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MEMORANDUM

SUBJECT: Reproductive and Developmental Toxicity Peer Review of Vinclozolin, December 3, 1997.

PC Code: 113201 Tox Chem No: 323C

TO: K. Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

THRU: David Anderson
Chairman, Reproductive/Developmental Toxicity Committee
Health Effects Division (7509C)

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BACKGROUND: The Health Effects Division (HED) Reproductive and Developmental Toxicity Assessment Review Committee's first meeting to evaluate the weight-of-evidence for developmental and reproductive toxicity of vinclozolin was held October 20, 1993.

At the first meeting, the Committee concluded that the critical effect level for risk assessments for developmental toxicity was 3 mg/kg/day (lowest dose tested) based upon decreased anogenital distance in males in a rat developmental study (Gray study, 1993, MRID 43170501).

A second meeting to evaluate the uncertainty factor was held on January 23, 1997. The *ad hoc* committee decided that an uncertainty factor of 100x was appropriate (William Burnam memo, 2/21/97).

The third meeting was held by the Reproductive and Developmental Toxicity Committee on December 3, 1997 to determine a suitable endpoint for the regulation of potential developmental effects of vinclozolin. The third meeting was held because new material had become available.

A statistical re-analysis of the anogenital distance data using

multiple comparison tests was made by Health Effects Division Science Analysis Branch. The re-analysis determined that decreased anogenital distance was statistically significant at 12 mg/kg/day and above (Mary Marion memo, 11/19/97).

In addition, two new studies with vinclozolin submitted by the registrant (BASF, 1997, MRID 43395701 and 43395702, Doc 012402) reported decreased anogenital distance in males at 200 mg/kg/day but not at 12 mg/kg/day.

SUMMARY:

The newly available data and previously considered data regarding the developmental and reproductive toxicity of vinclozolin were evaluated by the Reproductive and Developmental Toxicity Committee in a weight-of-the evidence approach.

The Committee concluded that the NOEL for developmental toxicity was 6 mg/kg/day and the LOEL for developmental toxicity was 12 mg/kg/day. The LOEL was based upon statistically significant decreases in male anogenital distance (Gray study) and increased hairless areas, reported as areolas (BASF studies).

The Committee reaffirmed the previous decision to remove the 10x uncertainty factor for protection of infants and children. This decision was reached because the mechanism for developmental toxicity is understood and a very sensitive indicator of toxicity was selected. A summary of the weight-of-evidence considerations follows in a separate section of the memo.

DEVELOPMENTAL AND REPRODUCTIVE STUDIES REVIEWED:

1. Gray, L.E. (1996). Internal EPA Report on: Update on Antiandrogenic Effects of the Fungicide Vinclozolin on Sex Differentiation of the LE Hooded Rat. EPA, HEERL, RTP, NC. MRID # unassigned. (6/10/96). Prepublication report.

This prepublication report is from a presentation by Dr. Gray to the EPA Science Advisory Panel (10/29/96) and consisted of summary tables and 3 journal articles. This report is a continuation of data made available by Gray in 1993.

Vinclozolin was administered to pregnant Long Evans Hooded rats by gavage in corn oil from gestation day 14 to postnatal day 3 at doses of 0, 3, 6, 12, 25, 50, or 100 mg/kg/day. Anogenital distance was measured in 4 blocks to allow one person to make all

the anogenital measurements. Organ weights, sperm counts, and other effects on the male reproductive system were also reported (see Table 1). Only 2 or 3 litters per treatment group were necropsied. Results from other studies by the author at the above doses as well as 200 mg/kg/day were also summarized.

Decreased anogenital distance (AGD) occurred with increasing doses of vinclozolin (Table 1). The mean AGD was 3.43, 3.18, 3.29, 3.23, 3.05, 2.55, and 2.10 mm for the 0, 3, 6, 12, 25, 50, and 100 mg/kg/day groups, respectively. Mean AGD in the 4 control groups varied widely, from 3.09 to 3.61 mm.

