

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

REVISED 7/18/96

Chemical Name: Vinclozolin ✓

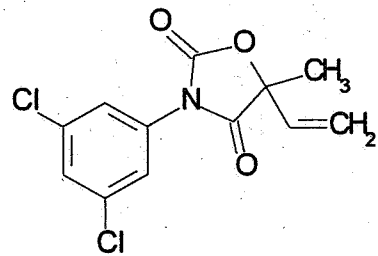
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The Health Effects Division Less-Than-Lifetime/Peer Review Committee considered the toxicity data available for this chemical at a meeting held August 15, 1995. Based on a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessments not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology data are presented. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Chemical Name: Vinclozolin



Reviewer:

Date: 8/1/96.

Section Head:

Date:

Branch Chief:

Date:

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Background:

The group met to discuss the Intermediate Occupational and Residential Exposure toxicity endpoint (1 week to several months) in response to a rebuttal by the registrant, BASF. The original endpoint selected was the same for the intermediate and long term

exposure endpoints, which was 4.8 mg/kg/day based on a NOEL of 1.2 mg/kg/day from a rat two year chronic study (MRID# 43254702) and a rat carcinogenicity study (MRID# 43254703) corrected for dermal absorption of 25% (i.e., 1.2 mg/kg/day/0.25 = 4.8 mg/kg/day).

The registrant suggested that a rat dermal developmental study (MRID# 43703301, NOEL = 60 mg/kg/day) or a 90-day rat feeding study (MRID# 42728801, NOEL = 4.4 mg/kg/day) corrected for dermal absorption would be acceptable for estimating intermediate term worker exposure (i.e., 4.4 mg/kg/day/0.25 = 17.6 mg/kg/day).

The following document presents the reevaluation (meeting of 7/18/96) of the toxicity endpoints for vinclozolin with reasons. Only the short term and intermediate term occupational and residential exposure endpoints have been changed from the previous TES document of 11/21/95.

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Dermal Absorption Data: Hawkins, DR et al. (January 3, 1991) MRID# 41824309, Study No. 91/10059 conducted by Huntingdon, England for BASF. HED Doc# 010261.

The data in the following Table 1 was extracted from Hawkins et al. (1991) and HED Doc# 010261. This dermal absorption data are required only for the route-to-route calculation using the Gray et al. (1993) data for short term, intermediate term and the 2-year oral chronic study in rats (MRID# 43254702) for the long term occupational and residential exposure assessment. The executive summaries for the studies to be used for short term, and intermediate term occupational and residential exposure are presented under the section on Acute Dietary Endpoint and long term occupational and residential exposure are presented under Long Term Occupational and Residential Exposure presented later in this document.

Since the percentage dermal absorption decreases with increasing dermal dose level to the skin, the percentage dermal absorption for a calculated human occupational and residential exposure should be found from the data in Table 1 at the corresponding dermal exposure in mg/kg. The calculated human exposure to the skin can be found in Row 1 or 2 of Table 1 and correspondingly the percentage absorption can be found in Row 4 or by plotting the data in Row 4 vs. dose level to determine the percentage for intermediate and long term exposure values. This will likely yield an overly conservative estimate of the human dose, but it is believed to be adequate for a preliminary assessment. If an unsatisfactory MOE results, then refinement of the percentage dermal absorption figures may be necessary.

If human dermal exposure is less than 0.10 mg/kg/day, then the Toxicology Branch-1 should be consulted for the appropriate percentage to use in the calculations.

Example calculation for an short and intermediate term occupational or residential human dermal exposure of 0.13 mg/kg/day\*: Human dermal dose (mg/kg/day) = 0.13 mg/kg/day X 25.2%/100 = 0.0328 mg/kg/day. MOE = NOEL/human exposure = (3 mg/kg/day)/(0.0328 mg/kg/day) = 91. \*Values not in Table 1 can be obtained from plotting the percentage absorption vs. exposure level in Table 1.

Table 1

Percentage dermal absorption and skin retention at various dermal doses of vinclozolin at 10 hours after a single application. Data taken from a dermal absorption study of vinclozolin on rats (MRID# 41824309).

