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

JUL 1 3 1993

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MEMORANDUM:

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Surject:

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.

Frim:

David G Anderson, PhD

David M. Underson 7/1/43

Section 3. Toxicology Branch-l Health Effects Division (H7509C)

Ter

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

T-71:

Karen Hamernik, PhD.

Head Section 3. Toxicology Branch-l

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 RtD.

Data submitted for review were:

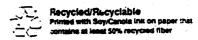
Hellwig, J. Report Reproduction Study with Reg. No. 83258 (Vinclozolin) in Rats Continuous Dietary Administration over 2-Gernerations (2 Litters in the First and 2 Litters in the Second Generation), Project No. 71R0375/88053; study conducted at BASF Aktiengesellschaft, Dept. Toxicology, D-W6700 Ludwigshaften,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

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Reg.

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).

\$10060

CONCLUSION:

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

Doses administered in the diet ware 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, Fl and F2 generations for 14 weeks. Two litters per generation were produced: Fla (F1 adults), Flb (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 FI, 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 PO (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.

Top control value

LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction in the F1 (97% of controls, $p \ge 0.05$), FX (96% of controls, $p \ge 0.05$), FY (94%* of controls, $p \le 0.05$) and FZ (98% of controls, $p \ge 0.05$) 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%, $p \le 0.001$) and absolute adrenal (119%, $p \le 0.05$) and 111%, $p \le 0.01$, respectively) weights were greater than controls in FY and FZ adult males and absolute adrenal (107%, $p \ge 0.05$) and absolute liver weights (109%, $p \le 0.05$) 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

of stehstically 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 Fla and Flb pups. The nominal increase in effects in these parameters at 1000 ppm were within historical control range and may not be biologically significant.

Fla and Flb pup survival was statistically significantly less than controls at 3000 ppm, at 0-4 day post partum (47%/92% and 60%/97%, respectively) and 4-21 post partum (86%/100% and 95%/98%, respectively). Cannibalism during lactation was increased at 3000 ppm. A body weight reduction occurred in Fla and Flb pups by day 1 at 3000 ppm (85% and 73%, both $p \le 0.01$, 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).

LFL: 300 ppm (30 mg/kg/day) for epididymal weight reduction (93%, $p \le 0.01$ of controls) in males and possibly liver weight increase in females (110%, $p \le 0.01$ of controls). At 1000 and 3000 ppm testis weights (110%, $p \le 0.01$ 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, $p \le 0.01$) and females (130%, $p \le 0.01$). 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.

<u>Core classification</u>: 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.

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. . 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.# 60244) 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. A. with week 27743 Section 3, Tox. Branch 1 (H7509C). Secondary reviewer: Karen Hamernik, PhD. L. Jewende 7/143 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.

MRID No.: 425813-01 & 425813-02 PC/No.: 113201.

DP Barcode No.: D186519. (Appendix II).

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3.5-

dichlorophenyl)-5-ethenyl-5-methyl-2,4-

oxazolidinedi-2,4-one].

STRUCTURE:

C1

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

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.

92/11251 & 71R0375/88053. Req. Doc. No. BASF STUDY NO .:

92/10596 (For 425813-01) and 11407 (For 425813-

02).

Report on the Reproduction Study with Reg. No. 83 REPORT TITLE:

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.

Dr. J Hellwig. AUTHOR(S):

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 PO, Fl and F2 generations for 14 weeks. Two litters per generation were Reproduction Bar SJ 4 Final Rep. Vincidzolin 92 1125 7180375 88053 429813 7145 im Jero 425813 92 0156513

produced: Fla (F1 adults), Flb (FX adults), F2a (F7 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. study was initiated December 22, 1988 and finished February 15, 1990.

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Agency.

LEL: 300 ppm (30 mg/kg/day) for epididymal weight reduction in the F1 (97% of controls, $p \ge 0.05$), FX (96% of controls, $p \ge$ 0.05), FY (94%* of controls, $p \le 0.05$) and FZ (98% of controls, p≥ 0.05) in males. Dose related lenticular degeneration was noced 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%, $p \le 0.001$) 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 ppmsabove.

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 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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of Statistically significant

Reproduction Rat 83:4 Final Rep. Vincipization 92 1135 7180375 88053 425813 9165 -m Into 425813-02 0186519

3000 ppm.

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

Fla and Flb 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 (86%/100% and 95%/98%, respectively). Cannibalism during lactation was increased at 3000 ppm. A body weight reduction occurred in Fla and Flb pups by day 1 at 3000 ppm (85% and 73%, both p \leq 0.01, respectively) on day 4 and day 21 post fartum at 1000 (76% to 81% for Fla and 89% and 84% for Flb, at the respective post partum days) and 300 ppm (76% and 73% for Fla; 72% and 67% for Flb, 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 Fla and 5.6%/0% for the Flb). Nipples were present on male Fla and Flb pups at 1000 and 3.00 ppm (Verbal comment by BASF).

Parental toxicity:

NOEJ .: 50 ppm (4.9 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 \leq 0.01 of controls). At 1000 and 3000 ppm testis weights (110%, $p \le 0.01$ 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, $p \le 0.01$) and females (130%, $p \le 0.01$). 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 femaleSat the rate of 3/24 at 1000 and 24/24 at 3000 ppm.

<u>Core classification</u>: 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. <u>Test material</u>: 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 + 126) 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 cm²). During mating males and females were housed in Makrolon cages, type M III (800 cm²). 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. Fla animals used for mating were also randomly assigned. Neither PO nor Fl litter mates were mated.
- 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 (PO and F1) and 2 (Fla, Flb, F2a and F2b) litters per generation in the rat. In addition, all Fla 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 (Fla) 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. Flb 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 Fla, Flb 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 F1 males at 1000 and 3000 ppm produced no pups.
- 24 animals per sex per group were selected for the PO

generation.

610060 24 animals per sex per group were selected from the Fla litters

for the F1 generation. Except at the 3000 ppm dose level, where all surviving Fla 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 Flb litters for the FX adult data on organ weights and histological data. Except at the 3000 ppm dose level, where all surviving Flb 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 may 32. Analyses of dietary concentrations were conducted on samples prepared on 11/25/88, 12/12/88, 12/22/88, 3/2/89, 6/7/89, 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 PO, 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 PO and F1 males and females in the form of cataracts at the HDT and antiandrogenicity 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 there 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 PO, Fla, (selected for the F1), Flb (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 PO and F1 males to week 28 and week 32, respectively. These parameters were determined for PO 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 PO, 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

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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 rale body weight reductions occurred from week 1 to 1 (93% of controls, p ≤ 0.05) and in F1 males from week 1 to 28 (80% of controls, p ≤ 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 ≤ 0.05) and nominally reduced by the end of the 10 weeks (96% of controls, p ≤ 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 up to week 4, 94% of controls), but it was nominally decreased at 3000 ppm up to week 4, 94% of controls), but it was nominally decreased at

Body weights of FX (adult Flb 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 efficienty calculations for the premating period.

Mean body weight gain in g over the time period T (pre-mating period).	mqq O	50 ppm	300 ppm	1000 ppm	3000 ppm.
PO males	297.8	318	313.0	297.4	271.2
PO females	133.2	135.1	146.4	131.1	125.3
Fl males	301.2	306.6	322.3	307.2	275.6
Fl females	144.2	146.3	151.2	146.9	177.4
Mean food consumption in	g/animal/day	y over the	time period T		
20	26.5	27.5	27.5	2 ± . 3	24.5
PO females	19.3	19.3	20.1	18.8	17.8
F1 males	26.0	26.4	27.3	26.3	23.9
71 females	19.0	19.1	19.9	18.9	19.4
Relative efficiency = (bo over time period T).	dy weight ga	ain over tim	me period T)/	(relative for	
PO males	11.2	11.5	11.4	11.3	11.0
PO females	6.90	6.22	7.28	6.97	7.04
Fl males	11.6	11.5	11.8	11.7	11.5
F1 females	7.59	7.66	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 70 males or females or 31 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 no modely decreased at 3000 ppm in males and females. The overall relative efficiency of food utilization was unchanged in the PO and F1 males and temales at all doce levels (Table A).

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

water consumption was statistically significantly increased : males and females at the 1000 and the 3000 ppm dose levels [Table 3]. The water consumption was statistically significantly increased in females at the 300 ppm and above (Table B)

Table 3: Mean water consumption for the pre-mating period for PO and Fl male and female adults.