Decreased AGD is an anti-androgenic effect which occurs in rats, but the relevance to humans is unknown. The study author believed that decreased AGD was significant at the low dose of 3 mg/kg/day, however, a statistical analysis by the HED Science Analysis Branch using multiple comparison tests reported significance at 12 mg/kg/day and above (Mary Marion memo, 11/19/97).

An increase in nipple areas occurred with increasing doses of vinclozolin (see Table 1), however, no histology was apparently performed. The frequencies for the nipple areas were 4.9%, 17.4%, 33.1%, 55.3%, 49%, 100% and 100% for the 0, 3, 6, 12, 25, 50, and 100 mg/kg/day, respectively.

Other effects on the male reproductive system included decreased seminal vesicle and prostate weights at 25 mg/kg/day and above; vaginal pouches, increased number of nipples, hypospadias, decreased sperm counts, and decreased fertility at 50 mg/kg/day and above; decreased caudal epididymal weight and increased number of ectopic testes at 100 mg/kg/day (Table 1).

The report included results from other studies by the author showing increased serum luteinizing hormone at 5 mg/kg/day and above; delayed puberty at 15 mg/kg/day and above; bladder stones, increased mortality, seminiferous tubular atrophy, testicular and epididymal granulomas, prostate agenesis, and increased serum testosterone at 100 mg/kg/day and above.

TABLE 1. SELECTED RESULTS FROM EARL GRAY'S VINCLOZOLIN SAP PRESENTATION

	DOSE (mg/kg/day)						
	0	3	6	12	25	50	100
Block 1 AGD in 2-day old LE pups[1]	3.40	3.23	3.24	2.98	2.85	2.55	2.10
Block 2 AGD in 2-DAY OLD LE pups	3.09	2.92	2.89	---	--	---	---
Block 3 AGD in 2-DAY OLD LE pups	3.61	3.12	3.50	3.17	3.12	---	---
Block 4 AGD in 2-DAY OLD LE pups	3.59	3.58	3.49	3.45	2.99	---	---
Blocks 1-4 AGD. 2-DAY OLD LE pups[2]	3.43	3.18	3.29	**3.23**	**3.05**	**2.55**	**2.10**
MALE PUPS/LITTER NECROPSIED at 12 months[3]	12/5	12/3	13/3	10/2	6/2	6/3	2/2
BODY WEIGHT (g)	660	667	655	717	701	716	643
SEMINAL VESICLES (g)	2.25	2.25	1.96*	2.18	**1.92****	**1.78****	**0.66****
VENTRAL PROSTATE (mg)	663	565	522	494	**359***	**275****	**69****
CAUDAL EPIDIDYMAL WT (mg)	322	310	294	319	300	287	**213****
CAUDAL EPIDIDYMAL SPERM COUNT x10^6	155	134	133	152	153	150	**67***
TESTIS SPERMATIDS (x10^6)	218	213	206	219	223	191	**175**
HYPOSPADIAS	0	0	0	0	0	**3/6**	**2/2**
EJACULATED SPERM of <10^6	0/14	0/13	1/13	0/10	0/6	**3/6**	**3/3**
FERTILITY	100%	100%	92%	100%	100%	**50%***	**0%****
EJACULATED SPERM (x10^6)	1.84	1.87	1.82	2.03	1.93	**0.18****	**0.0****
NO. ECTOPIC TESTES/MALES EXAM.	0/22	0/13	0/13	0/14	0/6	0/11	**2/10**
NO. VAGINAL POUCH/EXAMINED	0/22	0/13	0/13	0/14	0/6	**1/11**	**6/11**
NO. NIPPLES (12 months of age)	0	0	0.15	0.2	0	**4.1****	**6.0****
NIPPLE AREAS (areolae) in 13-day old pups (histo not performed in all doses)[4]	4.9%	17.4%	33.1%*	55.3%*	49%*	100%*	100%*