Dose level (mg/kg)	0.13	1.3	13	130
Dose level (mg/cm <sup>2</sup> )	0.002	0.02	0.2	2.0
Percentage vinclozolin absorbed 10 hours after a single application (% of mg/kg)				
% absorbed through and retained in treated skin	25.2	19.5	6.16	4.42

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Acute Dietary Endpoint (One day)

Studies Selected - Guideline Nos.: Gray et al. (1993) and Kelce et al. (1993) research of the anti-androgenicity of vinclozolin. The summaries were presented to the Developmental and Reproductive Peer Review Committee for Vinclozolin.

MRID#: None.

Summaries:

L Earl Gray, JM Ostby and W Kelce (1993) Anti-androgenic Effects of the Fungicide Vinclozolin on Sex Differentiation of the Rat. (Prepublication paper, submitted for publication 12/93 to (0000) Toxicology Applied Pharmacology 00, 00-00).

Study conducted at the EPA Laboratories at HERL, RTP as part of a screen for chemicals causing effects on reproduction.

The LEL of 3 mg/kg/day was chosen by the Developmental and Reproduction Peer Review Committee as lowest dose level for developmental toxicity. The committee recognized at that time that since the developmental effects were caused by late gestational and/or early postnatal dosing, for the developmental effects to occur would require accumulated levels of test material and that the effects may not be seen from acute dosing at 3 mg/kg/day.

An *ad hoc* group composed of Karl Baetcke, Elizabeth Doyle and David G Anderson met and chose a NOEL of 3 mg/kg/day based on the sensitive nature of the anogenital distance (AGD) in rats to anti-androgens and that only 6 litters at 3 mg/kg/day were used in Gray's studies to determine the AGD and that the use of a corn oil vehicle in Gray's studies may have increased absorption versus the carboxymethylcellulose vehicle used in the BASF studies.

Vinclozolin was administered to LE Hooded rats by gavage in corn oil from post coital day 14 to post natal day 3 (postcoital day 23=postnatal day 1). The study was conducted in 3 sets; (1) approximately 5 pregnant rats per dose level at 0, 100 and 200 mg/kg/day, (2) approximately 3 dams per dose level at 0 (5 rats in control group) 3, 6, 12, 25 and 50 mg/kg/day, and (3) 6 dams per dose level at 0, 3 and 6 mg/kg/day.

Details on 10 additional litters studied have not been reported to OPP, but interim reports on the reproductive effects have been made available to OPP for group 1 to day 380, group 2 animals to day 56 and for group 3 animals to post natal day 13 as reported in the above referenced paper. Group 1 animals show the typical hypospadias, reduced sex organ weights, etc., demonstrated in the study of reproduction conducted by BASF (MRID# 425813-01) and reported in HED Doc# 010380. In addition, caudal epididymal sperm count was statistically significantly lower than controls at 50 mg/kg/day and serum testosterone decreased (64% and 67% of controls) at 100 and 200 mg/kg/day, respectively, at 11 months of age.

The lowest effect level was demonstrated at 3 mg/kg/day in the combined study 2 and 3 where anogenital distance (AGD) was statistically significant reduced in males on postnatal day 2. The AGD in experiment 2 was 95.0% and 95.3% of controls at 3 and 6 mg/kg/day, respectively, and in experiment 3 it was 93.6% and 93.0% of controls at 3 and 6 mg/kg/day, respectively. The AGD at 3 and 6 mg/kg/day was shown to be reduced when combined for statistical analysis in a two way ANOVA with dose (2 DF) and block (study 2 versus study 3) as the main effects. There was a significant block effect, but the block by treatment interaction

was not significant by the statistical methods used. These results indicate that treatment consistently reduced AGD from study 2 to study 3 by the same amount, but the absolute values of AGD for both control and dosed males were higher in study 2 than study 3. The lowest effect level was 3 mg/kg/day (LDT) for AGD in males, but no NOEL was produced.

Although, nipple development was nominally increased at 3 and 6 mg/kg/day and higher at day 13, the increases were not statistically significant.

Androgen receptor binding inhibition in developing males *in utero* is thought to cause the effects in rats from vinclozolin treatment. The effects are similar to those found for flutamide and finasteride (Imperato-McGinley, 1992) in rats.

