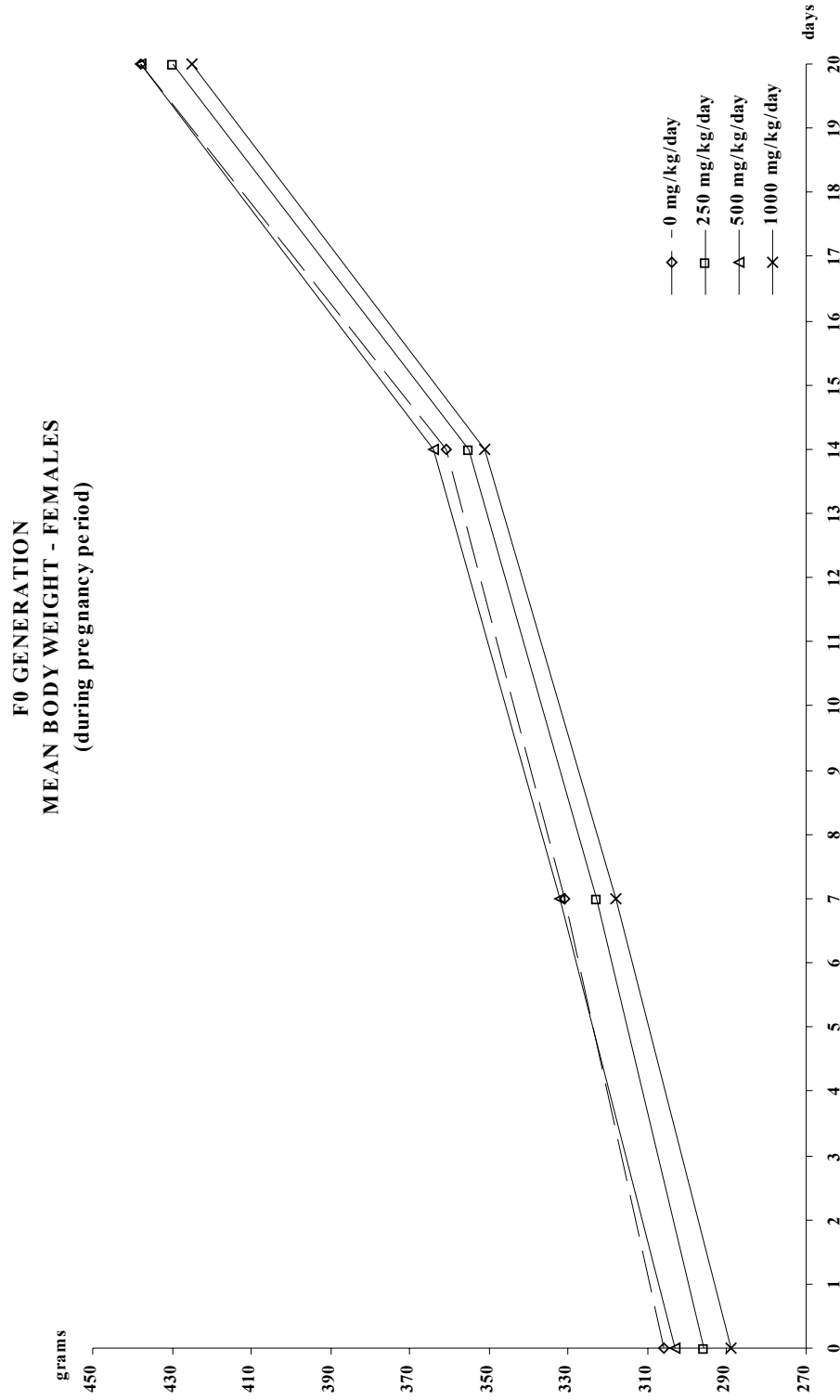


Figure 8

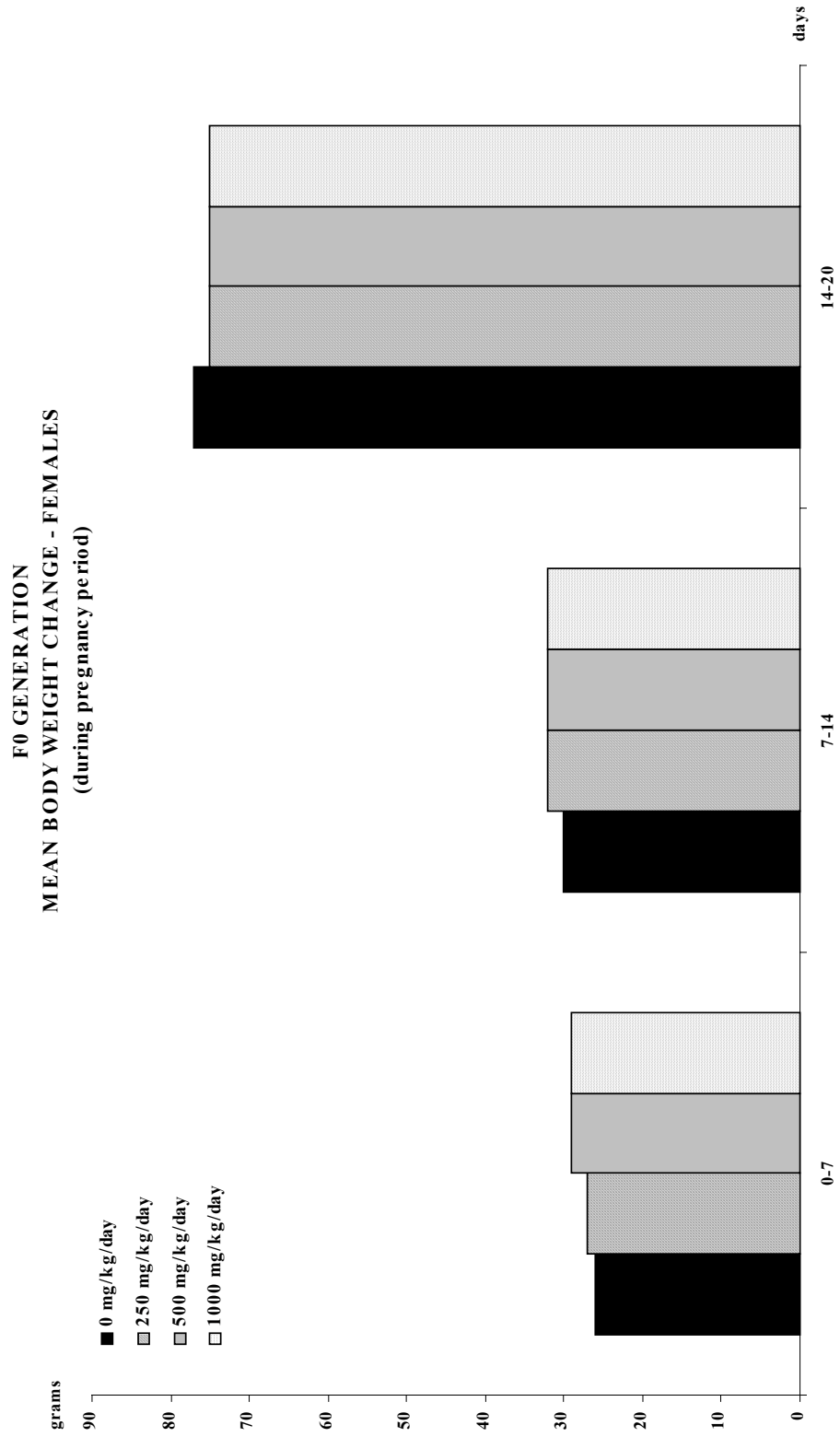


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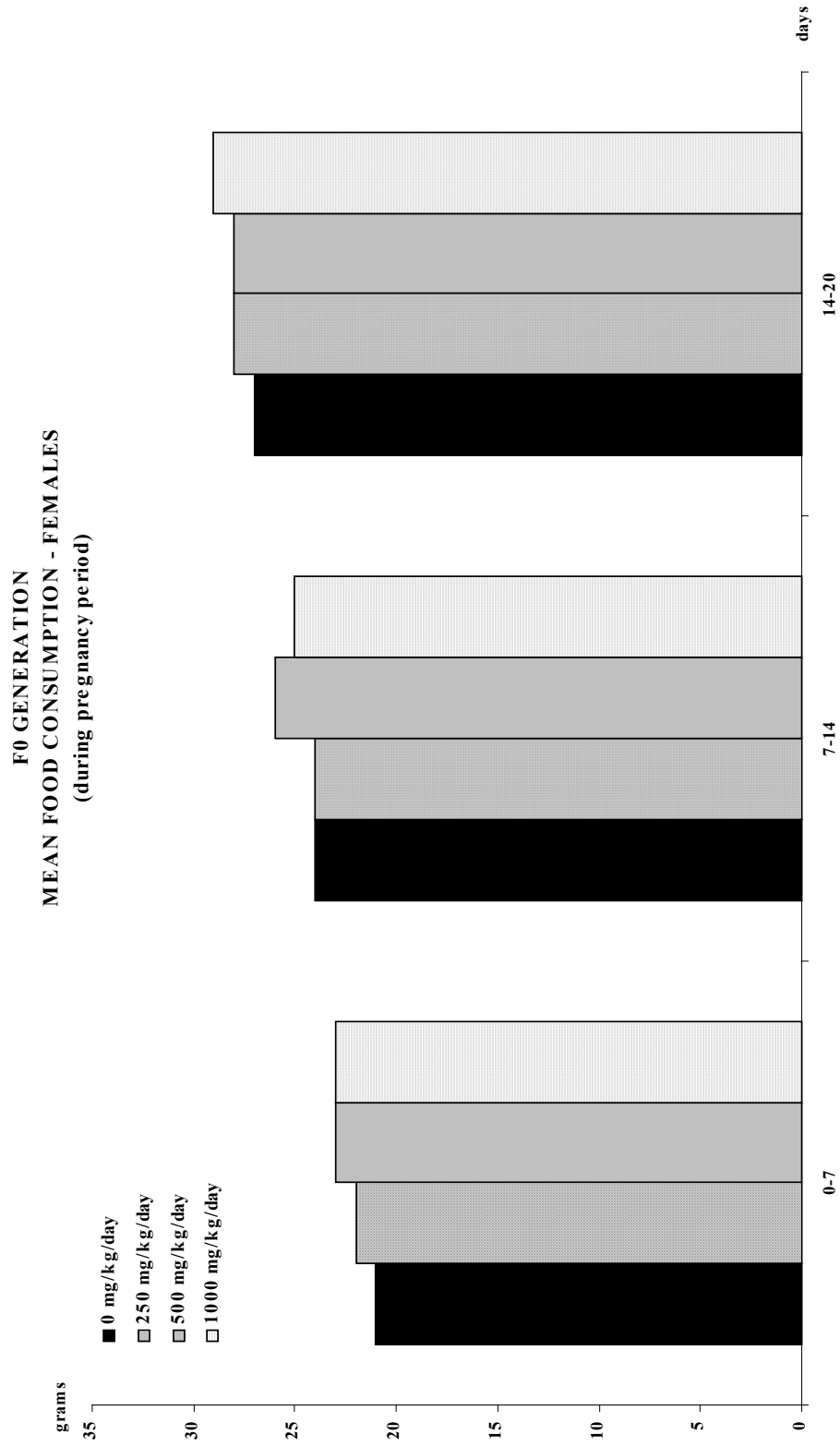


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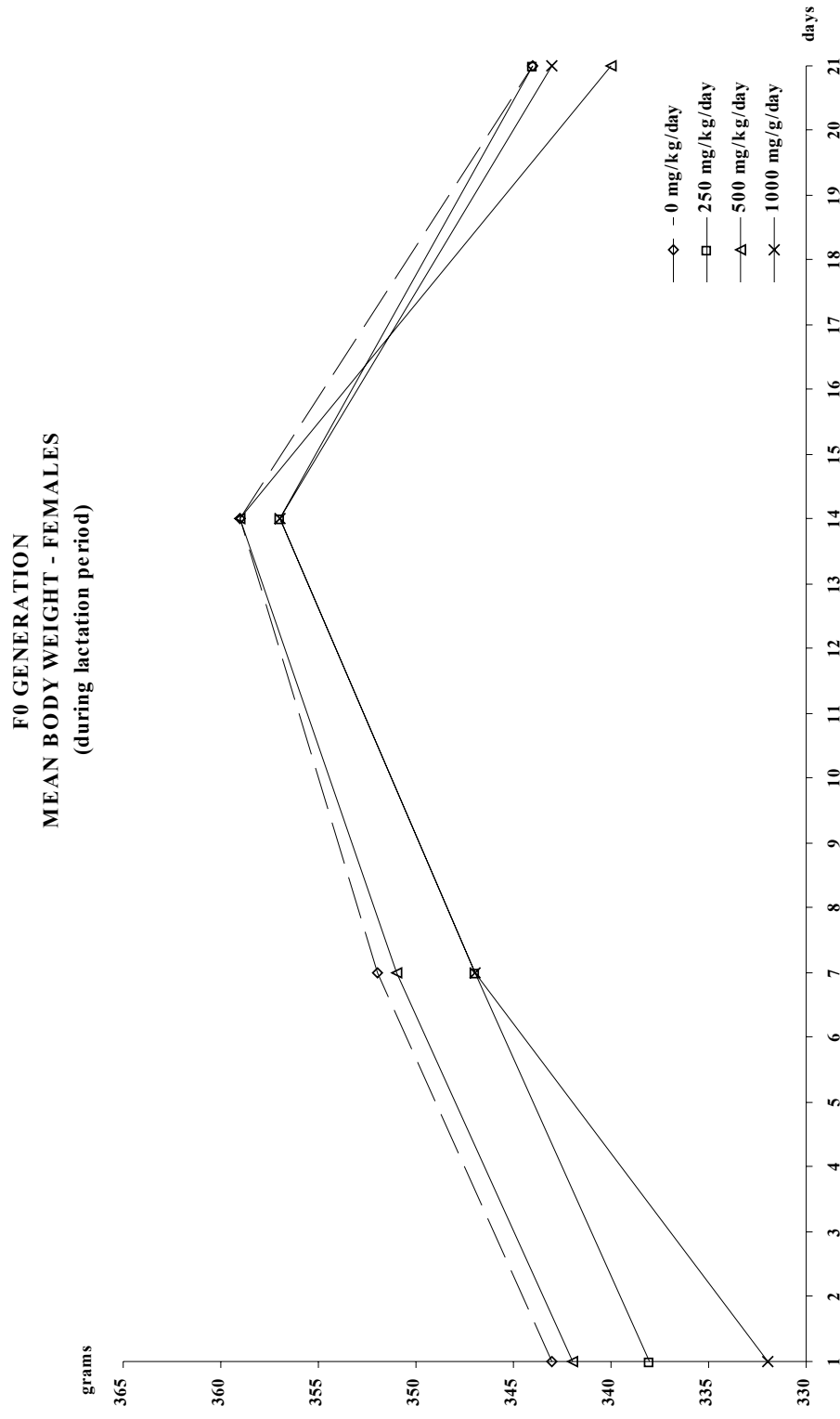


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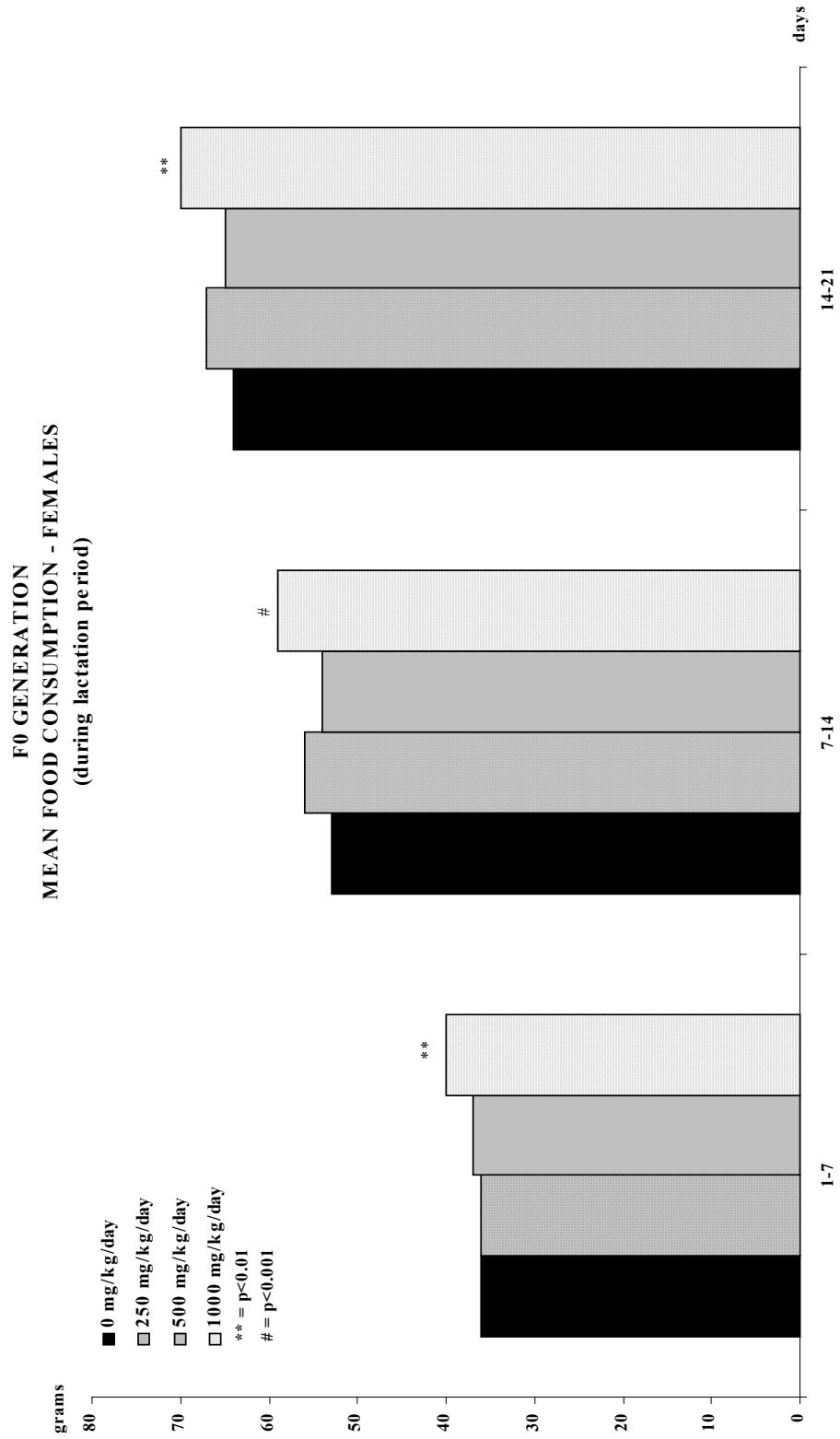


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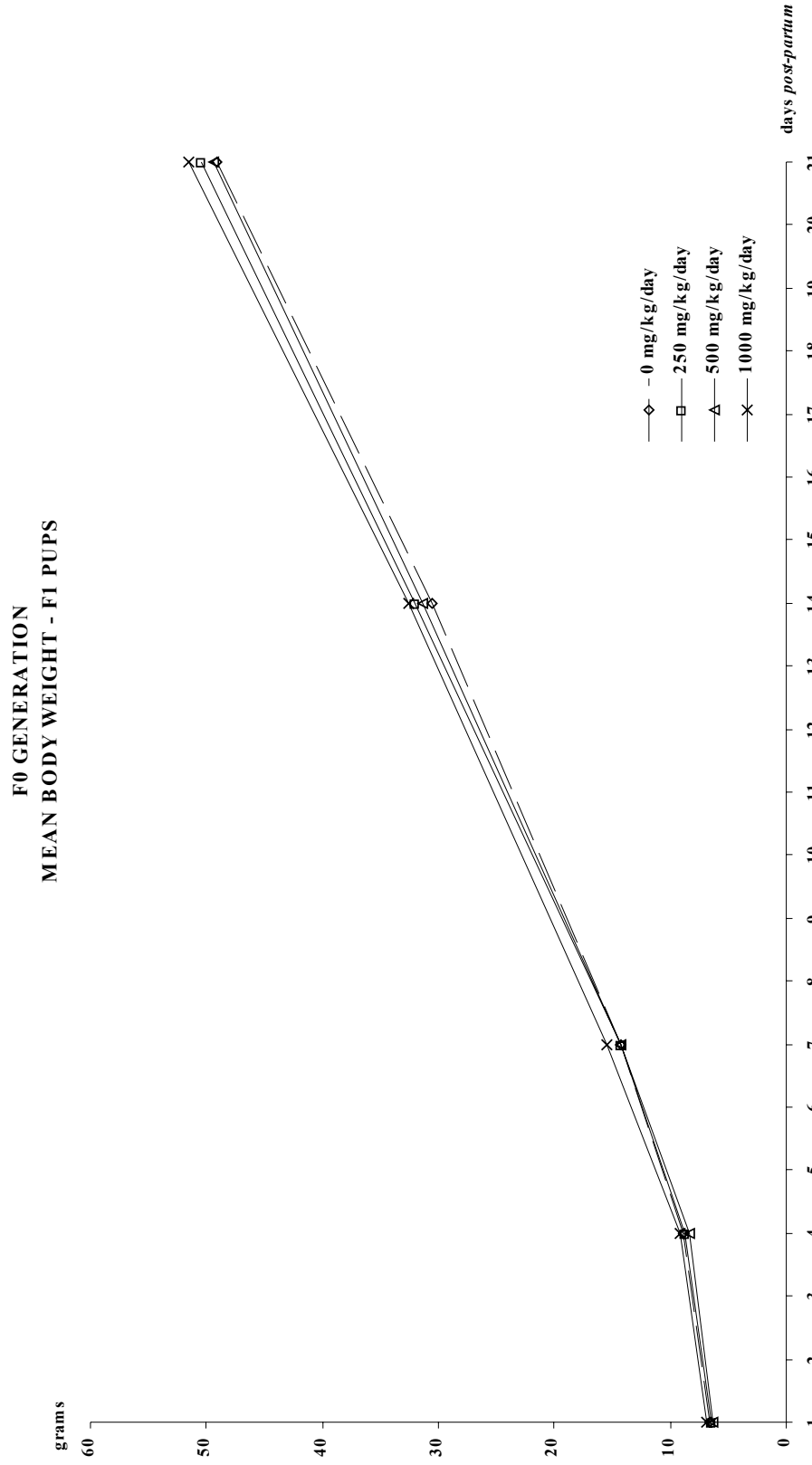


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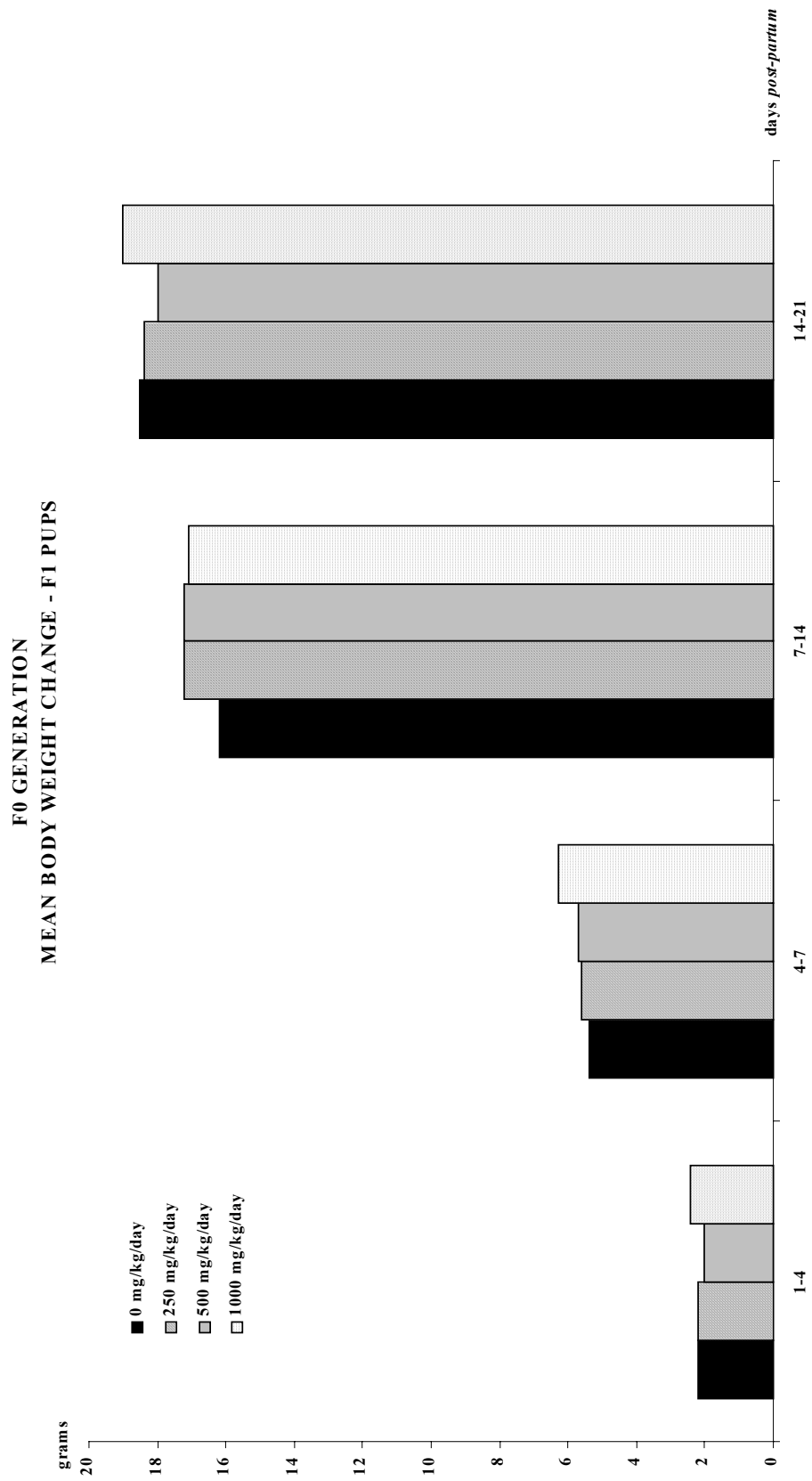


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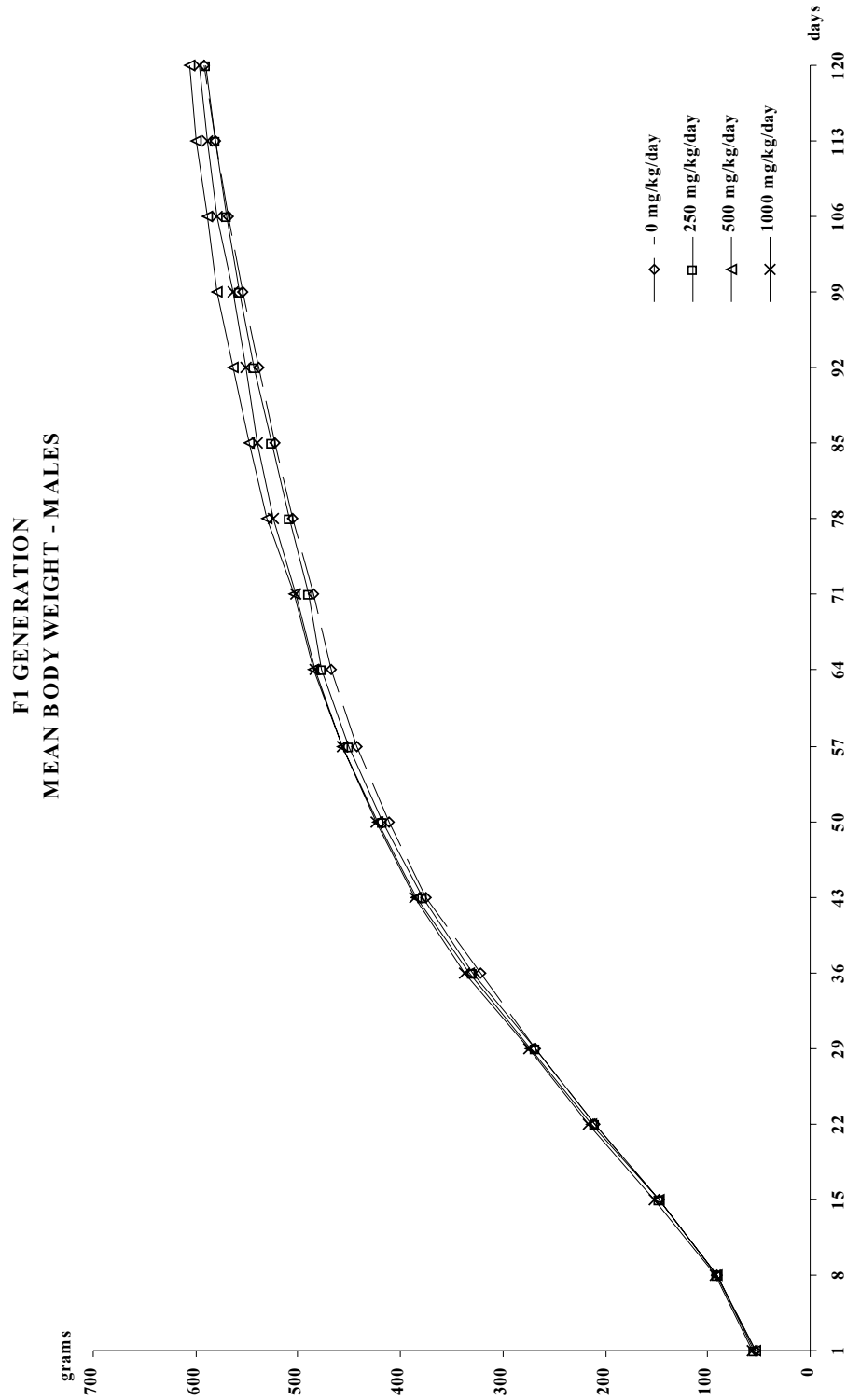


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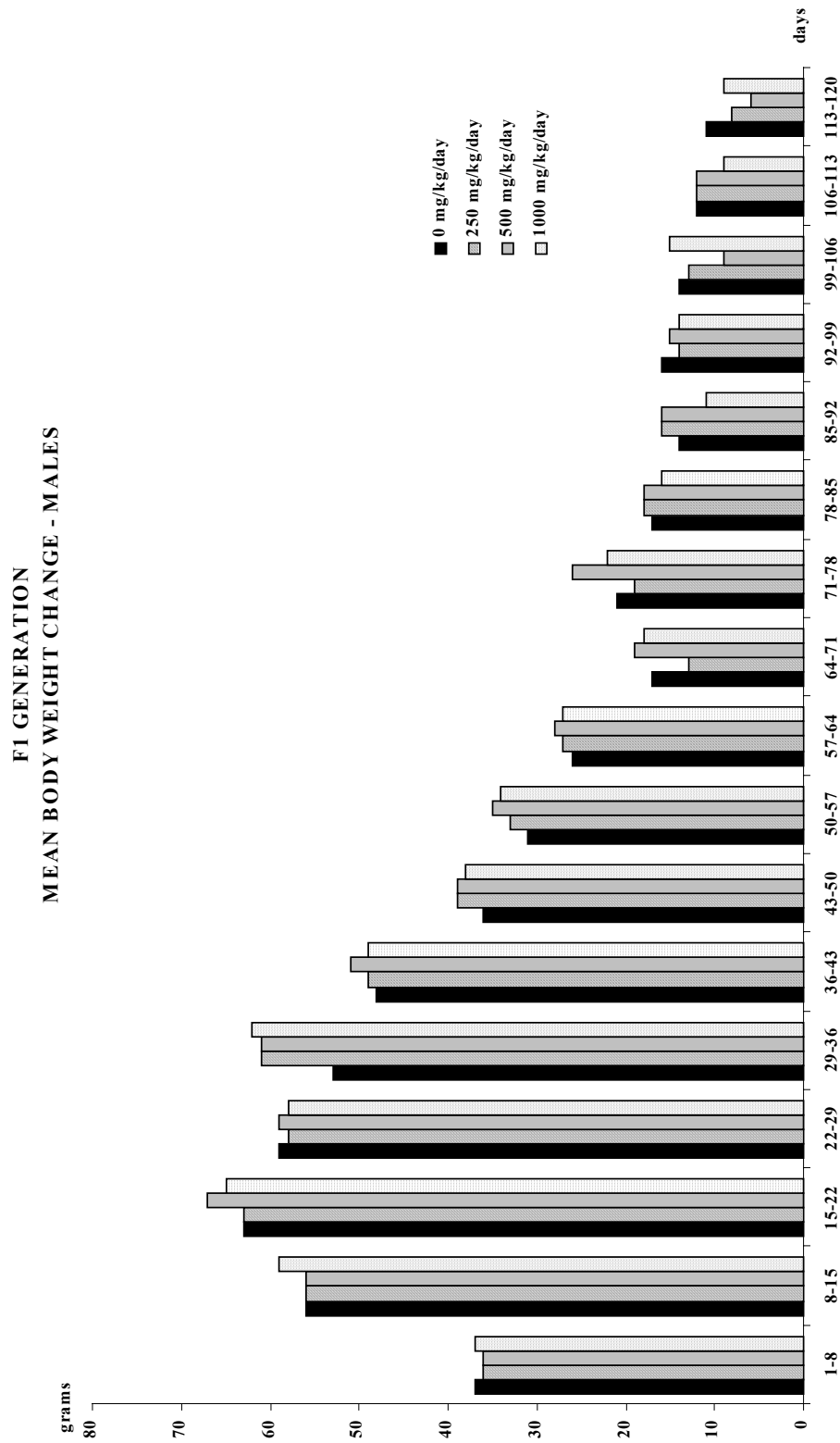


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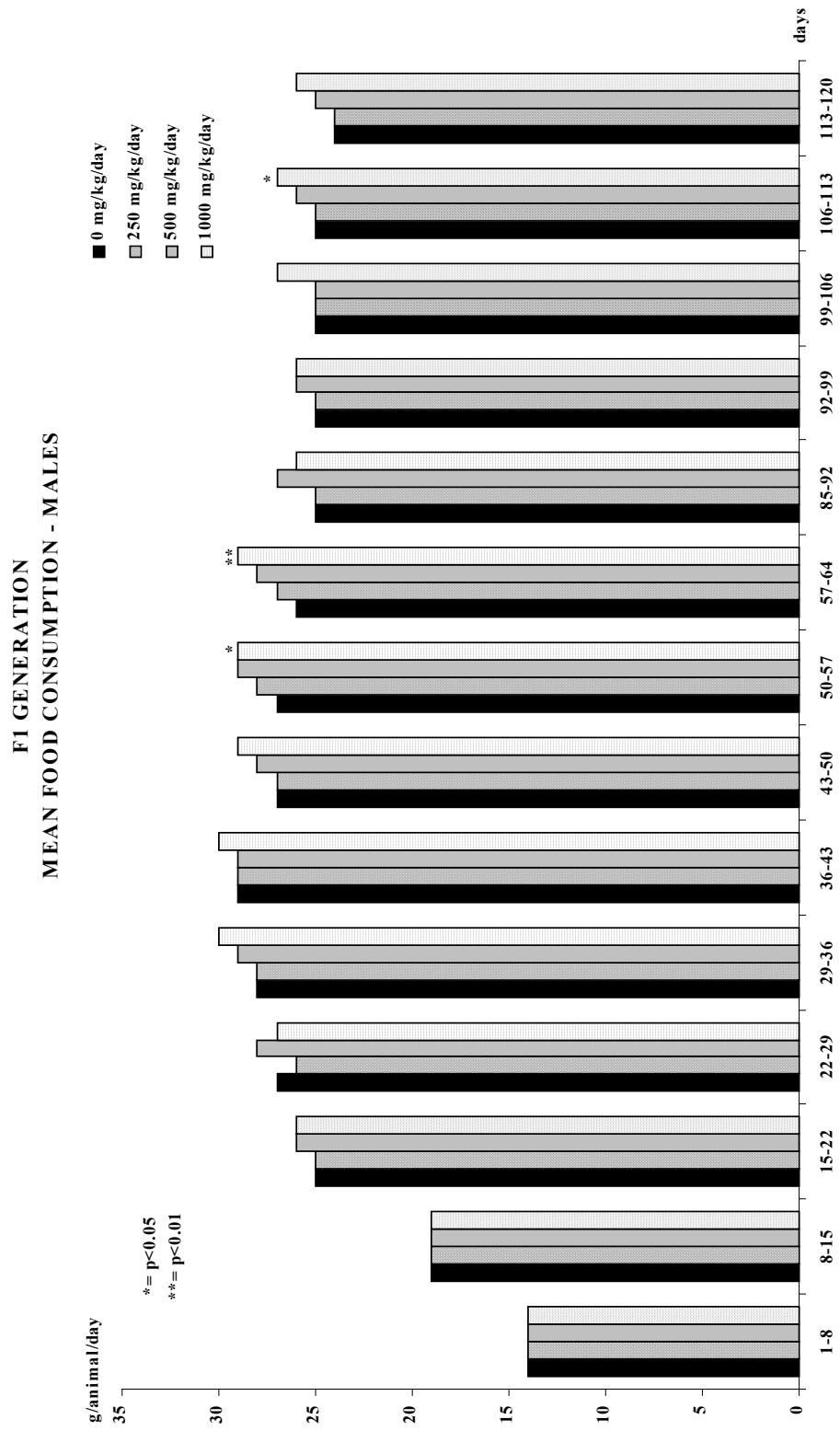


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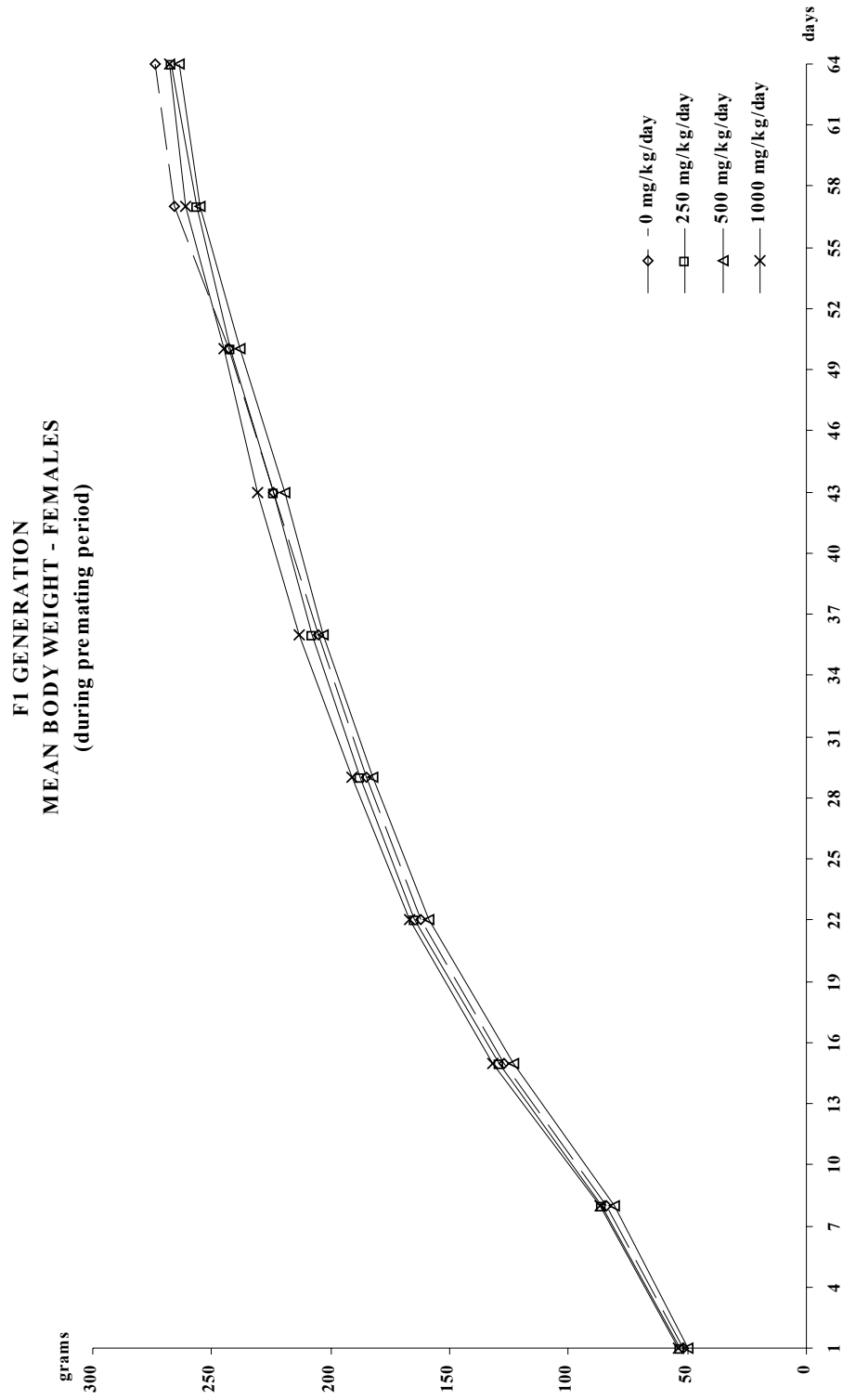


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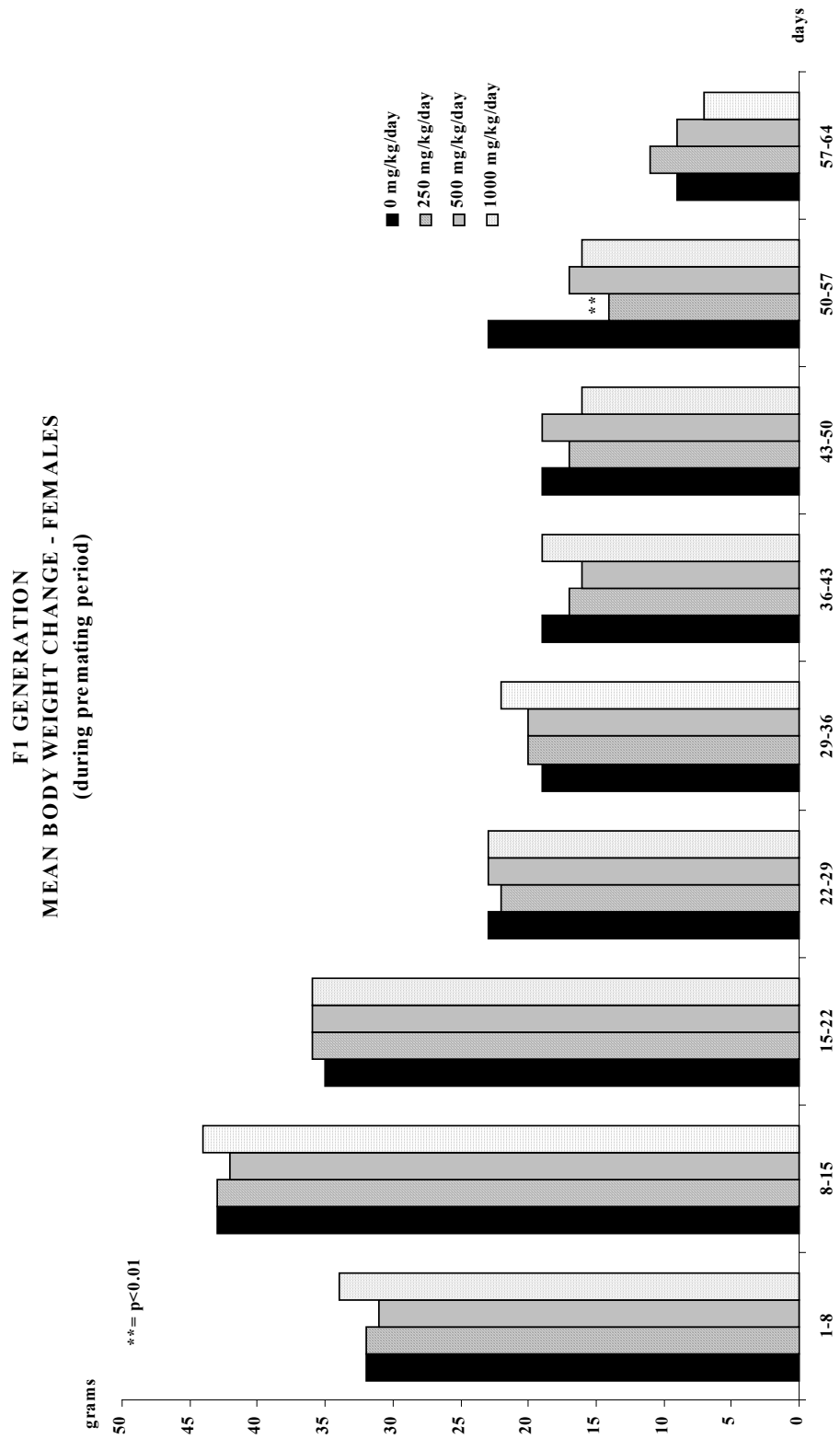


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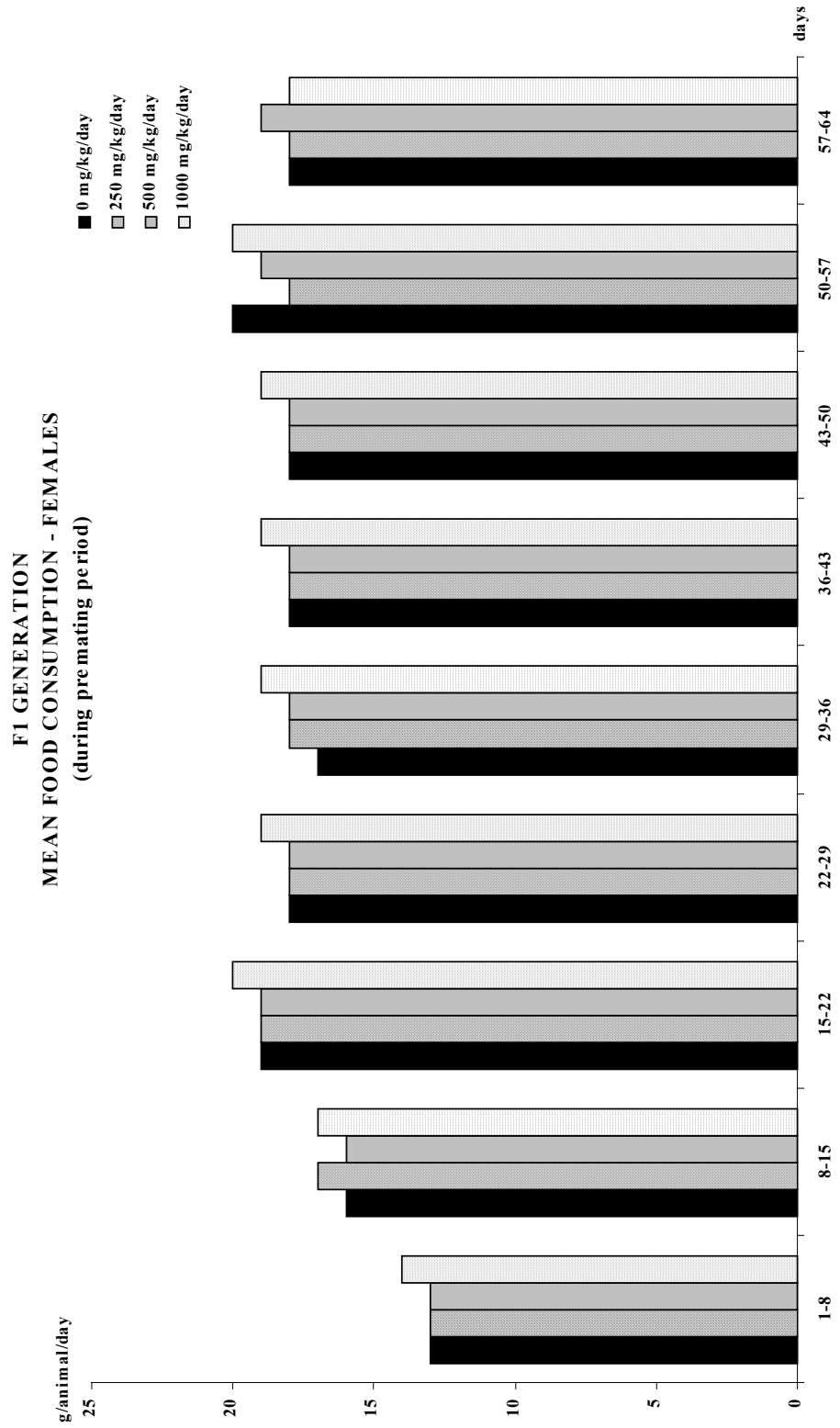


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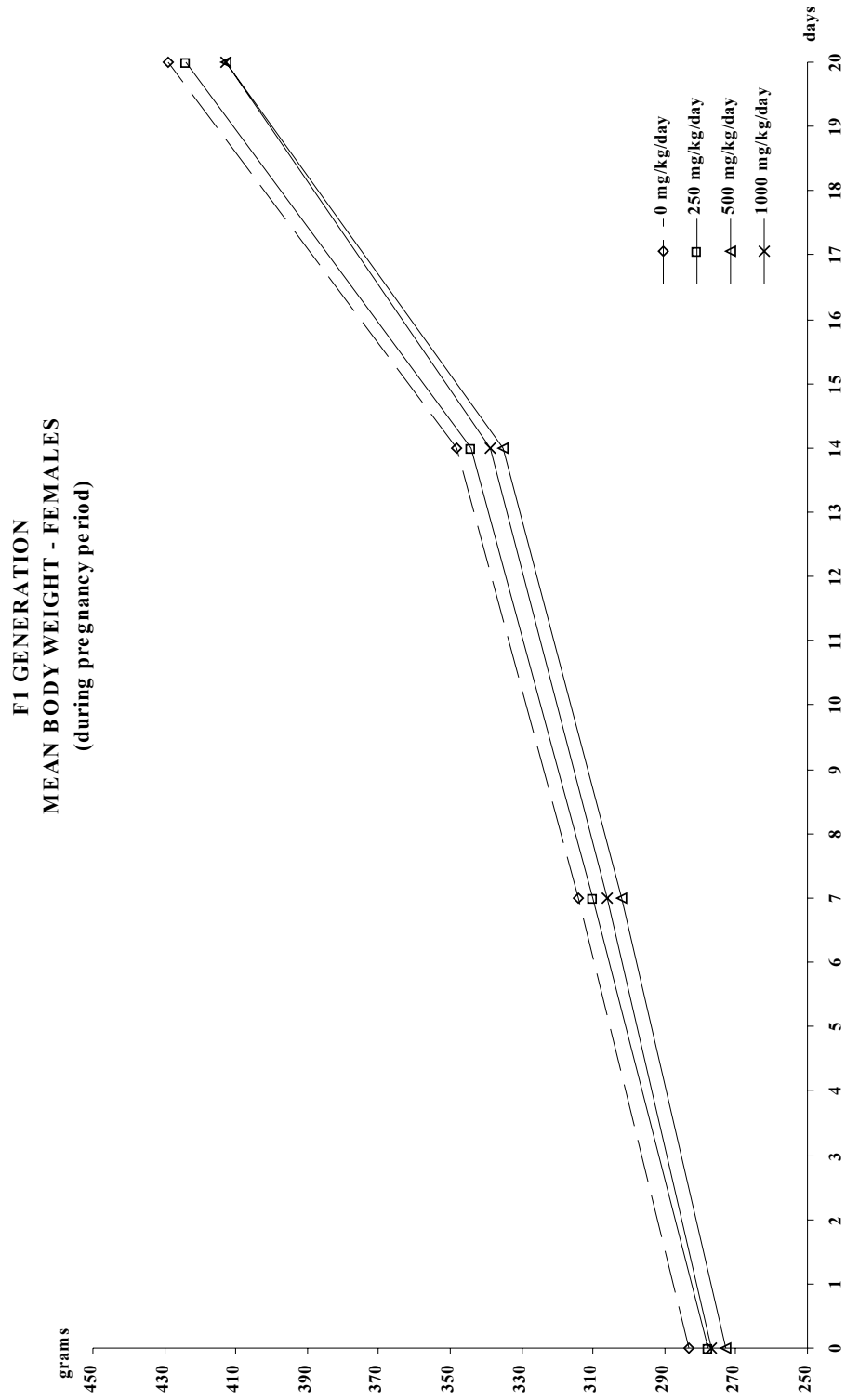


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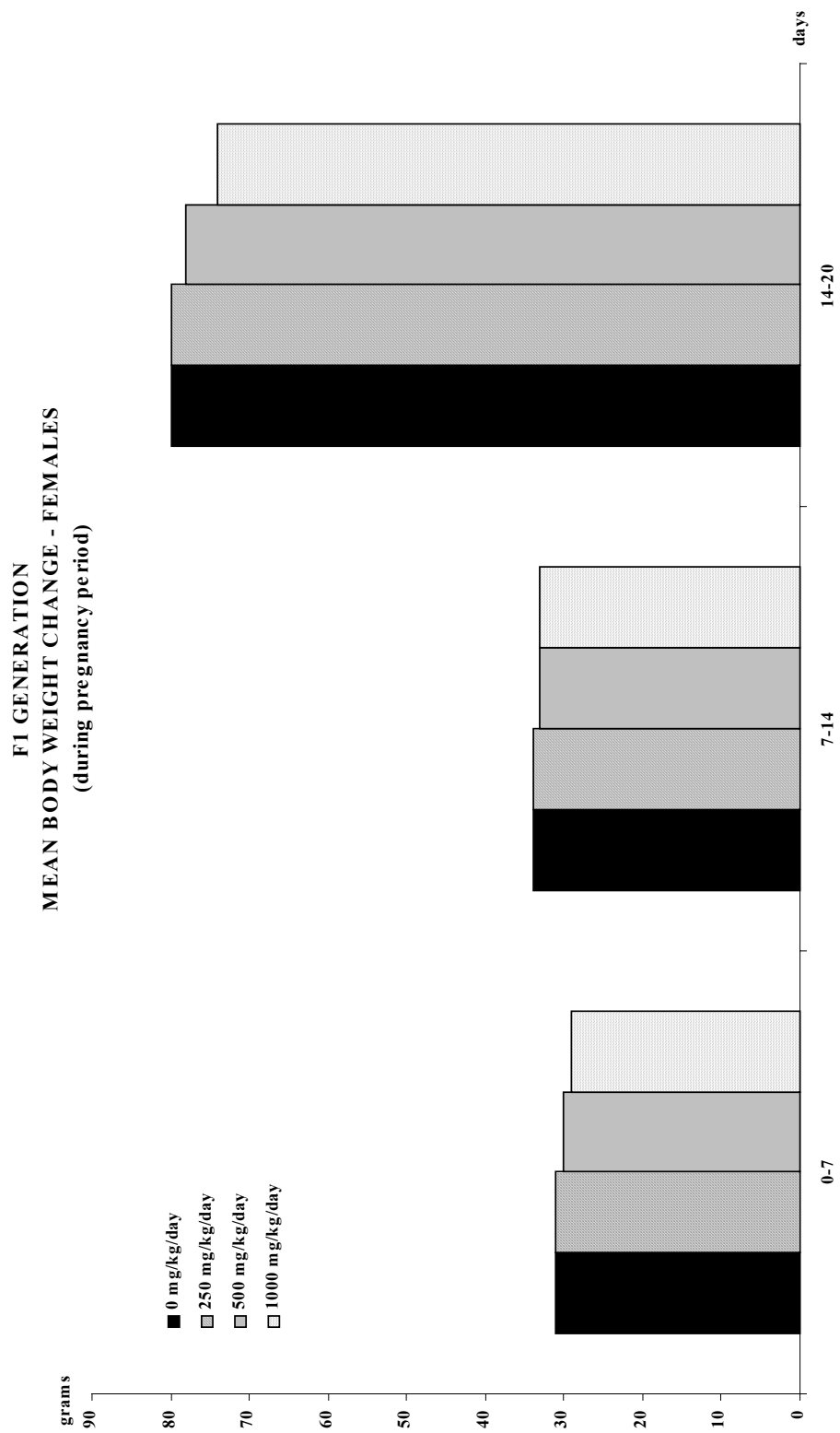


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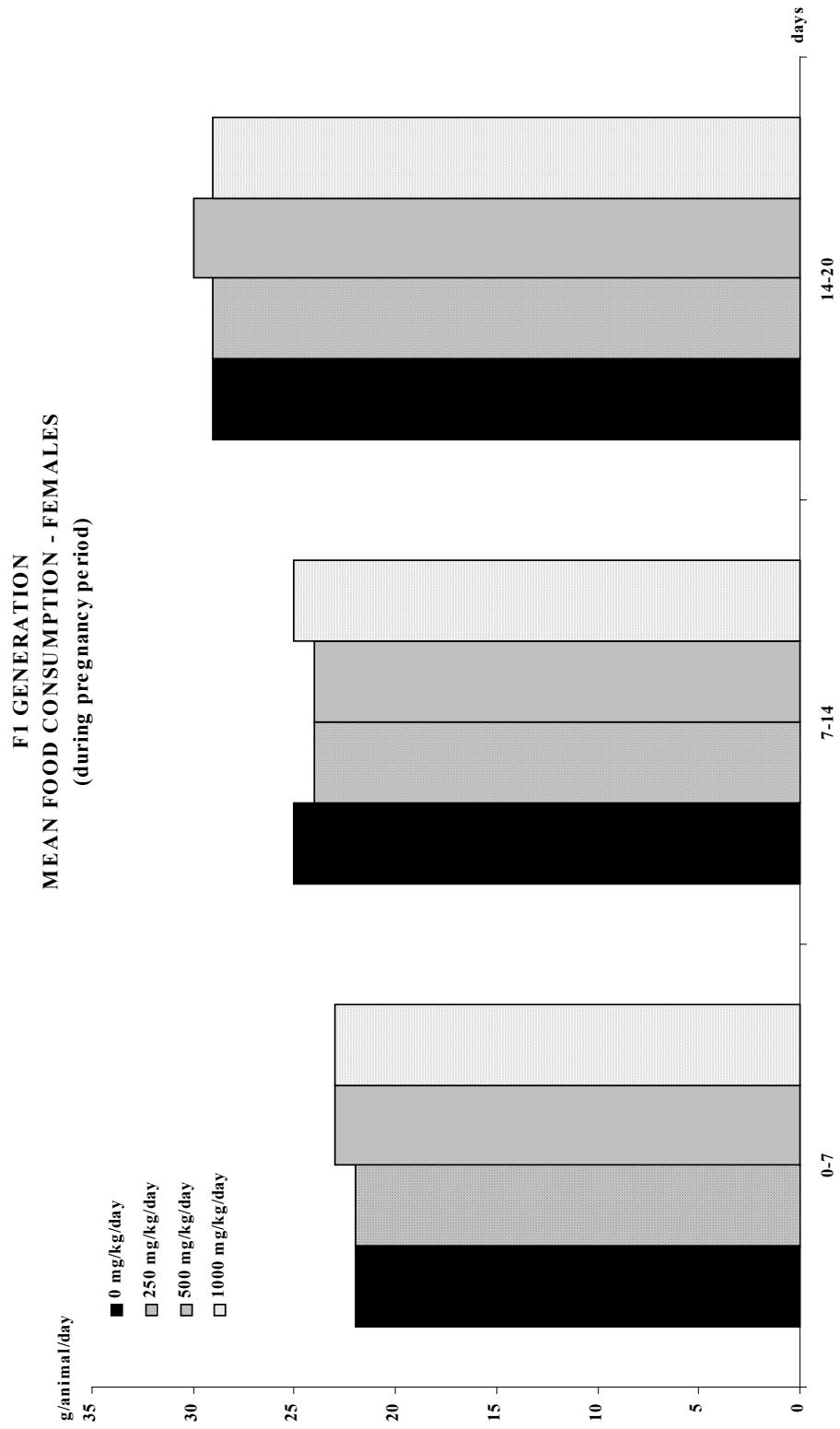


