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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 13 1993

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: EPA ID # 007969-00057; Vinclozolin; Review of the Final Report of the Effects of Vinclozolin on a Two-generation Study of Reproduction in the Rat (MRID# 425813-01) and a Summary Report of Prenatal and Reproductive Toxicity (MRID# 425813-02).

PC No.: 113201. DP Barcode No.: D186519.
TcxChem No.: 323C. Submission No.: S433258.
Case No.: 011409. Action No.: 400 Data-Misc. Not requested.

From: David G Anderson, PhD David G Anderson 7/7/93
Section 3, Toxicology Branch-I
Health Effects Division (H7509C)

To: Susan Lewis/Julie Fairfax PM 21
Fungicide and Herbicide Branch
Registration Division (H7505C)

Thru: Karen Hamernik, PhD. K. Hamernik 7/14/93
Head Section 3, Toxicology Branch-I
Health Effects Division (H7509C).

CC Karen Whitby

This study on the effects of vinclozolin on reproduction does not change the NOEL of 2.5 mg/kg/day which forms the basis of the RfD.

Data submitted for review were:

Hellwig, J. Report Reproduction Study with Reg. No. 83258 (Vinclozolin) in Rats Continuous Dietary Administration over 2-Gernerations (2 Litters in the First and 2 Litters in the Second Generation). Project No. 71R0375/88053; study conducted at BASF Aktiengesellschaft, Dept. Toxicology, D-W6700 Ludwigshaften, Germany; Reg. Doc. BASF No. 92/11251, 10/21/93 (7 volumes) 2901 pages for BASF (MRID# 425813-01).

and

Ben van Ravenzwaay, B. Discussion of Prenatal and Reproduction Toxicity of Reg.

No. 83 258 (Vinclozolin); Reg. Doc. No. 92/11407, November/1992, 47 pages (MRID# 425813-02).

D186519

CONCLUSION:

1. MRID# 425813-01. Conclusions from the DER on the 2-Generation Study on Reproduction (83-4).

Doses administered in the diet were 0, 50, 300, 1000 or 3000 ppm of vinclozolin (technical, 99.2%) (Males = 0, 4.9, 30, 96 or 290 mg/kg/day; Females = 0, 5.3, 31, 101 or 290 mg/kg/day) to 24 Wistar rats per sex per group through the P0, F1 and F2 generations for 14 weeks. Two litters per generation were produced: F1a (F1 adults), F1b (FX adults), F2a (FY adults) and F2b (FZ adults). FY and FZ adults were dosed only at 50 and 300 ppm because no F2 pups were produced at higher dose levels. The study was initiated December 22, 1988 and finished February 15, 1990.

Offspring Toxicity:

NOEL: 50 ppm (4.9 mg/kg/day)(LDT). Absolute Epididymal weights were statistically significantly decreased at 50 ppm in FY adults only, but they were nominally and/or statistically significantly decreased at all dose levels in the F1, FX and FZ adult males. Absolute epididymal weights (95%)* were statistically significantly less than controls at 50 ppm in FY adults only, but nominally less than controls in P0 (97%), F1 (99.8%), FX (96%)* and FZ (99%)* adults.

The effect at 50 ppm was minimal and considered sufficiently close to a NOEL. To determine the functional meaning of this decreased epididymal weight, sperm function tests may be necessary. These sperm function tests are being held in reserve and should not be conducted prior to consultation with the Agency.

% of control value

LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction in the F1 (97% of controls, $p \geq 0.05$), FX (96% of controls, $p \geq 0.05$), FY (94%* of controls, $p \leq 0.05$) and FZ (98% of controls, $p \geq 0.05$) in males. Dose related lenticular degeneration was noted in 1-2/24 F1 males and 1-3/24 females. These effects occurred in nearly all F1 and FX males and females at the HDT. Absolute testis (106%-107%, $p \leq 0.001$) and absolute adrenal (119%, $p \leq 0.05$ and 111%, $p \leq 0.01$, respectively) weights were greater than controls in FY and FZ adult males and absolute adrenal (107%, $p \geq 0.05$) and absolute liver weights (109%, $p \leq 0.05$) were greater than controls in F1 adult females, but not relative adrenal or liver weight. An increased incidence of testicular Leydig cell hyperplasia occurred in F1 (7/24) males at 300 ppm and above.

At 1000 and 3000 ppm pseudohermaphroditism, anomalies and functional deficit occurred in adult male reproductive organs, such as aberrant Wolffian duct, bilateral Muellerian duct, reduced/absent prostate, seminal vesicle, bulbo-urethral gland. In addition, atrophic seminiferous tubules, aspermia/ oligospermia and reduced penis size were noted. Hypospadia occurred in all male offspring only at the 1000 and 3000 ppm dose levels. Increased ovarian lipidosis and ovarian interstitial cell hypertrophy occurred at 1000 and

* statistically significant

3000 ppm. Frequent compound related single cell liver necrosis was noted in F1 and FX adult males (23/29 and 48/49) and in FX female adults (15/40) at 3000 ppm. Central hypertrophy of the liver occurred in the F1 (6/24 at 1000 ppm and 18/26 at 3000 ppm) and in FX females adults (2/24 and 35/40 at 1000 and 3000 ppm , respectively). and single cell liver necrosis occurred in FX female adult offspring (15/40) at 3000 ppm.

Adult male offspring (genital and reproductive tract malformations) sired no offspring at 1000 and 3000 ppm and fertility in adult F1 female offspring may have been reduced at 3000 ppm.

Pinna unfolding, eye opening, auditory canal opening was affected at 3000 ppm and the gripping reflex may have been affected during lactation for F1a and F1b pups. The nominal increase in effects in these parameters at 1000 ppm were within historical control range and may not be biologically significant.

F1a and F1b pup survival was statistically significantly less than controls at 3000 ppm, at 0-4 days post partum (47%/92% and 60%/97%, respectively) and 4-21 post partum days (86%/100% and 95%/98%, respectively). Cannibalism during lactation was increased at 3000 ppm. A body weight reduction occurred in F1a and F1b pups by day 1 at 3000 ppm (85% and 73%, both $p \leq 0.01$, respectively) on day 4 and day 21 post partum at 1000 (76% to 81% for F1a and 89% and 84% for F1b, at the respective post partum days) and 3000 ppm (76% and 73% for F1a; 72% and 67% for F1b, at the respective lactational days). A compound related increase in litter incidence over controls occurred in dilated renal pelvis or hydroureter in pups at 3000 ppm (46%/13% for the F1a and 5.6%/0% for the F1b). Nipples were present on male F1a and F1b pups at 1000 and 3000 ppm (Verbal comment by BASF).

Parental toxicity:

NOEL: 50 ppm (4.9 mg/kg/day).

LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction (93%, $p \leq 0.01$ of controls) in males and possibly liver weight increase in females (110%, $p \leq 0.01$ of controls). At 1000 and 3000 ppm testis weights (110%, $p \leq 0.01$ at 1000 ppm) and Leydig cell hyperplasia were increased (10/24 at 1000 ppm) and adrenal weights were increased in males (125% at 1000 ppm, $p \leq 0.01$) and females (130%, $p \leq 0.01$). Lipidosis of the adrenal occurred in females at 1000 (19/24) and 3000 ppm (24/24) and in males at 3000 ppm (24/24). Pituitary vacuolation cells (castration cells) occurred in all males at 3000 ppm. A dose related increased incidence of lenticular degeneration occurred in females at the 3 highest dose levels (only 1/24 at 300 ppm). Single cell necrosis of the liver occurred in most males and females at 3000 ppm and central hypertrophy occurred in both males and females at the rate of 3/24 at 1000 and 24/24 at 3000 ppm.

Core classification: Minimum. This study is acceptable under guideline 83-4 for reproduction in the rat.

The affect on the epididymal weight was minimal at the LDT and 50 ppm was considered to be the NOEL, however, the possible need for sperm parameter studies is reserved.

2. (MRID# 425813-02) - Summarized in the Appendix II of the DER on Reproduction.

The report summarized prenatal toxicity in the rat, rabbit and mouse, all of which have been reviewed elsewhere (Rat, HED Doc.# 007909; Rabbit, HED Doc.# 008311; Mouse, HED Doc.# 000244). Studies on reproduction were summarized, one study from the 1970s (Reviewed in HED Doc.# 000244) and and one from 1992 (MRID# 425813-02). A summary of the hormone studies and receptor binding studies were also related to a posulated mechanism of action. The NOEL/LEL for the developmental and reproductive effects of vinclozolin were stated. A list of 24 references supporting the summaries were also submitted. These references included previously submitted interim reports and final reports prenatal, studies on reproduction, studies on hormone receptor binding and 6 literature references to antiandrogens.

Only the summaries on the hormone receptor binding relative to mibolerone were reviewed, but no conclusions could be made because no details were presented .

CMemo Reproductive effects of Vinclozolin/71S0375/88053,92/11251,425813-01 and Summary Data/92/11407,425813-02/D186519 on the prenatal and literature references /B:\VINCLV43.23C\CMREPSRA.T93/DANDERSON/4/20/93&7/7/93.*

Primary reviewer: David G Anderson, PhD. D. Anderson 7/7/93
Section 3, Tox. Branch 1 (H7509C).
Secondary reviewer: Karen Hamernik, PhD. K. Hamernik 7/12/93
Section 3, Tox. Branch 1 (H7509C).

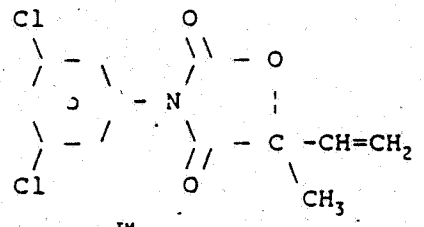
DATA EVALUATION REPORT

STUDY TYPE: Reproduction/Rat/(83-4)/92/11251/71R0375/38053/425813-01 & Summary/'-02.

ToxChem No.: 323C. Submission No.: S433258.
PC No.: 113201. MRID No.: 425813-01 & 425813-02 (Appendix II).
DP Barcode No.: D186519.

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan™ (41 to 50% vinclozolin), Curalan (Turf)™, Ornalin™, Reg no. 83 258.

SPONSOR: BASF Corp. Chemicals Div., Ag. Chem., PO Box 13528, Research Triangle Park, NC 27709-3528.

TESTING FACILITY: BASF Aktiengesellschaft, Dept. Toxicology, 6700 Ludwigshafen, Federal Republic of Germany.

STUDY NO.: 92/11251 & 71R0375/88053. Reg. Doc. No. BASF 92/10596 (For 425813-01) and 11407 (For 425813-02).

REPORT TITLE: **Report on the Reproduction Study with Reg. No. 83 258 (Vinclozolin) in Rats with Continuous Dietary Administration Over 2-Generations (2 litters in the First and 2 litters in the Second Generation) Project No.: 71R0375/88053 (MRID# 425813-01). Summary of Reproductive Effects and Hormone Studies (MRID# 425813-02) in Appendix II.**

AUTHOR(S): Dr. J Hellwig.

REPORT ISSUED: October 21, 1992.

CONCLUSION: Doses administered in the diet were 0, 50, 300, 1000 or 3000 ppm of vinclozolin (technical, 99.2%) (Males = 0, 4.9, 30, 96 or 290 mg/kg/day; Females = 0, 5.3, 31, 101 or 290 mg/kg/day) to 24 Wistar rats per sex per group through the P0, F1 and F2 generations for 14 weeks. Two litters per generation were

produced: F1a (F1 adults), F1b (FX adults), F2a (FY adults) and F2b (FZ adults). FY and FZ adults were dosed only at 50 and 300 ppm because no F2 pups were produced at higher dose levels. The study was initiated December 22, 1988 and finished February 15, 1990.

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The effect at 50 ppm was minimal and considered sufficiently close to a NOEL. To determine the functional meaning of this decreased epididymal weight, sperm function tests may be necessary. These sperm function tests are being held in reserve and should not be conducted prior to consultation with the Agency.

[1] % of control value

LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction in the F1 (97% of controls, $p \geq 0.05$), FX (96% of controls, $p \geq 0.05$), FY (94%* of controls, $p \leq 0.05$) and FZ (98% of controls, $p \geq 0.05$) in males. Dose related lenticular degeneration was noted in 1-2/24 F1 males and 1-3/24 females. These effects occurred in nearly all F1 and FX males and females at the HDT. Absolute testis (106%-107%, $p \leq 0.001$) and absolute adrenal (119%, $p \leq 0.05$ and 111%, $p \leq 0.01$, respectively) weights were greater than controls in FY and FZ adult males and absolute adrenal (107%, $p \geq 0.05$) and absolute liver weights (109%, $p \leq 0.05$) were greater than controls in F1 adult females, but not relative adrenal or liver weight. An increased incidence of testicular Leydig cell hyperplasia occurred in F1 (7/24) males at 300 ppm & above.

At 1000 and 3000 ppm pseudohermaphroditism, anomalies and functional deficit occurred in adult male reproductive organs, such as aberrant Wolffian duct, bilateral, Muellerian duct, reduced/absent prostate, seminal vesicle, & bulbo-urethral gland. In addition, atrophic seminiferous tubules, aspermia/oligospermia and reduced penis size were noted. Hypospadia occurred in all male offspring only at the 1000 and 3000 ppm dose levels. Increased ovarian lipidosis and ovarian interstitial cell hypertrophy occurred at 1000 and 3000 ppm. Frequent compound related single cell liver necrosis was noted in F1 and FX adult males (23/29 and 48/49) and in FX female adults (15/40) at 3000 ppm. Central hypertrophy of the liver occurred in the F1 (6/24 at 1000 ppm and 18/26 at 3000 ppm) and in FX female adults (2/24 and 35/40 at 1000 and 3000 ppm , respectively), and single cell liver necrosis occurred in FX female adult offspring (15/40) at 3000 ppm.

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* Statistically significant

3000 ppm.

Pinna unfolding, eye opening, auditory canal opening was affected at 3000 ppm and the gripping reflex may have been affected during lactation for F1a and F1b pups. The nominal increase in effects in these parameters at 1000 ppm were within historical control range and may not be biologically significant.

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Parental toxicity:
NOEL: 50 ppm (4.9 mg/kg/day).
LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction (93%, $p \leq 0.01$ of controls) in males and possibly liver weight increase in females (110%, $p \leq 0.01$ of controls). At 1000 and 3000 ppm testis weights (110%, $p \leq 0.01$ at 1000 ppm) and Leydig cell hyperplasia were increased (10/24 at 1000 ppm) and adrenal weights were increased in males (125% at 1000 ppm, $p \leq 0.01$) and females (130%, $p \leq 0.01$). Lipidosis of the adrenal occurred in females at 1000 (19/24) and 3000 ppm (24/24) and in males at 3000 ppm (24/24). Pituitary vacuolation cells (castration cells) occurred in all males at 3000 ppm. A dose related increased incidence of lenticular degeneration occurred in females at the 3 highest dose levels (only 1/24 at 300 ppm). Single cell necrosis of the liver occurred in most males and females at 3000 ppm and central hypertrophy occurred in both males and females at the rate of 3/24 at 1000 and 24/24 at 3000 ppm.

Core classification: Minimum. This study is acceptable under guideline 83-4 for reproduction in the rat.

The affect on the epididymal weight was minimal at the LDT and 50 ppm was considered to be the NOEL, however, the possible need for sperm parameter studies is reserved.

A. MATERIALS:

1. Test material: Vinclozolin, Description: Solid; Batch No.: N 183; Purity - 99.2% a.i.

2. Test animals: Species: Rats, Strain: Wistar (Chbb = THOM(SPF)), Age: 5 weeks at study initiation, Weight: Males -

134.4 (122 - 144) g, Females - 119.3 (108 - 130) g at study initiation, Source: Karl Thomae, Biberach an der Riss, FRG. Animals were acclimatized for 6 days after receipt.

3. Environment: The animal room was maintained at 20 to 24° C; Relative humidity was 30-70%; Light:dark = 12:12, starting at 6:00 AM. Rooms were disinfected with Autex apparatus, fully automatic. Final disinfecting used formaldehyde and ammonia. Each week walls and floor were disinfected with 0.5% Mikro-Quat.

Pre-mated animals were housed individually in stainless steel wire mesh cages (800 cm^2). During mating males and females were housed in Makrolon cages, type M III (800 cm^2). From day 18 of pregnancy to day 14 after birth, females and litters were also housed in Makrolon type M II cages. The latter were supplied with cellulose wadding as nesting material toward the end of pregnancy.

B. STUDY DESIGN:

1. Animal Assignment - Twenty-four animals per sex were assigned randomly to each group using a randomization program software, which randomizes according to body weight. F1a animals used for mating were also randomly assigned. Neither P0 nor F1 litter mates were mated.