Mean water consumption(c)/day	0 ppm	50 com	300 pput	_000 ,_m	3100 s.
PO males	26.1	26.4	27.1	28.2-	ca.2*
PO females	19.7	20.0	21.5**	21.4*	24.2**
F1 males	25.3	25.2	27.3	28.1*	29 7**
F1 females	20.3	19.3	21.8*	12.5**	23.5**

- * Statistically significant, p ≤ 0.05. ** Statistically significant, p ≤ 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 rertility indexes and length of gestation. The male mating and fertility indexes used for the Fla and Flb litters were defined in Table 048 and 049, reproduced from the submitted report, in the Appendix II. The female mating and fertility indexes were defined in Table 050 for the Fla litters and 051 for the Flb litters.
- a. Results on Fertility and Mating PO Male fertility was statistically significantly affected only at the 3000 ppm dose level for the Fla mating only (Table 048). The male fertility was nominally reduced for the Flb mating (Table 049). The Number of PO males not proving fertility were statistically significantly increased for the Fla mating, but not for the mating. None of Fl males proved their fertility for the F2 F2b matings at 1000 or 3000 ppm (Tables 145 and 146, reprod. in the Appendix II). PO female fertility was statistically significantly lower than control for the Fla litters, but not the Flb litters (Table 050 and 051) at the 3000 ppm dose level.

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The mating index was not significantly reduced in males or females producing either Fla or Flb litters (Table 043, 049, 050 and 051). The effect on Fl male fertility may have been test material related, but effects on PO females were probably incidental to the study at the 3000 ppm iose 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 24/2; 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.

<u>Table C.</u> Calculated mean test materia, consumption for various periods caring the study. Tenerally the dose levels determined during the pre-mating period for the PI are used for assessment purposes.)

	50 ppm (mean in mg kt/day)	300 ppm (mean in mg/kg/dar)	1000 ppm (mean in mg/kg/day)	3000 ppm (mean in mg/kg/day)
PO males (pre-mating	4.9	29.6	96.5	286.0
PO females pre-mating)	5.3	31.4	101.2	291.8
PO females Fla litters) Gestation Lactation*	4.3 8.2	25.1 47.3	83.8 150.4	237.2 249.8
PO females Flb litters) Gestation Lactation*	4 7.≘	·23.8 -44.6	79'.9 151.:	227.1 274.5
F1 males (pre-mating	4.5	27.0	96.0	314.0
Fl females cre-maring)	5.2	29.5	104.7	335.0
F1 females F2a litters) Gestation Lactation*	4.1 7.5	24.4 43.0		
F1 females F2b litters) Gestation Lactation=	3.9 7.2	23.1 39.3	_	_

^{*} Post natal days O through 14 only.

b. Pup weights for the Fla. Flb. 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 Fla litters and 063 and 064 for Fla litters, represided from the submitted report, in the

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⁻ Insufficient number of F1 delivered; insemination prevented by male malformations.

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Appendix II). At the 3000 ppm dose level body weights of Fla 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 Flb 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 Fla pups were statistically significant only on and after day 4, however the body weight of Flb pups were statistically significantly reduced throughout lactation starting at day 1. There were no pup weight decrements at 50 or 300 ppm in the Fla, Flb, F2a or F2b pups. There were no F2a or F2b pups at higher dose levels.

Males pups were slightly heavier than female rups 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 3irth and Pup Viability The number of Fla and Flb pups per litter were decreased at birth (74% of controls for the Fla and 77% of controls for the Flb) and during lactation with the largest number of pups dying by day 4 (37% of controls for the Fla and 47% of controls for the Flb), only at the 3000 ppm dose level (Tables 054 and 057, produced from the submitted report and presented in Appendix II).

F?a and F2b pups were not affected at the 50 and 300 ppm dose levels studied.

d. <u>Developmental Stages</u> and <u>Behavior for the Fla. Flb. F2a and F2b Offspring</u> - 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 Flz and Flb 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 Fla and Flb 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 Flb, but not Fla litters. ACO was statistically significantly lower in the Fla 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.

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Hematology and Clinical Chemistry - Blood was drawn from the recro-orbital venus plexus from 12 animals per sex from the PC and F1 generations at 196/197 and 224/225 days, respectively. The following parameters were studied. Hematological Parameters leukocytes (WBC) erythrocytes (F3C) hemoglobin (HGB) hematocrit (HCT) platelets (PLT).

Hematological Parameters leukocytes (WBC) erythrocytes (RBC) hemoglobin (HGB) hematocrit (HCT) platelets (PLT)

Clinical Chemistry Parameters
Blood Chemistry
total bilirubin
sodium
potassium
inorg. phosphate
calcium
urea
creatinine

mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin conc. (MCHC) retoculocytes thromboplastin time

total protein albumin globulins triglycerides cholesterol glucose

Enzymes
alanine aminotransferase
aspartate aminotransferase
alkaline phosphatase

Results - Consistent decreases in HCT and HGB occurred in PO and Fl females at 1000 ppm and above. Consistent elevations occurred in treatinine and cholesterol at 3000 ppm in PO and Fl 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 PO male hematology. Slight but statistically significant dose related decreases in nematocrit at 300 ppm and above and hemoglobin concentration at 1000 ppm and above occurred in PO females (HCT=94% at 300 ppm; HCT=91% at 3000 ppm and HRG=96% at 1000 ppm; HBG=92% at 3000 ppm of controls). The HCT, RBC and HGE in Fl females behaved similarly to the PO 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 Fl females. No other hematological effects were clearly dose related.

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

5. Sacrifice and Pathology -

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All animals that died and that were sacrificed on schedule in all PO, Fl, 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 PO, Fl 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 ights, 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 PO 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 PO groups (125% at 1000 ppm of controls), Fl (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 PO, Fl 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 PO, Fl, FX and FZ males, which appeared to be dose related. The epididymal weights were statistically significant at higher dose levels in the PO, Fl, 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

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

Dose group- PO males, body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Eody 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	17.3	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
Bod· · · , g sr n	432.2 49.6 24	425.1 39.8 24	446.7 44.8 24	430.3 37.3 24	364.6** 30.7 49
Live SD n	15.6 3.5 24	15.3 3.8 24	15.8 2.5 24	14.9 2.6 24	15.5 2.0 49
Testis, g SD n	3.44 0.26 24	3.46 0.27 24	3.69 0.36 24	3.65 0.37 24	2.72** 0.50 44
Epididymis, mg SD n	1302.3 117.4 24	1252.8 91.6 24	1260.8 120.6 24	1099.2** 94.9 24	540.1** 242.9 44
Adrenal gland, mg SD n	70.3 9.6 24	73.0 8.8 24	83.5 12.2 24	104.3** 18.7 24	190.** 38.5 49
Dose group→ FY males (adult F2a), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 բբա	3000 ppm .
Body wt., g SD n	424.8 37.1 24	418.6 30.0 24	437.5 47.6 24		•
Liver, g SD n	14.8 2.6 24	14.5 2.1 24	16.0 2.5 24	-	
Testis, g SD n	3.47 0.32 24	3.45 0.21 24	3.67** 0.31 24		-
Spididymis, mg SD n	1269.8 92.5 24	1212.4* 71.0 24	1195.8** 89.3 24		•
Adrenal gland, mg - SD n	81.2 12.0 24	79.5 10.9 24	89.9* 11.6 24	_	-
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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		and the second s
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	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 Fl groups at the 1000 and 3000 ppm dose levels.

Table E. Effects on terminal body weight and selected target organ weights in the FO and F1 parental females, FX (F1c females adults), FY (all female F2a adults) and FZ (all female F2b adults).

Dose group→ PO females, body wt. & absolute crgan 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	9.5 0.3 21	10.0 1.1 24	10.6* 1.8 24	10.5* 0.8 22	13.2**
Adrenal gland wt., mg SD n	110.3 11.2 21	108.8 16.9 24	114.7 15.6 24	143.6** 16.4 24	131.2** 24.5 21
Fl female (Fla adults), body wt. & absolute organ wt.	Control, 0	50 ppm	300 ppm	1000 ppm	3000 ppm
Body wt., g SD n	303.5 24.5 23	305.0 23.5 23	319.6 28.1 22	•	-
Liver wt., g sd n	9.5 1.3 23	9.7 1.0 23	10.4* 1.3 22	-	-
Adrenal gland wt., mg	94.2 8.5 23	92. 9.7 23	101.2*	-	-

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FX female (non-mate, Flb adults), body wt. & absolute organ wt.	Control, 0	50 ppm	3CO ppm	10 00 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	3CO 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 Fla and Flb 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 Fl 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 Fl 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 (Fl=24/24) (FX=20/24), reduced sizes of seminal vesicles (Fl=19/24) (FX=21/24), prostate (Fl=19/24) (FX=18/24), bulbo-urethral gland (Fl=15/24) (FX=13/24) and reduced penis size (Fl=23/24) (FX=21/24) were seen in Fl and FX males at 1000 ppm. Nipples were noted in Fl 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 1:68, 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 Fla and Flb 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 Fl 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 PO, Fl 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 Fl and 2/24 FX males and in only 1/24 PO 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, PO, 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 PO males and females and F1 and FX males. Lipidosis was noted in adrenals at 3000 ppm in PO, 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 PO, 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 ppn (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 Fla (selected for the Fl generation) and Flb (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 purs were delivered at 1000 or 3000

ppm from the Fl 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 Fl 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 Fla 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 cffspring 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 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 anogenital region through a vagina-like opening into the exterior.