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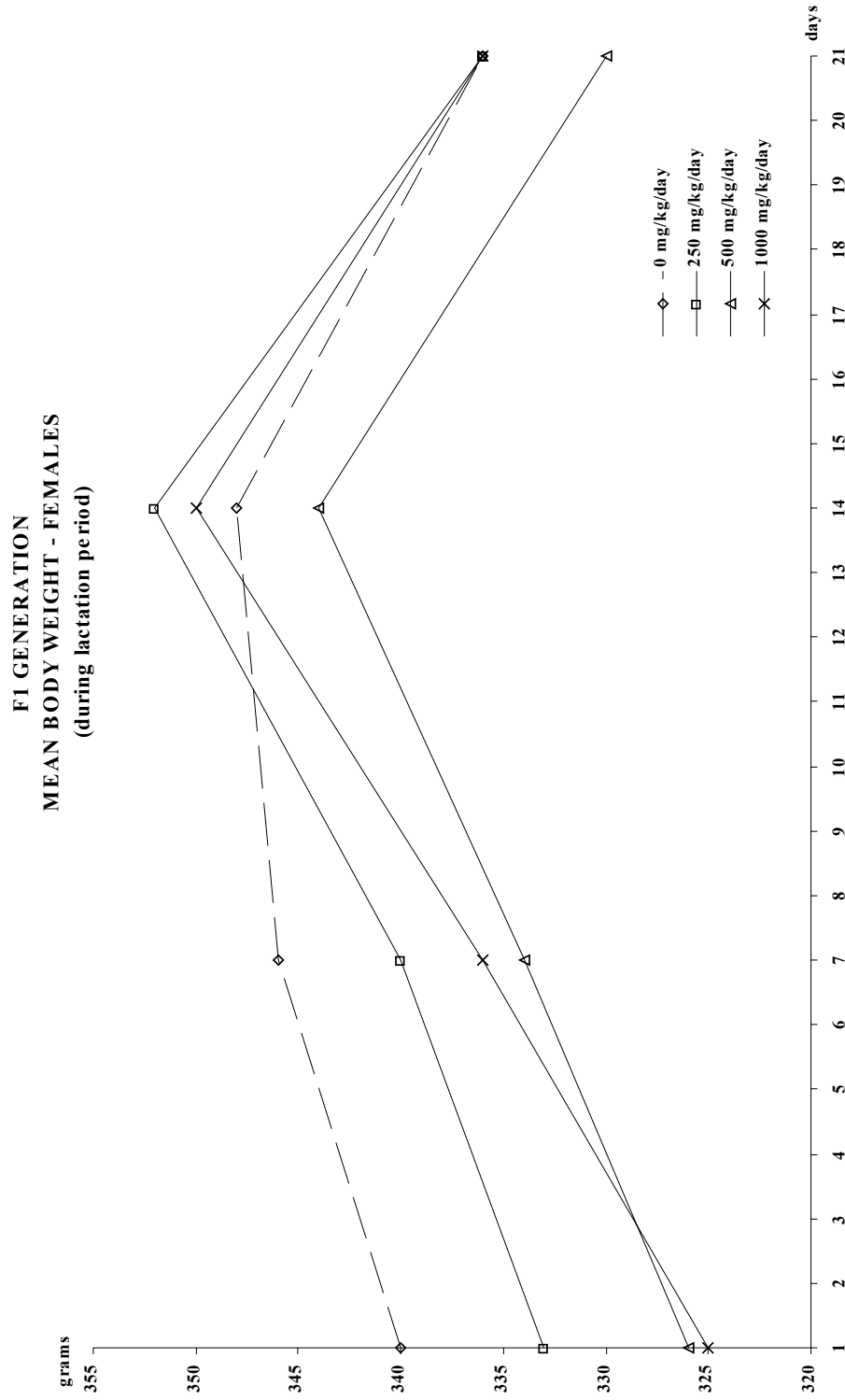


Figure 24

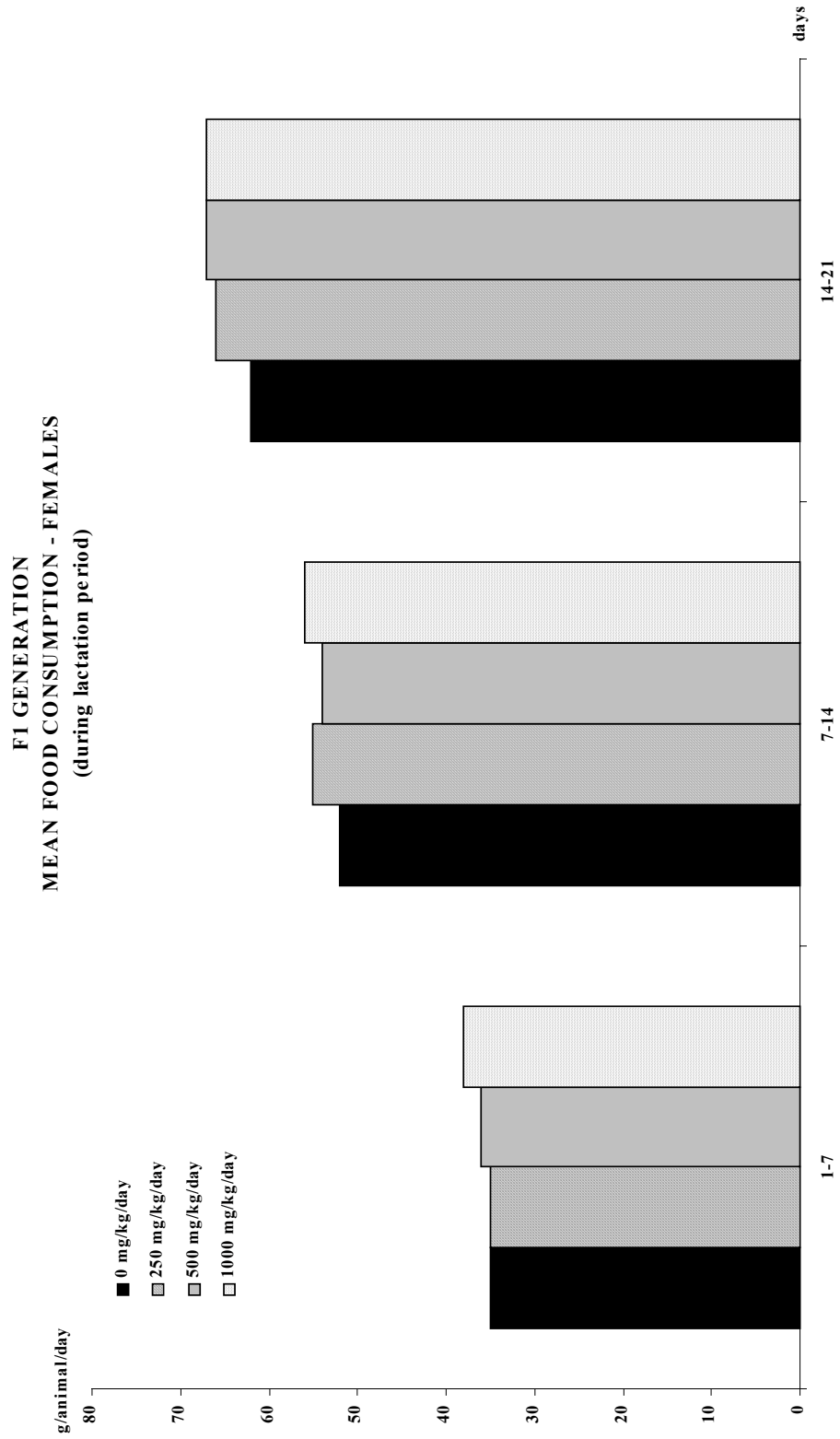


Figure 25

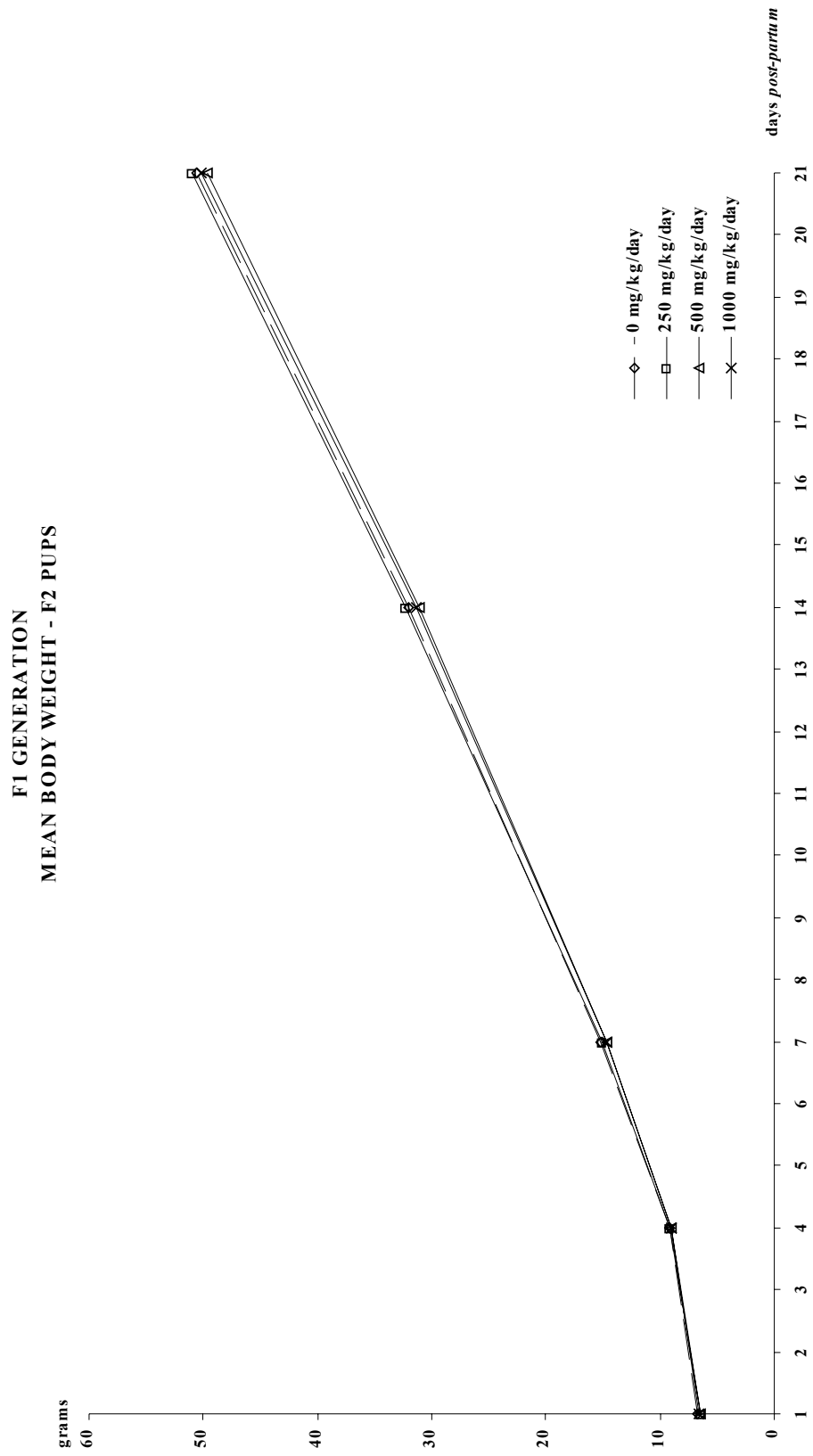


Figure 26

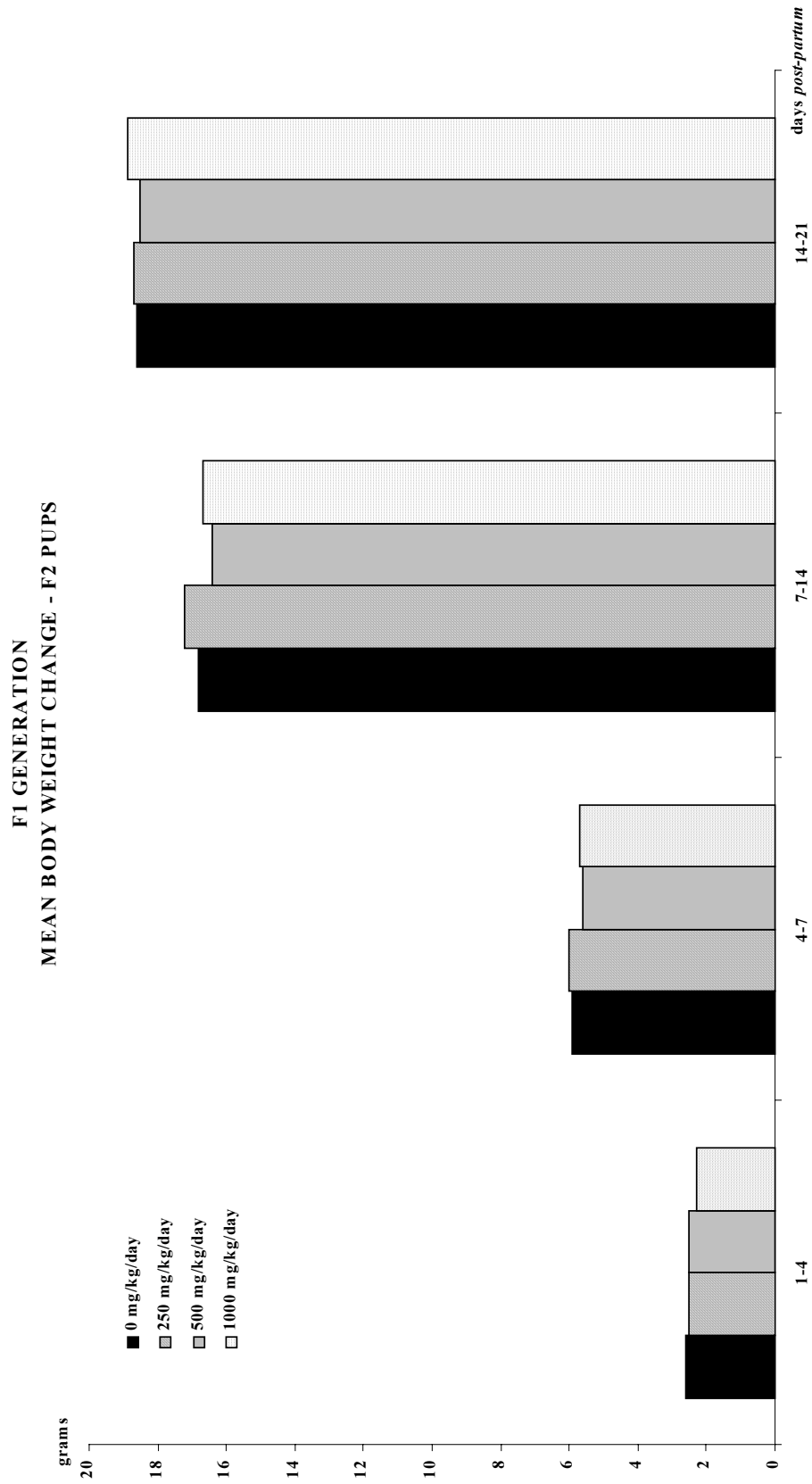


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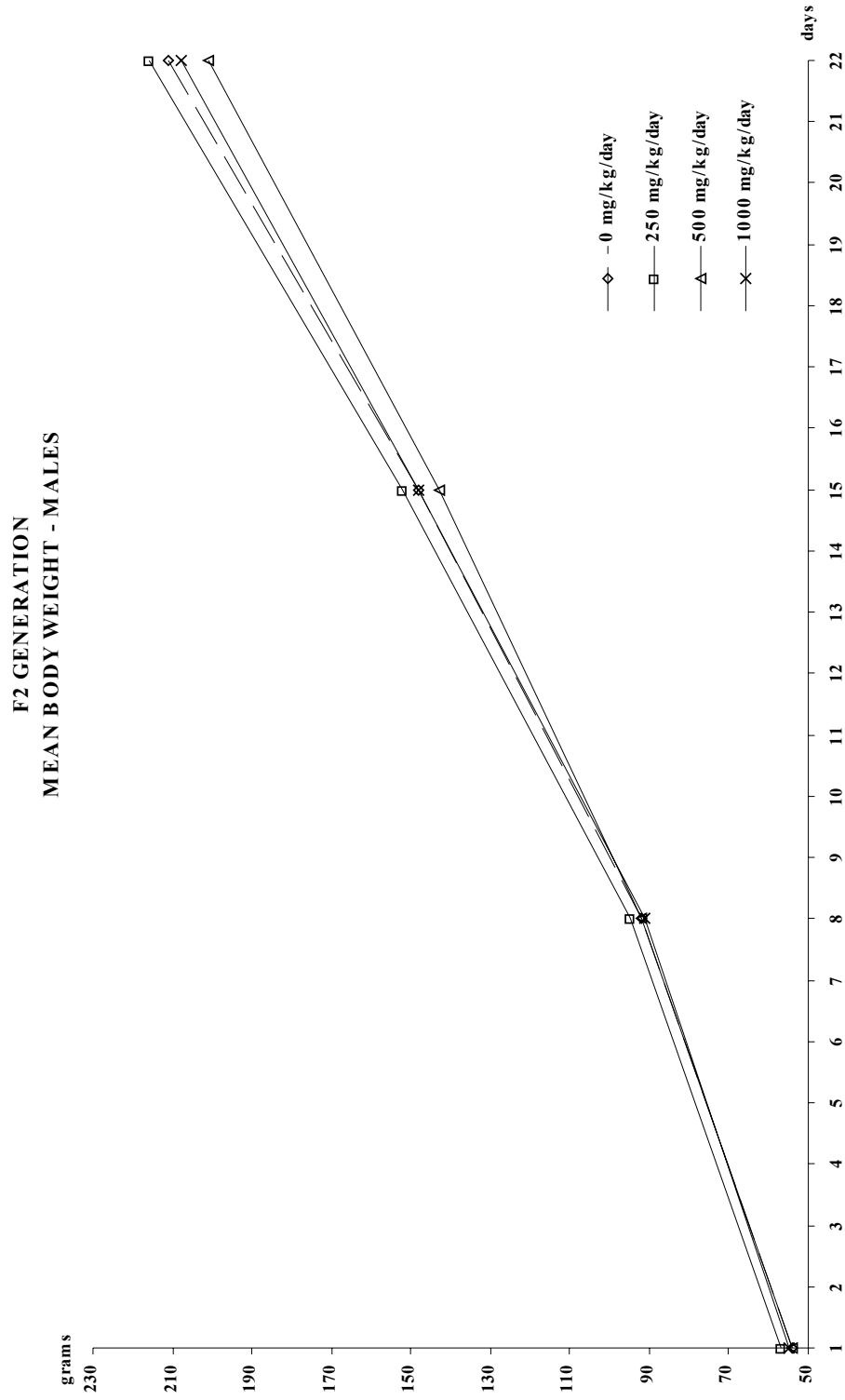


Figure 28

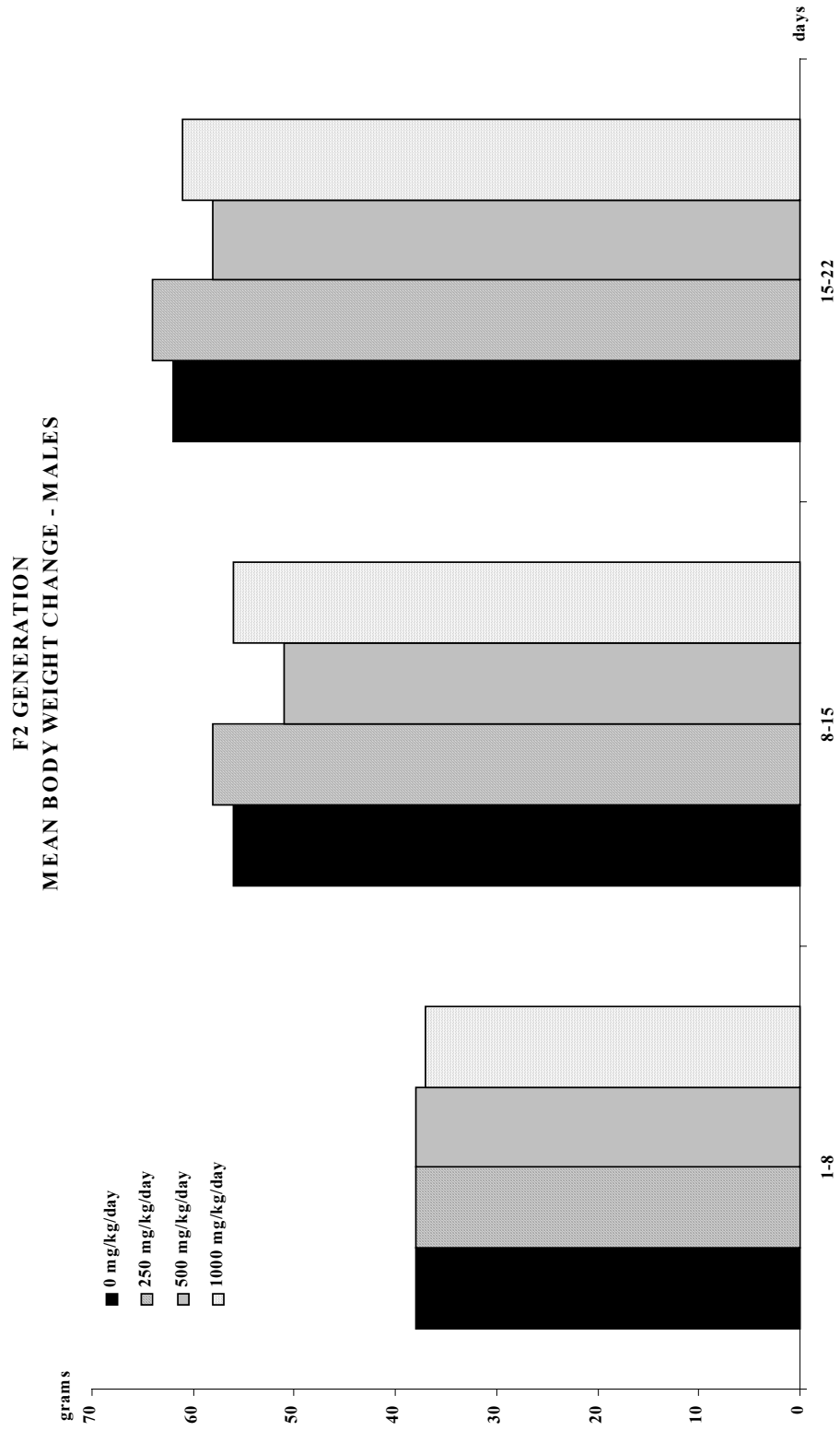


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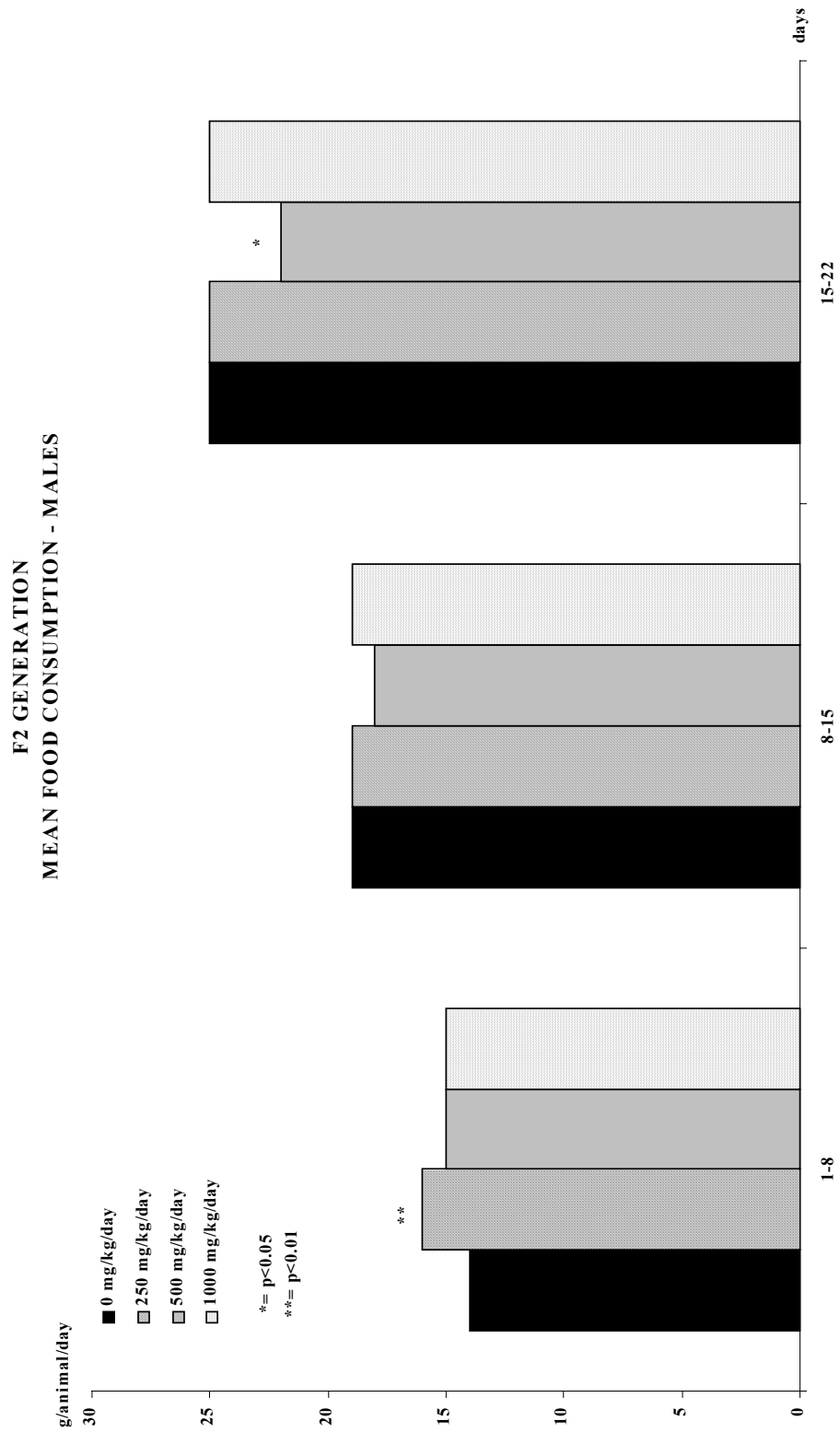


Figure 30

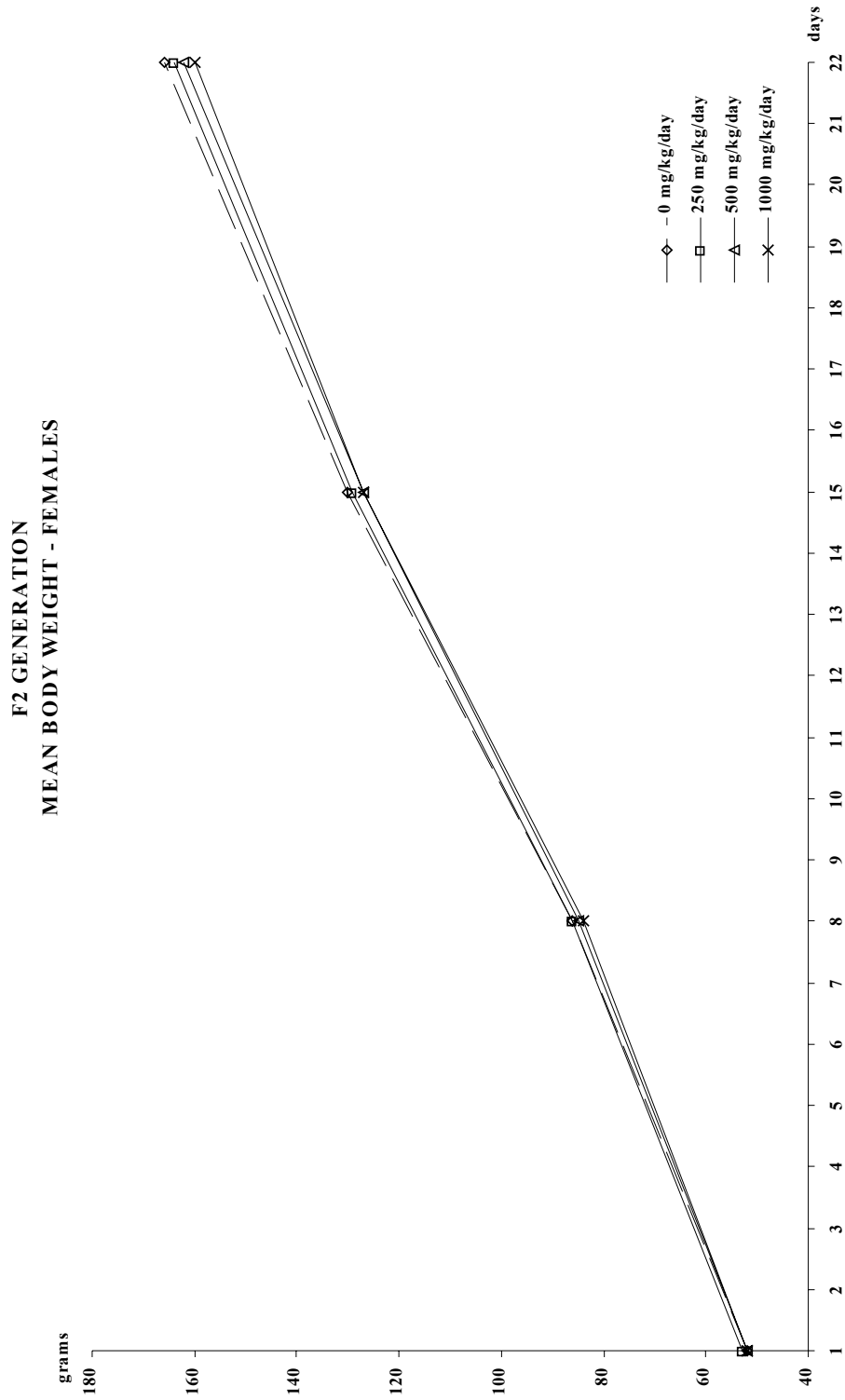


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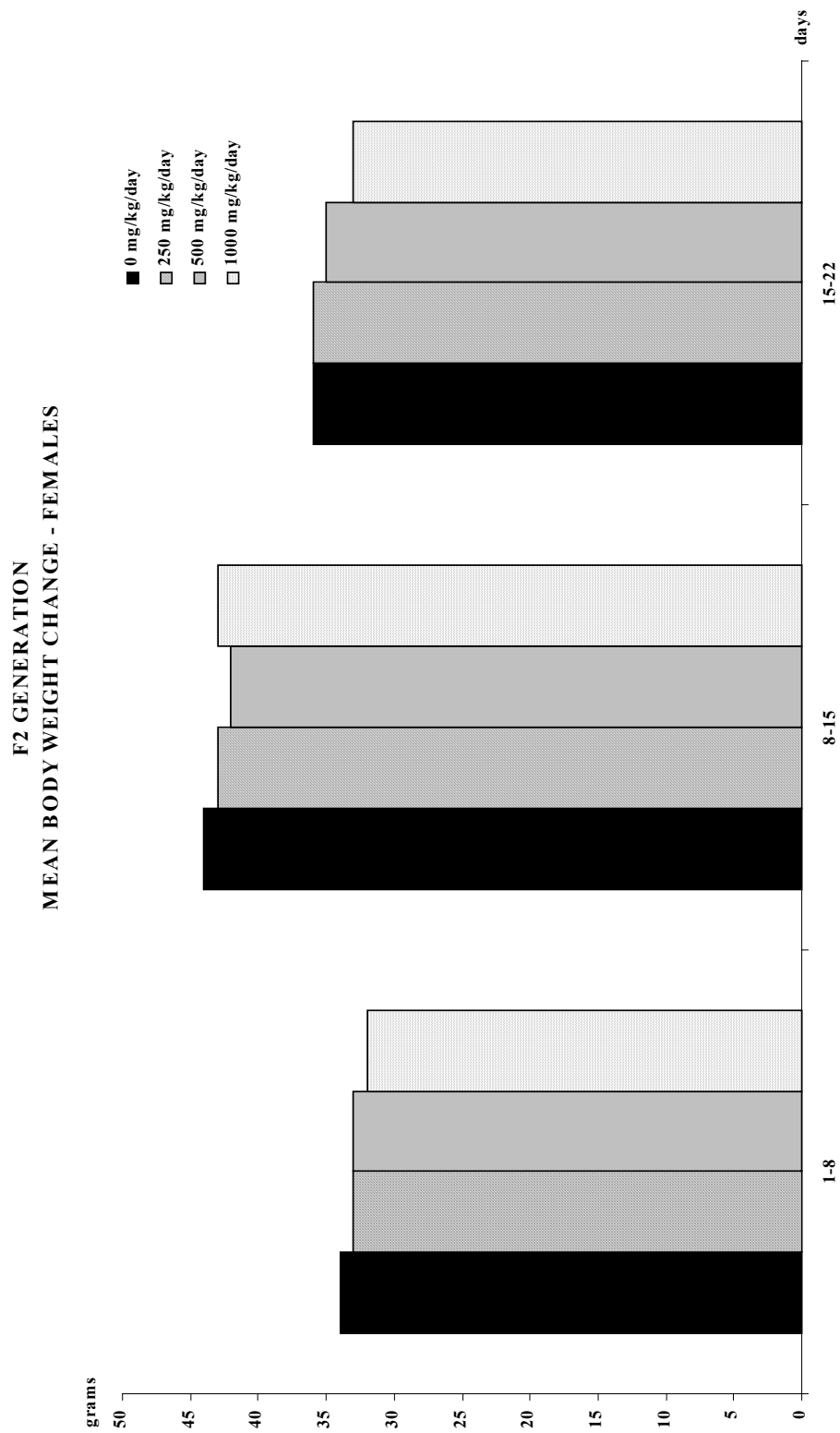


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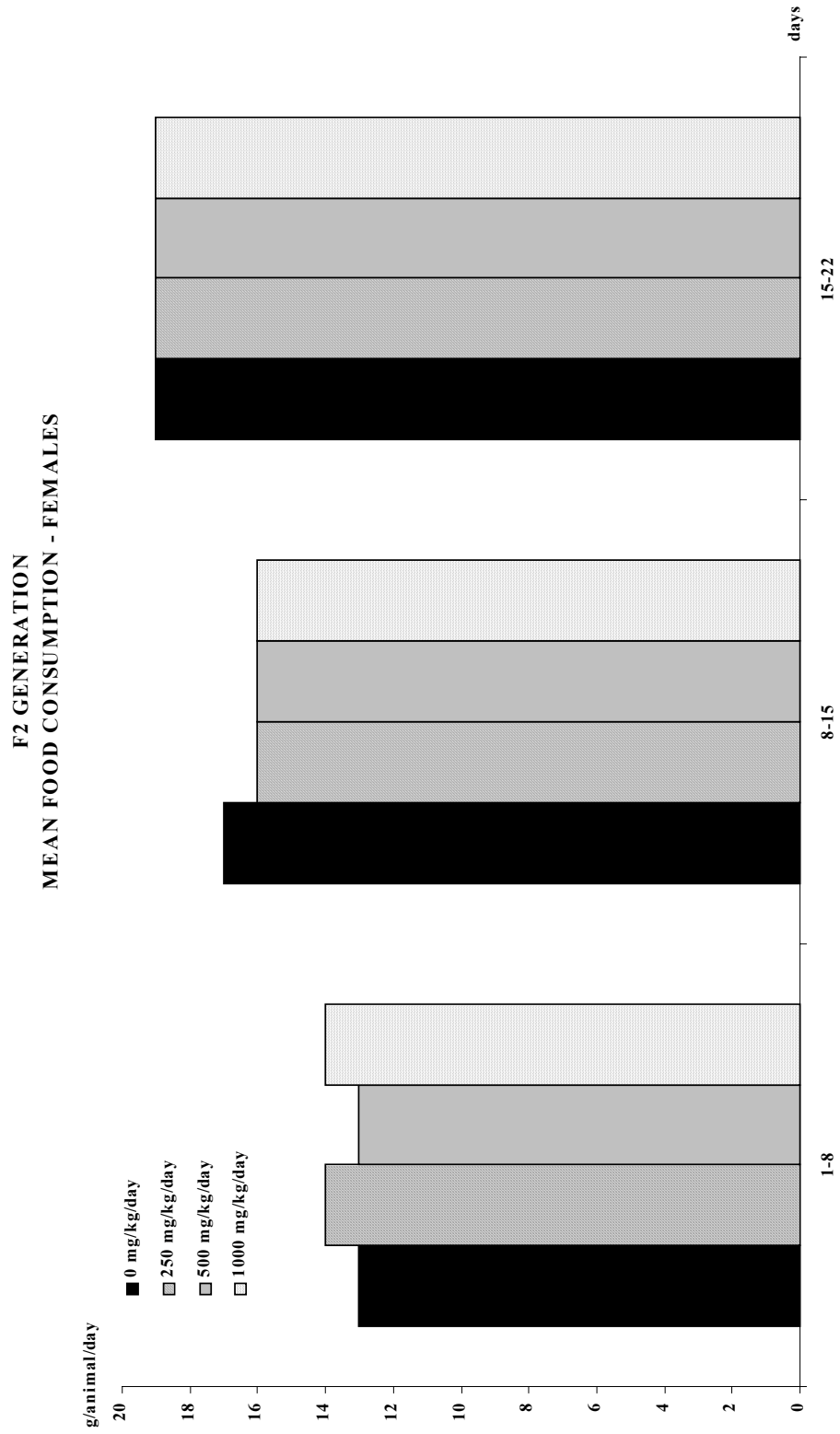


Table: 1

F0 GENERATION
CLINICAL SIGNS (Summary table/Males)

| MALES | | | | |
|---|----|-----|-----|------|
| Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
| Mortality | | | | |
| FINAL SACRIFICE | 25 | 25 | 25 | 25 |
| General aspect | | | | |
| PILOERECTOR | 0 | 0 | 1 | 0 |
| Breathing | | | | |
| LOUD BREATHING | 0 | 0 | 1 | 0 |
| Secretion/Excretion | | | | |
| PITYALISM | 0 | 0 | 0 | 2 |
| CHROMODACRYORRHEA | 1 | 0 | 0 | 0 |
| SOILED UROGENITAL AREA | 0 | 0 | 0 | 1 |
| PITYALISM immediately post-dosing | 2 | 7 | 19 | 23 |
| PITYALISM 1 hour post-dosing | 2 | 2 | 5 | 8 |
| PITYALISM 4 hour post-dosing | 0 | 0 | 0 | 1 |
| REGURGITATION | 1 | 0 | 0 | 1 |
| Skin | | | | |
| AREA OF HAIR LOSS ON HINDLIMB | 1 | 1 | 0 | 0 |
| AREA OF HAIR LOSS ON FORELIMB | 5 | 2 | 1 | 0 |
| AREA OF HAIR LOSS ON ABDOMEN | 1 | 1 | 0 | 0 |
| Miscellaneous | | | | |
| ABNORMAL GROWTH OF TEETH (cut regulary) | 0 | 0 | 1 | 0 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 18 | 16 | 5 | 2 |

Table: 2

F0 GENERATION

CLINICAL SIGNS (Summary table/Females/Premating period)

FEMALES

| Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
|----------------------------------|----|-----|-----|------|
| Secretion/Excretion | | | | |
| CHROMODACRYORRHEA | 0 | 0 | 1 | 0 |
| PIYALISM immediately post-dosing | 2 | 6 | 3 | 13 |
| Skin | | | | |
| AREA OF HAIR LOSS ON HINDLIMB | 0 | 0 | 0 | 1 |
| AREA OF HAIR LOSS ON FORELIMB | 0 | 0 | 6 | 3 |
| AREA OF HAIR LOSS ON BACK | 0 | 1 | 0 | 0 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 23 | 19 | 16 | 9 |

Table: 3

F0 GENERATION

CLINICAL SIGNS (Summary table/Females/Pregnancy period)

| Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
|----------------------------------|----|-----|-----|------|
| Mortality | | | | |
| FINAL SACRIFICE (no delivery) | 2 | 4 | 3 | 0 |
| Secretion/Excretion | | | | |
| CHROMODACRYORRHEA | 0 | 0 | 1 | 0 |
| PTYALISM immediately post-dosing | 2 | 7 | 11 | 19 |
| REGURGITATION | 1 | 1 | 0 | 0 |
| Skin | | | | |
| AREA OF HAIR LOSS ON HINDLIMB | 1 | 0 | 0 | 1 |
| AREA OF HAIR LOSS ON FORELIMB | 1 | 0 | 9 | 4 |
| AREA OF HAIR LOSS ON ABDOMEN | 1 | 0 | 0 | 0 |
| AREA OF HAIR LOSS ON BACK | 0 | 1 | 0 | 1 |
| CUTANEOUS LESION ON ABDOMEN | 0 | 0 | 0 | 1 |
| Miscellaneous | | | | |
| MASS ON UPPER FORELIMB DORSAL | 0 | 0 | 0 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 20 | 16 | 7 | 3 |

Table: 4

F0 GENERATION

CLINICAL SIGNS (Summary table/Females/Lactation period)

| Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
|-----------------------------------|----|-----|-----|------|
| Mortality | | | | |
| DECISION OF SACRIFICE | 0 | 1 | 3 | 0 |
| FINAL SACRIFICE | 23 | 20 | 19 | 25 |
| Secretion/Excretion | | | | |
| PITYALISM immediately post-dosing | 0 | 1 | 2 | 11 |
| Skin | | | | |
| AREA OF HAIR LOSS ON HINDLIMB | 0 | 0 | 0 | 1 |
| AREA OF HAIR LOSS ON FORELIMB | 1 | 0 | 7 | 4 |
| AREA OF HAIR LOSS ON ABDOMEN | 1 | 0 | 0 | 0 |
| AREA OF HAIR LOSS ON BACK | 0 | 1 | 0 | 1 |
| Pregnancy condition | | | | |
| BLOOD IN VAGINA | 0 | 0 | 1 | 0 |
| Miscellaneous | | | | |
| MASS ON UPPER FORELIMB DORSAL | 0 | 0 | 0 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 22 | 19 | 12 | 9 |

Table: 5

F0 GENERATION
BODY WEIGHTS (Mean values/Grams/Males)

MALES

| | | Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
|-----|----|-------------------|-------|-----|-----|------|
| Day | 1 | MEAN | 203 d | 202 | 205 | 202 |
| | | S.D. | 9 | 7 | 8 | 10 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 8 | MEAN | 274 d | 271 | 275 | 271 |
| | | S.D. | 13 | 11 | 12 | 13 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 15 | MEAN | 326 d | 324 | 330 | 327 |
| | | S.D. | 19 | 16 | 15 | 19 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 22 | MEAN | 371 d | 371 | 377 | 372 |
| | | S.D. | 26 | 25 | 22 | 23 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 29 | MEAN | 402 d | 400 | 407 | 402 |
| | | S.D. | 30 | 22 | 25 | 28 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 36 | MEAN | 426 d | 426 | 434 | 429 |
| | | S.D. | 32 | 25 | 28 | 33 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 43 | MEAN | 450 d | 448 | 461 | 453 |
| | | S.D. | 36 | 28 | 31 | 37 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 50 | MEAN | 470 d | 470 | 484 | 473 |
| | | S.D. | 38 | 30 | 33 | 41 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 57 | MEAN | 487 d | 487 | 500 | 488 |
| | | S.D. | 41 | 31 | 33 | 42 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 64 | MEAN | 504 d | 502 | 512 | 501 |
| | | S.D. | 42 | 34 | 38 | 43 |
| | | N | 25 | 25 | 25 | 25 |
| Day | 71 | MEAN | 521 d | 519 | 529 | 517 |
| | | S.D. | 44 | 33 | 40 | 45 |
| | | N | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 5 (continued)

F0 GENERATION
BODY WEIGHTS (Mean values/Grams/Males)

MALES

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|-------------------|------|--|-------|-----|-----|------|
| Day 78 | MEAN | | 525 d | 527 | 534 | 520 |
| | S.D. | | 45 | 32 | 39 | 44 |
| | N | | 25 | 25 | 25 | 25 |
| Day 85 | MEAN | | 541 d | 543 | 548 | 532 |
| | S.D. | | 45 | 34 | 43 | 43 |
| | N | | 25 | 25 | 25 | 25 |
| Day 92 | MEAN | | 558 d | 560 | 561 | 545 |
| | S.D. | | 48 | 36 | 46 | 43 |
| | N | | 25 | 25 | 25 | 25 |
| Day 99 | MEAN | | 572 d | 571 | 570 | 558 |
| | S.D. | | 51 | 35 | 50 | 43 |
| | N | | 25 | 25 | 25 | 25 |
| Day 106 | MEAN | | 584 d | 582 | 580 | 566 |
| | S.D. | | 51 | 37 | 52 | 44 |
| | N | | 25 | 25 | 25 | 25 |
| Day 113 | MEAN | | 599 d | 599 | 590 | 577 |
| | S.D. | | 54 | 39 | 55 | 43 |
| | N | | 25 | 25 | 25 | 25 |
| Day 120 | MEAN | | 596 d | 601 | 593 | 573 |
| | S.D. | | 60 | 27 | 63 | 36 |
| | N | | 15 | 15 | 15 | 15 |

Statistical key: d=ANOVA + Dunnett-test

Table: 6

F0 GENERATION
BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|---------------------|-------|------|------|------|
| Day 1 TO 8 | MEAN | 71 d | 69 | 70 | 69 |
| | S.D. | 8 | 8 | 7 | 9 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 35.0 | 34.3 | 34.1 |
| Day 8 TO 15 | MEAN | 52 d | 53 | 55 | 55 |
| | S.D. | 11 | 10 | 8 | 9 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 19.1 | 19.7 | 19.9 |
| Day 15 TO 22 | MEAN | 45 d | 47 | 48 | 45 |
| | S.D. | 11 | 15 | 9 | 8 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 13.8 | 14.4 | 14.4 |
| Day 22 TO 29 | MEAN | 31 d | 29 | 30 | 31 |
| | S.D. | 7 | 17 | 6 | 8 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 8.3 | 8.0 | 8.0 |
| Day 29 TO 36 | MEAN | 24 d | 27 | 26 | 26 |
| | S.D. | 6 | 7 | 5 | 8 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 6.0 | 6.6 | 6.4 |
| Day 36 TO 43 | MEAN | 24 d | 22 | 27 | 24 |
| | S.D. | 8 | 12 | 5 | 7 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 5.6 | 5.1 | 6.2 |
| Day 43 TO 50 | MEAN | 20 d | 22 | 24 | 21 |
| | S.D. | 7 | 6 | 7 | 8 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 4.3 | 4.8 | 5.1 |
| Day 50 TO 57 | MEAN | 17 d | 17 | 16 | 14 |
| | S.D. | 6 | 5 | 6 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 3.7 | 3.6 | 3.4 |
| Day 57 TO 64 | MEAN | 17 d | 16 | 12* | 14 |
| | S.D. | 6 | 5 | 11 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 3.6 | 3.2 | 2.3 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05

Table: 6 (continued)

F0 GENERATION
BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|-------|-------|-------|
| Day 64 TO 71 | MEAN | 16 d | 16 | 17 | 16 |
| | S.D. | 6 | 7 | 4 | 7 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 3.2 | 3.3 | 3.3 | 3.1 |
| Day 71 TO 78 | MEAN | 4 d | 8 | 4 | 3 |
| | S.D. | 6 | 5 | 7 | 10 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 0.8 | 1.6 | 0.9 | 0.5 |
| Day 78 TO 85 | MEAN | 16 d | 16 | 15 | 12 |
| | S.D. | 5 | 6 | 8 | 6 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 3.0 | 3.0 | 2.7 | 2.4 |
| Day 85 TO 92 | MEAN | 17 d | 17 | 13* | 13* |
| | S.D. | 5 | 4 | 6 | 5 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 3.1 | 3.2 | 2.4 | 2.5 |
| Day 92 TO 99 | MEAN | 15 d | 11 | 9* | 13 |
| | S.D. | 7 | 8 | 9 | 3 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 2.6 | 1.9 | 1.6 | 2.4 |
| Day 99 TO 106 | MEAN | 12 d | 11 | 10 | 8 |
| | S.D. | 4 | 5 | 8 | 3 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 2.1 | 1.9 | 1.7 | 1.5 |
| Day 106 TO 113 | MEAN | 15 d | 17 | 9** | 10* |
| | S.D. | 5 | 6 | 7 | 4 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 2.5 | 2.9 | 1.6 | 1.8 |
| Day 85 TO 113 | MEAN | 58 d | 56 | 41# | 45** |
| | S.D. | 15 | 9 | 19 | 5 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 10.7 | 10.3 | 7.4 | 8.5 |
| Day 1 TO 71 | MEAN | 318 d | 317 | 324 | 315 |
| | S.D. | 42 | 33 | 37 | 39 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 156.8 | 157.6 | 157.9 | 155.8 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01 # = p<0.001

Table: 6 (continued)

F0 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 | |
|---------------------|----------|-------|-------|-------|-------|-----|
| Day | 1 TO 113 | MEAN | 396 d | 397 | 385 | 375 |
| | | S.D. | 52 | 38 | 52 | 38 |
| | | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 195.4 | 197.2 | 187.3 | 185.5 | |

Statistical key: d=ANOVA + Dunnett-test

Table: 7

F0 GENERATION

BODY WEIGHTS (Mean values/Grams/Females/Premating period)

FEMALES

| | | Dose: (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------|------|-------------------|-------|-----|-----|------|
| Day 1 | MEAN | | 160 d | 156 | 157 | 156 |
| | S.D. | | 13 | 9 | 9 | 9 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 | MEAN | | 189 d | 186 | 188 | 189 |
| | S.D. | | 15 | 13 | 11 | 14 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 | MEAN | | 204 d | 205 | 209 | 207 |
| | S.D. | | 17 | 15 | 14 | 17 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 | MEAN | | 224 d | 224 | 227 | 226 |
| | S.D. | | 17 | 18 | 18 | 19 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 | MEAN | | 238 d | 237 | 242 | 242 |
| | S.D. | | 20 | 19 | 20 | 21 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 | MEAN | | 253 d | 248 | 254 | 252 |
| | S.D. | | 21 | 21 | 20 | 23 |
| | N | | 25 | 25 | 25 | 25 |
| Day 43 | MEAN | | 261 d | 261 | 268 | 265 |
| | S.D. | | 21 | 21 | 20 | 25 |
| | N | | 25 | 25 | 25 | 25 |
| Day 50 | MEAN | | 270 d | 266 | 273 | 267 |
| | S.D. | | 23 | 22 | 23 | 27 |
| | N | | 25 | 25 | 25 | 25 |
| Day 57 | MEAN | | 287 d | 283 | 287 | 277 |
| | S.D. | | 34 | 24 | 20 | 27 |
| | N | | 25 | 25 | 25 | 25 |
| Day 64 | MEAN | | 300 d | 291 | 294 | 284 |
| | S.D. | | 39 | 26 | 16 | 27 |
| | N | | 25 | 25 | 25 | 25 |
| Day 71 | MEAN | | 303 d | 294 | 301 | 286 |
| | S.D. | | 36 | 26 | 21 | 27 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 8

F0 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Females/Premating period)

FEMALES

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|---------------------|-------|------|------|------|
| Day 1 TO 8 | MEAN | 30 d | 30 | 31 | 33 |
| | S.D. | 6 | 8 | 5 | 7 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 18.6 | 19.3 | 20.1 |
| Day 8 TO 15 | MEAN | 15 d | 19 | 21* | 18 |
| | S.D. | 8 | 7 | 7 | 5 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 8.0 | 10.2 | 10.9 |
| Day 15 TO 22 | MEAN | 19 d | 19 | 18 | 19 |
| | S.D. | 8 | 6 | 7 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 9.5 | 9.5 | 8.8 |
| Day 22 TO 29 | MEAN | 15 d | 13 | 15 | 16 |
| | S.D. | 7 | 6 | 7 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 6.5 | 5.8 | 6.6 |
| Day 29 TO 36 | MEAN | 15 d | 11 | 12 | 10* |
| | S.D. | 5 | 6 | 7 | 5 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 6.3 | 4.7 | 5.0 |
| Day 36 TO 43 | MEAN | 8 d | 13** | 13# | 13** |
| | S.D. | 4 | 5 | 5 | 5 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 3.2 | 5.2 | 5.3 |
| Day 43 TO 50 | MEAN | 9 d | 5* | 6 | 3# |
| | S.D. | 5 | 5 | 6 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 3.4 | 2.0 | 2.1 |
| Day 50 TO 57 | MEAN | 17 d | 17 | 13 | 10 |
| | S.D. | 16 | 10 | 7 | 7 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 6.1 | 6.3 | 5.0 |
| Day 57 TO 64 | MEAN | 13 d | 8 | 7 | 7 |
| | S.D. | 11 | 9 | 8 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 4.5 | 2.8 | 2.7 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01 # = p<0.001

Table: 8 (continued)

F0 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Females/Premating period)

FEMALES

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|------|------|------|------|
| Day 64 TO 71 | MEAN | 3 d | 4 | 8 | 2 | |
| | S.D. | | 9 | 9 | 10 | 9 |
| | N | | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 1.1 | 1.3 | 2.6 | 0.6 |
| Day 1 TO 71 | MEAN | 143 d | 139 | 145 | 130 | |
| | S.D. | | 27 | 21 | 18 | 23 |
| | N | | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 89.4 | 89.2 | 92.4 | 83.3 |

Statistical key: d=ANOVA + Dunnett-test

Table: 9

F0 GENERATION

BODY WEIGHT (Mean values/grams/Females/Pregnancy period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|-------|-----|-----|------|
| DAY 0 | MEAN | 306 d | 296 | 303 | 289 |
| | S.D. | 34 | 27 | 24 | 29 |
| | N | 23 | 21 | 22 | 25 |
| DAY 7 | MEAN | 331 d | 323 | 332 | 318 |
| | S.D. | 37 | 28 | 27 | 30 |
| | N | 23 | 21 | 22 | 25 |
| DAY 14 | MEAN | 361 d | 355 | 364 | 351 |
| | S.D. | 39 | 30 | 31 | 29 |
| | N | 23 | 21 | 22 | 25 |
| DAY 20 | MEAN | 438 d | 430 | 438 | 425 |
| | S.D. | 45 | 35 | 38 | 32 |
| | N | 23 | 21 | 22 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 10

F0 GENERATION

BODY WEIGHT CHANGE (Mean values/grams/Females/Pregnancy period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|------|------|------|
| DAYS 0 TO 7 | MEAN | 26 d | 27 | 29 | 29 |
| | S.D. | 10 | 7 | 11 | 8 |
| | N | 23 | 21 | 22 | 25 |
| mean percent change | MEAN% | 8.5 | 9.3 | 9.6 | 10.2 |
| DAYS 7 TO 14 | MEAN | 30 d | 32 | 32 | 32 |
| | S.D. | 6 | 7 | 6 | 7 |
| | N | 23 | 21 | 22 | 25 |
| mean percent change | MEAN% | 9.1 | 9.9 | 9.6 | 10.2 |
| DAYS 14 TO 20 | MEAN | 77 d | 75 | 75 | 75 |
| | S.D. | 8 | 8 | 11 | 11 |
| | N | 23 | 21 | 22 | 25 |
| mean percent change | MEAN% | 21.3 | 21.1 | 20.5 | 21.4 |
| DAYS 0 TO 20 | MEAN | 132 d | 134 | 136 | 136 |
| | S.D. | 15 | 14 | 25 | 12 |
| | N | 23 | 21 | 22 | 25 |
| mean percent change | MEAN% | 43.5 | 45.5 | 44.9 | 47.5 |

Statistical key: d=ANOVA + Dunnett-test

Table: 11

F0 GENERATION

BODY WEIGHT (Mean values/grams/Females/Lactation period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|-------|-----|-----|------|
| DAY 1 | MEAN | 343 d | 338 | 342 | 332 |
| | S.D. | 39 | 28 | 29 | 32 |
| | N | 23 | 21 | 22 | 25 |
| DAY 7 | MEAN | 352 d | 347 | 351 | 347 |
| | S.D. | 36 | 23 | 23 | 29 |
| | N | 23 | 21 | 19 | 25 |
| DAY 14 | MEAN | 359 d | 357 | 359 | 357 |
| | S.D. | 33 | 17 | 25 | 24 |
| | N | 23 | 20 | 19 | 25 |
| DAY 21 | MEAN | 344 d | 344 | 340 | 343 |
| | S.D. | 29 | 18 | 24 | 24 |
| | N | 23 | 20 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 12

F0 GENERATION

BODY WEIGHT CHANGE (Mean values/grams/Females/Lactation period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|---------------------|-------|-----|-----|------|
| DAYS 1 TO 7 | MEAN | 9 d | 9 | 12 | 14 |
| | S.D. | 13 | 12 | 8 | 10 |
| | N | 23 | 21 | 19 | 25 |
| | mean percent change | MEAN% | 2.8 | 2.8 | 3.7 |
| DAYS 7 TO 14 | MEAN | 7 d | 11 | 8 | 10 |
| | S.D. | 11 | 13 | 12 | 12 |
| | N | 23 | 20 | 19 | 25 |
| | mean percent change | MEAN% | 2.5 | 3.1 | 3.0 |
| DAYS 14 TO 21 | MEAN | -15 d | -13 | -19 | -14 |
| | S.D. | 13 | 9 | 11 | 13 |
| | N | 23 | 20 | 19 | 25 |
| | mean percent change | MEAN% | 0.3 | 0.8 | 0.3 |
| DAYS 1 TO 14 | MEAN | 16 d | 20 | 20 | 24 |
| | S.D. | 17 | 15 | 12 | 16 |
| | N | 23 | 20 | 19 | 25 |
| | mean percent change | MEAN% | 1.5 | 2.2 | 1.7 |
| DAYS 1 TO 21 | MEAN | 1 d | 7 | 1 | 11 |
| | S.D. | 20 | 17 | 12 | 19 |
| | N | 23 | 20 | 19 | 25 |
| | mean percent change | MEAN% | 1.3 | 2.2 | 1.5 |

Statistical key: d=ANOVA + Dunnett-test

Table: 13

F0 GENERATION
FOOD CONSUMPTION (Mean values/Grams per day/Males)

MALES

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|-------------------|------|------|----|-----|-----|------|
| Day 1 TO 8 | MEAN | 26 d | 26 | 26 | 27 | 27 |
| | S.D. | | 2 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 TO 15 | MEAN | 28 d | 28 | 28 | 29 | 30 |
| | S.D. | | 3 | 4 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 TO 22 | MEAN | 27 d | 27 | 27 | 28 | 29 |
| | S.D. | | 5 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 TO 29 | MEAN | 26 d | 26 | 26 | 27 | 28 |
| | S.D. | | 3 | 3 | 2 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 TO 36 | MEAN | 26 d | 26 | 26 | 26 | 27 |
| | S.D. | | 3 | 4 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 TO 43 | MEAN | 25 d | 24 | 24 | 26 | 26 |
| | S.D. | | 3 | 3 | 2 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 43 TO 50 | MEAN | 24 d | 24 | 26 | 26 | 26 |
| | S.D. | | 3 | 3 | 2 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 50 TO 57 | MEAN | 25 d | 25 | 25 | 26 | 26 |
| | S.D. | | 2 | 2 | 2 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 57 TO 64 | MEAN | 25 d | 25 | 25 | 25 | 27 |
| | S.D. | | 3 | 2 | 3 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 64 TO 71 | MEAN | 24 d | 24 | 24 | 24 | 25 |
| | S.D. | | 3 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 85 TO 92 | MEAN | 24 d | 24 | 25 | 24 | 25 |
| | S.D. | | 3 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 13 (continued)