2. Study Purpose and Protocol - The study is designed to provide information on the toxic effects of vinclozolin on the organs of reproduction, mating behavior, conception, parturition, lactation and growth and development, developmental stages and behavioral tests of offspring, such as pinna unfolding on day 4 post partum, opening of the auditory canal and gripping reflex on post partum day 13, eye opening on day 15 post partum, pupillary reflex on day 20 postpartum and a hearing test on day 21 post partum. The study was conducted for 2-generations (P0 and F1) and 2 (F1a, F1b, F2a and F2b) litters per generation in the rat. In addition, all F1a animals were raised and randomly selected for mating to produce the F2a and F2b litters when they were sufficiently mature to be sexed accurately. In order to have sufficient F1 (F1a) animals to produce the F2a and F2b litters, litters were not reduced to 8 pups per litter at lactational day 4 as suggested by the guidelines. F1b animals were designated the FX animals and raised for 14 weeks. F2a and F2b animals were randomly selected for the FY and FZ animals, respectively. No F2 pups were delivered at the 1000 or 3000 ppm dose levels. Matings were 1:1 overnight or until vaginal sperm was detected or up to 3 weeks. Males not producing a F1a, F1b or F2a or F2b litter were reevaluated for fertility with a fertile control animal, except F1 males at the 1000 and 3000 ppm dose levels. F1 males at 1000 and 3000 ppm had severely malformed genital organs (hypoplastic penises, paraphimosis and hypospadia) and could not impregnate females. F1 males at 1000 and 3000 ppm produced no pups.

- 24 animals per sex per group were selected for the P0

generation.

- 24 animals per sex per group were selected from the F1a litters for the F1 generation. Except at the 3000 ppm dose level, where all surviving F1a pups, 29 males and 37 females were raised for at least 14 weeks (the sex could not be definitively determined) and selected for the HDT F1 generation. 24 animals per sex per group were selected from the F1b litters for the FX adult data on organ weights and histological data. Except at the 3000 ppm dose level, where all surviving F1b pups, 50 males and 41 females were raised for at least 14 weeks (the sex could not be definitively determined) and selected for the FX animals.
- 24 animals per sex per group were selected from the F2a litters for the FY adult data on organ weights and histological data, except at the 1000 and 3000 ppm dose level, where no pups were produced. 24 animals per sex per group were selected from the F2b litters for the FZ adult data on organ weights and histological data, except at the 1000 and 3000 ppm dose level, where no pups were produced.

3. Diet preparation - Diet was prepared at least every 32 days, and stored at room temperature until used. Samples of the diet were collected every month initially and every 3 months later in the study and were analyzed. Samples of treated food were analyzed for homogeneity, stability and concentration at ≈ 22° C. Samples of diet were stored at -23° C until assayed.

Results - The overall homogeneity analyses ranged from 91.4% to 107% of nominal. Stability determinations indicated that test material was stable within the diet with analytical results of 100% of nominal on day 0, 93.6% of nominal on day 10 and 94.4% of nominal on day 32. Analyses of dietary concentrations were conducted on samples prepared on 11/25/88, 12/12/88, 12/22/88, 3/2/89, 6/[illegible]/89, 9/12/89 and 12/26/89. All were within an acceptable range of 86.4% to 104% of nominal.

4. Animals receive food and water ad libitum. Rats were fed Kliba maintenance diet rat/mouse/hamster GLP 343 meal supplied by Klingentalmühle AG, CH-4303 Kaiseraugst, Switzerland. Tap water was also supplied.

5. Statistics - The data were evaluated statistically using the computer systems of the Department of Toxicology of BASF, Aktiengesellschaft.

Dunnett's test was used for all parametric data and Fisher's Exact Test was used for developmental stages, mating and fertility indexes, gestation, live birth, viability and lactation indexes.

6. Data presented in the submitted report was quality assurance

audited throughout the study and signed by H Fleig, Head of QA on 10/23/92.

C. METHODS AND RESULT FOR P0, F1 and F2 GENERATIONS: (Numbered tables were copied from the submitted report and are reproduced and presented in Appendix I. Lettered tables were constructed from data in the submitted report)

1. Observations - Animals were inspected daily for signs of toxicity and mortality.

Results - Toxicity - Toxicity was observed in P0 and F1 males and females in the form of cataracts at the HDT and anti-androgenicity at the two highest dose levels. At the 1000 and 3000 ppm dose level, no pups were born from the F1 females

Hypospadia and hypoplasia of the penis was observed in all but 1 or 2 F1 males at 1000 and 3000 ppm. A vaginal like orifice was seen in all but 1 or 2 F1 males and paraphimosis in most F1 males at 1000 ppm and 4 at 3000 ppm. Hypoplastic testes were seen in most F1 males at 3000 ppm. Cataracts were seen in 1 F0 male and 5 F0 females after 10 weeks at 3000 ppm. Cataracts were seen in 3/26 males starting at week 10 and 11/26 F1 males starting at week 15. Cataracts started in F1 females at 3000 ppm at week 7 (1/26) and progressed to 12/26 by week 12.

Mortality (Survival) - Among adult animals, mortality was small (0-1 per dose level), except among F1 males where 4 adult animal deaths at 3000 ppm at week 7, 10, 12 and 30 may have been test material related. However, adult mortality does not appear to be test material related in either males or females, except perhaps in the 4 F1 adult male deaths at 3000 ppm.

2. Body Weight, Food and Water Consumption - Body weights and body weight gain were determined weekly for P0, F1a, (selected for the F1), F1b (selected for the FX), F2a (selected for the FY) and F2b (selected for the FZ) males and females from initiation of dosing after weaning to week 10 or 11 (mating). These parameters were determined for P0 and F1 males to week 28 and week 32, respectively. These parameters were determined for P0 and F1 females through mating, gestation, lactation and through at least week 24. These parameters were determined in FX through week 15, in FY through week 12 and in FZ through week 12 in males and females. Body weight data for males and females at sacrifice are presented in Tables D and E.

Results for P0, F1 and FX Adult Males and Females - Although significant decreases occurred in body weight, the relative efficiency of food utilization did not change. Therefore, apparently no toxic body weight decrements occurred (Table A). However, the body weight decrement may have been related to androgen receptor inhibition in the muscles of males and in

females. Body weights of F2 adult litters were not changed at 50 and 300 ppm and no animals were studied at higher dose levels.

P0 male body weight reductions occurred from week 1 to [illegible] (93% of controls, $p \leq 0.05$) and in F1 males from week 1 to 28 (80% of controls, $p \leq 0.05$) at 3000 ppm. Male body weight gain was infrequently statistically significantly decreased during the same period. The body weights at 50 and 300 ppm dose levels were nominally elevated through out the same period. P0 female body weights were statistically significantly reduced for the first 2 weeks (95% of controls, $p \leq 0.05$) and nominally reduced by the end of the 10 weeks (96% of controls, $p \leq 0.05$). F1 female body weight was statistically significantly decreased at 3000 ppm up to week 4, 94% of controls), but it was nominally decreased at 3000 ppm at the end of 14 weeks.

Body weights of FX (adult F1b animals) males and Females followed a pattern of decrease similar to the body weights of F1 males and Females. No effects occurred on the body weights of FY (adult F2a) and FZ (adult F2b) animals raised for 14 weeks at 50 and 300 ppm.

Table A.

Body weight gain, food consumption data and food efficiency calculations for the pre-mating period.

Mean body weight gain in g over the time period T (pre-mating period).	0 ppm	50 ppm	300 ppm	1000 ppm	3000 ppm
P0 males	297.8	318..	313.3	297.4	271.2
P0 females	133.2	135.1	146.4	131.1	125.3
F1 males	301.2	306.6	322.3	307.2	275.6
F1 females	144.2	146.3	151.2	146.9	177.4
Mean food consumption in g/animal day over the time period T.					
P0	26.5	27.5	27.5	26.3	24.6
P0 females	19.3	19.8	20.1	18.8	17.8
F1 males	26.0	26.4	27.3	26.3	23.9
F1 females	19.0	19.1	19.9	18.9	19.4
Relative efficiency = (body weight gain over time period T)/(relative food consumed over time period T).					
P0 males	11.2	11.5	11.4	11.3	11.0
P0 females	6.90	6.82	7.28	6.97	7.04
F1 males	11.6	11.5	11.8	11.7	11.5
F1 females	7.59	7.65	8.10	7.77	9.14

Relative food efficiency is only meaningful when compared with controls and other dose groups within a given grouping for P0 males or females or F1 males or females because of comparability of the data used in the calculations.

Results from Diet and Water Consumption Stud

The food consumption was unchanged to n[illegible]nally decreased at 3000 ppm in males and females. The overall relative efficiency of food utilization was unchanged in the P0 and F1 males and females at all dose levels (Table A).

Test material consumption was determined during the pre-mating period for the P0 and F1 adults. The mean consumption for the pre-mating P0 generation is generally used for assessment purposes. Therefore the mean dose administered at the NOEL/LEL is 4.9 mg/kg/day for P0 males and 5.3 mg/kg/day for P0 females at 50 ppm; and at the 300 ppm, 29.6 or 30 mg/kg/day for P0 males and 31.4 or 31 mg/kg/day f[illegible] females (Table C).

Water consumption was statistically significantly increased i[illegible] males and females at the 1000 and the 3000 ppm dose levels (Table B). The water consumption was statistically significantly increased in females at the 300 ppm and above (Table B)

Table B: Mean water consumption for the pre-mating period for P0 and F1 male and female adults.

Mean water consumption(g)/day	0 ppm	50 ppm	300 ppm	1000 ppm	3000 p[illegible]
P0 males	26.1	26.4	27.1	28.2*	28.2*
P0 females	19.7	20.0	21.5**	21.4*	24.2**
F1 males	25.9	25.2	27.3	28.1*	28.7**
F1 females	20.3	19.8	21.8*	22.6**	23.6**

* Statistically significant, $p \leq 0.05$. ** Statistically significant, $p \leq 0.01$.

3. Reproductive Parameters and Litter Data - The following data related to the reproductive potential of adult males and/or females, were collected: mating and fertility indexes and length of gestation. The male mating and fertility indexes used for the F1a and F1b litters were defined in Table 048 and 049, repro[illegible]uced from the submitted report, in the Appendix II. The female mating and fertility indexes were defined in Table 050 for the F1a litters and 051 for the F1b litters.

a. Results on Fertility and Mating - P0 Male fertility was statistically significantly affected only at the 3000 ppm dose level for the F1a mating only (Table 048). The male fertility was nominally reduced for the F1b mating (Table 049). The Number of P0 males not proving fertility were statistically significantly increased for the F1a mating, but not for the mating. None of F1 males proved their fertility for the F2 F2b matings at 1000 or 3000 ppm (Tables 145 and 146, reprod. in the Appendix II). P0 female fertility was statistically significantly lower than control for the F1a litters, but not the F1b litters (Table 050 and 051) at the 3000 ppm dose level.

The mating index was not significantly reduced in males or females producing either F1a or F1b litters (Table 048, 049, 050 and 051). The effect on P0 male fertility may have been test material related, but effects on P0 females were probably incidental to the study at the 3000 ppm dose level.

The male and female mating and fertility indexes producing the F2a and F2b litters were 0 or close to 0 at the 1000 and 3000 ppm dose level (Tables 144, 145, 146 and 147). These indexes were unaffected at the 50 and 300 ppm dose level. When the F1 females at 1000 and 3000 ppm were reevaluated for fertility with a proven male 24/24 were pregnant at 1000 ppm and 20/26 were pregnant at 3000 ppm. Thus the fertility of F1 females also may have been affected at the 1000 ppm dose level.

Table C. Calculated mean test material consumption for various periods during the study. Generally the dose levels determined during the pre-mating period for the P0 are used for assessment purposes.)

	50 ppm (mean in mg/kg/day)	300 ppm (mean in mg/kg/day)	1000 ppm (mean in mg/kg/day)	3000 ppm (mean in mg/kg/day)
P0 males (pre-mating	4.9	29.6	96.5	286.0
P0 females pre-mating)	5.3	31.4	101.2	291.8
P0 females F1a litters)				
Gestation	4.3	25.1	83.8	237.2
Lactation*	8.2	47.3	150.4	249.8
P0 females F1b litters)				
Gestation	4.1	23.8	79.9	227.1
Lactation*	7.8	44.6	151.1	274.5
F1 males (pre-mating	4.8	27.0	96.0	314.0
F1 females pre-mating)	5.3	29.5	104.7	335.0
F1 females F2a litters)				
Gestation	4.1	24.4	-	-
Lactation*	7.5	43.0	-	-
F1 females F2b litters)				
Gestation	3.9	23.1	-	-
Lactation*	7.2	39.3	-	-

* Post natal days 0 through 14 only.
- Insufficient number of F1 delivered; insemination prevented by male malformations.

b. Pup weights for the F1a, F1b, F2a and F2b during Lactation (reported only as litter means) - Pup weights were recorded individually but reported as litter means for day 1, 4, 7, 14, and 21 (weaning).

Results - Statistically significant body weight reductions compared with control values occurred for male and female pups at 1000 and 3000 ppm dose levels (Table 059 and 060 for F1a litters and 063 and 064 for F1b litters, reproduced from the submitted report, in the

Appendix II). At the 3000 ppm dose level body weights of F1a males and female pups were 85% of controls at day 1 and 73% of controls at day 21. At the 3000 ppm dose level, body weights of F1b males and females were 84% of controls at day 1 and 67% of controls at day 21. At the 1000 ppm dose level, body weights of F1a pups were statistically significant only on and after day 4, however the body weight of F1b pups were statistically significantly reduced throughout lactation starting at day 1 . There were no pup weight decrements at 50 or 300 ppm in the F1a, F1b, F2a or F2b pups. There were no F2a or F2b pups at higher dose levels.

Males pups were slightly heavier than female pups throughout lactation as is generally the case. Thus, if anti-androgenicity cause differentially reduced muscle mass in males, it was compensated by an increase in body fat and/or fluid retention.

c. Average Number of Pups at Birth and Pup Viability The number of F1a and F1b pups per litter were decreased at birth (74% of controls for the F1a and 77% of controls for the F1b) and during lactation with the largest number of pups dying by day 4 (37% of controls for the F1a and 47% of controls for the F1b), only at the 3000 ppm dose level (Tables 054 and 057, produced from the submitted report and presented in Appendix II).

F2a and F2b pups were not affected at the 50 and 300 ppm dose levels studied.

d. Developmental Stages and Behavior for the F1a, F1b, F2a and F2b Offspring - Developmental stages such as pinna unfolding (PU), auditory canal opening (ACO), eye opening (EO) and pupil constriction (PC) and behavior such as gripping reflex (GR) was determined on pups up to weaning. The data were inappropriately presented as percentage of pups meeting the criteria rather percentage of litters with pup(s) meeting the criteria.

Results - The data for the F1a and F1b litters can be found in Tables 067 and 068, reproduced in the Appendix. Pinnae unfolding, auditory canal opening, eye opening and the gripping flex appeared to be affected outside the historical control range and statistically significant at 3000 ppm in the F1a and F1b pups. At 1000 ppm PU and EO were comparable with controls in the percentage pups meeting the criteria. These values were at low end of the criteria with the historical control range and statistically significant in F1b, but not F1a litters. ACO was statistically significantly lower in the F1a at 1000 ppm, but this also was comparable with the historical control range.

F2a pups showed statistically significantly, but slightly decreased percentage pups with PU and EO at 300 ppm, but again these were within the historical control range.

Other values were statistically significantly lower than controls, but did not appear to be dose related or test material related.

The effects at 3000 ppm were considered to be the only test material related effects occurring in the these parameters.

Hematology and Clinical Chemistry - Blood was drawn from the retro-orbital venus plexus from 12 animals per sex from the P0 and F1 generations at 196/197 and 224/225 days, respectively. The following parameters were studied. Hematological Parameters leukocytes (WBC) erythrocytes (RBC) hemoglobin (HGB) hematocrit (HCT) platelets (PLT).

Hematological Parameters	
leukocytes (WBC)	mean corpuscular volume (MCV)
erythrocytes (RBC)	mean corpuscular hemoglobin
hemoglobin (HGB)	(MCH) mean corpuscular
hematocrit (HCT)	hemoglobin conc. (MCHC)
platelets (PLT)	reticulocytes thromboplastin
	time

Clinical Chemistry Parameters	
Blood Chemistry	total protein
total bilirubin	albumin
sodium	globulins
potassium	triglycerides
inorg. phosphate	cholesterol
calcium	glucose
urea	
creatinine	Enzymes
	alanine aminotransferase
	aspartate aminotransferase
	alkaline phosphatase

Results - Consistent decreases in HCT and HGB occurred in P0 and F1 females at 1000 ppm and above. Consistent elevations occurred in creatinine and cholesterol at 3000 ppm in P0 and F1 males and females. Other statistically significant changes occurred, but they were either not clearly dose related or they occurred in only one generation or the biological significance could be questioned.

No dose related effects occurred in P0 male hematology. Slight but statistically significant dose related decreases in hematocrit at 300 ppm and above and hemoglobin concentration at 1000 ppm and above occurred in P0 females (HCT=94% at 300 ppm; HCT=91% at 3000 ppm and HBG=96% at 1000 ppm; HBG=92% at 3000 ppm of controls). The HCT, RBC and HGB in F1 females behaved similarly to the P0 females, except no effects occurred at 300 ppm. The decrement in RBC may have been dose related at 300 ppm and above, but it was not clearly so. The clotting time was reduced at 3000 ppm to 81% of controls in F1 females. No other hematological effects were clearly dose related.

Creatinine and cholesterol were clearly elevated at 3000 ppm in P0 and F1 males and females and cholesterol at 1000 and 3000 ppm in P0 females. Total protein and globulin were statistically significantly elevated at 3000 ppm in F1 males and total protein, albumin, globulin and triglycerides were elevated F1 females at 3000 ppm. Sodium and chloride were slightly, but statistically significantly depressed at 300 ppm and above in P0 females.