Reproduction Rat: 83-4-Final Rep . Vinclozolin/92.1125.71R0375 88053:425813-01&Sum Info 425813-02 D186519.

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 Fla and Flb 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 Fla, Flb, F2a or F2b

pups.

Fla and Flb 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 Fla and Flb 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 PO, F1 and FX males and FO 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.

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- 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. (Movember 1992) Discussion of Prenatal and Reproduction Toxicity of Reg. No. 258 (Vinclosolin), Reg Doc. No. BASF 92/11407.]

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 vinclozclin, 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 9.244 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 0.30244 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 0.1000067 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

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

Reproduction.Rat.83-4 Final Rep. Vinclozatin 92 1125 7180375 88053 425812-0185um into 401813-012 0116519

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 summa ? 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, 3 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 (sponsir's definitions), extracted from the submitted report. The values are in general agreement those arrived at by Toxicclog: Branck-1. The F2 generation effects at 4.9 mg/kg/day are for epididytal 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-amirogens with androgen receptors from various sources.

Chemical and reaction time (Knupper.	Binding affinities relative to				
4/27/90).	Flutamide fibolerine				
Vinclozolin 2 hours 12 hours	55% I.4%				
119 208 (metabolite, see fig.1 2 hours 12 hours	48 2.0% A				

Reproduction Rat 83-4 Fnal Rep. Vincozolin 92 1125 71R0375 58053 425513-018Sum Into 425813-02 0186519

Tuble 3. Vincipzolin dissociation constants (Ka mmoles/1) relative to mitclerone over the three studies. The methods used to derive these results were not stated.

Androgen receptor source/reference	Vincissolin relative to mibolarone Kd (mmoles/1)	Vinclozolin binding as a % of mibolerone	Mibolerone Ki 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, 3 3/92)	28	(13)	C.244 ± 0.114	(91%)
Rat prostate, in vivo study (Knuppen, 3/3/92)	100	(0.0253)	0.026 ± 0.016	(925)

These units, Kd (nmoles/1), must be in error for the relative vinclozolin binding affinity presented in the submitted report. These units are not consistent with the pext 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 binting reported in the submitted summary for

vinclozolin relative to mibolarone and flutamida.

Table C. Binding affinities of various anti-androgens.

Experiment	Vincitzolin Vincitation relative to flutamide (% mibolerane (%	Mibolerane Kd nmoles/l	119 208 Kd (nmcles/1)
LNCAP cells (Knuppen, 3 3/92)	91% 1%	0.244 = 114	
Rat prostate (Knuppen, 3 3/92)	92% 0.026%	0.026 : 0.016	. • .

Table 2. NOEL in mg/kg day from the recent developmental toxicity studies and the study on reproduction (Sponsor suggested effect levels .

	faternal toxicity	Feto/emoryo toxicity	Anti-androgen effects	Reproduction
Developmental/rat/tral	: :30	150	15	ļ
Developmental/rabbit/oral	50	200		
Developmental/rat/dermal	50	!	50	-
2-Gen. reproduction	4.9	29	4.9 (PO/F1) <4.9 (F2)	29

Reproduction:Rat 83-4 Final Rep. Vinclozolin 92 1125 71R0375 88053 425813-01\$Sum Inte 425813-02 D185519

Figure 1. The major metabolite, two major decomposition products of winclocolin and four other chemicals demonstrating anti-androgenisity two drugs and I pesticides).

//\
pH > 5.0 // Slowly at \
pH < 5.5 \
// C1

M1 reversible hydrolysis product 2-[[(3,5-dichlorophenyl)carbamoyl]cxy]-2-methyl-3-butanoic acid); forms rapidly at alkaline pH > 8.0, Szetc et al., 1989. Irreversible degradation product, referred to as Compound 23 in the metapolism study and M2 by Szeto et al., 1989.

RU 23 908

Flutamide

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

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

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C10380

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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).*

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(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER OR WITH PUPS / FETUSES IN WIERO (D) MALE FERTILITY INDEX - X 100 MALES PLACED WITH FEMALES X 100 (B) NALE MATIRE INDEX - ----- K HALES WITH CONFIRMED MATIRE TOO

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	1657 620	6 TEST GROUP 11	TEST GROUP 12	1651 GROUP 13	16 ST GROUP 14 3,000 PPH
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BASP Department of Toxicology

PATHOLOGY REPORT

7180375/88053

Req. No. 83 258: 2-Generation Reproduction Study in Rats, Oral Application

Oct/19/1992 CECE acopat system

RESULTS AND DISCUSSION

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

PENIS

BEST AVAILABLE GOPE

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 sales of dose group 14, three cross sections through the urogenital tract

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 attampt 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 Mueilerian 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 membrawe and they open into a common cavity covered by a non stratifying epithelium,

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PATHOLOGY REPORT

Reg. No. 83 258: 2-Generation Reproduction Study in Rats, Oral Application

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acopat system

RESULTS AND DISCUSSION

Name of the lesion

010380

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

Groups 10 11 12 13 14

10 11 12 13 14 10 11 12 13 14 male rats (level I)

		(1	eser Il	male rats	(level II)
Animals in selected gro	ou p		29		25
Ductus deferens (level Ductus deferens-like du	I) ict (level II)	28		
unilateral bilaterai			5 23		24 2 22
Muellerian duct unilateral bilateral			20 1 19		16 3 13
Both ducts present unilateral bilateral			18 5 13	1	15 4 11
Not otherwise specified unilateral	duct	and the second s	• •		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

		-			Gro	ups			•		
Name of the lesion	10	11	12 88	13	14	10 fer	11	12 rate	13	14	
Animals in selected group	24	24	24	24	29	24	24	24	24	26	
Vacuolation of cells						• •					



EASF Department of Toxicology PATHOLOGY REPORT	26
Reg. No. 83 258: 2-Generation Reproduct- ion Study in Rats, Oral Application	71R0375/98053 Oct/19/1992 CEGE acopat system
RESULTS AND DISCUSSION	010380

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

	•				G	COUDS			
Name of the lesion				- 10 fem	11	12 Fats	13	14	•
Animals in selected	group			 		24	,	7.	
Lipidosis of ovarian	interstitial	cells,	NOS		1		_ 	<u> </u>	
		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	minimal	•	i	•	2	6	
			slight	•	•	• 1	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 sicroscopically 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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PATHOLOGY REPORT

Reg. No. 83 258: 2-Generation Reproduction Study in Rats, Oral Application

7180375/98053

Oct/19/1392 CEGE accpat

RESULTS AND DISCUSSION

3. FX animals (dose groups XO to X4)

010380

System

- A. Weight parameters
- a. Absolute weights

The mean terminal body weight was statistically significantly decreased in the

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

The females of coups 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 sanner.

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.

D. 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

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

In the males of groups 13 and 14; 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.

3. Gross observations

As in the animals of the FI 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.

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Reg. No. 33 258: I-Generation Reproduction Study in Rats. Oral Application

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RESULTS AND DISCUSSION

Again, as in the males of the Fl generation parental animals, the most striking finding in all the males of group X4 (3000 pgm) was the presence of one or two grossly visible flotal structures (miled "Muellarian flots" for diagnostic purpose), extending between approximately the neck of the urinary pladder, accompanying the inerhra and opening in the inegenital region through a vaginative opening into the exterior. These ducts contained either water-like or purpose.

In these animals, the seminal vesicle (48/49), the pristate (49/49) and the bulbo-urethral gland (49/49) were entirely assent, and the restes (35/49), applications (49/49), and penis (48/43) of trese animals seemed to be reduced in size. Hypospadia was noted in all but one make rat of this group. In addition, the seminal vesicle of one remaining make 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-trethral 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).

Adnesions between testes and epididyeides were noted in individual males of group X4, most likely indicative for inflammatory reactions. In two males of this group, an epididymal auscess was noted furing 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 nited 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 (1003 ppm), and in nine of the sale rats of group X2 (300 ppm).