F0 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Males)

MALES

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|-------------------|------|------|----|-----|-----|------|
| Day 92 TO 99 | MEAN | 24 d | 24 | 24 | 24 | 26* |
| | S.D. | | 3 | 2 | 3 | 2 |
| | N | | 25 | 24 | 25 | 25 |
| Day 99 TO 106 | MEAN | 25 d | 25 | 25 | 25 | 27** |
| | S.D. | | 3 | 2 | 3 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 106 TO 113 | MEAN | 24 d | 25 | 25 | 25 | 26 |
| | S.D. | | 3 | 2 | 3 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 1 TO 71 | MEAN | 26 d | 26 | 26 | 26 | 27 |
| | S.D. | | 2 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01

Table: 14

F0 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Females/Premating period)

FEMALES

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|-------------------|------|------|----|-----|-----|------|
| Day 1 TO 8 | MEAN | 18 d | 18 | 18 | 19 | 19 |
| | S.D. | 2 | 1 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 8 TO 15 | MEAN | 18 d | 18 | 18 | 19 | 19 |
| | S.D. | 1 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 15 TO 22 | MEAN | 19 d | 19 | 19 | 19 | 20* |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 22 TO 29 | MEAN | 18 d | 18 | 18 | 19 | 20* |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 29 TO 36 | MEAN | 18 d | 18 | 18 | 19 | 20 |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 36 TO 43 | MEAN | 17 d | 18 | 18 | 19* | 19** |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 43 TO 50 | MEAN | 17 d | 18 | 18 | 19 | 19* |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 50 TO 57 | MEAN | 19 d | 19 | 19 | 19 | 19 |
| | S.D. | 4 | 3 | 2 | 2 | |
| | N | 24 | 25 | 25 | 25 | |
| Day 57 TO 64 | MEAN | 20 d | 20 | 20 | 19 | 19 |
| | S.D. | 5 | 3 | 2 | 2 | |
| | N | 24 | 25 | 25 | 25 | |
| Day 64 TO 71 | MEAN | 18 d | 18 | 18 | 19 | 18 |
| | S.D. | 3 | 2 | 3 | 3 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 1 TO 71 | MEAN | 18 d | 18 | 18 | 19 | 19 |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01

Table: 15

F0 GENERATION

FOOD CONSUMPTION (Mean values/grams per day/Females/Pregnancy period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|------|-----|-----|------|
| DAYS 0 TO 7 | MEAN | 21 d | 22 | 23 | 23 |
| | S.D. | 3 | 3 | 3 | 3 |
| | N | 23 | 20 | 22 | 25 |
| DAYS 7 TO 14 | MEAN | 24 d | 24 | 26 | 25 |
| | S.D. | 3 | 3 | 4 | 3 |
| | N | 23 | 21 | 21 | 25 |
| DAYS 14 TO 20 | MEAN | 27 d | 28 | 28 | 29 |
| | S.D. | 3 | 2 | 3 | 3 |
| | N | 23 | 21 | 22 | 25 |
| DAYS 0 TO 20 | MEAN | 24 d | 25 | 25 | 26 |
| | S.D. | 3 | 2 | 3 | 3 |
| | N | 23 | 21 | 22 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 16

F0 GENERATION

FOOD CONSUMPTION (Mean values/grams per day/Females/Lactation period)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|------|-----|-----|------|
| DAYS 1 TO 7 | MEAN | 36 d | 36 | 37 | 40** |
| | S.D. | 5 | 8 | 4 | 3 |
| | N | 23 | 21 | 19 | 25 |
| DAYS 7 TO 14 | MEAN | 53 d | 56 | 54 | 59# |
| | S.D. | 7 | 4 | 5 | 3 |
| | N | 23 | 20 | 19 | 25 |
| DAYS 14 TO 21 | MEAN | 64 d | 67 | 65 | 70** |
| | S.D. | 8 | 6 | 8 | 5 |
| | N | 23 | 20 | 19 | 25 |
| DAYS 1 TO 14 | MEAN | 44 d | 46 | 46 | 50# |
| | S.D. | 6 | 4 | 5 | 3 |
| | N | 23 | 20 | 19 | 25 |
| DAYS 1 TO 21 | MEAN | 51 d | 53 | 52 | 56# |
| | S.D. | 6 | 4 | 5 | 3 |
| | N | 23 | 20 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test ** = p<0.01 # = p<0.001

Table 17

**F0 GENERATION
SUMMARY OF REPRODUCTIVE DATA**

| Dose-level (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|---------|---------|---------|---------|
| | | Group 1 | Group 2 | Group 3 | Group 4 |
| Paired males + females | n | 25 + 25 | 25 + 25 | 25 + 25 | 25 + 25 |
| Pairs able to mate | n | 25 | 25 | 25 | 25 |
| Mating index | % | 100 | 100 | 100 | 100 |
| Mean number of days of pairing before mating | n | 3.28 | 2.76 | 2.52 | 2.72 |
| Pregnant female partners | n | 23 | 21 | 22 | 25 |
| Fertility index | % | 92 | 84 | 88 | 100 |
| Females with live concepti | n | 23 | 21 | 22 | 25 |
| Gestation index | % | 100 | 100 | 100 | 100 |

Table: 18

F0 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|------|--------|-------|-------|-------|
| Females on Study | N | 25 | 25 | 25 | 25 |
| Females Mated | N | 25 f | 25 | 25 | 25 |
| Mating Index | % | 100.0 | 100.0 | 100.0 | 100.0 |
| Females Pregnant | N | 23 f | 21 | 22 | 25 |
| Female Fertility Index | % | 92.0 | 84.0 | 88.0 | 100.0 |
| Females with Liveborn | N | 23 f | 21 | 22 | 25 |
| Gestation Index | % | 100.0 | 100.0 | 100.0 | 100.0 |
| Females Surviving Delivery | N | 23 f | 21 | 22 | 25 |
| Duration of Gestation | MEAN | 21.7 d | 21.5 | 21.5 | 21.8 |
| S.D. | | 0.6 | 0.5 | 0.5 | 0.4 |
| with Stillborn Pups | N | 0 f | 0 | 0 | 0 |
| % | | 0.0 | 0.0 | 0.0 | 0.0 |
| with all Stillborn | N | 0 f | 0 | 0 | 0 |
| % | | 0.0 | 0.0 | 0.0 | 0.0 |
| with Entire Liveborn Litter Dying and/or Missing, Cannibalized, Culled | | | | | |
| days 0-4 | N | 0 f | 0 | 3 | 0 |
| % | | 0.0 | 0.0 | 13.6 | 0.0 |
| days 0-21 | N | 0 f | 1 | 3 | 0 |
| % | | 0.0 | 4.8 | 13.6 | 0.0 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test

Table: 18 (continued)

F0 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|------|--------|-------|-------|-------|
| Litters with Liveborn Pups | N | 23 | 21 | 22 | 25 |
| Pups Delivered (total) | N | 328 | 296 | 327 | 354 |
| | MEAN | 14.3 d | 14.1 | 14.9 | 14.2 |
| | S.D. | 2.2 | 2.3 | 2.3 | 2.0 |
| Liveborn | N | 328 f | 296 | 327 | 354 |
| Live Birth Index | % | 100.0 | 100.0 | 100.0 | 100.0 |
| Stillborn | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| Uncertain | N | 0 | 0 | 0 | 0 |
| Culled day 4 | | 136 | 107 | 117 | 145 |
| Culled (total) | N | 136 | 107 | 117 | 146 |
| Cannibalized | N | 4 | 15 | 24 | 7 |
| Missing | N | 1 | 0 | 0 | 0 |
| Died | N | 13 | 20 | 32 | 2 |
| Liveborn, not culled prior to day 21 | N | 192 | 189 | 210 | 209 |
| Pups Dying, Missing, and/or Cannibalized | | | | | |
| day 0 | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| days 1-4 | N | 8 f | 21** | 58# | 8 |
| | % | 2.4 | 7.1 | 17.7 | 2.3 |
| days 5-7 | N | 8 f | 12 | 5 | 0** |
| | % | 2.4 | 4.1 | 1.5 | 0.0 |
| days 8-14 | N | 2 f | 2 | 1 | 1 |
| | % | 0.6 | 0.7 | 0.3 | 0.3 |
| days 15-21 | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| Pups Surviving 4 days Viability Index | N | 320 f | 275** | 269# | 346 |
| | % | 97.6 | 92.9 | 82.3 | 97.7 |
| Pups Surviving 21 days Lactation Index | N | 174 f | 154 | 146 | 199** |
| | % | 94.6 | 91.7 | 96.1 | 99.5 |
| Implantation Sites per Litter | N | 343 | 314 | 344 | 379 |
| | MEAN | 14.9 d | 15.0 | 15.6 | 15.2 |
| | S.D. | 2.2 | 2.1 | 2.1 | 1.9 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test ** = p<0.01 # = p<0.001

Table: 18 (continued)

F0 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|----------------------------------|------|--------|------|------|------|
| Live Pups/Litter | | | | | |
| day 1 | MEAN | 14.2 d | 14.0 | 14.4 | 14.1 |
| | S.D. | 2.2 | 2.3 | 2.2 | 1.9 |
| day 4 preculling | MEAN | 13.9 d | 13.1 | 14.2 | 13.8 |
| | S.D. | 2.0 | 2.1 | 2.0 | 2.0 |
| day 4 postculling | MEAN | 8.0 d | 8.0 | 8.0 | 8.0 |
| | S.D. | 0.0 | 0.0 | 0.0 | 0.2 |
| day 7 | MEAN | 7.7 d | 7.4 | 7.7 | 8.0 |
| | S.D. | 1.1 | 1.6 | 0.6 | 0.0 |
| day 14 | MEAN | 7.6 d | 7.7 | 7.7 | 8.0 |
| | S.D. | 1.1 | 0.7 | 0.7 | 0.2 |
| day 21 | MEAN | 7.6 d | 7.7 | 7.7 | 8.0 |
| | S.D. | 1.1 | 0.7 | 0.7 | 0.2 |
| Pup Weight/Litter (grams) | | | | | |
| day 1 | MEAN | 6.6 d | 6.5 | 6.3 | 6.8 |
| | S.D. | 0.7 | 0.6 | 0.6 | 0.6 |
| day 4 preculling | MEAN | 8.9 d | 8.7 | 8.4 | 9.1 |
| | S.D. | 1.4 | 1.6 | 1.2 | 1.2 |
| day 4 postculling | MEAN | 8.9 d | 8.8 | 8.5 | 9.2 |
| | S.D. | 1.3 | 1.6 | 1.3 | 1.2 |
| day 7 | MEAN | 14.3 d | 14.3 | 14.2 | 15.5 |
| | S.D. | 2.3 | 3.2 | 2.4 | 1.8 |
| day 14 | MEAN | 30.6 d | 32.0 | 31.4 | 32.5 |
| | S.D. | 3.3 | 2.9 | 3.6 | 2.5 |
| day 21 | MEAN | 49.1 d | 50.4 | 49.4 | 51.5 |
| | S.D. | 5.4 | 4.0 | 6.1 | 4.2 |
| Sex Ratio - Male Pups:Total Pups | | | | | |
| day 0 | N | 172 f | 141 | 157 | 194 |
| | % | 52.4 | 47.6 | 48.0 | 54.8 |
| day 21 | N | 92 f | 73 | 75 | 99 |
| | % | 52.9 | 47.4 | 51.4 | 49.7 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test

Table: 19

F0 GENERATION
SUMMARY OF PUP WEIGHTS (grams)

| Dose: (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|-------------------|------------------------------|------|-------|-----|-----|------|
| day 1 | males | MEAN | 6.8 d | 6.7 | 6.5 | 7.0 |
| | | S.D. | 0.7 | 0.6 | 0.7 | 0.7 |
| | | N | 23 | 21 | 22 | 25 |
| 1 | females | MEAN | 6.4 d | 6.4 | 6.0 | 6.5 |
| | | S.D. | 0.6 | 0.6 | 0.6 | 0.6 |
| | | N | 23 | 21 | 22 | 25 |
| 1 | males+females | MEAN | 6.6 d | 6.5 | 6.3 | 6.8 |
| | | S.D. | 0.7 | 0.6 | 0.6 | 0.6 |
| | | N | 23 | 21 | 22 | 25 |
| day 4 | males preculling | MEAN | 9.1 d | 9.0 | 8.7 | 9.3 |
| | | S.D. | 1.4 | 1.6 | 1.3 | 1.2 |
| | | N | 23 | 21 | 19 | 25 |
| 4 | females preculling | MEAN | 8.6 d | 8.5 | 8.1 | 8.9 |
| | | S.D. | 1.4 | 1.6 | 1.2 | 1.2 |
| | | N | 23 | 21 | 19 | 25 |
| 4 | males+females preculling | MEAN | 8.9 d | 8.7 | 8.4 | 9.1 |
| | | S.D. | 1.4 | 1.6 | 1.2 | 1.2 |
| | | N | 23 | 21 | 19 | 25 |
| day 4 | males postculling | MEAN | 9.2 d | 9.1 | 8.8 | 9.4 |
| | | S.D. | 1.3 | 1.6 | 1.4 | 1.2 |
| | | N | 23 | 21 | 19 | 25 |
| 4 | females postculling | MEAN | 8.6 d | 8.5 | 8.2 | 9.0 |
| | | S.D. | 1.3 | 1.6 | 1.2 | 1.3 |
| | | N | 23 | 21 | 19 | 25 |
| 4 | males+females postculling | MEAN | 8.9 d | 8.8 | 8.5 | 9.2 |
| | | S.D. | 1.3 | 1.6 | 1.3 | 1.2 |
| | | N | 23 | 21 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 19 (continued)

F0 GENERATION
SUMMARY OF PUP WEIGHTS (grams)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|--------|------|------|------|
| day 7 males | MEAN | 14.7 d | 15.5 | 14.7 | 15.9 |
| | S.D. | 2.2 | 2.3 | 2.5 | 1.7 |
| | N | 23 | 19 | 19 | 25 |
| 7 females | MEAN | 14.0 d | 13.9 | 13.7 | 15.1 |
| | S.D. | 2.6 | 3.1 | 2.3 | 2.1 |
| | N | 23 | 21 | 19 | 25 |
| 7 males+females | MEAN | 14.3 d | 14.3 | 14.2 | 15.5 |
| | S.D. | 2.3 | 3.2 | 2.4 | 1.8 |
| | N | 23 | 21 | 19 | 25 |
| day 14 males | MEAN | 31.1 d | 32.8 | 32.0 | 33.1 |
| | S.D. | 2.9 | 2.9 | 3.9 | 2.5 |
| | N | 23 | 19 | 19 | 25 |
| 14 females | MEAN | 30.0 d | 31.4 | 30.7 | 32.0 |
| | S.D. | 3.8 | 3.2 | 3.5 | 2.8 |
| | N | 23 | 20 | 19 | 25 |
| 14 males+females | MEAN | 30.6 d | 32.0 | 31.4 | 32.5 |
| | S.D. | 3.3 | 2.9 | 3.6 | 2.5 |
| | N | 23 | 20 | 19 | 25 |
| day 21 males | MEAN | 50.1 d | 51.7 | 50.5 | 52.4 |
| | S.D. | 4.9 | 4.1 | 6.7 | 4.5 |
| | N | 23 | 19 | 19 | 25 |
| 21 females | MEAN | 48.1 d | 49.5 | 48.2 | 50.6 |
| | S.D. | 6.1 | 4.3 | 5.9 | 4.4 |
| | N | 23 | 20 | 19 | 25 |
| 21 males+females | MEAN | 49.1 d | 50.4 | 49.4 | 51.5 |
| | S.D. | 5.4 | 4.0 | 6.1 | 4.2 |
| | N | 23 | 20 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 19 (continued)

F0 GENERATION
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|--------|------|------|-------|
| day 1- 4 males | MEAN | 2.3 d | 2.3 | 2.0 | 2.3 |
| | S.D. | 0.8 | 1.3 | 0.8 | 0.8 |
| | N | 23 | 21 | 19 | 25 |
| females | MEAN | 2.2 d | 2.1 | 1.9 | 2.4 |
| | S.D. | 0.9 | 1.3 | 0.8 | 0.8 |
| | N | 23 | 21 | 19 | 25 |
| males+females | MEAN | 2.2 d | 2.2 | 2.0 | 2.4 |
| | S.D. | 0.8 | 1.2 | 0.8 | 0.7 |
| | N | 23 | 21 | 19 | 25 |
| day 4- 7 males | MEAN | 5.5 d | 6.2 | 5.9 | 6.5** |
| | S.D. | 1.1 | 1.0 | 1.2 | 0.9 |
| | N | 23 | 19 | 19 | 25 |
| females | MEAN | 5.4 d | 5.4 | 5.5 | 6.1 |
| | S.D. | 1.5 | 1.8 | 1.3 | 0.9 |
| | N | 23 | 21 | 19 | 25 |
| males+females | MEAN | 5.4 d | 5.6 | 5.7 | 6.3 |
| | S.D. | 1.3 | 1.8 | 1.2 | 0.8 |
| | N | 23 | 21 | 19 | 25 |
| day 4-21 males | MEAN | 40.9 d | 42.4 | 41.8 | 43.0 |
| | S.D. | 4.1 | 3.3 | 5.9 | 3.9 |
| | N | 23 | 19 | 19 | 25 |
| females | MEAN | 39.5 d | 40.9 | 40.0 | 41.7 |
| | S.D. | 5.3 | 3.2 | 5.2 | 3.5 |
| | N | 23 | 20 | 19 | 25 |
| males+females | MEAN | 40.2 d | 41.5 | 41.0 | 42.3 |
| | S.D. | 4.6 | 3.1 | 5.4 | 3.5 |
| | N | 23 | 20 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test ** = p<0.01

Table: 19 (continued)

F0 GENERATION

SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------|------|--------|------|------|------|
| day 7-14 males | MEAN | 16.4 d | 17.3 | 17.3 | 17.2 |
| | S.D. | 1.9 | 1.7 | 2.3 | 1.5 |
| | N | 23 | 19 | 19 | 25 |
| females | MEAN | 16.0 d | 17.1 | 17.1 | 16.9 |
| | S.D. | 1.9 | 1.6 | 2.2 | 1.4 |
| | N | 23 | 20 | 19 | 25 |
| males+females | MEAN | 16.2 d | 17.2 | 17.2 | 17.1 |
| | S.D. | 1.8 | 1.5 | 2.2 | 1.4 |
| | N | 23 | 20 | 19 | 25 |
| day 14-21 males | MEAN | 19.0 d | 18.9 | 18.5 | 19.3 |
| | S.D. | 2.4 | 2.1 | 3.6 | 2.4 |
| | N | 23 | 19 | 19 | 25 |
| females | MEAN | 18.1 d | 18.1 | 17.5 | 18.6 |
| | S.D. | 2.7 | 1.8 | 3.1 | 2.0 |
| | N | 23 | 20 | 19 | 25 |
| males+females | MEAN | 18.5 d | 18.4 | 18.0 | 19.0 |
| | S.D. | 2.5 | 1.9 | 3.3 | 2.1 |
| | N | 23 | 20 | 19 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table 20

F0 GENERATION
MEAN VALUES OF ANOGENITAL DISTANCE
ON DAY 1 POST-PARTUM

| Dose-level (mg/kg/day) | | Male | | | | Female | | | |
|----------------------------------|------|------|------|------|------|--------|------|------|------|
| | | 0 | 250 | 500 | 1000 | 0 | 250 | 500 | 1000 |
| AGD | Mean | 4.71 | 4.62 | 4.47 | 4.64 | 2.84 | 2.77 | 2.63 | 2.68 |
| | SD | 0.43 | 0.33 | 0.39 | 0.30 | 0.36 | 0.24 | 0.26 | 0.37 |
| PW | Mean | 6.80 | 6.70 | 6.50 | 7.00 | 6.40 | 6.40 | 6.00 | 6.50 |
| | SD | 0.70 | 0.60 | 0.70 | 0.70 | 0.60 | 0.60 | 0.60 | 0.60 |
| AGD/PW | Mean | 0.69 | 0.69 | 0.70 | 0.67 | 0.44 | 0.44 | 0.44 | 0.42 |
| | SD | 0.06 | 0.07 | 0.09 | 0.07 | 0.06 | 0.06 | 0.05 | 0.07 |
| AGD/Cube root of body weight (a) | Mean | 2.48 | 2.45 | 2.40 | 2.43 | 1.53 | 1.50 | 1.45 | 1.44 |
| | SD | 0.18 | 0.17 | 0.21 | 0.15 | 0.18 | 0.14 | 0.14 | 0.20 |

AGD: anogenital distance (mm)

PW: pup weight (grams)

AGD/PW: anogenital distance normalized to pup body weight

(a): the anogenital distance is normalized to the cube root of pup body weight

Table: 21

F0 GENERATION

ASSESSMENT OF REFLEX AND PHYSICAL DEVELOPMENT (Mean data)

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|-------|-------|------|-------|
| SURFACE RIGHTING day 5 | | | | | |
| Number of pups tested | N | 182 | 163 | 152 | 200 |
| Number of pups exhibiting positive response | N | 182 f | 157* | 147* | 198 |
| | % | 100.0 | 96.3 | 96.7 | 99.0 |
| CLIFF AVOIDANCE day 11 | | | | | |
| Number of pups tested | N | 174 | 154 | 146 | 199 |
| Number of pups exhibiting positive response | N | 169 f | 154 | 139 | 189 |
| | % | 97.1 | 100.0 | 95.2 | 95.0 |
| AIR RIGHTING day 17 | | | | | |
| Number of pups tested | N | 174 | 154 | 146 | 199 |
| Number of pups exhibiting positive response | N | 172 f | 152 | 143 | 199 |
| | % | 98.9 | 98.7 | 97.9 | 100.0 |

Statistical key: f=Fishers exact test * = p<0.05

Table: 22

F0 GENERATION

SUMMARY OF MACROSCOPIC POSTMORTEM OBSERVATIONS OF PUPS DEAD

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------------------------|---|-------|------|------|-------|
| Litters Evaluated | N | 2 | 4 | 8 | 1 |
| Pups Evaluated | N | 13 | 11 | 10 | 2 |
| GENERAL | | | | | |
| Litter Incidence | N | 2 | 3 | 4 | 1 |
| Pup Incidence | N | 10 | 4 | 4 | 1 |
| O AUTOLYSIS | | | | | |
| Pup Incidence | N | 10 f | 4 | 4 | 1 |
| | % | 76.9 | 36.4 | 40.0 | 50.0 |
| Litter Incidence | N | 2 f | 3 | 4 | 1 |
| | % | 100.0 | 75.0 | 50.0 | 100.0 |
| TOTAL PUPS DEAD OBSERVATIONS | | | | | |
| Pup Incidence | N | 10 f | 4 | 4 | 1 |
| | % | 76.9 | 36.4 | 40.0 | 50.0 |
| Litter Incidence | N | 2 f | 3 | 4 | 1 |
| | % | 100.0 | 75.0 | 50.0 | 100.0 |

Statistical key: f=Fishers exact test

Table: 22 (continued)

F0 GENERATION

**SUMMARY OF MACROSCOPIC POSTMORTEM OBSERVATIONS OF PUPS SACRIFICED
AFTER WEANING**

| Dose: (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|-----|-----|-----|------|
| Litters Evaluated | N | 23 | 20 | 19 | 25 |
| Pups Evaluated | N | 118 | 98 | 91 | 145 |
| GONADS | | | | | |
| Litter Incidence | N | 0 | 0 | 0 | 1 |
| Pup Incidence | N | 0 | 0 | 0 | 1 |
| V SMALL TESTIS | | | | | |
| Pup Incidence | N | 0 f | 0 | 0 | 1 |
| | % | 0.0 | 0.0 | 0.0 | 0.7 |
| Litter Incidence | N | 0 f | 0 | 0 | 1 |
| | % | 0.0 | 0.0 | 0.0 | 4.0 |
| TOTAL PUPS SACRIFICED OBSERVATIONS | | | | | |
| Pup Incidence | N | 0 f | 0 | 0 | 1 |
| | % | 0.0 | 0.0 | 0.0 | 0.7 |
| Litter Incidence | N | 0 f | 0 | 0 | 1 |
| | % | 0.0 | 0.0 | 0.0 | 4.0 |

Statistical key: f=Fishers exact test

Table 23

F0 GENERATION
SUMMARY OF EPIDIDYMAL SPERM COUNT MOTILITY
TESTICULAR SPERM HEAD COUNT AND DAILY SPERM PRODUCTION

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|-------|-------|-------|-------|
| <u>EPIDIDYMIS</u> | | | | |
| Number of spermatozoa ($10^3/\text{mm}^3$ grams of sperm) | | | | |
| Mean | 923 | 938 | 935 | 918 |
| Sd | 200 | 205 | 159 | 194 |
| n | 25 | 25 | 25 | 24 |
| Epididymal sperm motility (%) | | | | |
| Motile | | | | |
| Mean | 99.7 | 100.0 | 98.6 | 97.6 |
| Sd | 1.5 | 0.0 | 4.0 | 6.6 |
| n | 25 | 25 | 25 | 25 |
| Non-motile | | | | |
| Mean | 0.3 | 0.0 | 1.4 | 2.4 |
| Sd | 1.5 | 0.0 | 4.0 | 6.6 |
| n | 25 | 25 | 25 | 25 |
| <u>TESTIS</u> | | | | |
| Number of sperm heads ($10^6/\text{g}$ of testis) | | | | |
| Mean | 114.8 | 109.0 | 108.1 | 109.8 |
| Sd | 18.7 | 13.1 | 18.6 | 16.5 |
| n | 25.0 | 25.0 | 25.0 | 25.0 |
| Daily sperm production rate ($10^6/\text{g}$ of testis/day) | | | | |
| Mean | 18.8 | 17.9 | 17.7 | 18.0 |
| Sd | 3.1 | 2.2 | 3.1 | 2.7 |
| n | 25.0 | 25.0 | 25.0 | 25.0 |

Table 24

F0 GENERATION
SUMMARY OF EPIDIDYMAL SPERM MORPHOLOGY
(expressed as %)

| Dose-levels (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|----|-----|-----|------|
| n | 25 | 25 | 25 | 25 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Normal | | | | |
| Mean % | 93 | 93 | 97 | 96 |
| Sd | 19 | 19 | 2 | 2 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Normally shaped head separated from flagellum | | | | |
| Mean % | 2 | 3 | 2 | 3 |
| Sd | 2 | 3 | 2 | 2 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head separated from flagellum | | | | |
| Mean % | 0 | 0 | 0 | 0 |
| Sd | 0 | 0 | 0 | 0 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head with normal flagellum | | | | |
| Mean % | 4 | 4 | 0 | 0 |
| Sd | 20 | 17 | 1 | 1 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head with abnormal flagellum | | | | |
| Mean % | 0 | 0 | 0 | 0 |
| Sd | 0 | 0 | 0 | 0 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Degenerative flagellar defect(s) with normal head | | | | |
| Mean % | 0 | 0 | 0 | 0 |
| Sd | 0 | 0 | 0 | 0 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Other flagellar defect(s) with normal head | | | | |
| Mean % | 0 | 0 | 1 | 1 |
| Sd | 0 | 1 | 1 | 1 |

Table: 25

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

FO PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|----------|-----------|-----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| ADRENAL GLANDS | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT (g): | | 0.05236 | 0.06020# | 0.05928# | 0.06628## |
| SD : | | 0.013 | 0.014 | 0.009 | 0.012 |
| MEAN % BODY : | | 0.00872 | 0.01013# | 0.01022## | 0.01167## |
| SD : | | 0.002 | 0.002 | 0.002 | 0.002 |
| | | | | | |
| BRAIN | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT (g): | | 2.08 | 2.14 | 2.08 | 2.08 |
| SD : | | 0.081 | 0.099 | 0.088 | 0.086 |
| MEAN % BODY : | | 0.34800 | 0.35931 | 0.35925 | 0.36688* |
| SD : | | 0.026 | 0.021 | 0.029 | 0.024 |
| | | | | | |
| EPIDIDYMIS, LEFT | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT (g): | | 0.77008 | 0.77092 | 0.77784 | 0.80988 |
| SD : | | 0.054 | 0.077 | 0.067 | 0.189 |
| MEAN % BODY : | | 0.12886 | 0.12947 | 0.13434 | 0.14209 |
| SD : | | 0.014 | 0.013 | 0.016 | 0.027 |
| | | | | | |
| EPIDIDYMIS, RIGHT | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT (g): | | 0.78148 | 0.78968 | 0.77492 | 0.77528 |
| SD : | | 0.053 | 0.092 | 0.062 | 0.056 |
| MEAN % BODY : | | 0.13072 | 0.13245 | 0.13383 | 0.13670 |
| SD : | | 0.013 | 0.014 | 0.015 | 0.012 |
| | | | | | |
| FINAL BODY WEIGHT | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT (g): | | 601.9 | 596.9 | 583.2 | 569.1# |
| SD : | | 55.28 | 37.92 | 54.07 | 41.37 |
| | | | | | |

 */**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL

#/#):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

Assigned control group(s) : 1,

Table: 25 (continued)

SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

FO PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-----------------|--------------|---------|-----------|-----------|-----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| KIDNEYS | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 3.58 | 3.96* | 4.12** | 4.34** |
| SD | : | 0.413 | 0.446 | 0.624 | 0.434 |
| MEAN % BODY | : | 0.59628 | 0.66246** | 0.70569** | 0.76341** |
| SD | : | 0.053 | 0.052 | 0.076 | 0.063 |
| | | | | | |
| LIVER | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 19.54 | 19.98 | 19.97 | 22.87** |
| SD | : | 2.79 | 2.21 | 2.82 | 2.75 |
| MEAN % BODY | : | 3.24 | 3.34 | 3.42 | 4.02** |
| SD | : | 0.272 | 0.236 | 0.267 | 0.369 |
| | | | | | |
| PITUITARY GLAND | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 0.01272 | 0.01424 | 0.01256 | 0.01336 |
| SD | : | 0.002 | 0.003 | 0.003 | 0.003 |
| MEAN % BODY | : | 0.00212 | 0.00239 | 0.00217 | 0.00233 |
| SD | : | 0.000 | 0.001 | 0.001 | 0.000 |
| | | | | | |
| PROSTATE | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 1.41 | 1.63# | 1.37 | 1.62 |
| SD | : | 0.272 | 0.320 | 0.285 | 0.396 |
| MEAN % BODY | : | 0.23582 | 0.27279 | 0.23656 | 0.28593** |
| SD | : | 0.054 | 0.053 | 0.054 | 0.069 |
| | | | | | |
| SEMINAL VESICLE | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 2.06 | 2.26 | 2.19 | 2.28 |
| SD | : | 0.309 | 0.595 | 0.439 | 0.574 |
| MEAN % BODY | : | 0.34605 | 0.37895 | 0.37615 | 0.40207 |
| SD | : | 0.066 | 0.098 | 0.073 | 0.100 |
| | | | | | |

#/#):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL

Assigned control group(s) : 1,

Table: 25 (continued)

SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

FO PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|----------------|--------------|---------|---------|---------|----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| SPLEEN | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 0.75304 | 0.76592 | 0.76560 | 0.75304 |
| SD | : | 0.111 | 0.127 | 0.131 | 0.121 |
| MEAN % BODY | : | 0.12472 | 0.12819 | 0.13194 | 0.13192 |
| SD | : | 0.011 | 0.019 | 0.023 | 0.016 |
| | | | | | |
| TESTIS, LEFT | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 1.78 | 1.73 | 1.78 | 1.75 |
| SD | : | 0.116 | 0.181 | 0.142 | 0.237 |
| MEAN % BODY | : | 0.29710 | 0.29005 | 0.30712 | 0.31052 |
| SD | : | 0.028 | 0.025 | 0.033 | 0.049 |
| | | | | | |
| TESTIS, RIGHT | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 1.76 | 1.76 | 1.76 | 1.79 |
| SD | : | 0.105 | 0.179 | 0.130 | 0.126 |
| MEAN % BODY | : | 0.29488 | 0.29427 | 0.30321 | 0.31497* |
| SD | : | 0.029 | 0.025 | 0.033 | 0.029 |
| | | | | | |
| THYROID GLANDS | n: | 25 | 25 | 25 | 25 |
| MEAN WEIGHT | (g): | 0.02196 | 0.02147 | 0.02228 | 0.02264 |
| SD | : | 0.004 | 0.007 | 0.004 | 0.008 |
| MEAN % BODY | : | 0.00366 | 0.00358 | 0.00384 | 0.00398 |
| SD | : | 0.001 | 0.001 | 0.001 | 0.001 |
| | | | | | |

*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL
Assigned control group(s) : 1,

Table: 25 (continued)

SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

FO PARENTS

SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| ADRENAL GLANDS | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT (g): | | 0.06820 | 0.06596 | 0.07145 | 0.07196 |
| SD : | | 0.010 | 0.011 | 0.011 | 0.012 |
| MEAN % BODY : | | 0.02153 | 0.02276 | 0.02288 | 0.02234 |
| SD : | | 0.004 | 0.006 | 0.004 | 0.004 |
| | | | | | |
| BRAIN | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT (g): | | 1.92 | 1.92 | 1.96 | 1.92 |
| SD : | | 0.069 | 0.065 | 0.080 | 0.072 |
| MEAN % BODY : | | 0.60900 | 0.66324 | 0.63755 | 0.59672 |
| SD : | | 0.108 | 0.148 | 0.132 | 0.046 |
| | | | | | |
| FINAL BODY WEIGHT | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT (g): | | 323.3 | 300.1 | 315.9 | 323.8 |
| SD : | | 47.31 | 51.02 | 44.85 | 25.75 |
| | | | | | |
| KIDNEYS | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT (g): | | 2.24 | 2.22 | 2.29 | 2.35 |
| SD : | | 0.185 | 0.160 | 0.207 | 0.224 |
| MEAN % BODY : | | 0.70673 | 0.77143 | 0.74388 | 0.72691 |
| SD : | | 0.110 | 0.198 | 0.160 | 0.060 |
| | | | | | |
| LIVER | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT (g): | | 14.87 | 14.75 | 15.40 | 15.71 |
| SD : | | 1.70 | 1.83 | 1.95 | 1.89 |
| MEAN % BODY : | | 4.67 | 5.15 | 5.03 | 4.85 |
| SD : | | 0.695 | 1.62 | 1.40 | 0.394 |
| | | | | | |

No statistically significant weight differences noted between treated groups and controls

Table: 25 (continued)

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

FO PARENTS

SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-----------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| OVARIES | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT | (g): | 0.16836 | 0.16683 | 0.16682 | 0.16432 |
| SD | : | 0.025 | 0.027 | 0.022 | 0.023 |
| MEAN % BODY | : | 0.05303 | 0.05727 | 0.05385 | 0.05108 |
| SD | : | 0.010 | 0.014 | 0.010 | 0.008 |
| | | | | | |
| PITUITARY GLAND | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT | (g): | 0.01576 | 0.01508 | 0.01609 | 0.01392 |
| SD | : | 0.003 | 0.003 | 0.005 | 0.003 |
| MEAN % BODY | : | 0.00494 | 0.00525 | 0.00519 | 0.00430 |
| SD | : | 0.001 | 0.002 | 0.002 | 0.001 |
| | | | | | |
| SPLEEN | n: | 25 | 24 | 21 | 25 |
| MEAN WEIGHT | (g): | 0.65800 | 0.63179 | 0.64467 | 0.63540 |
| SD | : | 0.084 | 0.093 | 0.094 | 0.112 |
| MEAN % BODY | : | 0.20816 | 0.21752 | 0.21003 | 0.19588 |
| SD | : | 0.043 | 0.055 | 0.057 | 0.028 |
| | | | | | |
| THYROID GLANDS | n: | 25 | 24 | 22 | 25 |
| MEAN WEIGHT | (g): | 0.01868 | 0.01750 | 0.01782 | 0.01824 |
| SD | : | 0.004 | 0.005 | 0.005 | 0.004 |
| MEAN % BODY | : | 0.00591 | 0.00610 | 0.00575 | 0.00565 |
| SD | : | 0.002 | 0.002 | 0.002 | 0.001 |
| | | | | | |
| UTERUS | n: | 23 | 20 | 19 | 25 |
| MEAN WEIGHT | (g): | 0.53978 | 0.58645 | 0.48321 | 0.57620 |
| SD | : | 0.096 | 0.231 | 0.102 | 0.218 |
| MEAN % BODY | : | 0.17203 | 0.20656 | 0.15988 | 0.18085 |
| SD | : | 0.040 | 0.083 | 0.048 | 0.078 |
| | | | | | |

 No statistically significant weight differences noted between treated groups and controls

Table: 26

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PUPS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 23 | 19 | 19 | 25 |
| FINAL BODY WEIGHT | n: | 23 | 19 | 19 | 25 |
| MEAN WEIGHT (g): | | 61.12 | 62.19 | 58.78 | 67.72# |
| SD : | | 10.37 | 9.29 | 9.69 | 8.89 |
| | | | | | |
| BRAIN | n: | 23 | 19 | 19 | 25 |
| MEAN WEIGHT (g): | | 1.48 | 1.50 | 1.50 | 1.52 |
| SD : | | 0.083 | 0.120 | 0.088 | 0.070 |
| MEAN % BODY : | | 2.47 | 2.45 | 2.61 | 2.28 |
| SD : | | 0.374 | 0.277 | 0.358 | 0.301 |
| | | | | | |
| SPLEEN | n: | 23 | 19 | 19 | 25 |
| MEAN WEIGHT (g): | | 0.29113 | 0.29411 | 0.29195 | 0.33728 |
| SD : | | 0.067 | 0.058 | 0.083 | 0.055 |
| MEAN % BODY : | | 0.47484 | 0.47150 | 0.49072 | 0.50023 |
| SD : | | 0.078 | 0.055 | 0.094 | 0.068 |
| | | | | | |
| THYMUS | n: | 23 | 19 | 19 | 25 |
| MEAN WEIGHT (g): | | 0.27943 | 0.25742 | 0.26916 | 0.28688 |
| SD : | | 0.069 | 0.044 | 0.059 | 0.039 |
| MEAN % BODY : | | 0.45524 | 0.41567 | 0.45738 | 0.42769 |
| SD : | | 0.068 | 0.053 | 0.062 | 0.062 |
| | | | | | |

 #/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL
 Assigned control group(s) : 1,

Table: 26 (continued)

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PUPS

SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 22 | 20 | 19 | 25 |
| FINAL BODY WEIGHT | n: | 22 | 20 | 19 | 25 |
| MEAN WEIGHT (g): | | 57.03 | 57.19 | 58.36 | 63.62* |
| SD : | | 10.42 | 9.36 | 7.54 | 7.26 |
| | | | | | |
| BRAIN | n: | 22 | 20 | 19 | 25 |
| MEAN WEIGHT (g): | | 1.46 | 1.42 | 1.46 | 1.49 |
| SD : | | 0.100 | 0.283 | 0.052 | 0.075 |
| MEAN % BODY : | | 2.62 | 2.52 | 2.54 | 2.36# |
| SD : | | 0.415 | 0.570 | 0.275 | 0.247 |
| | | | | | |
| SPLEEN | n: | 22 | 20 | 19 | 25 |
| MEAN WEIGHT (g): | | 0.27086 | 0.34270 | 0.29342 | 0.31180 |
| SD : | | 0.066 | 0.258 | 0.061 | 0.053 |
| MEAN % BODY : | | 0.47119 | 0.60651 | 0.50102 | 0.49254 |
| SD : | | 0.070 | 0.458 | 0.070 | 0.076 |
| | | | | | |
| THYMUS | n: | 22 | 20 | 19 | 25 |
| MEAN WEIGHT (g): | | 0.27668 | 0.27025 | 0.27705 | 0.30156 |
| SD : | | 0.076 | 0.045 | 0.056 | 0.037 |
| MEAN % BODY : | | 0.48115 | 0.47447 | 0.47531 | 0.47740 |
| SD : | | 0.092 | 0.050 | 0.079 | 0.060 |
| | | | | | |

#/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL

Assigned control group(s) : 1,

Table: 27

```

-----
NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
FO PARENTS
-----
ORGAN/FINDING          DOSE GROUP:  1    2    3    4
                      ANIM.EXAM.: 25   25   25   25
-----
ADRENAL GLANDS        :
- REDUCED IN SIZE    :  -    1    -    -
.....
EPIDIDYMIS, RIGHT    :
- ENLARGED           :  -    -    -    1
.....
KIDNEYS              :
- GREY/GREEN COLOR   :  -    1    1    4
- PALENESS           :  -    -    -    2
.....
LIVER                 :
- ACCENTUATED LOBULAR PATTERN :  3    -    -    -
- ENLARGED           :  -    -    -    3
- PALENESS           :  -    1    -    1
.....
SEMINAL VESICLES     :
- ENLARGED           :  -    -    -    1
.....
SPLEEN               :
- GRANULAR SURFACE   :  -    -    -    2
.....
THYROID GLANDS       :
- ENLARGED           :  -    1    -    -
.....
    
```


Table: 27 (continued)

```

-----
NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS                                     FEMALE
FO PARENTS
-----
ORGAN/FINDING          DOSE GROUP:   1   2   3   4
                    ANIM.EXAM.: 25  25  25  25
-----
ADRENAL GLANDS          :
- ENLARGED              :   -   1   -   -
.....
KIDNEYS                 :
- SEROUS CYSTS          :   -   -   -   1
.....
MANDIBUL. LYMPH NODE    :
- FOCI REDDISH/PURPLISH :   1   -   -   -
- REDDISH COLOR         :   -   -   -   1
.....
PALPABLE MASSES         :
- MASSES GREYISH/WHITISH :  -   -   -   1
.....
SKIN                    :
- ALOPECIA              :   1   -   1   -
.....
THYMUS                  :
- REDDISH COLOR         :   1   -   -   -
- REDUCED IN SIZE       :   3   5   7   5
.....
THYROID GLANDS         :
- REDUCED IN SIZE       :   -   1   -   1
.....
UTERUS                  :
- DILATATION            :   2   3   -   4
- MASSES REDDISH/PURPLISH :   -   -   1   -
- SEROUS CONTENTS       :   2   4   -   5
.....
VAGINA                  :
- TRANSLUCENT CONTENTS  :   -   -   1   -
.....
    
```

Table: 28

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS

| SEX : | | | | | MALE |
|---------------------------|----|----|----|----|------|
| DOSE GROUP: | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | 25 | 25 | 25 | 25 | |
| ADRENAL GLANDS : | 25 | - | - | 24 | |
| - Vacuol.Cortical cell: | - | - | - | 2 | |
| - Altered Cell Foci : | - | - | - | 1 | |
| EPIDIDYMIS, RIGHT : | 25 | - | - | 25 | |
| - Spermatic granuloma : | - | - | - | 1 | |
| KIDNEYS : | - | - | - | 6 | |
| - Tubular Basophilia : | - | - | - | 4 | |
| - Peritubular Fibrosis: | - | - | - | 3 | |
| - Aci.Glob.Cor.Tub.Ep.: | - | - | - | 5 | |
| - Proteinaceous casts : | - | - | - | 1 | |
| - Inters.Mono.Cel.Agg.: | - | - | - | 2 | |
| LIVER : | 1 | - | - | 3 | |
| - Hepatocel.Hypertrop.: | - | - | - | 3 | |
| PITUITARY GLAND : | 25 | - | - | 25 | |
| - Development. Cyst(S): | 1 | - | - | - | |
| PROSTATE : | 25 | - | - | 25 | |
| - Inters.Mono.Cel.Agg.: | 7 | - | - | 6 | |
| - Subacute Prostatitis: | - | - | - | 1 | |
| SPLEEN : | - | - | - | 2 | |
| - Capsular Thickening : | - | - | - | 1 | |
| TESTES : | 25 | - | - | 25 | |
| - Tailed sperm.norm.n.: | 25 | - | - | 25 | |
| - Round sperm.norm.nu.: | 25 | - | - | 25 | |
| - Spermatoocytes norm.n.: | 25 | - | - | 25 | |
| - Spermato gon.norm.n. : | 25 | - | - | 25 | |
| - Dif.stag.sper.cyc.p.: | 25 | - | - | 25 | |
| - Desquamat.spermatoc.: | 8 | - | - | 1 | |
| - Deg.seminifer.tubul.: | 2 | - | - | 2 | |

Table: 28 (continued)

| ----- | | | | |
|--|----|----|----|--------|
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX | | | | |
| STATUS AT NECROPSY: K0, INCL. DEATHS | | | | |
| ----- | | | | |
| SEX : | | | | FEMALE |
| DOSE GROUP: | 1 | 2 | 3 | 4 |
| NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | |
| MANDIBUL. LYMPH NODE : | 1 | - | - | 1 |
| - Plasmocytosis : | 1 | - | - | 1 |
| - Sinusal hemorrhage : | 1 | - | - | 1 |
| ----- | | | | |
| OVARIES : | 25 | - | - | 25 |
| - Proestrus : | 5 | - | - | 9 |
| - Estrus : | 3 | - | - | 2 |
| - Metestrus : | 7 | - | - | 8 |
| - Diestrus : | 9 | - | - | 6 |
| - Few corpora lutea : | 1 | - | - | - |
| - Few follic.develop. : | 1 | - | - | - |
| ----- | | | | |
| PALPABLE MASSES : | - | - | - | 1 |
| - Mammary ductul.carc.: | - | - | - | 1 |
| ----- | | | | |
| PITUITARY GLAND : | 24 | - | - | 25 |
| - Development. Cyst(S): | 1 | - | - | - |
| ----- | | | | |
| THYMUS : | 4 | - | - | 5 |
| - Lymphoid Depletion : | 1 | - | - | 2 |
| - Interstit.hemorrhage: | 3 | - | - | - |
| ----- | | | | |
| THYROID GLANDS : | - | - | - | 1 |
| - Development. Cyst(s): | - | - | - | 1 |
| ----- | | | | |
| UTERUS : | 25 | - | - | 25 |
| - Proestrus : | 5 | - | - | 9 |
| - Estrus : | 3 | - | - | 2 |
| - Metestrus : | 7 | - | - | 8 |
| - Diestrus : | 9 | - | - | 6 |
| - End.epith.c.atrophy : | 1 | - | - | - |
| - Yell.pigm.lad.macro.: | 2 | - | - | - |
| - Dilated Lumen : | 2 | - | - | 6 |
| ----- | | | | |

Table: 28 (continued)

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS

| SEX : | FEMALE | | | |
|-------------------------|--------|----|----|----|
| DOSE GROUP: | 1 | 2 | 3 | 4 |
| NO. ANIMALS: | 25 | 25 | 25 | 25 |
| VAGINA : | 25 | - | - | 24 |
| - Proestrus : | 5 | - | - | 8 |
| - Estrus : | 3 | - | - | 2 |
| - Metestrus : | 7 | - | - | 8 |
| - Diestrus : | 9 | - | - | 6 |
| - Mucific.Vagin.Epith.: | 1 | - | - | - |

Table: 29

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, MALE

| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING |
|---|---|
| | ANIMAL NO: B29204 |
| LIVER - 01: Accentuated lobular pattern. | - NOT SPECIFIED. |
| | ANIMAL NO: B29207 |
| LIVER - 01: Accentuated lobular pattern. | - NOT SPECIFIED. |
| | ANIMAL NO: B29224 |
| LIVER - 01: Accentuated lobular pattern. | - NOTHING ABNORMAL DISCOVERED. |

Table: 29 (continued)

 CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29607

THYMUS
 - 01: Reduced in size. - NOTHING ABNORMAL DISCOVERED.

ANIMAL NO: B29608

THYMUS
 - 01: Right lobe: reddish color. - Interstitial hemorrhage, grade 2.

ANIMAL NO: B29609

SKIN
 - 01: Alopecia, diffuse, (a). - NOTHING ABNORMAL DISCOVERED.

THYMUS
 - 01: Reduced in size. - Lymphoid depletion, grade 2.

ANIMAL NO: B29611

MANDIBUL. LYMPH NODE
 - 01: Foci reddish/purplish, many, - Sinusal hemorrhage,
 punctiform, (a). bilateral, grade 2.

ANIMAL NO: B29614

UTERUS
 - 01: Both horns: dilatation, serous - Proestrus. Dilated lumen, grade 2.
 contents.

Table: 29 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29616

.....

THYMUS

- 01: Reduced in size.

- NOTHING ABNORMAL DISCOVERED.

.....

ANIMAL NO: B29620

.....

UTERUS

- 01: Both horns: dilatation, serous - Proestrus. Dilated lumen, grade 4.
contents.

.....

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 2, MALE |
|--|-----------------------------------|--------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29228 |
| | | |
| KIDNEYS | | |
| - 01: Grey/green color. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29238 |
| | | |
| ADRENAL GLANDS | | |
| - 01: Right: reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29240 |
| | | |
| LIVER | | |
| - 01: Paleness. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29241 |
| | | |
| THYROID GLANDS | | |
| - 01: Enlarged. | - NOT SPECIFIED. | |
| | | |

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 2, FEMALE |
|--|-----------------------------------|----------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29626 |
| ADRENAL GLANDS | | |
| - 01: Enlarged. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29629 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29631 |
| UTERUS | | |
| - 01: Both horns: serous contents. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29638 |
| UTERUS | | |
| - 01: Both horns: dilatation, serous contents. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29640 |
| THYROID GLANDS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |

Table: 29 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 2, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29642

THYMUS

- 01: Reduced in size. - NOT SPECIFIED.

ANIMAL NO: B29643

THYMUS

- 01: Reduced in size. - NOT SPECIFIED.

UTERUS

- 01: Both horns: dilatation, serous - NOT SPECIFIED.
contents.

ANIMAL NO: B29644

THYMUS

- 01: Reduced in size. - NOT SPECIFIED.

ANIMAL NO: B29648

THYMUS

- 01: Reduced in size. - NOT SPECIFIED.

ANIMAL NO: B29649

UTERUS

- 01: Both horns: dilatation, serous - NOT SPECIFIED.
contents.

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 3, MALE |
|--|-----------------------------------|--------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29267 |
| | | |
| KIDNEYS | | |
| - 01: Grey/green color. | - NOT SPECIFIED. | |
| | | |

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 3, FEMALE |
|--|-----------------------------------|----------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29655 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29657 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29658 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29660 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29663 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29664 |
| THYMUS | | |
| - 01: Reduced in size. | - NOT SPECIFIED. | |
| | | |

Table: 29 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 3, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29665

SKIN

- 01: Forelimbs, alopecia, approx 1 cm long, approx 0.5 cm wide, (a). - NOT SPECIFIED.

ANIMAL NO: B29668

UTERUS

- 01: Right horn: cranial part, mass reddish/purplish, approx 1.5 cm long, approx 1 cm wide, firm, homogenous. - NOT SPECIFIED.

ANIMAL NO: B29670

THYMUS

- 01: Reduced in size. - NOT SPECIFIED.

ANIMAL NO: B29673

VAGINA

- 01: Translucent contents, thick. - NOT SPECIFIED.

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 4, MALE |
|--|---|----------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29276 |
| KIDNEYS - 01: Paleness. | - Tubular basophilia, bilateral,grade 3. | |
| SPLEEN - 01: Granular surface. | - Capsular thickening,grade 2. | |
| | | ANIMAL NO: B29277 |
| SPLEEN - 01: Granular surface. | - NOTHING ABNORMAL DISCOVERED. | |
| | | ANIMAL NO: B29278 |
| KIDNEYS - 01: Grey/green color. | - Acidophilic globules in cortical tubular epithelium, bilateral,grade 2. | |
| LIVER - 01: Enlarged. | - Hepatocellular hypertrophy,grade 3. | |
| | | ANIMAL NO: B29280 |
| KIDNEYS - 01: Grey/green color. | - Acidophilic globules in cortical tubular epithelium, bilateral,grade 3. | |
| SEMINAL VESICLES - 01: Enlarged. | - NOTHING ABNORMAL DISCOVERED. | |

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 4, MALE |
|--|--|----------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29281 |
| KIDNEYS | | |
| - 01: Grey/green color. | - Acidophilic globules in cortical tubular epithelium, bilateral, grade 2. | |
| LIVER | | |
| - 01: Enlarged. | - Hepatocellular hypertrophy, grade 2. | |
| | | ANIMAL NO: B29285 |
| KIDNEYS | | |
| - 01: Grey/green color. | - Acidophilic globules in cortical tubular epithelium, bilateral, grade 3. | |
| | | ANIMAL NO: B29289 |
| LIVER | | |
| - 01: Enlarged. | - NOT SPECIFIED. | |
| | | ANIMAL NO: B29294 |
| KIDNEYS | | |
| - 01: Paleness. | - Acidophilic globules in cortical tubular epithelium, bilateral, grade 3. | |

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 4, MALE |
|--|-----------------------------------|------------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29295 |
| LIVER | | |
| - 01: Paleness. | - | NOTHING ABNORMAL DISCOVERED. |
| | | |
| | | ANIMAL NO: B29298 |
| EPIDIDYMIS, RIGHT | | |
| - 01: Enlarged. | - | NOTHING ABNORMAL DISCOVERED. |
| | | |

Table: 29 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 4, FEMALE |
|--|--|----------------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29676 |
| KIDNEYS | | |
| - 01: Left: serous cyst, approx 0.2 cm in diameter. | - NOTHING ABNORMAL DISCOVERED. | |
| THYMUS | | |
| - 01: Reduced in size. | - Lymphoid depletion, grade 2. | |
| | | ANIMAL NO: B29681 |
| THYMUS | | |
| - 01: Reduced in size. | - NOTHING ABNORMAL DISCOVERED. | |
| | | ANIMAL NO: B29682 |
| THYROID GLANDS | | |
| - 01: Reduced in size. | - NOTHING ABNORMAL DISCOVERED. | |
| | | ANIMAL NO: B29685 |
| UTERUS | | |
| - 01: Both horns: dilatation, serous contents. | - Proestrus. Dilated lumen, grade 4. | |
| | | ANIMAL NO: B29686 |
| MANDIBUL. LYMPH NODE | | |
| - 01: Reddish color. | - Sinusal hemorrhage, bilateral, grade 2. | |

Table: 29 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 4, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

UTERUS

- 01: Both horns: dilatation, serous - Proestrus. Dilated lumen, grade 3.
contents.

ANIMAL NO: B29688
.....

UTERUS

- 01: Both horns: dilatation, serous - Proestrus. Dilated lumen, grade 2.
contents.

ANIMAL NO: B29690
.....

THYMUS

- 01: Reduced in size. - NOTHING ABNORMAL DISCOVERED.

ANIMAL NO: B29694
.....

THYMUS

- 01: Reduced in size - NOTHING ABNORMAL DISCOVERED.

UTERUS

- 01: Both horns: serous contents. - Proestrus.

ANIMAL NO: B29695
.....

UTERUS

- 01: both horns: dilatation, serous - Proestrus. Dilated lumen, grade 4.
contents.

Table: 29 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 4, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29696
.....

PALPABLE MASSES

- 01: Observed in vivo, 2213: mass - Mammary ductular
greyish/whitish, approx 2 cm carcinoma, (malignant neoplasm).
long, approx 1 cm wide, firm,
homogenous, (811 812).
.....

ANIMAL NO: B29698
.....

THYMUS

- 01: Reduced in size. - Lymphoid depletion, grade 2.
.....