[1] Table 2, page 4. 2-day old male LE pups. [2] Values differ slightly between Gray SAP presentation and Gray, et al, 1993
[3] Table 4, page 6. Male offspring, necropsied at 12 months.
[4] Figure 2. 13-day old male offspring, male LE pups, Blocks 1-4.
* $p<0.05$ ** $p<0.01$ according to study report

TABLE 1, continued. SELECTED RESULTS FROM EARL GRAY'S VINCLOZOLIN SAP PRESENTATION

	DOSE (mg/kg/day)				
	0	5	15	25	100
AGE AT PREPUTIAL SEPARATION[1]	40.7	41.1	41.8*	44.4*	47.8*
CAUDAL EPIDIDYMAL WT[2]	291	278	235*	248*	211*
PAIRED EPIDIDYMAL WT[3]	1.57	1.56	1.44*	1.49	1.35*
SERUM LH (ng/mL)[4]	0.15	0.25*	0.33*	0.36*	0.42*
SERUM TESTOSTERONE (ng/mL)[5]	2.24	1.82	1.96	1.83	3.27*

[1]from Figure 7, F0 male LE rats
[2]from Figure 8, F0 male LE rats
[3]from Figure 9, F0 male LE rats
[4]from Figure 10, F0 male LE rats
[5]from Figure 11, F0 male LE rats
* $p<0.05$ according to study report

2. Hellwig, J. (1997) Reg No. 83 258 - Pre-/postnatal toxicity Study in Long Evans Rats after Oral Administration (Gavage) Dept of Toxicology BASF Akiengesellschaft, FRG. MRID# 44395702. 9/1/97. Unpublished.

and **Hellwig, J. (1997). (1997). Reg No. 83 258 - Pre-/postnatal toxicity Study in Wistar Rats after Oral Administration (Gavage). Dept of Toxicology BASF Akiengesellschaft, FRG. MRID# 44395701. 9/1/97. Unpublished.**

The registrant (BASF) sponsored developmental studies in LE and Wistar rats following Dr. Gray's protocol, including postnatal dosing to include the entire period of sexual differentiation. A similar vehicle (olive oil compared to corn oil) was used. The 2 studies were an attempt to duplicate Dr. Gray's report of decreased anogenital distance (AGD) in LE rats at the low dose of 3 mg/kg/day.

Vinclozolin was administered to pregnant LE and Wistar rats by gavage in olive oil from gestation day 14 to postnatal day 3 at doses of 0, 1, 3, 6, 12, or 200 mg/kg/day in LE rats and 0, 3, 12, or 200 mg/kg/day in Wistar rats. AGD was measured on live pups on day 2, as in the Gray study. About half the male pups were then sacrificed, fixed in Bouin's solution and the AGD remeasured. The study was conducted in 2 blocks separated by 1 day. Results are shown in Table 2.

The only biologically significant maternal effect was decreased

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weight gain in Wistar rats (-90%), accompanied by decreased food consumption in the 200 mg/kg/day group. The maternal NOEL is 12 mg/kg/day and the maternal LOEL is 200 mg/kg/day based on decreased weight gain and food consumption in LE rats.

The AGD or AGD-index were statistically significantly reduced only at 200 mg/kg/day in fixed and live pups from each strain. In addition, all the male pups in both strains had ambiguous genitalia at the 200 mg/kg/day dose level only. Also in both strains at 200 mg/kg/day, live birth index was decreased (Wistar & LE: 88%-83% versus 98%-93% in controls, respectively) and number of stillborn were increased (Wistar & LE: 12% & 17% versus 2.2% & 6.8% in controls, respectively) as well as pups that died (38% & 15% versus 1.5% & 8.1% in controls, respectively) and decreased survival day 0 to 2 (58% & 65% versus 98% & 92% in controls, respectively). Day 2 pup weights were reduced (25%, male, and 27%, female, of control in Wistar rats and at day 22 they were reduced (14% of control, $p \leq 0.05$ in Wistar female rats, but only nominally reduced from control in Long Evans rats at day 2 and day 22) at 200 mg/kg/day. The areolas/nipple anlagen was present on a litter basis (statistical analyses not conducted) and % pup basis ($p \leq 0.05$) at 200 and 12 mg/kg/day in both strains (48.1% versus 11.3% in control in Wistar pups and 61.3% versus 31.1% in control in Long Evans pups).