Nearly a quarter of the males (12/49, one more than seed clinically) and six out of the fourty females of the high fome 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 14. From the gross sorphological appearance, it was not interpreted to be a tusor - 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

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Lenticular segeneration was noted in almost all male (47.49) and in all female rats of dose group x4, in 4 sales and sany females (11.74) of dose group x3, and in two male and one female rat of dose group x2.

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Reg. No. 83 258: 2-Generation	Reprod	iuct-				71R0375/8805
ion Study in Rats, Oral Appli	cation					acopat system
TUCTORICE OF MICHOGGODIA DELLA						
INCIDENCE OF MICROSCOPIC FIND FO GENERATION PARENTAL ANIMAL			4			
FU GENERATION PARENTAL ANIMAL	5					010380
Sacrifice group	K1					
Sex	M					
Ocse group	20	91		4.5		
Animals in selected Group	24	24	<u> </u>	23	04	
Picstate	24	24	24	24	24	
- Secretion reduced	1	41	4.9	24	24	
Seminal vesicle	24	24	24			
- Acinar atrophy	1	.4.4	44	2.4	24	
Secretion reduced	1	•		•	• 4	
Cagulation glands	24	24	24	2	4	
Acinar atrophy	1		24	24	24	
Secretion reduced	ī	•	•		:	
estes	24	24	24	24	6	
Leydig cell hyperpl.		1	• •	10	24	
Tub. atrophy, focal		•	•	10	16	
Tub. atrophy, diff.	ī	•	•	•	3	
pididymides	24	24	24	24	24	
Exfoliat. germ cells	1				44	
Aspermia	•	●	•			
yes	24	24	24	24	24	
Lentic. degeneration			•	1		
lver	24	24	24	24	22	
Central hypertrophy		-	• •	3		
Single cell necrosis			•		24	
Fatty change, interm.		•	•	•	20	e de la companya de
Fatty change, focal		3	3	:	22	
Facty change, periph	•	15	. 7	12	4	
Lymphoid cell aggreg	23	24	20		2	
Bile duct prolifer.	••	• •		24	24	
Fibrosis, focal	•	•	•	3	•	
Congestion	, , ,		. •	•	•	4
renal cortex	24	24	24		:	
Lipidosis	• •	• •	44	24	24	
Lipogenic pigment	, •		•	• •	24	X .
Extracortical nodule	· · · · · · · · · · · · · · · · · · ·	•		•	1	
Cyst(s)	•		1		4	
Calcification, focal	i		•	1	•	
Congestion	• .	•	•	• • •		
renal medulla	 -				<u> </u>	
tuitary gland	24.	24	24	24	24	
Vacuolation of cells	24	24	24	24	24	· · · · · · · · · · · · · · · · · · ·
Cyst	5	2	6	6	24	X
	. 7	3		4	- 11	4. *
dneys						

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Reg. No. 83 258: 2-Generation ion Study in Rats, Oral Appli	Reproduce	ict-					56 R0375/88053 9/1992 CEGE t system
INCIDENCE OF MICROSCOPIC FIND FO GENERATION PARENTAL ANIMAL							u10380
Sacrifice group Sex	K1					" - 	
Dose group	. М ЭО	01	02	11		8	
Animals in selected Group	2.4	24	24	24	04		
Heart - Myofibrosis, focal	1				24		

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Reg. No. 93 258: 2-Generation on Study in Rats, Oral Appl:	cation	uct-	•				::.19/1992 CEGI
					7.	ac	CDAT SYSTEM
INCIDENCE OF MICROSCOPIC FIND	INGS						010380
FO GENERATION PARENTAL ANIMAL	5				and the second		010900
Sacrifice group	K1					4	
Sex	F						
Dose group	00	91	0.2	03	04		
Animals in selected Group	24	24	24	24	24	-	
Cvaries	24	23	24	24	24		
- Lipidosis			•	22	24	200	
- Follicular cyst	•				4		
- Reduced maturation	•	18 °	•		2		
- Lipogenio pigment	18	23	24	2.4	21		
Terus	2.4	23	24	24	24		
- State of pregnancy	•		•	2			
- Luminal dilation	5 .	8	9	6	5		
Congestion			•		1	, 3	
lervix.	24	23	24	24	24		
State of pregnancy	•	•	•	2	•		
Congestion	•				1		
agina	24	23	24	24	24		
State of pregnancy	•		•	2 .	•		
Congestion	•				1		
• 1.11	_ 24	24	24	24.	24		
Lentic. degeneration			1	20	24		and the second second
Central hypertrophy	24	24	24	24	24		
Single cell necrosis		•	•	3	24		
Necrosis, focal	•	•			19		* 1
Fatty change, focal		•	. •		1		
Fatty change, periph	1	• 1	•	•			* ,
Lymphoid cell aggreg	8	11	5	•	7		
Bile duct prolifer.	23	24.	24	24	23		
Remodeling parenchym	ì		•	•	1	2 to 1	
crenal cortex	24	24				· · · · · · · · · · · · · · · · · · ·	
Lipidosis	• •	49.	24	24	24		
Lipogenic pigment	•		•	19	24		
Extracortical nodule	i	•	•	:	2 .	100	
Congestion	•	i	•	, 2	3		
cenal medulia	24	24	24	-:-			
Calcification, focal			44	24	24		*
tuitary gland	24	24	24	~;			
Hyperplasia, focal	1			24	24	· · .	
7acuolation of cells	i	•	`•	.•	•		
Cyst	7	7		3	3		· · · · · · · · · · · · · · · · · · ·
Malformation		•	1	.3	4		

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INCIDENCE OF MICROSCOPIC FINDIN FO GENERATION PARENTAL ANIMALS	IGS					U103	
Sacrifice group	Kl						
Sex	F						
Dose group	00	J1	02	03	34		
Animals in selected Group	24	2.4	24	24	24		
Mammary gland							
- Fibroadenom.			•	•	* *		
Pancreas	1		•		•		
- Edema, interstitial	- 1	•	•	•			
Duodenum							
Jejunum		· · · · · · · · · · · · · · · · · · ·					
Ileum .					l		
Cecus				· · · · ·	1		
Colon		• • • • • • • • • • • • • • • • • • • •	•		1		
Rectum	<u> </u>				1		

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INCIDENCE OF MICROSCOPIC FIND	INGS			•		
FI GENERATION PARENTAL ANIMAL	s				3 .	
						0103
Sacrifice group	Fl					
Sex .	M					
Cose group	10	11	12	13	14	
Animals in selected Group	24	. 24	24	24	29	
Penis		•	•	24	29	
Organ size reduced			•		27	
rogenital tract I		•	•	•	29	
Ductus deferens		•	. •	•	28	
With cell. debris		•	• '	•	5	
With spermia Muellerian duct	•	•	•	•	20	
		•	•:	•	20	
with cell. debris	•	•	•		5	
rogenital tract II		<u> </u>			- 6	
D. defer, -like duct	•	•	•	15	25	
. with cell. debris	•	•	•		24	
with spermia	, e . •		•	•	6	
Muellerian duct	•		•	• '	17.	•
with cell. debris				. • .	15	
with spermia		. •	•	•	3	
Duct (NOS)	•	•		v 2	13	
ogenital tract III	 					
D. deferlike duct	•		•	•	5	
vith spermia		•		•	4	
Muellerian duct		€.•	•	• •	4	
Vagina-like orifice	•	• •		•	2	
with cell. debris	•	•	•		4	
with spermia	•	•		•	2	
OSTATE SPECKIA			<u> </u>		2	
	24	24	24	24	29	
Organ not detectable Acinar atrophy	•	•	•		28	
Secretion reduced	•	•	·	1	1	
Absence of secretion	• 1	• .	1	11	1	
	•	•	**	4 :		
Thronic inflammation				14		<u> </u>
	24	24	24	24	29	
organ not detectable	•				· 7 -	
cinar atrophy	•	•	•	•	22	
ecretion reduced				18	21	
bsence of secretion	• **.	• •			1	
hronic inflammation	• ' i		•	11	4	
uminal cell. debris	•		•	•	. 3	•
uminal spermia					6	
		24	24	24	29	
gulation glands	24	4.5		4.2		_
gulation glands	24	. 45				
quiation glands rqan not detectable ecretion reduced	24	•	2	3	29	
igulation glands organ not detectable ecretion reduced hronic inflammation bo-usethral gland	2.4					