Table 30

Summary table - F0 parents

**Total number of primordial follicles counted for the two ovaries
Number of animals with up to ten or a multiple of ten primordial follicles**

| Dose-level (mg/kg/day) | 0 | 1000 |
|--|---------|---------|
| $0 \leq n \leq 10$ | 4 / 25 | 2 / 25 |
| $10 < n \leq 20$ | 13 / 25 | 7 / 25 |
| $20 < n \leq 30$ | 4 / 25 | 10 / 25 |
| $30 < n \leq 40$ | 1 / 25 | 3 / 25 |
| $40 < n \leq 50$ | 3 / 25 | 3 / 25 |
| Total number of animals | 25 / 25 | 25 / 25 |
| Number of animals with up to 50 primordial follicles | 25 / 25 | 25 / 25 |

Table 31

Summary table - F0 parents

**Total number of growing follicles counted for the two ovaries
Number of animals with up to three or a multiple of three growing follicles**

| Dose-level (mg/kg/day) | 0 | 1000 |
|--|---------|---------|
| $0 \leq n \leq 3$ | 24 / 25 | 25 / 25 |
| $3 < n \leq 6$ | 1 / 25 | 0 / 25 |
| Total number of animals | 25 / 25 | 25 / 25 |
| Number of animals with up to 6 growing follicles | 25 / 25 | 25 / 25 |

Table: 32

F1 GENERATION
CLINICAL SIGNS (Summary table/Males)

| MALES | | | | |
|---|----|-----|-----|------|
| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
| Mortality | | | | |
| DECISION OF SACRIFICE | 1 | 0 | 0 | 0 |
| FOUND DEAD (after treatment) | 0 | 0 | 1 | 0 |
| FINAL SACRIFICE | 24 | 25 | 24 | 25 |
| General aspect | | | | |
| ROUND BACK | 1 | 0 | 0 | 0 |
| EMACIATED APPEARANCE | 1 | 0 | 0 | 0 |
| PILOERECTOR | 1 | 0 | 0 | 0 |
| COLD TO THE TOUCH | 1 | 0 | 0 | 0 |
| Behaviour | | | | |
| HYPOKINESIA | 1 | 0 | 0 | 0 |
| Breathing | | | | |
| DYSPNEA | 1 | 0 | 0 | 0 |
| Secretion/Excretion | | | | |
| PITYALISM immediately post-dosing | 11 | 21 | 24 | 25 |
| PITYALISM 1 hour post-dosing | 0 | 5 | 6 | 9 |
| REGURGITATION | 1 | 1 | 0 | 0 |
| CHROMODACRYORRHEA | 1 | 0 | 1 | 0 |
| SOFT FAECES | 0 | 0 | 1 | 0 |
| Skin | | | | |
| CUTANEOUS LESION ON NECK DORSAL AREA | 0 | 3 | 4 | 3 |
| CUTANEOUS LESION ON NECK VENTRAL AREA | 1 | 0 | 0 | 0 |
| Miscellaneous | | | | |
| ABNORMAL GROWTH OF TEETH (cut regulary) | 0 | 1 | 3 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 10 | 3 | 0 | 0 |

Table: 33

F1 GENERATION

CLINICAL SIGNS (Summary table/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|----|-----|-----|------|
| Mortality | | | | |
| FOUND DEAD (after treatment) | 0 | 0 | 0 | 1 |
| FINAL SACRIFICE (no mating) | 1 | 1 | 0 | 3 |
| Secretion/Excretion | | | | |
| PITYALISM immediately post-dosing | 2 | 10 | 17 | 22 |
| REGURGITATION | 0 | 1 | 0 | 1 |
| CHROMODACRYORRHEA | 1 | 0 | 0 | 0 |
| Skin | | | | |
| CUTANEOUS LESION ON NECK DORSAL AREA | 1 | 0 | 0 | 0 |
| AREA OF HAIR LOSS ON THORAX | 0 | 0 | 0 | 1 |
| AREA OF HAIR LOSS ON NECK VENTRAL AREA | 0 | 0 | 0 | 1 |
| AREA OF HAIR LOSS ON FORELIMB | 0 | 0 | 0 | 1 |
| Miscellaneous | | | | |
| NECROSED TAIL | 1 | 0 | 0 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 20 | 15 | 8 | 3 |

Table: 34

F1 GENERATION

CLINICAL SIGNS (Summary table/Females/Pregnancy period)

| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|----------------------------------|----|-----|-----|------|
| Mortality | | | | |
| FINAL SACRIFICE (no delivery) | 3 | 3 | 3 | 1 |
| Secretion/Excretion | | | | |
| PTYALISM immediately post-dosing | 0 | 2 | 4 | 10 |
| Miscellaneous | | | | |
| NECROSED TAIL | 1 | 0 | 0 | 2 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 23 | 22 | 21 | 10 |

Table: 35

F1 GENERATION

CLINICAL SIGNS (Summary table/Females/Lactation period)

| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|----|-----|-----|------|
| Mortality | | | | |
| FINAL SACRIFICE | 21 | 20 | 22 | 19 |
| DECISION SACRIFICE (dead litter) | 0 | 1 | 0 | 1 |
| Breathing | | | | |
| DYSPNEA | 0 | 0 | 1 | 0 |
| LOUD BREATHING | 0 | 0 | 1 | 0 |
| ABDOMINAL BREATHING | 0 | 0 | 1 | 0 |
| Secretion/Excretion | | | | |
| PTYALISM immediately post-dosing | 0 | 2 | 4 | 9 |
| Skin | | | | |
| AREA OF HAIR LOSS ON NECK VENTRAL AREA | 0 | 0 | 0 | 1 |
| Miscellaneous | | | | |
| NECROSED TAIL | 1 | 0 | 0 | 2 |
| ABNORMAL GROWTH OF TEETH (cut regulary) | 1 | 0 | 0 | 0 |
| MASS ON MAMMARY GLAND | 0 | 0 | 0 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 19 | 19 | 18 | 9 |

Table: 36

F1 GENERATION
BODY WEIGHTS (Mean values/Grams/Males)

MALES

| | | Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------|------|------------------|-------|-----|-----|------|
| Day 1 | MEAN | | 54 d | 55 | 54 | 56 |
| | S.D. | | 5 | 5 | 8 | 6 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 | MEAN | | 91 d | 91 | 91 | 93 |
| | S.D. | | 8 | 8 | 12 | 10 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 | MEAN | | 147 d | 147 | 147 | 152 |
| | S.D. | | 14 | 11 | 21 | 17 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 | MEAN | | 210 d | 211 | 214 | 217 |
| | S.D. | | 18 | 14 | 30 | 24 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 | MEAN | | 269 d | 268 | 273 | 275 |
| | S.D. | | 23 | 19 | 39 | 29 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 | MEAN | | 322 d | 329 | 333 | 337 |
| | S.D. | | 35 | 22 | 46 | 33 |
| | N | | 25 | 25 | 25 | 25 |
| Day 43 | MEAN | | 375 d | 378 | 384 | 386 |
| | S.D. | | 32 | 24 | 50 | 37 |
| | N | | 24 | 25 | 25 | 25 |
| Day 50 | MEAN | | 411 d | 417 | 422 | 423 |
| | S.D. | | 36 | 26 | 55 | 39 |
| | N | | 24 | 25 | 25 | 25 |
| Day 57 | MEAN | | 442 d | 450 | 457 | 457 |
| | S.D. | | 40 | 31 | 59 | 43 |
| | N | | 24 | 25 | 25 | 25 |
| Day 64 | MEAN | | 468 d | 477 | 485 | 484 |
| | S.D. | | 42 | 34 | 64 | 45 |
| | N | | 24 | 25 | 25 | 25 |
| Day 71 | MEAN | | 485 d | 490 | 504 | 502 |
| | S.D. | | 43 | 34 | 68 | 46 |
| | N | | 24 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 36 (continued)

F1 GENERATION
BODY WEIGHTS (Mean values/Grams/Males)

MALES

| | | Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---------|------|------------------|-------|-----|-----|------|
| Day 78 | MEAN | | 506 d | 509 | 530 | 524 |
| | S.D. | | 47 | 37 | 70 | 50 |
| | N | | 24 | 25 | 25 | 25 |
| Day 85 | MEAN | | 523 d | 526 | 548 | 540 |
| | S.D. | | 48 | 40 | 70 | 50 |
| | N | | 24 | 25 | 25 | 25 |
| Day 92 | MEAN | | 538 d | 543 | 564 | 551 |
| | S.D. | | 49 | 41 | 71 | 50 |
| | N | | 24 | 25 | 25 | 25 |
| Day 99 | MEAN | | 554 d | 557 | 579 | 564 |
| | S.D. | | 51 | 45 | 73 | 52 |
| | N | | 24 | 25 | 24 | 25 |
| Day 106 | MEAN | | 568 d | 570 | 589 | 579 |
| | S.D. | | 53 | 48 | 78 | 56 |
| | N | | 24 | 25 | 24 | 25 |
| Day 113 | MEAN | | 580 d | 581 | 600 | 588 |
| | S.D. | | 54 | 46 | 82 | 57 |
| | N | | 24 | 25 | 24 | 25 |
| Day 120 | MEAN | | 591 d | 590 | 606 | 597 |
| | S.D. | | 56 | 47 | 83 | 58 |
| | N | | 24 | 25 | 24 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 37

F1 GENERATION
BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|------|------|------|------|
| Day 1 TO 8 | MEAN | 37 d | 36 | 36 | 37 |
| | S.D. | 5 | 3 | 5 | 5 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 68.6 | 67.0 | 67.3 | 67.0 |
| Day 8 TO 15 | MEAN | 56 d | 56 | 56 | 59 |
| | S.D. | 7 | 6 | 9 | 8 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 61.6 | 61.4 | 62.0 | 63.1 |
| Day 15 TO 22 | MEAN | 63 d | 63 | 67 | 65 |
| | S.D. | 7 | 5 | 10 | 9 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 43.0 | 43.3 | 45.4 | 42.5 |
| Day 22 TO 29 | MEAN | 59 d | 58 | 59 | 58 |
| | S.D. | 7 | 7 | 11 | 10 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 27.9 | 27.3 | 27.6 | 26.9 |
| Day 29 TO 36 | MEAN | 53 d | 61 | 61 | 62 |
| | S.D. | 22 | 6 | 8 | 8 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 19.9 | 22.7 | 22.3 | 22.7 |
| Day 36 TO 43 | MEAN | 48 d | 49 | 51 | 49 |
| | S.D. | 10 | 7 | 8 | 9 |
| | N | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | 14.7 | 14.9 | 15.4 | 14.5 |
| Day 43 TO 50 | MEAN | 36 d | 39 | 39 | 38 |
| | S.D. | 9 | 5 | 8 | 9 |
| | N | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | 9.6 | 10.4 | 10.0 | 9.8 |
| Day 50 TO 57 | MEAN | 31 d | 33 | 35 | 34 |
| | S.D. | 6 | 7 | 8 | 6 |
| | N | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | 7.6 | 7.8 | 8.2 | 8.0 |
| Day 57 TO 64 | MEAN | 26 d | 27 | 28 | 27 |
| | S.D. | 6 | 7 | 9 | 5 |
| | N | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | 5.9 | 5.9 | 6.0 | 5.9 |

Statistical key: d=ANOVA + Dunnett-test

Table: 37 (continued)

F1 GENERATION
BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|---------------------|-------|--|-------|-------|--------|-------|
| Day 64 TO 71 | MEAN | | 17 d | 13 | 19 | 18 |
| | S.D. | | 6 | 8 | 8 | 5 |
| | N | | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 3.7 | 2.8 | 4.0 | 3.8 |
| Day 71 TO 78 | MEAN | | 21 d | 19 | 26 | 22 |
| | S.D. | | 12 | 11 | 8 | 7 |
| | N | | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 4.2 | 3.9 | 5.2 | 4.3 |
| Day 78 TO 85 | MEAN | | 17 d | 18 | 18 | 16 |
| | S.D. | | 9 | 7 | 8 | 7 |
| | N | | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 3.4 | 3.5 | 3.5 | 3.0 |
| Day 85 TO 92 | MEAN | | 14 d | 16 | 16 | 11 |
| | S.D. | | 6 | 6 | 11 | 17 |
| | N | | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | | 2.8 | 3.1 | 3.0 | 2.1 |
| Day 92 TO 99 | MEAN | | 16 d | 14 | 15 | 14 |
| | S.D. | | 5 | 6 | 5 | 14 |
| | N | | 24 | 25 | 24 | 25 |
| mean percent change | MEAN% | | 3.0 | 2.5 | 2.8 | 2.5 |
| Day 99 TO 106 | MEAN | | 14 d | 13 | 9 | 15 |
| | S.D. | | 6 | 8 | 19 | 7 |
| | N | | 24 | 25 | 24 | 25 |
| mean percent change | MEAN% | | 2.5 | 2.4 | 1.6 | 2.6 |
| Day 106 TO 113 | MEAN | | 12 d | 12 | 12 | 9 |
| | S.D. | | 6 | 6 | 8 | 7 |
| | N | | 24 | 25 | 24 | 25 |
| mean percent change | MEAN% | | 2.1 | 2.1 | 1.9 | 1.6 |
| Day 113 TO 120 | MEAN | | 11 d | 8 | 6 | 9 |
| | S.D. | | 7 | 6 | 25 | 4 |
| | N | | 24 | 25 | 24 | 25 |
| mean percent change | MEAN% | | 1.8 | 1.4 | 1.1 | 1.5 |
| Day 1 TO 113 | MEAN | | 526 d | 527 | 546 | 533 |
| | S.D. | | 54 | 44 | 75 | 53 |
| | N | | 24 | 25 | 24 | 25 |
| mean percent change | MEAN% | | 980.5 | 968.9 | 1006.6 | 956.9 |

Statistical key: d=ANOVA + Dunnett-test

Table: 37 (continued)

F1 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 | |
|---------------------|---------|-------|-------|-------|-------|-----|
| Day | 1 TO 64 | MEAN | 414 d | 422 | 430 | 428 |
| | | S.D. | 43 | 32 | 58 | 42 |
| | | N | 24 | 25 | 25 | 25 |
| mean percent change | MEAN% | 772.0 | 775.9 | 797.5 | 769.0 | |

Statistical key: d=ANOVA + Dunnett-test

Table: 38

F1 GENERATION
BODY WEIGHTS (Mean values/Grams/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|--|-------|-----|-----|------|
| Day 1 | MEAN | | 52 d | 53 | 50 | 54 |
| | S.D. | | 5 | 4 | 7 | 5 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 | MEAN | | 84 d | 86 | 81 | 87 |
| | S.D. | | 9 | 8 | 8 | 8 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 | MEAN | | 127 d | 129 | 123 | 132 |
| | S.D. | | 13 | 11 | 12 | 12 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 | MEAN | | 162 d | 165 | 159 | 167 |
| | S.D. | | 14 | 12 | 13 | 14 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 | MEAN | | 185 d | 188 | 182 | 191 |
| | S.D. | | 16 | 14 | 14 | 16 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 | MEAN | | 205 d | 208 | 203 | 213 |
| | S.D. | | 19 | 17 | 16 | 20 |
| | N | | 25 | 25 | 25 | 25 |
| Day 43 | MEAN | | 224 d | 224 | 219 | 231 |
| | S.D. | | 19 | 21 | 17 | 22 |
| | N | | 25 | 25 | 25 | 25 |
| Day 50 | MEAN | | 243 d | 242 | 238 | 245 |
| | S.D. | | 22 | 23 | 20 | 24 |
| | N | | 25 | 25 | 25 | 24 |
| Day 57 | MEAN | | 266 d | 256 | 255 | 261 |
| | S.D. | | 28 | 28 | 25 | 29 |
| | N | | 25 | 25 | 25 | 24 |
| Day 64 | MEAN | | 274 d | 267 | 264 | 268 |
| | S.D. | | 26 | 29 | 21 | 29 |
| | N | | 25 | 25 | 25 | 24 |

Statistical key: d=ANOVA + Dunnett-test

Table: 39

F1 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|---------------------|-------|------|------|------|
| Day 1 TO 8 | MEAN | 32 d | 32 | 31 | 34 |
| | S.D. | 5 | 4 | 4 | 5 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 61.5 | 60.6 | 63.4 |
| Day 8 TO 15 | MEAN | 43 d | 43 | 42 | 44 |
| | S.D. | 5 | 5 | 5 | 5 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 51.6 | 50.3 | 51.4 |
| Day 15 TO 22 | MEAN | 35 d | 36 | 36 | 36 |
| | S.D. | 5 | 6 | 5 | 7 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 27.8 | 28.5 | 29.3 |
| Day 22 TO 29 | MEAN | 23 d | 22 | 23 | 23 |
| | S.D. | 4 | 4 | 4 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 14.3 | 13.6 | 14.8 |
| Day 29 TO 36 | MEAN | 19 d | 20 | 20 | 22 |
| | S.D. | 7 | 7 | 6 | 7 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 10.4 | 10.7 | 11.1 |
| Day 36 TO 43 | MEAN | 19 d | 17 | 16 | 19 |
| | S.D. | 4 | 7 | 5 | 6 |
| | N | 25 | 25 | 25 | 25 |
| | mean percent change | MEAN% | 9.2 | 7.9 | 8.0 |
| Day 43 TO 50 | MEAN | 19 d | 17 | 19 | 16 |
| | S.D. | 8 | 6 | 6 | 8 |
| | N | 25 | 25 | 25 | 24 |
| | mean percent change | MEAN% | 8.5 | 7.7 | 8.7 |
| Day 50 TO 57 | MEAN | 23 d | 14** | 17 | 16 |
| | S.D. | 10 | 10 | 11 | 10 |
| | N | 25 | 25 | 25 | 24 |
| | mean percent change | MEAN% | 9.4 | 5.8 | 7.3 |
| Day 57 TO 64 | MEAN | 9 d | 11 | 9 | 7 |
| | S.D. | 11 | 11 | 8 | 8 |
| | N | 25 | 25 | 25 | 24 |
| | mean percent change | MEAN% | 3.4 | 4.3 | 3.7 |

Statistical key: d=ANOVA + Dunnett-test ** = p<0.01

Table: 39 (continued)

F1 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 | |
|---------------------|---------|-------|-------|-------|-------|-----|
| Day | 1 TO 64 | MEAN | 222 d | 213 | 214 | 215 |
| | | S.D. | 26 | 28 | 19 | 28 |
| | | N | 25 | 25 | 25 | 24 |
| mean percent change | MEAN% | 431.1 | 400.5 | 432.8 | 401.7 | |

Statistical key: d=ANOVA + Dunnett-test

Table: 40

F1 GENERATION

BODY WEIGHT (Mean values/grams/Females/Pregnancy period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|-------|-----|-----|------|
| DAY 0 | MEAN | 283 d | 278 | 273 | 277 |
| | S.D. | 25 | 30 | 22 | 28 |
| | N | 21 | 21 | 22 | 20 |
| DAY 7 | MEAN | 314 d | 310 | 302 | 306 |
| | S.D. | 28 | 30 | 27 | 29 |
| | N | 21 | 21 | 22 | 20 |
| DAY 14 | MEAN | 348 d | 344 | 335 | 339 |
| | S.D. | 31 | 30 | 31 | 30 |
| | N | 21 | 21 | 22 | 20 |
| DAY 20 | MEAN | 429 d | 424 | 413 | 413 |
| | S.D. | 37 | 32 | 39 | 32 |
| | N | 21 | 21 | 22 | 20 |

Statistical key: d=ANOVA + Dunnett-test

Table: 41

F1 GENERATION

BODY WEIGHT CHANGE (Mean values/grams/Females/Pregnancy period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|------|------|------|
| DAYS 0 TO 7 | MEAN | 31 d | 31 | 30 | 29 |
| | S.D. | 9 | 9 | 9 | 6 |
| | N | 21 | 21 | 22 | 20 |
| mean percent change | MEAN% | 11.1 | 11.5 | 10.8 | 10.7 |
| DAYS 7 TO 14 | MEAN | 34 d | 34 | 33 | 33 |
| | S.D. | 7 | 6 | 8 | 6 |
| | N | 21 | 21 | 22 | 20 |
| mean percent change | MEAN% | 11.0 | 11.2 | 10.8 | 10.8 |
| DAYS 14 TO 20 | MEAN | 80 d | 80 | 78 | 74 |
| | S.D. | 12 | 7 | 14 | 10 |
| | N | 21 | 21 | 22 | 20 |
| mean percent change | MEAN% | 23.1 | 23.3 | 23.4 | 22.1 |
| DAYS 0 TO 20 | MEAN | 146 d | 145 | 141 | 137 |
| | S.D. | 21 | 15 | 21 | 12 |
| | N | 21 | 21 | 22 | 20 |
| mean percent change | MEAN% | 51.9 | 52.9 | 51.5 | 49.8 |

Statistical key: d=ANOVA + Dunnett-test

Table: 42

F1 GENERATION

BODY WEIGHT (Mean values/grams/Females/Lactation period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|-------|-----|-----|------|
| DAY 1 | MEAN | 340 d | 333 | 326 | 325 |
| | S.D. | 38 | 28 | 31 | 32 |
| | N | 21 | 21 | 22 | 20 |
| DAY 7 | MEAN | 346 d | 340 | 334 | 336 |
| | S.D. | 34 | 28 | 30 | 28 |
| | N | 21 | 20 | 22 | 19 |
| DAY 14 | MEAN | 348 d | 352 | 344 | 350 |
| | S.D. | 34 | 30 | 31 | 26 |
| | N | 21 | 20 | 22 | 19 |
| DAY 21 | MEAN | 336 d | 336 | 330 | 336 |
| | S.D. | 24 | 23 | 28 | 21 |
| | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table: 43

F1 GENERATION

BODY WEIGHT CHANGE (Mean values/grams/Females/Lactation period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|-----|-----|------|
| DAYS 1 TO 7 | MEAN | 6 d | 8 | 8 | 12 |
| | S.D. | 16 | 10 | 13 | 10 |
| | N | 21 | 20 | 22 | 19 |
| mean percent change | MEAN% | 1.9 | 2.5 | 2.7 | 3.9 |
| DAYS 7 TO 14 | MEAN | 3 d | 12* | 10 | 13* |
| | S.D. | 16 | 11 | 10 | 8 |
| | N | 21 | 20 | 22 | 19 |
| mean percent change | MEAN% | 1.4 | 3.0 | 2.8 | 4.0 |
| DAYS 14 TO 21 | MEAN | -12 d | -15 | -14 | -13 |
| | S.D. | 18 | 13 | 14 | 8 |
| | N | 21 | 20 | 22 | 19 |
| mean percent change | MEAN% | -0.1 | 0.6 | 0.6 | 1.4 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05

Table: 44

F1 GENERATION
FOOD CONSUMPTION (Mean values/Grams per day/Males)

MALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|--|------|-----|-----|------|
| Day 1 TO 8 | MEAN | | 14 d | 14 | 14 | 14 |
| | S.D. | | 3 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 TO 15 | MEAN | | 19 d | 19 | 19 | 19 |
| | S.D. | | 2 | 2 | 3 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 TO 22 | MEAN | | 25 d | 25 | 26 | 26 |
| | S.D. | | 2 | 2 | 3 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 TO 29 | MEAN | | 27 d | 26 | 28 | 27 |
| | S.D. | | 2 | 2 | 4 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 TO 36 | MEAN | | 28 d | 28 | 29 | 30 |
| | S.D. | | 3 | 2 | 4 | 3 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 TO 43 | MEAN | | 29 d | 29 | 29 | 30 |
| | S.D. | | 3 | 2 | 4 | 3 |
| | N | | 24 | 25 | 25 | 25 |
| Day 43 TO 50 | MEAN | | 27 d | 27 | 28 | 29 |
| | S.D. | | 4 | 2 | 3 | 3 |
| | N | | 24 | 25 | 25 | 25 |
| Day 50 TO 57 | MEAN | | 27 d | 28 | 29 | 29* |
| | S.D. | | 3 | 2 | 3 | 2 |
| | N | | 24 | 25 | 25 | 25 |
| Day 57 TO 64 | MEAN | | 26 d | 27 | 28 | 29** |
| | S.D. | | 3 | 2 | 3 | 3 |
| | N | | 24 | 25 | 25 | 25 |
| Day 85 TO 92 | MEAN | | 25 d | 25 | 27 | 26 |
| | S.D. | | 3 | 3 | 3 | 3 |
| | N | | 24 | 24 | 25 | 25 |
| Day 92 TO 99 | MEAN | | 25 d | 25 | 26 | 26 |
| | S.D. | | 3 | 2 | 3 | 3 |
| | N | | 24 | 25 | 24 | 25 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01

Table: 44 (continued)

F1 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Males)

MALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|------|----|-----|-----|------|
| Day 99 TO 106 | MEAN | 25 d | 25 | 25 | 25 | 27 |
| | S.D. | | 3 | 3 | 4 | 4 |
| | N | | 24 | 25 | 24 | 25 |
| Day 106 TO 113 | MEAN | 25 d | 25 | 25 | 26 | 27* |
| | S.D. | | 2 | 2 | 5 | 3 |
| | N | | 24 | 25 | 24 | 25 |
| Day 113 TO 120 | MEAN | 24 d | 24 | 24 | 25 | 26 |
| | S.D. | | 3 | 2 | 6 | 3 |
| | N | | 24 | 25 | 24 | 25 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05

Table: 45

F1 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|------|----|-----|-----|------|
| Day 1 TO 8 | MEAN | 13 d | 13 | 13 | 13 | 14 |
| | S.D. | | 2 | 1 | 2 | 2 |
| | N | | 25 | 25 | 24 | 25 |
| Day 8 TO 15 | MEAN | 16 d | 17 | 17 | 16 | 17 |
| | S.D. | | 2 | 1 | 1 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 TO 22 | MEAN | 19 d | 19 | 19 | 19 | 20 |
| | S.D. | | 2 | 1 | 1 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 TO 29 | MEAN | 18 d | 18 | 18 | 18 | 19 |
| | S.D. | | 1 | 1 | 1 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 29 TO 36 | MEAN | 17 d | 18 | 18 | 18 | 19 |
| | S.D. | | 2 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 36 TO 43 | MEAN | 18 d | 18 | 18 | 18 | 19 |
| | S.D. | | 1 | 2 | 1 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 43 TO 50 | MEAN | 18 d | 18 | 18 | 18 | 19 |
| | S.D. | | 1 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 24 |
| Day 50 TO 57 | MEAN | 20 d | 18 | 18 | 19 | 20 |
| | S.D. | | 2 | 3 | 3 | 3 |
| | N | | 25 | 25 | 25 | 24 |
| Day 57 TO 64 | MEAN | 18 d | 18 | 18 | 19 | 18 |
| | S.D. | | 3 | 3 | 2 | 2 |
| | N | | 25 | 25 | 25 | 24 |

Statistical key: d=ANOVA + Dunnett-test

Table: 46

F1 GENERATION

FOOD CONSUMPTION (Mean values/grams per day/Females/Pregnancy period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|------|-----|-----|------|
| DAYS 0 TO 7 | MEAN | 22 d | 22 | 23 | 23 |
| | S.D. | 3 | 3 | 3 | 3 |
| | N | 21 | 21 | 22 | 20 |
| DAYS 7 TO 14 | MEAN | 25 d | 24 | 24 | 25 |
| | S.D. | 3 | 3 | 4 | 3 |
| | N | 21 | 21 | 22 | 20 |
| DAYS 14 TO 20 | MEAN | 29 d | 29 | 30 | 29 |
| | S.D. | 4 | 3 | 3 | 3 |
| | N | 21 | 21 | 22 | 20 |

Statistical key: d=ANOVA + Dunnett-test

Table: 47

F1 GENERATION

FOOD CONSUMPTION (Mean values/grams per day/Females/Lactation period)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|------|-----|-----|------|
| DAYS 1 TO 7 | MEAN | 35 d | 35 | 36 | 38 |
| | S.D. | 4 | 7 | 5 | 4 |
| | N | 21 | 20 | 22 | 19 |
| DAYS 7 TO 14 | MEAN | 52 d | 55 | 54 | 56 |
| | S.D. | 5 | 5 | 5 | 5 |
| | N | 21 | 20 | 22 | 19 |
| DAYS 14 TO 21 | MEAN | 62 d | 66 | 67 | 67 |
| | S.D. | 7 | 6 | 7 | 5 |
| | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table 48

F 1 GENERATION
SUMMARY OF CLEAVAGE OF THE BALANOPREPUTIAL GLAND

Sex: male

| | Dose-level (mg/kg/day) | | | |
|------------------------|------------------------|-------|-------|-------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Mean age of appearance | 35 | 34 | 35 | 35 |
| SD | 2 | 2 | 2 | 2 |
| Mean body weight on | | | | |
| positive days (grams) | 135.0 | 132.6 | 136.8 | 138.3 |
| SD | 15.9 | 13.2 | 15.1 | 20.8 |

Table 49

**F 1 GENERATION
SUMMARY OF VAGINAL OPENING**

Sex: female

| | Dose-level (mg/kg/day) | | | |
|--|------------------------|-------|-------|-------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Mean age of appearance | 34 | 34 | 35 | 33 |
| SD | 3 | 3 | 2 | 2 |
| Mean body weight on positive days (grams) | 114.1 | 116.4 | 117.6 | 114.7 |
| SD | 17.7 | 17.1 | 11.1 | 17.5 |

Table 50

F 1 GENERATION
SUMMARY OF ACOUSTIC STARTLE RESPONSE

Sex: male

| | Dose-level (mg/kg/day) | | | |
|-----------------------------|------------------------|-----|-----|------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Total of positive responses | 25 | 25 | 25 | 25 |
| % of positive responses | 100 | 100 | 100 | 100 |

Sex: female

| | Dose-level (mg/kg/day) | | | |
|-----------------------------|------------------------|-----|-----|------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Total of positive responses | 25 | 25 | 25 | 25 |
| % of positive responses | 100 | 100 | 100 | 100 |

Table 52

**F1 GENERATION
SUMMARY OF MOTOR ACTIVITY
(First trial)**

Sex: male

| | | Dose-level (mg/kg/day) | | | |
|---|------------|------------------------|-----|-----|------|
| | | 0 | 250 | 500 | 1000 |
| | n | 25 | 25 | 25 | 25 |
| Movements within the front of the cage | Mean | 58 | 69 | 72 | 79 |
| | SD | 29 | 17 | 18 | 18 |
| | Mean/1 min | 6 | 7 | 7 | 8 |
| | SD/1min | 3 | 2 | 2 | 2 |
| Back and forth movements | Mean | 32 | 40 | 45 | 47 |
| | SD | 11 | 5 | 11 | 10 |
| | Mean/1 min | 3 | 4 | 4 | 5 |
| | SD/1min | 1 | 1 | 1 | 1 |
| Movements within the back of the cage | Mean | 64 | 70 | 74 | 78 |
| | SD | 24 | 19 | 21 | 20 |
| | Mean/1 min | 6 | 7 | 7 | 8 |
| | SD/1min | 2 | 2 | 2 | 2 |
| Vertical movements | Mean | 84 | 106 | 108 | 105 |
| | SD | 33 | 22 | 23 | 21 |
| | Mean/1 min | 8 | 11 | 11 | 11 |
| | SD/1min | 3 | 2 | 2 | 2 |

Table 53

**F1 GENERATION
SUMMARY OF MOTOR ACTIVITY
(First trial)**

Sex: female

| | | Dose-level (mg/kg/day) | | | |
|---|------------|------------------------|-----|-----|------|
| | | 0 | 250 | 500 | 1000 |
| | n | 25 | 25 | 25 | 25 |
| Movements within the front of the cage | Mean | 96 | 112 | 100 | 106 |
| | SD | 25 | 23 | 19 | 29 |
| | Mean/1 min | 10 | 11 | 10 | 11 |
| | SD/1min | 2 | 2 | 2 | 3 |
| Back and forth movements | Mean | 46 | 59 | 54 | 55 |
| | SD | 12 | 9 | 11 | 14 |
| | Mean/1 min | 5 | 6 | 5 | 5 |
| | SD/1min | 1 | 1 | 1 | 1 |
| Movements within the back of the cage | Mean | 92 | 105 | 102 | 101 |
| | SD | 25 | 25 | 19 | 28 |
| | Mean/1 min | 9 | 10 | 10 | 10 |
| | SD/1min | 3 | 2 | 2 | 3 |
| Vertical movements | Mean | 118 | 137 | 134 | 111 |
| | SD | 27 | 21 | 32 | 32 |
| | Mean/1 min | 12 | 14 | 13 | 11 |
| | SD/1min | 3 | 2 | 3 | 3 |

Table 54

**F1 GENERATION
SUMMARY OF MOTOR ACTIVITY
(Second trial)**

Sex: male

| | | Dose-level (mg/kg/day) | | | |
|---|------------|------------------------|-----|-----|------|
| | | 0 | 250 | 500 | 1000 |
| | n | 25 | 25 | 25 | 25 |
| Movements within the front of the cage | Mean | 65 | 64 | 69 | 66 |
| | SD | 22 | 18 | 13 | 18 |
| | Mean/1 min | 7 | 6 | 7 | 7 |
| | SD/1min | 2 | 2 | 1 | 2 |
| Back and forth movements | Mean | 37 | 41 | 41 | 44 |
| | SD | 11 | 11 | 9 | 12 |
| | Mean/1 min | 4 | 4 | 4 | 4 |
| | SD/1min | 1 | 1 | 1 | 1 |
| Movements within the back of the cage | Mean | 67 | 63 | 67 | 70 |
| | SD | 21 | 18 | 22 | 19 |
| | Mean/1 min | 7 | 6 | 7 | 7 |
| | SD/1min | 2 | 2 | 2 | 2 |
| Vertical movements | Mean | 88 | 94 | 93 | 95 |
| | SD | 30 | 20 | 19 | 15 |
| | Mean/1 min | 9 | 9 | 9 | 10 |
| | SD/1min | 3 | 2 | 2 | 1 |

Table 55

**F1 GENERATION
SUMMARY OF MOTOR ACTIVITY
(Second trial)**

Sex: female

| | | Dose-level (mg/kg/day) | | | |
|---|------------|------------------------|-----|-----|------|
| | | 0 | 250 | 500 | 1000 |
| | n | 25 | 25 | 25 | 25 |
| Movements within the front of the cage | Mean | 89 | 100 | 100 | 107 |
| | SD | 26 | 21 | 30 | 24 |
| | Mean/1 min | 9 | 10 | 10 | 11 |
| | SD/1min | 3 | 2 | 3 | 2 |
| Back and forth movements | Mean | 45 | 52 | 52 | 56 |
| | SD | 12 | 9 | 13 | 13 |
| | Mean/1 min | 5 | 5 | 5 | 6 |
| | SD/1min | 1 | 1 | 1 | 1 |
| Movements within the back of the cage | Mean | 90 | 88 | 86 | 97 |
| | SD | 31 | 21 | 26 | 26 |
| | Mean/1 min | 9 | 9 | 9 | 10 |
| | SD/1min | 3 | 2 | 3 | 3 |
| Vertical movements | Mean | 109 | 118 | 115 | 126 |
| | SD | 16 | 21 | 22 | 27 |
| | Mean/1 min | 11 | 12 | 12 | 13 |
| | SD/1min | 2 | 2 | 2 | 3 |

Table 56

**F1 GENERATION
SUMMARY OF REPRODUCTIVE DATA**

| Dose-level (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|---------|---------|---------|-----------|
| | | Group 1 | Group 2 | Group 3 | Group 4 |
| Paired males + females | n | 24+25 | 25+25 | 25+25 | 25+24 (a) |
| Pairs able to mate | n | 25 | 24 | 25 | 23 |
| Female mating index * | % | 100 | 96 | 100 | 96 |
| Mean number of days of pairing before mating | n | 3.1 | 3.5 | 2.6 | 2.4 |
| Pregnant female partners * | n | 22 | 22 | 22 | 22 |
| Fertility index * | % | 88 | 92 | 88 | 96 |
| Females with no delivery | | 0 | 1 | 0 | 0 |
| Females with live concepti | n | 21 | 21 | 22 | 20 |
| Gestation index | % | 95.5 | 95.5 | 100 | 91 |

* including pregnant female with no detection of sperm at vaginal lavage

(a) female found dead before mating

Table: 57

F1 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|------|--------|------|-------|------|
| Females on Study | N | 25 | 25 | 25 | 25 |
| Females Mated | N | 25 f | 24 | 25 | 23 |
| Mating Index | % | 100.0 | 96.0 | 100.0 | 92.0 |
| Females Pregnant | N | 22 f | 22 | 22 | 22 |
| Female Fertility Index | % | 88.0 | 91.7 | 88.0 | 95.7 |
| Females with Liveborn | N | 21 f | 21 | 22 | 20 |
| Gestation Index | % | 95.5 | 95.5 | 100.0 | 90.9 |
| Females Surviving Delivery | N | 21 f | 21 | 22 | 20 |
| Duration of Gestation | MEAN | 21.5 d | 21.6 | 21.6 | 21.6 |
| | S.D. | 0.5 | 0.5 | 0.5 | 0.5 |
| with Stillborn Pups | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| with all Stillborn | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| with Entire Liveborn Litter Dying and/or Missing, Cannibalized, Culled | | | | | |
| days 0-4 | N | 0 f | 1 | 0 | 1 |
| | % | 0.0 | 4.8 | 0.0 | 5.0 |
| days 0-21 | N | 0 f | 1 | 0 | 1 |
| | % | 0.0 | 4.8 | 0.0 | 5.0 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test

Table: 57 (continued)

F1 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|------|--------|-------|-------|-------|
| Litters with Liveborn Pups | N | 21 | 21 | 22 | 20 |
| Pups Delivered (total) | N | 287 | 288 | 301 | 280 |
| | MEAN | 13.7 d | 13.7 | 13.7 | 14.0 |
| | S.D. | 2.6 | 1.8 | 1.9 | 1.9 |
| Liveborn | N | 287 f | 288 | 301 | 280 |
| Live Birth Index | % | 100.0 | 100.0 | 100.0 | 100.0 |
| Stillborn | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| Uncertain | N | 0 | 0 | 0 | 0 |
| Culled day 4 | | 116 | 113 | 116 | 108 |
| Culled (total) | N | 116 | 113 | 116 | 108 |
| Cannibalized | N | 5 | 4 | 4 | 9 |
| Missing | N | 0 | 0 | 0 | 0 |
| Died | N | 6 | 12 | 5 | 12 |
| Liveborn, not culled prior to day 21 | N | 171 | 175 | 185 | 172 |
| Pups Dying, Missing, and/or Cannibalized | | | | | |
| day 0 | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| days 1-4 | N | 7 f | 15 | 9 | 20** |
| | % | 2.4 | 5.2 | 3.0 | 7.1 |
| days 5-7 | N | 1 f | 0 | 0 | 1 |
| | % | 0.3 | 0.0 | 0.0 | 0.4 |
| days 8-14 | N | 3 f | 1 | 0 | 0 |
| | % | 1.0 | 0.3 | 0.0 | 0.0 |
| days 15-21 | N | 0 f | 1 | 0 | 0 |
| | % | 0.0 | 0.3 | 0.0 | 0.0 |
| Pups Surviving 4 days Viability Index | N | 280 f | 273 | 292 | 260** |
| | % | 97.6 | 94.8 | 97.0 | 92.9 |
| Pups Surviving 21 days Lactation Index | N | 160 f | 158 | 176 | 151 |
| | % | 97.6 | 98.8 | 100.0 | 99.3 |
| Implantation Sites per Litter | N | 299 | 302 | 309 | 301 |
| | MEAN | 14.2 d | 14.4 | 14.0 | 15.1 |
| | S.D. | 2.5 | 1.6 | 1.9 | 1.7 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test ** = p<0.01

Table: 57 (continued)

F1 GENERATION
SUMMARY OF REPRODUCTIVE AND LITTER DATA

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|----------------------------------|------|--------|------|------|------|
| Live Pups/Litter | | | | | |
| day 1 | MEAN | 13.5 d | 13.7 | 13.7 | 14.0 |
| | S.D. | 2.7 | 1.9 | 1.9 | 1.9 |
| day 4 preculling | MEAN | 13.3 d | 13.6 | 13.3 | 13.7 |
| | S.D. | 2.8 | 1.6 | 1.8 | 1.9 |
| day 4 postculling | MEAN | 7.8 d | 8.0 | 8.0 | 8.0 |
| | S.D. | 0.9 | 0.0 | 0.0 | 0.0 |
| day 7 | MEAN | 7.8 d | 8.0 | 8.0 | 7.9 |
| | S.D. | 0.9 | 0.0 | 0.0 | 0.2 |
| day 14 | MEAN | 7.6 d | 7.9 | 8.0 | 7.9 |
| | S.D. | 1.0 | 0.2 | 0.0 | 0.2 |
| day 21 | MEAN | 7.6 d | 7.9 | 8.0 | 7.9 |
| | S.D. | 1.0 | 0.3 | 0.0 | 0.2 |
| Pup Weight/Litter (grams) | | | | | |
| day 1 | MEAN | 6.7 d | 6.5 | 6.5 | 6.6 |
| | S.D. | 0.6 | 0.6 | 0.5 | 0.6 |
| day 4 preculling | MEAN | 9.2 d | 9.1 | 9.0 | 9.0 |
| | S.D. | 1.4 | 1.0 | 0.9 | 1.4 |
| day 4 postculling | MEAN | 9.2 d | 9.1 | 9.1 | 9.0 |
| | S.D. | 1.4 | 1.0 | 1.0 | 1.4 |
| day 7 | MEAN | 15.2 d | 15.1 | 14.6 | 14.6 |
| | S.D. | 2.2 | 1.6 | 1.6 | 2.2 |
| day 14 | MEAN | 32.0 d | 32.3 | 31.1 | 31.3 |
| | S.D. | 4.2 | 2.1 | 2.9 | 2.5 |
| day 21 | MEAN | 50.6 d | 51.0 | 49.6 | 50.2 |
| | S.D. | 6.7 | 3.9 | 5.5 | 3.7 |
| Sex Ratio - Male Pups:Total Pups | | | | | |
| day 0 | N | 144 f | 147 | 155 | 146 |
| | % | 50.5 | 51.0 | 51.5 | 52.1 |
| day 21 | N | 83 f | 79 | 86 | 76 |
| | % | 51.9 | 50.0 | 48.9 | 50.3 |

Statistical key: d=ANOVA + Dunnett-test f=Fishers exact test

Table: 58

F1 GENERATION
SUMMARY OF PUP WEIGHTS (grams)

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------------------------------|------|-------|-----|-----|------|
| day 1 | males | MEAN | 6.9 d | 6.7 | 6.6 | 6.8 |
| | | S.D. | 0.6 | 0.6 | 0.5 | 0.6 |
| | | N | 21 | 21 | 22 | 20 |
| 1 | females | MEAN | 6.5 d | 6.3 | 6.4 | 6.3 |
| | | S.D. | 0.6 | 0.6 | 0.5 | 0.6 |
| | | N | 21 | 21 | 22 | 20 |
| 1 | males+females | MEAN | 6.7 d | 6.5 | 6.5 | 6.6 |
| | | S.D. | 0.6 | 0.6 | 0.5 | 0.6 |
| | | N | 21 | 21 | 22 | 20 |
| day 4 | males preculling | MEAN | 9.5 d | 9.3 | 9.2 | 9.2 |
| | | S.D. | 1.5 | 1.0 | 1.0 | 1.4 |
| | | N | 21 | 20 | 22 | 19 |
| 4 | females preculling | MEAN | 8.9 d | 8.8 | 8.9 | 8.7 |
| | | S.D. | 1.3 | 1.0 | 0.9 | 1.4 |
| | | N | 21 | 20 | 22 | 19 |
| 4 | males+females preculling | MEAN | 9.2 d | 9.1 | 9.0 | 9.0 |
| | | S.D. | 1.4 | 1.0 | 0.9 | 1.4 |
| | | N | 21 | 20 | 22 | 19 |
| day 4 | males postculling | MEAN | 9.5 d | 9.3 | 9.3 | 9.2 |
| | | S.D. | 1.5 | 1.0 | 1.0 | 1.3 |
| | | N | 21 | 20 | 22 | 19 |
| 4 | females postculling | MEAN | 8.9 d | 8.8 | 8.9 | 8.7 |
| | | S.D. | 1.3 | 1.0 | 1.0 | 1.4 |
| | | N | 21 | 20 | 22 | 19 |
| 4 | males+females postculling | MEAN | 9.2 d | 9.1 | 9.1 | 9.0 |
| | | S.D. | 1.4 | 1.0 | 1.0 | 1.4 |
| | | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table: 58 (continued)

F1 GENERATION
SUMMARY OF PUP WEIGHTS (grams)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|--------|------|------|------|
| day 7 males | MEAN | 15.6 d | 15.6 | 15.0 | 15.0 |
| | S.D. | 2.3 | 1.7 | 1.6 | 2.1 |
| | N | 21 | 20 | 22 | 19 |
| 7 females | MEAN | 14.6 d | 14.6 | 14.4 | 14.2 |
| | S.D. | 2.3 | 1.5 | 1.6 | 2.4 |
| | N | 21 | 20 | 22 | 19 |
| 7 males+females | MEAN | 15.2 d | 15.1 | 14.6 | 14.6 |
| | S.D. | 2.2 | 1.6 | 1.6 | 2.2 |
| | N | 21 | 20 | 22 | 19 |
| day 14 males | MEAN | 32.5 d | 33.0 | 31.4 | 32.0 |
| | S.D. | 4.5 | 2.4 | 3.0 | 2.5 |
| | N | 21 | 20 | 22 | 19 |
| 14 females | MEAN | 31.4 d | 31.6 | 30.8 | 30.6 |
| | S.D. | 4.0 | 2.0 | 2.9 | 2.6 |
| | N | 21 | 20 | 22 | 19 |
| 14 males+females | MEAN | 32.0 d | 32.3 | 31.1 | 31.3 |
| | S.D. | 4.2 | 2.1 | 2.9 | 2.5 |
| | N | 21 | 20 | 22 | 19 |
| day 21 males | MEAN | 51.5 d | 52.1 | 50.3 | 51.2 |
| | S.D. | 7.2 | 4.4 | 5.8 | 3.6 |
| | N | 21 | 20 | 22 | 19 |
| 21 females | MEAN | 49.6 d | 49.9 | 49.0 | 49.1 |
| | S.D. | 6.2 | 3.6 | 5.5 | 4.1 |
| | N | 21 | 20 | 22 | 19 |
| 21 males+females | MEAN | 50.6 d | 51.0 | 49.6 | 50.2 |
| | S.D. | 6.7 | 3.9 | 5.5 | 3.7 |
| | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table: 58 (continued)

F1 GENERATION
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|--------|------|------|------|
| day 1- 4 males | MEAN | 2.7 d | 2.5 | 2.6 | 2.4 |
| | S.D. | 0.9 | 0.7 | 0.7 | 1.0 |
| | N | 21 | 20 | 22 | 19 |
| females | MEAN | 2.5 d | 2.4 | 2.5 | 2.3 |
| | S.D. | 0.8 | 0.6 | 0.6 | 1.0 |
| | N | 21 | 20 | 22 | 19 |
| males+females | MEAN | 2.6 d | 2.5 | 2.5 | 2.3 |
| | S.D. | 0.8 | 0.6 | 0.6 | 1.0 |
| | N | 21 | 20 | 22 | 19 |
| day 4- 7 males | MEAN | 6.1 d | 6.3 | 5.7 | 5.8 |
| | S.D. | 1.0 | 1.0 | 1.0 | 1.0 |
| | N | 21 | 20 | 22 | 19 |
| females | MEAN | 5.7 d | 5.8 | 5.5 | 5.5 |
| | S.D. | 1.2 | 0.8 | 0.9 | 1.1 |
| | N | 21 | 20 | 22 | 19 |
| males+females | MEAN | 5.9 d | 6.0 | 5.6 | 5.7 |
| | S.D. | 1.0 | 0.9 | 1.0 | 1.0 |
| | N | 21 | 20 | 22 | 19 |
| day 4-21 males | MEAN | 42.0 d | 42.8 | 41.0 | 41.9 |
| | S.D. | 5.9 | 4.0 | 5.1 | 2.7 |
| | N | 21 | 20 | 22 | 19 |
| females | MEAN | 40.7 d | 41.1 | 40.1 | 40.4 |
| | S.D. | 5.1 | 3.4 | 4.8 | 3.0 |
| | N | 21 | 20 | 22 | 19 |
| males+females | MEAN | 41.4 d | 42.0 | 40.5 | 41.2 |
| | S.D. | 5.5 | 3.6 | 4.9 | 2.7 |
| | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table: 58 (continued)

F1 GENERATION
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|------------------|------|--------|------|------|------|
| day 7-14 males | MEAN | 16.8 d | 17.4 | 16.4 | 17.0 |
| | S.D. | 2.4 | 1.6 | 1.7 | 1.2 |
| | N | 21 | 20 | 22 | 19 |
| females | MEAN | 16.8 d | 17.0 | 16.5 | 16.4 |
| | S.D. | 2.4 | 1.2 | 1.6 | 1.1 |
| | N | 21 | 20 | 22 | 19 |
| males+females | MEAN | 16.8 d | 17.2 | 16.4 | 16.7 |
| | S.D. | 2.3 | 1.3 | 1.6 | 1.1 |
| | N | 21 | 20 | 22 | 19 |
| day 14-21 males | MEAN | 19.0 d | 19.1 | 18.9 | 19.1 |
| | S.D. | 3.1 | 2.3 | 3.2 | 1.6 |
| | N | 21 | 20 | 22 | 19 |
| females | MEAN | 18.2 d | 18.3 | 18.2 | 18.6 |
| | S.D. | 2.6 | 2.0 | 3.0 | 1.9 |
| | N | 21 | 20 | 22 | 19 |
| males+females | MEAN | 18.6 d | 18.7 | 18.5 | 18.9 |
| | S.D. | 2.8 | 2.1 | 3.0 | 1.7 |
| | N | 21 | 20 | 22 | 19 |

Statistical key: d=ANOVA + Dunnett-test

Table 59

F1 GENERATION
MEAN VALUES OF ANOGENITAL DISTANCE
ON DAY 1 POST-PARTUM

| Dose-level (mg/kg/day) | | Male | | | | Female | | | |
|----------------------------------|------|------|------|------|------|--------|------|------|------|
| | | 0 | 250 | 500 | 1000 | 0 | 250 | 500 | 1000 |
| AGD | Mean | 4.57 | 4.56 | 4.54 | 4.63 | 2.80 | 2.72 | 2.81 | 2.90 |
| | SD | 0.39 | 0.42 | 0.43 | 0.38 | 0.35 | 0.32 | 0.29 | 0.35 |
| PW | Mean | 6.90 | 6.70 | 6.60 | 6.80 | 6.50 | 6.30 | 6.40 | 6.30 |
| | SD | 0.60 | 0.60 | 0.50 | 0.60 | 0.60 | 0.60 | 0.50 | 0.60 |
| AGD/PW | Mean | 0.67 | 0.69 | 0.69 | 0.69 | 0.44 | 0.44 | 0.45 | 0.47 |
| | SD | 0.06 | 0.10 | 0.08 | 0.09 | 0.06 | 0.07 | 0.06 | 0.09 |
| AGD/Cube root of body weight (a) | Mean | 2.41 | 2.42 | 2.42 | 2.45 | 1.51 | 1.47 | 1.51 | 1.57 |
| | SD | 0.18 | 0.25 | 0.23 | 0.21 | 0.18 | 0.19 | 0.17 | 0.22 |

AGD: anogenital distance (mm)

PW: pup weight (grams)

AGD/PW: anogenital distance normalized to pup body weight

(a): the anogenital distance is normalized to the cube root of pup body weight

Table: 60

F1 GENERATION

ASSESSMENT OF REFLEX AND PHYSICAL DEVELOPMENT (Mean data)

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|-------|------|------|------|
| SURFACE RIGHTING day 5 | | | | | |
| Number of pups tested | N | 164 | 160 | 176 | 152 |
| Number of pups exhibiting positive response | N | 159 f | 155 | 172 | 147 |
| | % | 97.0 | 96.9 | 97.7 | 96.7 |
| CLIFF AVOIDANCE day 11 | | | | | |
| Number of pups tested | N | 160 | 159 | 176 | 151 |
| Number of pups exhibiting positive response | N | 158 f | 158 | 169 | 148 |
| | % | 98.8 | 99.4 | 96.0 | 98.0 |
| AIR RIGHTING day 17 | | | | | |
| Number of pups tested | N | 160 | 158 | 176 | 151 |
| Number of pups exhibiting positive response | N | 155 f | 152 | 170 | 150 |
| | % | 96.9 | 96.2 | 96.6 | 99.3 |

Statistical key: f=Fishers exact test

Table: 61

F1 GENERATION

SUMMARY OF MACROSCOPIC POSTMORTEM OBSERVATIONS OF PUPS DEAD

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|-------------------------------------|---|-------|-----|------|------|
| Litters Evaluated | N | 3 | 1 | 4 | 4 |
| Pups Evaluated | N | 6 | 1 | 5 | 4 |
| GENERAL | | | | | |
| Litter Incidence | N | 3 | 0 | 2 | 3 |
| Pup Incidence | N | 4 | 0 | 3 | 3 |
| O AUTOLYSIS | | | | | |
| Pup Incidence | N | 4 f | 0 | 3 | 3 |
| | % | 66.7 | 0.0 | 60.0 | 75.0 |
| Litter Incidence | N | 3 f | 0 | 2 | 3 |
| | % | 100.0 | 0.0 | 50.0 | 75.0 |
| TOTAL PUPS DEAD OBSERVATIONS | | | | | |
| Pup Incidence | N | 4 f | 0 | 3 | 3 |
| | % | 66.7 | 0.0 | 60.0 | 75.0 |
| Litter Incidence | N | 3 f | 0 | 2 | 3 |
| | % | 100.0 | 0.0 | 50.0 | 75.0 |

Statistical key: f=Fishers exact test

Table: 61 (continued)

F1 GENERATION

**SUMMARY OF MACROSCOPIC POSTMORTEM OBSERVATIONS OF PUPS SACRIFICED
 AFTER WEANING**

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|-----|-----|-----|------|
| Litters Evaluated | N | 21 | 20 | 22 | 19 |
| Pups Evaluated | N | 107 | 103 | 122 | 101 |
| TOTAL PUPS SACRIFICED OBSERVATIONS | | | | | |
| Pup Incidence | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |
| Litter Incidence | N | 0 f | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 |

Statistical key: f=Fishers exact test

Table 62

F1 GENERATION
SUMMARY TABLE:
EPIDIDYMAL SPERM COUNT AND MOTILITY
TESTICULAR SPERM HEAD COUNT AND DAILY SPERM PRODUCTION

| Dose-level (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|-------|------|-------|------|
| <u>EPIDIDYMIS</u> | | | | |
| Number of spermatozoa ($10^3/\text{mm}^3$ grams of sperm) | | | | |
| Mean | 725 | 673 | 701 | 688 |
| Sd | 150 | 197 | 97 | 177 |
| n | 22 | 24 | 23 | 24 |
| ----- | | | | |
| Epididymal sperm motility (%) | | | | |
| Motile | | | | |
| Mean | 84.6 | 87.1 | 93.3 | 88.3 |
| Sd | 34.1 | 31.6 | 22.0 | 29.4 |
| n | 24 | 25 | 24 | 25 |
| ----- | | | | |
| Non-motile | | | | |
| Mean | 11.3 | 5.0 | 2.5 | 4.8 |
| Sd | 29.1 | 17.7 | 9.3 | 13.6 |
| n | 24 | 25 | 24 | 25 |
| <u>TESTIS</u> | | | | |
| Number of sperm heads ($10^6/\text{g}$ of testis) | | | | |
| Mean | 100.6 | 97.8 | 105.3 | 99.8 |
| Sd | 36.7 | 32.3 | 27.2 | 38.9 |
| n | 24.0 | 25.0 | 24.0 | 25.0 |
| ----- | | | | |
| Daily sperm production rate ($10^6/\text{g}$ of testis/day) | | | | |
| Mean | 16.5 | 16.0 | 17.3 | 16.4 |
| Sd | 6.0 | 5.3 | 4.5 | 6.4 |
| n | 24.0 | 25.0 | 24.0 | 25.0 |

Table 63

F1 GENERATION
SUMMARY OF EPIDIDYMAL SPERM MORPHOLOGY
(expressed as %)

| Dose-levels (mg/kg/day) | 0 | 250 | 500 | 1000 |
|---|----|-----|-----|------|
| n | 24 | 25 | 24 | 25 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Normal | | | | |
| Mean % | 84 | 86 | 86 | 88 |
| Sd | 30 | 28 | 27 | 24 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Normally shaped head separated from flagellum | | | | |
| Mean % | 11 | 4 | 5 | 8 |
| Sd | 24 | 9 | 7 | 19 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head separated from flagellum | | | | |
| Mean % | 0 | 0 | 0 | 0 |
| Sd | 1 | 0 | 0 | 1 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head with normal flagellum | | | | |
| Mean % | 1 | 1 | 4 | 1 |
| Sd | 1 | 2 | 15 | 2 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Mis-shapen head with abnormal flagellum | | | | |
| Mean % | 0 | 0 | 0 | 0 |
| Sd | 1 | 0 | 0 | 1 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Degenerative flagellar defect(s) with normal head | | | | |
| Mean % | 1 | 0 | 0 | 0 |
| Sd | 2 | 0 | 0 | 0 |
| <hr style="border-top: 1px dashed black;"/> | | | | |
| Other flagellar defect(s) with normal head | | | | |
| Mean % | 0 | 0 | 1 | 0 |
| Sd | 1 | 1 | 1 | 1 |

Table: 64

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| FINAL BODY WEIGHT | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT | (g): | 589.4 | 588.2 | 605.8 | 594.2 |
| SD | : | 55.22 | 48.84 | 85.04 | 58.45 |
| | | | | | |
| ADRENAL GLANDS | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT | (g): | 0.06454 | 0.06024 | 0.06825 | 0.06924 |
| SD | : | 0.012 | 0.009 | 0.012 | 0.010 |
| MEAN % BODY | : | 0.01097 | 0.01029 | 0.01142 | 0.01171 |
| SD | : | 0.002 | 0.002 | 0.002 | 0.002 |
| | | | | | |
| PITUITARY GLAND | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT | (g): | 0.01283 | 0.01384 | 0.01396 | 0.01460# |
| SD | : | 0.004 | 0.003 | 0.003 | 0.003 |
| MEAN % BODY | : | 0.00217 | 0.00237 | 0.00234 | 0.00246# |
| SD | : | 0.001 | 0.001 | 0.001 | 0.001 |
| | | | | | |
| PROSTATE | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT | (g): | 1.47 | 1.48 | 1.38 | 1.41 |
| SD | : | 0.311 | 0.249 | 0.230 | 0.279 |
| MEAN % BODY | : | 0.25136 | 0.25239 | 0.23059 | 0.23740 |
| SD | : | 0.057 | 0.043 | 0.043 | 0.040 |
| | | | | | |
| SEMINAL VESICLES | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT | (g): | 1.71 | 1.94 | 1.86 | 1.92 |
| SD | : | 0.295 | 0.567 | 0.422 | 0.436 |
| MEAN % BODY | : | 0.29278 | 0.33038 | 0.31650 | 0.32424 |
| SD | : | 0.055 | 0.085 | 0.113 | 0.073 |
| | | | | | |

 #/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

Assigned control group(s) : 1,

Table: 64 (continued)

SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| TESTIS, RIGHT | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 1.84 | 1.75 | 1.86 | 1.82 |
| SD : | | 0.137 | 0.337 | 0.226 | 0.255 |
| MEAN % BODY : | | 0.31441 | 0.29746 | 0.31004 | 0.30958 |
| SD : | | 0.036 | 0.059 | 0.040 | 0.050 |
| | | | | | |
| EPIDIDYMIS, RIGHT | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 0.75575 | 0.70512 | 0.75008 | 0.71244 |
| SD : | | 0.041 | 0.148 | 0.113 | 0.127 |
| MEAN % BODY : | | 0.12915 | 0.12002 | 0.12492 | 0.12065 |
| SD : | | 0.012 | 0.025 | 0.018 | 0.022 |
| | | | | | |
| EPIDIDYMIS, LEFT | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 0.71683 | 0.69636 | 0.71904 | 0.68980 |
| SD : | | 0.110 | 0.123 | 0.123 | 0.120 |
| MEAN % BODY : | | 0.12299 | 0.11863 | 0.11980 | 0.11693 |
| SD : | | 0.023 | 0.021 | 0.021 | 0.021 |
| | | | | | |
| TESTIS, LEFT | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 1.79 | 1.77 | 1.84 | 1.84 |
| SD : | | 0.317 | 0.390 | 0.210 | 0.171 |
| MEAN % BODY : | | 0.30842 | 0.30222 | 0.30679 | 0.31198 |
| SD : | | 0.065 | 0.067 | 0.037 | 0.042 |
| | | | | | |
| BRAIN | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 2.06 | 2.13 | 2.13* | 2.11 |
| SD : | | 0.085 | 0.096 | 0.123 | 0.085 |
| MEAN % BODY : | | 0.35257 | 0.36390 | 0.35648 | 0.35851 |
| SD : | | 0.034 | 0.030 | 0.038 | 0.034 |
| | | | | | |

#/#):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL

Assigned control group(s) : 1,

Table: 64 (continued)

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PARENTS

SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|------------------|--------------|---------|-----------|-----------|-----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| LIVER | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 18.89 | 18.94 | 21.58# | 23.95## |
| SD : | | 2.45 | 2.32 | 4.16 | 4.10 |
| MEAN % BODY : | | 3.20 | 3.21 | 3.54## | 4.01## |
| SD : | | 0.225 | 0.245 | 0.317 | 0.389 |
| | | | | | |
| KIDNEYS | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 3.38 | 3.73 | 4.13## | 5.34## |
| SD : | | 0.341 | 0.449 | 0.640 | 5.39 |
| MEAN % BODY : | | 0.57406 | 0.63368## | 0.68399## | 0.90836## |
| SD : | | 0.043 | 0.046 | 0.068 | 0.958 |
| | | | | | |
| SPLEEN | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 0.80125 | 0.80256 | 0.78238 | 0.79776 |
| SD : | | 0.147 | 0.082 | 0.125 | 0.145 |
| MEAN % BODY : | | 0.13556 | 0.13677 | 0.13070 | 0.13493 |
| SD : | | 0.019 | 0.013 | 0.023 | 0.025 |
| | | | | | |
| THYROID GLANDS | n: | 24 | 25 | 24 | 25 |
| MEAN WEIGHT (g): | | 0.02792 | 0.02812 | 0.02929 | 0.02884 |
| SD : | | 0.005 | 0.004 | 0.005 | 0.004 |
| MEAN % BODY : | | 0.00474 | 0.00480 | 0.00489 | 0.00488 |
| SD : | | 0.001 | 0.001 | 0.001 | 0.001 |
| | | | | | |

 #/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL
 Assigned control group(s) : 1,

Table: 64 (continued)

SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PARENTS

SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| FINAL BODY WEIGHT | n: | 25 | 24 | 25 | 23 |
| MEAN WEIGHT (g): | | 325.2 | 319.2 | 314.8 | 330.3 |
| SD | : | 24.95 | 25.46 | 24.50 | 41.34 |
| | | | | | |
| ADRENAL GLANDS | n: | 25 | 24 | 25 | 23 |
| MEAN WEIGHT (g): | | 0.07164 | 0.06800 | 0.06944 | 0.07435 |
| SD | : | 0.013 | 0.011 | 0.007 | 0.012 |
| MEAN % BODY | : | 0.02200 | 0.02145 | 0.02218 | 0.02277 |
| SD | : | 0.003 | 0.004 | 0.003 | 0.004 |
| | | | | | |
| PITUITARY GLAND | n: | 25 | 24 | 25 | 23 |
| MEAN WEIGHT (g): | | 0.01372 | 0.01350 | 0.01268 | 0.01374 |
| SD | : | 0.003 | 0.003 | 0.002 | 0.002 |
| MEAN % BODY | : | 0.00423 | 0.00422 | 0.00406 | 0.00420 |
| SD | : | 0.001 | 0.001 | 0.001 | 0.001 |
| | | | | | |
| OVARIES | n: | 25 | 24 | 25 | 23 |
| MEAN WEIGHT (g): | | 0.16352 | 0.17179 | 0.16752 | 0.16278 |
| SD | : | 0.027 | 0.028 | 0.031 | 0.024 |
| MEAN % BODY | : | 0.05047 | 0.05417 | 0.05312 | 0.04941 |
| SD | : | 0.008 | 0.010 | 0.008 | 0.006 |
| | | | | | |
| UTERUS | n: | 21 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 0.55738 | 0.57725 | 0.53832 | 0.54653 |
| SD | : | 0.130 | 0.161 | 0.141 | 0.122 |
| MEAN % BODY | : | 0.17316 | 0.18101 | 0.17120 | 0.16970 |
| SD | : | 0.040 | 0.052 | 0.041 | 0.038 |
| | | | | | |

No statistically significant weight differences noted between treated groups and controls

Table: 64 (continued)

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS

STATUS AT NECROPSY: K0

F1 PARENTS

SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|----------------|------------------|---------|----------|---------|-----------|
| | NO. ANIMALS: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| BRAIN | n: | 25 | 24 | 25 | 23 |
| | MEAN WEIGHT (g): | 1.96 | 1.98 | 1.93 | 1.93 |
| | SD : | 0.082 | 0.072 | 0.091 | 0.077 |
| | MEAN % BODY : | 0.60409 | 0.62437 | 0.61693 | 0.59275 |
| | SD : | 0.040 | 0.046 | 0.039 | 0.065 |
| | | | | | |
| LIVER | n: | 25 | 24 | 25 | 23 |
| | MEAN WEIGHT (g): | 14.85 | 15.07 | 15.26 | 16.34* |
| | SD : | 1.87 | 2.31 | 2.01 | 2.34 |
| | MEAN % BODY : | 4.58 | 4.71 | 4.86 | 4.97# |
| | SD : | 0.562 | 0.571 | 0.588 | 0.666 |
| | | | | | |
| KIDNEYS | n: | 25 | 24 | 25 | 23 |
| | MEAN WEIGHT (g): | 2.24 | 2.34 | 2.30 | 2.49** |
| | SD : | 0.178 | 0.242 | 0.226 | 0.284 |
| | MEAN % BODY : | 0.69219 | 0.73338 | 0.73050 | 0.76202## |
| | SD : | 0.061 | 0.075 | 0.048 | 0.097 |
| | | | | | |
| SPLEEN | n: | 25 | 24 | 25 | 23 |
| | MEAN WEIGHT (g): | 0.69032 | 0.66046 | 0.66288 | 0.64943 |
| | SD : | 0.085 | 0.117 | 0.095 | 0.089 |
| | MEAN % BODY : | 0.21254 | 0.20705 | 0.21106 | 0.19905 |
| | SD : | 0.023 | 0.034 | 0.029 | 0.034 |
| | | | | | |
| THYROID GLANDS | n: | 25 | 24 | 25 | 23 |
| | MEAN WEIGHT (g): | 0.01876 | 0.02108 | 0.01856 | 0.02109 |
| | SD : | 0.004 | 0.004 | 0.003 | 0.004 |
| | MEAN % BODY : | 0.00580 | 0.00666* | 0.00589 | 0.00638 |
| | SD : | 0.001 | 0.001 | 0.001 | 0.001 |
| | | | | | |

 #/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL

*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL

Assigned control group(s) : 1,

Table: 65

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
 STATUS AT NECROPSY: K0
 F2 PUPS
 SEX: MALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 21 | 20 | 22 | 19 |
| FINAL BODY WEIGHT | n: | 21 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 60.36 | 59.56 | 58.30 | 59.43 |
| SD : | | 10.42 | 9.20 | 10.59 | 6.68 |
| | | | | | |
| BRAIN | n: | 21 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 1.47 | 1.52 | 1.48 | 1.46 |
| SD : | | 0.082 | 0.080 | 0.090 | 0.089 |
| MEAN % BODY : | | 2.53 | 2.60 | 2.60 | 2.49 |
| SD : | | 0.571 | 0.369 | 0.366 | 0.236 |
| | | | | | |
| SPLEEN | n: | 21 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 0.30976 | 0.29550 | 0.28986 | 0.28868 |
| SD : | | 0.069 | 0.094 | 0.067 | 0.054 |
| MEAN % BODY : | | 0.51115 | 0.49513 | 0.49713 | 0.48601 |
| SD : | | 0.075 | 0.132 | 0.074 | 0.072 |
| | | | | | |
| THYMUS | n: | 21 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 0.27990 | 0.26085 | 0.24605 | 0.26621 |
| SD : | | 0.052 | 0.044 | 0.060 | 0.038 |
| MEAN % BODY : | | 0.46760 | 0.43939 | 0.42093 | 0.45180 |
| SD : | | 0.062 | 0.057 | 0.059 | 0.079 |
| | | | | | |

 No statistically significant weight differences noted between treated groups and controls

Table: 65 (continued)

 SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
 STATUS AT NECROPSY: K0
 F2 PUPS
 SEX: FEMALE

| ORGAN | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-------------------|--------------|---------|---------|---------|---------|
| | NO. ANIMALS: | 20 | 20 | 22 | 19 |
| FINAL BODY WEIGHT | n: | 20 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 57.08 | 57.20 | 57.51 | 56.23 |
| SD : | | 7.25 | 6.91 | 8.99 | 6.87 |
| | | | | | |
| BRAIN | n: | 20 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 1.47 | 1.45 | 1.46 | 1.43 |
| SD : | | 0.054 | 0.062 | 0.104 | 0.063 |
| MEAN % BODY : | | 2.61 | 2.57 | 2.58 | 2.57 |
| SD : | | 0.301 | 0.293 | 0.359 | 0.250 |
| | | | | | |
| SPLEEN | n: | 20 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 0.30160 | 0.28370 | 0.29495 | 0.26279 |
| SD : | | 0.061 | 0.049 | 0.067 | 0.045 |
| MEAN % BODY : | | 0.52560 | 0.50103 | 0.51809 | 0.46954 |
| SD : | | 0.072 | 0.090 | 0.116 | 0.073 |
| | | | | | |
| THYMUS | n: | 20 | 20 | 22 | 19 |
| MEAN WEIGHT (g): | | 0.27560 | 0.26730 | 0.27350 | 0.26832 |
| SD : | | 0.056 | 0.042 | 0.052 | 0.046 |
| MEAN % BODY : | | 0.48156 | 0.47045 | 0.48307 | 0.47633 |
| SD : | | 0.066 | 0.076 | 0.115 | 0.049 |
| | | | | | |

 No statistically significant weight differences noted between treated
 groups and controls

Table: 66

```

-----
NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
F1 PARENTS
-----
ORGAN/FINDING          DOSE GROUP:  1    2    3    4
                    ANIM.EXAM.: 25  25  25  25
-----
ADRENAL GLANDS        :
- REDUCED IN SIZE     :  -    1    -    -
.....
TESTES                 :
- ENLARGED             :  -    1    -    -
- REDUCED IN SIZE     :  2    2    1    2
- SOFT                 :  1    1    1    2
- TRANSLUCENT ASPECT  :  -    1    -    1
.....
EPIDIDYMIDES          :
- REDUCED IN SIZE     :  2    3    1    3
- TRANSLUCENT ASPECT  :  -    1    -    1
.....
LIVER                  :
- ACCENTUATED LOBULAR PATTERN :  -    -    -    1
- ENLARGED             :  -    -    -    2
.....
KIDNEYS               :
- DILATED PELVIS      :  1    -    1    1
- ENLARGED             :  -    -    -    1
- GREY/GREEN COLOR    :  -    -    1    1
- IRREGULAR COLOR     :  -    1    1    1
- MASSES GREYISH/WHITISH :  -    -    -    1
- PALENESS            :  1    -    3    -
.....
SPLEEN                :
- ENLARGED             :  1    -    -    1
- REDUCED IN SIZE     :  1    -    -    -
.....
THYMUS                :
- FOCI REDDISH/PURPLISH :  1    -    -    -
- REDUCED IN SIZE     :  -    1    -    -
.....
LUNGS                 :
- DILATATION          :  -    -    1    -
- FOAMY CONTENTS      :  -    -    1    -
.....
ADIPOSE TISSUE        :
- NODULES REDDISH/PURPLISH :  -    -    1    -
-----
    
```


Table: 66 (continued)

NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS MALE
F1 PARENTS

| ORGAN/FINDING | DOSE GROUP: | 1 | 2 | 3 | 4 |
|-----------------|-------------|----|----|----|----|
| | ANIM.EXAM.: | 25 | 25 | 25 | 25 |
| ----- | | | | | |
| URINARY BLADDER | : | | | | |
| - THICKENED | : | - | - | - | 1 |

.....

