



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

DEC 1 1989

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 7969-53. DER for an Interim Report of a Two-Generation Study of Vinclozolin on Reproduction in the rat/89/0200 (MRID No. 411228-01).

Tox. Chem. No.: 323C.
Project No.: 9-1609.
Record No.: 246454.

To: S Lewis/J Stone, PM 21
Registration Division (H7505C)

From: David G Anderson, PhD. *David G Anderson 11/21/89*
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Marion Copley, DVM *Marion Copley 11/21/89*
Section Head, Section 2
Toxicology Branch I (IRS)
Health Effects Division (H7509C).

and

Karl P Baetcke, PhD
Chief Toxicology Branch 1 (IRS)
Health Effects Division (H7509C) *Karl P Baetcke 11/21/89*

CONCLUSIONS:

These conclusions are tentative because the submitted interim report only included effects on the F0 parental generation from initial dosing to mating, and gestation and lactation period to weaning for the first litter.

Doses administered in the feed to Chbb: THOM-SPF Wistar rats; 0, 50, 300, 1000, or 3000 ppm, (Mean premating equivalents; 0, 4.9, 29.6, 96.5, or 286 mg/kg/day for males, and 0, 5.3, 31.4, 101.2, or 292 mg/kg/day for females, respectively).

Parental Effects:

NOEL: 300 ppm (30 mg/kg/day).

LEL: 1000 ppm (96 mg/kg/day) for possible male infertility, and

statistically significant male infertility at 3000 ppm. Probable female body weight decrements, decreased food consumption and efficiency of food utilization during the first week of gestation and lactation at 3000 ppm.

Offspring Effects:

NOEL: 300 ppm (25 mg/kg/day for parental females, mean dosage for gestation).

LEL: 1000 ppm (86 mg/kg/day for parental females, mean dosage for gestation) for pseudohermaphrodisim in males, developmental delays, reduced male and female pup weight, increased pup death at pd day 1-4, and throughout lactation, and increased stillbirths.

Requested Action:

The registration Division requested that the Toxicology Branch 1 (IRS) review preliminary data on a 2-generation study of reproduction with Vinclozolin.

C. COMMENTS:

This interim report on the study of reproduction in the rat suggests that the NOEL for pseudohermaphrodisim in male pups is as low as 25 mg/kg/day (300 ppm). However, the NOEL for male reproductive potential also occurred at the 300 ppm dose level (30 mg/kg/day). It is likely that the data on the fertility of males from the F1 generation when completed will occur at even lower dose levels, and that testicular histopathology will occur at even lower dose levels than the effects on the male fertility in the F1 generation. It should be noted that previous preliminary developmental toxicity studies had indicated a NOEL of 15 mg/kg/day for the same effect.

The study included the premating, mating, gestation, and lactation periods for the F0 and F1a pups. The final report can be expected during the first half of 1991.

Cover memo on a preliminary data on reproduction/A:\VINCLV13.23C\CMINTREP.RAT/D Anderson/10/28/89.

Primary reviewer: David G Anderson, PhD.
Section 2, Tox. Branch 1 (IRS) (H7509C).
Secondary reviewer: Marion P Copley, DVM.
Section 2, Tox. Branch 1 (IRS) (H7509C).

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David G Anderson 11/21/89
Marion Copley 11/23/89

DATA EVALUATION REPORT

STUDY TYPE: Interim Report on Reproduction Study/Rat/89/0200.

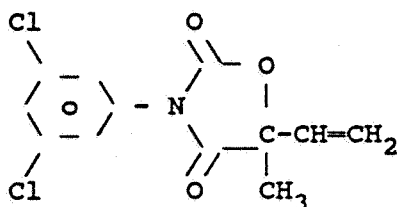
MRID No.: 411228-01.

TOX. CHEM. No.: 323C

TEST MATERIAL: Vinclozolin.

SYNONYMS: 3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidine-2,4-dione., Ronilan.

STRUCTURE:



SPONSOR: BASF Corp. Chemicals Div., Agricultural Chemicals,
100 Cherry Hill Road, Parsippany, NJ 07054.

TESTING FACILITY: BASF Aktiengesellschaft, Dept. Toxicology, 6700
Ludwigshafen/Rhein, West Germany.