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ion Study in Rats, Oral Appli	cation	466				Oct/19/1992 CEG
		سبنى				acopat system
INCIDENCE OF MICROSCOPIC FINE	INGS					
FI GENERATION PARENTAL ANIMAL	.s					010380
						240380
Sacrifice group	Fl					
Sex	М	100				
Dose group	10	11	1.2	13	14	
Animals in selected Group	24	2.1	24	24	29	
Testes	24	21	24	24	29	
- Leydig cell tumour					4	
- Leydig cell hyperpl.	2		- 7	17	24	
- Cystic rete testis			•		1	
Tub. acrophy, focal			1	5	13	
Tub. accopny, diff.		1	•		11	
Tub. mineralization	7.8 1	· •		•	6	
Chronic inflammation				•	7	
pididymides	24	24	24	24	29	
Atrophy, diffuse					10	
Aspermia	1	1			10	
Oligospermia		_	Ť.	•	6	
Chronic inflammation		•	•	•	9	
Abscess		•	•	•		
yes .	24	24	24	24	- 1	
Lentic, degeneration	7.7		2		29	
iver	24	24	24	9	29	
Focal hyperplasia	4.9	44	24	24	29	
Altered foci (NOS)	•		•	•	1.	
-Eosinophilic foci	•	- A ★ *		•	12	
-Basophilic foci			•	,	. 11	
Central hypertrophy	•	•	•	•	1	
Single cell necrosis	ו	•		4 .	28	
Paner 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	
renal cortex	24	23	24	. 24	29	
Lipidosis	•			2	29	_
Lipogenic pigment		•			2	•
Extracortical nodule				-	. 3	•
Cyst(s)			7 7	•	1	
Calcification, focal	1	\$ 1	•	•		
Congestion	,	•	•	•		
Hematopoiesis		•	• •	•		
renal medulla	24	23	34			
Calcification, focal	67	- 23	24	24	29.	
Lymphoid cells	•		•	•	1	
cuitary gland				•	1	
Vacuolation of cells	24	24	24	24	29	
Cast	4- 31	2	6	19	28	•
			6	2	- 8	

PATHOLOGY REPORT Reg. No. 83 258: 2-Generation ion Study in Rats, Ocal Appli	Reprod	uct-				71R0175/88053 Oct/19/1992 CEGE account system
INCIDENCE OF MICROSCOPIC FIND F1 GENERATION PARENTAL ANIMAL						010 3 8(
Sacrifice group	Fl					
Sex () A Section () The Company of	M					
lose group	10	11	12	13	. 14	
unimals in selected Group	24	24	24	24	29	
Lidneys	•		-	5	1	
Hyperplasia, urothel		•		4	1	
Nephritis, interst.				3	1	
Nephropathy			<u> </u>	2		
rinary bladder	•	•	•	8		
Carcinoma, trans.cell	3.	•		1		计可以转换 医抗原虫毒蛋白酶
Papilloma, trans.cell				3		
Hyperplasia ungs	<u> </u>	•	•	- 4		
	•		•	•	, 1	
Interstit. pneumonia	• •	•			1	
Dilation	• 1	.,•	•	•	1	
Liac lymph nodes		· · · · ·	•	•	1	
Lymphadenitis simpl.	•		1	1	3	1
enal lymph nodes	* * *		1	_1_	3	
Hyperemia	•	• •	•	2	2	
Lymphadenitis simpl.	•	•		1	•	
guino-femoral lnn.	•	•	•			1
Lymphadenitis simpl.	•	. •	•	•	1	
in	2			•	_1	
Inflammation, focal			. 2	1	1	
Alopecia, focal	•	•	Ţ	•	1.	
Necrosis, focal	4	•	T	I,		

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Reg. No. 83 258: 2-Generation	Reprod	uct-					/19/1992 CEGE
ion Study in Rats, Oral Applic	ation					400	
INCIDENCE OF MICROSCOPIC FINDS	NCC	· · · · · · · · · · · · · · · · · · ·					
FI GENERATION PARENTAL ANIMALS							U1038
The second secon	. ,						070001
Sacrifice group	51			···		-	
Sex	?				* * *		
Dose group	10	11	1.2	13	14		The second second
Animals selected Group	24	24	24	24	37		
Ovaries	23	24	21	24	26		
- Cipic is	•	1		3	9		
- Cys+ ; corpus luteum	1		2		1		
- Follicular cyst	2	2		•			
- Reduced maturation	1		ì	•	1		
- Cystic rete tubule	1		•		. •		
- Lipogenic pigment	23	23	24	24	23		A Commence of the
Uterus	23	24	24	2.1	26		
- State of pregnay	1		2	24	20	5 S	
- Luminal dilation	1	7	6	**	2		
Cervix	23	24	24	24	26		
- State of ocerancy	1		2	24	20		
Vagina	23	24	24	24	26		•
- State of pregnancy	1		2	24	20		
Eyes	24	24	24	24	26		
- Lentic. diceneration				22	26		
Liver	2.4	24	24	24	26		
- Altered foci (NOS)				• •	3		•
Eosinophilic foci			•	•	3		
- Central hypertrophy		· · · ·	•	6	18		
- Fatty change, periph	9	4	2 5	•	1		
- Lymphoid cell aggreg	24	24	22	21	26		
- Bile duct prolifer.	1.		1	4.4	1		
- Congestion			. •	•	. •		
Adrenal cortex	24	24	24	24	36		
- Lipidosis	4.7	6.4	. 49	•	26		
- Lipogenic pigment		•	•	. 8	26		
- Extracortical nodule	•	• •	• •	•	12		
- Cyst(s)	* *	- ;	•	•	. 6	*	
- Calcification, focal	•	1	3	•	:	* .	
- Congestion	•	•		•	2		e e e e e e e e e e e e e e e e e e e
Adrenal medulla	24	24	34		5		
Pituitary gland	24	24	24	24	26		
- Hyperpiasia, focal		. 44	24	23	26		
Vacuolation of cells	1	· ·		• 1	. 1		
- Cyst		;	1 2	•			
	10	. 5	5		11	•	

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Reg. No. 83 258; 2-Generation ion Study in Rats, Ocal Applic	Reprod	uct-				7180375/38053 Oct/19/1992 CEGE acopat system
INCIDENCE OF MICROSCOPIC FINDS F1 GENERATION PARENTAL ANIMALS	NGS			3		
Sacrifice group	FI					010380
Sex						
Dose group	15	11	. 12			
Animals in selected Group	24	24	24	13		• • • • • • • • • • • • • • • • • • • •
Manmary gland			- 44	24		
- Fibroadenoma	•	5	•		•	
Skin				•		
- Alopecia, focal	<u>:</u>	•	2 2			

### CIDENCE OF MICROSCOPIC FINDINGS - FX ANIMALS #### ANIMALS #### ANIMALS #### ANIMALS ##### ANIMALS ###################################		7190775 (000					
Reg. No. 83 258: 2-Generation	Repro	duct-				0	Ct /19/1905
ion Study in Rats, Oral Appli	cation						
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INCIDENCE OF MICKOSCUPIC FIND	INGS -	FX ANI	MALS			4.	ប់រំពន្ធ
Sacrifice group	Fl						92000
Sex							• • • • • • • • • • • • • • • • • • •
Dose group		ХÌ	¥2				
Animals in selected Group				-			
Penis						· · · · · · · · · · · · · · · · · · ·	
- Organ size reduced				,••	-,		
Urogenital tract I			······································				
Ductus deferens				•	·		
		•		•			
" With spermia				•			
- Muellerian duct	•	•		-			
with cell. debris							
With spermia			•				
rogenital tract II	•		•	21		-	
						1	
. Vith spermia	•	•					
	.•*	•	•			•	
with cell. debris	•						
with spermia							
rogenital tract III	•	•	•				
							in the second
with spermia							
Vagina-like orifice			•				the state of the state of
with cell. debris					2		
" with spermia					2	s.	
ostate	24	24	24	24	49		
Organ not detectable	S 4		•		46	> ~	•
Acinar atrophy					. 3		
Secretion reduced	•		2	9	3		
Absence of secretion				ĩ	•		A
Chronic inflammation				4	•		
minal 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				R			•
Luminal cell. debris			_		2		
Luminal spermia	. 4			•** . -	5		
agulation glands	24	24	24	24	49		
Organ not detectable	•		. 1.		49		
Secretion reduced		•		12	43		
Absence of secretion		< -	-	1		• • •	**************************************
Phronic inflagmation	•	-	•	. 3	•	**	
bo-urethral gland .			•	24	49		
organ not detectable) -	_	. •	7	49		
ecretion reduced	. / T	•			~3		