Table: 66 (continued)

```

-----
NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS                                     FEMALE
F1 PARENTS
-----
ORGAN/FINDING          DOSE GROUP:   1     2     3     4
                    ANIM.EXAM.:  25   25   25   25
-----
ADRENAL GLANDS          :
- FOCI BROWNISH/BLACKISH :   1     -     -     -
.....
UTERUS                  :
- SEROUS CONTENTS       :   2     2     3     1
.....
THYROID GLANDS         :
- ENLARGED              :   -     1     -     -
.....
ILEUM                   :
- DISTENDED WITH GAS    :   -     1     -     -
- WHITISH COLOR        :   1     -     -     -
.....
ADIPOSE TISSUE         :
- NODULES YELLOWISH    :   1     -     -     -
.....
    
```

Table: 67

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS
 F1 PARENTS

| | SEX : | | | | | MALE |
|-------------------------|-------|----|----|----|----|------|
| DOSE GROUP: | | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | | 25 | 25 | 25 | 25 | |
| ----- | | | | | | |
| ADRENAL GLANDS : | | 24 | 1 | - | 25 | |
| - Acces. adrenal cort.: | | 1 | - | - | 2 | |
| - Inters.Mono.Cel.Agg.: | | 3 | - | - | 5 | |
| - Sinusoidal Ectasia : | | 12 | - | - | 11 | |
| - Cyst(s) : | | 1 | - | - | 2 | |
| - Vacuol.Cortical cell: | | - | - | - | 5 | |
| - Altered Cell Foci : | | - | - | - | 1 | |
| - Cystic Degeneration : | | - | - | - | 1 | |
| - Lipomatosis : | | - | - | - | 1 | |
| ----- | | | | | | |
| PITUITARY GLAND : | | 24 | - | - | 25 | |
| - Vacuolated Cells : | | 10 | - | - | 8 | |
| - Development. Cyst(S): | | - | - | - | 1 | |
| ----- | | | | | | |
| PROSTATE : | | 24 | 3 | 2 | 25 | |
| - Hypersecretion : | | - | - | - | 1 | |
| - Atroph.Tub.Alv.Units: | | - | - | - | 1 | |
| - Epithel.Cell Atrophy: | | 9 | 3 | - | 12 | |
| - Inters.Mono.Cel.Agg.: | | 5 | 1 | 2 | 8 | |
| - Granulocyte Infiltr.: | | 1 | - | - | 1 | |
| - Acute Prostatitis : | | - | - | 1 | 1 | |
| - Subacute Prostatitis: | | 4 | 1 | - | 5 | |
| ----- | | | | | | |
| SEMINAL VESICLES : | | 24 | 2 | 2 | 25 | |
| - Inters.Mono.Cel.Agg.: | | 1 | - | - | - | |

Table: 67 (continued)

 NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS
 F1 PARENTS

| SEX : | | | | | MALE |
|-------------------------|----|----|----|----|------|
| DOSE GROUP: | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | 25 | 25 | 25 | 25 | |
| TESTIS, RIGHT : | 24 | 25 | 24 | 25 | |
| - Tail.Sperm.Norm.Num.: | 24 | 22 | 23 | 22 | |
| - Reduc.Tailed.Sperma.: | - | 3 | 1 | 3 | |
| - Round Sperm.Norm.Nu.: | 24 | 22 | 23 | 22 | |
| - Reduc.Round spermat.: | - | 3 | 1 | 3 | |
| - Spermatoc.Norm.Numb.: | 24 | 22 | 23 | 22 | |
| - Spermatocy.Reduced : | - | 3 | 1 | 3 | |
| - Spermatog.Normal Nu.: | 24 | 22 | 23 | 22 | |
| - Spermatogonia Reduc.: | - | 3 | 1 | 3 | |
| - Diff.Stag.Cycl.Pres.: | 24 | 22 | 23 | 23 | |
| - Diff.Stag.Cycl.Dist.: | - | 3 | 1 | 2 | |
| - Deg./Necr.Cel.Sloug.: | 9 | 4 | 8 | 6 | |
| - Sem.tub.lin.Sert.c. : | 8 | 7 | 9 | 12 | |
| - Vacuol.semin.tubules: | 7 | 5 | 4 | 3 | |
| - Vacuol.sertoli cells: | 1 | 2 | 3 | 2 | |
| - Degener.germ.epith. : | 1 | 1 | - | 1 | |
| - Retained Spermatids : | - | - | 1 | - | |
| - Multinucl.Giant Cel.: | - | 1 | - | 1 | |
| - Spermatic Granuloma : | - | 1 | - | - | |
| EPIDIDYMIS, RIGHT : | 24 | 3 | 2 | 25 | |
| - Oligospermia : | - | 2 | 1 | 1 | |
| - Exfol.Sperm.Sloughed: | - | - | 1 | - | |
| - Aspermia : | - | - | - | 1 | |
| - Inters.Mono.Cel.Agg.: | 2 | - | - | 1 | |
| LIVER : | - | - | - | 2 | |
| - Alt.cel.foci acid. : | - | - | - | 1 | |
| - Alt.cel.foci clear : | - | - | - | 1 | |
| - Mononuclear Cel.Agg.: | - | - | - | 2 | |
| - Hepatocel.Hypertrop.: | - | - | - | 2 | |

Table: 67 (continued)

```

-----
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
F1 PARENTS
-----
                SEX      :
                DOSE GROUP:  1    2    3    4
                NO.ANIMALS: 25   25  25  25
-----
KIDNEYS          :  1    -    1    4
- Dilated Pelvis :  1    -    -    1
- Nephroblastoma :  -    -    -    1
- Tubular Basophilia :  1    -    1    2
- Peritubular Fibrosis:  1    -    1    2
- Tubular Dilatation :  -    -    1    -
- Aci.Glob.Cor.Tub.Ep.:  -    -    1    3
- Deg./Necr.C.Sloughed:  -    -    1    -
- Inters.Mono.Cel.Agg.:  1    -    1    2
-----
SPLEEN           :  1    -    -    1
- Lymphoid Cel.Hyperp.:  1    -    -    1
- Extramed.hematopoi. :  -    -    -    1
-----
THYMUS           :  1    -    -    -
- Capillary hemorrhage:  1    -    -    -
-----
    
```

Table: 67 (continued)

```

-----
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
F1 PARENTS
-----
                SEX      :                               FEMALE
                DOSE GROUP:      1      2      3      4
                NO. ANIMALS:    25    25    25    25
-----
ADRENAL GLANDS      :      25      -      -      24
- Cort.Cel.Hypertrophy:      -      -      -      1
- Acces. adrenal cort.:      -      -      -      3
- Inters.Mono.Cel.Agg.:      -      -      -      5
- Sinusoidal Ectasia :      22      -      -      18
- Cystic Degeneration :      -      -      -      1
- Lipomatosis       :      1      -      -      1
-----
PITUITARY GLAND     :      25      -      -      24
- Cyst(s)           :      1      -      -      1
- Development. Cyst(S):      1      -      -      2
-----
OVARIES             :      25      3      3      24
- Proestrus         :      5      1      1      5
- Estrus            :      2      1      -      5
- Metestrus         :      7      -      -      1
- Diestrus          :      8      -      2      9
- Pregn.Corpora Lutea :      -      -      -      2
-----
UTERUS              :      25      3      3      24
- Infold.end.epithel. :      -      -      -      1
- Proestrus         :      5      1      -      5
- Estrus            :      2      -      -      3
- Metestrus         :      6      -      -      1
- Diestrus          :      7      -      -      9
- Yell.pigm.lad.macro.:     10      1      -      13
- Dilated Lumen     :      5      1      -      1
- Morphology of Pregn.:      1      1      -      2
- Mineralization    :      1      -      -      -
-----
VAGINA              :      25      3      3      24
- Proestrus         :      5      1      1      5
- Estrus            :      2      1      -      5
- Metestrus         :      7      -      -      1
- Diestrus          :      8      -      2      9
- Mucific.Vagin.Epith.:      2      1      -      4
- Epithel.Cel.Hyperpl.:      1      1      -      -
-----

```

Table: 67 (continued)

```

-----
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
F1 PARENTS
-----
                SEX          :                               FEMALE
                DOSE GROUP:    1      2      3      4
                NO.ANIMALS:   25    25    25    25
-----
PALPABLE MASSES      :      -      -      -      1
- Mammary Fibroadenoma:      -      -      -      1
-----
ADIPOSE TISSUE       :      1      -      -      -
- Fat Necrosis       :      1      -      -      -
-----
    
```

Table: 68

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               MALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
ADRENAL GLANDS      :   24    1    -    25
- Inters.Mono.Cel.Agg.
  GRADE 1 :   3     -    -    5
                TOTAL AFFECTED :   3     -    -    5
                MEAN SEVERITY :  1.0     -    -    1.0
.....
- Sinusoidal Ectasia
  GRADE 1 :   9     -    -    9
  GRADE 2 :   3     -    -    2
                TOTAL AFFECTED :  12     -    -   11
                MEAN SEVERITY :  1.3     -    -   1.2
.....
- Vacuol.Cortical cell
  GRADE 2 :   -     -    -    5
                TOTAL AFFECTED :   -     -    -    5
                MEAN SEVERITY :   -     -    -   2.0
.....
- Altered Cell Foci
  GRADE 1 :   -     -    -    1
                TOTAL AFFECTED :   -     -    -    1
                MEAN SEVERITY :   -     -    -   1.0
.....
- Cystic Degeneration
  GRADE 1 :   -     -    -    1
                TOTAL AFFECTED :   -     -    -    1
                MEAN SEVERITY :   -     -    -   1.0
.....
- Lipomatosis
  GRADE 1 :   -     -    -    1
                TOTAL AFFECTED :   -     -    -    1
                MEAN SEVERITY :   -     -    -   1.0
-----
    
```


Table: 68 (continued)

 SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS

| | | | | | |
|------------------------|-----|-----|-----|-----|------|
| SEX : | | | | | MALE |
| DOSE GROUP: | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | 25 | 25 | 25 | 25 | |
| ----- | | | | | |
| PITUITARY GLAND : | 24 | - | - | 25 | |
| - Vacuolated Cells | | | | | |
| GRADE 1 : | 8 | - | - | 7 | |
| GRADE 2 : | 2 | - | - | 1 | |
| TOTAL AFFECTED : | 10 | - | - | 8 | |
| MEAN SEVERITY : | 1.2 | - | - | 1.1 | |
| ----- | | | | | |
| PROSTATE : | 24 | 3 | 2 | 25 | |
| - Hypersecretion | | | | | |
| GRADE 2 : | - | - | - | 1 | |
| TOTAL AFFECTED : | - | - | - | 1 | |
| MEAN SEVERITY : | - | - | - | 2.0 | |
| | | | | | |
| - Atroph.Tub.Alv.Units | | | | | |
| GRADE 2 : | - | - | - | 1 | |
| TOTAL AFFECTED : | - | - | - | 1 | |
| MEAN SEVERITY : | - | - | - | 2.0 | |
| | | | | | |
| - Epithel.Cell Atrophy | | | | | |
| GRADE 1 : | 5 | 1 | - | 2 | |
| GRADE 2 : | 2 | - | - | 8 | |
| GRADE 3 : | 2 | 1 | - | 2 | |
| GRADE 4 : | - | 1 | - | - | |
| TOTAL AFFECTED : | 9 | 3 | - | 12 | |
| MEAN SEVERITY : | 1.7 | 2.7 | - | 2.0 | |
| | | | | | |
| - Inters.Mono.Cel.Agg. | | | | | |
| GRADE 1 : | 5 | - | 1 | 8 | |
| GRADE 2 : | - | 1 | 1 | - | |
| TOTAL AFFECTED : | 5 | 1 | 2 | 8 | |
| MEAN SEVERITY : | 1.0 | 2.0 | 1.5 | 1.0 | |
| | | | | | |

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               MALE
                DOSE GROUP:    1     2     3     4
                NO.ANIMALS:   25   25   25   25
-----
PROSTATE        CONT'D.    24    3    2    25
- Granulocyte Infiltr.
  GRADE 1 :      1     -     -     1
                TOTAL AFFECTED :    1     -     -     1
                MEAN SEVERITY :   1.0     -     -     1.0
.....
- Acute Prostatitis
  GRADE 1 :      -     -     -     1
  GRADE 2 :      -     -     1     -
                TOTAL AFFECTED :      -     -     1     1
                MEAN SEVERITY :      -     -     2.0  1.0
.....
- Subacute Prostatitis
  GRADE 1 :      -     -     -     1
  GRADE 2 :      2     1     -     2
  GRADE 3 :      1     -     -     2
  GRADE 4 :      1     -     -     -
                TOTAL AFFECTED :      4     1     -     5
                MEAN SEVERITY :   2.8  2.0     -     2.2
-----
SEMINAL VESICLES :    24    2    2    25
- Inters.Mono.Cel.Agg.
  GRADE 1 :      1     -     -     -
                TOTAL AFFECTED :      1     -     -     -
                MEAN SEVERITY :   1.0     -     -     -
-----
TESTIS, RIGHT    :    24   25   24   25
- Reduc.Tailed.Sperma.
  GRADE 1 :      -     -     -     1
  GRADE 4 :      -     1     -     1
  GRADE 5 :      -     2     1     1
                TOTAL AFFECTED :      -     3     1     3
                MEAN SEVERITY :      -   4.7   5.0   3.3
.....
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               MALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
TESTIS, RIGHT  CONT'D.   24   25   24   25
- Reduc.Round spermat.
    GRADE 1 :   -   -   -   1
    GRADE 4 :   -   1   -   1
    GRADE 5 :   -   2   1   1

    TOTAL AFFECTED :   -   3   1   3
    MEAN SEVERITY  :   -  4.7  5.0  3.3
.....
- Spermatocy.Reduced
    GRADE 1 :   -   -   -   1
    GRADE 4 :   -   1   -   1
    GRADE 5 :   -   2   1   1

    TOTAL AFFECTED :   -   3   1   3
    MEAN SEVERITY  :   -  4.7  5.0  3.3
.....
- Spermatogonia Reduc.
    GRADE 1 :   -   -   -   1
    GRADE 4 :   -   1   -   1
    GRADE 5 :   -   2   1   1

    TOTAL AFFECTED :   -   3   1   3
    MEAN SEVERITY  :   -  4.7  5.0  3.3
.....
- Diff.Stag.Cycl.Dist.
    GRADE 4 :   -   1   -   1
    GRADE 5 :   -   2   1   1

    TOTAL AFFECTED :   -   3   1   2
    MEAN SEVERITY  :   -  4.7  5.0  4.5
.....
- Deg./Necr.Cel.Sloug.
    GRADE 1 :   9   3   5   2
    GRADE 2 :   -   1   3   4

    TOTAL AFFECTED :   9   4   8   6
    MEAN SEVERITY  :  1.0  1.3  1.4  1.7
-----
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               MALE
                DOSE GROUP:    1     2     3     4
                NO.ANIMALS:    25   25   25   25
-----
TESTIS, RIGHT  CONT'D.      24   25   24   25
- Sem.tub.lin.Sert.c.
    GRADE 1 :    8     4     8     9
    GRADE 2 :    -     -     -     1
    GRADE 4 :    -     1     -     1
    GRADE 5 :    -     2     1     1

    TOTAL AFFECTED :    8     7     9    12
    MEAN SEVERITY  :    1.0  2.6  1.4  1.7
.....
- Vacuol.semin.tubules
    GRADE 1 :    7     5     4     3

    TOTAL AFFECTED :    7     5     4     3
    MEAN SEVERITY  :    1.0  1.0  1.0  1.0
.....
- Vacuol.sertoli cells
    GRADE 1 :    1     -     3     1
    GRADE 3 :    -     2     -     1

    TOTAL AFFECTED :    1     2     3     2
    MEAN SEVERITY  :    1.0  3.0  1.0  2.0
.....
- Degener.germ.epith.
    GRADE 1 :    1     1     -     1

    TOTAL AFFECTED :    1     1     -     1
    MEAN SEVERITY  :    1.0  1.0     -  1.0
.....
- Retained Spermatids
    GRADE 1 :    -     -     1     -

    TOTAL AFFECTED :    -     -     1     -
    MEAN SEVERITY  :    -     -  1.0     -
.....
- Multinucl.Giant Cel.
    GRADE 1 :    -     1     -     1

    TOTAL AFFECTED :    -     1     -     1
    MEAN SEVERITY  :    -  1.0     -  1.0
-----
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               MALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
TESTIS, RIGHT  CONT'D.   24   25   24   25
- Spermatic Granuloma
  GRADE 2 :      -     1     -     -
                TOTAL AFFECTED :      -     1     -     -
                MEAN SEVERITY :      -     2.0   -     -
-----
EPIDIDYMIS, RIGHT      :   24     3     2   25
- Oligospermia
  GRADE 3 :      -     -     1     -
  GRADE 4 :      -     2     -     1
                TOTAL AFFECTED :      -     2     1     1
                MEAN SEVERITY :      -     4.0   3.0   4.0
-----
- Exfol.Sperm.Sloughed
  GRADE 3 :      -     -     1     -
                TOTAL AFFECTED :      -     -     1     -
                MEAN SEVERITY :      -     -     3.0   -
-----
- Aspermia
  GRADE 5 :      -     -     -     1
                TOTAL AFFECTED :      -     -     -     1
                MEAN SEVERITY :      -     -     -     5.0
-----
- Inters.Mono.Cel.Agg.
  GRADE 1 :     1     -     -     -
  GRADE 2 :     1     -     -     1
                TOTAL AFFECTED :     2     -     -     1
                MEAN SEVERITY :   1.5     -     -     2.0
-----
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX      :                               MALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
LIVER          :   -   -   -   2
- Alt.cel.foci acid.
    GRADE 1    :   -   -   -   1
                TOTAL AFFECTED :   -   -   -   1
                MEAN SEVERITY  :   -   -   -   1.0
.....
- Alt.cel.foci clear
    GRADE 1    :   -   -   -   1
                TOTAL AFFECTED :   -   -   -   1
                MEAN SEVERITY  :   -   -   -   1.0
.....
- Mononuclear Cel.Agg.
    GRADE 1    :   -   -   -   1
    GRADE 2    :   -   -   -   1
                TOTAL AFFECTED :   -   -   -   2
                MEAN SEVERITY  :   -   -   -   1.5
.....
- Hepatocel.Hypertrop.
    GRADE 2    :   -   -   -   1
    GRADE 3    :   -   -   -   1
                TOTAL AFFECTED :   -   -   -   2
                MEAN SEVERITY  :   -   -   -   2.5
-----
KIDNEYS       :   1   -   1   4
- Dilated Pelvis
    GRADE 2    :   -   -   -   1
    GRADE 3    :   1   -   -   -
                TOTAL AFFECTED :   1   -   -   1
                MEAN SEVERITY  :  3.0   -   -   2.0
.....
    
```

Table: 68 (continued)

 SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS

| | | | | | |
|------------------------|---------|-----|----|-----|------|
| SEX : | | | | | MALE |
| DOSE GROUP: | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | 25 | 25 | 25 | 25 | |
| ----- | | | | | |
| KIDNEYS | CONT'D. | 1 | - | 1 | 4 |
| - Tubular Basophilia | | | | | |
| GRADE 1 : | | - | - | - | 2 |
| GRADE 2 : | | 1 | - | - | - |
| GRADE 3 : | | - | - | 1 | - |
| TOTAL AFFECTED : | | 1 | - | 1 | 2 |
| MEAN SEVERITY : | | 2.0 | - | 3.0 | 1.0 |
| | | | | | |
| - Peritubular Fibrosis | | | | | |
| GRADE 1 : | | - | - | - | 2 |
| GRADE 2 : | | 1 | - | - | - |
| GRADE 3 : | | - | - | 1 | - |
| TOTAL AFFECTED : | | 1 | - | 1 | 2 |
| MEAN SEVERITY : | | 2.0 | - | 3.0 | 1.0 |
| | | | | | |
| - Tubular Dilatation | | | | | |
| GRADE 2 : | | - | - | 1 | - |
| TOTAL AFFECTED : | | - | - | 1 | - |
| MEAN SEVERITY : | | - | - | 2.0 | - |
| | | | | | |
| - Aci.Glob.Cor.Tub.Ep. | | | | | |
| GRADE 2 : | | - | - | - | 1 |
| GRADE 3 : | | - | - | - | 1 |
| GRADE 4 : | | - | - | 1 | 1 |
| TOTAL AFFECTED : | | - | - | 1 | 3 |
| MEAN SEVERITY : | | - | - | 4.0 | 3.0 |
| | | | | | |
| - Deg./Necr.C.Sloughed | | | | | |
| GRADE 3 : | | - | - | 1 | - |
| TOTAL AFFECTED : | | - | - | 1 | - |
| MEAN SEVERITY : | | - | - | 3.0 | - |
| | | | | | |

Table: 68 (continued)

 SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0, INCL. DEATHS

| | | | | | |
|---------------------------|---------|-----|----|-----|------|
| SEX : | | | | | MALE |
| DOSE GROUP: | 1 | 2 | 3 | 4 | |
| NO. ANIMALS: | 25 | 25 | 25 | 25 | |
| ----- | | | | | |
| KIDNEYS | CONT'D. | 1 | - | 1 | 4 |
| - Inters. Mono. Cel. Agg. | | | | | |
| GRADE 1 : | | 1 | - | - | 2 |
| GRADE 2 : | | - | - | 1 | - |
| TOTAL AFFECTED : | | 1 | - | 1 | 2 |
| MEAN SEVERITY : | | 1.0 | - | 2.0 | 1.0 |
| ----- | | | | | |

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               FEMALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
ADRENAL GLANDS      :   25   -   -   24
- Cort.Cel.Hypertrophy
  GRADE 2 :         -   -   -   1
    TOTAL AFFECTED :         -   -   -   1
    MEAN SEVERITY  :         -   -   -   2.0
.....
- Inters.Mono.Cel.Agg.
  GRADE 1 :         -   -   -   5
    TOTAL AFFECTED :         -   -   -   5
    MEAN SEVERITY  :         -   -   -   1.0
.....
- Sinusoidal Ectasia
  GRADE 1 :        14   -   -   14
  GRADE 2 :         8   -   -   4
    TOTAL AFFECTED :        22   -   -   18
    MEAN SEVERITY  :        1.4   -   -   1.2
.....
- Cystic Degeneration
  GRADE 1 :         -   -   -   1
    TOTAL AFFECTED :         -   -   -   1
    MEAN SEVERITY  :         -   -   -   1.0
.....
- Lipomatosis
  GRADE 1 :         1   -   -   1
    TOTAL AFFECTED :         1   -   -   1
    MEAN SEVERITY  :        1.0   -   -   1.0
-----
PITUITARY GLAND    :   25   -   -   24
- Cyst(s)
  GRADE 1 :         1   -   -   1
    TOTAL AFFECTED :         1   -   -   1
    MEAN SEVERITY  :        1.0   -   -   1.0
-----
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               FEMALE
                DOSE GROUP:   1     2     3     4
                NO.ANIMALS:  25   25   25   25
-----
UTERUS           :   25    3    3    24
- Infold.end.epithel.
  GRADE 3       :    -    -    -    1
                TOTAL AFFECTED :    -    -    -    1
                MEAN SEVERITY  :    -    -    -    3.0
.....
- Yell.pigm.lad.macro.
  GRADE 1       :    3    -    -    3
  GRADE 2       :    5    1    -    8
  GRADE 3       :    2    -    -    2
                TOTAL AFFECTED :   10    1    -   13
                MEAN SEVERITY  :   1.9  2.0    -   1.9
.....
- Dilated Lumen
  GRADE 1       :    2    -    -    1
  GRADE 2       :    2    1    -    -
  GRADE 3       :    1    -    -    -
                TOTAL AFFECTED :    5    1    -    1
                MEAN SEVERITY  :   1.8  2.0    -   1.0
.....
- Mineralization
  GRADE 1       :    1    -    -    -
                TOTAL AFFECTED :    1    -    -    -
                MEAN SEVERITY  :   1.0    -    -    -
-----
VAGINA           :   25    3    3    24
- Mucific.Vagin.Epith.
  GRADE 2       :    1    1    -    2
  GRADE 3       :    1    -    -    1
  GRADE 4       :    -    -    -    1
                TOTAL AFFECTED :    2    1    -    4
                MEAN SEVERITY  :   2.5  2.0    -   2.8
.....
    
```

Table: 68 (continued)

```

-----
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-----
                SEX           :                               FEMALE
                DOSE GROUP:    1     2     3     4
                NO.ANIMALS:    25   25   25   25
-----
VAGINA          CONT'D.      25    3    3    24
- Epithel.Cel.Hyperpl.
                GRADE 2 :     -    1    -    -
                GRADE 3 :     1    -    -    -