STUDY NO.: 89/0200, BASF Project No. 71R0375/88053.

REPORT TITLE: Preliminary Information, Two-generation
Reproduction Toxicity Study of Reg. No. 83-
258 in Rats. Dietary Administration.

AUTHOR(S): J Fellwig.

REPORT ISSUED: May 19, 1989.

CORE GRADE: Supplementary because the report is an interim
report.

CONCLUSIONS:

These conclusions are tentative because of the interim nature of the submitted report; included were effects on the F0 parental generation from initial dosing to mating, and gestation and lactation period for the first litter through weaning, only.

Doses administered in the feed to Chbb: THOM-SPF Wistar rats; 0, 50, 300, 1000, or 3000 ppm, (Mean pre-mating equivalents; 0, 4.9, 29.6, 96.5, or 286 mg/kg/day for males, and 0, 5.3, 31.4, 101.2, or 292 mg/kg/day for females, respectively).

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LEL: 1000 ppm (96 mg/kg/day) for possible male infertility, and statistically significant male infertility at 3000 ppm. Probable female body weight decrements, decreased food consumption and efficiency of food utilization during the first week of gestation and lactation at 3000 ppm.

Offspring Effects:

NOEL: 300 ppm (25 mg/kg/day for parental females, mean dosage for gestation).

LEL: 1000 ppm (86 mg/kg/day for parental females, mean dosage for gestation) for pseudohermaphroditism in males, developmental delays, reduced male and female pup weight, increased pup death at pd day 1-4, and throughout lactation, and increased stillbirths.

A. MATERIALS:

1. Test compound: Vinclozolin, technical. Purity >about 99.2%,
2. Test animals: Species: Rats, Strain: Wistar (Chbb: THOM-SPF), Weight: males-120-170 g, females-100-150 g, Source: Dr. K. Thomae GmbH, Biberach/Riss, FGR.
3. Environment: Humidity 30-70%. Temperature 20-24 degrees C. Light:dark = 12:12.

B. SUMMARY OF FINDINGS:

Vinclozolin was administered in the feed to approximately 25 Wistar (Chbb: THOM-SPF) rats/sex/group at 0, 50, 300, 1000, or 3000 ppm throughout a 2-generation study on reproduction. This is a interim report of the findings which include the first litter to weaning. Although, parental body weight gain decrements occurred during the first 10 weeks of the premating period (9.8% in males and 5.2% in females), food consumption was correspondingly lowered such that there was no evidence of reduced efficiency of food utilization for males or females rats during the premating period. During the first week of the gestation for the Fla litters body weight, food consumption and food efficiency were all reduced compared to controls at the HDT. During the first week of lactation for the Fla litters body weight, food consumption and food efficiency were all reduced from control values at the HDT. These toxic effects on dams may have been expressed due to the extra stress of gestation and lactation. However, even under these stresses, the later part of gestation and lactation demonstrated no differences in food efficiency from control values. Both body weights and food

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consumption were statistically significantly reduced in parental females during gestation and lactation at the HDT.

Male fertility was slightly reduced at 1000, and 3000 ppm dose levels according to the fertility index but not the mating index. The fertility index was defined as $[(\text{number of males proving to be fertile})/(\text{number of males placed with females})] * 100$. The mating index was defined as $[(\text{number of males with confirmed mating})/(\text{number males placed with females})] * 100$.

The results indicate that the males mated but that the sperm was probably inadequate for fertilization at the HDT and probably also at the next lower dose level as well. However, it should be noted that a female component could have contributed to the apparent male infertility as well. The data also indicated that longer cohabitation was required for mating in some animals at the HDT. This latter effect may not be exclusively due to the male component.

The results from the parental animals and the offspring are presented in Table A.

Fewer offspring were delivered at the HDT, $p < 0.01$. There were also fewer live births, $p < 0.01$, and more stillbirths, $p < 0.01$ at the HDT. A statistically significant number of pups died and were cannibalized prior to weaning. Pup appeared to die most frequently on post gestational days (pd) 1-4, but pup deaths occurred throughout the lactational period. Male and female pup weights were statistically lower from pd 4 to pd 21 at the two highest dose levels, and throughout lactation at the HDT.