PATHOLOGY REPORT Reg. No. 83 258: 2-Genera				, , , , , , , , , , , , , , , , , , , 			79 [20375/8805]
ion Study in Rats, Oral A	tion Repro	gircs-					19/1992 CEGE
ICB SEES, SEELS, SEEL A	polication	•	·		4	_ ಕದಾ	4
INCIDENCE OF MICHOSCOPIC	PINDINGS -	PY AND	MAI C				
		** 101	.com.s				01038
Sacrifice group	Fl					•	
Sex					* .		
Dose group	X0	X1	X2	X3	X4		
Animals in selected Group	24	24	24	24	49		
Restes	24	24	24	24	49		
Leydig cell hyperpl.		•		19	38		
Tub. atrophy, focal	•		•	1	33		
Tub. atrophy, diff.	•	•		.•	16		
Tubular grant cells	e e e	•	:•		4 %		
Tub. mineralization	•	٠		•	2	in de	
Chronic inflammation pididymides					- 6		
Attophy, diffuse	24	24	24	24	43		
Exfoliat. germ cells	•	•		•	3		
Aspermia	•				4		
Oligospermia	•	•		•	12	100	
Chronic lefterment	•	•	•	1	14		
Chronic Inflammation		<u> </u>	•		9		
-	24	24	24	24	49		
Lentic. degeneration			2	4	47		
Altered foci (NOS)	24	24	24	24	49		
-Zosinophilic foci	•		•	•	2		
Central hypertrophy		•	•	•	. 2		
Single cell necrosis	. • .	• ,	. •	2	49		1.5
Fatty change, interm.			•	• •	48	*	
Necrosis, focal		•	, ÷	•	4		e w
Patty change, focal	•	1	• .	1	:		•
Patty change, periph	2	2	2	1	· .		•
Lymphoid cell aggreg	22	22	19	21	31		
Bile duct prolifer.	24	24	. 24	24	49		
Fibrosis, focal			•	1	4		
Peliosis, focal	· ·	• .	•	• .	1	*	
renal cortex					1		*
Lipidosis	24	24	24	24	49		
Extracortical nodule	•	•	•	1	49		
Calcification, focal	•	1	, .	2	4.		
renel medulla	•			•	2		
Lymphoid cells		24	24	24	48		· ·
turtesh draug			•		. 2		
Vacuation of	24	24	24	24	49		
Vacuolation of cells	5	1	6	8	47		
Cyst Malformation	. 5	2.	7	3	8		A STATE OF THE STA
	<u> </u>	1		<u>i</u>	1		
dneys	•	•		1	1		
Hyperplasia, urothel		•	•	1	•		
Nephritis, interst.			•	•	1		
Nephropathy	_			1			

PATHOLOGY REPORT Reg. No. 83 258: 2-Generation ion Study in Rats, Oral Appli	Reprod	uct-		- 14 - 14 - 14 - 14 - 14 - 14 - 14 - 14		71R0375/8805 Oct/19/1992 CEGI acopat system
INCIDENCE OF MICROSCOPIC FIND	INGS -	PX ANI	MALS			010380
Sacrifice group Sex	F.			<u> </u>		
Dose group	X3	X1	va			
Animals in selected Group	24	24	X2	Х3	X 4	
Urinary bladder		- 44	24	24	19	
- Hyperplasia	•	•	• •	1	•	•
Lungs		•				
- Chronic congestion	•		•	1	•	
Seart						
- Myodegeneration	•	•	•	1	•	
Mediastinal lymph n.	****		•			
Congestion, chronic.	•	•	•	I	•	
Iliac lymph nodes.					<u> </u>	
- Lymphadenitis simpl.	•	•	•	2		
ikin	•	•	•	- 2	•	
Alopecia, focal		•	•	· 2	7	

PATHOLOGY PEPORT Reg. No. 83 258: 2-Generation	n Reproc	uct-			· · · · · · · · · · · · · · · · · · ·	120375/38651
ion Study in Rats, Oral Appl	ication			,		Oct/19/1992 CECI acopat system
INCIDENCE OF MICROSCOPIC PIN	DINGS -	PX AND	MALS			010380
Sacrifice group	Fl			1		
Sex						
Dose group	X0	. X1	X2	X3	X4	
Animals in selected Group	24	24	24	24	40	
Ovaries	24	24	24	24	40	
- Lipidosis	•	•	1	20	38	
- Cystic corpus luteum	•	•	•	•	2	
- Follicular cyst	•	•	• ,	•	1	
- Cystic rete tubule	1	4	•	1		
- Cipogenis pigment	23	20	2.4	22	40	<u> </u>
Sterus	24	24	24	24	40	
- Luminal dilation	1	3	41	•	9	
Congestion	1_	•	•			
ervix	.24	24	24	24	40	
Congestica	1					
/agina	24	24	24	24	40	
Congestica	1				•	
700	24	24	24	24	40	
Lentic. degeneration			1_	11	40	
	24	24	24	24	40	
Altered foci (NOS)	•	•	1	•	1	
-Zosinopailie foci	.•	•	•	•	.1	
-Clear cell foci		•	1	•	S• 1	*
Central hypertrophy	•	•	•	. 2	35	
Single cell necrosis	•			•	15	
Necrosis, focal	1	• •,	•		1	
Patty change, focal	3	1	3 .,	1	1	
Fatty charge, periph	5	7	5	5	3	
Lymphoid cell aggreg	22	2.4	24	23	40	
Bile duct prolifer.		1			4	
drenal cortex	24	21	24	24	40	
Lipidosis		•	•	7	40	
Extracort.cal nodule	.1.	. 1	1	. •	7	
Cyst(s)	•			•	2	
Calcification, focal		•			å	
renal medulla	24	24	- 24	24	40	
tuitary gland	23	24	24	24	40	
Vacuolatica of cells	• • .	•	1	•	1	
Cyst	4	:4 .	2	4	3	
Malformation					1	

BASP Department of Toxicology PATHOLOGY REPORT Reg. No. 33 258: 1-Generation R ion Study in Rats. Oral Applica	eproc	luct-					32 0375/38053 /1992 CEGE system
INCIDENCE OF MICROSCOPIC FINDING	GS -	EX ANIM	ALS				010380
Sacrifice group Sex	£1						
Ocse group	F XO	X1	X2	х3	Xá		
Animals in selected Group	2.4	24	::	24	40		
Lungs - Chronic congestion	1		•	•			
liac lymph nodes - Lymphacenitis simpl.	•		•	1	•		
Skin - Inčlammation, Eccal		•	•	1			

200 No 03 755. 3 0							71RC37S/38O53
Reg. No. 83 258: 2-Generation	a Reprod	ncs-				Oct.	19/1392 CEGE
:on Study in Rats, Oral Appl	ication				•		
INCIDENCE OF MICROSCOPIC FIN	DINGS -	PY ANI	MALS				01038
Sacrifice group	K1						
Sex	M			P			
Dose group		Y1	¥2	70	Yl		
Animals in selected Group	24	24	24	24	24	24	
Prostate	24	24	24				
Seminal resicle	24	24	24		•		
- Secretion reduced	•		1		•	•	
Coagulation glands	24	24	24	-	•	-	
- Secretion reduced			1	•	•	•	
Ovaries			-	24	24		
- Lipidosis			•		24	24	
- Cystic .cete tubule	- 1	•	•	2	•	2	
Lipoqenic pigment		•	•	15	•	•	
terus			•	24	24		
Luminal dilation	•			3`	4.5	24	
err.x				24	24	6	
89158		. 1	•	24		24	
estes	2.4	24	24	- 44	24	24	
Leydig cell hyperpl.	• •		1	•		• 1	
Tub. atrophy, focal		i	1	•	•	•	
Dididymides	24	24	24	`	•	•	
yes	24	24	24	24		•	
Lentic. degeneration	•		4.9	45	24	24	an en en
ives	24	24	24		-:	3	
Alzered foci (NOS)	**	4.5	44	24	24	24	A Company
-Basophilic foci	•	•	•	•	• .	1	
Necrosis, focal	a italia da f G	.*	•	. •	•	. 1	
Patty change, focal	2		1	• "	•	. •	•
Ficty change, periph		•	1	•	3		
Lymphoid cell aggreg	21	21	23	12	11	12	
Bile duct prolifer.	24	24	24	24	24	24	
ienal cortex		•				•	
Extracortical nodule	24	2.4	24	24	24	24	
Ensergerest undate	•	:	.•	•	•	1	
Eypertrophy, focal Cyst(s)		•	2			•	
		2					
cenal medulia	. 24	24	24	24	24	24	
tuitary gland	24	24	24	24	24	24	· · · · · · · · · · · · · · · · · · ·
Vacuolation of cells	14.	10	14	•			
Cvst	<u> </u>	3		2	1	1	
iac lympa nodes			1				
Lymphadenitis simpl.			1	· ·	-	•	* *
:8		•	1				
Necrosis, focal	5.2%		1	-	•	. •	• • •