                TOTAL AFFECTED :     1    1    -    -
                MEAN SEVERITY :    3.0  2.0  -    -
-----
    
```

Table: 69

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29302
.....

TESTES
- 01: REDUCED IN SIZE, SOFT. - no macro/micro correlation
EPIDIDYMIDES
- 01: REDUCED IN SIZE. - no macro/micro correlation
.....

ANIMAL NO: B29303
.....

TESTES
- 01: LEFT, REDUCED IN SIZE. - NOT SUBMITTED FOR EXAMINATION.
EPIDIDYMIDES
- 01: LEFT, REDUCED IN SIZE. - NOT SUBMITTED FOR EXAMINATION.
.....

ANIMAL NO: B29304
.....

KIDNEYS
- 01: PALENESS. - NOT SPECIFIED.
SPLEEN
- 01: REDUCED IN SIZE. - NOT SPECIFIED.
.....

ANIMAL NO: B29314
.....

SPLEEN
- 01: ENLARGED. - Lymphoid cell hyperplasia, grade 2
.....

ANIMAL NO: B29315
.....

KIDNEYS
- 01: RIGHT: DILATED PELVIS. - Dilated pelvis, unilateral, grade 3.
.....

Table: 69 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 1, MALE |
|---|-----------------------------------|--------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | |
| | | ANIMAL NO: B29320 |
| | | |
| THYMUS | | |
| - 01: FOCI REDDISH/PURPLISH, SEVERAL, UP TO 0.1 CM IN DIAMETER. | - Capillary hemorrhage, grade 3. | |
| | | |

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29702
.....

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - Proestrus, residual morphology of
pseudo-pregnancy.

ADIPOSE TISSUE

- 01: OVARIAN REGION, NODULE - Fat necrosis, grade 2.
YELLOWISH, APPROX 0.5 CM IN
DIAMETER, (A).
.....

ANIMAL NO: B29703
.....

ILEUM

- 01: MUCOSA: WHITISH COLOR. - NOTHING ABNORMAL DISCOVERED.
.....

ANIMAL NO: B29706
.....

ADRENAL GLANDS

- 01: LEFT: FOCUS BROWNISH/BLACKISH, - NOTHING ABNORMAL DISCOVERED.
APPROX 0.2 CM IN DIAMETER.
.....

ANIMAL NO: B29722
.....

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - Proestrus.
.....

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 2, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29328
.....

THYMUS

- 01: RIGHT LOBE: REDUCED IN SIZE. - NOT SPECIFIED.
.....

ANIMAL NO: B29333
.....

TESTIS, RIGHT

FDG.01, TESTES

- Reduced number of tailed

FDG.01, TESTES

- Reduced number of tailed

EPIDIDYMIS, RIGHT

FDG.01, EPIDIDYMIDES

- Oligospermia, grade 4.

TESTES

- 01: SOFT, REDUCED IN SIZE.

- SEE UNDER: TESTIS, RIGHT.

EPIDIDYMIDES

- 01: REDUCED IN SIZE.
.....

- SEE UNDER: EPIDIDYMIS, RIGHT.
.....

ANIMAL NO: B29340
.....

TESTIS, RIGHT

FDG.01, TESTES

- Seminiferous tubules lined by

FDG.01, TESTES

- Seminiferous tubules lined by

TESTES

- 01: RIGHT: TRANSLUCENT ASPECT.

- SEE UNDER: TESTIS, RIGHT.

EPIDIDYMIDES

- 01: RIGHT: REDUCED IN SIZE.
.....

- NOT SUBMITTED FOR EXAMINATION.
.....

ANIMAL NO: B29341
.....

ADRENAL GLANDS

- 01: RIGHT: REDUCED IN SIZE.

- NOTHING ABNORMAL DISCOVERED.

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 2, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

TESTES

- 01: LEFT: ENLARGED. - NOT SUBMITTED FOR EXAMINATION.

.....

ANIMAL NO: B29346

KIDNEYS

- 01: IRREGULAR COLOR. - NOT SPECIFIED.

.....

ANIMAL NO: B29350

TESTIS, RIGHT

FDG.01, TESTES

- Reduced number of tailed

FDG.01, TESTES

- Reduced number of tailed

EPIDIDYMIS, RIGHT

FDG.01, EPIDIDYMIDES

- Oligospermia, grade 4.

TESTES

- 01: REDUCED IN SIZE.

- SEE UNDER: TESTIS, RIGHT.

EPIDIDYMIDES

- 01: REDUCED IN SIZE, TRANSLUCENT ASPECT.

- SEE UNDER: EPIDIDYMIS, RIGHT.

.....

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 2, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29727

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - NOT SPECIFIED.

ANIMAL NO: B29738

THYROID GLANDS

- 01: LEFT: ENLARGED. - NOTHING ABNORMAL DISCOVERED.

ANIMAL NO: B29739

ILEUM

- 01: DISTENDED WITH GAS. - NOTHING ABNORMAL DISCOVERED.

ANIMAL NO: B29747

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - NOT SPECIFIED.

Table: 69 (continued)

| ----- | |
|--|--|
| CORRELATION TABLE: NECROPSY - MICROSCOPY | |
| DOSE GROUP 3, MALE | |
| ----- | |
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING |
| | ANIMAL NO: B29354 |
| | |
| KIDNEYS | |
| - 01: PALENESS. | - NOT SPECIFIED. |
| | |
| | ANIMAL NO: B29357 |
| | |
| TESTIS, RIGHT | |
| FDG.01, TESTES | - Reduced number of tailed |
| FDG.01, TESTES | - Reduced number of tailed |
| EPIDIDYMIS, RIGHT | |
| FDG.01, EPIDIDYMIDES | - Oligospermia, grade 3. Exfoliated |
| FDG.01, EPIDIDYMIDES | - Oligospermia, grade 3. Exfoliated |
| TESTES | |
| - 01: REDUCED IN SIZE, SOFT. | - SEE UNDER: TESTIS, RIGHT. |
| EPIDIDYMIDES | |
| - 01: REDUCED IN SIZE. | - SEE UNDER: EPIDIDYMIS, RIGHT. |
| KIDNEYS | |
| - 01: PALENESS. | - Tubular basophilia, bilateral, grade 3. Peritubular fibrosis, bilateral, grade 3. Acidophilic globules in cortical tubular epithelium, bilateral, grade 4. Degenerated/necrotic cells sloughed in tubular lumens, bilateral, grade 3. Tubular dilatation, bilateral, grade 2. |
| | |

Table: 69 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 3, MALE |
|--|-----------------------------------|--------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29359 |
| | | |
| KIDNEYS | | |
| - 01: GREY/GREEN COLOR. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29363 |
| | | |
| KIDNEYS | | |
| - 01: RIGHT: DILATED PELVIS. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29369 |
| | | |
| KIDNEYS | | |
| - 01: PALENESS. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29370 |
| | | |
| KIDNEYS | | |
| - 01: IRREGULAR COLOR. | - NOT SPECIFIED. | |
| | | |
| | | ANIMAL NO: B29372 |
| | | |
| ADIPOSE TISSUE | | |
| - 01: PANCREATIC REGION, NODULE | - NOT SPECIFIED. | |
| REDDISH/PURPLISH, APPROX 0.4 | | |
| CM IN DIAMETER, (A). | | |
| | | |

Table: 69 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 3, MALE |
|--|-----------------------------------|--------------------|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | | ANIMAL NO: B29375 |
| LUNGS | | |
| - 01: DILATATION, FOAMY CONTENTS. | - NOT SPECIFIED. | |
| | | |

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 3, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29757

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - NOT SPECIFIED.

ANIMAL NO: B29771

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - NOT SPECIFIED.

ANIMAL NO: B29773

UTERUS

- 01: RIGHT HORN, BOTH HORNS: SEROUS - NOTHING ABNORMAL DISCOVERED.
CONTENTS.

Table: 69 (continued)

| CORRELATION TABLE: NECROPSY - MICROSCOPY | | DOSE GROUP 4, MALE |
|--|-----------------------------------|--|
| NECROPSY OBSERVATION | CORRESPONDING MICROSCOPIC FINDING | |
| | ANIMAL NO: B29381 | |
| TESTIS, RIGHT | | |
| FDG.01, TESTES | - | Reduced number of tailed |
| FDG.01, TESTES | - | Reduced number of tailed |
| EPIDIDYMIS, RIGHT | | |
| FDG.01, EPIDIDYMIDES | - | Aspermia, grade 5. |
| TESTES | | |
| - 01: SOFT, REDUCED IN SIZE. | - | SEE UNDER: TESTIS, RIGHT. |
| EPIDIDYMIDES | | |
| - 01: REDUCED IN SIZE. | - | SEE UNDER: EPIDIDYMIS, RIGHT. |
| | | |
| | ANIMAL NO: B29387 | |
| KIDNEYS | | |
| - 01: RIGHT: MASS GREYISH/WHITISH, APPROX 4.5 CM LONG, APPROX 3.5 CM WIDE, FIRM, HOMOGENOUS, NODULAR. | - | Nephroblastoma, bilateral, (malignant neoplasm). |
| - 02: LEFT: MASS GREYISH/WHITISH, APPROX 3 CM LONG, APPROX 2 CM WIDE, FIRM, HOMOGENOUS, NODULAR. | - | Nephroblastoma, bilateral, (malignant neoplasm). |
| - 03: LEFT: ENLARGED. | - | Nephroblastoma, bilateral, (malignant neoplasm). |
| SPLEEN | | |
| - 01: ENLARGED. | - | Lymphoid cell hyperplasia, grade 2. Extramedullary hematopoiesis, grade 2. |
| URINARY BLADDER | | |
| - 01: MUCOSA: THICKENED. | - | NOTHING ABNORMAL DISCOVERED. |
| | | |

Table: 69 (continued)

 CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 4, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29390

LIVER
 - 01: ENLARGED. - Hepatocellular hypertrophy,
 centri-lobular, grade 2.

ANIMAL NO: B29391

TESTIS, RIGHT
 FDG.01, TESTES - Reduced number of tailed
 FDG.01, TESTES - Reduced number of tailed
 EPIDIDYMIS, RIGHT
 FDG.01, EPIDIDYMIDES - Oligospermia, grade 4.
 TESTES
 - 01: RIGHT: REDUCED IN SIZE, SOFT. - SEE UNDER: TESTIS, RIGHT.
 EPIDIDYMIDES
 - 01: RIGHT: REDUCED IN SIZE. - SEE UNDER: EPIDIDYMIS, RIGHT.
 KIDNEYS
 - 01: IRREGULAR COLOR. - Acidophilic globules in cortical
 tubular epithelium,
 bilateral, grade 4.

ANIMAL NO: B29398

TESTES
 - 01: LEFT: TRANSLUCENT ASPECT. - NOT SUBMITTED FOR EXAMINATION.
 EPIDIDYMIDES
 - 01: LEFT: REDUCED IN SIZE,
 TRANSLUCENT ASPECT. - NOT SUBMITTED FOR EXAMINATION.
 KIDNEYS
 - 01: RIGHT: DILATED PELVIS. - Dilated pelvis, unilateral, grade
 2.

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 4, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29399
.....

LIVER

- 01: ENLARGED, ACCENTUATED LOBULAR PATTERN. - Hepatocellular hypertrophy, centri-lobular, grade 3.

KIDNEYS

- 01: GREY/GREEN COLOR. - Acidophilic globules in cortical tubular epithelium, bilateral, grade 3.
.....

Table: 69 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 4, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: B29776
.....

UTERUS

- 01: BOTH HORNS: SEROUS CONTENTS. - Proestrus, with morphology of
previous pseudo-pregnancy.
.....

ANIMAL NO: B29777
.....

GENERAL OBSERVATION

- 01: DIED AFTER TREATMENT. - NOT SPECIFIED.
.....

ANIMAL NO: B29785
.....

PALPABLE MASSES

- 01: MASS WHITISH, APPROX 1.5 CM - Mammary Fibroadenoma, (benign
LONG, APPROX 1.5 CM WIDE, neoplasm).
FIRM, HOMOGENEOUS.
.....

ANIMAL NO: B29789
.....

GENERAL OBSERVATION

- 01: CLINICAL OBSERVATIONS NOT SEEN - NOT SPECIFIED.
AT NECROPSY, NECROSED TAIL.
.....

Table 70

Summary table - F1 parents

**Total number of primordial follicles counted for the two ovaries
Number of animals with up to ten or a multiple of ten primordial follicles**

| Dose-level (mg/kg/day) | 0 | 1000 |
|--|---------|---------|
| $0 \leq n \leq 10$ | 5 / 25 | 9 / 24 |
| $10 < n \leq 20$ | 13 / 25 | 9 / 24 |
| $20 < n \leq 30$ | 2 / 25 | 4 / 24 |
| $30 < n \leq 40$ | 4 / 25 | 1 / 24 |
| $40 < n \leq 50$ | 1 / 25 | 0 / 24 |
| $50 < n \leq 60$ | 0 / 25 | 1 / 24 |
| Total number of animals | 25 / 25 | 24 / 24 |
| Number of animals with up to 60 primordial follicles | 25 / 25 | 23 / 24 |

Table 71

Summary table - F1 parents

**Total number of growing follicles counted for the two ovaries
Number of animals with up to three or a multiple of three growing follicles**

| Dose-level (mg/kg/day) | 0 | 1000 |
|---|---------|---------|
| $0 \leq n \leq 3$ | 17 / 25 | 20 / 24 |
| $3 < n \leq 6$ | 6 / 25 | 3 / 24 |
| $6 < n \leq 9$ | 1 / 25 | 1 / 24 |
| $9 < n \leq 12$ | 1 / 25 | 0 / 24 |
| Total number of animals | 25 / 25 | 24 / 24 |
| Number of animals with up to 12 growing follicles | 23 / 25 | 23 / 24 |

Table: 72

F2 GENERATION
CLINICAL SIGNS (Summary table/Males)

MALES

| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--|----|-----|-----|------|
| Mortality | | | | |
| FINAL SACRIFICE | 25 | 25 | 25 | 25 |
| General aspect | | | | |
| ROUND BACK | 0 | 0 | 0 | 1 |
| PILOERECTOR | 0 | 0 | 0 | 1 |
| Secretion/Excretion | | | | |
| PTIALISM immediately post-dosing | 2 | 8 | 4 | 13 |
| Miscellaneous | | | | |
| ABNORMAL GROWTH OF TEETH (cut regular) | 0 | 0 | 0 | 1 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 23 | 17 | 21 | 12 |

Table: 73

F2 GENERATION

CLINICAL SIGNS (Summary table/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|-----------------------------------|----|-----|-----|------|
| Mortality | | | | |
| FINAL SACRIFICE | 24 | 25 | 25 | 25 |
| FOUND DEAD (after treatment) | 1 | 0 | 0 | 0 |
| Secretion/Excretion | | | | |
| PITYALISM immediately post-dosing | 0 | 2 | 3 | 11 |
| Normal | | | | |
| NO REMARKABLE OBSERVATIONS | 25 | 23 | 22 | 14 |

Table: 74

F2 GENERATION
BODY WEIGHTS (Mean values/Grams/Males)

MALES

| | | Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------|------|------------------|-------|-----|-----|------|
| Day 1 | MEAN | | 54 d | 57 | 54 | 55 |
| | S.D. | | 5 | 5 | 7 | 5 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 | MEAN | | 92 d | 95 | 92 | 91 |
| | S.D. | | 7 | 7 | 10 | 12 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 | MEAN | | 148 d | 152 | 143 | 148 |
| | S.D. | | 11 | 11 | 16 | 19 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 | MEAN | | 211 d | 216 | 201 | 208 |
| | S.D. | | 15 | 16 | 24 | 25 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table: 75

F2 GENERATION
BODY WEIGHT CHANGE (Mean values/Grams/Males)

MALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|-------|-------|-------|
| Day 1 TO 8 | MEAN | 38 d | 38 | 38 | 37 |
| | S.D. | 3 | 4 | 5 | 8 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 71.7 | 66.5 | 71.1 | 66.8 |
| Day 8 TO 15 | MEAN | 56 d | 58 | 51* | 56 |
| | S.D. | 6 | 5 | 9 | 8 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 61.4 | 61.1 | 55.7 | 61.7 |
| Day 15 TO 22 | MEAN | 62 d | 64 | 58 | 61 |
| | S.D. | 6 | 6 | 13 | 8 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 42.2 | 41.8 | 40.8 | 41.5 |
| Day 1 TO 22 | MEAN | 157 d | 159 | 147 | 154 |
| | S.D. | 13 | 13 | 22 | 21 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 294.9 | 280.5 | 276.4 | 280.7 |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05

Table: 76

F2 GENERATION

BODY WEIGHTS (Mean values/Grams/Females/Premating period)

FEMALES

| | | Dose (mg/kg/day) | 0 | 250 | 500 | 1000 |
|--------|------|------------------|-------|-----|-----|------|
| Day 1 | MEAN | | 52 d | 53 | 52 | 52 |
| | S.D. | | 5 | 5 | 7 | 4 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 | MEAN | | 86 d | 86 | 85 | 84 |
| | S.D. | | 7 | 7 | 10 | 7 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 | MEAN | | 130 d | 129 | 127 | 127 |
| | S.D. | | 10 | 12 | 15 | 10 |
| | N | | 25 | 25 | 25 | 25 |
| Day 22 | MEAN | | 166 d | 164 | 162 | 160 |
| | S.D. | | 14 | 14 | 15 | 13 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d-ANOVA + Dunnett-test

Table: 77

F2 GENERATION

BODY WEIGHT CHANGE (Mean values/Grams/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---------------------|-------|-------|-------|-------|-------|
| Day 1 TO 8 | MEAN | 34 d | 33 | 33 | 32 |
| | S.D. | 4 | 3 | 5 | 4 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 65.2 | 61.6 | 63.6 | 62.2 |
| Day 8 TO 15 | MEAN | 44 d | 43 | 42 | 43 |
| | S.D. | 5 | 8 | 6 | 5 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 50.9 | 49.5 | 48.9 | 50.8 |
| Day 15 TO 22 | MEAN | 36 d | 36 | 35 | 33 |
| | S.D. | 6 | 5 | 6 | 6 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 27.5 | 27.8 | 28.2 | 26.3 |
| Day 1 TO 22 | MEAN | 114 d | 111 | 110 | 108 |
| | S.D. | 12 | 12 | 11 | 12 |
| | N | 25 | 25 | 25 | 25 |
| mean percent change | MEAN% | 218.4 | 208.9 | 212.4 | 209.4 |

Statistical key: d=ANOVA + Dunnett-test

Table: 78

F2 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Males)

MALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|------|------|-----|-----|------|
| Day 1 TO 8 | MEAN | 14 d | 16** | 15 | 15 | |
| | S.D. | 2 | 3 | 1 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 8 TO 15 | MEAN | 19 d | 19 | 18 | 19 | |
| | S.D. | 2 | 2 | 2 | 2 | |
| | N | 25 | 25 | 25 | 25 | |
| Day 15 TO 22 | MEAN | 25 d | 25 | 22* | 25 | |
| | S.D. | 2 | 2 | 4 | 3 | |
| | N | 25 | 25 | 25 | 25 | |

Statistical key: d=ANOVA + Dunnett-test * = p<0.05 ** = p<0.01

Table: 79

F2 GENERATION

FOOD CONSUMPTION (Mean values/Grams per day/Females/Premating period)

FEMALES

| Dose (mg/kg/day) | | | 0 | 250 | 500 | 1000 |
|------------------|------|--|------|-----|-----|------|
| Day 1 TO 8 | MEAN | | 13 d | 14 | 13 | 14 |
| | S.D. | | 1 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |
| Day 8 TO 15 | MEAN | | 17 d | 16 | 16 | 16 |
| | S.D. | | 1 | 2 | 2 | 1 |
| | N | | 25 | 25 | 25 | 25 |
| Day 15 TO 22 | MEAN | | 19 d | 19 | 19 | 19 |
| | S.D. | | 2 | 2 | 2 | 2 |
| | N | | 25 | 25 | 25 | 25 |

Statistical key: d=ANOVA + Dunnett-test

Table 80

F 2 GENERATION
SUMMARY OF CLEAVAGE OF THE BALANOPREPUTIAL GLAND

Sex: male

| | Dose-level (mg/kg/day) | | | |
|------------------------|------------------------|-------|-------|-------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Mean age of appearance | 36 | 35 | 35 | 36 |
| SD | 2 | 1 | 2 | 3 |
| Mean body weight on | | | | |
| positive days (grams) | 148.3 | 140.0 | 139.8 | 147.9 |
| SD | 21.5 | 11.0 | 14.0 | 16.1 |

Table 81

**F 2 GENERATION
SUMMARY OF VAGINAL OPENING**

Sex: female

| | Dose-level (mg/kg/day) | | | |
|------------------------|------------------------|-------|-------|-------|
| | 0 | 250 | 500 | 1000 |
| n | 25 | 25 | 25 | 25 |
| Mean age of appearance | 35 | 34 | 34 | 33 |
| SD | 3 | 2 | 4 | 2 |
| Mean body weight on | | | | |
| positive days (grams) | 124.1 | 119.0 | 112.2 | 109.9 |
| SD | 19.4 | 17.2 | 18.0 | 13.8 |

Table: 82

F2 GENERATION
SUMMARY OF NECROPSY OBSERVATIONS

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|--------------------------------|---|-----|-----|-----|------|
| MALES | N | 25 | 25 | 25 | 25 |
| KIDNEY | N | 1 | 2 | 2 | 1 |
| KIDNEY: DILATED PELVIS | N | 1 f | 2 | 2 | 1 |
| | % | 4.0 | 8.0 | 8.0 | 4.0 |
| INTESTINES | N | 0 | 1 | 0 | 0 |
| INTESTINES: DISTENDED WITH GAS | N | 0 f | 1 | 0 | 0 |
| | % | 0.0 | 4.0 | 0.0 | 0.0 |
| NO REMARKABLE OBSERVATIONS | | 24 | 22 | 23 | 24 |

Statistical key: f=Fishers exact test

Table: 83

F2 GENERATION
SUMMARY OF NECROPSY OBSERVATIONS

| Dose (mg/kg/day) | | 0 | 250 | 500 | 1000 |
|---|---|------|-----|------|------|
| FEMALES | N | 25 | 25 | 25 | 25 |
| TRACHEA | N | 1 | 0 | 0 | 0 |
| TRACHEA: FOAMY CONTENTS | N | 1 f | 0 | 0 | 0 |
| | % | 4.0 | 0.0 | 0.0 | 0.0 |
| LUNGS | N | 1 | 0 | 0 | 0 |
| LUNG: FOAMY CONTENTS | N | 1 f | 0 | 0 | 0 |
| | % | 4.0 | 0.0 | 0.0 | 0.0 |
| LUNG: REDDISH COLOR | N | 1 f | 0 | 0 | 0 |
| | % | 4.0 | 0.0 | 0.0 | 0.0 |
| LIVER | N | 0 | 0 | 1 | 0 |
| LIVER: BROWNISH NODULE(S) | N | 0 f | 0 | 1 | 0 |
| | % | 0.0 | 0.0 | 4.0 | 0.0 |
| UTERUS | N | 3 | 2 | 5 | 3 |
| UTERUS: SEROUS CONTENTS IN UTERINE HORN | N | 3 f | 2 | 5 | 3 |
| | % | 12.0 | 8.0 | 20.0 | 12.0 |
| UTERUS: DILATATION OF UTERINE HORN | N | 2 f | 0 | 0 | 0 |
| | % | 8.0 | 0.0 | 0.0 | 0.0 |
| NO REMARKABLE OBSERVATIONS | | 21 | 23 | 20 | 22 |

Statistical key: f=Fishers exact test

APPENDICES

1. Analytical certificates of the test item

TOTAL FINA ELF

Raffinerie des Flandres

BULLETIN D'ANALYSE

Produit 2325 Client
C.I.T.
Destinataire Lib. produit ETBE
Moyen d'expédition ROUTE Destination EVREUX

| Prélèvement Lieu | Date | Détermination | Norme de référence | Unité de mesure | Résultat |
|---------------------|------|--------------------------|-----------------------|--------------------|----------|
| BAC | B026 | 308596 du 19/06/2003 | | | |
| | | PROPYLENE % | IFP-9412-1 | % pds | 0 |
| | | PROPANE | IFP-9412-1 | % pds | 0 |
| | | PROPADIENE | IFP-9412-1 | % pds | 0 |
| | | CYCLOPROPANE | IFP-9412-1 | % pds | 0 |
| | | ISOBUTANE | IFP-9412-1 | % pds | 0 |
| | | (ISO+1)BUTENE | IFP-9412-1 | % pds | 0 |
| | | BUTADIENE-1,3 | IFP-9412-1 | % pds | 0 |
| | | N-BUTANE | IFP-9412-1 | % pds | 0 |
| | | BUTENE-2-T | IFP-9412-1 | % pds | 0 |
| | | ETHANOL | IFP-9412-1 | % pds | 0 |
| | | 3-M-BUTENE-1 | IFP-9412-1 | % pds | 0 |
| | | I-PENTANE | IFP-9412-1 | % pds | 0 |
| | | PENTENE-1 | IFP-9412-1 | % pds | 0 |
| | | 2-M-BUTENE-1 | IFP-9412-1 | % pds | 0 |
| | | N-PENTANE | IFP-9412-1 | % pds | 0 |
| | | D.E.E. | IFP-9412-1 | % pds | 0 |
| | | T.B.A. | IFP-9412-1 | % pds | 0 |
| | | 2M2-BUTENE | IFP-9412-1 | % pds | 0 |
| | | E.T.B.E. | IFP-9412-1 | % pds | 99,97 |
| | | E.S.B.E. | IFP-9412-1 | % pds | 0 |
| | | M.T.B.E. | IFP-9412-1 | % pds | 0 |
| | | M.S.B.E. | IFP-9412-1 | % pds | 0 |
| | | S.B.A. | IFP-9412-1 | % pds | 0 |
| | | T-PENTENE-2 | IFP-9412-1 | % pds | 0 |
| | | E.T.A.E. | IFP-9412-1 | % pds | 0 |
| | | SOMME C4 | IFP-9412-1 | % pds | 0 |
| | | SOMME C5 ET + DIMERES | IFP-9412-1 | % pds | 0 |

PAGE 1 / 1

POUR TOTAL FINA ELF RAFFINERIE DES FLANDRES :

Le jeudi - 26/06/03

Raffinerie des Flandres - BP 79
59279 LOON PLAGE
Tél 03 28 26 35 00

TotalFinaElf France
Société Anonyme au capital de 623 728 035 EUR
Siège social : 24 cours Michelet
92800 Puteaux - France
SIREN : 542 034 921 RCS Nanterre

TOTAL FINA ELF

RAFFINAGE ET MARKETING
DIRECTION RECHERCHE
Centre de Recherche de SOLAIZE

MEMO

Destinataire / To : JP. GENNART (RM/RAF/HSE)

Expéditeur / From : C. CHAMBON

Tél. : 04-78-02-61-70

Fax : 04-78-02-60-89

Date : 26/09/2002

Copies :

Référence : RM/RAF/RECH/CRES/CMA - 2002/403 cc/cc

OBJET / Subject : Characterization of a purified ETBE sample
Service request # RM/RAF/RECH/CRES/CMA-2002/365
(Analyse Shift # B16272)

In order to study the toxicity of ETBE on the reproduction, the Research Center of Solaize has been requested to characterize a sample of purified ETBE. The initial ETBE, supplied by Feyzin Refinery was purified by a subcontractor.

Analysis was done by gas chromatography according to an internal method (reference MA0146). The compounds identification was realised by gas chromatography coupled with a mass spectrometer detector.

As this kind of analysis is not done frequently by the Research Center, the repeatability of the method applied to an ETBE sample is unknown. Also, measurement precision cannot be provided.

The results and the chromatogram obtained are presented in the following pages.

No EtOH presence has been detected by GC-MS : it means that if EtOH is present, its content level is lower than 0.01% mass/mass.

Accessibilité :
B.P. 22
69360 - SOLAIZE
(France)

CONFIDENTIEL

TOTALFINAELF

LIBRE

DOC/AQ 049 Rév. 1

RM/RAF/RECH/CRES/CMA - 2002/403 cc/cc

2/3

| Compounds | Content % m/m | Content % v/v |
|------------------------------------|------------------|------------------|
| n-butane | 0.03 | 0.05 |
| Isopentane | 0.43 | 0.53 |
| Isobutene + 1-butene | 0.01 | 0.01 |
| Trans-2-butene | 0.12 | 0.15 |
| Cis-2-butene | 0.25 | 0.30 |
| 3-méthyl-1-butene | 0.13 | 0.15 |
| C ₅ -olefin | 0.03 | 0.03 |
| C ₆ -olefin | 0.04 | 0.05 |
| C ₇ -olefin | 0.15 | 0.16 |
| C ₈ -olefin | 0.05 | 0.05 |
| C ₈ -olefin | 0.03 | 0.03 |
| ABT (Tertio butyl alcool) | 0.06 | 0.06 |
| ETBE | 98.37 min. | 98.14 |
| ESBE (Ethyl sec. butyl ether) | 0.15 | 0.15 |
| C ₇ Oxygenated compound | 0.04 | 0.04 |
| C ₇ Oxygenated compound | 0.08 | 0.08 |
| Unknown compound | 0.01 | |

It is important to notice that the results in % v/v have been obtained using average density for the unknown compounds (C8-olefins for example).

Analysis was realised by D. FADEL (+33-(0)4-78-02-62-63) and S. JACQUETTON (+33-(0)4-78-02-63-40).

C. CHAMBON

2. Determination of ETHYL TERTIARY BUTYL ETHER (ETBE) in the dosage forms

Determination of ETHYL TERTIARY BUTYL ETHER (ETBE) in the dosage forms

Principle

An aliquot of each dosage form was diluted then analyzed by Gas Liquid Chromatography with Flame Ionization Detection (FID). The concentration of the test item was determined from a calibration curve of peak area against concentration of ETHYL TERTIARY BUTYL ETHER (ETBE) in standard solutions (external standard calibration).

The analytical procedure used was validated according to CIT procedures before a previous study with the same test item (*CIT/Study No. 24168 RSR*). The validation data demonstrated the suitability of the method for analysis of the dosage form; a summary of validation results were presented in the *Study report No. 24168 RSR*.

Sample preparation

An aliquot (1 mL) of each dosage form under magnetic stirring was sampled (weighed accurately) in a tube and diluted ten-fold with diethyl ether. Subsequently, serial dilutions in diethyl ether were carried out to achieve target concentrations in a range 5-200 µg/mL of test item.

From the aliquot of dosage form sampled (weighed accurately), the real volume of the aliquot analyzed was determined (taking into account the density of each preparation) and the value of the first dilution factor was calculated.

Chromatographic conditions (GLC/ECD)

| | |
|-------------|---|
| Column | : DB5 (J&W Scientific) length = 30 m inner diameter = 0.53 mm film thickness = 5 µm |
| Vector gas | : Helium pressure = 10 psi flow-rate = 15 mL/min |
| Autosampler | : Varian 8100 or Varian CP-8400 |
| Injector | : temperature = 250°C split mode injection leak flow rate = 150 mL/min (split ratio = 1/10) injected volume = 2 µL |
| Detector | : Flame Ionization Detection temperature = 300°C Air flow rate = 300 mL/min Hydrogen flow rate = 30 mL/min make-up flow rate (Helium) = 10 mL/min |
| Oven | : Varian 3400 or Varian CP-3800 |

Column temperature : initial temperature = 50°C (3 min)
final temperature = 200°C
ramp = 25°C/min

Data acquisition software : Multichrom 2 (Fisons Instruments)

Retention time : ETHYL TERTIARY BUTYL ETHER (ETBE), approx 2 min

Analysis time : 3 min

Calibration curve

Peak areas were determined for standard solutions ranging from 5 µg/mL to 200 µg/mL of ETHYL TERTIARY BUTYL ETHER (ETBE). A calibration curve was obtained by linear regression analysis of peak areas against concentrations.

The regression analysis of the calibration data gave an equation of the following form:

$$Y = a X + b$$

where: Y = peak area of ETHYL TERTIARY BUTYL ETHER (ETBE) (µVs),
X = concentration of ETHYL TERTIARY BUTYL ETHER (ETBE) (mg/mL),
a = slope value
b = intercept

Assay

Diluted samples of dosage form were analyzed by Gas Liquid Chromatography with FID detection.

Each sample was diluted appropriately, and one injection was performed for each final dilution.

The ETHYL TERTIARY BUTYL ETHER (ETBE) peak area was determined for each sample and the concentration of the test item was calculated using the equation obtained from the calibration data.

All the results are expressed as mg/mL of ETHYL TERTIARY BUTYL ETHER (ETBE).

Results

The results are presented in Tables 1 to 5.

Table 1: HOMOGENEITY OF THE TEST ITEM (Batch No. S02-08-159-13/1) IN THE DOSAGE FORMS

| Nominal concentration (mg/mL) | Sampling level | Obtained concentration (mg/mL) | | | Mean (n=6) CV [1] |
|-------------------------------------|-------------------|-----------------------------------|---------|------|-------------------------|
| | | Assay 1 | Assay 2 | Mean | |
| 62.5 | Top | 56.2 | 59.4 | 57.8 | 60.3 |
| | Middle | 61.2 | 59.4 | 60.3 | CV = 4 % |
| | Bottom | 61.0 | 64.3 | 62.7 | -4% |
| 250 | Top | 196 | 230 | 213 | 228 |
| | Middle | 241 | 246 | 244 | CV = 8 % |
| | Bottom | 216 | 236 | 226 | -9% |

CV: coefficient of variation (100 x SD/mean)

[1] Deviation from nominal value (%)

Table 2: HOMOGENEITY OF THE TEST ITEM (Batch No. 308 596) IN THE DOSAGE FORMS

| Nominal concentration (mg/mL) | Sampling level | Obtained concentration (mg/mL) | | | Mean (n=6) CV [1] |
|-------------------------------|----------------|--------------------------------|---------|------|-------------------------|
| | | Assay 1 | Assay 2 | Mean | |
| 62.5 | Top | 51.2 | 61.4 | 56.3 | 62.4 |
| | Middle | 67.3 | 62.6 | 65.0 | CV = 10 % |
| | Bottom | 68.8 | 63.2 | 66.0 | 0% |
| 250 | Top | 208 | 261 | 235 | 240 |
| | Middle | 241 | 249 | 245 | CV = 7 % |
| | Bottom | 246 | 236 | 241 | -4% |

CV: coefficient of variation (100 x SD/mean)

[1] Deviation from nominal value (%)

**Table 3: STABILITY OF TEST ITEM (Batch No. 308 596)
IN THE DOSAGE FORMS STORED AT ROOM TEMPERATURE**

| Nominal concentration (mg/mL) | Sampling day | Obtained concentration (mg/mL) | | | Deviation from nominal value |
|-------------------------------|--|--------------------------------|---------|-------|------------------------------|
| | | Assay 1 | Assay 2 | Mean | |
| 62.5 | day 0 | | | 62.4* | 0% |
| | day 4 | 62.1 | 58.8 | 60.5 | -3% |
| | day 9 | 60.2 | 58.8 | 59.5 | -5% |
| | <i>Deviation on day 9 from initial value on day 0:</i> | | | | <i>-5%</i> |
| 250 | day 0 | | | 240* | -4% |
| | day 4 | 232 | 263 | 248 | -1% |
| | day 9 | 247 | 221 | 234 | -6% |
| | <i>Deviation on day 9 from initial value on day 0:</i> | | | | <i>-3%</i> |

*: Mean value of homogeneity at day 0

Table 4: CONCENTRATION OF THE TEST ITEM IN ADMINISTERED DOSAGE FORMS FOR THE F0 GENERATION

| Group | Nominal concentration (mg/mL) | Actual concentration (F0 generation) (mg/mL) | | | | | |
|----------|---------------------------------------|--|-------------|--------------|-------------|------------|------------|
| | | Week 1 | Week 2 | Week 6 | Week 10 | Week 14 | Week 18 |
| 1 | 0 | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ |
| | <i>Deviation from nominal value :</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> |
| | | [66.5-59.4]* | | [57.7-58.0]* | | | |
| 2 | 62.5 | 63.0 | 64.6 | 57.9 | 66.5 | 58.0 | 63.6 |
| | <i>Deviation from nominal value :</i> | <i>1%</i> | <i>3%</i> | <i>-7%</i> | <i>6%</i> | <i>-7%</i> | <i>2%</i> |
| | | [127-139]* | | | | | |
| 3 | 125 | 133 | 124 | 113 | 130 | 128 | 133 |
| | <i>Deviation from nominal value :</i> | <i>6%</i> | <i>-1%</i> | <i>-10%</i> | <i>4%</i> | <i>2%</i> | <i>6%</i> |
| | | [235-274]* | | [232-252]* | | | [258-264]* |
| 4 | 250 | 255 | 226 | 242 | 226 | 227 | 261 |
| | <i>Deviation from nominal value :</i> | <i>2%</i> | <i>-10%</i> | <i>-3%</i> | <i>-10%</i> | <i>-9%</i> | <i>4%</i> |

*: individual values of replicate determinations used to the mean value (written below)

BLQ: Below Limit of Quantification (< 0.1 mg/mL)

nc: not calculated

Table 5: CONCENTRATION OF THE TEST ITEM IN ADMINISTERED DOSAGE FORMS FOR THE F1 GENERATION

| Group | Nominal concentration (mg/mL) | Actual concentration (F1 generation) (mg/mL) | | | | |
|----------|---------------------------------------|--|-----------|------------|-----------|--------------|
| | | Week 1 | Week 6 | Week 9 | Week 13 | Week 17 |
| 1 | 0 | BLQ | BLQ | BLQ | BLQ | BLQ |
| | <i>Deviation from nominal value :</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> | <i>nc</i> |
| 2 | 62.5 | 63.6 | 64.9 | 57.7 | 59.6 | 65.3 |
| | <i>Deviation from nominal value :</i> | 2% | 4% | -8% | -5% | 4% |
| | | | | [117-121]* | | [64.2-66.4]* |
| 3 | 125 | 133 | 135 | 119 | 125 | 132 |
| | <i>Deviation from nominal value :</i> | 6% | 8% | -5% | 0% | 6% |
| | | [258-264]* | | | | [136-128]* |
| 4 | 250 | 261 | 237 | 265 | 234 | 233 |
| | <i>Deviation from nominal value :</i> | 4% | -5% | 6% | -6% | -7% |
| | | | | | | [227-238]* |

*: individual values of replicate determinations used to the mean value (written below)

BLQ: Below Limit of Quantification (< 0.1 mg/mL)

nc: not calculated

3. Diet formula

Ref: A04

COMPLETE DIET

RAT AND MOUSE MAINTENANCE DIET

Appearance: 15 mm diameter pellets or powder

Conditioning: 20 kg double paper bag with aluminium on the outside

Daily portion: Rat 15-25 g, Mouse 5-10 g, water *ad libitum*.

FORMULA %

| | |
|---|------|
| Cereals and cereal biproducts | 83.9 |
| Vegetable protein (soya bean meal, yeast) | 8 |
| Animal protein (fish) | 4 |
| Vitamin and mineral mixture | 4.1 |

AVERAGE ANALYSIS %

| | |
|---------------------------------|------|
| Calorific value (KCal/kg) | 2900 |
| Moisture | 12 |
| Proteins | 16 |
| Lipids | 3 |
| Carbohydrates (N.F.E.) | 60 |
| Fibre | 4 |
| Minerals (ash) | 5 |

| | MINERALS (calculated in mg/kg) | | |
|----------|--------------------------------|----------|-------|
| | Nat val. | CMV val. | Total |
| P | 5900 | 0 | 5900 |
| Ca | 3300 | 5000 | 8300 |
| K | 6700 | 0 | 6700 |
| Na | 900 | 1600 | 2500 |
| Mg | 1900 | 100 | 2000 |
| Mn | 20 | 40 | 60 |
| Fe | 90 | 150 | 240 |
| Cu | Traces | 15 | 16 |
| Zn | 40 | 45 | 85 |
| Co | T | 1.5 | 1.5 |
| I | 0.3 | 0 | 0.3 |

AMINO ACID VALUES

(calculated in mg/kg)

| | |
|------------------|------|
| Arginine | 9800 |
| Cystine | 2300 |
| Lysine | 7700 |
| Methionine | 2800 |
| Tryptophan | 1900 |
| Glycine | 8100 |

FATTY ACID VALUES

(calculated in mg/kg)

| | |
|------------------------|--------|
| Palmitic acid | 4000 |
| Palmitoleic acid | 600 |
| Stearic acid | Traces |
| Oleic acid | 6400 |
| Linoleic acid | 12400 |
| Linolenic acid | 90 |

| | VITAMINS (calculated per kg) | | |
|-------------|------------------------------|----------|---------|
| | Nat val. | CMV val. | Total |
| Vitamin A | Traces | 7500 IU | 7500 IU |
| Vitamin D3 | Traces | 1000 IU | 1000 IU |
| Vitamin B1 | 6 mg | 1 mg | 7 mg |
| Vitamin B2 | 2 mg | 4.5 mg | 6.5 mg |
| Vitamin B3 | 10 mg | 6.5 mg | 16.5 mg |
| Vitamin B6 | 1.3 mg | 1.3 mg | 2.6 mg |
| Vitamin B12 | 0.01 mg | 0.01 mg | 0.02 mg |
| Vitamin E | 15 mg | 15 mg | 30 mg |
| Vitamin K3 | 0.25 mg | 2.25 mg | 2.5 mg |
| Vitamin PP | 60 mg | 15 mg | 75 mg |
| Folic acid | 0.5 mg | 0 mg | 0.5 mg |
| Biotin | 0.04 mg | 0 mg | 0.04 mg |
| Choline | 1200 mg | 400 mg | 1600 mg |

Available under quality "Control Ref.: A04 C "

SAFE, 7 rue Galliéni, Villemoisson, 91360 Epinay-sur-Orge

Tel: 01.69.04.03.57 - Fax: 01.69.04.81.97

(Ref. Doc. UAR: 2000)

4. F0 generation - clinical history (individual findings/males)

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|--|---|--|
| B29201 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29202 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29203 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29204 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29205 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29206 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29207 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29208 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29209 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29210 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29211 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29212 | Normal Mortality Secretion/Excretion Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing AREA OF HAIR LOSS ON HINDLIMB, R AREA OF HAIR LOSS ON FORELIMB, B AREA OF HAIR LOSS ON FORELIMB, R | 1 to 13, 15 to 16, 18, 20, 22 to 82 120 14 17, 19, 21 83 to end 83 to 118 119 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|--|--|--|
| B29213 | Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B AREA OF HAIR LOSS ON ABDOMEN | 1 to 65, 95 to end 120 84 to 94 66 to 94 |
| B29214 | Normal Mortality Secretion/Excretion Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE CHROMODACRYORRHEA AREA OF HAIR LOSS ON FORELIMB, B | 1 to 65, 72 to 79 120 66 to 71 80 to end |
| B29215 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29216 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29217 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29218 | Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 1 to 83, 95 to 118 120 84 to 94, 119 to end |
| B29219 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29220 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29221 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 1 to 20, 22 to 70, 72 to 80, 82 to 119, 121 121 71, 81, 120 21 |
| B29222 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE REGURGITATION | 1 to 75, 79 to end 121 76 to 78 |
| B29223 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|------------------------------------|--|---------------------------------------|
| B29223 (CONTINUED) Mortality | FINAL SACRIFICE | 121 |
| B29224 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 121 |
| B29225 Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 1 to 82, 95 to end 121 83 to 94 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 250 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|---|
| B29226 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29227 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29228 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29229 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 20, 22 to 80, 92 to end 117 21, 81 to 91 |
| B29230 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 80, 92 to end 117 81 to 91 |
| B29231 | Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B AREA OF HAIR LOSS ON ABDOMEN | 1 to 64 117 65 to end 77 to end |
| B29232 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 9, 12, 14 to 20, 22 to end 117 10 to 11, 13, 21 |
| B29233 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 13, 15 to 19, 21 to end 117 14, 20 |
| B29234 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 1 to 13, 15 to 16, 18 to 65, 67 to end 117 14, 66 17 |
| B29235 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29236 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 250 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|--|
| B29237 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29238 | Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE AREA OF HAIR LOSS ON HINDLIMB, B AREA OF HAIR LOSS ON FORELIMB, B | 1 to 58 120 59 to 60 61 to end |
| B29239 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29240 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29241 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29242 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29243 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29244 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 13, 15 to 65, 67 to end 120 14, 66 |
| B29245 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 120 |
| B29246 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 121 |
| B29247 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 1 to 9, 11, 13 to 14, 16 to end 121 10, 12 15 |
| B29248 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 121 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 250 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|---------------------|--|-----------------|
| B29249 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 121 |
| B29250 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 121 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|--|---|--|
| B29251 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 1 to 16, 18 to 71, 74 to 79, 92 to end 117 72 to 73, 80 to 91 17 |
| B29252 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 80, 96 to end 117 81 to 95 |
| B29253 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 79, 81 to end 117 80 |
| B29254 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 9, 11 to 13, 15 to 58, 64 to 66, 68 to 79, 83 to end 117 10, 14, 59 to 63, 67, 80 to 82 |
| B29255 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29256 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 1 to end 117 |
| B29257 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 80, 96 to end 117 71, 81 to 95 |
| B29258 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 1 to 12, 15, 17 to 19, 21 to 33, 35 to 58, 64 to 66, 68 to 79, 83 to end 117 13 to 14, 20, 34, 59 to 63, 67, 80 to 82 16 |
| B29259 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 1 to 13, 15 to 92, 96 to end 117 14, 93 to 95 |
| B29260 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 12, 15 to 58, 64 to 92, 96 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|---|--|
| B29260 (CONTINUED) | | |
| Mortality | FINAL SACRIFICE | 117 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 13 to 14, 59 to 63, 93 to 95 |
| B29261 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 15, 17 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM 1 hour post-dosing | 16 |
| B29262 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 10, 12, 14 to 58, 67 to 90, 119 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 11, 13, 59 to 66, 93 to 95 |
| Skin | AREA OF HAIR LOSS ON FORELIMB, L | 91 to 118 |
| B29263 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 10, 14 to 19, 21 to 33, 35 to 58, 66 to 71, 73 to 79, 92, 96 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 11 to 13, 20, 34, 59 to 65, 72, 80 to 91, 93 to 95 |
| B29264 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to end |
| Mortality | FINAL SACRIFICE | 120 |
| B29265 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 12, 14 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 13 |
| B29266 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 12, 14 to 58, 67 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Breathing | LOUD BREATHING | 59 to 66 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 13, 59 to 66 |
| B29267 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 58, 67 to 79, 81 to 90, 120 |
| Mortality | FINAL SACRIFICE | 120 |
| General aspect | PILLOERECTION | 114 to 119 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 59 to 66, 80 |
| Miscellaneous | ABNORMAL GROWTH OF TEETH (cut regulary) | 91 to 117 |
| B29268 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 13, 15 to 65, 67 to 71, 73 to 92, 96 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|---|---|
| B29268 (CONTINUED) | | |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 14, 66, 72, 93 to 95 |
| B29269 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 10, 14 to 79, 83 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 11 to 13, 80 to 82 |
| B29270 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to end |
| Mortality | FINAL SACRIFICE | 120 |
| B29271 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 11, 14 to 15, 17 to 34, 67 to 80, 83 to end |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 12 to 13, 35 to 66, 81 to 82 16 |
| B29272 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 11, 14 to 16, 18 to 34, 66 to 71, 73 to 79, 96 to 119, 121 |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 12 to 13, 35 to 65, 72, 80 to 95, 120 17 |
| B29273 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 9, 11 to 34, 66 to 119, 121 |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 10, 35 to 65, 120 |
| B29274 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 92, 96 to 119, 121 |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 93 to 95, 120 |
| B29275 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to end |
| Mortality | FINAL SACRIFICE | 121 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|
| B29276 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing |
| | | 1 to 64, 66, 68 to 69, 72 to 91, 117 117 65, 67, 70 to 71, 92 to 116 67 |
| B29277 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing |
| | | 1 to 9, 11, 15 to 58, 66 to 67, 69 to 70, 75 to 79, 92, 96 to 101, 116 to end 117 10, 12 to 14, 59 to 65, 68, 71 to 74, 80 to 91, 93 to 95, 102 to 115 68 |
| B29278 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing |
| | | 1 to 12, 15 to 58, 66 to 67, 69 to 101, 116 to end 117 13 to 14, 59 to 65, 68, 102 to 115 68 |
| B29279 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 1 to 63, 65 to end 117 64 |
| B29280 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 1 to 68, 70 to end 117 69 |
| B29281 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing |
| | | 1 to 10, 12, 15 to 33, 35 to 58, 73, 116 to end 117 11, 13 to 14, 34, 59 to 72, 74 to 115 67 |
| B29282 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE |
| | | 1 to 10, 13, 15, 18 to 19, 21 to 58, 67 to 69, 71 to 80, 83 to end 117 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|--|---|
| B29282 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing | 11 to 12, 14, 20, 59 to 66, 70, 81 to 82 16 to 17, 20 |
| B29283 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 12, 14 to 33, 35 to 58, 66 to 82, 92 to 101, 117 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 117 13, 34, 59 to 65, 83 to 91, 102 to 116 |
| B29284 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 12, 14 to 19, 21 to 33, 35 to 58, 67 to 68, 70 to 72, 74 to 101, 117 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 117 13, 20, 34, 59 to 66, 69, 73, 102 to 116 |
| B29285 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to end 117 |
| B29286 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 11, 14 to 15, 17 to 34, 69 to 71, 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing PTYALISM 1 hour post-dosing PTYALISM 4 hour post-dosing | 120 12 to 13, 21, 35 to 68, 72 to 119 16, 67 16 |
| B29287 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 13, 15 to 58, 66 to 74, 83 to end 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 14, 59 to 65, 75 to 82 |
| B29288 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 9, 11 to 12, 14 to 20, 22 to 58, 66 to 71, 73 to 79, 83 to end 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 10, 13, 59 to 65, 72, 80 to 82 |
| B29289 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to end 120 |
| B29290 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 13, 15 to 58, 66 to 101, 116 to end 120 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|----------------------------------|--|
| B29290 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 14, 59 to 65, 102 to 115 |
| B29291 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 71, 78 to 101, 116, 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 120 |
| | | 72 to 77, 102 to 115, 117 to 119 |
| B29292 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 12, 14 to 34, 66 to 80, 83 to 101, 120 |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM | 59 |
| | PTYALISM immediately post-dosing | 13, 35 to 65, 81 to 82, 102 to 119 |
| B29293 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 9, 11 to 15, 17 to 20, 22 to 34, 66 to 71, 73 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM | 21, 35 to 65 |
| | SOILED UROGENITAL AREA | 72 |
| | PTYALISM immediately post-dosing | 10 |
| | PTYALISM 1 hour post-dosing | 16 |
| B29294 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 58, 66 to 69, 71 to 74, 77 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 59 to 65, 70, 75 to 76 |
| B29295 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 12, 14 to 63, 65, 67 to 79, 92 to end |
| Mortality | FINAL SACRIFICE | 120 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 13, 64, 66, 80 to 91 |
| B29296 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 9, 11 to 12, 15 to 33, 35 to 63, 67 to 101, 116 to 119, 121 |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 10, 13 to 14, 34, 64 to 66, 102 to 115, 120 |
| B29297 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 13, 15, 17 to 68, 70 to 119, 121 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Males)

MALES Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|----------------------------------|--|
| B29297 (CONTINUED) | | |
| Mortality | FINAL SACRIFICE | 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 14, 69, 120 |
| | PTYALISM 1 hour post-dosing | 16 |
| B29298 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 19, 21 to 105, 107 to 119, 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 121 |
| | REGURGITATION | 20, 120 |
| | | 106 |
| B29299 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 92, 96 to 101, 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 121 |
| | | 93 to 95, 102 to 120 |
| B29300 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE | 1 to 12, 15 to 58, 66 to 79, 96 to 101, 116 to 119, 121 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 121 |
| | | 13 to 14, 59 to 65, 80 to 95, 102 to 115, 120 |

5. F0 generation - clinical history (individual findings/females/premating period)

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------|--|-------------------|
| B29601 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29602 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29603 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29604 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29605 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29606 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29607 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29608 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29609 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 9, 11 to 72 |
| B29610 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29611 | Normal Secretion/Excretion NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 77, 79 78 |
| B29612 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29613 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29614 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29615 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29616 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29617 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29618 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29619 | Normal Secretion/Excretion NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 72 73 |
| B29620 | Normal NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 77 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------|-------------------------------------|---------------|
| B29621 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29622 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 82 |
| B29623 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29624 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29625 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 250 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|---------------------------------------|--|------------------------------|
| B29626 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29627 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29628 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29629 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29630 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29631 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 12, 14 to 73 13 |
| B29632 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29633 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29634 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 84 |
| B29635 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29636 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29637 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29638 | Normal Secretion/Excretion Skin | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing AREA OF HAIR LOSS ON BACK | 1 to 9, 11 to 72 10 73 |
| B29639 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29640 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 72 |
| B29641 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29642 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 9, 11 to 74 10 |
| B29643 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 9, 11 to 73 10 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 250 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------|-------------------------------|---|
| B29644 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 1 to 13, 15 to 71 14 |
| B29645 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 71 |
| B29646 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 1 to 12, 14 to 72, 74 13, 73 |
| B29647 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 77 |
| B29648 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 71 |
| B29649 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 72 |
| B29650 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 71 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 500 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|---------------------|---|--------------------|
| B29651 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 65 |
| | Secretion/Excretion | CHROMODACRYORRHEA PTYALISM immediately post-dosing | 67 to 73 66, 73 |
| B29652 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 74 |
| B29653 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29654 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29655 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29656 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29657 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29658 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29659 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 78 |
| B29660 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 62 |
| | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 63 to 71 |
| B29661 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 53 |
| | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 54 to 77 |
| B29662 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 79 |
| | Secretion/Excretion | PTYALISM immediately post-dosing | 80 |
| B29663 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 61 |
| | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 62 to 74 |
| B29664 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 53 |
| | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 54 to 72 |
| B29665 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 62 |
| | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 63 to 71 |
| B29666 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29667 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 61 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|--------------------------------------|---|---------------|
| B29667 (CONTINUED) Skin | AREA OF HAIR LOSS ON FORELIMB, B | 62 to 74 |
| B29668 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29669 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29670 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29671 Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 72 73 |
| B29672 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29673 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29674 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29675 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 1000 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|-------------------------------|---|---|
| B29676 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 72 73 |
| B29677 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 73 |
| B29678 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 11, 14 to 63, 65 to 70, 72 12 to 13, 64, 71 |
| B29679 | Normal Skin | NO REMARKABLE CLINICAL OBSERVATIONS AREA OF HAIR LOSS ON FORELIMB, B | 1 to 62 63 to 71 |
| B29680 | Normal Skin | NO REMARKABLE CLINICAL OBSERVATIONS AREA OF HAIR LOSS ON HINDLIMB, R AREA OF HAIR LOSS ON HINDLIMB, B AREA OF HAIR LOSS ON FORELIMB, B | 1 to 44 45 to 62 63 to 71 54 to 71 |
| B29681 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29682 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29683 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 10, 12 to 65, 67 to 70, 72 to 74 11, 66, 71 |
| B29684 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 10, 12 to 66, 68 to 72, 74 11, 67, 73 |
| B29685 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 71 |
| B29686 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 10, 12 to 67, 69 to 72 11, 68 |
| B29687 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 58, 67 to 74 59 to 66 |
| B29688 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 11, 13 to 73 12 |
| B29689 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 72 73 to 74 |
| B29690 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 63, 65, 67 to 72 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Premating period)

FEMALES Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|----------------------------------|-------------------------------------|
| B29690 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 64, 66, 73 |
| B29691 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 73 |
| B29692 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 71 |
| B29693 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 64, 66 to 72 65 |
| B29694 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 73 |
| B29695 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 73 |
| B29696 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 73 74 |
| B29697 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 9, 12 to 73 10 to 11 |
| B29698 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 9, 11 to 73 10 |
| B29699 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 1 to 62 63 to 71 |
| B29700 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 1 to 78 |

6. F0 generation - clinical history (individual findings/females/pregnancy period)

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|--------------------------------------|---|--------------------------------|
| B29601 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29602 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29603 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29604 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29605 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 22 |
| B29606 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29607 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29608 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29609 Normal Skin | NO REMARKABLE CLINICAL OBSERVATIONS AREA OF HAIR LOSS ON FORELIMB, B AREA OF HAIR LOSS ON ABDOMEN | 0 to 9 11 to 21 10 to 21 |
| B29610 Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS REGURGITATION | 0, 4 to 21 1 to 3 |
| B29611 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29612 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29613 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29614 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29615 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29616 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29617 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29618 Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 20 0 |
| B29619 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to 20 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|-------------------------------------|---------------|
| B29619 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 |
| B29620 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 4 |
| Mortality | FINAL SACRIFICE (no delivery) | 29 |
| Skin | AREA OF HAIR LOSS ON HINDLIMB, B | 5 to end |
| B29621 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29622 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29623 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29624 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| Mortality | FINAL SACRIFICE (no delivery) | 27 |
| B29625 Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 250 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|-------------------------------|---|-------------------------------|
| B29626 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 15, 19 to 20 16 to 18 |
| B29627 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29628 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 5, 16 to 20 6 to 15 |
| B29629 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29630 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE (no delivery) | 0 to end 26 |
| B29631 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE (no delivery) | 0 to end 27 |
| B29632 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29633 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29634 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29635 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29636 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 16, 20 17 to 19 |
| B29637 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29638 | Skin | AREA OF HAIR LOSS ON BACK | 0 to 20 |
| B29639 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29640 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29641 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 20 |
| B29642 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 12, 15 to 20 13 to 14 |
| B29643 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 13, 15 to 20 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 250 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|----------------------------------|-------------------------------------|
| B29643 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 14 |
| B29644 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |
| B29645 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | Mortality | FINAL SACRIFICE (no delivery) |
| | | 0 to end 27 |
| B29646 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | Secretion/Excretion | PTYALISM immediately post-dosing |
| | | 0 to 4, 9 to 21 5 to 8 |
| B29647 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | Mortality | FINAL SACRIFICE (no delivery) |
| | | 0 to end 29 |
| B29648 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | Secretion/Excretion | PTYALISM immediately post-dosing |
| | | 0 to 15, 17 to 21 16 |
| B29649 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |
| B29650 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | Secretion/Excretion | REGURGITATION |
| | | 0, 2 to 20 1 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|
| B29651 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS CHROMODACRYORRHEA PTYALISM immediately post-dosing |
| | | 9 to 21 0 to 8 0, 3 to 4, 6 to 8 |
| B29652 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |
| B29653 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 0 to 7, 9 to 20 8 |
| B29654 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 0 to 1, 4 to 21 2 to 3 |
| B29655 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |
| B29656 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE (no delivery) PTYALISM immediately post-dosing |
| | | 0 to 18, 21 to end 27 19 to 20 |
| B29657 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |
| B29658 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 20 |
| B29659 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 3 to 20 0 to 2 |
| B29660 | Skin | AREA OF HAIR LOSS ON FORELIMB, B |
| | | 0 to 21 |
| B29661 | Skin | AREA OF HAIR LOSS ON FORELIMB, B |
| | | 0 to 20 |
| B29662 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing |
| | | 0, 6 to 11, 13 to 21 1 to 5, 12 |
| B29663 | Skin | AREA OF HAIR LOSS ON FORELIMB, B |
| | | 0 to 20 |
| B29664 | Skin | AREA OF HAIR LOSS ON FORELIMB, B |
| | | 0 to 20 |
| B29665 | Secretion/Excretion Skin | PTYALISM immediately post-dosing AREA OF HAIR LOSS ON FORELIMB, B |
| | | 8 to 10, 13 0 to 20 |
| B29666 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0, 3, 5 to 8 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|----------------------------------|---|
| B29666 (CONTINUED) | | |
| Mortality | FINAL SACRIFICE (no delivery) | 27 |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 2, 4, 9 to 10 |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 11 to end |
| B29667 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 0 to 19 |
| B29668 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| B29669 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 7, 11 to 20 0, 8 to 10 |
| B29670 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 8, 11 to 12, 15 to 21 9 to 10, 13 to 14 |