Developmental stages such as auditory canal opening on pd day 13, eye opening on post partum day 15, pinna unfolding, gripping-reflex, acoustical startle, and pupil constriction were determined. Only auditory canal opening and the pinna unfolding were affected (See Table A). The organ/skeleton observations noted were not specifically identified but probably included: dilated renal pelvis, dilated ureters, hypoplasia of the testes, absence of hind legs, incisors sloped, and indefinite external sex. The indefinite external sex syndrome was called pseudohermaphrodism (decreased anal-genital distance in males only) in previous studies.

The final report can be expected during the first half of 1991.

C. COMMENTS.

This interim report on the study of reproduction in the rat suggests that the NOEL for pseudohermaphrodism in male pups may be as low as 25 mg/kg/day (300 ppm). However, the NOEL for male reproductive potential also occurred at the 300 ppm dose level (30 mg/kg/day). It is likely that the data on the fertility of males from the F1 generation when completed will occur at even lower dose levels, and that testicular histopathology will occur at even lower dose levels than the effects on the male fertility

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in the F1 generation. It should be noted that previous preliminary developmental toxicity studies had indicated a NOEL of 15 mg/kg/day for the same effect.

Table A.

Fertility and mating indexes of males producing the Fla litters, incidence of pseudohermaphrodisim in male pups, developmental delays, and total incidences of externally observed malformations.

Dose groups (ppm)	0	50	300	1000	3000
Males placed with females	24	24	24	24	24
Males without confirmed mating	0	0	0	0	1
Mating index	100%	100%	100%	100%	95.8%
Infertile males	1	0	0	2	7*
Males proving fertility	23	24	24	22	17*
Fertility index	95.8%	100%	100%	91.7%	70.8%
Male pups, obvious pseudohermaphrodisim					
pups	0%	0%	0%	5.1%***	42.9%***
litters	0%	0%	0%	31.8%***	69.2%***
Auditory canal opening					
litters tested	22	24	24	21	10
pups tested	289	311	315	302	70
pups reaching criteria	97.2%	92.6%	99.0%	89.4%***	68.6%***
Total pup external organ/skeletal obs.					
pup incidence	1.9%	3.5%	2.4%	8.7%***	49.2%***
litter incidence	21.7%	20.8%	25.0%	59.1%*	76.9%***

* Statistically significant, $p < 0.05$.

** Statistically significant, $p < 0.01$.

DER for the interim report of the study on reproduction/
B:\VINCLOZO3.23C\INTREPRO.RA2/D Anderson/10/25/89.

Tox. Cem. No. 323C, Vinclozolin, 3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidine-2,4-dione
Accession/ File Last Updated: 10/27/89 Tox

Study/Lab/Study#/Date Material MRID No.

Prelim. 2-Gen. Vincloz 411228-01
R-pro/Rat olin,
BASF Germany Tech.,
89/0200 99.2%
5/19/89.

Results

Category

Doc. No.

Interim report: Includes the NA
F0 & 1st litter to weaning.

Supplementary
because it is
an interim
report.

Doses adm. in the feed to
Chbb: THOM-SPF Wistar rats; 0,
50, 300, 1000, or 3000 ppm,
(Mean premating equivalents;
0, 4.9, 29.6, 96.5, or 286
mg/kg/day for males, and 0,
5.3, 31.4, 101.2, or 292
mg/kg/day for females).

Parental Effects:

NOEL: 300 ppm (30 mg/kg/day).
LEL: 1000 ppm (96 mg/kg/day)
for poss. male infertility, &
male infertility at 3000 ppm.
Probable female BWT decr.,
decr. food cons. & eff. of
food util. during the first wk
of gest. & lact. at 3000 ppm.

Offspring Effects:

NOEL: 300 ppm (25 mg/kg/day
for parental females, av.
dosage for gestation).
LEL: 1000 ppm (86 mg/kg/day
for F0 females, av. dosage for
gest.) for pseudohermaphroditism
in males, devel. delays, red.
male and female pup wt, incr.
pup death at pd day 1-4, and
throughout lact., and incr.
stillbirths.

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