The developmental NOEL in the current study is 6 mg/kg/day and the developmental LOEL is 12 mg/kg/day, based on significant increase in areolas/nipple anlagen in both strains.

The study is unacceptable for a non-guideline perinatal study of developmental toxicity in rats. Because of lack of significant effects on AGD at lower dose levels, the acceptability of the study must wait for confirmation of the analytical concentrations of vinclozolin dosages.

TABLE 2. SELECTED RESULTS FROM BASF VINCLOZOLIN STUDY - LONG EVANS RATS

	DOSE (mg/kg/day)					
	0	1	3	6	12	200
AGD day 2 live pups	3.72	3.86	3.67	3.54	3.70	**2.48****
AGD day 2, Bouin fixed pups	3.13	3.09	2.97	2.99	3.03	**1.74****
AGD day 22, live pups	15.69	15.42	15.01	14.95	14.63	**11.70****
AG Index day 22, live pups	0.26	0.26	0.28	0.27	0.27	**0.20**
% males with areolas day 12 (no histology performed)	31.1	36.4	44.5	35.7	**61.3***	**100.0****

SELECTED RESULTS FROM BASF VINCLOZOLIN STUDY - WISTAR RATS

	DOSE (mg/kg/day)					
	0	1	3	6	12	200
AGD day 2, live pups	3.93	---	4.20	---	3.94	**2.07****
AGD day 2, Bouin fixed pups	3.21	---	3.31	---	3.25	**1.68****
AGD day 22 live pups	16.89	---	16.34	---	17.11	**10.93****
AG Index day 2 live pups	0.51	---	0.51	---	0.49	**0.36****
AG Index day 2, Bouin fixed pups	0.41	---	0.41	---	0.40	**0.30****
AG Index day 22, live pups	0.27	---	0.27	---	0.26	**0.20****
% males with areolas day 12 (no histology performed)	11.3	---	8.3	---	**48.1***	**100.0****

* $p \leq 0.05$ ** $p \leq 0.01$

3. **Qualitative Risk Assessment, Vinclozolin (Mary Marion memo, 11/19/97).** This is a reanalysis of anogenital distance (AGD) results from the Gray developmental study using multiple comparison tests. Statistical significance was reported for the 12 mg/kg/day and above groups.

4. **Transmittal of the Final Report of the FIFRA Scientific Advisory Panel Meeting held October 29-30, 1996 (Larry Dorsey memo, 12/6/96).** The Scientific Advisory (SAP) Panel reported that decreased anogenital distance (AGD) in rats is the most sensitive endpoint for anti-androgenic effects of vinclozolin. The SAP Panel said that decreased AGD alone had uncertain significance, but was important when other anti-androgenic effects occurred.

5. **Developmental and Reproductive Toxicity Peer Review of Vinclozolin (Elizabeth A. Doyle and David G. Anderson memo, 10/7/94).** This memo reported conclusions of the first meeting of the HED Peer Review Committee for Reproductive and Developmental Toxicity regarding developmental toxicity of vinclozolin held on October 20, 1993.

At this meeting, the Committee concluded that the critical effect level for risk assessments for developmental toxicity was 3 mg/kg/day (lowest dose tested) based upon decreased anogenital distance in males in a rat developmental study (Gray study, 1993, MRID 43170501).

A number of developmental and reproductive studies were reviewed at this meeting. Tables 3-7 summarize qualitative results of these studies as described in the Peer Review memo.