(2000)

5. Sacrifice and Pathology -

All animals that died and that were sacrificed on schedule in all P0, F1, FX, FY and FZ animals were subject to gross pathological examination. Gross lesions were fixed in 4% buffered formalin and examined grossly, except in the case of the male testes which were fixed in Bouin's fixative. The epididymides, seminal vesicles, coagulating gland, prostate, pituitary, eyes, liver, adrenals and bone marrow were examined microscopically in the male. The ovaries, cervix and vagina, uterus, pituitary, eyes, liver, adrenals and bone marrow were examined microscopically in females. In addition, the testes, epididymides, liver and adrenals were weighed.

Results - a. Organ weights - Absolute organ weights were statistically significantly elevated in the determined organs of males and females of P0, F1 and FX animals at 3000 ppm and in some groups at the 300 ppm dose level (Table D and E). The relative liver and adrenal weights followed similar upward trends as the absolute organ weights, but in contrast with the elevated absolute organ weight, i some groups from some generations, the relative organs weights were not statistically significantly different from controls. The relative liver and adrenal gland weights do not change the NOEL/LEL, thus, relative organ weights are not presented. Brain weights were not determined.

Generally absolute liver weights were statistically significantly elevated at the 3000 ppm dose level in males (0% to 114% of controls) (Table D) and in females (0% to 177% of controls) (Table E) when studied. Absolute testis weights were generally elevated at 1000 (110% of controls) and 3000 ppm (115% of controls in the P0 males, but when exposed *in utero* these testis weights were decreased at 3000 ppm in F1 (77% of controls) and FX (79% of controls) males (Table D). Absolute adrenal weights in males were increased at 1000 ppm and 3000 ppm in P0 groups (125% at 1000 ppm of controls), F1 (130% at 1000 ppm of controls), FX (148% at 1000 ppm of controls) (Table D). Absolute adrenal weights in females (Table E) followed the same pattern in P0, F1 and FX male groups. In the FY and FZ males (Table D), absolute testes weights and adrenal weights were statistically significantly increased at the 300 ppm dose level (HDT for the FY and FZ animals). Absolute adrenal weights were statistically significantly increased at 300 ppm in FY (109% of controls) and FZ (111% of controls) females (Table E).

The epididymal weights were nominally or statistically significantly depressed at all dose levels. Although a statistically significant depression occurred only in FY males at 50 ppm, a nominal depression occurred in P0, F1, FX and FZ males, which appeared to be dose related. The epididymal weights were statistically significant at higher dose levels in the P0, F1, FX and FZ males, but not all at the same dose levels (Table D). In the opinion of this reviewer, it was only due to the precision of the epididymal weight data that the dose related response was detected at the LDT. The CV for this data varied from 5.9% to 9.0% in controls and the 50 ppm dose groups, which is very good for an organ weight of ≈1 g.

The epididymal weight decrease was probably the result of the anti-androgenicity of vinclozolin. The functional meaning of these

slight epididymal weight decreases can only be determined by the sperm paramenters that may have been affected during transit since no histopathology was expected or demonstrated.

Table 9. Effects on terminal body weight and selected target organ weights in the P0 and F1 parental males, FX (F1b adult males), FY (all F2a adult males) and FZ (all F2b adult males).

Dose group→ P0 males, body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g	530.6	558.4	556.4	530.5	500.0
SD	57.0	51.9	44.2	52.7	53.3
n	23	24	24	24	22
Liver, g	16.3	17.6	17.4	16.1	18.6**
SD	2.6	2.9	1.9	2.1	2.5
n	23	24	24	24	22
Testis, g	3.60	3.69	3.75	3.97**	4.13**
SD	0.20	0.24	0.27	0.26	0.36
n	23	24	24	24	22
Epididymis, mg	1472.2	1433.3	1367.1**	1318.8**	1063.2**
SD	103.6	110.6	98.8	114.4	123.2
n	23	24	24	24	22
Adrenal gland, mg	73.5	76.2	81.1	91.6**	154.8**
SD	10.2	8.5	13.6	15.3	37.5
n	23	24	24	24	22
Dose group→ F1 males (adult F1a), body wt. & absolute organ wt.	**Control, 0**	**50 ppm**	**300 ppm**	**1000 ppm**	**3000 ppm**
Body wt., g	543.0	548.2	568.	494.7*	431.9**
SD	59.0	79.1	66.6	52.5	50.2
n	24	24	22	24	25
Liver, g	17.0	17.6	18.7	16.0	15.7
SD	2.7	3.2	2.3	2.7	3.0
n	24	24	22	24	25
Testis, g	3.76	3.80	3.96	3.66	2.90**
SD	0.24	0.30	0.32	0.49	0.68
n	23	24	22	24	22
Epididymis, mg	1366.9	1363.9	1327.1	1147.3	870.2**
SD	88.1	105.9	75.9	144.6	972.0
n	23	24	22	24	22
Adrenal gland, mg	66.6	70.9	79.	86.8**	158.6**
SD	8.1	12.4	10.6	13.7	34.9
n	24	23	22	24	25

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Dose group→ FX males (non-mated adult F1b), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g	432.2	425.1	446.7	430.3	364.6**
SD	49.6	39.8	44.8	37.3	30.7
n	24	24	24	24	49
Liver, g	15.6	15.3	15.8	14.9	15.5
SD	3.5	3.8	2.5	2.6	2.0
n	24	24	24	24	49
Testis, g	3.44	3.46	3.69	3.65	2.72**
SD	0.26	0.27	0.36	0.37	0.50
n	24	24	24	24	44
Epididymis, mg	1302.3	1252.8	1260.8	1099.2**	540.1**
SD	117.4	91.6	120.6	94.9	242.9
n	24	24	24	24	44
Adrenal gland, mg	70.3	73.0	83.5	104.3**	190.**
SD	9.6	8.8	12.2	18.7	38.5
n	24	24	24	24	49

Dose group→ FY males (adult F2a), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g	424.8	418.6	437.5	-	-
SD	37.1	30.0	47.6		
n	24	24	24		
Liver, g	14.8	14.5	16.0	-	-
SD	2.6	2.1	2.5		
n	24	24	24		
Testis, g	3.47	3.45	3.67**	-	-
SD	0.32	0.21	0.31		
n	24	24	24		
Epididymis, mg	1269.8	1212.4*	1195.8**	-	-
SD	92.5	71.0	89.3		
n	24	24	24		
Adrenal gland, mg	81.2	79.5	89.9*	-	-
SD	12.0	10.9	11.6		
n	24	24	24		

Continued, next page

Dose group→ FZ males (adult F2b), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	388.3 38.2 24	406.6 35.3 24	424.6** 47.3 24	-	-
Liver, g SD n	13.9 2.0 24	14.7 2.3 24	16.3** 3.2 24	-	-
Testis, g SD n	3.33 0.23 24	3.44 0.21 24	3.67** 0.32 24	-	-
Epididymis, mg SD n	1217.2 [illegible] [illegible]	1200.8 78.9 24	1198.9 107.4 24	-	-
Adrenal gland, mg SD n	78.1 10.0 24	78.5 10.3 24	93.1** 12.0 24	-	-

SD = Standard deviation; n = Number of animals; * = Statistically significance, $p \leq 0.05$; ** = Statistically significance, $p \leq 0.01$; - = Missing data due to reproductive toxicity in the F1 groups at the 1000 and 3000 ppm dose levels.

Table E. Effects on terminal body weight and selected target organ weights in the F0 and F1 parental females, FX (F1b females adults), FY (all female F2a adults) and FZ (all female F2b adults).

Dose group→ P0 females, body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	299.2 20.7 21	301.3 25.2 24	311.6 22.5 24	287.7 20.3 22	285.6 21.3 21
Liver wt., g sd n	9.6 0.8 21	10.0 1.1 24	10.6* 1.8 24	10.5* 0.8 22	13.2** 1.4 21
Adrenal gland wt., mg SD n	110.0 11.2 21	108.8 16.9 24	114.7 15.6 24	143.6** 16.4 24	131.2** 24.5 21
F1 female (F1a adults), body wt. & absolute organ wt.	**Control, 0**	**50 ppm**	**300 ppm**	**1000 ppm**	**3000 ppm**
Body wt., g SD n	303.5 24.6 23	305.0 23.5 23	319.6 28.1 22	-	-
Liver wt., g sd n	9.5 1.0 23	9.7 1.0 23	10.4* 1.3 22	-	-
Adrenal gland wt., mg SD n	94.2 8.5 23	92. 9.7 23	101.2* 11.7 22	-	-

Continued on the next page

FX female (non-mate, F1b adults), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	247.9 27.6 23	246.3 19.7 24	265.3* 33.2 24	253.3 16.9 23	251.9 18.7 40
Liver wt., g sd n	7.5 1.2 23	7.3 0.6 24	7.8 1.0 24	8.6* 0.6 23	13.3** 1.8 40
Adrenal gland wt., mg SD n	85.7 13.3 23	86.1 8.1 24	92.9 11.8 24	113.5** 16.1 23	132.0** 23.6 40
Dose group → FY female (F2a adults), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	241.8 16.8 24	239.5 17.6 24	247.8 26.0 24	-	-
Liver wt., g sd n	7.3 0.6 24	7.4 0.7 24	8.0* 0.8 24	-	-
Adrenal gland wt., mg SD n	92.3 11.8 24	90.5 13.0 24	100.4* 10.0 24		
FZ female (F2b adults), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	232.2 26.2 24	234.4 24.0 24	247.0 27.8 24	-	-
Liver wt., g sd n	7.3 0.9 24	7.4 0.8 24	8.0* 1.1 24	-	-
Adrenal gland wt., mg SD n	93.5 11.7 24	88.6 9.8 24	103.5** 11.6 24	-	-

SD = Standard deviation; n = Number of animals; * = Statistically significance, $p \leq 0.05$; ** = Statistically significance, $p \leq 0.01$; - = Missing data due to reproductive toxicity in the F1 groups at the 1000 and 3000 ppm dose levels.

b. Gross Necropsy and Microscopic Examination -

i. Results from Gross pathology - Gross examination was conducted. Gross pathology was generally related to the anti-androgenicity of vinclozolin, however, the relationship of the adrenal enlargement, eye cataracts and liver toxicity to this anti-androgenicity has not been directly related. However, liver and adrenal toxicity have been noted in studies of other anti-androgens such as flutamide.

The PO generation males and females showed discolored adrenals and cataracts at the 3000 ppm dose level only.

Reduced size and mal development of male reproductive organs were seen at 1000 and 3000 ppm, such as the seminal vesicles, prostate, bulbo-urethral gland, hypospadia (nearly all males in the F1 and FX groups) and penis. Discolored adrenals generally were seen at 1000 and 3000 ppm and cataracts were seen at 300, 1000 and 3000 ppm. The cataracts were seen in males and females at 300 ppm and above. Reduced testes size, epididymal size and the presence of Muellerian ducts were seen only at 3000 ppm in the F1 and FX males. All gross pathology was seen at the same or higher dose levels than the histopathology.

Feminization of F1a and F1b pups occurred to such an extent that pups could not be sexed. Pups were raised to adulthood in order to determine which animals to cohabit for mating trials. The adult F1 males demonstrated hypospadia and hypoplastic penis in all 29/29 males at 3000 ppm. Paraphimosis (6/29), vagina like orifice (28/29) and hypoplastic testes (29/29) in F1 adult males at 3000 ppm. FX males demonstrated similar findings in all males dosed at 3000 ppm. Ectopic testes or undescended testes were not reported in this study, but they have been reported from dosing in utero with other anti-androgens and other studies with vinclozolin. At 1000 ppm, hypospadia (F1=24/24)(FX=20/24), reduced sizes of seminal vesicles (F1=19/24)(FX=21/24), prostate (F1=19/24)(FX=18/24), bulbo-urethral gland (F1=15/24)(FX=13/24) and reduced penis size (F1=23/24)(FX=21/24) were seen in F1 and FX males at 1000 ppm. Nipples were noted in F1 and FX males at 1000 and 3000 ppm.

ii. Microscopic examination - Test material related findings occurred in the reproductive organs of males and females. Males were more sensitive to vinclozolin than females. A description of these malformations of the reproductive organs and other organs are presented on pages 1464 through 1468, reproduced in Appendix I. Detailed microscopic findings are reported in Tables reproduced from the submitted report. The following pages on microscopic examination are reproduced in Appendix I. PO males: pages 1495 and 1496. PO females: page 1498. F1 adult males: page 1506, 1507 and 1508. F1 adult females: pages 1509 and 1510. FX adult males: pages 1518, 1519 and 1520. FX adult females: page 1521 and 1522. FY adult males: page 1528 and 1529. FY adult females: none reported. FZ adult males: page 1534. FZ adult females: none reported.

PO males were affected less than males dosed in utero. PO males showed Leydig cell hyperplasia (10/24) at 1000 ppm and above (16/24), atrophy of seminiferous tubules of the testes (3/24) at 3000 ppm and reduced secretion in the prostate (2/24) at 3000 ppm. The pituitary demonstrated castration cells (vacuolation) in all PO males at the HDT (Tables on page 1495, reproduced in Appendix I). Feminization of F1a and F1b pups occurred to such a degree that pups could not be sexed. Pups were raised to adulthood in order to determine which animals to be cohabited for mating trials at 1000 and 3000 ppm.

Feminization of F1 and FX adult males at the 1000 and 3000 ppm dose levels was also apparent (Table on page 1506, 1507, 1518, 1519 and 1520, reproduced in the Appendix). Ductus deferens and

Muellerian ducts were both present in the 18/29 males at 3000 ppm. Also at 3000 ppm, seminal vesicles were missing or reduced in size and vaginal pouches were present. Most of the Muellerian ducts contained sperm and cellular debris. Since none of the males demonstrated ovaries, but all demonstrated testes, these males were pseudohermaphrodites. In many of the these animals the prostate and seminal vesicles, coagulating gland, bulbo-urethral gland were missing or reduced in size at 3000 ppm. At 1000 ppm, generally reduced secretion was present in these organs. Hypospadia was demonstrated at 1000 ppm and above.

Lipidosis and interstitial cell hyperplasia of the ovary occurred at 1000 and 3000 ppm in P0, F1 and FX females (Tables on page 1497,, 1509 and 1522, reproduced in Appendix I). No other dose related histopathology was reported on the female reproductive organs.

Lenticular degeneration occurred in 2/24 F1 and 2/24 FX males and in only 1/24 P0 and 1/24 FX females at 300 ppm. The frequency was increased at higher dose levels and in most animals at 3000 ppm (Tables on Page 1495, 1507 and 1519 for males and 1497, 1509 and 1521 for females, reproduced in Appendix I). Cataracts were noted in FY (0/24 for males and 3/24 for females) and FZ (2/24 for males and 1/24 for females) adults only at 300 ppm (Tables on page 1528 and 1534, reproduced in the Appendix). The highest dose level groups for the FY and FZ was 300 ppm. Lenticular degeneration is histological term, BASF used to characterize cataracts and lens histopathology.

Microscopically, P0, F1 and FX male and female livers and adrenal organs were affected only at the 1000 and 3000 ppm (Tables on 1495, 1507 and 1519 for males and 1497, 1509 and 1521 for females, reproduced in Appendix I). There was no nephropathy reported for any group to correlate with the increased water consumption. Central hypertrophy of the liver was affected at 1000 ppm while necrosis and fatty changes occurred only at 3000 ppm in P0 males and females and F1 and FX males. Lipidosis was noted in adrenals at 3000 ppm in P0, F1 and FX males and females and in some males and female animals at 1000 pm. Lipogenic pigment was seen in the adrenals only at 3000 ppm in P0, F1 and FX males and females. The F1a and F1b pups demonstrated dilated renal pelvis and hydroureters only at 3000 ppm (Tables 070 and 073, reproduced in Appendix I).

D. ABSTRACT AND DISCUSSION:

A study of the effects of vinclozolin in approximately 24 Wistar rats per sex per group were conducted for 2 generations at 0, 50, 150, 500, 1000 or 4500 ppm (0, 4.9, 30, 96 or 290 for males and 0, 5.3, 31, 101 or 290 mg/kg/day for females). Animals from both the F1a (selected for the F1 generation) and F1b (FX adults) litters were raised to maturity because the sex was indeterminate at the 1000 and 3000 ppm dose level. Similarly the F2a (FY adults) and F2b (FZ adults) litters were raised to maturity (approximately 14 weeks). No pups were delivered at 1000 or 3000

ppm from the F1 parents, therefore, these dose levels are absent in the F2a and F2b litters and FY and FZ adults.

Body weights, but not efficiency in males of the PO and F1 generations were depressed slightly at 3000 ppm. Although the lack of effects on efficiency would appear to argue against a toxic effect on body weight, the extent of the effect of this anti-androgen on appetite, muscle mass, body water retention and fat deposition is unknown and efficiency of food utilization may not be a good index of toxic effects of anti-androgens.

Water consumption was statistically significantly decreased in adult PO and F1 female groups at 300 ppm and in all adult groups at 1000 and 3000 ppm. Increased water consumption was less definitive in other chronic studies. No histological correlate in the kidneys were found for the increase in water consumption. Pups at 3000 ppm demonstrated hydroureter and dilated renal pelvis.