| B29671 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 1, 3 to 7, 9 to 20 2, 8 |
| B29672 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 0 to 11 12 to 21 |
| B29673 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Mortality | FINAL SACRIFICE (no delivery) | 0 to end 27 |
| B29674 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| B29675 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Skin | AREA OF HAIR LOSS ON FORELIMB, L | 0 to 11 12 to 20 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 1000 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|-------------------------------|---|---|
| B29676 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29677 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 5, 7, 11 to 20 6, 8 to 10 |
| B29678 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 3 to 19 0 to 2, 20 to 21 |
| B29679 | Skin | AREA OF HAIR LOSS ON FORELIMB, B | 0 to 21 |
| B29680 | Skin | AREA OF HAIR LOSS ON HINDLIMB, B AREA OF HAIR LOSS ON FORELIMB, B | 0 to 21 0 to 21 |
| B29681 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0, 2 to 4, 6 to 9, 12 to 21 1, 5, 10 to 11 |
| B29682 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 1 to 2, 4 to 8, 11 to 12, 20 0, 3, 9 to 10, 13 to 19, 21 |
| B29683 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0, 2 to 5, 12 to 17 1, 6 to 11, 18 to 21 |
| B29684 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 9, 12 to 17, 20 to 21 10 to 11, 18 to 19 |
| B29685 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 11, 13 to 21 12 |
| B29686 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 3, 10 to 20 4 to 9 |
| B29687 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 21 |
| B29688 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 4, 9 to 10, 14 to 18 5 to 8, 11 to 13, 19 to 21 |
| B29689 | Normal Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS PTYALISM immediately post-dosing | 0 to 1, 8 to 20 2 to 7 |
| B29690 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to 2, 9 to 20 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Pregnancy period)

Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|---|---|
| B29690 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 3 to 8, 21 |
| B29691 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 2, 9 to 21 3 to 8 |
| B29692 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 1 to 3, 7 to 20 0, 4 to 6 |
| B29693 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 6, 10 to 21 7 to 9 |
| B29694 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 0 to 8 9 to 21 |
| B29695 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 2, 13 to 21 3 to 12 |
| B29696 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 3 to 13 0 to 2 |
| Miscellaneous | MASS ON UPPER FORELIMB DORSAL left side 1 x 1 cm | 14 to 20 |
| B29697 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 2, 12 to 18 4 to 11, 19 to 21 |
| Skin | CUTANEOUS LESION ON ABDOMEN | 3 to 8 |
| B29698 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 5, 9 6 to 8, 11 to 12, 19 to 21 |
| Skin | AREA OF HAIR LOSS ON BACK | 10 to 21 |
| B29699 | Secretion/Excretion | PTYALISM immediately post-dosing |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 12 0 to 20 |
| B29700 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS |
| | | 0 to 21 |

7. F0 generation - clinical history (individual findings/females/lactation period)

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|---------------------|---|----------------------------|
| B29601 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 24 |
| B29602 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29603 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29604 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 24 |
| B29605 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29606 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29607 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29608 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29609 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B AREA OF HAIR LOSS ON ABDOMEN | 22 0 to end 0 to end |
| B29610 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29611 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29612 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29613 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29614 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 0 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------------------|--|----------------|
| B29614 (CONTINUED) Mortality | FINAL SACRIFICE | 25 |
| B29615 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29616 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29617 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29618 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29619 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29621 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29622 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29623 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29625 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 250 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|---------------------|-------------------------------------|---------------|
| B29626 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 1 to end |
| | Mortality | DECISION OF SACRIFICE | 8 |
| | | Dead litter | |
| | Secretion/Excretion | PTYALISM immediately post-dosing | 0 |
| B29627 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 25 |
| B29628 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 25 |
| B29629 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29632 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29633 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 25 |
| B29634 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29635 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29636 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29637 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29638 | Mortality | FINAL SACRIFICE | 25 |
| | Skin | AREA OF HAIR LOSS ON BACK | 0 to end |
| B29639 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 22 |
| B29640 | Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| | Mortality | FINAL SACRIFICE | 25 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 250 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|-------------------------------|--|----------------|
| B29641 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29642 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29643 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29644 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29646 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29648 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29649 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29650 Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 500 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|-------------------------------|
| B29651 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29652 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29653 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29654 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29655 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29657 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29658 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29659 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29660 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 22 0 to end |
| B29661 | Mortality Skin | DECISION OF SACRIFICE Dead litter AREA OF HAIR LOSS ON FORELIMB, B | 4 0 to end |
| B29662 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 0 to 17, 24 24 18 to 23 |
| B29663 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 25 0 to end |
| B29664 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 22 0 to end |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 500 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED | |
|---------|--|---|-------------------------------|
| B29665 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 22 0 to end |
| B29667 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29668 | Normal Mortality Pregnancy condition | NO REMARKABLE CLINICAL OBSERVATIONS DECISION OF SACRIFICE poor clinical condition of the litter BLOOD IN VAGINA | 0 to 1 2 2 |
| B29669 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29670 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 23 |
| B29671 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 0 to 20, 25 25 21 to 24 |
| B29672 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 23 0 to end |
| B29674 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 22 |
| B29675 | Normal Mortality Skin | NO REMARKABLE CLINICAL OBSERVATIONS DECISION OF SACRIFICE poor clinical condition of the litter AREA OF HAIR LOSS ON FORELIMB, L | 2 to end 3 0 to 1 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 1000 mg/kg/day

| ANIMAL# | | OBSERVATIONS | DAYS OBSERVED |
|---------|--|--|------------------------------|
| B29676 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29677 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29678 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 8 to end 25 0 to 7 |
| B29679 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B | 23 0 to end |
| B29680 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON HINDLIMB, B AREA OF HAIR LOSS ON FORELIMB, B | 23 0 to end 0 to end |
| B29681 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 0, 10 to end 23 1 to 9 |
| B29682 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 8 to end 23 0 to 7 |
| B29683 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing | 5 to end 25 0 to 4 |
| B29684 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |
| B29685 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 23 |
| B29686 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 23 |
| B29687 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE | 0 to end 25 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------|--|---|
| B29688 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 0 to 1, 6 to 23, 25 25 2 to 5, 24 |
| B29689 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 0 to 12, 14 to 15, 17 to end 25 13, 16 |
| B29690 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 6 to end 25 0 to 5 |
| B29691 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 0 to 7, 9 to 16, 23, 25 25 8, 17 to 22, 24 |
| B29692 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE |
| | | 0 to end 22 |
| B29693 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 0 to 8, 10 to end 25 9 |
| B29694 | Mortality Skin | FINAL SACRIFICE AREA OF HAIR LOSS ON FORELIMB, B |
| | | 25 0 to end |
| B29695 | Normal Mortality | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE |
| | | 0 to end 25 |
| B29696 | Mortality Miscellaneous | FINAL SACRIFICE MASS ON UPPER FORELIMB DORSAL left side 1 x 1 cm MASS ON UPPER FORELIMB DORSAL left side 2 x 1 cm |
| | | 25 0 to 10 11 to end |
| B29697 | Normal Mortality Secretion/Excretion | NO REMARKABLE CLINICAL OBSERVATIONS FINAL SACRIFICE PTYALISM immediately post-dosing |
| | | 7, 9 to 20, 25 25 0 to 6, 8, 21 to 24 |
| B29698 | Mortality | FINAL SACRIFICE |
| | | 25 |

F0 GENERATION

CLINICAL HISTORY (Individual findings/Females/Lactation period)

Dose: 1000 mg/kg/day

| ANIMAL# | OBSERVATIONS | DAYS OBSERVED |
|---------------------|-------------------------------------|---------------|
| B29698 (CONTINUED) | | |
| Secretion/Excretion | PTYALISM immediately post-dosing | 0 to 5 |
| Skin | AREA OF HAIR LOSS ON BACK | 0 to end |
| B29699 | | |
| Mortality | FINAL SACRIFICE | 22 |
| Skin | AREA OF HAIR LOSS ON FORELIMB, B | 0 to end |
| B29700 | | |
| Normal | NO REMARKABLE CLINICAL OBSERVATIONS | 0 to end |
| Mortality | FINAL SACRIFICE | 22 |

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On behalf of:

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ENI S.p.A.
Fortum Oil and Gas Oy
Lyondell Chemical Europe Inc.
Oxeno Olefinchemie GmbH
Repsol Petróleo, S.A.
TOTAL France S.A.

TEST ITEM

ETHYL TERTIARY BUTYL ETHER (ETBE)
CAS No. 637-92-3

STUDY TITLE

**TWO-GENERATION STUDY
(REPRODUCTION AND FERTILITY EFFECTS)
BY ORAL ROUTE (GAVAGE) IN RATS**

STUDY DIRECTOR

Wassila Gaoua

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Volume 2

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8. F0 generation - body weight (individual values/grams/males)

F0 GENERATION

BODY WEIGHTS (Individual values/Grams/Males)

MALES Dose: 0 mg/kg/day

| Animal No. | Day of STUDY | |
|------------|--------------|-----|
| | 113 | 120 |
| B29201 | 577 | - |
| B29202 | 600 | - |
| B29203 | 569 | - |
| B29204 | 711 | - |
| B29205 | 593 | - |
| B29206 | 642 | - |
| B29207 | 684 | - |
| B29208 | 617 | - |
| B29209 | 598 | - |
| B29210 | 601 | - |
| B29211 | 622 | 638 |
| B29212 | 546 | 557 |
| B29213 | 631 | 643 |
| B29214 | 547 | 545 |
| B29215 | 556 | 564 |
| B29216 | 540 | 549 |
| B29217 | 521 | 527 |
| B29218 | 640 | 648 |
| B29219 | 555 | 571 |
| B29220 | 678 | 697 |
| B29221 | 605 | 614 |
| B29222 | 586 | 596 |
| B29223 | 647 | 660 |
| B29224 | 632 | 646 |
| B29225 | 475 | 480 |
| MEAN | 599 | 596 |
| S.D. | 54 | 60 |
| N | 25 | 15 |

F0 GENERATION

BODY WEIGHTS (Individual values/Grams/Males)

MALES Dose: 250 mg/kg/day

| Animal No. | Day of STUDY | |
|------------|--------------|-----|
| | 113 | 120 |
| B29226 | 585 | - |
| B29227 | 569 | - |
| B29228 | 555 | - |
| B29229 | 596 | - |
| B29230 | 572 | - |
| B29231 | 694 | - |
| B29232 | 546 | - |
| B29233 | 607 | - |
| B29234 | 642 | - |
| B29235 | 693 | - |
| B29236 | 668 | 684 |
| B29237 | 575 | 587 |
| B29238 | 589 | 595 |
| B29239 | 571 | 584 |
| B29240 | 588 | 595 |
| B29241 | 578 | 585 |
| B29242 | 585 | 591 |
| B29243 | 607 | 614 |
| B29244 | 585 | 589 |
| B29245 | 611 | 617 |
| B29246 | 576 | 577 |
| B29247 | 563 | 574 |
| B29248 | 605 | 603 |
| B29249 | 618 | 619 |
| B29250 | 589 | 596 |
| MEAN | 599 | 601 |
| S.D. | 39 | 27 |
| N | 25 | 15 |

F0 GENERATION

BODY WEIGHTS (Individual values/Grams/Males)

MALES Dose: 500 mg/kg/day

| Animal No. | Day of STUDY | |
|------------|--------------|-----|
| | 113 | 120 |
| B29251 | 574 | - |
| B29252 | 561 | - |
| B29253 | 569 | - |
| B29254 | 671 | - |
| B29255 | 636 | - |
| B29256 | 542 | - |
| B29257 | 620 | - |
| B29258 | 556 | - |
| B29259 | 569 | - |
| B29260 | 640 | - |
| B29261 | 642 | 655 |
| B29262 | 609 | 614 |
| B29263 | 651 | 666 |
| B29264 | 586 | 600 |
| B29265 | 558 | 566 |
| B29266 | 471 | 471 |
| B29267 | 574 | 575 |
| B29268 | 645 | 647 |
| B29269 | 567 | 583 |
| B29270 | 607 | 620 |
| B29271 | 513 | 523 |
| B29272 | 709 | 703 |
| B29273 | 619 | 618 |
| B29274 | 517 | 513 |
| B29275 | 536 | 542 |
| MEAN | 590 | 593 |
| S.D. | 55 | 63 |
| N | 25 | 15 |

F0 GENERATION

BODY WEIGHTS (Individual values/Grams/Males)

MALES Dose: 1000 mg/kg/day

| Animal No. | Day of STUDY | |
|------------|--------------|-----|
| | 113 | 120 |
| B29276 | 507 | - |
| B29277 | 556 | - |
| B29278 | 663 | - |
| B29279 | 635 | - |
| B29280 | 610 | - |
| B29281 | 607 | - |
| B29282 | 581 | - |
| B29283 | 509 | - |
| B29284 | 582 | - |
| B29285 | 626 | - |
| B29286 | 577 | 577 |
| B29287 | 558 | 564 |
| B29288 | 537 | 542 |
| B29289 | 595 | 602 |
| B29290 | 592 | 593 |
| B29291 | 582 | 561 |
| B29292 | 650 | 665 |
| B29293 | 528 | 533 |
| B29294 | 538 | 543 |
| B29295 | 570 | 578 |
| B29296 | 564 | 570 |
| B29297 | 632 | 624 |
| B29298 | 545 | 558 |
| B29299 | 542 | 555 |
| B29300 | 535 | 538 |
| MEAN | 577 | 573 |
| S.D. | 43 | 36 |
| N | 25 | 15 |

9. F0 generation - body weight change (individual values/grams/males)

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/Grams/Males)

MALES Dose: 0 mg/kg/day

| ANIMAL# | Day OF STUDY | | |
|---------|--------------|------|-------|
| | 85-113 | 1-71 | 1-113 |
| B29201 | 36 | 328 | 386 |
| B29202 | 43 | 311 | 379 |
| B29203 | 46 | 311 | 372 |
| B29204 | 91 | 374 | 488 |
| B29205 | 77 | 295 | 393 |
| B29206 | 57 | 353 | 434 |
| B29207 | 80 | 369 | 488 |
| B29208 | 67 | 328 | 411 |
| B29209 | 65 | 298 | 393 |
| B29210 | 52 | 332 | 400 |
| B29211 | 90 | 340 | 433 |
| B29212 | 43 | 289 | 342 |
| B29213 | 59 | 347 | 420 |
| B29214 | 47 | 279 | 354 |
| B29215 | 50 | 295 | 361 |
| B29216 | 51 | 275 | 341 |
| B29217 | 48 | 252 | 315 |
| B29218 | 62 | 340 | 435 |
| B29219 | 54 | 282 | 356 |
| B29220 | 73 | 379 | 477 |
| B29221 | 52 | 339 | 404 |
| B29222 | 61 | 295 | 374 |
| B29223 | 52 | 364 | 434 |
| B29224 | 62 | 363 | 437 |
| B29225 | 40 | 209 | 276 |
| MEAN | 58 | 318 | 396 |
| S.D. | 15 | 42 | 52 |
| N | 25 | 25 | 25 |

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/Grams/Males)

MALES Dose: 250 mg/kg/day

| ANIMAL# | Day OF STUDY | | |
|---------|--------------|------|-------|
| | 85-113 | 1-71 | 1-113 |
| B29226 | 50 | 309 | 387 |
| B29227 | 47 | 289 | 365 |
| B29228 | 47 | 292 | 356 |
| B29229 | 79 | 281 | 377 |
| B29230 | 52 | 279 | 364 |
| B29231 | 77 | 377 | 488 |
| B29232 | 48 | 278 | 355 |
| B29233 | 45 | 336 | 409 |
| B29234 | 64 | 361 | 434 |
| B29235 | 63 | 392 | 486 |
| B29236 | 57 | 385 | 470 |
| B29237 | 45 | 304 | 373 |
| B29238 | 68 | 303 | 383 |
| B29239 | 50 | 300 | 375 |
| B29240 | 56 | 307 | 386 |
| B29241 | 48 | 301 | 378 |
| B29242 | 57 | 309 | 382 |
| B29243 | 54 | 333 | 415 |
| B29244 | 61 | 309 | 387 |
| B29245 | 67 | 334 | 421 |
| B29246 | 52 | 308 | 376 |
| B29247 | 51 | 270 | 349 |
| B29248 | 54 | 326 | 405 |
| B29249 | 49 | 338 | 417 |
| B29250 | 53 | 314 | 389 |
| MEAN | 56 | 317 | 397 |
| S.D. | 9 | 33 | 38 |
| N | 25 | 25 | 25 |

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/Grams/Males)

MALES Dose: 500 mg/kg/day

| ANIMAL# | Day OF STUDY | | |
|---------|--------------|------|-------|
| | 85-113 | 1-71 | 1-113 |
| B29251 | 46 | 300 | 371 |
| B29252 | 40 | 289 | 349 |
| B29253 | 14 | 337 | 369 |
| B29254 | 64 | 375 | 450 |
| B29255 | 47 | 353 | 426 |
| B29256 | 31 | 286 | 339 |
| B29257 | 57 | 340 | 426 |
| B29258 | 58 | 276 | 345 |
| B29259 | 47 | 305 | 358 |
| B29260 | 55 | 354 | 438 |
| B29261 | 47 | 375 | 442 |
| B29262 | 73 | 316 | 399 |
| B29263 | 57 | 373 | 443 |
| B29264 | 22 | 330 | 378 |
| B29265 | 28 | 315 | 362 |
| B29266 | 13 | 254 | 276 |
| B29267 | 34 | 332 | 362 |
| B29268 | 54 | 355 | 440 |
| B29269 | 36 | 295 | 370 |
| B29270 | 50 | 340 | 406 |
| B29271 | 16 | 283 | 312 |
| B29272 | 68 | 387 | 489 |
| B29273 | 41 | 358 | 416 |
| B29274 | -5 | 296 | 325 |
| B29275 | 42 | 278 | 323 |
| MEAN | 41 | 324 | 385 |
| S.D. | 19 | 37 | 52 |
| N | 25 | 25 | 25 |

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/Grams/Males)

MALES Dose: 1000 mg/kg/day

| ANIMAL# | Day OF STUDY | | |
|---------|--------------|------|-------|
| | 85-113 | 1-71 | 1-113 |
| B29276 | 40 | 269 | 321 |
| B29277 | 46 | 296 | 351 |
| B29278 | 39 | 387 | 438 |
| B29279 | 52 | 344 | 417 |
| B29280 | 39 | 330 | 401 |
| B29281 | 39 | 345 | 396 |
| B29282 | 53 | 306 | 388 |
| B29283 | 46 | 250 | 308 |
| B29284 | 42 | 329 | 377 |
| B29285 | 46 | 353 | 423 |
| B29286 | 45 | 332 | 380 |
| B29287 | 47 | 310 | 354 |
| B29288 | 41 | 281 | 335 |
| B29289 | 37 | 353 | 393 |
| B29290 | 43 | 330 | 389 |
| B29291 | 45 | 333 | 392 |
| B29292 | 47 | 387 | 442 |
| B29293 | 56 | 269 | 327 |
| B29294 | 42 | 267 | 333 |
| B29295 | 51 | 318 | 380 |
| B29296 | 48 | 303 | 383 |
| B29297 | 49 | 359 | 416 |
| B29298 | 37 | 300 | 344 |
| B29299 | 48 | 257 | 348 |
| B29300 | 44 | 269 | 330 |
| MEAN | 45 | 315 | 375 |
| S.D. | 5 | 39 | 38 |
| N | 25 | 25 | 25 |

10. F0 generation - body weight (individual values/grams/females/premating period)

11. F0 generation - body weight change (individual values/grams/females/premating period)

12. F0 generation - body weight (individual values/grams/females/pregnancy period)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Pregnancy period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|-----|-----|-----|
| | | 0 | 7 | 14 | 20 |
| B29601 | SP | 288 | 314 | 348 | 420 |
| B29602 | SP | 323 | 341 | 373 | 450 |
| B29603 | SP | 383 | 410 | 447 | 541 |
| B29604 | SP | 323 | 354 | 391 | 469 |
| B29605 | SP | 291 | 310 | 339 | 407 |
| B29606 | SP | 317 | 355 | 384 | 457 |
| B29607 | SP | 277 | 299 | 323 | 395 |
| B29608 | SP | 271 | 280 | 309 | 383 |
| B29609 | SP | 276 | 302 | 334 | 399 |
| B29610 | SP | 275 | 306 | 330 | 400 |
| B29611 | SP | 300 | 310 | 353 | 434 |
| B29612 | SP | 282 | 310 | 341 | 414 |
| B29613 | SP | 301 | 327 | 358 | 435 |
| B29614 | SP | 296 | 318 | 344 | 422 |
| B29615 | SP | 386 | 411 | 434 | 523 |
| B29616 | SP | 294 | 332 | 363 | 435 |
| B29617 | SP | 279 | 305 | 334 | 412 |
| B29618 | SP | 366 | 404 | 443 | 540 |
| B29619 | SP | 342 | 363 | 395 | 468 |
| B29620 | SNB | 371 | 392 | 393 | 391 |
| B29621 | SP | 284 | 316 | 347 | 424 |
| B29622 | SP | 310 | 322 | 339 | 419 |
| B29623 | SP | 300 | 351 | 375 | 443 |
| B29624 | SNB | 264 | 284 | 302 | 304 |
| B29625 | SP | 265 | 284 | 306 | 383 |
| MEAN | | 306 | 331 | 361 | 438 |
| S.D. | | 34 | 37 | 39 | 45 |
| N | | 23 | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Pregnancy period)

Dose: 250 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|-----|-----|-----|
| | | 0 | 7 | 14 | 20 |
| B29626 | UPL | 302 | 337 | 369 | 448 |
| B29627 | SP | 289 | 326 | 366 | 434 |
| B29628 | SP | 285 | 313 | 353 | 438 |
| B29629 | SP | 338 | 375 | 413 | 495 |
| B29630 | SNB | 343 | 334 | 337 | 343 |
| B29631 | SNB | 314 | 345 | 346 | 337 |
| B29632 | SP | 280 | 310 | 329 | 402 |
| B29633 | SP | 261 | 283 | 317 | 390 |
| B29634 | SP | 320 | 339 | 359 | 431 |
| B29635 | SP | 278 | 312 | 339 | 403 |
| B29636 | SP | 304 | 334 | 383 | 454 |
| B29637 | SP | 290 | 321 | 348 | 415 |
| B29638 | SP | 335 | 372 | 406 | 497 |
| B29639 | SP | 276 | 303 | 334 | 414 |
| B29640 | SP | 296 | 317 | 357 | 422 |
| B29641 | SP | 283 | 307 | 336 | 409 |
| B29642 | SP | 312 | 331 | 357 | 440 |
| B29643 | SP | 345 | 363 | 394 | 483 |
| B29644 | SP | 317 | 353 | 384 | 459 |
| B29645 | SNB | 315 | 346 | 348 | 334 |
| B29646 | SP | 273 | 300 | 333 | 404 |
| B29647 | SNB | 332 | 350 | 334 | 328 |
| B29648 | SP | 300 | 315 | 346 | 409 |
| B29649 | SP | 232 | 261 | 288 | 352 |
| B29650 | SP | 295 | 315 | 347 | 427 |
| MEAN | | 296 | 323 | 355 | 430 |
| S.D. | | 27 | 28 | 30 | 35 |
| N | | 21 | 21 | 21 | 21 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Pregnancy period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|-----|-----|-----|
| | | 0 | 7 | 14 | 20 |
| B29651 | SP | 281 | 314 | 349 | 431 |
| B29652 | SP | 287 | 322 | 356 | 425 |
| B29653 | SP | 283 | 315 | 342 | 410 |
| B29654 | SP | 324 | 371 | 409 | 496 |
| B29655 | SP | 269 | 291 | 321 | 400 |
| B29656 | SNB | 293 | 331 | 354 | 346 |
| B29657 | SP | 286 | 313 | 333 | 389 |
| B29658 | SP | 296 | 343 | 381 | 459 |
| B29659 | SP | 332 | 341 | 375 | 436 |
| B29660 | SP | 287 | 327 | 359 | 440 |
| B29661 | UPL | 345 | 362 | 390 | 472 |
| B29662 | SP | 330 | 342 | 364 | 427 |
| B29663 | SP | 295 | 324 | 349 | 416 |
| B29664 | SP | 305 | 330 | 365 | 446 |
| B29665 | SP | 323 | 369 | 417 | 517 |
| B29666 | SNB | 322 | 329 | 329 | 337 |
| B29667 | SP | 336 | 365 | 402 | 477 |
| B29668 | UPL | 346 | 391 | 432 | 505 |
| B29669 | SP | 305 | 331 | 361 | 436 |
| B29670 | SP | 300 | 336 | 373 | 462 |
| B29671 | SP | 271 | 292 | 320 | 388 |
| B29672 | SP | 276 | 298 | 326 | 377 |
| B29673 | SNB | 296 | 325 | 333 | 339 |
| B29674 | SP | 288 | 308 | 336 | 416 |
| B29675 | UPL | 295 | 316 | 344 | 416 |
| MEAN | | 303 | 332 | 364 | 438 |
| S.D. | | 24 | 27 | 31 | 38 |
| N | | 22 | 22 | 22 | 22 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Pregnancy period)

Dose: 1000 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|----|------------------|-----|-----|-----|
| | | 0 | 7 | 14 | 20 |
| B29676 | SP | 299 | 329 | 361 | 429 |
| B29677 | SP | 271 | 301 | 349 | 420 |
| B29678 | SP | 279 | 304 | 328 | 419 |
| B29679 | SP | 291 | 333 | 359 | 424 |
| B29680 | SP | 263 | 299 | 344 | 406 |
| B29681 | SP | 256 | 277 | 303 | 372 |
| B29682 | SP | 291 | 321 | 353 | 431 |
| B29683 | SP | 269 | 289 | 318 | 401 |
| B29684 | SP | 329 | 345 | 379 | 461 |
| B29685 | SP | 233 | 264 | 296 | 374 |
| B29686 | SP | 282 | 306 | 341 | 433 |
| B29687 | SP | 345 | 365 | 394 | 483 |
| B29688 | SP | 339 | 380 | 411 | 463 |
| B29689 | SP | 266 | 299 | 338 | 417 |
| B29690 | SP | 315 | 343 | 374 | 457 |
| B29691 | SP | 284 | 310 | 346 | 420 |
| B29692 | SP | 293 | 318 | 346 | 428 |
| B29693 | SP | 323 | 348 | 381 | 475 |
| B29694 | SP | 287 | 336 | 376 | 450 |
| B29695 | SP | 257 | 286 | 316 | 382 |
| B29696 | SP | 273 | 301 | 328 | 390 |
| B29697 | SP | 262 | 281 | 311 | 376 |
| B29698 | SP | 292 | 323 | 362 | 434 |
| B29699 | SP | 290 | 331 | 364 | 421 |
| B29700 | SP | 339 | 373 | 387 | 468 |
| MEAN | | 289 | 318 | 351 | 425 |
| S.D. | | 29 | 30 | 29 | 32 |
| N | | 25 | 25 | 25 | 25 |

SP=Fin sac/Pg

13. F0 generation - body weight change (individual values/grams/females/pregnancy period)
Fin sac:final sacrifice
Prem sac:prematurely sacrificed
Pg:pregnant
NotPg:not pregnant

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Pregnancy period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|--------|---------|--------|
| | | 0 - 7 | 7 - 14 | 14 - 20 | 0 - 20 |
| B29601 | SP | 26 | 35 | 72 | 132 |
| B29602 | SP | 18 | 32 | 76 | 126 |
| B29603 | SP | 27 | 36 | 95 | 158 |
| B29604 | SP | 31 | 37 | 78 | 146 |
| B29605 | SP | 19 | 28 | 68 | 116 |
| B29606 | SP | 38 | 30 | 73 | 141 |
| B29607 | SP | 22 | 24 | 72 | 117 |
| B29608 | SP | 10 | 29 | 74 | 112 |
| B29609 | SP | 26 | 32 | 65 | 123 |
| B29610 | SP | 31 | 24 | 70 | 125 |
| B29611 | SP | 10 | 44 | 80 | 134 |
| B29612 | SP | 28 | 31 | 74 | 132 |
| B29613 | SP | 27 | 30 | 78 | 135 |
| B29614 | SP | 22 | 26 | 78 | 127 |
| B29615 | SP | 25 | 23 | 88 | 137 |
| B29616 | SP | 37 | 32 | 72 | 140 |
| B29617 | SP | 25 | 29 | 78 | 133 |
| B29618 | SP | 38 | 39 | 96 | 174 |
| B29619 | SP | 20 | 33 | 73 | 126 |
| B29620 | SNB | 20 | 1 | -3 | 19 |
| B29621 | SP | 32 | 31 | 77 | 140 |
| B29622 | SP | 12 | 18 | 80 | 109 |
| B29623 | SP | 52 | 24 | 68 | 143 |
| B29624 | SNB | 20 | 18 | 2 | 40 |
| B29625 | SP | 20 | 22 | 77 | 118 |
| MEAN | | 26 | 30 | 77 | 132 |
| S.D. | | 10 | 6 | 8 | 15 |
| N | | 23 | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Pregnancy period)

Dose: 250 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|--------|---------|--------|
| | | 0 - 7 | 7 - 14 | 14 - 20 | 0 - 20 |
| B29626 | UPL | 35 | 31 | 79 | 145 |
| B29627 | SP | 37 | 39 | 69 | 145 |
| B29628 | SP | 28 | 40 | 85 | 152 |
| B29629 | SP | 37 | 38 | 82 | 157 |
| B29630 | SNB | -10 | 3 | 6 | -1 |
| B29631 | SNB | 31 | 1 | -9 | 23 |
| B29632 | SP | 30 | 18 | 73 | 122 |
| B29633 | SP | 21 | 35 | 72 | 128 |
| B29634 | SP | 19 | 20 | 72 | 111 |
| B29635 | SP | 34 | 26 | 65 | 125 |
| B29636 | SP | 29 | 49 | 72 | 150 |
| B29637 | SP | 31 | 27 | 67 | 125 |
| B29638 | SP | 37 | 35 | 91 | 162 |
| B29639 | SP | 26 | 31 | 80 | 138 |
| B29640 | SP | 21 | 40 | 65 | 126 |
| B29641 | SP | 25 | 29 | 73 | 127 |
| B29642 | SP | 19 | 27 | 82 | 128 |
| B29643 | SP | 18 | 30 | 89 | 138 |
| B29644 | SP | 36 | 31 | 75 | 142 |
| B29645 | SNB | 31 | 2 | -14 | 19 |
| B29646 | SP | 28 | 33 | 71 | 132 |
| B29647 | SNB | 18 | -15 | -6 | -4 |
| B29648 | SP | 15 | 31 | 64 | 110 |
| B29649 | SP | 29 | 27 | 64 | 120 |
| B29650 | SP | 21 | 31 | 80 | 132 |
| MEAN | | 27 | 32 | 75 | 134 |
| S.D. | | 7 | 7 | 8 | 14 |
| N | | 21 | 21 | 21 | 21 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Pregnancy period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | | |
|---------|-----|------------------|--------|---------|--------|
| | | 0 - 7 | 7 - 14 | 14 - 20 | 0 - 20 |
| B29651 | SP | 33 | 35 | 82 | 150 |
| B29652 | SP | 35 | 34 | 69 | 138 |
| B29653 | SP | 32 | 27 | 69 | 128 |
| B29654 | SP | 47 | 38 | 87 | 171 |
| B29655 | SP | 22 | 31 | 79 | 131 |
| B29656 | SNB | 39 | 23 | -8 | 54 |
| B29657 | SP | 27 | 20 | 56 | 103 |
| B29658 | SP | 47 | 38 | 79 | 163 |
| B29659 | SP | 9 | 33 | 62 | 105 |
| B29660 | SP | 40 | 33 | 81 | 153 |
| B29661 | UPL | 17 | 29 | 82 | 127 |
| B29662 | SP | 12 | 21 | 63 | 96 |
| B29663 | SP | 29 | 25 | 67 | 121 |
| B29664 | SP | 25 | 36 | 80 | 141 |
| B29665 | SP | 47 | 47 | 101 | 195 |
| B29666 | SNB | 7 | 0 | 8 | 15 |
| B29667 | SP | 30 | 37 | 75 | 141 |
| B29668 | UPL | 45 | 41 | 73 | 159 |
| B29669 | SP | 26 | 30 | 75 | 130 |
| B29670 | SP | 36 | 38 | 89 | 163 |
| B29671 | SP | 21 | 28 | 68 | 117 |
| B29672 | SP | 22 | 28 | 51 | 101 |
| B29673 | SNB | 29 | 8 | 6 | 43 |
| B29674 | SP | 20 | 28 | 80 | 128 |
| B29675 | UPL | 20 | 28 | 73 | 121 |
| MEAN | | 29 | 32 | 75 | 136 |
| S.D. | | 11 | 6 | 11 | 25 |
| N | | 22 | 22 | 22 | 22 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Pregnancy period)

Dose: 1000 mg/kg/day

| FEMALE# | DAY OF PREGNANCY | | | | |
|---------|------------------|--------|---------|--------|-----|
| | 0 - 7 | 7 - 14 | 14 - 20 | 0 - 20 | |
| B29676 | SP | 30 | 31 | 68 | 129 |
| B29677 | SP | 30 | 48 | 71 | 149 |
| B29678 | SP | 25 | 24 | 91 | 139 |
| B29679 | SP | 42 | 26 | 65 | 133 |
| B29680 | SP | 36 | 45 | 62 | 143 |
| B29681 | SP | 21 | 26 | 69 | 115 |
| B29682 | SP | 30 | 32 | 77 | 140 |
| B29683 | SP | 20 | 29 | 83 | 132 |
| B29684 | SP | 16 | 34 | 82 | 132 |
| B29685 | SP | 31 | 32 | 78 | 141 |
| B29686 | SP | 24 | 35 | 92 | 152 |
| B29687 | SP | 20 | 29 | 89 | 138 |
| B29688 | SP | 42 | 31 | 52 | 124 |
| B29689 | SP | 33 | 39 | 79 | 151 |
| B29690 | SP | 28 | 31 | 83 | 142 |
| B29691 | SP | 27 | 35 | 74 | 136 |
| B29692 | SP | 25 | 28 | 82 | 135 |
| B29693 | SP | 25 | 33 | 94 | 152 |
| B29694 | SP | 49 | 40 | 74 | 163 |
| B29695 | SP | 29 | 30 | 66 | 124 |
| B29696 | SP | 27 | 27 | 63 | 117 |
| B29697 | SP | 19 | 30 | 65 | 114 |
| B29698 | SP | 32 | 39 | 71 | 142 |
| B29699 | SP | 41 | 33 | 57 | 131 |
| B29700 | SP | 33 | 15 | 81 | 129 |
| MEAN | | 29 | 32 | 75 | 136 |
| S.D. | | 8 | 7 | 11 | 12 |
| N | | 25 | 25 | 25 | 25 |

SP=Fin sac/Pg

14. F0 generation - body weight (individual values/grams/females/lactation period)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Lactation period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY POSTPARTUM | | | |
|---------|-----|----------------|-----|-----|-----|
| | | 1 | 7 | 14 | 21 |
| B29601 | SP | 321 | 344 | 334 | 317 |
| B29602 | SP | 350 | 356 | 372 | 353 |
| B29603 | SP | 433 | 439 | 438 | 425 |
| B29604 | SP | 377 | 371 | 366 | 346 |
| B29605 | SP | 317 | 329 | 332 | 315 |
| B29606 | SP | 367 | 344 | 356 | 338 |
| B29607 | SP | 320 | 342 | 329 | 319 |
| B29608 | SP | 315 | 345 | 354 | 326 |
| B29609 | SP | 306 | 316 | 333 | 330 |
| B29610 | SP | 321 | 324 | 338 | 334 |
| B29611 | SP | 323 | 347 | 360 | 370 |
| B29612 | SP | 326 | 358 | 385 | 348 |
| B29613 | SP | 332 | 345 | 345 | 342 |
| B29614 | SP | 304 | 307 | 321 | 323 |
| B29615 | SP | 399 | 404 | 397 | 387 |
| B29616 | SP | 344 | 352 | 374 | 342 |
| B29617 | SP | 313 | 332 | 356 | 333 |
| B29618 | SP | 438 | 441 | 438 | 401 |
| B29619 | SP | 386 | 389 | 390 | 371 |
| B29620 | SNB | | | | |
| B29621 | SP | 330 | 323 | 339 | 316 |
| B29622 | SP | 319 | 334 | 332 | 315 |
| B29623 | SP | 345 | 341 | 346 | 331 |
| B29624 | SNB | | | | |
| B29625 | SP | 304 | 313 | 323 | 332 |
| MEAN | | 343 | 352 | 359 | 344 |
| S.D. | | 39 | 36 | 33 | 29 |
| N | | 23 | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Lactation period)

Dose: 250 mg/kg/day

| FEMALE# | | DAY POSTPARTUM | | | |
|---------|-----|----------------|-----|-----|-----|
| | | 1 | 7 | 14 | 21 |
| B29626 | UPL | 362 | 363 | | |
| B29627 | SP | 348 | 368 | 368 | 354 |
| B29628 | SP | 333 | 346 | 349 | 352 |
| B29629 | SP | 403 | 388 | 391 | 381 |
| B29630 | SNB | | | | |
| B29631 | SNB | | | | |
| B29632 | SP | 330 | 341 | 352 | 325 |
| B29633 | SP | 304 | 315 | 342 | 337 |
| B29634 | SP | 355 | 374 | 368 | 337 |
| B29635 | SP | 330 | 364 | 348 | 336 |
| B29636 | SP | 359 | 354 | 384 | 365 |
| B29637 | SP | 325 | 336 | 352 | 343 |
| B29638 | SP | 374 | 382 | 373 | 346 |
| B29639 | SP | 325 | 322 | 349 | 344 |
| B29640 | SP | 340 | 352 | 370 | 356 |
| B29641 | SP | 319 | 326 | 353 | 337 |
| B29642 | SP | 331 | 331 | 339 | 335 |
| B29643 | SP | 372 | 359 | 367 | 368 |
| B29644 | SP | 360 | 361 | 365 | 354 |
| B29645 | SNB | | | | |
| B29646 | SP | 323 | 332 | 347 | 337 |
| B29647 | SNB | | | | |
| B29648 | SP | 332 | 350 | 367 | 344 |
| B29649 | SP | 270 | 296 | 313 | 290 |
| B29650 | SP | 312 | 333 | 353 | 343 |
| MEAN | | 338 | 347 | 357 | 344 |
| S.D. | | 28 | 23 | 17 | 18 |
| N | | 21 | 21 | 20 | 20 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Lactation period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY POSTPARTUM | | | |
|---------|-----|----------------|-----|-----|-----|
| | | 1 | 7 | 14 | 21 |
| B29651 | SP | 318 | 328 | 336 | 322 |
| B29652 | SP | 326 | 341 | 354 | 312 |
| B29653 | SP | 307 | 326 | 316 | 297 |
| B29654 | SP | 385 | 392 | 411 | 398 |
| B29655 | SP | 320 | 339 | 348 | 317 |
| B29656 | SNB | | | | |
| B29657 | SP | 328 | 342 | 330 | 325 |
| B29658 | SP | 356 | 367 | 385 | 362 |
| B29659 | SP | 340 | 358 | 369 | 351 |
| B29660 | SP | 343 | 362 | 381 | 340 |
| B29661 | UPL | 364 | | | |
| B29662 | SP | 331 | 345 | 351 | 342 |
| B29663 | SP | 335 | 353 | 354 | 333 |
| B29664 | SP | 347 | 354 | 376 | 349 |
| B29665 | SP | 400 | 416 | 398 | 381 |
| B29666 | SNB | | | | |
| B29667 | SP | 358 | 360 | 372 | 352 |
| B29668 | UPL | 409 | | | |
| B29669 | SP | 350 | 347 | 372 | 350 |
| B29670 | SP | 358 | 355 | 358 | 341 |
| B29671 | SP | 307 | 324 | 341 | 338 |
| B29672 | SP | 302 | 329 | 336 | 314 |
| B29673 | SNB | | | | |
| B29674 | SP | 328 | 329 | 335 | 336 |
| B29675 | UPL | 323 | | | |
| MEAN | | 342 | 351 | 359 | 340 |
| S.D. | | 29 | 23 | 25 | 24 |
| N | | 22 | 19 | 19 | 19 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT (Individual values/grams/Females/Lactation period)

Dose: 1000 mg/kg/day

| FEMALE# | | DAY POSTPARTUM | | | |
|---------|----|----------------|-----|-----|-----|
| | | 1 | 7 | 14 | 21 |
| B29676 | SP | 361 | 374 | 361 | 331 |
| B29677 | SP | 319 | 330 | 346 | 351 |
| B29678 | SP | 321 | 324 | 350 | 345 |
| B29679 | SP | 350 | 351 | 363 | 344 |
| B29680 | SP | 318 | 320 | 351 | 337 |
| B29681 | SP | 291 | 296 | 319 | 312 |
| B29682 | SP | 344 | 353 | 362 | 350 |
| B29683 | SP | 274 | 313 | 325 | 306 |
| B29684 | SP | 362 | 371 | 396 | 366 |
| B29685 | SP | 282 | 298 | 309 | 307 |
| B29686 | SP | 343 | 352 | 367 | 344 |
| B29687 | SP | 385 | 391 | 395 | 373 |
| B29688 | SP | 370 | 384 | 385 | 362 |
| B29689 | SP | 321 | 343 | 357 | 339 |
| B29690 | SP | 362 | 369 | 362 | 347 |
| B29691 | SP | 319 | 344 | 359 | 343 |
| B29692 | SP | 337 | 346 | 356 | 334 |
| B29693 | SP | 366 | 383 | 387 | 394 |
| B29694 | SP | 355 | 386 | 399 | 374 |
| B29695 | SP | 295 | 315 | 334 | 305 |
| B29696 | SP | 281 | 321 | 343 | 340 |
| B29697 | SP | 301 | 317 | 320 | 304 |
| B29698 | SP | 335 | 346 | 341 | 335 |
| B29699 | SP | 355 | 370 | 357 | 379 |
| B29700 | SP | 365 | 376 | 378 | 353 |
| MEAN | | 332 | 347 | 357 | 343 |
| S.D. | | 32 | 29 | 24 | 24 |
| N | | 25 | 25 | 25 | 25 |

SP=Fin sac/Pg

15. F0 generation - body weight change (individual values/grams/females/lactation period)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Lactation period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | | | |
|---------|-----|------------------|--------|---------|--------|--------|
| | | 1 - 7 | 7 - 14 | 14 - 21 | 1 - 14 | 1 - 21 |
| B29601 | SP | 23 | -10 | -16 | 13 | -4 |
| B29602 | SP | 6 | 16 | -20 | 22 | 3 |
| B29603 | SP | 6 | -1 | -13 | 5 | -8 |
| B29604 | SP | -7 | -5 | -20 | -11 | -31 |
| B29605 | SP | 11 | 3 | -16 | 14 | -2 |
| B29606 | SP | -23 | 12 | -18 | -11 | -29 |
| B29607 | SP | 22 | -13 | -10 | 10 | -1 |
| B29608 | SP | 30 | 9 | -27 | 39 | 12 |
| B29609 | SP | 10 | 17 | -3 | 27 | 25 |
| B29610 | SP | 3 | 15 | -5 | 17 | 13 |
| B29611 | SP | 24 | 13 | 10 | 36 | 46 |
| B29612 | SP | 32 | 26 | -37 | 58 | 22 |
| B29613 | SP | 13 | 0 | -3 | 13 | 10 |
| B29614 | SP | 3 | 15 | 2 | 17 | 19 |
| B29615 | SP | 6 | -7 | -10 | -1 | -12 |
| B29616 | SP | 8 | 22 | -32 | 29 | -2 |
| B29617 | SP | 19 | 24 | -23 | 43 | 20 |
| B29618 | SP | 2 | -2 | -37 | 0 | -37 |
| B29619 | SP | 3 | 2 | -19 | 4 | -15 |
| B29620 | SNB | | | | | |
| B29621 | SP | -7 | 16 | -23 | 9 | -14 |
| B29622 | SP | 16 | -2 | -17 | 13 | -4 |
| B29623 | SP | -5 | 6 | -16 | 1 | -14 |
| B29624 | SNB | | | | | |
| B29625 | SP | 9 | 10 | 10 | 18 | 28 |
| MEAN | | 9 | 7 | -15 | 16 | 1 |
| S.D. | | 13 | 11 | 13 | 17 | 20 |
| N | | 23 | 23 | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Lactation period)

Dose: 250 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | | | |
|---------|-----|------------------|--------|---------|--------|--------|
| | | 1 - 7 | 7 - 14 | 14 - 21 | 1 - 14 | 1 - 21 |
| B29626 | UPL | 0 | | | | |
| B29627 | SP | 20 | 0 | -14 | 20 | 6 |
| B29628 | SP | 13 | 3 | 3 | 16 | 19 |
| B29629 | SP | -14 | 3 | -11 | -11 | -22 |
| B29630 | SNB | | | | | |
| B29631 | SNB | | | | | |
| B29632 | SP | 11 | 11 | -27 | 22 | -6 |
| B29633 | SP | 11 | 28 | -5 | 38 | 33 |
| B29634 | SP | 19 | -6 | -31 | 13 | -18 |
| B29635 | SP | 35 | -17 | -12 | 18 | 6 |
| B29636 | SP | -6 | 30 | -19 | 24 | 6 |
| B29637 | SP | 11 | 16 | -9 | 27 | 18 |
| B29638 | SP | 8 | -9 | -27 | -1 | -28 |
| B29639 | SP | -4 | 27 | -5 | 24 | 19 |
| B29640 | SP | 11 | 18 | -14 | 30 | 16 |
| B29641 | SP | 7 | 27 | -16 | 34 | 19 |
| B29642 | SP | 0 | 8 | -4 | 8 | 4 |
| B29643 | SP | -13 | 8 | 1 | -5 | -4 |
| B29644 | SP | 1 | 5 | -12 | 6 | -6 |
| B29645 | SNB | | | | | |
| B29646 | SP | 9 | 15 | -10 | 24 | 14 |
| B29647 | SNB | | | | | |
| B29648 | SP | 18 | 17 | -23 | 35 | 12 |
| B29649 | SP | 26 | 16 | -22 | 42 | 20 |
| B29650 | SP | 21 | 20 | -10 | 41 | 31 |
| MEAN | | 9 | 11 | -13 | 20 | 7 |
| S.D. | | 12 | 13 | 9 | 15 | 17 |
| N | | 21 | 20 | 20 | 20 | 20 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Lactation period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | | | |
|---------|-----|------------------|--------|---------|--------|--------|
| | | 1 - 7 | 7 - 14 | 14 - 21 | 1 - 14 | 1 - 21 |
| B29651 | SP | 9 | 8 | -13 | 17 | 4 |
| B29652 | SP | 15 | 13 | -42 | 28 | -14 |
| B29653 | SP | 19 | -10 | -19 | 9 | -10 |
| B29654 | SP | 7 | 20 | -14 | 27 | 13 |
| B29655 | SP | 19 | 10 | -31 | 29 | -3 |
| B29656 | SNB | | | | | |
| B29657 | SP | 15 | -12 | -5 | 2 | -2 |
| B29658 | SP | 11 | 19 | -23 | 30 | 6 |
| B29659 | SP | 18 | 11 | -18 | 29 | 11 |
| B29660 | SP | 19 | 19 | -40 | 38 | -3 |
| B29661 | UPL | | | | | |
| B29662 | SP | 14 | 6 | -10 | 21 | 11 |
| B29663 | SP | 18 | 1 | -21 | 19 | -2 |
| B29664 | SP | 7 | 22 | -27 | 29 | 2 |
| B29665 | SP | 16 | -18 | -17 | -2 | -19 |
| B29666 | SNB | | | | | |
| B29667 | SP | 3 | 11 | -19 | 14 | -5 |
| B29668 | UPL | | | | | |
| B29669 | SP | -3 | 26 | -22 | 23 | 0 |
| B29670 | SP | -3 | 3 | -17 | 0 | -17 |
| B29671 | SP | 16 | 18 | -3 | 34 | 31 |
| B29672 | SP | 27 | 7 | -22 | 35 | 12 |
| B29673 | SNB | | | | | |
| B29674 | SP | 1 | 6 | 1 | 7 | 8 |
| B29675 | UPL | | | | | |
| MEAN | | 12 | 8 | -19 | 20 | 1 |
| S.D. | | 8 | 12 | 11 | 12 | 12 |
| N | | 19 | 19 | 19 | 19 | 19 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

BODY WEIGHT CHANGE (Individual values/grams/Females/Lactation period)

Dose: 1000 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | | | |
|---------|----|------------------|--------|---------|--------|--------|
| | | 1 - 7 | 7 - 14 | 14 - 21 | 1 - 14 | 1 - 21 |
| B29676 | SP | 13 | -12 | -30 | 0 | -30 |
| B29677 | SP | 11 | 16 | 5 | 27 | 32 |
| B29678 | SP | 3 | 26 | -5 | 29 | 25 |
| B29679 | SP | 1 | 12 | -19 | 13 | -6 |
| B29680 | SP | 2 | 31 | -13 | 33 | 19 |
| B29681 | SP | 5 | 23 | -7 | 28 | 21 |
| B29682 | SP | 9 | 9 | -11 | 18 | 7 |
| B29683 | SP | 39 | 12 | -19 | 51 | 32 |
| B29684 | SP | 10 | 25 | -30 | 34 | 4 |
| B29685 | SP | 16 | 11 | -2 | 27 | 25 |
| B29686 | SP | 8 | 16 | -23 | 24 | 1 |
| B29687 | SP | 5 | 4 | -21 | 9 | -12 |
| B29688 | SP | 14 | 0 | -23 | 15 | -8 |
| B29689 | SP | 21 | 14 | -18 | 36 | 18 |
| B29690 | SP | 7 | -7 | -15 | 0 | -15 |
| B29691 | SP | 25 | 15 | -16 | 40 | 24 |
| B29692 | SP | 10 | 9 | -22 | 19 | -3 |
| B29693 | SP | 18 | 3 | 7 | 21 | 28 |
| B29694 | SP | 31 | 13 | -26 | 44 | 19 |
| B29695 | SP | 20 | 19 | -30 | 39 | 9 |
| B29696 | SP | 40 | 22 | -3 | 62 | 59 |
| B29697 | SP | 16 | 3 | -16 | 19 | 3 |
| B29698 | SP | 12 | -6 | -6 | 6 | 0 |
| B29699 | SP | 15 | -13 | 22 | 2 | 24 |
| B29700 | SP | 11 | 2 | -25 | 13 | -12 |
| MEAN | | 14 | 10 | -14 | 24 | 11 |
| S.D. | | 10 | 12 | 13 | 16 | 19 |
| N | | 25 | 25 | 25 | 25 | 25 |

SP=Fin sac/Pg

16. F0 generation - food consumption (individual values/grams per day/males)

F0 GENERATION

FOOD CONSUMPTION (Individual values/Grams per day/Males)

MALES Dose: 250 mg/kg/day

| Animal No. | Day of Study | | | | | | | | | | | | | |
|------------|--------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|---------|
| | 1-8 | 8-15 | 15-22 | 22-29 | 29-36 | 36-43 | 43-50 | 50-57 | 57-64 | 64-71 | 85-92 | 92-99 | 99-106 | 106-113 |
| B29226 | 28 | 31 | 27 | 28 | 27 | 27 | 28 | 27 | 25 | 23 | 26 | 22 | 25 | 25 |
| B29227 | 24 | 27 | 26 | 25 | 25 | 25 | 26 | 25 | 26 | 24 | 25 | 24 | 25 | 24 |
| B29228 | 23 | 25 | 23 | 22 | 23 | 23 | 23 | 22 | 22 | 18 | 21 | 20 | 22 | 22 |
| B29229 | 26 | 29 | 27 | 24 | 24 | 22 | 23 | 22 | 23 | 23 | 24 | 24 | 24 | 25 |
| B29230 | 25 | 23 | 25 | 24 | 24 | 23 | 25 | 24 | 23 | 23 | 24 | 24 | 25 | 24 |
| B29231 | 29 | 31 | 31 | 30 | 31 | 29 | 27 | 27 | 29 | 30 | 30 | 29 | 31 | 31 |
| B29232 | 24 | 26 | 25 | 23 | 23 | 23 | 24 | 23 | 22 | 23 | 23 | 22 | 23 | 27 |
| B29233 | 25 | 28 | 28 | 25 | 26 | 25 | 26 | 26 | 24 | 23 | 24 | 25 | 24 | 24 |
| B29234 | 29 | 32 | 31 | 31 | 29 | 29 | 31 | 29 | 30 | 27 | 27 | 28 | 28 | 27 |
| B29235 | 29 | 44 | 25 | 34 | 40 | 29 | 32 | 32 | 30 | 28 | 28 | 25 | 27 | 28 |
| B29236 | 28 | 29 | 31 | 29 | 30 | 28 | 31 | 30 | 30 | 26 | 29 | 27 | 30 | 29 |
| B29237 | 26 | 29 | 28 | 25 | 28 | 12 | 28 | 28 | 26 | 24 | 25 | 23 | 25 | 27 |
| B29238 | 25 | 27 | 26 | 25 | 26 | 25 | 23 | 23 | 22 | 22 | 22 | | 23 | 24 |
| B29239 | 25 | 24 | 25 | 24 | 25 | 22 | 23 | 22 | 23 | 21 | 22 | 22 | 22 | 23 |
| B29240 | 26 | 29 | 29 | 27 | 23 | 22 | 22 | 25 | 24 | 24 | 25 | 23 | 26 | 27 |
| B29241 | 25 | 27 | 26 | 26 | 25 | 26 | 27 | 26 | 26 | 26 | 27 | 25 | 26 | 26 |
| B29242 | 27 | 29 | 28 | 27 | 26 | 26 | 25 | 24 | 25 | 24 | 25 | 25 | 26 | 25 |
| B29243 | 24 | 26 | 26 | 28 | 27 | 26 | 27 | 26 | 25 | 25 | 26 | 27 | 26 | 24 |
| B29244 | 28 | 29 | 26 | 25 | 23 | 24 | 25 | 25 | 24 | 25 | 23 | 25 | 25 | 26 |
| B29245 | 24 | 28 | 28 | 25 | 24 | 24 | 24 | 24 | 24 | 24 | 24 | 23 | 24 | 25 |
| B29246 | 23 | 25 | 25 | 24 | 23 | 22 | 22 | 23 | 23 | 22 | 21 | 21 | 22 | 22 |
| B29247 | 27 | 27 | 25 | 24 | 24 | 24 | 24 | 24 | 23 | 25 | 24 | 25 | 24 | 24 |
| B29248 | 26 | 29 | 30 | 30 | 27 | 25 | 26 | 25 | 24 | 21 | 23 | 22 | 24 | 23 |
| B29249 | 26 | 27 | 28 | 27 | 27 | 26 | 25 | 25 | 25 | 24 | 26 | 24 | 23 | 25 |
| B29250 | 24 | 27 | 27 | 26 | 25 | 24 | 24 | 25 | 24 | 21 | 22 | 21 | 25 | 24 |
| MEAN | 26 | 28 | 27 | 26 | 26 | 24 | 26 | 25 | 25 | 24 | 25 | 24 | 25 | 25 |
| S.D. | 2 | 4 | 2 | 3 | 4 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| N | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 24 | 25 | 25 |

17. F0 generation - food consumption
(individual values/grams per day/females/premating period)

F0 GENERATION

FOOD CONSUMPTION (Individual values/Grams per day/Females/Premating period)

FEMALES Dose: 0 mg/kg/day

| Animal No. | Day of Study | | | | | | | | | |
|------------|--------------|------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 1-8 | 8-15 | 15-22 | 22-29 | 29-36 | 36-43 | 43-50 | 50-57 | 57-64 | 64-71 |
| B29601 | 17 | 19 | 20 | 18 | 19 | 17 | 19 | 21 | 23 | 18 |
| B29602 | 18 | 18 | 18 | 19 | 18 | 16 | 16 | 19 | 22 | 19 |
| B29603 | 20 | 21 | 24 | 23 | 23 | 20 | 23 | 24 | 28 | 24 |
| B29604 | 16 | 17 | 19 | 18 | 18 | 18 | 20 | 19 | 17 | 16 |
| B29605 | 16 | 18 | 20 | 19 | 18 | 18 | 19 | 19 | 18 | 17 |
| B29606 | 17 | 17 | 18 | 20 | 19 | 19 | 18 | 21 | 25 | 20 |
| B29607 | 17 | 18 | 18 | 16 | 17 | 16 | 15 | 15 | 15 | 16 |
| B29608 | 17 | 17 | 16 | 17 | 17 | 15 | 15 | 15 | 14 | 14 |
| B29609 | 18 | 18 | 18 | 18 | 19 | 17 | 17 | 15 | 18 | 20 |
| B29610 | 17 | 18 | 18 | 16 | 17 | 16 | 16 | 17 | 17 | 17 |
| B29611 | 16 | 18 | 17 | 17 | 16 | 15 | 15 | 17 | 16 | 17 |
| B29612 | 19 | 18 | 16 | 16 | 18 | 16 | 16 | 19 | 22 | 16 |
| B29613 | 20 | 18 | 18 | 17 | 17 | 16 | 16 | 18 | 16 | 17 |
| B29614 | 18 | 18 | 19 | 19 | 18 | 17 | 18 | 19 | 21 | 19 |
| B29615 | 22 | 21 | 21 | 23 | 23 | 21 | 21 | 23 | 27 | 24 |
| B29616 | 18 | 18 | 19 | 19 | 18 | 16 | 16 | 17 | 17 | 18 |
| B29617 | 17 | 18 | 16 | 16 | 17 | 15 | 15 | 16 | 16 | 16 |
| B29618 | 22 | 19 | 20 | 21 | 21 | 20 | 20 | 28 | 28 | 17 |
| B29619 | 19 | 19 | 20 | 19 | 20 | 20 | 18 | 27 | 26 | 19 |
| B29620 | 18 | 18 | 20 | 18 | 19 | 18 | 18 | 22 | 22 | 22 |
| B29621 | 19 | 19 | 20 | 19 | 20 | 18 | 17 | 18 | 17 | 17 |
| B29622 | 18 | 18 | 18 | 17 | 16 | 18 | 16 | 16 | 15 | 17 |
| B29623 | 23 | 22 | 21 | 20 | 21 | 20 | 19 | MV | | 22 |
| B29624 | 16 | 17 | 17 | 18 | 17 | 16 | 16 | 10 | 22 | 15 |
| B29625 | 17 | 17 | 16 | 16 | 15 | 13 | 13 | 17 | 8 | 12 |
| MEAN | 18 | 18 | 19 | 18 | 18 | 17 | 17 | 19 | 20 | 18 |
| S.D. | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 4 | 5 | 3 |
| N | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 24 | 24 | 25 |

MV=MISSING VALUE

18. F0 generation - food consumption
(individual values/grams per day/females/pregnancy period)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Pregnancy period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | |
|---------|-----|------------------|--------|---------|
| | | 0 - 7 | 7 - 14 | 14 - 20 |
| B29601 | SP | 22 | 25 | 27 |
| B29602 | SP | 20 | 27 | 27 |
| B29603 | SP | 27 | 28 | 29 |
| B29604 | SP | 21 | 23 | 25 |
| B29605 | SP | 20 | 22 | 23 |
| B29606 | SP | 24 | 25 | 25 |
| B29607 | SP | 19 | 19 | 24 |
| B29608 | SP | 16 | 18 | 27 |
| B29609 | SP | 22 | 23 | 26 |
| B29610 | SP | 21 | 22 | 28 |
| B29611 | SP | 19 | 24 | 28 |
| B29612 | SP | 24 | 26 | 29 |
| B29613 | SP | 21 | 22 | 26 |
| B29614 | SP | 22 | 22 | 25 |
| B29615 | SP | 25 | 25 | 28 |
| B29616 | SP | 24 | 28 | 29 |
| B29617 | SP | 21 | 21 | 24 |
| B29618 | SP | 28 | 31 | 37 |
| B29619 | SP | 23 | 24 | 28 |
| B29620 | SNB | 24 | 23 | 20 |
| B29621 | SP | 23 | 27 | 29 |
| B29622 | SP | 19 | 19 | 23 |
| B29623 | SP | 14 | 25 | 25 |
| B29624 | SNB | 17 | 19 | 18 |
| B29625 | SP | 17 | 18 | 22 |
| MEAN | | 21 | 24 | 27 |
| S.D. | | 3 | 3 | 3 |
| N | | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Pregnancy period)

Dose: 250 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | |
|---------|-----|------------------|--------|---------|
| | | 0 - 7 | 7 - 14 | 14 - 20 |
| B29626 | UPL | 26 | 28 | 29 |
| B29627 | SP | 20 | 25 | 29 |
| B29628 | SP | 19 | 23 | 28 |
| B29629 | SP | 26 | 28 | 30 |
| B29630 | SNB | 17 | 20 | 21 |
| B29631 | SNB | 24 | 24 | 19 |
| B29632 | SP | 23 | 23 | 27 |
| B29633 | SP | 19 | 21 | 24 |
| B29634 | SP | | 20 | 24 |
| B29635 | SP | 23 | 24 | 26 |
| B29636 | SP | 28 | 31 | 31 |
| B29637 | SP | 23 | 23 | 28 |
| B29638 | SP | 25 | 25 | 30 |
| B29639 | SP | 23 | 25 | 30 |
| B29640 | SP | 22 | 25 | 28 |
| B29641 | SP | 22 | 23 | 27 |
| B29642 | SP | 19 | 20 | 25 |
| B29643 | SP | 24 | 25 | 32 |
| B29644 | SP | 26 | 25 | 27 |
| B29645 | SNB | 24 | 24 | 19 |
| B29646 | SP | 21 | 23 | 30 |
| B29647 | SNB | 25 | 34 | 18 |
| B29648 | SP | 20 | 22 | 28 |
| B29649 | SP | 20 | 21 | 22 |
| B29650 | SP | 24 | 26 | 27 |
| MEAN | | 22 | 24 | 28 |
| S.D. | | 3 | 3 | 2 |
| N | | 20 | 21 | 21 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Pregnancy period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY OF PREGNANCY | | |
|---------|-----|------------------|--------|---------|
| | | 0 - 7 | 7 - 14 | 14 - 20 |
| B29651 | SP | 22 | 24 | 27 |
| B29652 | SP | 23 | 25 | 26 |
| B29653 | SP | 24 | 23 | 23 |
| B29654 | SP | 28 | 29 | 29 |
| B29655 | SP | 22 | 22 | 29 |
| B29656 | SNB | 23 | 25 | 21 |
| B29657 | SP | 19 | 23 | 25 |
| B29658 | SP | 25 | 27 | 32 |
| B29659 | SP | 23 | 27 | 24 |
| B29660 | SP | 18 | 24 | 29 |
| B29661 | UPL | 25 | | 32 |
| B29662 | SP | 21 | 22 | 24 |
| B29663 | SP | 24 | 25 | 26 |
| B29664 | SP | 23 | 24 | 30 |
| B29665 | SP | 25 | 32 | 37 |
| B29666 | SNB | 22 | 20 | 21 |
| B29667 | SP | 25 | 27 | 26 |
| B29668 | UPL | 29 | 33 | 32 |
| B29669 | SP | 18 | 32 | 25 |
| B29670 | SP | 22 | 27 | 29 |
| B29671 | SP | 20 | 21 | 26 |
| B29672 | SP | 21 | 24 | 23 |
| B29673 | SNB | 20 | 22 | 17 |
| B29674 | SP | 21 | 23 | 29 |
| B29675 | UPL | 22 | 22 | 26 |
| MEAN | | 23 | 26 | 28 |
| S.D. | | 3 | 4 | 3 |
| N | | 22 | 21 | 22 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Pregnancy period)

Dose: 1000 mg/kg/day

| FEMALE# | DAY OF PREGNANCY | | | |
|---------|------------------|--------|---------|----|
| | 0 - 7 | 7 - 14 | 14 - 20 | |
| B29676 | SP | 23 | 26 | 30 |
| B29677 | SP | 27 | 28 | 30 |
| B29678 | SP | 19 | 22 | 28 |
| B29679 | SP | 23 | 27 | 30 |
| B29680 | SP | 26 | 31 | 32 |
| B29681 | SP | 20 | 21 | 24 |
| B29682 | SP | 23 | 23 | 29 |
| B29683 | SP | 17 | 20 | 29 |
| B29684 | SP | 25 | 28 | 32 |
| B29685 | SP | 21 | 22 | 27 |
| B29686 | SP | 24 | 28 | 32 |
| B29687 | SP | 26 | 28 | 33 |
| B29688 | SP | 28 | 30 | 26 |
| B29689 | SP | 23 | 27 | 32 |
| B29690 | SP | 26 | 27 | 30 |
| B29691 | SP | 21 | 23 | 27 |
| B29692 | SP | 20 | 24 | 30 |
| B29693 | SP | 21 | 22 | 29 |
| B29694 | SP | 26 | 30 | 33 |
| B29695 | SP | 21 | 22 | 25 |
| B29696 | SP | 22 | 23 | 26 |
| B29697 | SP | 19 | 21 | 24 |
| B29698 | SP | 25 | 27 | 28 |
| B29699 | SP | 25 | 27 | 30 |
| B29700 | SP | 30 | 27 | 26 |
| MEAN | | 23 | 25 | 29 |
| S.D. | | 3 | 3 | 3 |
| N | | 25 | 25 | 25 |

SP=Fin sac/Pg

19. F0 generation - food consumption
(individual values/grams per day/females/lactation period)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Lactation period)

Dose: 0 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | |
|---------|-----|------------------|--------|---------|
| | | 1 - 7 | 7 - 14 | 14 - 21 |
| E29601 | SP | 36 | 52 | 61 |
| E29602 | SP | 38 | 56 | 67 |
| E29603 | SP | 29 | 40 | 52 |
| E29604 | SP | 33 | 45 | 55 |
| E29605 | SP | 41 | 55 | 68 |
| E29606 | SP | 24 | 44 | 58 |
| E29607 | SP | 40 | 55 | 63 |
| E29608 | SP | 38 | 57 | 66 |
| E29609 | SP | 36 | 57 | 73 |
| E29610 | SP | 33 | 53 | 64 |
| E29611 | SP | 30 | 35 | 37 |
| E29612 | SP | 45 | 63 | 72 |
| E29613 | SP | 37 | 54 | 71 |
| E29614 | SP | 36 | 57 | 71 |
| E29615 | SP | 27 | 44 | 58 |
| E29616 | SP | 39 | 59 | 66 |
| E29617 | SP | 39 | 63 | 72 |
| E29618 | SP | 38 | 56 | 63 |
| E29619 | SP | 34 | 55 | 65 |
| E29620 | SNB | | | |
| E29621 | SP | 36 | 55 | 63 |
| E29622 | SP | 38 | 54 | 70 |
| E29623 | SP | 39 | 54 | 68 |
| E29624 | SNB | | | |
| E29625 | SP | 32 | 47 | 60 |
| MEAN | | 36 | 53 | 64 |
| S.D. | | 5 | 7 | 8 |
| N | | 23 | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Lactation period)

Dose: 250 mg/kg/day

| FEMALE# | DAY OF LACTATION | | | |
|---------|------------------|--------|---------|----|
| | 1 - 7 | 7 - 14 | 14 - 21 | |
| B29626 | UPL | 22 | | |
| B29627 | SP | 43 | 62 | 72 |
| B29628 | SP | 38 | 53 | 64 |
| B29629 | SP | 23 | 51 | 71 |
| B29630 | SNB | | | |
| B29631 | SNB | | | |
| B29632 | SP | 39 | 55 | 67 |
| B29633 | SP | 27 | 54 | 62 |
| B29634 | SP | 39 | 53 | 60 |
| B29635 | SP | 40 | 55 | 71 |
| B29636 | SP | 38 | 62 | 76 |
| B29637 | SP | 38 | 59 | 68 |
| B29638 | SP | 51 | 47 | 56 |
| B29639 | SP | 36 | 58 | 68 |
| B29640 | SP | 40 | 60 | 69 |
| B29641 | SP | 33 | 56 | 69 |
| B29642 | SP | 23 | 54 | 69 |
| B29643 | SP | 35 | 55 | 75 |
| B29644 | SP | 45 | 58 | 67 |
| B29645 | SNB | | | |
| B29646 | SP | 37 | 55 | 61 |
| B29647 | SNB | | | |
| B29648 | SP | 37 | 59 | 70 |
| B29649 | SP | 44 | 59 | 65 |
| B29650 | SP | 32 | 46 | 52 |
| MEAN | | 36 | 56 | 67 |
| S.D. | | 8 | 4 | 6 |
| N | | 21 | 20 | 20 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Lactation period)

Dose: 500 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | |
|---------|-----|------------------|--------|---------|
| | | 1 - 7 | 7 - 14 | 14 - 21 |
| B29651 | SP | 33 | 53 | 66 |
| B29652 | SP | 34 | 50 | 44 |
| B29653 | SP | 37 | 52 | 68 |
| B29654 | SP | 35 | 53 | 63 |
| B29655 | SP | 43 | 59 | 67 |
| B29656 | SNB | | | |
| B29657 | SP | 33 | 51 | 67 |
| B29658 | SP | 38 | 61 | 75 |
| B29659 | SP | 37 | 56 | 61 |
| B29660 | SP | 45 | 66 | 75 |
| B29661 | UPL | | | |
| B29662 | SP | 35 | 54 | 66 |
| B29663 | SP | 36 | 53 | 68 |
| B29664 | SP | 37 | 62 | 75 |
| B29665 | SP | 39 | 54 | 63 |
| B29666 | SNB | | | |
| B29667 | SP | 31 | 44 | 64 |
| B29668 | UPL | | | |
| B29669 | SP | 29 | 48 | 55 |
| B29670 | SP | 45 | 62 | 75 |
| B29671 | SP | 33 | 48 | 60 |
| B29672 | SP | 38 | 54 | 60 |
| B29673 | SNB | | | |
| B29674 | SP | 35 | 54 | 63 |
| B29675 | UPL | | | |
| MEAN | | 37 | 54 | 65 |
| S.D. | | 4 | 5 | 8 |
| N | | 19 | 19 | 19 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

FOOD CONSUMPTION (Individual values/grams per day/Females/Lactation period)

Dose: 1000 mg/kg/day

| FEMALE# | | DAY OF LACTATION | | |
|---------|----|------------------|--------|---------|
| | | 1 - 7 | 7 - 14 | 14 - 21 |
| B29676 | SP | 45 | 62 | 71 |
| B29677 | SP | 43 | 63 | 76 |
| B29678 | SP | 41 | 59 | 71 |
| B29679 | SP | 39 | 58 | 68 |
| B29680 | SP | 34 | 57 | 63 |
| B29681 | SP | 37 | 58 | 70 |
| B29682 | SP | 41 | 63 | 74 |
| B29683 | SP | 36 | 55 | 66 |
| B29684 | SP | 42 | 65 | 78 |
| B29685 | SP | 38 | 56 | 70 |
| B29686 | SP | 41 | 63 | 68 |
| B29687 | SP | 41 | 60 | 72 |
| B29688 | SP | 40 | 61 | 70 |
| B29689 | SP | 43 | 67 | 75 |
| B29690 | SP | 41 | 60 | 71 |
| B29691 | SP | 43 | 64 | 72 |
| B29692 | SP | 38 | 58 | 68 |
| B29693 | SP | 37 | 57 | 70 |
| B29694 | SP | 45 | 62 | 65 |
| B29695 | SP | 42 | 57 | 64 |
| B29696 | SP | 34 | 54 | 61 |
| B29697 | SP | 39 | 55 | 67 |
| B29698 | SP | 40 | 55 | 65 |
| B29699 | SP | 41 | 61 | 81 |
| B29700 | SP | 43 | 59 | 64 |
| MEAN | | 40 | 59 | 70 |
| S.D. | | 3 | 3 | 5 |
| N | | 25 | 25 | 25 |

SP=Fin sac/Pg

20. F0 generation - pairing and mating data (individual values)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

PAIRING AND MATING DATA (Individual values)

Dose: 0 mg/kg/day

| Female No. | Period of pairing Male No. | Partner female status | Mating date | Number of days of pairing before mating |
|------------|-------------------------------|--------------------------|----------------|---|
| B29601 | B29201 | SP | 13-JUN-03 | 4 |
| B29602 | B29202 | SP | 11-JUN-03 | 2 |
| B29603 | B29203 | SP | 10-JUN-03 | 1 |
| B29604 | B29204 | SP | 13-JUN-03 | 4 |
| B29605 | B29205 | SP | 12-JUN-03 | 3 |
| B29606 | B29206 | SP | 10-JUN-03 | 1 |
| B29607 | B29207 | SP | 12-JUN-03 | 3 |
| B29608 | B29208 | SP | 12-JUN-03 | 3 |
| B29609 | B29209 | SP | 11-JUN-03 | 2 |
| B29610 | B29210 | SP | 10-JUN-03 | 1 |
| B29611 | B29211 | SP | 18-JUN-03 | 9 |
| B29612 | B29212 | SP | 11-JUN-03 | 2 |
| B29613 | B29213 | SP | 10-JUN-03 | 1 |
| B29614 | B29214 | SP | 13-JUN-03 | 4 |
| B29615 | B29215 | SP | 13-JUN-03 | 4 |
| B29616 | B29216 | SP | 12-JUN-03 | 3 |
| B29617 | B29217 | SP | 12-JUN-03 | 3 |
| B29618 | B29218 | SP | 10-JUN-03 | 1 |
| B29619 | B29219 | SP | 12-JUN-03 | 3 |
| B29620 | B29220 | SNB | 16-JUN-03 | 7 |
| B29621 | B29221 | SP | 11-JUN-03 | 2 |
| B29622 | B29222 | SP | 21-JUN-03 | 12 |
| B29623 | B29223 | SP | 11-JUN-03 | 2 |
| B29624 | B29224 | SNB | 12-JUN-03 | 3 |
| B29625 | B29225 | SP | 11-JUN-03 | 2 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

F0 GENERATION

PAIRING AND MATING DATA (Individual values)

Dose: 250 mg/kg/day

| Female No. | Period of pairing Male No. | Partner female status | Mating date | Number of days of pairing before mating |
|------------|-------------------------------|--------------------------|----------------|---|
| B29626 | B29226 | UPL | 10-JUN-03 | 1 |
| B29627 | B29227 | SP | 13-JUN-03 | 4 |
| B29628 | B29228 | SP | 12-JUN-03 | 3 |
| B29629 | B29229 | SP | 10-JUN-03 | 1 |
| B29630 | B29230 | SNB | 13-JUN-03 | 4 |
| B29631 | B29231 | SNB | 12-JUN-03 | 3 |
| B29632 | B29232 | SP | 10-JUN-03 | 1 |
| B29633 | B29233 | SP | 12-JUN-03 | 3 |
| B29634 | B29234 | SP | 23-JUN-03 | 14 |
| B29635 | B29235 | SP | 10-JUN-03 | 1 |
| B29636 | B29236 | SP | 11-JUN-03 | 2 |
| B29637 | B29237 | SP | 10-JUN-03 | 1 |
| B29638 | B29238 | SP | 12-JUN-03 | 3 |
| B29639 | B29239 | SP | 10-JUN-03 | 1 |
| B29640 | B29240 | SP | 11-JUN-03 | 2 |
| B29641 | B29241 | SP | 10-JUN-03 | 1 |
| B29642 | B29242 | SP | 13-JUN-03 | 4 |
| B29643 | B29243 | SP | 12-JUN-03 | 3 |
| B29644 | B29244 | SP | 10-JUN-03 | 1 |
| B29645 | B29245 | SNB | 10-JUN-03 | 1 |
| B29646 | B29246 | SP | 13-JUN-03 | 4 |
| B29647 | B29247 | SNB | 16-JUN-03 | 7 |
| B29648 | B29248 | SP | 10-JUN-03 | 1 |
| B29649 | B29249 | SP | 11-JUN-03 | 2 |
| B29650 | B29250 | SP | 10-JUN-03 | 1 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

PAIRING AND MATING DATA (Individual values)

Dose: 500 mg/kg/day

| Female No. | Period of pairing Male No. | Partner female status | Mating date | Number of days of pairing before mating |
|------------|-------------------------------|--------------------------|----------------|---|
| B29651 | B29251 | SP | 12-JUN-03 | 3 |
| B29652 | B29252 | SP | 13-JUN-03 | 4 |
| B29653 | B29253 | SP | 10-JUN-03 | 1 |
| B29654 | B29254 | SP | 10-JUN-03 | 1 |
| B29655 | B29255 | SP | 10-JUN-03 | 1 |
| B29656 | B29256 | SNB | 10-JUN-03 | 1 |
| B29657 | B29257 | SP | 10-JUN-03 | 1 |
| B29658 | B29258 | SP | 12-JUN-03 | 3 |
| B29659 | B29259 | SP | 17-JUN-03 | 8 |
| B29660 | B29260 | SP | 10-JUN-03 | 1 |
| B29661 | B29261 | UPL | 16-JUN-03 | 7 |
| B29662 | B29262 | SP | 19-JUN-03 | 10 |
| B29663 | B29263 | SP | 13-JUN-03 | 4 |
| B29664 | B29264 | SP | 11-JUN-03 | 2 |
| B29665 | B29265 | SP | 10-JUN-03 | 1 |
| B29666 | B29266 | SNB | 10-JUN-03 | 1 |
| B29667 | B29267 | SP | 13-JUN-03 | 4 |
| B29668 | B29268 | UPL | 10-JUN-03 | 1 |
| B29669 | B29269 | SP | 10-JUN-03 | 1 |
| B29670 | B29270 | SP | 10-JUN-03 | 1 |
| B29671 | B29271 | SP | 12-JUN-03 | 3 |
| B29672 | B29272 | SP | 10-JUN-03 | 1 |
| B29673 | B29273 | SNB | 10-JUN-03 | 1 |
| B29674 | B29274 | SP | 10-JUN-03 | 1 |
| B29675 | B29275 | UPL | 10-JUN-03 | 1 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

F0 GENERATION

PAIRING AND MATING DATA (Individual values)

Dose: 1000 mg/kg/day

| Female No. | Period of pairing Male No. | Partner female status | Mating date | Number of days of pairing before mating |
|------------|-------------------------------|--------------------------|----------------|---|
| B29676 | B29276 | SP | 12-JUN-03 | 3 |
| B29677 | B29277 | SP | 12-JUN-03 | 3 |
| B29678 | B29278 | SP | 11-JUN-03 | 2 |
| B29679 | B29276 | SP | 10-JUN-03 | 1 |
| B29680 | B29280 | SP | 10-JUN-03 | 1 |
| B29681 | B29281 | SP | 10-JUN-03 | 1 |
| B29682 | B29282 | SP | 10-JUN-03 | 1 |
| B29683 | B29283 | SP | 13-JUN-03 | 4 |
| B29684 | B29284 | SP | 13-JUN-03 | 4 |
| B29685 | B29285 | SP | 10-JUN-03 | 1 |
| B29686 | B29286 | SP | 11-JUN-03 | 2 |
| B29687 | B29287 | SP | 13-JUN-03 | 4 |
| B29688 | B29288 | SP | 12-JUN-03 | 3 |
| B29689 | B29289 | SP | 13-JUN-03 | 4 |
| B29690 | B29290 | SP | 12-JUN-03 | 3 |
| B29691 | B29291 | SP | 12-JUN-03 | 3 |
| B29692 | B29292 | SP | 10-JUN-03 | 1 |
| B29693 | B29293 | SP | 11-JUN-03 | 2 |
| B29694 | B29294 | SP | 12-JUN-03 | 3 |
| B29695 | B29295 | SP | 12-JUN-03 | 3 |
| B29696 | B29296 | SP | 13-JUN-03 | 4 |
| B29697 | B29297 | SP | 12-JUN-03 | 3 |
| B29698 | B29298 | SP | 12-JUN-03 | 3 |
| B29699 | B29299 | SP | 10-JUN-03 | 1 |
| B29700 | B29300 | SP | 17-JUN-03 | 8 |

SP=Fin sac/Pg

21. F0 generation - estrous stages

F0 GENERATION

ESTROUS STAGES

Dose: 0 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| B29601 | MET | EST | PRO | PRO | DI | PRO | PRO | DI | DI | PRO | DI | DI | PRO | DI | DI | MET | DI | PRO | |
| B29602 | EST | DI | PRO | PRO | EST | PRO | PRO | PRO | PRO | DI | DI | DI | DI | DI | DI | DI | DI | DI | DI |
| B29603 | PRO | EST | DI | PRO | MET | EST | PRO | PRO | PRO | PRO | DI | DI | DI | PRO | PRO | MET | DI | DI | |
| B29604 | DI | PRO | DI | PRO | MET | EST | DI | PRO | MET | EST | DI | PRO | PRO | EST | DI | DI | PRO | EST | |
| B29605 | EST | DI | PRO | PRO | EST | DI | PRO | PRO | EST | DI | EST | PRO | EST | DI | DI | PRO | EST | MET | |
| B29606 | EST | DI | PRO | PRO | EST | PRO | PRO | PRO | PRO | PRO | PRO | DI | PRO | MET | DI | DI | DI | PRO | |
| B29607 | PRO | MET | EST | PRO | DI | PRO | EST | DI | DI | PRO | PRO | EST | PRO | DI | EST | EST | MET | MET | |
| B29608 | EST | PRO | PRO | PRO | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | DI | PRO | MET | EST | MET | |
| B29609 | PRO | MET | PRO | EST | MET | PRO | PRO | EST | PRO | PRO | DI | EST | DI | PRO | PRO | EST | MET | MET | |
| B29610 | PRO | DI | PRO | EST | EST | EST | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | MET | MET | PRO | MET | |
| B29611 | EST | PRO | PRO | PRO | EST | DI | PRO | PRO | EST | DI | EST | PRO | EST | DI | PRO | MET | EST | DI | |
| B29612 | PRO | PRO | PRO | EST | MET | PRO | PRO | PRO | DI | PRO | DI | DI | MET | DI | PRO | EST | MET | DI | |
| B29613 | EST | DI | PRO | DI | EST | EST | DI | PRO | PRO | EST | EST | PRO | PRO | PRO | EST | DI | MET | MET | |
| B29614 | EST | PRO | PRO | PRO | EST | DI | PRO | PRO | PRO | PRO | PRO | DI | PRO | DI | DI | DI | DI | DI | |
| B29615 | PRO | PRO | PRO | EST | PRO | PRO | PRO | PRO | MET | PRO | DI | DI | EST | DI | DI | MET | DI | DI | |
| B29616 | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | DI | PRO | MET | EST | MET | |
| B29617 | DI | MET | PRO | EST | PRO | DI | DI | PRO | EST | DI | PRO | PRO | EST | DI | DI | DI | EST | MET | |
| B29618 | EST | PRO | PRO | PRO | MET | PRO | DI | MET | EST | PRO | PRO | DI | MET | EST | EST | PRO | PRO | MET | |
| B29619 | EST | EST | PRO | PRO | MET | PRO | PRO | MET | MET | PRO | DI | EST | DI | MET | DI | DI | DI | PRO | |
| B29620 | PRO | EST | PRO | PRO | MET | PRO | PRO | PRO | PRO | PRO | DI | DI | DI | DI | EST | EST | MET | DI | |