6. **RfD Peer Review Report of Vinclozolin (Henry Spencer memo, 12/21/95).** This memo reported conclusions of the 8/3/95 RfD Peer Review Committee. The RfD was 0.012 mg/kg/day based upon a NOEL of 1.2 mg/kg/day in the 2-year feeding/carcinogenicity study in rats (MRID 43254702). The LOEL of 2.3 mg/kg/day was based upon increased incidence of lenticular degeneration of the eyes. An uncertainty factor of 100x was used to account for interspecies extrapolation and intraspecies variability.

The RfD report described the **chronic 1-year dog study**. In the chronic dog study the NOEL was 2.4 mg/kg/day and LOEL was 4.8 mg/kg/day based upon increased relative testes weight, prostate atrophy, and increased bilirubin in males.

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In the **rabbit developmental study**, groups of 15 or 20 Himalayan Chbb:HM rabbits received doses of 0, 50, 200, 400, or 800 mg/kg/day vinclozolin in CMC in water from gestation day 6 through 28. The maternal NOEL was 50 mg/kg/day and the maternal LOEL was 200 mg/kg/day based upon increases in liver and adrenal weights. The developmental NOEL was 200 mg/kg/day and the developmental LOEL was 400 mg/kg/day based upon early resorptions (increased postimplantation loss), fetal weight increase, decreased live litter size, and possibly increased skeletal anomalies. No anti-androgenic effects were seen.

7. Toxicology Endpoint Selection Document, revised 6/2/97, for the meeting of 8/15/95. This document includes endpoints "for the general population (including infants and children) and for females 13+ years".

8. DER for the full report of four developmental toxicity studies of vinclozolin in the rat (David Anderson memo, 5/7/90, Document 007909). This memo is the review for 4 developmental studies with vinclozolin (MRID 41132201). These 4 studies were conducted to verify decreased anogenital distance (AGD) in male rats in a study originally conducted in Japan.

The NOEL for developmental toxicity was 15 mg/kg/day, the lowest dose tested and the LOEL was 50 mg/kg/day, based on decreased AGD in male rats. The maternal NOEL was <600 mg/kg/day and the maternal LOEL was 600 mg/kg/day based on increases in liver and adrenal weights; organ weights were not determined at lower weights.

9. Kelce, W.R., et al. (1994). Environmental Hormone Disruptors: Evidence that Vinclozolin Developmental Toxicity is Mediated by Antiandrogenic Metabolites. Toxicology and Applied Pharmacology 126. 276-285

This journal article was part of the Gray report. The article reported results of *in vitro* studies into possible mechanisms for the developmental abnormalities caused by vinclozolin. Two vinclozolin metabolites, M1 and M2, were found to be effective antagonists to the androgen receptor while parent vinclozolin was a weak competitor. Neither vinclozolin, M1, nor M2 inhibited testosterone synthesis.

The report showed that vinclozolin metabolites, M1 and/or M2, are

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competitive antagonists at the androgen receptor. This competitive inhibition is the likely mechanism for the anti-androgenic effects seen in the *in vivo* studies.

WEIGHT-OF-THE-EVIDENCE CONSIDERATIONS:

1. Numerous effects in **rat** developmental and reproductive studies demonstrated the anti-androgenic effects of vinclozolin at the following dose levels.

2. Decreased anogenital distance (AGD) in male rats occurred as low at **12 mg/kg/day** with a NOEL of 6 mg/kg/day. Alone, this effect would be of uncertain concern for human risk assessment, but when taken into consideration with other effects occurring at higher dose levels, it provides a sensitive indicator for anti-androgenic effects.

3. There was consideration of a lower NOEL based on possibly decreased AGD at lower doses in the Gray study. A lower NOEL was not selected because:

> The decrease in AGD in the Gray study was statistically significant (using multiple comparison tests) at 12 mg/kg/day and above.
>
> There was wide variation for AGD in the different control groups in the Gray study and a larger number of litters in each block in the BASF study.
>
> Not all data from the Gray study was available for review.