Of the hormone levels tested, vinclozolin at 4500 ppm for 6 months was found to induce statistically significant elevations of ACTH, corticosterone, testosterone, DHEA and LH in males and ACTH and LH in females (MRID# 425884-01). Aldosterone was 157% of controls in males and 45% of controls in females in the 6 months study. Since the LH levels in females were only doubled and FSH was unchanged, the apparent elevation in females may have been due to the timing of the blood collection and the estrous cycles in some of the females, i.e., the LH may have been elevated due to ovulatory release. There were no studies conducted on the estrous cycles to determine the timing of possible ovulation of these females.

The fertility of the PO males and the fertility index for PO females was slightly decreased at the 3000 ppm dose level. The number of males proving fertility was statistically significantly reduced only for the F1a mating and only 2 males failed when remated to fertile females. However, the case was much different when F1 males were mated. F1 males were apparently not capable of fertilizing females to produce the F2 generation at 1000 and 3000 ppm because no offspring were delivered. The Sponsor indicated that malformed male genitalia was the reason for the failure of females to deliver offspring. There was no other indication whether this may have been due to inadequate sperm, hypospadia, small penis size or failure to adequately stimulate the female (Wilson et al, 1963 and Wilson et al, 1965), but all these factors may have contributed to the F1 male infertility at 1000 and 3000 ppm. Severity of the hypospadia could account for all the male infertility. Fertility was unaffected at 50 and 300 ppm. Female fertility may have been affected at the 3000 ppm dose level because 6 PO females failed to conceive with control males of proven fertility.

In addition to malformed genitalia, which probably acted as inadequate sperm delivery system, adult males at 1000 and 3000 ppm had malformations of the internal organs of reproduction. The testing laboratory called these internal malformations, Muellerian ducts (embryological origin of the vagina, uterus and uterine tubes), mostly at 3000 ppm. They extended from the neck of the urinary bladder, accompanying the ureter and opening in the ano-genital region through a vagina-like opening into the exterior.

These ducts contained either water like or puss like contents. Seminal vesicles and prostates were absent in these animals and testes, epididymides and penises were reduced in size. No report of ectopic or undescended testes were reported, but they have been reported from in utero dosing with other anti-androgens.

A body weight reduction occurred in F1a and F1b pups during lactation from day 4 through day 21 at 1000 and 3000 ppm. Body weights were reduced at day 1 after birth at 3000 ppm. No body weight effects occurred at 50, 300 ppm in F1a, F1b, F2a or F2b pups.

F1a and F1b pup survival was significantly depressed at 1000 nd 3000 ppm starting at day 4 of lactation. Cannibalism during lactation was increased at 3000 ppm. The F1a and F1b pups demonstrated dilated renal pelvis and hydroureter only at 3000 ppm. Observation of cataracts were noted as early week 8 in females at 300 ppm. These cataracts appeared to be dose related with a NOEL/LEL = 50 ppm/300 ppm in males and females. Liver toxicity in the form of single cell necrosis was noted at 3000 ppm with liver weight increases occurring at 300 ppm in some groups from some generations.

Absolute adrenal weight increases were noted in FY and FZ males and F1, FY and FZ females at 300 ppm and above and lipidosis was noted at 1000 ppm and above. Relative adrenal weights were statistically significantly increased only at 1000 ppm and 3000 ppm in P0, F1 and FX males and P0 and FX females, the only male and female groups studied at 1000 and 3000 ppm. Lipidosis of the interstitial cells were noted in the ovary at 1000 and 3000 ppm. An increased incidence of hepatocellular hypertrophy and necrosis occurred in the liver of males and females at 3000 ppm. In the case of the adrenal, calculating the relative organ weights with the variable body weights of groups may have masked real organ weight increases. Relative weights of the testis and the epididymis are not relevant.

F. BIBLIOGRAPHY:

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Wilson, JR, N Adler, and B LeBoeuf (1965). The effects of intromission frequency on successful pregnancy in the female rat. Proc. Nat. Acad. Sci. 53, 1392-1395.

G. APPENDIX I: Tables 048, 049, 050, 051, 054, 057, 059, 060, 061, 062, 063, 064, 067, 068, 070, 073, 144, 145, 146, 147; pathology descriptions on page 1464 through 1468; and Tables on pages 1495, 1496, 1497, 1498, 1506, 1507, 1508, 1509, 1510, 1518, 1519, 1520, 1521, 1522, 1528 and 1534 of the submitted document, copied from the submitted report and referenced in the DER.

H. **APPENDIX II**: Summary of MRID# 425813-02; [van Ravenzwaay, Ben. (November 1992) Discussion of Prenatal and Reproduction Toxicity of Reg. No. 258 (Vinclozolin), Reg Doc. No. BASF 92/11407.] 010380

The report summarized prenatal toxicity in the rat, rabbit and mouse, all of which have been reviewed elsewhere (Rat, HED Doc.# 007909; Rabbit, HED Doc.# 008311; Mouse, HED Doc.# 000244). Studies on reproduction were summarized, one study from the 1970s (Reviewed in HED Doc.# 000244) and one from 1992 (Reviewed in the DER). A summary of the hormone studies and receptor binding studies were also related to a postulated mechanism of action. The NOEL/LEL for the developmental and reproductive effects of vinclozolin were stated. A list of 24 references supporting the summaries were also submitted. These references included previously submitted interim reports and final reports on prenatal studies, studies on reproduction, studies on hormone receptor binding and 6 literature references to anti-androgens.

The literature references will not be reviewed in this document. The data reviewed previously on prenatal toxicity in the rat, rabbit and mouse, referenced above, will not be reviewed again. The study on reproduction has already been reviewed in the DER. However, summary data not previously reviewed is presented on relative binding of vinclozolin, a major urinary metabolite (119 208), flutamide and RU 23-980 to androgen receptors. The structures of these compounds are presented in Figure 1.

The summary reported weak interactions of vinclozolin with the androgen receptors in human mammary cells, MCF-7 cells, compared with mibolerone, a synthetic anabolic steroid related to testosterone and additional binding results from receptors in a LNCAP cell line derived from human prostate and in rat prostate. The report indicated that the Kd for mibolerone was 0.244 nmoles/l in the LNCAP cell line derived from human prostate. The report further stated that the vinclozolin Kd was 1% of mibolerone and 91% of flutamide. This should mean that the Kd for vinclozolin in the LNCAP cell line is 0.00244 nmoles/l.

The report further indicated that the Kd for mibolerone was 0.026 nmoles/l in the in vivo rat prostate study. The report indicated that the vinclozolin Kd was 0.026% of mibolerone and 92% of flutamide. This should mean that the Kd for vinclozolin in the in vivo rat prostate study is 0.0000067 nmoles/l. This would imply that the rat prostate receptor bound vinclozolin more tightly than the human prostate receptor. It follows then that if other conditions are equal, vinclozolin should be less effective in humans than in rats. However, the calculated relative Kd for vinclozolin as presented by the sponsor (Table 3) does not support the calculations in this paragraph. Thus without addition data and

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[1] Kd (nmoles/l) = Binding affinity = Dissociation constant = [receptor][test material]/[receptor-test material]. [HR]/[H] = -1/kd[HR] + [R0]/Kd, H = hormone concentration, HR = hormone-receptor concentration, R0 = receptor concentration and R = free receptor concentration.

information, none of the experimental or calculated Kd's can be used.

These results have little meaning without the experimental details and additional information, such as conditions for the binding and the nature of the binding curves. The summary presented by the sponsor contained no details of the methods used to compared the binding affinities or the methods used to obtain the affinities. The data (Tables A, B and C) are presented as given, and the validity cannot be determined at this time.

A summary of the maternal NOEL, prenatal, reproductive and anti-androgenicity NOEL are given in Table D (sponsor's definitions), extracted from the submitted report. The values are in general agreement those arrived at by Toxicology Branch-1. The F2 generation effects at 4.9 mg/kg/day are for epididymal weight reduction. The sponsor may be requested to determine the functional meaning of this epididymal weight reduction in an additional study.

Table A. Relative binding affinities of various anti-androgens with androgen receptors from various sources.

Chemical and reaction time (Knupper, 4/27/90).	Binding affinities relative to	
	Flutamide	Fibclerone
Vinclozolin 2 hours 12 hours	65% 40%	1.4% 1.1%
119 208 (metabolite, see fig.1) 2 hours 12 hours	4% 2%	1.0% 1.0%

Table B. Vinclozolin dissociation constants (Kd nmoles/l) relative to mibolerone over the three studies. The methods used to derive these results were not stated.

Androgen receptor source/reference	Vinclozolin relative to mibolerone Kd (nmoles/l)*	Vinclozolin binding as a % of mibolerone	Mibolerone Kd nmoles/l	Vinclozolin binding as a % of flutamide
MCF-7 cells, in vitro study (Knuppen, 4/27/90)	180	-	-	-
MCF-7 cells, in vitro study (Knuppen, 4/9/91)	25	-	-	-
LNCAP cells, in vitro study (Knuppen, 8/3/92)	28	(1%)**	0.244 ± 0.11%	(91%)
Rat prostate, in vivo study (Knuppen, 8/3/92)	100	(0.026%)	0.026 ± 0.016	(92%)

* These units, Kd (nmoles/l), must be in error for the relative vinclozolin binding affinity presented in the submitted report. These units are not consistent with the next column also selected from the submitted report. They may be the relative binding among the 4 studies with the study in the rat prostate being set at an arbitrary 100.

** Values in parenthesis are the percentage binding reported in the submitted summary for vinclozolin relative to mibolerone and flutamide.

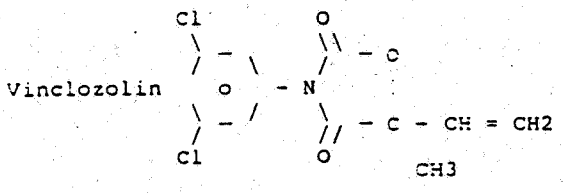
Table C. Binding affinities of various anti-androgens.

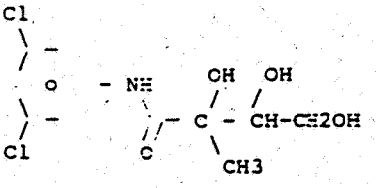
Experiment	Vinclozolin relative to flutamide (%	Vinclozolin relative to mibolerone (%	Mibolerone Kd nmoles/l	119 208 Kd (nmoles/l)
LNCAP cells (Knuppen, 8/3/92)	91%	1%	0.244 ± 11%	-
Rat prostate (Knuppen, 8/3/92)	92%	0.026%	0.026 ± 0.016	-

Table D. NOEL in mg/kg day from the recent developmental toxicity studies and the study on reproduction (Sponsor suggested effect levels).

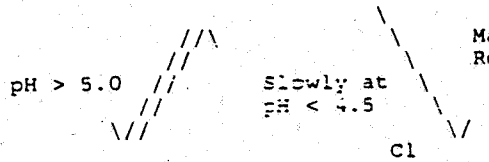
	Maternal toxicity	Feto/embryo toxicity	Anti-androgen effects	Reproduction
Developmental/rat/oral	300	150	15	-
Developmental/rabbit/oral	30	200	-	-
Developmental/rat/dermal	60	-	60	-
2-Gen. reproduction	4.9	29	4.9 (P0/F1) <4.9 (F2)	29

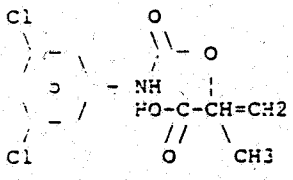
Figure 1. The major metabolite, two major decomposition products of vinclozolin and four other chemicals demonstrating anti-androgenicity (two drugs and 2 pesticides).



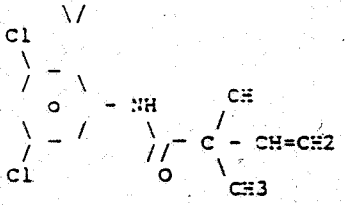


Major urinary metabolite (compound 25). Referred to 119 208 in this report.

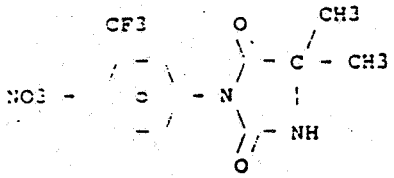




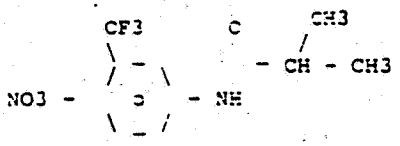
M1 reversible hydrolysis product [2-[[(3,5-dichlorophenyl)carbamoyl]oxy]-2-methyl-3-butanoic acid]; forms rapidly at alkaline pH > 8.0, Szeto et al., 1989.



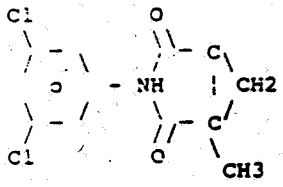
Irreversible degradation product, referred to as Compound 23 in the metabolism study and M2 by Szeto et al., 1989.



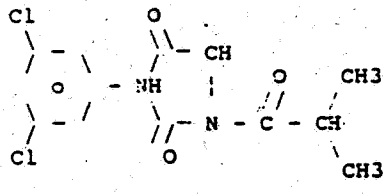
RU 23 908



Flutamide



Procymidone; [N-(3,5-dichlrophenyl)-1,2-dimethyl-cyclopropane-1,2-dicarboximide].



Glycophene, iprodione, Anfor, BSI, Chipco and Rovral; [3-(3,5-dichlorophenyl)-N-(1-imidazolidinecarbo nide].

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010380

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Knuppen, R. (Orig. Germ. 11/27/91) Study of possible binding of Reg. No. 83 258 (vinclozolin), Reg. No. 119 208 (metabolite BF 352-22) to the androgen and glucocorticoid receptors in the cytosol from MCF-7 cells and from prostate and liver tissues of the rat (Proj. No. 21B0375/889033); Oct. 13, 1992 (original German report: Nov. 27, 1991). Conducted at the Medical University of Lübeck, D-W-2400 Lübeck, FRG. Reg. Doc. No. BASF 92/11229.

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Szeto, Sunny Y, Nick E Burlinson, James E Rahe and Peter Oloffs. (1989) Kinetics of hydrolysis of the dicarboximide fungicide vinclozolin. J. Agric. Food Chem. 37, 523-529.

DER for Repro/Vinclozolin MRID# 425813-01 & Summary -02/D1816519/ B:\VINCLV43.23C\DREPSUMI.MFO/DANDERSON/3/22/93,4/20/93. (Recovered 6/3/93. resubmitted 6/10/93; Edited 7/7/93).*

13-MAR-92 PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS TABLE : 048
88053F1A ORAL ADMINISTRATION (DIET) / F0 MALES
SUMMARY OF MALE REPRODUCTION DATA (F1A LITTER)

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
MALES ON STUDY	N	24	24	24	24	24
MALES PLACED WITH FEMALES	N	24	24	24	24	24
	%	100	100	100	100	100
MALES WITH CONFIRMED MATING (A)	N	24	24	24	24	23
MALE MATING INDEX (B)	%	100	100	100	100	96
MALES WITHOUT CONFIRMED MATING	N	0	0	0	0	1
	%	0	0	0	0	4
MALES PROVING THEIR FERTILITY (C)	N	23	24	24	22	17 a
MALE FERTILITY INDEX (D)	%	96	100	100	92	71
MALES WHICH DID NOT PROVE THEIR FERTILITY	N	1	0	0	2	7 a
	%	4	0	0	8	29

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER

(B) MALE MATING INDEX = $\frac{\text{NUMBER OF MALES WITH CONFIRMED MATING}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER OR WITH PUPS / FETUSES IN UTERO

(D) MALE FERTILITY INDEX = $\frac{\text{NUMBER OF MALES PROVING THEIR FERTILITY}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

92/11251 0213

26

30

C10380

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 MALES
SUMMARY OF MALE REPRODUCTION DATA (F1B LITTER)

TABLE : 049

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
MALES ON STUDY	N	24	24	24	24	24
MALES PLACED WITH FEMALES	N	24	24	24	24	23
	%	100	100	100	100	96
MALES WITH CONFIRMED MATING (A)	N	24	24	24	24	22
MALE MATING INDEX (B)	%	100	100	100	100	96
MALES WITHOUT CONFIRMED MATING	N	0	0	0	0	1
	%	0	0	0	0	4
MALES PROVING THEIR FERTILITY (C)	N	21	23	23	22	19
MALE FERTILITY INDEX (D)	%	88	96	96	92	83
MALES WHICH DID NOT PROVE THEIR FERTILITY	N	3	1	1	2	4
	%	12	4	4	8	17

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER

(B) MALE MATING INDEX = $\frac{\text{NUMBER OF MALES WITH CONFIRMED MATING}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER OR WITH PUPS / FETUSES IN UTERO

(D) MALE FERTILITY INDEX = $\frac{\text{NUMBER OF MALES PROVING THEIR FERTILITY}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