PATHOLOGY REPORT						7	1R0375/88053
Reg. No. 83 258: 2-Generation ion Study in Rats, Cral Appli		uct-			:	Oct/	19/1992 CEGE
ion Study in Rats, Ctal Appli	CATION				·	acop	
INCIDENCE OF MICROSCOPIC FIND	INGS -	FZ ANI!	MALS				V10380
Sacrifice group	K1	 					
Sex	М	Y		P			and the second of the second
Dose group	20	Z1	22	20	21	72	
Animals in selected Group	24	2.4	24	24	24	24	
Prostate	24	24	24				
Seminal vesicle	2.1	24	24		•	•	
Coaquiation glands	2.4	24	24	· · · · · · · · · · · · · · · · · · ·	•		
Ovaries /				24	24	24	
- Lipidosis						2	
- Cystic rete tubule			<u>.</u>	i	•	•	•
- Lipogenic pigment			•	22	19	24	
Uterus			······································	24	24	24	
- Luminal dilation	> -			5	3	6	
Cervix				24	24	24	
/agina				24	24	24	
estes	24	24	24				
Leydig cell hyperpl.	2		2	•	•	•	
Tub. atrophy, focal	1		2			•	
Spididymides	24	24	24		•		
yes	24	24	24	24	24	24	
Lentic, degeneration			2	•		1	
iver	2.4	24	24	24.	24	24	rin artisti da la como c
Altered foci (NOS)			2		44	45	-
-Eosinophilic foci		•	ī	•	•	•	
-Basophilic foci	•	•	î	:•	• .	· .	
Necrosis, focal	*	· •.	i	•	•	•	
Fatty change, focal	2	i	3	2	•	•	
Fatty change, periph	19	22	20	9	7	•	
Lymphoid cell aggreg	24	24	23	24	24	11	
Bile duct prolifer.	. 43		4.0	43	44	24	
drenal cortex	24	24	24	24	24		
Extracortical nodule	47	1		44 .		24	
Hypertrophy, focal	1		•	s .*	•		
drenal - dulla	24	24	7.4		1_		
ituitary gland	24	24	24	<u>24</u>	24	24	
Vacuolation of cells	4	5	6	49	44	24	* *,