4. Also supporting the evidence for an anti-androgenic effect at 12 mg/kg/day was an increased number of "areolas" (BASF studies) in male rats. Since these areas were not examined histologically, they should be described as "hairless areas" until confirming histopathology has been performed, although they do provide supportive evidence for an anti-androgenic effect at 12 mg/kg/day.

The Gray study reported an increased number of "nipples" (statistically significant) at 50 and 100 mg/kg/day. Although these animals received a necropsy, it could not be determined whether the nipples received a histological examination.

The Gray study also reported a dose-related increase in "nipple areas" in 13-day old pups in all treatment groups. The lower dose levels were not examined histologically.

The reports of "nipples", "nipple areas", and "areolas" give support for a NOEL of 6 mg/kg/day based on decreased AGD, although histological confirmation, expected from both laboratories will provide stronger evidence.

5. In general, the dose-response curve was shallow. Following are the main developmental effects reported in the developmental and reproductive studies:

Occurring at **5-15 mg/kg/day** and above in male rats was an increase in serum luteinizing hormone.

At **25-31 mg/kg/day** and above in male rats, variations in parental and/or offspring organ weights (adrenal, epididymis, liver, testis, seminal vesicles, and ventral prostate) occurred.

At **50 mg/kg/day** and above in male rats, an increase in hypospadias and a decreased sperm count in offspring occurred.

At **101 mg/kg/day** and above, offspring in the rat reproduction study sired no pups due to functional malformations in males. Abnormalities in males included pseudohermaphroditism, atrophic seminiferous tubules, reduced penis size, aberrant Wolffian duct, bilateral Muellerian duct, and reduced or absent prostate, seminal vesicle, or bulbourethral gland. In female rats, abnormalities included ovarian lipidosis and ovarian interstitial cell hypertrophy.

At **300-400 mg/kg/day**, dilated renal pelvis, dilated ureter, hydroureter, hydronephrosis, 14th rib, and delays in maturation also occurred.

In the **rabbit** developmental study, developmental effects seen at 400 mg/kg/day and above included an increase in early resorptions with a resulting decreased litter size, and skeletal anomalies. At 800 mg/kg/day, abortions also occurred. No anti-androgenic effects were noted.

6. The developmental and reproductive effects were evident in the rat studies, with no anti-androgenic effects in the rabbit developmental study. However, the mechanism for anti-androgenicity is believed to be antagonistic binding to the androgen receptor by vinclozolin metabolites. Since the androgen receptor is widely conserved across species lines, anti-androgenic effects would be expected in humans. In addition, in the chronic dog study, increased relative testes weight and prostate atrophy occurred.

With the above considerations, and careful evaluation of all the data submitted regarding developmental and reproductive toxicity of vinclozolin, the NOEL for developmental toxicity was determined to be 6 mg/kg/day with a LOEL for developmental toxicity of 12 mg/kg/day. Since the mechanism for the effect is understood, and

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a very sensitive indicator for developmental toxicity was selected, it was felt that the 10x uncertainty factor for protection of infants and children should be removed.

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APPENDIX

Tables 3-7 are qualitative summaries of studies reviewed in the first meeting of the Reproductive and Developmental Peer Committee (10/20/93).

TABLE 3. VINCLOZOLIN RAT GAVAGE DEVELOPMENTAL STUDY (MRID 41132204)

	DOSE (mg/kg/day)								
	0	15	50	50	100	200	400	600	1000
	MATERNAL TOXICITY								
↑ adrenal, liver wts	-	NT	NT	NT	NT	NT	NT	+	+
	DEVELOPMENTAL TOXICITY								
↓ AGD distance	-	-	+	+	+	+	+	+	+
dilated renal pelvis	-	-	-	-	-	-	+	+	+
hydroureter	-	-	-	-	-	-	+	+	+
14th rib	-	-	-	-	-	-	+	+	+
↓ fetal wt	-	-	-	-	-	-	-	-	+