TABLE : 050

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Females on Study	N	24	24	24	24	24
Females Mated	N	24	24	24	24	23
Female Mating Index	%	100	100	100	100	96
Mating days until day 0 pc	MEAN	2.0	2.2	2.3	2.2	2.7
	S.D.	0.86	1.01	0.94	0.96	3.23
	N	24	24	24	24	23
days 1 to 4	N	24	24	24	24	21
	%	100	100	100	100	91
days 5 to 8	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
days 9 to 14	N	0	0	0	0	2
	%	0.0	0.0	0.0	0.0	8.7
days 15 to 21	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
Females Pregnant	N	23	24	24	22	17a
Female Fertility Index	%	96	100	100	92	74
Duration of Gestation (Days)	MEAN	22.0	21.8	21.9	21.7	21.7
	S.D.	0.37	0.44	0.28	0.48	0.47
Females with Liveborn	N	23	24	24	22	17
Gestation Index	%	100	100	100	100	100
with Stillborn Pups	N	4	5	4	3	5
	%	17	21	17	14	29
with all Stillborn	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
Pups Delivered	MEAN	14.0	14.0	14.5	15.2	10.8b
	S.D.	2.65	2.32	2.07	2.07	4.50
	TOTAL	321	336	347	335	184
Liveborn	N	315	331	342	330	171b
Live Birth Index	%	98	99	99	99	93
Stillborn	N	6	5	5	5	13b
	%	1.9	1.5	1.4	1.5	7.1

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

TABLE : 051

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Females on Study	N	24	24	24	24	23
Females Mated	N	24	24	24	24	22
Female Mating Index	%	100	100	100	100	96
Mating days until day 0 pc	MEAN	1.9	2.1	2.7	2.3	3.3
	S.D.	0.97	1.18	3.09	1.08	3.73
	N	24	24	24	24	22
days 1 to 4	N	24	24	23	24	19
	%	100	100	96	100	86
days 5 to 8	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	4.5
days 9 to 14	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	4.5
days 15 to 21	N	0	0	1	0	1
	%	0.0	0.0	4.2	0.0	4.5
Females Pregnant	N	21	23	23	22	19
Female Fertility Index	%	88	96	96	92	86
Duration of Gestation (Days)	MEAN	21.7	21.8	21.7	21.7	21.5
	S.D.	0.46	0.42	0.47	0.48	0.51
Females with Liveborn	N	21	23	23	22	19
Gestation Index	%	100	100	100	100	100
with Stillborn Pups	N	5	11	11	5	9
	%	24	48	48	23	47
with all Stillborn	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
Pups Delivered	MEAN	15.2	16.1	15.9	16.2	11.8b
	S.D.	3.20	2.83	2.16	1.97	5.45
	TOTAL	319	371	365	357	225
Liveborn	N	308	355	350	349	214
Live Birth Index	%	97	96	96	98	95
Stillborn	N	11	16	15	8	11
	%	3.4	4.3	4.1	2.2	4.9

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT

9-OCT-9.

88053F1A

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF LITTER DATA

TABLE : 054

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Pups Dead						
day 0	N	13	4a	3b	4a	14
	%	4.1	1.2	0.9	1.2	8.2
days 1 to 4	N	13	16	18	22	77b
	%	4.1	4.8	5.3	6.7	45
days 5 to 7	N	0	0	4	2	8b
	%	0.0	0.0	1.2	0.6	4.7
days 8 to 14	N	0	0	2	0	2
	%	0.0	0.0	0.6	0.0	1.2
days 15 to 21	N	0	0	0	2	1
	%	0.0	0.0	0.0	0.6	0.6
Pups Surviving days 0 to 4 Viability Index	N	289	311	321	304	80b
	%	92	94	94	92	47
Pups Surviving days 4 to 21 Lactation Index	N	289	311	315a	300	69b
	%	100	100	98	99	86
Live Pups/Litter						
day 0	MEAN	13.7	13.8	14.3	15.0	10.1b
	S.D.	2.70	2.34	2.09	1.98	4.75
	TOTAL	315	331	342	330	171
day 4	MEAN	12.6	13.0	13.4	13.8	4.7b
	S.D.	4.21	2.46	2.78	3.50	4.41
	TOTAL	289	311	321	304	80
day 7	MEAN	12.6	13.0	13.2	13.7	4.2b
	S.D.	4.21	2.46	2.78	3.45	4.28
	TOTAL	289	311	317	302	72
day 14	MEAN	12.6	13.0	13.1	13.7	4.1b
	S.D.	4.21	2.46	2.77	3.45	4.37
	TOTAL	289	311	316	302	70
day 21	MEAN	12.6	13.0	13.1	13.6	4.1b
	S.D.	4.21	2.46	2.77	3.44	4.28
	TOTAL	289	311	315	300	69

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT. Pups Dead = Pups Died + Sacrificed Moribund + Cannibalized

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF LITTER DATA

TABLE : 056

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
(Total Number of) Litters	N	21	23	23	22	19
Litters with Liveborn Pups	N	21	23	23	22	19
	%	100	100	100	100	100
Litters with Stillborn Pups	N	5	11	11	5	9
	%	24	48	48	23	47
Litters with all Stillborn Pups	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
Pups Delivered (total)	N	319	371	365	357	225
	MEAN	15.2	16.1	15.9	16.2	11.8b
	S.D.	3.20	2.83	2.16	1.97	5.45
Pups Liveborn	N	308	355	350	349	214
	%	97	96	96	98	95
Pups Stillborn	N	11	16	15	8	11
	%	3.4	4.3	4.1	2.2	4.9
Pups Died	N	10	16	13	26a	70b
	%	3.1	4.3	3.6	7.3	31
Pups Sacrificed Moribund	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0
Pups Cannibalized	N	3	2	6	9	55b
	%	0.9	0.5	1.6	2.5	24
Pups Accidental Death	N	0	0	1	0	0
	%	0.0	0.0	0.3	0.0	0.0
Pups Sacrificed, Maternal Death	N	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / FO FEMALES (F1B LITTER)
SUMMARY OF LITTER DATA

TABLE : 057

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Pups Dead						
day 0	N	1	6	1	1	6a
	%	0.3	1.7	0.3	0.3	2.8
days 1 to 4	N	7	8	15	22a	80b
	%	2.3	2.3	4.3	6.3	37
days 5 to 7	N	3	2	2	3	4
	%	1.0	0.6	0.6	0.9	1.9
days 8 to 14	N	2	2	0	5	2
	%	0.6	0.6	0.0	1.4	0.9
days 15 to 21	N	0	0	1	4	1
	%	0.0	0.0	0.3	1.1	0.5
Pups Surviving days 0 to 4 Viability Index	N	300	341	334	326a	128b
	%	97	96	95	93	60
Pups Surviving days 4 to 21 Lactation Index	N	295	337	330	314	121a
	%	98	99	99	96	95
Live Pups/Litter						
day 0	MEAN	14.7	15.4	15.2	15.9	11.3b
	S.D.	3.29	2.86	2.04	1.91	5.22
	TOTAL	308	366	350	349	214
day 4	MEAN	14.3	14.8	14.5	14.8	6.7b
	S.D.	3.28	2.66	2.19	3.76	5.26
	TOTAL	300	341	334	326	128
day 7	MEAN	14.1	14.7	14.4	14.7	6.5b
	S.D.	3.15	2.58	2.13	3.72	5.11
	TOTAL	297	339	332	323	124
day 14	MEAN	14.0	14.7	14.4	14.5	6.4b
	S.D.	3.04	2.59	2.13	3.66	4.95
	TOTAL	296	337	332	318	122
day 21	MEAN	14.0	14.7	14.3	14.3	6.4b
	S.D.	3.04	2.59	2.17	3.67	4.89
	TOTAL	295	337	330	314	121

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT. Pups Dead = Pups Died + Sacrificed Moribund + Cannibalized

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

			TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
day 1	males	MEAN	6.4	6.4	6.4	6.1	5.4b
		S.D.	0.49	0.52	0.55	0.36	0.55
		N	22	24	24	22	12
	females	MEAN	6.1	6.1	6.2	5.8	5.2b
		S.D.	0.60	0.46	0.55	0.41	0.57
		N	22	24	24	22	14
	males+females	MEAN	6.2	6.2	6.3	5.9	5.3b
		S.D.	0.55	0.47	0.53	0.39	0.52
		N	22	24	24	22	14
day 4	males	MEAN	9.2	9.3	9.3	8.2a	7.0b
		S.D.	1.19	1.24	1.10	0.88	1.22
		N	22	24	24	21	10
	females	MEAN	9.1	8.9	9.0	8.0a	6.8b
		S.D.	1.24	1.10	1.20	0.89	1.20
		N	22	24	24	21	11
	males+females	MEAN	9.1	9.1	9.2	8.1a	6.8b
		S.D.	1.19	1.14	1.12	0.89	1.36
		N	22	24	24	21	11
day 7	males	MEAN	13.6	13.9	13.9	12.1a	9.6b
		S.D.	1.94	2.15	1.74	1.39	1.83
		N	22	24	24	21	10
	females	MEAN	13.4	13.4	13.5	11.7b	9.7b
		S.D.	1.76	1.91	1.80	1.38	2.02
		N	22	24	24	21	10
	males+females	MEAN	13.5	13.6	13.7	11.9a	9.2b
		S.D.	1.78	1.99	1.76	1.38	2.42
		N	22	24	24	21	11

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHTS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHTS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

TABLE : 060

			TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
day 14	males	MEAN	26.2	26.9	27.2	22.0b	18.1b
		S.D.	3.50	4.24	3.67	2.44	2.67
		N	22	24	24	21	10
	females	MEAN	25.8	26.2	26.4	21.3b	17.9b
		S.D.	3.42	3.90	3.68	2.23	3.26
		N	22	24	24	21	10
	males+females	MEAN	26.0	26.5	26.8	21.7b	18.0b
		S.D.	3.33	4.02	3.63	2.36	2.84
		N	22	24	24	21	10
day 21	males	MEAN	43.6	44.2	44.7	36.3b	31.3b
		S.D.	6.34	7.95	6.12	4.13	6.17
		N	22	24	24	21	10
	females	MEAN	42.1	42.3	42.6	35.2b	31.2b
		S.D.	6.52	6.90	5.90	3.75	6.32
		N	22	24	24	21	10
	males+females	MEAN	42.8	43.2	43.6	35.8b	31.4b
		S.D.	6.80	7.33	5.91	3.95	6.06
		N	22	24	24	21	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHTS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHTS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

TABLE : 061

			TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
DAYS 1 TO 4							
	males	MEAN	2.9	2.9	2.9	2.2a	1.5b
		S.D.	0.77	0.78	0.67	0.61	0.90
		N	22	24	24	21	10
	females	MEAN	2.9	2.8	2.8	2.1b	1.4b
		S.D.	0.68	0.71	0.71	0.59	0.91
		N	22	24	24	21	11
	males+females	MEAN	2.9	2.9	2.8	2.2b	1.3b
		S.D.	0.69	0.73	0.66	0.60	1.02
		N	22	24	24	21	11
DAYS 4 TO 7							
	males	MEAN	4.4	4.6	4.6	3.8	2.6b
		S.D.	0.94	1.09	0.77	0.63	0.67
		N	22	24	24	21	10
	females	MEAN	4.4	4.5	4.5	3.7a	2.7b
		S.D.	0.74	0.95	0.81	0.58	0.96
		N	22	24	24	21	10
	males+females	MEAN	4.4	4.6	4.5	3.8	2.4b
		S.D.	0.80	1.01	0.76	0.59	1.11
		N	22	24	24	21	11
DAYS 7 TO 14							
	males	MEAN	12.6	13.1	13.3	9.9b	8.5b
		S.D.	2.41	2.39	2.10	1.17	1.78
		N	22	24	24	21	10
	females	MEAN	12.4	12.8	13.0	9.6b	8.2b
		S.D.	2.77	2.26	2.25	1.30	1.98
		N	22	24	24	21	10
	males+females	MEAN	12.5	12.9	13.1	9.8b	8.3b
		S.D.	2.54	2.30	2.27	1.44	2.00
		N	22	24	24	21	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHT GAINS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHT GAINS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1A LITTER)
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

TABLE : 062

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
DAYS 14 TO 21						
males	MEAN	17.4	17.3	17.5	14.3b	13.2b
	S.D.	2.97	3.62	2.69	1.97	3.80
	N	22	24	24	21	10
females	MEAN	16.4	16.1	16.2	13.9a	13.2b
	S.D.	2.22	3.13	2.41	1.86	3.75
	N	22	24	24	21	10
males+females	MEAN	16.9	16.7	16.8	14.1b	13.3b
	S.D.	2.56	3.42	2.48	1.90	3.68
	N	22	24	24	21	10
DAYS 1 TO 21						
males	MEAN	37.2	37.8	38.2	30.3b	25.8b
	S.D.	6.10	7.62	5.81	3.89	6.05
	N	22	24	24	21	10
females	MEAN	36.0	36.2	36.4	29.4b	25.7b
	S.D.	5.34	6.59	5.56	3.49	6.15
	N	22	24	24	21	10
males+females	MEAN	36.6	36.9	37.3	29.8b	25.9b
	S.D.	5.60	7.02	5.59	3.70	5.90
	N	22	24	24	21	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHT GAINS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHT GAINS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

17-AUG-92

88053F1B

PROJ.NO. 71R0375/8803: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

TABLE 1 063

			TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
day 1	males	MEAN	6.4	6.4	6.3	6.2	5.3b
		S.D.	0.55	0.38	0.49	0.42	0.49
		N	21	23	23	22	16
	females	MEAN	6.1	6.1	6.0	5.9	5.2b
		S.D.	0.58	0.36	0.37	0.44	0.47
		N	21	23	23	22	16
	males+females	MEAN	6.2	6.3	6.2	6.0	5.2b
		S.D.	0.54	0.36	0.44	0.42	0.43
		N	21	23	23	22	17
day 4	males	MEAN	9.1	9.1	8.8	8.2b	6.5b
		S.D.	1.08	0.67	0.92	0.84	0.79
		N	21	23	23	21	14
	females	MEAN	8.6	8.7	8.3	7.8a	6.3b
		S.D.	1.17	0.68	0.86	0.89	1.03
		N	21	23	23	21	14
	males+females	MEAN	8.9	8.9	8.6	8.0b	6.4b
		S.D.	1.10	0.64	0.89	0.83	0.87
		N	21	23	23	21	14
day 7	males	MEAN	13.2	13.1	12.9	11.8b	8.5b
		S.D.	1.74	1.21	1.28	1.38	1.37
		N	21	23	23	21	14
	females	MEAN	12.7	12.5	12.2	11.1b	8.3b
		S.D.	1.87	1.30	1.26	1.44	1.48
		N	21	23	23	21	14
	males+females	MEAN	13.0	12.8	12.6	11.5b	8.5b
		S.D.	1.78	1.23	1.21	1.35	1.31
		N	21	23	23	21	14

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHTS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHTS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

92/11251 0228

040380

PROJ.NO. 7180375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

			TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
day 14	males	MEAN	25.3	24.0	25.1	22.1b	16.6b
		S.D.	3.56	2.96	2.85	3.14	3.16
		N	21	23	23	21	14
	females	MEAN	24.6	23.7	23.9	21.1b	16.2b
		S.D.	3.87	2.87	3.03	3.17	2.88
		N	21	23	23	21	14
	males+females	MEAN	24.9	24.3	24.6	21.6b	16.5b
		S.D.	3.66	2.89	2.88	3.07	2.80
		N	21	23	23	21	14
day 21	males	MEAN	40.8	40.9	41.5	36.3	26.9b
		S.D.	7.06	5.17	5.87	6.11	5.76
		N	21	23	23	21	14
	females	MEAN	39.2	38.5	38.9	34.3a	26.8b
		S.D.	6.90	4.77	5.66	5.80	5.35
		N	21	23	23	21	14
	males+females	MEAN	40.0	39.8	40.3	35.4a	26.9b
		S.D.	6.90	4.94	5.71	5.87	5.03
		N	21	23	23	21	14

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

NOTE: MALE OR FEMALE WEIGHTS BASED ON SEX IDENTIFIED DURING REARING OR AT NECROPSY;
COMBINED WEIGHTS BASED ON ALL PUPS (INCLUDING THOSE WITH "UNCERTAIN" SEX)

67/

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / FO FEMALES (F1A LITTER)
SUMMARY OF PUP PHYSICAL DEVELOPMENT AND REFLEX DATA

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
PINNA UNFOLDING						
Litters tested	M	22	24	24	21	11
Pups tested	M	289	311	321	303	73
Pups reaching criteria	M	262	280	287	261	51b
	%	91	90	89	86	70
AUDITORY CANAL OPENING						
Litters tested	M	22	24	24	21	10
Pups tested	M	289	311	315	302	70
Pups reaching criteria	M	281	288a	312	270b	48b
	%	97	93	99	89	69
EYE OPENING						
Litters tested	M	22	24	24	21	10
Pups tested	M	289	311	315	302	70
Pups reaching criteria	M	270	285	299	288	67
	%	93	92	95	95	96
GRIPPING-REFLEX						
Litters tested	M	22	24	24	21	10
Pups tested	M	289	311	315	302	70
Pups reaching criteria	M	289	309	315	302	70
	%	100	99	100	100	100
ACOUSTIC STARTLE						
Litters tested	M	22	24	24	21	10
Pups tested	M	289	311	316	300	70
Pups reaching criteria	M	289	311	316	300	70
	%	100	100	100	100	100
PUPIL CONSTRICTION						
Litters tested	M	22	24	24	21	10
Pups tested	M	289	311	315	300	70
Pups reaching criteria	M	289	311	315	300	70
	%	100	100	100	100	100