Last Page

71

tation Materia. MRID# Results Documents 23-w) 2-2en. Vinctozatin, 425813-11 \$ Documents are per Agree 0, 50, 300, 1700 or 7000 and 64	• • •	•		010380	Core
Signal 2 form. ***Total Control Contr	1 tatton	Materia.	MRID#		Grade Coc-
Section 2 and 1 an	(53-4) Z-Gen.	Vinctozatin,			"Life"
JULY 2017 19 49 23 11 12 A KER ratio set sealor group through the PC 3 and 52 personal to 11 weeks in an ordinary and 12 personal make produced at higher sold and 12 personal to which are sold and 12 personal to the person	ecroquet on/	"ech. 99.2%	425813-:2	technical 20 2 Mass = 0 4 5 10 36 or 290 materials from the	مرابد کست
prematicals of 10 areas. Two critis per generation were produced. Fig. 21 activities, 12 activit			1	A STATE OF THE STA	
Description of the substance of the substance of the substance of the process of the substance of the substa				Generations for a exect and chars per deneration were conducted by	14
The state of an office features of 1.388 and restand features 15, 1930. ***********************************				1 TO FE BOUTS, TES AT BOUTS: 305 FZ adults: EV and 27 adults and 1	
The STUD was not and Discontinuous College and Institute Fermann 15, 1930 This college and the spiritual college and the Study and Monthly and the spiritual college and the				, OFFY AS 53 ANG 300 SIM Secause TO F2 pubs were produced to home does as a line	
statistically significantly secretaged at 30 comm. PV soluts only, but they were home all, your statistics in grifficantly secretaged at 30 communities in the 51 pc griff 2 could make 1 mg embot in 50 gpm was minimal and considered successful control costs to 3000. To secretize the function intermediate making of this decretage decide, making of communities and initial statistics are secretized and communities. An embodied and statistics are secretized and communities and initial statistics and sold in the secretized making and intermediate and initial statistics. Sold in 51 pc graph of communities and control consideration with the specific control cont		1		The study was intrated December 12, 1988 and faished February 15, 1990	
statistically significantly secretaged at 30 comm. RV adults only, but they were mornally in our stratection is griphically tecretaged at 30 commissions in the 51 pc grid of 2 could make 1 membrane the function maken and considered successival posses is 1405. To setermine the function making of this decretage decoding an edged iscent function responsable making of the decretage and of the set			. :	Differing Tough, NGE: 57 com 4 9 mo kg day 4 DTI -	
romails and or statectals ignificantly becassed at all other everts in the 11 pt profit and the state of 50 ppm and amount and considered surfacement cases in a VOE. It becames the function are as monecaster, meas some most cases are cased and making the cases of the cases and control of the cases. The state of the cases are cased and cases are cased and cases are cased and cases. The case of the cases are cased and cases are cased and cases. The case of the cases are cased and cases are cased and cases are cased and cases. The case of the case of the cases are cased and cases are cased and cases are cased and cases. The case of the case of the case of the cases are cased and cases are cased and cases are cased and cases. The case of the case of the case of the cases are cased and cases are cased and cases are cased and cases. The case of the case of the cases are cased and cased and cases are cased and cased and cases are cased and cased and cased are cased as cased are cased are cased as cased are cased as cased and cased are cased and cased are cased as cased are cased as cased are cased as cased and cased are cased as cased are cased as cased and cased are cased as cased are cased as cased and cased are cased as cased are cased as cased and cased are cased as cased are cased as cased and cased are cased as cased and cased are cased as cased			1	Statisticary significantly pagrases if 50 coming by adults and a second significant	
profile sout Teach Teach Teach and Spipm was immeral and considered succious to loss to a Volla. It is reminized the function making of this decreased education and egyt is seem function rests are being red in responsible to the control on the 10 pages. 181, 100 com 30 my 40 pay, not residely making reduction in the 11 37% by committing at 2.135 my 45 pay, not residely making reduction in the 11 37% by committing at 2.135 my 45 pay. The pages are stated entitles the 11 pages and 12.24 making at 2.24 making at				"COMPAN, AND OF STATISTICAN'S EQUIPMENTLY SECRETARIA AT All state to the months are	
Does 13 No.5. It is estimate the functional meaning of this decreased expolarity and in issue and including to be implicated not to consultation with the Agency and in issue, and including to be implicated not to consultation with the Agency to the provided of the provided not to an activity and the provided not to an activity and to the provided not to an activity and to the provided not to activity and to the provided not provided not to the provided not provided				and the soult makes the effect at 50 ppm was minimal and considered a second	100
Adject Seem function less that is necessary. These seem function tests are sering and in reserve and should not be consulted bond to consultation with the Aperts (1975) and in the producted bond to consultation with the Aperts (1975) and 1975 and		•		2-058 12 a 1-05. I selection the functional meaning of the recreased and a	
till 107 cm 30 mg 40 ps. Int middly making resolution in the 21 37% cm 101 mg 21 32% cm 101 mg 21 mg 21 mg 21 32% cm 101 22% cm 101 mg 21 32% cm 101 22% cm				ARGET SCOTT SUPERCOTTESTS THAN THE RECESSORY. These sports function there is	
LEL JOS com 30 mg kg pay for stindrows, o a cold pay has distinance 51's controlled a pay of the control of the cold pay of th				neid in reserve and should not be attributed prior to consultation with the Advance	
control of a 10 feb of tentrols, a 2 to 25, FY 34-9 of countries of 5 to 10 feb of 23 feb of tentrol of 24 feb of 25		:- 		· Company of the second of the	
control of a 10 feb of tentrols, a 2 to 25, FY 34-9 of countries of 5 to 10 feb of 23 feb of tentrol of 24 feb of 25				LEL 300 com 30 mg 4g bay for epididymal weight reduction in the F1 197% %	
permission will price in 12.54 makes and 12.44 makes are translated in permission and 12.45 makes and families at the mDT. Associate tests 12.64 makes and families at the mDT. Associate tests 12.64 makes and families at the mDT. Associate tests 12.64 makes and families at the mDT. Associate tests 12.64 makes and families at the mDT. Associate tests 12.65 makes are provided at the most and associate test and associate test as 2.65 makes 12.65 makes are provided at 12.65 makes at 12.65 makes 12.			٠.,	- CONTINUES A A GENERAL SECTION OF CONTINUES A > 0.55; FV GARAGE CONTINUES AS A CONTINUE AS A C	•
TREATMENT AND ASSETTING THE CASE THE CASE AND THE POST ADSIGNATION OF THE CASE AND THE POST ADSIGNATION OF THE CASE AND TH		:		1 15 and 12 and 15 threat & 2 2 1 05, in males. Done to stand the contract	
Secret 1 194 St. 2013 and abstrate actional 1198, p. 3. 005 and 1119 bit 3 controlled actional 1198, p. 3. 005 and 1119 bit 3 cold and absolute integrity 1109 bit 3 cold as actional progress (1099 b) 3 cold associate integrity 1109 bit 3 cold as actional progress (1099 b) 3 cold and actional progress of cold and solute integrity 1109 bit 3 cold and actional progress of cold and solute integrity 1109 bit 3 cold and actional progress of cold and action actional progress of cold and actional progress of cold and actional progress of cold and actional actional progress of cold and actional actional progress of cold and actional actional progress action actional actional progress of cold and actional actional progress of cold and actional actional actional progress of cold actional actional actional progress of cold actional actio				regeneration was noted and 2.4.5° makes and 1.3.24 termines. These attacks	
Section 2. A series are grayer transcribed by any 2 and 25 but makes and 355 but the 2 per series at 10 ± 2.00 and absolute liner weaptrs (10%), 0 ≤ 0.00 and 250 but and assolute liner weaptrs (10%), 0 ≤ 0.00 and 250 but and 250 but liner weaptrs (10%), 0 ≤ 0.00 and 250 but liner and 2 but liner weaptrs are trained or her weaptr and 2 but liner an			P 2 7 7 7	101-111 T T43F + 1 T T A Tides and famales at the HOT Absolute and	
Discourse arrans 11 miles is 2015 and absolute here weights 1099, o ≤ 005; were protecting to 11 miles in 2015 and absolute here weights 1099, o ≤ 005; were protecting in 2010 and absolute here weights 1099, o ≤ 005; were protecting in 2010 and absolute here weights 1000 and about makes in 1800 and about makes at 300 commodities. An increased no tende in 1800 and about makes at 300 commodities, and about makes at 300 commodities, and about makes and functional certor obtained in about make the about the triples. Seemal vesicle/bubble-weights grand in about makes about the triples and indicated increased about the triples. Seemal vesicle/bubble-weights (and indicated increased about the about the 1900 and 3000 commodities exists increased its area indicated and areas interesting and hostification of the 1900 and 3000 commodities and increased and 1900 commodities and increased and 1900 commodities a			1 1 1 1	and abstitute adrenal (1°9%, o < 3.05 and 3.5% o <	
and proteins and the part of t	150			* ** ** ** * * * * * * * * * * * * * *	
Age trater fram commission is in 21 audit fermaes, but not relative agreen or ner weight An increased in center of the course and processed in center of 17 and makes at 300 commission and processed in the course of 17 and and the commission and processed in the course of 17 and and and and the course of 17 and	- i			2050 Le 30'enil 1. The 1 ≥ 0.05 and absolute their weights 1095 or 3.05	
An increased indicates in texticular laving cell hyperplasia contined in F1 7.24 mass at 100 and 3000 porm base and textification of the companion of the compa				were proster than portror sun FT abut females, but not relative adrenal or over weight.	200
At 100 and 3000 ppm isseudine ingans, such as aberrant Andrian dust, patient Wile en an dust, resided bases to create a compactive ingans, such as aberrant Andrian dust, patient Wile en an dust, resided bases to create an acceptance regards, such as aberrant Andrian dust, patient Wile en an dust, resided and cook and			1	An increased indicance of testicular levidig cell hyperplasia occurred in Ft. 7.14	
Vice enand duct, recluded basent protestes, seminal vesicle? bubbouvertinal gland in Noticin atrodition atrodi	* * * * * * * * * * * * * * * * * * * *				ľ,
Vice 4-an duct, reduced absert private, seminal escale/bubouvertral gland south attoring seminers tubued, ascernals registering and reduced pensitize were noted. Impostable about a deburged in all make offspring-only at the 1000 and 2000 ppm base eless. Increased statem indoes and owners interestical sed historicity required in 1500 and 2000 ppm base eless. There are offspring-only at the 1000 and 2000 ppm 1500 pp				At 1200 and 3000 ppm isseppmermaphroditism, anomalies and functional period	
Accordance in processor a became in all modes, aspermal engasperma and reduced bens like when roted in processor a became in all modes and ovarian interstitualized hiperrecry tocurred at 1000 and 2000 per requert compound related single cell her hecrosis was noted in \$1 and \$1 and meet 20 and 48.99 and in FX female acturs in \$2.00 and 18.00 and				Scarred in adult male reproductive organs, such as aberrant Anothio dues sustained	
Age of Cited impostance in contract in all make offspring-only at the 1000 and 3000 commotive election from the contract in the 1000 and 1000 commotive in the contract in th				The email duct, reduced absent ortifate, seminal vesicles bubb-urethral gland	
commons in 1000 and 1000 commons and ovarian intersitial zell historrowny columns at 1000 and 1000 commons and selected single cell their necrosis was noted in F1 and F4 abut makes 23 28 and 48 49) and in F4 female abuts 15 40 at 1000 commons in Jertim historrophy of the ver occurred in the F1 824 at 1000 commons and in F2 females abuts 12 42 and 18 40 at 1000 commons and in F2 females abuts 12 42 and 18 40 at 1000 commons are recommended in F2 female abuts inflating in respectively. Indising at 1000 commons are recommons and reproductive tract maintenances are no prisoning and recommons are recommons and recommons are recommons and recommons are recommons and recommons and recommons are recommendation and recommendation			* .	-dustion attound seminismus tubues, aspermist bigospermis and reduced ben's tize	
ANAILABLE COPT PEGS 1 AVAILABLE COPT BEST AVAILABLE COPT ANAILABLE COPT AVAILABLE COPT AV	•		the state of the state of	were noted impostiable topured in all male offspring-only at the 1000 and 3000	
Assignment of the state of the part and the state of the verification of the state	1000	i	i i	DETRICATE BASE TOTAL TOT	
15.50 at 3000 com. Incident Noverthops of the Ner occurred in the F1.50.4 at 1000 com. and 18.64 at 1000 com. and in FX females adults 12.24 and 35.00 at 1000 and 3000 com. The F1.50 com and 1000 com. About mak circoming gental and reproductive tract malformations, sized no offscring at 1000 into 3000 com and ferrituding certain about F1 female offscring may have been reduced at 1000 com. Phase antitioning ever obering feature of the female offscring may have been reduced at 1000 com. Phase antitioning ever obering feature of the female offscring may have been affected during, actation for F2 and F6 closes. The nominalist corease in effects in these parameters at 1000 cpm were within historical control range and may have been affected during, actation for F2 and F6 closes. The nominalist corease in effects in these parameters at 1000 cpm were within historical control range and may have be longically regulated indicated accreased weight and survival at 1000 com and 3000 cpm, respectively. A compound related increase in fitter indicated over controls occurred in deared renal petivis or involvement in puss at 3000 cpm, 46% 13% for the F1 and 5.6%.0% for the F1b. Nopoles were present on male F1a and F1b closes at 1000 and 3000 ppm (Verbal comment by BASF). Parents towarty: NOEL 50 com is 3 mg/kg/day). LEL: 300 sport (30 mg/kg/day) to 1000 cpm, p ≤ 0.01 at 1000 cpm, and Laving cell hypercases were weight increase in females (110%, p ≤ 0.01 at 1000 cpm, and Laving cell hypercases were moreased in females at 1000 cpm, and 124 at 1000 cpm, and accreased in males (125% at 1000 cpm, and females (130%, p ≤ 0.01) in celdoss of the accrease occurred in females at 1000 cpm, and cell females at 1000 cpm, and cell females at 3000 cpm, and cell females at 1000 cpm, and cell females at 3000 cpm, and cell females at 1000 cpm, and cell females at 3000 cpm, and cell females at 1000 cpm, and cell females at 1	$V = \epsilon$			request compound related single cell wer necrosis	-
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2.25 K. COO and 25 CA EL DAG mm.				3.74 or 1000 and 11.11 or 1000	į
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Core.c.assification: Minimum Thir study is acceptable under guideline 33.4 for			•		7

The atfect of the sold-dimar weight was minimal at the LDT and 50 com-

was considered to be the NCEL, however, the possible need for sperm parameter

Studies siteserved