TABLE 4. VINCLOZOLIN RAT DERMAL DEVELOPMENTAL STUDY (MRID 41413001)

	DOSE (mg/kg/day)			
	0	60	180	360
	MATERNAL TOXICITY			
↑ adrenal wts	-	+	+	+
↑ liver wts	-	-	-	+
	DEVELOPMENTAL TOXICITY			
↓ AGD distance	-	-	+	+
dilated renal pelvis	-	-	-	+
hydroureter	-	-	-	+

- means negative, + means positive

TABLE 5. VINCLOZOLIN RAT FEEDING DEVELOPMENTAL STUDY (MRID 41413001)

	DOSE (mg/kg/day)			
	0	23	111	394
	MATERNAL TOXICITY			
↑ adrenal wts	-	+	+	+
↓ body wt	-	-	-	+
↓ pituitary wt	-	-	-	+
↑ ovarian wts	-	-	-	+
	DEVELOPMENTAL TOXICITY			
↓ AGD distance	-	-	+	+
external pseudohermaphroditism	-	-	-	+
↓ fetal wt	-	-	-	+
dilated ureter	-	-	-	+
hydronephrosis	-	-	-	+
delayed ossification	-	-	-	+

- means negative, + means positive

TABLE 6. VINCLOZOLIN RABBIT GAVAGE DEVELOPMENTAL STUDY (MRID 41709301)

	DOSE (mg/kg/day)				
	0	50	200	400	800
	MATERNAL TOXICITY				
↑ liver and adrenal wts	-	-	+	+	+
↓ food consumption	-	-	-	+	+
↓ body wts	-	-	-	+	+
	DEVELOPMENTAL TOXICITY				
anti-androgenic effects	-	-	-	-	-
early resorptions	-	-	-	+	+
↓ live litter size	-	-	-	+	+
skeletal anomalies	-	-	-	+	+
abortions	-	-	-	-	+

- means negative, + means positive

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TABLE 7. VINCLOZOLIN RAT REPRODUCTION STUDY (MRID 42581301)

	DOSE (mg/kg/day)				
	0	5	31	101	290
	PARENTAL TOXICITY				
↓ epididymal wt	-	-	+	+	+
↑ testis wts	-	-	-	+	+
Leydig cell hyperplasia	-	-	-	+	+
lenticular degeneration (F)	-	-	-	+	+
↑ liver wts (F)	-	-	+	+	+
single-cell liver necrosis	-	-	-	-	+
↑ adrenal wts	-	-	-	+	+
adrenal lipidosis (F)	-	-	-	+	+
pituitary vacuolation cells (castration cells) (M)	-	-	-	-	+
	OFFSPRING TOXICITY				
↓ epididymal wts	-	-	+	+	+
↑ testis wts	-	-	+	+	+
Leydig cell hyperplasia	-	-	+	+	+
lenticular degeneration	-	-	-	-	+
↑ liver wts	-	-	+	+	+
single-cell liver necrosis	-	-	-	-	+
↑ adrenal weights	-	-	+	+	+
pseudohermaphroditism	-	-	-	+	+
functional deficits in male reproductive organs [1]	-	-	-	+	+
hypospadia	-	-	-	+	+
ovarian lipidosis	-	-	-	+	+
ovarian interstitial cell hypertrophy	-	-	-	+	+
delayed pinna unfolding, eye opening, auditory canal opening	-	-	-	-	+
dilated renal pelvis or hydroureter	-	-	-	-	+
↓ body weight	-	-	-	-	+
↓ pup survival	-	-	-	-	+

[1] **Aberrant Wolffian duct; bilateral Muellerian duct; reduced or absent prostate, seminal vesicle, or bulbourethral gland; atrophic seminiferous tubules, aspermia/oligospermia, reduced penis size.**

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