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

PROJ.NO. 71R03/5/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF PUP PHYSICAL DEVELOPMENT AND REFLEX DATA

TABLE : 068

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
PINNA UNFOLDING						
Litters tested	#	21	23	23	21	14
Pups tested	#	301	341	335	323	124
Pups reaching criteria	#	222	310b	279b	283b	35b
	%	74	91	83	88	28
AUDITORY CANAL OPENING						
Litters tested	#	21	23	23	21	14
Pups tested	#	295	337	332	317	121
Pups reaching criteria	#	240	307b	296b	268	56b
	%	81	91	89	85	46
EYE OPENING						
Litters tested	#	21	23	23	21	14
Pups tested	#	295	337	332	317	122
Pups reaching criteria	#	251	286	298	294b	84b
	%	85	85	90	93	69
GRIPPING-REFLEX						
Litters tested	#	21	23	23	21	14
Pups tested	#	295	337	332	317	122
Pups reaching criteria	#	295	337	332	316	104b
	%	100	100	100	100	85
ACOUSTIC STARTLE						
Litters tested	#	21	23	23	21	14
Pups tested	#	295	337	330	315	122
Pups reaching criteria	#	295	337	330	315	122
	%	100	100	100	100	100
PUPIL CONSTRICTION						
Litters tested	#	21	23	23	21	14
Pups tested	#	295	337	330	315	122
Pups reaching criteria	#	295	337	330	315	121
	%	100	100	100	100	99

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

PROJ.NO. /IR0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS — TABLE : 070
ORAL ADMINISTRATION (DIET) / FO FEMALES (F1A LITTER)
SUMMARY OF PUP NECROPSY OBSERVATIONS

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Litters Evaluated	N	23	24	24	22	13
Pups Evaluated	N	265	285	293	276	63
Live	N	259	280	288	271	50
Stillborn	N	6	5	5	5	13
HEART: DILATATION OF BOTH VENTRICLES (GLOBULAR-SHAPED HEART)						
Pup Incidence	N	0	0	0	1	5b
	%	0.0	0.0	0.0	0.4	7.9
Litter Incidence	N	0	0	0	1	3a
	%	0.0	0.0	0.0	4.5	23
HEART: LEFT VENTRICLE ENLARGED						
Pup Incidence	N	0	0	0	2	1
	%	0.0	0.0	0.0	0.7	1.6
Litter Incidence	N	0	0	0	1	1
	%	0.0	0.0	0.0	4.5	7.7
DILATED RENAL PELVIS						
Pup Incidence	N	8	1a	1a	4	17b
	%	3.0	0.4	0.3	1.4	27
Litter Incidence	N	3	1	1	4	6a
	%	13	4.2	4.2	18	46
HYDROURETER						
Pup Incidence	N	2	1	0	1	5b
	%	0.8	0.4	0.0	0.4	7.9
Litter Incidence	N	2	1	0	1	2
	%	8.7	4.2	0.0	4.5	15
HYPOPLASIA OF TESTES						
Pup Incidence	N	0	1	0	0	0
	%	0.0	0.4	0.0	0.0	0.0
Litter Incidence	N	0	1	0	0	0
	%	0.0	4.2	0.0	0.0	0.0
ABSENCE OF HINDLIMB(S) (LESION)						
Pup Incidence	N	1	0	0	1	0
	%	0.4	0.0	0.0	0.4	0.0
Litter Incidence	N	1	0	0	1	0
	%	4.3	0.0	0.0	4.5	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

PROJ.NO. 71R0375/80053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F0 FEMALES (F1B LITTER)
SUMMARY OF PUP NECROPSY OBSERVATIONS

TABLE : 073

		TEST GROUP 00 0 PPM	TEST GROUP 01 50 PPM	TEST GROUP 02 300 PPM	TEST GROUP 03 1,000 PPM	TEST GROUP 04 3,000 PPM
Litters Evaluated	#	21	23	23	22	18
Pups Evaluated	#	268	321	311	300	81
Live	#	257	305	296	292	70
Stillborn	#	11	16	15	8	11
HEART: DILATATION OF BOTH VENTRICLES (GLOBULAR-SHAPED HEART)						
Pup Incidence	#	0	0	0	0	3a
	%	0.0	0.0	0.0	0.0	3.7
Litter Incidence	#	0	0	0	0	3
	%	0.0	0.0	0.0	0.0	17
HEART: RIGHT VENTRICLE ENLARGED						
Pup Incidence	#	0	0	0	0	9b
	%	0.0	0.0	0.0	0.0	11
Litter Incidence	#	0	0	0	0	5a
	%	0.0	0.0	0.0	0.0	28
HEART: LEFT VENTRICLE ENLARGED						
Pup Incidence	#	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	1.2
Litter Incidence	#	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	5.6
DILATED RENAL PELVIS						
Pup Incidence	#	0	2	0	0	16b
	%	0.0	0.6	0.0	0.0	20
Litter Incidence	#	0	2	0	0	6b
	%	0.0	8.7	0.0	0.0	33
HYDROURETER						
Pup Incidence	#	0	0	0	0	4b
	%	0.0	0.0	0.0	0.0	4.9
Litter Incidence	#	0	0	0	0	3
	%	0.0	0.0	0.0	0.0	17
KINKY TAIL						
Pup Incidence	#	0	0	0	1	0
	%	0.0	0.0	0.0	0.3	0.0
Litter Incidence	#	0	0	0	1	0
	%	0.0	0.0	0.0	4.5	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.

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PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS — TABLE 1 144
ORAL ADMINISTRATION (DIET) / F1 MALES
88053F2A
SUMMARY OF MALE REPRODUCTION DATA (F2A LITTER)

		TEST GROUP 10 0 PPM	TEST GROUP 11 50 PPM	TEST GROUP 12 300 PPM	TEST GROUP 13 1,000 PPM	TEST GROUP 14 3,000 PPM
MALES ON STUDY	N	24	24	23	24	26
MALES PLACED WITH FEMALES	N	24	23	23	24	26
	%	100	96	100	100	100
MALES WITH CONFIRMED MATING (A)	N	23	23	23	1 b	0 b
MALE MATING INDEX (B)	%	96	100	100	4	0
MALES WITHOUT CONFIRMED MATING	N	1	0	0	23 b	26 b
	%	4	0	0	96	100
MALES PROVING THEIR FERTILITY (C)	N	23	22	19	0 b	0 b
MALE FERTILITY INDEX (D)	%	96	96	83	0	0
MALES WHICH DID NOT PROVE THEIR FERTILITY	N	1	1	4	24 b	26 b
	%	4	4	17	100	100

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER

(B) MALE MATING INDEX = $\frac{\text{NUMBER OF MALES WITH CONFIRMED MATING}}{\text{NUMBER OF MALES PLACED WITH FEMALES}} \times 100$

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER OR WITH PUPS / FETUSES IN UTERO

(D) MALE FERTILITY INDEX = $\frac{\text{NUMBER OF MALES PROVING THEIR FERTILITY}}{\text{NUMBER OF MALES PLACED WITH FEMALES}} \times 100$

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F1 FEMALES (F2A LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 10 0 PPM	TEST GROUP 11 50 PPM	TEST GROUP 12 300 PPM	TEST GROUP 13 1,000 PPM	TEST GROUP 14 3,000 PPM
Females on Study	N	24	23	24	24	26
Females Mated	N	23	23	24	1b	0b
Female Mating Index	%	96	100	100	4.2	0.0
Mating days until day 0 pc	MEAN	2.3	2.9	2.8	16.0b	
	S.D.	1.05	3.05	1.35	0.00	
	N	23	23	24	1	
days 1 to 4	N	23	22	23	0a	
	%	100	96	96	0.0	
days 5 to 8	N	0	0	1	0	
	%	0.0	0.0	4.2	0.0	
days 9 to 14	N	0	0	0	0	
	%	0.0	0.0	0.0	0.0	
days 15 to 21	N	0	1	0	1a	
	%	0.0	4.3	0.0	100	
Females Pregnant	N	23	22	20	0a	
Female Fertility Index	%	100	96	83	0.0	
Duration of Gestation (Days)	MEAN	22.2	22.0a	22.0		
	S.D.	0.39	0.21	0.32		
Females with Liveborn	N	23	22	20		
Gestation Index	%	100	100	100		
with Stillborn Pups	N	13	5a	6		
	%	57	23	30		
with all Stillborn	N	0	0	0		
	%	0.0	0.0	0.0		
Pups Delivered	MEAN	12.7	13.5	13.4		
	S.D.	3.59	3.43	4.44		
	TOTAL	291	298	267	0	0
Liveborn	N	274	292a	258		
Live Birth Index	%	94	98	97		
Stillborn	N	17	6a	9		
	%	5.8	2.0	3.4		

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F1 FEMALES (F2B LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 10 0 PPM	TEST GROUP 11 50 PPM	TEST GROUP 12 300 PPM	TEST GROUP 13 1,000 PPM	TEST GROUP 14 3,000 PPM
Females on Study	N	24	23	24	24	26
Females Mated	N	24	23	24	1b	0b
Female Mating Index	%	100	100	100	4.2	0.0
Mating days until day 0 pc	MEAN	2.0	2.6	2.8	19.0b	
	S.D.	0.91	1.12	1.65	0.00	
	N	24	23	24	1	
days 1 to 4	N	24	23	22	0a	
	%	100	100	92	0.0	
days 5 to 8	N	0	0	2	0	
	%	0.0	0.0	8.3	0.0	
days 9 to 14	N	0	0	0	0	
	%	0.0	0.0	0.0	0.0	
days 15 to 21	N	0	0	0	1a	
	%	0.0	0.0	0.0	100	
Females Pregnant	N	24	23	21	0a	
Female Fertility Index	%	100	100	88	0.0	
Duration of Gestation (Days)	MEAN	22.0	21.7a	22.0		
	S.D.	0.29	0.45	0.38		
Females with Liveborn	N	24	23	21		
Gestation Index	%	100	100	100		
with Stillborn Pups	N	5	5	6		
	%	21	22	29		
with all Stillborn	N	0	0	0		
	%	0.0	0.0	0.0		
Pups Delivered	MEAN	15.2	14.3	13.1		
	S.D.	2.30	3.64	4.65		
	TOTAL	364	329	276	0	0
Liveborn	N	352	320	265		
Live Birth Index	%	97	97	96		
Stillborn	N	12	9	11		
	%	3.3	2.7	4.0		

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01.
THE INDICES ARE DEFINED IN THE TEXT

PROJ.NO. 71R0375/88053: 2-GENERATION REPRODUCTION STUDY IN RATS
ORAL ADMINISTRATION (DIET) / F1 MALES
SUMMARY OF MALE REPRODUCTION DATA (F2B LITTER)

88053F2B

		TEST GROUP 10 0 PPM	TEST GROUP 11 50 PPM	TEST GROUP 12 300 PPM	TEST GROUP 13 1,000 PPM	TEST GROUP 14 3,000 PPM
MALES ON STUDY	N	24	24	23	24	26
MALES PLACED WITH FEMALES	N %	24 100	23 96	23 100	24 100	26 100
MALES WITH CONFIRMED MATING (A)	N	24	23	23	1 b	0 b
MALE MATING INDEX (B)	%	100	100	100	4	0
MALES WITHOUT CONFIRMED MATING	N %	0 0	0 0	0 0	23 b 96	26 b 100
MALES PROVING THEIR FERTILITY (C)	N	24	23	20	0 b	0 b
MALE FERTILITY INDEX (D)	%	100	100	87	0	0
MALES WHICH DID NOT PROVE THEIR FERTILITY	N %	0 0	0 0	3 13	24 b 100	26 b 100

SIGNIFICANTLY DIFFERENT FROM CONTROL: a - P<0.05; b - P<0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER

(B) MALE MATING INDEX = $\frac{\text{NUMBER OF MALES WITH CONFIRMED MATING}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER OR WITH PUPS / FETUSES IN UTERO

(D) MALE FERTILITY INDEX = $\frac{\text{NUMBER OF MALES PROVING THEIR FERTILITY}}{\text{NUMBER OF MALES PLACED WITH FEMALES}}$ X 100

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Moreover, whenever glandular tissue was present, chronic inflammation was noted considerably often in dose groups 13 and/or 14 in the prostate glands, the seminal vesicles, and the coagulation glands.

PENIS

The grossly observed reduction of the size of the penis, was verified in most cases only in dose group 14 (27/29). An attempt to verify the clinically observed hypospadia was not made as the clinical observation will even have more diagnostic power than pathology when pathology failed to verify it.

UROGENITAL TRACT

In order to investigate the nature of the grossly observed "Muellerian ducts" in the males of dose group 14, three cross sections through the urogenital tract were performed.
Level I was most appropriate for the detection of either a unilateral or bilateral ductus deferens and/or a uni- or bilateral duct, containing an epithelium that resembles structures of a Muellerian duct.
Level II was primarily worth to demonstrate, whether the "ductus deferens like duct" has entered "normally" into the urethra or not and - if it had not reached the urethra - where the aberrant "ductus deferens-like duct" and the "Muellerian duct" were running to the anogenital region.
Level III was made only in randomly selected representative individuals. It was prepared for the only purpose to demonstrate the further conduct of aberrant duct(s) to the outside in the anogenital region. No attempt was made to correlate hypospadia with a meaningful histologic finding, as its clinical and gross observation was taken as a sufficient proof for its existence.

In level I of the urogenital tract most animals had both a ductus deferens and a Muellerian duct, bilateral in most cases. Unilateral means that either the ductus deferens or the Muellerian duct were unilaterally present on the slide. The contents of the ducts were either a fluid containing spermia or a puzz like debris resembling the uterine contents of a pyometra. A variety of different combinations of the contents for both ducts were noted uni- and/or bilaterally.

In level II it becomes obvious that most of the ducts described in level I do not enter the urethra - what would at last be expected of the ductus deferens. In many cases the one or the other or both ducts parallel the urethra and run in the direction of the anogenital region. The contents of these ducts are comparable with what was seen at level I as well concerning the cellular material as their uni- or bilateral occurrence in either of the ducts.

In animal No. 725, level III demonstrates best the hermaphrodite condition of all males having both an aberrant ductus deferens (or ductus deferens like duct) and a Muellerinan duct. In this animal longitudinal sections were performed through the anogenital region between the vagina-like orifice through which the grossly described ducts seem to reach the outside of the animal body and the area caudal to level II (bulbo-urethral gland). One of the serial sections shows two ducts lying one upon another - one resembling a ductus deferens, one resembling a primitive uterine horn (Muellerian duct). They are separated by a membrane and they open into a common cavity covered by a non stratifying epithelium.

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RESULTS AND DISCUSSION

thus resembling a vagina. This vagina-like cavity opens to the outside. The duct resembling a ductus deferens contains spermia, the duct resembling a uterus contains a puzz-like debris, morphologically identical to what is seen in pyometra.

Text Table No. 13: Incidences of Selected Microscopic Findings in the Urogenital Tract

Name of the lesion	Groups 10 male rats (level I)	11	12	13	14	10 male rats (level II)	11	12	13	14
Animals in selected group	29					25				
Ductus deferens (level I)	28									
Ductus deferens-like duct (level II)										
unilateral	5					24				
bilateral	23					2				
						22				
Muellerian duct	20									
unilateral	1					16				
bilateral	19					3				
						13				
Both ducts present	18									
unilateral	5					15				
bilateral	13					4				
						11				
Not otherwise specified duct										
unilateral						1				
						1				

PITUITARY GLAND

Vacuolation of cells in the anterior part of the pituitary was seen in male rats of all groups including the control group. In dose groups 13 and 14, however, the incidences were considerably higher than in the other treatment groups including the control group. With the exception of one female rat of group 12 (animal No. 654), no vacuolation of the pituitary cells was reported in female rats of any other group.

Text Table No. 14: Microscopic Incidences of Cellular Vacuolation in the Pituitary Gland

Name of the lesion	Groups 10 male rats	11	12	13	14	10 female rats	11	12	13	14
Animals in selected group	24	24	24	24	29	24	24	24	24	26
Vacuolation of cells	4	2	6	19	28	.	.	1	.	.

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OVARIES

Lipidosis of the ovarian interstitial cells was observed in some females of dose groups 13 and 14 with a dose depending increase in incidence. Although as well the number of animals affected as the graded severity was lower than in the corresponding animals of the F0 generation, lipidosis of the ovarian interstitial cells is regarded as a treatment related effect in the F1 generation, too. One female rat of dose group 11 (animal No. 643) also showed minimal (grade 1) lipidosis of the ovarian interstitail cells. As no such finding was reported from dose group 12, this is regarded to be rather an incidental finding of possibly spontaneous etiology than a clearly treatment related effect.

Text Table No. 15: Microscopic Incidences and Graded Severities of Ovarian Lipidosis

Name of the lesion	Groups 10 female rats	11	12	13	14
Animals in selected group	23	24	24	24	26
Lipidosis of ovarian interstitial cells, NOS	.	1	.	3	8
- , minimal	.	1	.	2	6
, slight	.	.	.	1	2

No further relevant findings were observed in the ovaries that seem to be related to the application of the test article.