| B29621 | PRO | EST | PRO | EST | MET | PRO | DI | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | MET | DI | |
| B29622 | PRO | PRO | EST | DI | MET | PRO | EST | PRO | PRO | DI | EST | DI | DI | PRO | EST | DI | MET | PRO | |
| B29623 | DI | DI | PRO | EST | DI | MET | PRO | PRO | DI | PRO | PRO | DI | DI | PRO | DI | DI | PRO | DI | |
| B29624 | EST | DI | PRO | PRO | EST | DI | PRO | EST | EST | DI | DI | PRO | EST | PRO | DI | DI | EST | MET | |
| B29625 | DI | DI | PRO | EST | MET | PRO | PRO | PRO | PRO | PRO | DI | DI | DI | DI | DI | PRO | MET | MET | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

Day 19: missing values

F0 GENERATION

ESTROUS STAGES

Dose: 0 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-------|-------|-------|-------|-----|-----|-------|-----|------|-----|-----|-----|-------|----|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| B29601 | MET | MET | EST | MET | PRO | PRO | DI+S | | | | | | | | | | |
| B29602 | DI | MET | DI | MET | DI+S | | | | | | | | | | | | |
| B29603 | MET | MET | MET | SPERM | | | | | | | | | | | | | |
| B29604 | MET | DI | EST | MET | MET | MET | EST+S | | | | | | | | | | |
| B29605 | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29606 | MET | MET | MET | EST+S | | | | | | | | | | | | | |
| B29607 | MET | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29608 | DI | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29609 | EST | MET | MET | PRO | DI+S | | | | | | | | | | | | |
| B29610 | EST | PRO | PRO | DI+S | | | | | | | | | | | | | |
| B29611 | DI | DI | MET | MET | MET | MET | PRO | MET | DI | DI | PRO | DI+S | | | | | |
| B29612 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29613 | MET | MET | MET | EST+S | | | | | | | | | | | | | |
| B29614 | MET | DI | PRO | MET | DI | PRO | DI+S | | | | | | | | | | |
| B29615 | DI | EST | MET | MET | MET | PRO | EST+S | | | | | | | | | | |
| B29616 | PRO | EST | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29617 | MET | EST | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29618 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29619 | MET | PRO | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29620 | MET | MET | DI | PRO | PRO | DI | DI | DI | MET | EST+S | | | | | | | |
| B29621 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29622 | MET | MET | MET | DI | DI | DI | DI | MET | DI | DI | MET | MET | MET | MET | MET | MET+S | |
| B29623 | MET | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29624 | DI | EST | MET | MET | PRO | EST+S | | | | | | | | | | | |
| B29625 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

CIT/Study No. 24859 RSR/ETHYL TERTIARY BUTYL ETHER (ETBE)/
TOTAL France S.A.

F0 GENERATION

ESTROUS STAGES

Dose: 250 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| B29626 | PRO | EST | EST | PRO | DI | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | EST | EST | MET | MET | PRO | |
| B29627 | EST | EST | PRO | PRO | MET | EST | PRO | PRO | PRO | EST | PRO | DI | PRO | EST | MET | DI | PRO | EST | |
| B29628 | EST | DI | PRO | EST | EST | PRO | PRO | PRO | EST | PRO | MET | MET | EST | PRO | MET | DI | EST | MET | |
| B29629 | EST | EST | PRO | DI | EST | EST | PRO | PRO | DI | PRO | EST | PRO | MET | PRO | EST | MET | DI | PRO | |
| B29630 | PRO | EST | DI | PRO | PRO | EST | DI | PRO | PRO | EST | EST | DI | PRO | PRO | EST | DI | PRO | MET | |
| B29631 | EST | DI | PRO | PRO | MET | PRO | MET | PRO | MET | DI | EST | DI | EST | DI | PRO | PRO | EST | MET | |
| B29632 | MET | PRO | EST | PRO | EST | PRO | EST | PRO | MET | PRO | EST | PRO | DI | PRO | EST | MET | DI | PRO | |
| B29633 | EST | PRO | PRO | PRO | EST | MET | PRO | PRO | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | MET | |
| B29634 | PRO | EST | PRO | DI | PRO | EST | PRO | PRO | PRO | EST | PRO | EST | PRO | EST | MET | MET | PRO | EST | |
| B29635 | EST | PRO | DI | DI | EST | EST | PRO | PRO | PRO | EST | EST | PRO | PRO | EST | DI | DI | MET | EST | |
| B29636 | DI | DI | PRO | EST | DI | DI | PRO | EST | DI | PRO | DI | EST | DI | DI | EST | DI | DI | MET | |
| B29637 | PRO | EST | DI | DI | MET | PRO | PRO | MET | MET | MET | MET | DI | DI | DI | PRO | DI | DI | PRO | |
| B29638 | EST | EST | PRO | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | DI | PRO | MET | EST | MET | |
| B29639 | PRO | PRO | EST | DI | MET | PRO | EST | DI | EST | PRO | EST | DI | PRO | PRO | EST | MET | MET | PRO | |
| B29640 | PRO | PRO | EST | DI | EST | DI | PRO | PRO | PRO | PRO | DI | DI | DI | MET | DI | PRO | MET | MET | |
| B29641 | PRO | PRO | EST | DI | DI | EST | EST | DI | PRO | PRO | EST | DI | DI | PRO | EST | MET | DI | PRO | |
| B29642 | PRO | EST | DI | DI | EST | EST | DI | PRO | EST | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | |
| B29643 | EST | DI | PRO | DI | EST | DI | PRO | PRO | DI | PRO | EST | DI | MET | DI | DI | DI | DI | DI | |
| B29644 | PRO | PRO | EST | DI | MET | PRO | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | MET | MET | PRO | |
| B29645 | DI | EST | PRO | EST | PRO | PRO | PRO | DI | EST | PRO | DI | DI | PRO | PRO | DI | DI | DI | PRO | |
| B29646 | PRO | DI | PRO | EST | EST | MET | DI | DI | PRO | EST | DI | DI | DI | EST | MET | MET | PRO | MET | |
| B29647 | PRO | PRO | PRO | EST | DI | PRO | PRO | PRO | PRO | PRO | DI | DI | DI | PRO | DI | DI | PRO | MET | |
| B29648 | PRO | EST | DI | DI | DI | PRO | MET | EST | PRO | PRO | PRO | DI | PRO | PRO | MET | DI | DI | PRO | |
| B29649 | PRO | PRO | PRO | EST | DI | PRO | EST | EST | DI | PRO | EST | EST | DI | DI | PRO | EST | MET | DI | |
| B29650 | PRO | DI | PRO | EST | PRO | PRO | PRO | PRO | PRO | DI | DI | DI | DI | DI | DI | DI | DI | DI | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

Day 19: missing values

F0 GENERATION

ESTROUS STAGES

Dose: 250 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-------|-------|-------|-------|-----|----|-------|----|----|-----|----|----|-----|-------|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| B29626 | MET | MET | MET | DI+S | | | | | | | | | | | | | |
| B29627 | DI | DI | EST | MET | MET | PRO | EST+S | | | | | | | | | | |
| B29628 | EST | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29629 | DI | DI | MET | EST+S | | | | | | | | | | | | | |
| B29630 | MET | MET | DI | DI | DI | DI | EST+S | | | | | | | | | | |
| B29631 | MET | EST | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29632 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29633 | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29634 | DI | PRO | EST | MET | DI | MET | MET | MET | DI | DI | DI | DI | MET | DI | DI | MET | MET+S |
| B29635 | DI | PRO | PRO | DI+S | | | | | | | | | | | | | |
| B29636 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29637 | MET | DI | PRO | MET+S | | | | | | | | | | | | | |
| B29638 | DI | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29639 | DI | DI | PRO | EST+S | | | | | | | | | | | | | |
| B29640 | EST | MET | DI | PRO | EST+S | | | | | | | | | | | | |
| B29641 | MET | MET | MET | EST+S | | | | | | | | | | | | | |
| B29642 | DI | DI | EST | MET | MET | PRO | EST+S | | | | | | | | | | |
| B29643 | EST | PRO | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29644 | DI | MET | DI | EST+S | | | | | | | | | | | | | |
| B29645 | DI | PRO | EST | DI+S | | | | | | | | | | | | | |
| B29646 | DI | DI | EST | DI | DI | PRO | EST+S | | | | | | | | | | |
| B29647 | DI | DI | MET | MET | MET | MET | DI | MET | DI | EST+S | | | | | | | |
| B29648 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29649 | EST | MET | MET | PRO | DI+S | | | | | | | | | | | | |
| B29650 | DI | DI | PRO | EST+S | | | | | | | | | | | | | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

CIT/Study No. 24859 RSR/ETHYL TERTIARY BUTYL ETHER (ETBE)/
TOTAL France S.A.

F0 GENERATION

ESTROUS STAGES

Dose: 500 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| B29651 | EST | DI | PRO | PRO | EST | DI | PRO | PRO | EST | DI | PRO | DI | EST | DI | DI | DI | EST | MET | |
| B29652 | PRO | EST | DI | DI | MET | EST | PRO | PRO | PRO | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | |
| B29653 | DI | PRO | EST | DI | DI | PRO | PRO | DI | DI | PRO | EST | DI | DI | PRO | EST | DI | DI | MET | |
| B29654 | PRO | PRO | EST | PRO | MET | PRO | EST | DI | PRO | PRO | EST | DI | DI | PRO | EST | MET | DI | PRO | |
| B29655 | EST | EST | PRO | MET | EST | DI | PRO | DI | PRO | PRO | MET | DI | DI | DI | PRO | MET | DI | DI | |
| B29656 | EST | EST | PRO | DI | EST | PRO | EST | PRO | EST | PRO | EST | DI | PRO | PRO | EST | MET | DI | PRO | |
| B29657 | EST | PRO | PRO | PRO | EST | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | DI | PRO | EST | DI | PRO | |
| B29658 | EST | DI | DI | PRO | EST | DI | MET | PRO | EST | PRO | PRO | PRO | EST | DI | DI | MET | EST | MET | |
| B29659 | DI | PRO | PRO | EST | DI | PRO | PRO | EST | EST | DI | EST | MET | EST | PRO | MET | PRO | EST | MET | |
| B29660 | PRO | PRO | EST | DI | MET | PRO | EST | DI | DI | PRO | EST | PRO | MET | PRO | EST | MET | DI | PRO | |
| B29661 | EST | DI | DI | PRO | EST | DI | PRO | PRO | PRO | EST | DI | DI | PRO | PRO | EST | DI | DI | DI | |
| B29662 | EST | MET | PRO | DI | DI | PRO | MET | MET | EST | PRO | MET | DI | DI | DI | MET | MET | PRO | MET | |
| B29663 | EST | EST | DI | DI | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | MET | DI | PRO | EST | |
| B29664 | PRO | DI | PRO | EST | DI | DI | PRO | PRO | PRO | PRO | PRO | DI | PRO | EST | MET | DI | MET | MET | |
| B29665 | DI | PRO | EST | DI | EST | PRO | EST | PRO | EST | PRO | EST | DI | DI | PRO | EST | MET | DI | PRO | |
| B29666 | EST | PRO | PRO | EST | EST | EST | EST | EST | EST | EST | EST | EST | PRO | EST | EST | MET | DI | PRO | |
| B29667 | PRO | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | EST | PRO | PRO | EST | DI | MET | PRO | EST | |
| B29668 | PRO | PRO | EST | DI | MET | EST | EST | DI | PRO | PRO | EST | DI | DI | PRO | EST | MET | DI | EST | |
| B29669 | PRO | EST | DI | MET | PRO | PRO | PRO | DI | EST | PRO | PRO | DI | DI | DI | PRO | MET | DI | EST | |
| B29670 | DI | PRO | EST | DI | DI | PRO | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | MET | DI | PRO | |
| B29671 | PRO | MET | PRO | EST | EST | MET | PRO | PRO | EST | PRO | DI | DI | PRO | PRO | DI | DI | EST | MET | |
| B29672 | EST | DI | PRO | PRO | EST | PRO | MET | MET | PRO | PRO | DI | DI | DI | DI | DI | DI | DI | | |
| B29673 | EST | DI | PRO | PRO | EST | PRO | PRO | DI | PRO | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | |
| B29674 | PRO | PRO | PRO | PRO | DI | PRO | PRO | PRO | MET | DI | DI | DI | DI | PRO | DI | DI | DI | DI | |
| B29675 | DI | PRO | PRO | EST | DI | PRO | PRO | PRO | EST | EST | PRO | DI | PRO | EST | EST | DI | DI | PRO | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

Day 19: missing values

B29672, day 18: missing value

F0 GENERATION

ESTROUS STAGES

Dose: 500 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-------|------|-------|-------|-----|----|------|------|-----|-------|----|----|----|----|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| B29651 | DI | EST | MET | MET | PRO | EST+S | | | | | | | | | | | |
| B29652 | DI | DI | EST | PRO | DI | EST | EST+S | | | | | | | | | | |
| B29653 | DI | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29654 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29655 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29656 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29657 | EST | EST | MET | DI+S | | | | | | | | | | | | | |
| B29658 | MET | DI | MET | DI | DI | DI+S | | | | | | | | | | | |
| B29659 | DI | MET | MET | MET | DI | MET | MET | DI | DI | EST | DI+S | | | | | | |
| B29660 | MET | MET | PRO | DI+S | | | | | | | | | | | | | |
| B29661 | DI | DI | MET | DI | DI | MET | DI | DI | DI | DI+S | | | | | | | |
| B29662 | MET | MET | MET | MET | MET | MET | MET | MET | DI | DI | MET | MET | MET+S | | | | |
| B29663 | DI | MET | EST | MET | MET | PRO | EST+S | | | | | | | | | | |
| B29664 | PRO | MET | DI | PRO | DI+S | | | | | | | | | | | | |
| B29665 | MET | DI | PRO | EST+S | | | | | | | | | | | | | |
| B29666 | EST | EST | EST | EST+S | | | | | | | | | | | | | |
| B29667 | MET | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | |
| B29668 | MET | DI | MET | EST+S | | | | | | | | | | | | | |
| B29669 | DI | DI | MET | EST+S | | | | | | | | | | | | | |
| B29670 | MET | DI | MET | DI+S | | | | | | | | | | | | | |
| B29671 | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29672 | MET | DI | PRO | EST+S | | | | | | | | | | | | | |
| B29673 | DI | DI | EST | DI+S | | | | | | | | | | | | | |
| B29674 | MET | DI | PRO | EST+S | | | | | | | | | | | | | |
| B29675 | MET | DI | PRO | EST+S | | | | | | | | | | | | | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

F0 GENERATION

ESTROUS STAGES

Dose: 1000 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| B29676 | PRO | DI | PRO | EST | DI | PRO | DI | EST | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | MET | |
| B29677 | EST | PRO | PRO | PRO | EST | PRO | PRO | PRO | EST | PRO | EST | PRO | EST | PRO | MET | MET | EST | MET | |
| B29678 | DI | PRO | EST | DI | MET | PRO | EST | EST | PRO | DI | EST | EST | DI | DI | PRO | EST | MET | DI | |
| B29679 | PRO | PRO | EST | DI | MET | EST | EST | EST | EST | PRO | PRO | DI | DI | EST | MET | MET | PRO | EST | |
| B29680 | DI | PRO | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | PRO | PRO | PRO | EST | MET | DI | PRO | |
| B29681 | DI | MET | EST | PRO | DI | PRO | EST | DI | DI | PRO | EST | PRO | PRO | PRO | EST | MET | DI | DI | |
| B29682 | EST | EST | EST | DI | PRO | PRO | EST | EST | PRO | PRO | EST | DI | DI | PRO | EST | MET | DI | PRO | |
| B29683 | EST | DI | DI | MET | EST | DI | DI | MET | EST | EST | PRO | DI | PRO | EST | DI | DI | DI | EST | |
| B29684 | PRO | EST | DI | DI | MET | EST | DI | PRO | PRO | EST | EST | PRO | PRO | EST | DI | DI | PRO | EST | |
| B29685 | EST | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | EST | PRO | PRO | EST | PRO | MET | PRO | EST | |
| B29686 | DI | MET | PRO | EST | PRO | PRO | PRO | EST | PRO | DI | EST | EST | DI | PRO | PRO | EST | MET | DI | |
| B29687 | PRO | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | DI | PRO | EST | DI | MET | DI | MET | PRO | EST |
| B29688 | EST | DI | PRO | PRO | EST | PRO | PRO | EST | EST | PRO | EST | EST | EST | PRO | DI | DI | EST | MET | |
| B29689 | EST | EST | PRO | DI | EST | EST | PRO | PRO | EST | EST | EST | DI | PRO | EST | DI | DI | PRO | EST | |
| B29690 | EST | PRO | DI | PRO | EST | PRO | DI | PRO | EST | DI | EST | PRO | EST | DI | DI | DI | EST | MET | |
| B29691 | EST | EST | PRO | PRO | EST | PRO | DI | PRO | EST | EST | EST | PRO | EST | DI | PRO | PRO | EST | MET | |
| B29692 | DI | PRO | EST | DI | DI | PRO | EST | DI | PRO | PRO | EST | DI | PRO | PRO | EST | DI | MET | PRO | |
| B29693 | PRO | EST | PRO | EST | PRO | PRO | PRO | PRO | EST | PRO | DI | PRO | EST | PRO | PRO | MET | EST | EST | |
| B29694 | EST | MET | PRO | PRO | EST | DI | PRO | PRO | EST | DI | DI | DI | EST | PRO | PRO | MET | EST | MET | |
| B29695 | EST | PRO | PRO | PRO | EST | PRO | MET | PRO | EST | PRO | PRO | PRO | EST | PRO | DI | DI | EST | DI | |
| B29696 | DI | DI | PRO | EST | DI | MET | EST | PRO | DI | EST | PRO | DI | DI | EST | EST | MET | PRO | EST | |
| B29697 | EST | PRO | PRO | PRO | EST | EST | PRO | PRO | EST | PRO | EST | EST | EST | PRO | DI | EST | EST | MET | |
| B29698 | EST | DI | PRO | PRO | EST | DI | PRO | PRO | EST | DI | EST | PRO | EST | DI | DI | EST | EST | MET | |
| B29699 | EST | EST | DI | PRO | EST | DI | PRO | PRO | EST | PRO | PRO | DI | DI | DI | DI | DI | DI | DI | |
| B29700 | PRO | EST | EST | DI | MET | PRO | EST | PRO | MET | PRO | EST | DI | DI | PRO | EST | MET | MET | MET | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

Day 19: missing values

F0 GENERATION

ESTROUS STAGES

Dose: 1000 mg/kg/day

| FEMALE# | DAY OF ESTROUS EVALUATION | | | | | | | | | | | | | | | | |
|---------|---------------------------|-----|-----|-------|-------|-------|-------|-----|-----|----|------|----|----|----|----|----|----|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| B29676 | PRO | EST | MET | MET | PRO | DI+S | | | | | | | | | | | |
| B29677 | MET | EST | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29678 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29679 | MET | MET | MET | DI+S | | | | | | | | | | | | | |
| B29680 | MET | MET | PRO | EST+S | | | | | | | | | | | | | |
| B29681 | MET | MET | PRO | DI+S | | | | | | | | | | | | | |
| B29682 | MET | DI | PRO | EST+S | | | | | | | | | | | | | |
| B29683 | DI | DI | EST | DI | DI | PRO | EST+S | | | | | | | | | | |
| B29684 | MET | MET | EST | MET | DI | PRO | EST+S | | | | | | | | | | |
| B29685 | MET | EST | PRO | EST+S | | | | | | | | | | | | | |
| B29686 | EST | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29687 | MET | PRO | EST | MET | MET | PRO | EST+S | | | | | | | | | | |
| B29688 | DI | MET | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29689 | MET | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | |
| B29690 | DI | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29691 | PRO | EST | MET | DI | PRO | EST+S | | | | | | | | | | | |
| B29692 | MET | MET | EST | EST+S | | | | | | | | | | | | | |
| B29693 | PRO | MET | MET | PRO | EST+S | | | | | | | | | | | | |
| B29694 | MET | EST | MET | MET | MET | DI+S | | | | | | | | | | | |
| B29695 | MET | EST | MET | MET | PRO | EST+S | | | | | | | | | | | |
| B29696 | DI | EST | EST | MET | DI | PRO | EST+S | | | | | | | | | | |
| B29697 | PRO | EST | MET | DI | PRO | DI+S | | | | | | | | | | | |
| B29698 | MET | EST | MET | MET | PRO | EST+S | | | | | | | | | | | |
| B29699 | DI | PRO | PRO | DI+S | | | | | | | | | | | | | |
| B29700 | DI | DI | DI | MET | DI | DI | DI | EST | MET | DI | DI+S | | | | | | |

DI=DIESTRUS MET=METESTRUS PRO=PROESTRUS EST=ESTRUS +S=SPERM

22. F0 generation - pregnancy status of females (individual data)

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION

PREGNANCY STATUS OF FEMALES (Individual data)

Dose: 0 mg/kg/day

| ANIMAL# | DATE PREGNANT | DATE OF DEL | SCHED. SAC | ACTUAL DEATH | STATUS CODES |
|---------|---------------|-------------|------------|--------------|---------------------------|
| B29601 | 13-JUN-03 | 4-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29602 | 11-JUN-03 | 3-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29603 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29604 | 13-JUN-03 | 5-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29605 | 12-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29606 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29607 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29608 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29609 | 11-JUN-03 | 3-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29610 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29611 | 18-JUN-03 | 9-JUL-03 | | 31-JUL-03 | Fin sac/Pg |
| B29612 | 11-JUN-03 | 3-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29613 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29614 | 13-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29615 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29616 | 12-JUN-03 | 3-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29617 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29618 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29619 | 12-JUN-03 | 3-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29620 | 16-JUN-03 | | | 15-JUL-03 | Fin sac/NotPg/No delivery |
| B29621 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29622 | 21-JUN-03 | 13-JUL-03 | | 4-AUG-03 | Fin sac/Pg |
| B29623 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29624 | 12-JUN-03 | | | 9-JUL-03 | Fin sac/NotPg/No delivery |
| B29625 | 11-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |

F0 GENERATION

PREGNANCY STATUS OF FEMALES (Individual data)

Dose: 250 mg/kg/day

| ANIMAL# | DATE PREGNANT | DATE OF DEL | SCHED. SAC | ACTUAL DEATH | STATUS CODES |
|---------|---------------|-------------|------------|--------------|---------------------------|
| B29626 | 10-JUN-03 | 1-JUL-03 | | 9-JUL-03 | Prem sac/Pg/Lactation |
| B29627 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29628 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29629 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29630 | 13-JUN-03 | | | 9-JUL-03 | Fin sac/NotPg/No delivery |
| B29631 | 12-JUN-03 | | | 9-JUL-03 | Fin sac/NotPg/No delivery |
| B29632 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29633 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29634 | 23-JUN-03 | 15-JUL-03 | | 6-AUG-03 | Fin sac/Pg |
| B29635 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29636 | 11-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29637 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29638 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29639 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29640 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29641 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29642 | 13-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29643 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29644 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29645 | 10-JUN-03 | | | 7-JUL-03 | Fin sac/NotPg/No delivery |
| B29646 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29647 | 16-JUN-03 | | | 15-JUL-03 | Fin sac/NotPg/No delivery |
| B29648 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29649 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29650 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |

F0 GENERATION

PREGNANCY STATUS OF FEMALES (Individual data)

Dose: 500 mg/kg/day

| ANIMAL# | DATE PREGNANT | DATE OF DEL | SCHED. SAC | ACTUAL DEATH | STATUS CODES |
|---------|---------------|-------------|------------|--------------|---------------------------|
| B29651 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29652 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29653 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29654 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29655 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29656 | 10-JUN-03 | | | 7-JUL-03 | Fin sac/NotPg/No delivery |
| B29657 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29658 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29659 | 17-JUN-03 | 8-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29660 | 10-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29661 | 16-JUN-03 | 7-JUL-03 | | 11-JUL-03 | Prem sac/Pg/Lactation |
| B29662 | 19-JUN-03 | 11-JUL-03 | | 4-AUG-03 | Fin sac/Pg |
| B29663 | 13-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29664 | 11-JUN-03 | 2-JUL-03 | | 24-JUL-03 | Fin sac/Pg |
| B29665 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29666 | 10-JUN-03 | | | 7-JUL-03 | Fin sac/NotPg/No delivery |
| B29667 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29668 | 10-JUN-03 | 2-JUL-03 | | 4-JUL-03 | Prem sac/Pg/Lactation |
| B29669 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29670 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29671 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29672 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29673 | 10-JUN-03 | | | 7-JUL-03 | Fin sac/NotPg/No delivery |
| B29674 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29675 | 10-JUN-03 | 1-JUL-03 | | 4-JUL-03 | Prem sac/Pg/Lactation |

F0 GENERATION

PREGNANCY STATUS OF FEMALES (Individual data)

Dose: 1000 mg/kg/day

| ANIMAL# | DATE PREGNANT | DATE OF DEL | SCHED. SAC | ACTUAL DEATH | STATUS CODES |
|---------|---------------|-------------|------------|--------------|--------------|
| B29676 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29677 | 12-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29678 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29679 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29680 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29681 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29682 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29683 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29684 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29685 | 10-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29686 | 11-JUN-03 | 2-JUL-03 | | 25-JUL-03 | Fin sac/Pg |
| B29687 | 13-JUN-03 | 5-JUL-03 | | 30-JUL-03 | Fin sac/Pg |
| B29688 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29689 | 13-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29690 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29691 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29692 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29693 | 11-JUN-03 | 3-JUL-03 | | 28-JUL-03 | Fin sac/Pg |
| B29694 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29695 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29696 | 13-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29697 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29698 | 12-JUN-03 | 4-JUL-03 | | 29-JUL-03 | Fin sac/Pg |
| B29699 | 10-JUN-03 | 1-JUL-03 | | 23-JUL-03 | Fin sac/Pg |
| B29700 | 17-JUN-03 | 9-JUL-03 | | 31-JUL-03 | Fin sac/Pg |

23. F0 generation - delivery and litter data

Fin sac: final sacrifice
Prem sac: prematurely sacrificed
Pg: pregnant
NotPg: not pregnant

F0 GENERATION
DELIVERY AND LITTER DATA

Dose: 0 mg/kg/day

| FEMALE# | LITTER DELIVERED | | | NUMBER OF LIVE PUPS | | | | | | | | | | TOTAL IMPLAN- TATIONS N | DURATION OF GESTATION (DAYS) N | | | |
|---------|------------------|-----------|------------|---------------------|------|----|------|----|-----|---|-----|----|-----|----------------------------------|---|----|------|------|
| | LIVE N | DEAD N | TOTAL N | DAYS | | | | | | | | | | | | | | |
| | | | | 1 | | 4 | | 4 | | 7 | | 14 | | | | 21 | | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | N | N | | | |
| B29601 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 15 | 21 |
| B29602 | SP | 15 | 0 | 15 | 7 | 8 | 7 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29603 | SP | 18 | 0 | 18 | 8 | 10 | 8 | 10 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 18 | 21 |
| B29604 | SP | 14 | 0 | 14 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29605 | SP | 14 | 0 | 14 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 23 |
| B29606 | SP | 14 | 0 | 14 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 21 |
| B29607 | SP | 12 | 0 | 12 | 7 | 5 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 12 | 22 |
| B29608 | SP | 10 | 0 | 10 | 4 | 6 | 4 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 11 | 22 |
| B29609 | SP | 12 | 0 | 12 | 11 | 1 | 11 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 14 | 22 |
| B29610 | SP | 10 | 0 | 10 | 7 | 3 | 7 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 11 | 22 |
| B29611 | SP | 16 | 0 | 16 | 9 | 7 | 9 | 7 | 4 | 4 | 1 | 2 | 1 | 2 | 1 | 2 | 16 | 21 |
| B29612 | SP | 14 | 0 | 14 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29613 | SP | 14 | 0 | 14 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29614 | SP | 17 | 0 | 17 | 11 | 6 | 11 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 19 | 21 |
| B29615 | SP | 19 | 0 | 19 | 11 | 8 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 19 | 22 |
| B29616 | SP | 14 | 0 | 14 | 5 | 9 | 5 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 21 |
| B29617 | SP | 16 | 0 | 16 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29618 | SP | 15 | 0 | 15 | 6 | 9 | 6 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 21 |
| B29619 | SP | 13 | 0 | 13 | 5 | 8 | 5 | 8 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 15 | 21 |
| B29620 | SNB | | | | | | | | | | | | | | | | | |
| B29621 | SP | 14 | 0 | 14 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29622 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29623 | SP | 14 | 0 | 14 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29624 | SNB | | | | | | | | | | | | | | | | | |
| B29625 | SP | 13 | 0 | 13 | 6 | 7 | 6 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 13 | 21 |
| TOTAL | | 328 | 0 | 328 | 327 | | 320 | | 184 | | 176 | | 174 | | 174 | | 343 | |
| MEAN | | 14.3 | 0.0 | 14.3 | 14.2 | | 13.9 | | 8.0 | | 7.7 | | 7.6 | | 7.6 | | 14.9 | 21.7 |
| S.D. | | 2.2 | 0.0 | 2.2 | 2.2 | | 2.0 | | 0.0 | | 1.1 | | 1.1 | | 1.1 | | 2.2 | 0.6 |
| N | | 23 | 23 | 23 | 23 | | 23 | | 23 | | 23 | | 23 | | 23 | | 23 | 23 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery

DAY 4 COLUMNS = PRE- AND POSTCULLING RESPECTIVELY

F0 GENERATION

DELIVERY AND LITTER DATA

Dose: 250 mg/kg/day

| FEMALE# | LITTER DELIVERED | | | NUMBER OF LIVE PUPS | | | | | | | | | | | | TOTAL IMPLAN- TATIONS N | DURATION OF GESTATION (DAYS) N | |
|---------|------------------|-----------|------------|---------------------|------|----|------|----|-----|----|-----|----|-----|---|-----|----------------------------------|---|------|
| | LIVE N | DEAD N | TOTAL N | DAYS | | | | | | | | | | | | | | |
| | | | | 1 | | 4 | | 7 | | 14 | | 21 | | | | | | |
| | | | | M | F | M | F | M | F | M | F | M | F | M | F | | | |
| B29626 | UPL | 14 | 0 | 14 | 3 | 11 | 3 | 9 | 3 | 5 | 0 | 1 | 0 | 0 | 0 | 0 | 15 | 21 |
| B29627 | SP | 14 | 0 | 14 | 8 | 5 | 8 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29628 | SP | 16 | 0 | 16 | 6 | 10 | 6 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 21 |
| B29629 | SP | 16 | 0 | 16 | 10 | 6 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 22 |
| B29630 | SNB | | | | | | | | | | | | | | | | | |
| B29631 | SNB | | | | | | | | | | | | | | | | | |
| B29632 | SP | 11 | 0 | 11 | 6 | 5 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 12 | 21 |
| B29633 | SP | 14 | 0 | 14 | 2 | 11 | 1 | 8 | 1 | 7 | 0 | 7 | 0 | 7 | 0 | 7 | 14 | 22 |
| B29634 | SP | 12 | 0 | 12 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29635 | SP | 10 | 0 | 10 | 5 | 5 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 10 | 22 |
| B29636 | SP | 15 | 0 | 15 | 7 | 8 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29637 | SP | 12 | 0 | 12 | 3 | 9 | 3 | 9 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 14 | 21 |
| B29638 | SP | 18 | 0 | 18 | 8 | 10 | 8 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 18 | 21 |
| B29639 | SP | 14 | 0 | 14 | 8 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29640 | SP | 12 | 0 | 12 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29641 | SP | 14 | 0 | 14 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 21 |
| B29642 | SP | 16 | 0 | 16 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 21 |
| B29643 | SP | 17 | 0 | 17 | 9 | 8 | 8 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 18 | 21 |
| B29644 | SP | 15 | 0 | 15 | 7 | 8 | 6 | 8 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 15 | 22 |
| B29645 | SNB | | | | | | | | | | | | | | | | | |
| B29646 | SP | 14 | 0 | 14 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 16 | 22 |
| B29647 | SNB | | | | | | | | | | | | | | | | | |
| B29648 | SP | 11 | 0 | 11 | 5 | 6 | 5 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 13 | 22 |
| B29649 | SP | 13 | 0 | 13 | 9 | 4 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29650 | SP | 18 | 0 | 18 | 6 | 12 | 5 | 8 | 4 | 4 | 3 | 2 | 3 | 2 | 3 | 2 | 19 | 21 |
| TOTAL | | 296 | 0 | 296 | 294 | | 275 | | 168 | | 156 | | 154 | | 154 | | 314 | |
| MEAN | | 14.1 | 0.0 | 14.1 | 14.0 | | 13.1 | | 8.0 | | 7.4 | | 7.7 | | 7.7 | | 15.0 | 21.5 |
| S.D. | | 2.3 | 0.0 | 2.3 | 2.3 | | 2.1 | | 0.0 | | 1.6 | | 0.7 | | 0.7 | | 2.1 | 0.5 |
| N | | 21 | 21 | 21 | 21 | | 21 | | 21 | | 21 | | 20 | | 20 | | 21 | 21 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

DAY 4 COLUMNS = PRE- AND POSTCULLING RESPECTIVELY

F0 GENERATION
DELIVERY AND LITTER DATA

Dose: 500 mg/kg/day

| FEMALE# | | LITTER DELIVERED | | | NUMBER OF LIVE PUPS | | | | | | | | | | TOTAL IMPLAN- TATIONS N | DURATION OF GESTATION (DAYS) N | | |
|---------|-----|------------------|-----------|------------|---------------------|----|------|----|-----|---|-----|---|-----|---|----------------------------------|---|------|------|
| | | LIVE N | DEAD N | TOTAL N | DAYS | | | | | | | | | | | | | |
| | | | | | 1 | | 4 | | 7 | | 14 | | 21 | | | | | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | | | | | |
| B29651 | SP | 16 | 0 | 16 | 8 | 8 | 8 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29652 | SP | 14 | 0 | 14 | 8 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29653 | SP | 15 | 0 | 15 | 8 | 7 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29654 | SP | 17 | 0 | 17 | 7 | 10 | 7 | 10 | 4 | 4 | 3 | 4 | 3 | 3 | 3 | 3 | 17 | 22 |
| B29655 | SP | 14 | 0 | 14 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29656 | SNB | | | | | | | | | | | | | | | | | |
| B29657 | SP | 9 | 0 | 9 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 11 | 22 |
| B29658 | SP | 17 | 0 | 17 | 4 | 12 | 4 | 12 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 21 |
| B29659 | SP | 16 | 0 | 16 | 11 | 5 | 11 | 5 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 16 | 21 |
| B29660 | SP | 13 | 0 | 13 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29661 | UPL | 18 | 0 | 18 | 8 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 19 | 21 |
| B29662 | SP | 14 | 0 | 14 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29663 | SP | 15 | 0 | 15 | 9 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 21 |
| B29664 | SP | 15 | 0 | 15 | 10 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29665 | SP | 17 | 0 | 17 | 9 | 8 | 9 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 18 | 21 |
| B29666 | SNB | | | | | | | | | | | | | | | | | |
| B29667 | SP | 20 | 0 | 20 | 8 | 9 | 8 | 7 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 20 | 22 |
| B29668 | UPL | 15 | 0 | 15 | 5 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 22 |
| B29669 | SP | 13 | 0 | 13 | 6 | 7 | 6 | 7 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 14 | 21 |
| B29670 | SP | 16 | 0 | 16 | 9 | 7 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 22 |
| B29671 | SP | 13 | 0 | 13 | 5 | 8 | 5 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29672 | SP | 12 | 0 | 12 | 5 | 7 | 5 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 13 | 22 |
| B29673 | SNB | | | | | | | | | | | | | | | | | |
| B29674 | SP | 14 | 0 | 14 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 21 |
| B29675 | UPL | 14 | 0 | 14 | 7 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 21 |
| TOTAL | | 327 | 0 | 327 | 317 | | 269 | | 152 | | 147 | | 146 | | 146 | | 344 | |
| MEAN | | 14.9 | 0.0 | 14.9 | 14.4 | | 14.2 | | 8.0 | | 7.7 | | 7.7 | | 7.7 | | 15.6 | 21.5 |
| S.D. | | 2.3 | 0.0 | 2.3 | 2.2 | | 2.0 | | 0.0 | | 0.6 | | 0.7 | | 0.7 | | 2.1 | 0.5 |
| N | | 22 | 22 | 22 | 22 | | 19 | | 19 | | 19 | | 19 | | 19 | | 22 | 22 |

SP=Fin sac/Pg SNB=Fin sac/NotPg/No delivery UPL=Prem sac/Pg/Lactation

DAY 4 COLUMNS = PRE- AND POSTCULLING RESPECTIVELY

F0 GENERATION
DELIVERY AND LITTER DATA

Dose: 1000 mg/kg/day

| FEMALE# | LITTER DELIVERED | | | NUMBER OF LIVE PUPS | | | | | | | | | | TOTAL IMPLAN- TATIONS N | DURATION OF GESTATION (DAYS) N | | | |
|---------|------------------|-----------|------------|---------------------|------|----|------|----|-----|---|-----|----|-----|----------------------------------|---|----|------|------|
| | LIVE N | DEAD N | TOTAL N | DAYS | | | | | | | | | | | | | | |
| | | | | 1 | | 4 | | 4 | | 7 | | 14 | | | | 21 | | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | N | N | | | |
| B29676 | SP | 10 | 0 | 10 | 7 | 3 | 7 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 11 | 22 |
| B29677 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29678 | SP | 17 | 0 | 17 | 12 | 5 | 12 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 22 |
| B29679 | SP | 10 | 0 | 10 | 4 | 6 | 4 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 11 | 22 |
| B29680 | SP | 14 | 0 | 14 | 2 | 12 | 2 | 12 | 2 | 6 | 2 | 6 | 2 | 5 | 2 | 5 | 14 | 22 |
| B29681 | SP | 13 | 0 | 13 | 8 | 5 | 8 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29682 | SP | 14 | 0 | 14 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29683 | SP | 14 | 0 | 14 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29684 | SP | 13 | 0 | 13 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 22 |
| B29685 | SP | 12 | 0 | 12 | 7 | 5 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29686 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29687 | SP | 17 | 0 | 17 | 10 | 7 | 10 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 17 | 22 |
| B29688 | SP | 17 | 0 | 17 | 8 | 9 | 8 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 19 | 22 |
| B29689 | SP | 16 | 0 | 16 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 21 |
| B29690 | SP | 15 | 0 | 15 | 6 | 9 | 6 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29691 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 22 |
| B29692 | SP | 15 | 0 | 15 | 8 | 7 | 8 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29693 | SP | 16 | 0 | 16 | 7 | 8 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 19 | 22 |
| B29694 | SP | 14 | 0 | 14 | 7 | 7 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29695 | SP | 15 | 0 | 15 | 7 | 8 | 7 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| B29696 | SP | 15 | 0 | 15 | 9 | 6 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 15 | 21 |
| B29697 | SP | 12 | 0 | 12 | 8 | 4 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 13 | 22 |
| B29698 | SP | 14 | 0 | 14 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 22 |
| B29699 | SP | 11 | 0 | 11 | 7 | 4 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 14 | 21 |
| B29700 | SP | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 4 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 16 | 22 |
| TOTAL | | 354 | 0 | 354 | 353 | | 346 | | 201 | | 200 | | 199 | | 199 | | 379 | |
| MEAN | | 14.2 | 0.0 | 14.2 | 14.1 | | 13.8 | | 8.0 | | 8.0 | | 8.0 | | 8.0 | | 15.2 | 21.8 |
| S.D. | | 2.0 | 0.0 | 2.0 | 1.9 | | 2.0 | | 0.2 | | 0.0 | | 0.2 | | 0.2 | | 1.9 | 0.4 |
| N | | 25 | 25 | 25 | 25 | | 25 | | 25 | | 25 | | 25 | | 25 | | 25 | 25 |

SP=Fin sac/Pg

DAY 4 COLUMNS = PRE- AND POSTCULLING RESPECTIVELY

24. F0 generation - daily litter survival

F0 GENERATION

DAILY LITTER SURVIVAL

Dose: 0 mg/kg/day

| FEMALE# | NUMBER OF LIVE PUPS | | | | | | | | | | | | | | | | | | | | | | | |
|---------|---------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | DAYS | | | | | | | | | | | | | | | | | | | | | | | |
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | 11 | | 12 | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | |
| B29601 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 |
| B29602 | 7 | 8 | 7 | 8 | 7 | 8 | 7 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29603 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| B29604 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29605 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29606 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29607 | 7 | 5 | 7 | 5 | 7 | 5 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29608 | 4 | 6 | 4 | 6 | 4 | 6 | 4 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29609 | 11 | 1 | 11 | 1 | 11 | 1 | 11 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 | 7 | 1 |
| B29610 | 7 | 3 | 7 | 3 | 7 | 3 | 7 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 |
| B29611 | 9 | 7 | 9 | 7 | 9 | 7 | 9 | 7 | 3 | 3 | 3 | 3 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| B29612 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29613 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29614 | 11 | 6 | 11 | 6 | 11 | 6 | 11 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29615 | 11 | 8 | 8 | 6 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 |
| B29616 | 5 | 9 | 5 | 9 | 5 | 9 | 5 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29617 | 7 | 9 | 7 | 9 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29618 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29619 | 5 | 8 | 5 | 8 | 5 | 8 | 5 | 8 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 |
| B29621 | 9 | 5 | 9 | 5 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29622 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29623 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29625 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| TOTAL | 171 | 156 | 168 | 154 | 166 | 154 | 166 | 154 | 95 | 87 | 95 | 86 | 92 | 84 | 92 | 82 | 92 | 82 | 92 | 82 | 92 | 82 | 92 | 82 |

F0 GENERATION
DAILY LITTER SURVIVAL

Dose: 250 mg/kg/day

| FEMALE# | NUMBER OF LIVE PUPS | | | | | | | | | | | | | | | | | | | | | | | |
|---------|---------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | DAYS | | | | | | | | | | | | | | | | | | | | | | | |
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | 11 | | 12 | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | |
| B29626 | 3 | 11 | 3 | 11 | 3 | 11 | 3 | 9 | 1 | 5 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| B29627 | 8 | 5 | 8 | 5 | 8 | 5 | 8 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29628 | 6 | 10 | 6 | 10 | 6 | 10 | 6 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29629 | 10 | 6 | 10 | 6 | 9 | 6 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29632 | 6 | 5 | 6 | 5 | 6 | 5 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29633 | 2 | 11 | 1 | 8 | 1 | 8 | 1 | 8 | 0 | 7 | 0 | 7 | 0 | 7 | 0 | 7 | 0 | 7 | 0 | 7 | 0 | 7 | 0 | 7 |
| B29634 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29635 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29636 | 7 | 8 | 7 | 7 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29637 | 3 | 9 | 3 | 9 | 3 | 9 | 3 | 9 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 |
| B29638 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29639 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29640 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29641 | 9 | 5 | 9 | 5 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29642 | 7 | 9 | 7 | 9 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29643 | 9 | 8 | 9 | 8 | 8 | 7 | 8 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29644 | 7 | 8 | 7 | 8 | 6 | 8 | 6 | 8 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 |
| B29646 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | |
| B29648 | 5 | 6 | 5 | 6 | 5 | 6 | 5 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29649 | 9 | 4 | 9 | 4 | 9 | 4 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29650 | 6 | 12 | 6 | 12 | 6 | 12 | 5 | 8 | 4 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 |
| TOTAL | 140 | 154 | 139 | 150 | 136 | 149 | 133 | 142 | 76 | 87 | 73 | 84 | 73 | 83 | 73 | 82 | 73 | 81 | 73 | 81 | 73 | 81 | 73 | 81 |

F0 GENERATION
DAILY LITTER SURVIVAL

Dose: 500 mg/kg/day

| FEMALE# | NUMBER OF LIVE PUPS | | | | | | | | | | | | | | | | | | | | | | | |
|---------|---------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | DAYS | | | | | | | | | | | | | | | | | | | | | | | |
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | 11 | | 12 | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | |
| B29651 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29652 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29653 | 8 | 7 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29654 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 3 | |
| B29655 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29657 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | |
| B29658 | 4 | 12 | 4 | 12 | 4 | 12 | 4 | 12 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29659 | 11 | 5 | 11 | 5 | 11 | 5 | 11 | 5 | 11 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | |
| B29660 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29661 | 8 | 9 | 3 | 4 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| B29662 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29663 | 9 | 6 | 9 | 6 | 9 | 6 | 8 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29664 | 10 | 5 | 9 | 5 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29665 | 9 | 8 | 9 | 8 | 9 | 8 | 9 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29667 | 8 | 9 | 8 | 9 | 8 | 9 | 8 | 7 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| B29668 | 5 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| B29669 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 3 | |
| B29670 | 9 | 7 | 9 | 7 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29671 | 5 | 8 | 5 | 8 | 5 | 8 | 5 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29672 | 5 | 7 | 5 | 7 | 5 | 7 | 5 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29674 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| B29675 | 7 | 7 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| TOTAL | 154 | 163 | 141 | 149 | 135 | 141 | 132 | 137 | 78 | 74 | 76 | 73 | 75 | 72 | 75 | 72 | 75 | 72 | 75 | 72 | 75 | 71 | 75 | 71 |

F0 GENERATION
DAILY LITTER SURVIVAL

Dose: 1000 mg/kg/day

| FEMALE# | NUMBER OF LIVE PUPS | | | | | | | | | | | | | | | | | | | | | | | |
|---------|---------------------|-----|-----|-----|-----|-----|-----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| | DAYS | | | | | | | | | | | | | | | | | | | | | | | |
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | | 11 | | 12 | |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | |
| B29676 | 7 | 3 | 7 | 3 | 7 | 3 | 7 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 | 5 | 3 |
| B29677 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29678 | 12 | 5 | 12 | 5 | 12 | 4 | 12 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29679 | 4 | 6 | 4 | 6 | 4 | 6 | 4 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29680 | 2 | 12 | 2 | 12 | 2 | 12 | 2 | 12 | 2 | 6 | 2 | 6 | 2 | 6 | 2 | 5 | 2 | 5 | 2 | 5 | 2 | 5 | 2 | 5 |
| B29681 | 8 | 5 | 8 | 5 | 8 | 5 | 8 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29682 | 9 | 5 | 9 | 5 | 9 | 5 | 9 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29683 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29684 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29685 | 7 | 5 | 7 | 5 | 7 | 5 | 7 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29686 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29687 | 10 | 7 | 10 | 7 | 10 | 7 | 10 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29688 | 8 | 9 | 8 | 9 | 8 | 9 | 8 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29689 | 7 | 9 | 7 | 9 | 7 | 9 | 7 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29690 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29691 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29692 | 8 | 7 | 8 | 7 | 8 | 7 | 8 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29693 | 7 | 8 | 7 | 8 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29694 | 7 | 7 | 7 | 7 | 7 | 6 | 7 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29695 | 7 | 8 | 7 | 8 | 7 | 8 | 7 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29696 | 9 | 6 | 6 | 5 | 6 | 5 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29697 | 8 | 4 | 8 | 4 | 8 | 4 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29698 | 10 | 4 | 10 | 4 | 10 | 4 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29699 | 7 | 4 | 7 | 4 | 7 | 4 | 7 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| B29700 | 9 | 6 | 9 | 6 | 9 | 6 | 9 | 6 | 4 | 5 | 4 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| TOTAL | 193 | 160 | 190 | 159 | 190 | 156 | 190 | 156 | 99 | 102 | 99 | 102 | 99 | 101 | 99 | 100 | 99 | 100 | 99 | 100 | 99 | 100 | 99 | 100 |

25. F0 generation - pup survival (individual data/lactation period)

F0 GENERATION

PUP SURVIVAL (Individual data/Lactation period)

Dose: 0 mg/kg/day

| FEMALE# | PUP # | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|----|------|----|------|------|----|----|----|----|----|----|----|----|---|--|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | | | | | | | | | | | | |
| B29601 | MP22 | MW24 | MW24 | MW24 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FP22 | FZ | 8 | FW24 | FW24 | FC | 4 | FC | 4 | | | | | | | | | | | | |
| B29602 | MP22 | MW22 | MW22 | MW22 | MC | 4 | MC | 4 | MC | 4 | FP22 | FW22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | | | |
| B29603 | MZ | 7 | MP22 | MW22 | MW22 | MC | 4 | MC | 4 | MC | 4 | FP22 | FW22 | FW22 | FZ | 6 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | | | |
| B29604 | MP22 | MW24 | MW24 | MW24 | MC | 4 | MC | 4 | FP22 | FW24 | FW24 | FW24 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | | | |
| B29605 | MP22 | MP22 | MW25 | MW25 | MC | 4 | MC | 4 | MC | 4 | MM | 1 | FP22 | FP22 | FW25 | FW25 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | | | |
| B29606 | MP22 | MP22 | MW22 | MW22 | MC | 4 | MC | 4 | MC | 4 | FP22 | FP22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | | | |
| B29607 | MP22 | MW25 | MW25 | MW25 | MC | 4 | FC | 4 | MC | 4 | MC | 4 | FP22 | FW25 | FW25 | FW25 | | | | | | | | | | | | | | | | | | | |
| B29608 | MW25 | MP22 | MW25 | MW25 | FP22 | FW25 | FW25 | FW25 | FC | 4 | FC | 4 | | | | | | | | | | | | | | | | | | | | | | | |
| B29609 | MP22 | MW22 | MW22 | MW22 | MW22 | MW22 | MW22 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FP22 | | | | | | | | | | | |
| B29610 | MP22 | MW22 | MW22 | MW22 | MC | 4 | MC | 4 | FP22 | MW22 | FW22 | FW22 | | | | | | | | | | | | | | | | | | | | | | | |
| B29611 | MD | 7 | MD | 5 | MD | 7 | MW22 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FW22 | FW22 | FD | 5 | FD | 7 | FC | 4 | FC | 4 | | | | | | | | | | |
| B29612 | MP22 | MW22 | MW22 | MW22 | FP22 | FW22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | |
| B29613 | MP22 | MP22 | MW22 | MW22 | MC | 4 | FP22 | FP22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | MC | 4 | | | | | | | | | |
| B29614 | MP22 | MW25 | MW25 | MW25 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FP22 | FW25 | FW25 | FW25 | FC | 4 | FC | 4 | FC | 4 | | | | | | | | | |
| B29615 | MD | 3 | MP22 | MD | 3 | MW25 | MW25 | MD | 2 | MD | 2 | MW25 | MC | 4 | MC | 4 | MD | 2 | FW25 | FD | 2 | FP22 | FD | 8 | FW25 | FC | 4 | FC | 4 | FD | 2 | | | | |
| B29616 | MP22 | MP22 | MW22 | MW22 | MC | 4 | FP22 | FP22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | |
| B29617 | MP22 | MW25 | MW25 | MW25 | MC | 4 | MC | 4 | MC | 4 | FC | 4 | FP22 | FW25 | FW25 | FW25 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | |
| B29618 | MP22 | MW22 | MW22 | MW22 | MC | 4 | MC | 4 | FP22 | FW22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | |
| B29619 | MP22 | MW22 | MW22 | MW22 | MC | 4 | FP22 | FW22 | FZ | 7 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | |
| B29621 | MP22 | MW25 | MW25 | MW25 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FP22 | FW25 | FW25 | FW25 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | | | |
| B29622 | MW22 | MW22 | MW22 | MW22 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FW22 | FW22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | |
| B29623 | MP22 | MW25 | MW25 | MW25 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | MC | 4 | FP22 | FW25 | FW25 | FW25 | | | | | | | | | | | | | | | |
| B29625 | MW22 | MP22 | MW22 | MW22 | MC | 4 | MC | 4 | FP22 | FW22 | FW22 | FW22 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | FC | 4 | |

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE D-DIED C-CULLED Z-CANNIBALIZED M-MISSING P-SELECTED PARENT W-SACRIFICED AFTER WEANING

CIT/Study No. 24859 RSR/ETHYL TERTIARY BUTYL ETHER (ETBE)/
TOTAL France S.A.

F0 GENERATION

PUP SURVIVAL (Individual data/Lactation period)

Dose: 250 mg/kg/day

| FEMALE# | PUP # | | | | | | | | | | | | | | | | | | | | | | |
|---------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|----|----|----|----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| B29626 | MD 6 | MD 5 | MZ 5 | FZ 6 | FD 4 | FZ 7 | FD 4 | FZ 8 | FD 6 | FD 6 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | |
| B29627 | MP22 | MP22 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW25 | FW25 | FC 4 | FD 1 | | | | | | | | | |
| B29628 | MP22 | MP22 | MW25 | MW25 | MC 4 | MC 4 | FP22 | FP22 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | |
| B29629 | MP22 | MZ 4 | MZ 4 | MW22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | FZ 4 | FW22 | FP22 | FW22 | FW22 | MD 3 | FC 4 | | | | | | | |
| B29632 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | | | | | | | | | | | | |
| B29633 | MD 1 | MD 2 | MD 5 | FW25 | FP22 | FW25 | FD 2 | FD 2 | FW25 | FD 2 | FW25 | FW25 | FW25 | FC 4 | | | | | | | | | |
| B29634 | MW22 | MW22 | MW22 | MW22 | MC 4 | MC 4 | FW22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | | | | | | | | | | | |
| B29635 | MP22 | MP22 | MW22 | MW22 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | | | | | | | | | | | | | |
| B29636 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FZ 2 | | | | | | | | |
| B29637 | MP22 | MW22 | MW22 | FP22 | FW22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | | | |
| B29638 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | |
| B29639 | MP22 | MW22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | | | | | | | | | |
| B29640 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | | | | |
| B29641 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FW22 | FP22 | FP22 | FW22 | FC 4 | | | | | | | | | |
| B29642 | MP22 | MP22 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | |
| B29643 | MP22 | MW25 | MW25 | MW25 | MC 4 | MD 3 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FD 3 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29644 | MP22 | MW22 | MD 3 | MD 6 | MW22 | MC 4 | MC 4 | FP22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29646 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FZ 9 | FW25 | | | | | | | | | |
| B29648 | MP22 | MW22 | MW22 | MW22 | MC 4 | FP22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | | | | | | | | | | | | |
| B29649 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | | | | | | | | | | |
| B29650 | MP22 | MZ 6 | MW22 | MZ 4 | MW22 | MC 4 | FD 5 | FD 5 | FW22 | FP22 | FZ 4 | FC 4 | FZ 4 | FC 4 | FZ 4 | FZ 4 | FC 4 | FC 4 | | | | | |

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE D-DIED C-CULLED Z-CANNIBALIZED P-SELECTED PARENT W-SACRIFICED AFTER WEANING

F0 GENERATION

PUP SURVIVAL (Individual data/Lactation period)

Dose: 500 mg/kg/day

| FEMALE# | PUP # | | | | | | | | | | | | | | | | | | | | | | |
|---------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| B29651 | MP22 | MP22 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | |
| B29652 | MP22 | MP22 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | | |
| B29653 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW22 | FP22 | FW22 | FZ 2 | FC 4 | FC 4 | | | | | | | | |
| B29654 | MP22 | MW22 | MW22 | MD 6 | MC 4 | MC 4 | MC 4 | FP22 | FW22 | FZ11 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29655 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | |
| B29657 | MP22 | MW22 | MW22 | MW22 | MW22 | MD 1 | MW22 | FP22 | FW22 | | | | | | | | | | | | | | |
| B29658 | MP22 | MP22 | MW25 | MW25 | FP22 | FP22 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FD 1 |
| B29659 | MW22 | MW22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FW22 | FW22 | FW22 | FZ 6 | FC 4 | | | | | | |
| B29660 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | FC 4 | | | | | | | | | | |
| B29661 | MD 2 | MZ 2 | MZ 2 | MZ 2 | MZ 3 | MZ 4 | MZ 4 | MD 2 | FZ 3 | FZ 4 | FD 2 | FZ 4 | FD 2 | FZ 3 | FD 2 | FZ 2 | FD 2 | FD 1 | | | | | |
| B29662 | MW24 | MW24 | MW24 | MW24 | FW24 | FW24 | FW24 | FW24 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | |
| B29663 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MD 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | |
| B29664 | MP22 | MW22 | MW22 | MW22 | MC 4 | MD 2 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW22 | FW22 | FW22 | FC 4 | | | | | | | | |
| B29665 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29667 | MP22 | MZ 7 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FZ 4 | FP22 | FW25 | FW25 | FZ 7 | FD 1 | FC 4 | FC 4 | FC 4 | FC 4 | FD 1 | FZ 4 | MD 1 | | |
| B29668 | MZ 2 | MB 2 | MZ 2 | MZ 2 | MZ 2 | MD 1 | FD 2 | FB 2 | FB 2 | FD 2 | FZ 2 | FB 2 | FD 1 | FD 1 | FD 1 | | | | | | | | |
| B29669 | MP22 | MW22 | MD 6 | MW22 | MC 4 | MC 4 | FP22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | | | | | | | | | | |
| B29670 | MP22 | MW23 | MW23 | MW23 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FD 3 | FW23 | FW23 | FW23 | FC 4 | FC 4 | | | | | | | |
| B29671 | MP22 | MP22 | MW25 | MW25 | MC 4 | FW25 | FP22 | FP22 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | | |
| B29672 | MP22 | MW23 | MW23 | MW23 | MC 4 | FP22 | FW23 | FW23 | FW23 | FC 4 | FC 4 | FC 4 | | | | | | | | | | | |
| B29674 | MP22 | MW22 | MW22 | MW22 | FP22 | FW22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | | |
| B29675 | MD 2 | MD 3 | MD 2 | MB 3 | MD 3 | MB 3 | MD 3 | FD 2 | FD 3 | FD 2 | FB 3 | FD 3 | FB 3 | FZ 3 | | | | | | | | | |

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE D-DIED C-CULLED Z-CANNIBALIZED B-SACRIFICED MORIBUND P-SELECTED PARENT W-SACRIFICED AFTER WEANING

F0 GENERATION

PUP SURVIVAL (Individual data/Lactation period)

Dose: 1000 mg/kg/day

| FEMALE# | PUP # | | | | | | | | | | | | | | | | | | | | | | |
|---------|-------|------|------|------|------|------|------|------|------|------|------|------|------|-------|------|------|------|------|----|----|----|----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| B29676 | MP22 | MW25 | MW25 | MW25 | MW25 | MC 4 | MC 4 | FP22 | FW25 | FW25 | | | | | | | | | | | | | |
| B29677 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | |
| B29678 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FZ 3 | FP22 | FW25 | FW25 | FW25 | | | | | |
| B29679 | MP22 | MW23 | MW23 | MW23 | FP22 | FW23 | FW23 | FW23 | FC 4 | FC 4 | | | | | | | | | | | | | |
| B29680 | MP22 | MW23 | FZ 8 | FW23 | FP22 | FW23 | FW23 | FW23 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29681 | MP22 | MW23 | MW23 | MW23 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW23 | FW23 | FW23 | FC 4 | | | | | | | | | | |
| B29682 | MP22 | MW23 | MW23 | MW23 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | MC 4 | FW23 | FW23 | FW23 | FC 4 | | | | | | | | | |
| B29683 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29684 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | | |
| B29685 | MP22 | MW23 | MW23 | MW23 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW23 | FW23 | FW23 | FC 4 | | | | | | | | | | |
| B29686 | MP22 | MW23 | MW23 | MW23 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW23 | FW23 | FW23 | FC 4 | FC 4 | | | | | | | | |
| B29687 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29688 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29689 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | |
| B29690 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29691 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | | | | | | | | |
| B29692 | MP22 | MP22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FP22 | FW22 | FW22 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29693 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MD 1 | FP22 | FD 3 | FW25 | FW25 | FC 4 | FW25 | FC 4 | FC 4 | | | | | | | |
| B29694 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FPZ 3 | | | | | | | | | |
| B29695 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | FC 4 | FC 4 | FC 4 | FC 4 | | | | | | | | |
| B29696 | MP22 | MW25 | MZ 2 | MW25 | MW25 | MC 4 | MC 4 | MZ 2 | MZ 2 | FP22 | FW25 | FW25 | FW25 | FC 4 | FZ 2 | | | | | | | | |
| B29697 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | FW25 | FP22 | FW25 | FW25 | | | | | | | | | | | |
| B29698 | MP22 | MW25 | MW25 | MW25 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FP22 | FW25 | FW25 | FW25 | | | | | | | | | |
| B29699 | MP22 | MW22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | FP22 | FW22 | FW22 | FW22 | | | | | | | | | | | | |
| B29700 | MW22 | MW22 | MW22 | MW22 | MC 4 | MC 4 | MC 4 | MC 4 | MC 4 | FW22 | FW22 | FW22 | FW22 | FC 4 | FC 6 | | | | | | | | |

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE D-DIED C-CULLED Z-CANNIBALIZED P-SELECTED PARENT W-SACRIFICED AFTER WEANING

26. F0 generation - individual clinical observations in pups

**F0 GENERATION
INDIVIDUAL CLINICAL OBSERVATIONS IN PUPS**

Dose-level: 0 mg/kg/day

| Female No. | Clinical observations | Pup No. | Sex | Day of lactation |
|------------|-------------------------------------|---------|-----|---------------------------|
| B29601 | No significant clinical observation | | | |
| B29602 | No significant clinical observation | | | |
| B29603 | No significant clinical observation | | | |
| B29604 | No significant clinical observation | | | |
| B29605 | No significant clinical observation | | | |
| B29606 | No significant clinical observation | | | |
| B29607 | No significant clinical observation | | | |
| B29608 | Cutaneous lesion on right hindlimb | 1 | M | From day 4 p.p. |
| B29609 | No significant clinical observation | | | |
| B29610 | No significant clinical observation | | | |
| B29611 | No significant clinical observation | | | |
| B29612 | No significant clinical observation | | | |
| B29613 | No significant clinical observation | | | |
| B29614 | Necrosis on right hindlimb | 4 | M | From day 7 to day 20 p.p. |
| B29615 | Emaciated appearance | 16 | F | From day 14 p.p. |
| | Necrosis on right hindlimb | 16 | F | From day 14 p.p. |
| B29616 | No significant clinical observation | | | |
| B29617 | No significant clinical observation | | | |
| B29618 | No significant clinical observation | | | |
| B29619 | Necrosis on left forelimb | 9 | F | From day 11 p.p. |
| B29621 | No significant clinical observation | | | |
| B29622 | Cutaneous lesion on back | 6 | M | Day 4 p.p. |
| B29623 | Necrosis on left hindlimb | 13 | F | From day 5 p.p. |
| B29625 | Cutaneous lesion on left hindlimb | 1 | M | From day 4 to day 14 p.p. |

p.p.: *post-partum*