OTHER ORGANS

All other findings noted microscopically in the other organs are regarded to have developed spontaneously. Their occurrence is interpreted not to be related to the appliaction of the test article.

It is worth to note, however, that in dose group 13 urothelial hyperplasia in the renal pelvis was noted in the kidneys of four out of five animals showing gross lesions in the kidneys (twice unilateral, twice bilateral). In addition, urothelial hyperplasia in the urinary bladder was noted in 4 out of 8 grossly altered organs, while in the 4 remaining grossly altered urinary bladders, transitional cell papillomas were diagnosed in three cases and a transitional cell carcinoma in one case. As both organs (kidneys and urinary bladder) were not protocol organs, the value of these findings remain uncertain. As no such findings were reported from dose group 14 or any other treatment group including the control, however, it seems most likely that these lesions represent an incidental cumulation of various findings in the same organ system.

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3. FX animals (dose groups X0 to X4)

A. Weight parameters

a. Absolute weights

The mean terminal body weight was statistically significantly decreased in the males of group X4 (3000 ppm).

The mean terminal body weight of the females of group X2 (300 ppm) is indicated to be increased with statistical significance, representing an incidental finding.

The females of groups X3 (1000 ppm) and X4 (3000 ppm) revealed statistically significantly increased liver weights showing relationship to dosing.

The absolute adrenal weights of male and female rats of groups X3 and X4 were increased with statistical significance in a dose responding manner.

In accordance to the decreased terminal body weight of the males, the weight of the testes of group X4 was also decreased with statistical significance.

A statistically significant decrease of the mean absolute weight of the epididymides was noted in dose groups X3 and X4, which showed dependency to dosing.

b. Relative weights

The relative liver weight was statistically significantly increased in males of group X4 and in females of groups X3 and X4. In the latter, a relationship to dosing was evident.

The same was true for the statistically significantly increased relative adrenal weights of male and female rats of dose groups X3 and X4.

In the males of groups X3 and X4, the mean weights of the epididymides were decreased dose dependently and with statistical significance.

With the exception of the statistically increased terminal body weight of female rats of dose group X2 (300 ppm), all of these weight changes are interpreted to represent compound related effects.

B. Gross observations

As in the animals of the F1 generation, eyes and adrenal glands are thought to be target organs in male and in female rats, whereas testes, epididymides, accessory genital organs (seminal vesicle, prostate, bulbo-urethral gland), and penis were additionally involved in males.

Again, as in the males of the F1 generation parental animals, the most striking finding in all the males of group X4 (3000 ppm) was the presence of one or two grossly visible ductal structures (called "Muellarian ducts" for diagnostic purpose), extending between approximately the neck of the urinary bladder, accompanying the urethra and opening in the anogenital region through a vagina-like opening into the exterior. These ducts contained either water-like or pus-like contents.
In these animals, the seminal vesicle (48/49), the prostate (49/49) and the bulbo-urethral gland (49/49) were entirely absent, and the testes (35/49), epididymides (49/49), and penis (48/49) of these animals seemed to be reduced in size. Hypospadia was noted in all but one male rat of this group. In addition, the seminal vesicle of one remaining male was reduced in size.

In group X3 (1000 ppm), reduction in the organ size was also noted in the seminal vesicle (21/24), prostate (18/24), bulbo-urethral gland (13/24), and penis (21/24). Twenty of the males of this group are reported to have hypospadia.

In no case was there a grossly visible reduction in the size of the testes (X3).

Adhesions between testes and epididymides were noted in individual males of group X4, most likely indicative for inflammatory reactions. In two males of this group, an epididymal abscess was noted during necropsy.

Enlargement of the adrenal glands was noted in all male and all female rats of dose group X4, and all male and female animals of this group exhibited adrenal discoloration comparable to the one noted in the F0 or F1 generation animals.

Discoloration of the adrenal glands was also noted in all male and all but one female rats of group X3 (1000 ppm), and in nine of the male rats of group X2 (300 ppm).

Nearly a quarter of the males (12/49, one more than seen clinically) and six out of the fourty females of the high dose group X4 (3000 ppm) had developed cataracts.

In the liver, a focal lesion (indicated as "focus" in the table) was noted in only one male of the high dose group X4. From the gross morphological appearence, it was not interpreted to be a tumor - in which case it had been attributed to as "mass".

All other gross lesions reported are interpreted to be incidental from their incidence or distribution over the groups.

C. Histopathology

EYES

Lenticular degeneration was noted in almost all male (47/49) and in all female rats of dose group X4, in 4 males and many females (11/24) of dose group X3, and in two male and one female rat of dose group X2.

INCIDENCE OF MICROSCOPIC FINDINGS
F0-GENERATION PARENTAL ANIMALS

010380

Sacrifice group	K1				
Sex	M				
Dose group	00	01	02	03	04
Animals in selected Group	24	24	24	24	24
Prostate	24	24	24	24	24
- Secretion reduced	1	.	.	.	2
Seminal vesicle	24	24	24	24	24
- Acinar atrophy	1	.	.	.	.
- Secretion reduced	1	.	.	2	4
Coagulation glands	24	24	24	24	24
- Acinar atrophy	1	.	.	.	.
- Secretion reduced	1	.	.	.	6
Testes	24	24	24	24	24
- Leydig cell hyperpl.	.	1	.	10	16
- Tub. atrophy, focal	.	.	.	1	3
- Tub. atrophy, diff.	1	.	.	.	1
Epididymides	24	24	24	24	24
- Exfoliat. germ cells	1	.	.	.	.
- Aspermia	.	.	.	.	1
Eyes	24	24	24	24	24
- Lentic. degeneration	.	.	.	1	22
Liver	24	24	24	24	24
- Central hypertrophy	.	.	.	3	24
- Single cell necrosis	.	.	.	.	20
- Fatty change, interm.	.	.	.	.	22
- Fatty change, focal	7	3	3	4	4
- Fatty change, periph	11	15	17	12	2
- Lymphoid cell aggreg	23	24	20	24	24
- Bile duct prolifer.	.	.	.	3	.
- Fibrosis, focal	.	.	.	1	.
- Congestion	1	.	.	.	.
Adrenal cortex	24	24	24	24	24
- Lipidosis	.	.	.	.	24
- Lipogenic pigment	.	.	.	.	1
- Extracortical nodule	2	1	1	.	4
- Cyst(s)	.	1	.	1	.
- Calcification, focal	1	.	.	.	.
- Congestion	.	.	.	.	1
Adrenal medulla	24	24	24	24	24
Pituitary gland	24	24	24	24	24
- Vacuolation of cells	5	2	6	6	24
- Cyst	7	3	5	4	11
Kidneys	1	.	.	.	.
- Nephropathy	1	.	.	.	.

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INCIDENCE OF MICROSCOPIC FINDINGS
F0 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	K1				
Sex	M				
Dose group	00	01	02	03	04
Animals in selected Group	24	24	24	24	24
Heart	1	.	.	.	.
- Myofibrosis, focal	1	.	.	.	.

INCIDENCE OF MICROSCOPIC FINDINGS
F0 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	K1				
Sex	F				
Dose group	00	01	02	03	04
Animals in selected Group	24	24	24	24	24
Ovaries	24	23	24	24	24
- Lipidosis	.	.	.	22	24
- Follicular cyst	.	.	.	.	4
- Reduced maturation	.	.	.	.	2
- Lipogenic pigment	18	23	24	24	21
Uterus	24	23	24	24	24
- State of pregnancy	.	.	.	2	.
- Luminal dilation	5	8	9	6	5
- Congestion	.	.	.	.	1
Cervix	24	23	24	24	24
- State of pregnancy	.	.	.	2	.
- Congestion	.	.	.	.	1
Vagina	24	23	24	24	24
- State of pregnancy	.	.	.	2	.
- Congestion	.	.	.	.	1
Eyes	24	24	24	24	24
- Lentic. degeneration	.	.	1	20	24
Liver	24	24	24	24	24
- Central hypertrophy	.	.	.	3	24
- Single cell necrosis	.	.	.	.	19
- Necrosis, focal	.	.	.	.	1
- Fatty change, focal	1	.	.	.	.
- Fatty change, periph	8	11	6	.	7
- Lymphoid cell aggreg	23	24	24	24	23
- Bile duct prolifer.	.	.	.	.	1
- Remodeling parenchym	1	.	.	.	.
Adrenal cortex	24	24	24	24	24
- Lipidosis	.	.	.	19	24
- Lipogenic pigment	.	.	.	.	2
- Extracortical nodule	1	.	.	2	3
- Congestion	.	1	1	.	
Adrenal medulla	24	24	24	24	24
- Calcification, focal	.	.	.	.	1
Pituitary gland	24	24	24	24	24
- Hyperplasia, focal	1	.	.	.	.
- Vacuolation of cells	1	.	.	.	3
- Cyst	7	7	6	3	2
- Malformation	.	.	1	.	.
Kidneys	.	.	1	.	.
- Nephropathy	.	.	1	.	.

[illegible]

92/11251 1437

INCIDENCE OF MICROSCOPIC FINDINGS
F0 GENERATION PARENTAL ANIMALS

U10380

Sacrifice group	K1				
Sex	F				
Dose group	00	01	02	03	04
Animals in selected Group	24	24	24	24	24
Mammary gland	.	.	.	1	.
- Fibroadenoma	.	.	.	1	.
Pancreas	1	.	.	.	.
- Edema, interstitial	1	.	.	.	.
Duodenum	.	.	.	.	1
Jejunum	.	.	.	.	1
Ileum	.	.	.	.	1
Cecum	.	.	.	.	1
Colon	.	.	.	.	1
Rectum	.	.	.	.	1

INCIDENCE OF MICROSCOPIC FINDINGS
F1 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	10	11	12	13	14
Animals in selected Group	24	24	24	24	29
Penis	.	.	.	24	29
- Organ size reduced	.	.	.	.	27
Urogenital tract I	.	.	.	.	29
- Ductus deferens	.	.	.	.	28
- " with cell. debris	.	.	.	.	5
- " with spermia	.	.	.	.	20
- Muellerian duct	.	.	.	.	20
- " with cell. debris	.	.	.	.	5
- " with spermia	.	.	.	.	6
Urogenital tract II	.	.	.	15	25
- D. defer.-like duct	.	.	.	.	24
- " with cell. debris	.	.	.	.	6
- " with spermia	.	.	.	.	17
- Muellerian duct	.	.	.	.	15
- " with cell. debris	.	.	.	.	3
- " with spermia	.	.	.	.	13
- Duct (NOS)	.	.	.	.	.
Urogenital tract III	.	.	.	.	9
- D. defer.-like duct	.	.	.	.	4
- " with spermia	.	.	.	.	4
- Muellerian duct	.	.	.	.	2
- Vagina-like orifice	.	.	.	.	4
- " with cell. debris	.	.	.	.	2
- " with spermia	.	.	.	.	2
Prostate	24	24	24	24	29
- Organ not detectable	.	.	.	.	28
- Acinar atrophy	.	.	.	1	1
- Secretion reduced	.	.	1	11	1
- Absence of secretion	.	.	.	4	.
- Chronic inflammation	.	.	.	14	.
Seminal vesicle	24	24	24	24	29
- Organ not detectable	.	.	.	.	7
- Acinar atrophy	.	.	.	.	22
- Secretion reduced	.	.	.	18	21
- Absence of secretion	.	.	.	.	1
- Chronic inflammation	.	.	.	11	4
- Luminal cell. debris	.	.	.	.	3
- Luminal spermia	.	.	.	.	6
Coagulation glands	24	24	24	24	29
- Organ not detectable	.	.	.	3	29
- Secretion reduced	.	.	2	14	.
- Chronic inflammation	.	.	.	13	.
Bulbo-urethral gland	.	.	.	15	29
- Organ not detectable	.	.	.	9	29

INCIDENCE OF MICROSCOPIC FINDINGS
F1 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	10	11	12	13	14
Animals in selected Group	24	24	24	24	29
Testes	24	24	24	24	29
- Leydig cell tumour	.	.	.	.	4
- Leydig cell hyperpl.	2	.	7	17	24
- Cystic rete testis	.	.	.	.	1
- Tub. atrophy, focal	.	.	1	5	13
- Tub. atrophy, diff.	.	1	.	.	11
- Tub. mineralization	.	.	.	.	6
- Chronic inflammation	.	.	.	.	7
Epididymides	24	24	24	24	29
- Atrophy, diffuse	.	.	.	.	10
- Aspermia	1	1	.	.	10
- Oligospermia	.	.	.	.	6
- Chronic inflammation	.	.	.	.	9
- Abscess	.	.	.	.	1
Eyes	24	24	24	24	29
- Lentic. degeneration	.	.	2	9	29
Liver	24	24	24	24	29
- Focal hyperplasia	.	.	.	.	1
- Altered foci (NOS)	.	.	.	.	12
- -Eosinophilic foci	.	.	.	.	11
- -Basophilic foci	.	.	.	.	1
- Central hypertrophy	.	.	.	4	28
- Single cell necrosis	.	.	.	1	23
- Fatty change,interm.	.	.	.	1	12
- Fatty change, focal	2	3	4	5	4
- Fatty change, periph	14	18	17	13	12
- Lymphoid cell aggreg	24	24	23	24	28
- Bile duct prolifer.	2	1	.	.	1
- Dystrophy, acute	.	.	.	.	1
Adrenal cortex	24	23	24	24	29
- Lipidosis	.	.	.	2	29
- Lipogenic pigment	.	.	.	.	2
- Extracortical nodule	.	.	.	.	3
- Cyst(s)	.	.	.	.	1
- Calcification, focal	.	.	.	.	1
- Congestion	.	.	.	.	1
- Hematopoiesis	.	.	.	.	1
Adrenal medulla	24	23	24	24	29
- Calcification, focal	.	.	.	.	1
- Lymphoid cells	.	.	.	.	1
Pituitary gland	24	24	24	24	29
- Vacuolation of cells	4	2	6	19	28
- Cyst	3	4	6	2	8
- Malformation	1	.	.	.	.

INCIDENCE OF MICROSCOPIC FINDINGS
F1 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	10	11	12	13	14
Animals in selected Group	24	24	24	24	29
Kidneys	.	.	.	5	1
- Hyperplasia, urothel	.	.	.	4	1
- Nephritis, interst.	.	.	.	3	1
- Nephropathy	.	.	.	2	.
Urinary bladder	.	.	.	8	.
- Carcinoma,trans.cell	.	.	.	1	.
- Papilloma,trans.cell	.	.	.	3	.
- Hyperplasia	.	.	.	4	.
Lungs	.	.	.	.	1
- Interstit. pneumonia	.	.	.	.	1
Ductus choledochus	.	.	.	.	1
- Dilation	.	.	.	.	1
Iliac lymph nodes	.	.	1	1	3
- Lymphadenitis simpl.	.	.	1	1	3
Renal lymph nodes	.	.	.	2	2
- Hyperemia	.	.	.	1	.
- Lymphadenitis simpl.	.	.	.	1	2
Inguino-femoral lnn.	.	.	.	.	1
- Lymphadenitis simpl.	.	.	.	.	1
Skin	2	.	2	1	1
- Inflammation, focal	.	.	1	.	1
- Alopecia, focal	1	.	1	1	.
- Necrosis, focal	.	.	1	.	1

INCIDENCE OF MICROSCOPIC FINDINGS
F1 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	F1				
Sex	F				
Dose group	10	11	12	13	14
Animals selected Group	24	24	24	24	37
Ovaries	23	24	24	24	26
- Lipidosis	.	1	.	3	9
- Cyst(s) corpus luteum	1	.	2	.	1
- Follicular cyst	2	2	.	.	1
- Reduced maturation	1	.	1	.	1
- Cystic rete tubule	1	.	.	.	.
- Lipogenic pigment	23	23	24	24	23
Uterus	23	24	24	24	26
- State of pregnancy	1	.	2	24	20
- Luminal dilation	1	7	6	.	2
Cervix	23	24	24	24	26
- State of pregnancy	1	.	2	24	20
Vagina	23	24	24	24	26
- State of pregnancy	1	.	2	24	20
Eyes	24	24	24	24	26
- Lentic. degeneration	.	.	.	22	26
Liver	24	24	24	24	26
- Altered foci (NOS)	.	.	.	.	3
- -Eosinophilic foci	.	.	.	.	3
- Central hypertrophy	.	.	.	6	18
- Fatty change, periph	9	4	2	.	1
- Lymphoid cell aggreg	24	24	22	21	26
- Bile duct prolifer.	1	.	1	.	1
- Congestion	.	1	.	.	.
Adrenal cortex	24	24	24	24	26
- Lipidosis	.	.	.	8	26
- Lipogenic pigment	.	.	.	.	12
- Extracortical nodule	.	.	.	.	6
- Cyst(s)	.	1	3	.	.
- Calcification, focal	.	.	1	.	2
- Congestion	.	1	.	2	5
Adrenal medulla	24	24	24	24	26
Pituitary gland	24	24	24	23	26
- Hyperplasia, focal	1	.	.	.	1
- Vacuolation of cells	.	.	1	.	.
- Cyst	10	5	5	3	11

BASF Department of Toxicology
PATHOLOGY REPORT
Reg. No. 83 258: 2-Generation Reproduction Study in Rats, Oral Application

TLR0375/88053
Oct/19/1992 CEGE
acopat system

INCIDENCE OF MICROSCOPIC FINDINGS
F1 GENERATION PARENTAL ANIMALS

010380

Sacrifice group	F1				
Sex	F				
Dose group	10	11	12	13	14
Animals in selected Group	24	24	24	24	37
Mammary gland	-	2	-	-	-
- Fibroadenoma	-	2	-	-	-
Skin	-	-	2	-	-
- Alopecia, focal	-	-	2	-	-

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INCIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	X0	X1	X2	X3	X4
Animals in selected Group	24	24	24	24	49
Penis	.	.	.	21	48
- Organ size reduced	.	.	.	.	48
Urogenital tract I	.	.	.	.	48
- Ductus deferens	.	.	.	.	48
- " with cell. debris	.	.	.	.	3
- " with spermia	.	.	.	.	41
- Muellerian duct	.	.	.	.	45
- " with cell. debris	.	.	.	.	4
- " with spermia	.	.	.	.	29
Urogenital tract II	.	.	.	21	49
- D. defer.-like duct	.	.	.	.	49
- " with cell. debris	.	.	.	.	5
- " with spermia	.	.	.	.	40
- Muellerian duct	.	.	.	.	42
- " with cell. debris	.	.	.	.	4
- " with spermia	.	.	.	.	32
Urogenital tract III	.	.	.	.	6
- Muellerian duct	.	.	.	.	3
- " with spermia	.	.	.	.	1
- Vagina-like orifice	.	.	.	.	3
- " with cell. debris	.	.	.	.	2
- " with spermia	.	.	.	.	2
Prostate	24	24	24	24	49
- Organ not detectable	.	.	.	.	46
- Acinar atrophy	.	.	.	.	3
- Secretion reduced	.	.	2	9	3
- Absence of secretion	.	.	.	1	.
- Chronic inflammation	.	.	.	4	.
Seminal vesicle	24	24	24	24	49
- Organ not detectable	.	.	.	.	23
- Acinar atrophy	.	.	.	1	26
- Secretion reduced	.	.	.	12	15
- Absence of secretion	.	.	.	1	11
- Chronic inflammation	.	.	.	8	4
- Luminal cell. debris	.	.	.	.	2
- Luminal spermia	.	.	.	.	5
Coagulation glands	24	24	24	24	49
- Organ not detectable	.	.	.	.	49
- Secretion reduced	.	.	.	12	.
- Absence of secretion	.	.	.	1	.
- Chronic inflammation	.	.	.	3	.
Bulbo-urethral gland	.	.	.	24	49
- Organ not detectable	.	.	.	7	49
- Secretion reduced	.	.	.	9	.

INCIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	X0	X1	X2	X3	X4
Animals in selected Group	24	24	24	24	49
Testes	24	24	24	24	49
- Leydig cell hyperpl.	.	.	.	19	38
- Tub. atrophy, focal	.	.	.	1	33
- Tub. atrophy, diff.	.	.	.	.	26
- Tubular giant cells	.	.	.	.	4
- Tub. mineralization	.	.	.	.	2
- Chronic inflammation	.	.	.	.	6
Epididymides	24	24	24	24	49
- Atrophy, diffuse	.	.	.	.	9
- Exfoliat. germ cells	.	.	.	.	4
- Aspermia	.	.	.	.	12
- Oligospermia	.	.	.	1	14
- Chronic inflammation	.	.	.	.	9
Eyes	24	24	24	24	49
- Lentic. degeneration	.	.	2	4	47
Liver	24	24	24	24	49
- Altered foci (NOS)	.	.	.	.	2
- -Eosinophilic foci	.	.	.	.	2
- Central hypertrophy	.	.	.	2	49
- Single cell necrosis	.	.	.	.	48
- Fatty change,interm.	.	.	.	.	4
- Necrosis, focal	.	1	.	1	1
- Fatty change, focal	2	2	2	1	1
- Fatty change, peripn	22	22	19	21	31
- Lymphoid cell aggreg	24	24	24	24	49
- Bile duct prolifer.	.	.	.	1	4
- Fibrosis, focal	.	.	.	.	1
- Peliosis, focal	.	.	.	.	1
Adrenal cortex	24	24	24	24	49
- Lipidosis	.	.	.	1	49
- Extracortical nodule	.	1	.	2	4
- Calcification, focal	.	.	.	.	2
Adrenal medulla	24	24	24	24	48
- Lymphoid cells	.	.	.	.	2
Pituitary gland	24	24	24	24	49
- Vacuolation of cells	5	1	6	8	47
- Cyst	5	2	7	3	8
- Malformation	.	1	.	1	1
Kidneys	.	.	.	1	1
- Hyperplasia, urothel	.	.	.	1	.
- Nephritis, interst.	.	.	.	.	1
- Nephropathy	.	.	.	1	.
- Pyelectasia	.	.	.	.	1

INCIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS

010380

Sacrifice group	F1				
Sex	M				
Dose group	X0	X1	X2	X3	X4
Animals in selected Group	24	24	24	24	49
Urinary bladder	.	.	.	1	.
- Hyperplasia	.	.	.	1	.
Lungs	.	.	.	1	.
- Chronic congestion	.	.	.	1	.
Heart	.	.	.	1	.
- Myodegeneration	.	.	.	1	.
Mediastinal lymph n.	.	.	.	1	.
- Congestion, chronic.	.	.	.	1	.
Iliac lymph nodes	.	.	.	2	.
- Lymphadenitis simpl.	.	.	.	2	.
Skin	.	.	.	2	7
- Alopecia, focal	.	.	.	2	.

INCIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS

010380

Sacrifice group	F1				
Sex	F				
Dose group	X0	X1	X2	X3	X4
Animals in selected Group	24	24	24	24	40
Ovaries	24	24	24	24	40
- Lipidosis	.	.	.	20	38
- Cystic corpus luteum	.	.	.	.	2
- Follicular cyst	.	.	.	.	1
- Cystic rete tubule	1	4	.	1	.
- Lipogenic pigment	23	20	24	22	40
Uterus	24	24	24	24	40
- Luminal dilation	1	3	4	.	9
- Congestion	1	.	.	.	.
Cervix	24	24	24	24	40
- Congestion	1	.	.	.	.
Vagina	24	24	24	24	40
- Congestion	1	.	.	.	.
Eyes	24	24	24	24	40
- Lentic. degeneration	.	.	1	11	40
Liver	24	24	24	24	40
- Altered foci (NOS)	.	.	1	.	1
- -Eosinophilic foci	.	.	.	.	1
- -Clear cell foci	.	.	1	.	.
- Central hypertrophy	.	.	.	2	35
- Single cell necrosis	.	.	.	.	15
- Necrosis, focal	1	.	.	.	1
- Fatty change, focal	3	1	3	1	1
- Fatty change, periph	5	7	5	5	3
- Lymphoid cell aggreg	22	24	24	23	40
- Bile duct prolifer.	.	1	.	.	4
Adrenal cortex	24	21	24	24	40
- Lipidosis	.	.	.	7	40
- Extracortical nodule	1	1	1	.	7
- Cyst(s)	.	.	.	.	2
- Calcification, focal	.	.	.	.	4
Adrenal medulla	24	24	24	24	40
Pituitary gland	23	24	24	24	40
- Vacuolation of cells	.	.	1	.	1
- Cyst	4	4	2	4	3
- Malformation	.	.	.	.	1

INCIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS

010380

Sacrifice group	F1				
Sex	F				
Dose group	X0	X1	X2	X3	X4
Animals in selected Group	24	24	24	24	40
Lungs	1	.	.	.	.
- Chronic congestion	1	.	.	.	.
Iliac lymph nodes	.	.	.	1	.
- Lymphadenitis simpl.	.	.	.	1	.
Skin	.	.	.	1	.
- Inflammation, focal	.	.	.	1	.

INCIDENCE OF MICROSCOPIC FINDINGS - FY ANIMALS

010380

Sacrifice group	K1					
Sex	M			F		
Dose group	Y0	Y1	Y2	Y0	Y1	Y2
Animals in selected Group	24	24	24	24	24	24
Prostate	24	24	24	.	.	.
Seminal vesicle	24	24	24	.	.	.
- Secretion reduced	.	.	1	.	.	.
Coagulation glands	24	24	24	.	.	.
- Secretion reduced	.	.	1	.	.	.
Ovaries	.	.	.	24	24	24
- Lipidosis	.	.	.	.	.	2
- Cystic rete tubule	.	.	.	2	.	.
- Lipogenic pigment	.	.	.	15	24	18
Uterus	.	.	.	24	24	24
- Luminal dilation	.	.	.	3	.	6
Cervix	.	.	.	24	24	24
Vagina	.	.	.	24	24	24
Testes	24	24	24	.	.	.
- Leydig cell hyperpl.	.	.	1	.	.	.
- Tub. atrophy, focal	.	1	1	.	.	.
Epididymides	24	24	24	.	.	.
Eyes	24	24	24	24	24	24
- Lentic. degeneration	.	.	.	.	.	3
Liver	24	24	24	24	24	24
- Altered foci (NOS)	.	.	.	.	.	1
- Basophilic foci	.	.	.	.	.	1
- Necrosis, focal	.	.	1	.	.	.
- Fatty change, focal	2	.	1	.	3	.
- Fatty change, periph	21	21	23	12	11	12
- Lymphoid cell aggreg	24	24	24	24	24	24
- Bile duct prolifer.	1	.	.	.	.	.
Adrenal cortex	24	24	24	24	24	24
- Extracortical nodule	.	.	.	.	.	1
- Hypertrophy, focal	.	.	2	.	.	.
- Cyst(s)	.	2	.	.	.	.
Adrenal medulla	24	24	24	24	24	24
Pituitary gland	24	24	24	24	24	24
- Vacuolation of cells	14	10	14	.	.	.
- Cyst	1	3	.	2	1	1
Iliac lymph nodes	.	.	1	.	.	.
- Lymphadenitis simpl.	.	.	1	.	.	.
Skin	.	.	1	.	.	.
- Necrosis, focal	.	.	1	.	.	.

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INCIDENCE OF MICROSCOPIC FINDINGS - F2 ANIMALS

Sacrifice group	K1					
Sex	M			F		
Dose group	20	21	22	20	21	22
Animals in selected Group	24	24	24	24	24	24
Prostate	24	24	24	.	.	.
Seminal vesicle	24	24	24	.	.	.
Coagulation glands	24	24	24	.	.	.
Ovaries	.	.	.	24	24	24
- Lipidosis	.	.	.	.	.	2
- Cystic rete tubule	.	.	.	1	.	.
- Lipogenic pigment	.	.	.	22	19	24
Uterus	.	.	.	24	24	24
- Luminal dilation	.	.	.	5	3	6
Cervix	.	.	.	24	24	24
Vagina	.	.	.	24	24	24
Testes	24	24	24	.	.	.
- Leydig cell hyperpl.	2	.	2	.	.	.
- Tub. atrophy, focal	1	.	2	.	.	.
Epididymides	24	24	24	.	.	.
Eyes	24	24	24	24	24	24
- Lentic. degeneration	.	.	2	.	.	1
Liver	24	24	24	24	24	24
- Altered foci (NOS)	.	.	2	.	.	.
- -Eosinophilic foci	.	.	1	.	.	.
- -Basophilic foci	.	.	1	.	.	.
- Necrosis, focal	.	.	1	.	.	.
- Fatty change, focal	2	1	3	2	2	.
- Fatty change, periph	19	22	20	9	7	11
- Lymphoid cell aggreg	24	24	23	24	24	24
- Bile duct prolifer.	.	.	.	.	1	.
Adrenal cortex	24	24	24	24	24	24
- Extracortical nodule	.	1	1	.	.	.
- Hypertrophy, focal	1	.	.	.	1	.
Adrenal - dulla	24	24	24	24	24	24
Pituitary gland	24	24	24	24	24	24
- Vacuolation of cells	4	5	6	.	.	.
- Cyst	4	2	3	3	2	2

Last Page

Chemical 3230. Vinclozolin: (3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione). Date [illegible].93.
PC# 113201.

010380

Citation	Material	MRID#	Results	Core Grade Documents
(83-4) 2-Gen. Reproduction/ Rat Proj.#7190375 33353. Study#92,11231 10/21/1992.	Vinclozolin, Tech. 99.2%	425813-11 & 425813-12	Doses administered in the diet were 0, 50, 300, 1000 or 3000 ppm of vinclozolin technical (99.2%). Males = 0, 4.9, 30, 96 or 290 mg/kg day, Females = 0, 5.3, 31, 101 or 290 mg/kg day. 24 Wistar rats per sex per group through the P0, F1 and F2 generations for 14 weeks. Two litters per generation were produced: F1a (F1 adults), F1b (FX adults), F2a (FY adults) and F2b (FZ adults). FY and FZ adults were dosed only at 50 and 300 ppm because no F2 pups were produced at higher dose levels. The study was initiated December 22, 1988 and finished February 15, 1990 Offspring Toxicity: NOEL 50 ppm (4.9 mg/kg/day) (LDT). Epididymal weights were statistically significantly decreased at 50 ppm in FY adults only, but they were nominally and/or statistically significantly decreased at all dose levels in the F1, FX and FZ adult males. The effect at 50 ppm was minimal and considered sufficiently close to a NOEL. To determine the functional meaning of this decreased epididymal weight, sperm function tests may be necessary. These sperm function tests are being held in reserve and should not be conducted prior to consultation with the Agency. LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction in the F1 (97% of controls, p ≥ 0.05), FX (95% of controls, p ≥ 0.05), FY (94%) of controls (p ≤ 0.05) and FZ (98% of controls, p ≥ 0.05) in males. Dose related lenticular degeneration was noted in 1/24 F1 males and 1/3/24 females. These effects occurred in nearly all F1 and FX males and females at the HDT. Absolute testis (106%, 107%, p ≤ 0.01) and absolute adrenal (119%, p ≤ 0.05 and 111%, p ≤ 0.01 respectively) weights were greater than controls in FY and FZ adult males and absolute adrenal (117%, p ≥ 0.05) and absolute liver weights (109%, p ≤ 0.05) were greater than controls in F1 adult females, but not relative adrenal or liver weight. An increased incidence of testicular Leydig cell hyperplasia occurred in F1 (7/24 males) at 300 ppm above. At 1000 and 3000 ppm pseudohermaphroditism, anomalies and functional deficit occurred in adult male reproductive organs, such as aberrant Wolffian duct, bilateral Muellerian duct, reduced/absent prostate, seminal vesicle/bulbo-urethral gland. In addition atrophic seminiferous tubules, aspermia/oligospermia and reduced penis size were noted. Hypospadia occurred in all male offspring only at the 1000 and 3000 ppm dose levels. Increased ovarian lipidosis and ovarian interstitial cell hypertrophy occurred at 1000 and 3000 ppm. Frequent compound related single cell liver necrosis was noted in F1 and FX adult males (23/29 and 48/49) and in FX female adults (15/40) at 3000 ppm. Central hypertrophy of the liver occurred in the F1 (6/24 at 1000 ppm and 18/28 at 3000 ppm) and in FX females adults (2/24 and 35/40 at 1000 and 3000 ppm, respectively) and single cell liver necrosis occurred in FX female adult offspring (15/40) at 3000 ppm. Adult male offspring genital and reproductive tract malformations, sired no offspring at 1000 and 3000 ppm and fertility in adult F1 female offspring may have been reduced at 1000 ppm. Pinna unfolding, eye opening/auditory canal opening was affected at 3000 ppm and the gripping reflex may have been affected during lactation for F1a and F1b pups. The nominal increase in effects in these parameters at 1000 ppm were within historical control range and may not be biologically significant. Effects on F1a and F1b pups to weaning were noted in decreased weight and survival at 1000 ppm and 3000 ppm, respectively. A compound related increase in litter incidence over controls occurred in dilated renal pelvis or hydroureter in pups at 3000 ppm (46%/13% for the F1a and 5.6%/0% for the F1b). Nipples were present on male F1a and F1b pups at 1000 and 3000 ppm (Verbal comment by BASF). Parental toxicity: NOEL 50 ppm (4.3 mg/kg/day). LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction (93%, p ≤ 0.01 of controls) in males and possibly liver weight increase in females (110%, p ≤ 0.01 of controls). At 1000 and 3000 ppm testis weights (110%, p ≤ 0.01 at 1000 ppm) and Leydig cell hyperplasia were increased (10/24 at 1000 ppm) and adrenal weights were increased in males (125% at 1000 ppm, p ≤ 0.01) and females (130%, p ≤ 0.01). Lipidosis of the adrenal occurred in females at 1000 (19/24) and 3000 ppm (24/24) and in males at 3000 ppm (24/24). Pituitary vacuolation cells (castration cells) occurred in all males at 3000 ppm. A dose related increased incidence of lenticular degeneration occurred in females at the 3 highest dose levels (only 1/24 at 300 ppm). Single cell necrosis of the liver occurred in most males and females at 3000 ppm and central hypertrophy occurred in both males and females at the rate of 3/24 at 1000 and 24/24 at 3000 ppm. Core classification: Minimum. This study is acceptable under guideline 83-4 for reproduction in the rat. The affect on the epididymal weight was minimal at the LDT and 50 ppm was considered to be the NOEL, however, the possible need for sperm parameter studies is reserved.	Minimum

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