The oral developmental study conducted by BASF used carboxymethylcellulose as a vehicle while the Gray et al. (1993) study used corn oil as a vehicle. The use of a corn oil vehicle instead of 0.5% carboxymethylcellulose as in the BASF studies may have contributed to the effects at a lower dose levels than in the BASF studies. Corn oil may increase absorption from the gut compared with carboxymethylcellulose vehicle. In addition, there were strain, protocol and methodology differences between the studies that may have contributed to the different dose levels at which effects were seen.

Reference:

Imperato-McGinley, J, RS Sanchez, JR Spencer, B Yee and ED Vaughn (1992). Comparison of effects of the 5-reductase inhibitor finasteride and the anti-androgen flutamide on prostate and genital differentiation: Dose-responses studies. *Endocrinology* 131(3): 1149-1156.

Endpoint and dose for use in risk assessment: 5.5 mg/kg/day.

Comments about the study and/or endpoint: The lowest effect level of 3 mg/kg/day could not be attained in rats by dosing rats with 3 mg/kg on a single day. The dose level would be expected to be higher, i.e., 5.5 mg/kg/day ( $3 \text{ mg/kg/day} \times 3.91/2.12 = 3 \times 1.8 = 5.5 \text{ mg/kg/day}$ ), in order to obtain the internal dose corresponding to 3 mg/kg in rats from dosing on multiple days.

Data from the metabolism study (MRID# 41824308, study# 90/0544 and MRID# 41824307, study# 90/0514, HED Doc.# 010261) indicate that the peak plasma levels in females occur 2 hours after dosing at 10 mg/kg, the smallest dose level for which data was reported. These plasma levels were 3.91 g/g-plasma, 2 hours after the last of 7 daily doses of 10 mg/kg and 2.12 g/g-plasma, 2 hours after a single 10 mg/kg dose. The plasma levels would be close to equilibrium levels in rats after 7 days of dosing. Thus, the ratio is  $(3.91 \text{ g/g}) / (2.12 \text{ g/g}) = 1.84$  and  $1.84 \times 3$

mg/kg/day = 5.5 mg/kg/day.

It is reasonable to further assume that the maximal developmental effects occur from the peak plasma levels of vinclozolin. However, it is unknown when the peak plasma levels of the anti-androgen metabolites would occur, but presumably these would be no higher than plasma levels of the parent vinclozolin. Therefore, the estimated acute endpoint for the dietary risk assessment for oral exposure for developmental effects is 5.5 mg/kg.

A risk assessment for this endpoint is required.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Study Selected - Guideline No.: See the Gray, Osby and Kelce (1993) study used for the acute dietary exposure (immediately above).

MRID#: No MRID#.

Summary: See summary under acute dietary endpoint (1 day).

Endpoint and dose for use in occupational or residential 1-day to 7 days exposure risk assessment: 3 mg/kg/day.

Comments about studies and/or endpoint: Although a dermal developmental toxicity study was conducted by BASF and was considered by the committee, there are uncertainties about most relevant study for effects on the anogenital distance (AGD). The discrepancy between Gray's oral data (Long Evans Hooded rat) and BASF's oral data (Wistar rat) on developmental toxicity, must be considered. The NOEL from neither dermal developmental toxicity study conducted by BASF accounts for this uncertainty or discrepancy. Therefore, the developmental toxicity end point from Gray's data was chosen as the most sensitive and corrected for dermal absorption.

TESC also notes that when BASF was considering conducting an additional dermal developmental toxicity study in the rat, they were advised verbally that the LE Hooded rat used by Gray et al. would facilitate comparison between the two laboratories.

This risk assessment is required.

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Intermediate Term Occupational or Residential (1 Week to Several Months)

Study Selected - Guideline No.: See the Gray, Osby and Kelce (1993) study used for the acute dietary exposure.

MRID#: No MRID#.

Summary: See summary under acute dietary endpoint (1 day).

Endpoint and dose for use in occupational or residential 1-day to 7 days exposure risk assessment: 3 mg/kg/day.

Comments about studies and/or endpoint:

The committee reviewed the available database and looked at the pros and cons of using a number of potentially applicable studies (including two rat dermal developmental studies (BASF) (MRID# 41413001 and 43703301), a two generation rat reproduction studies (MRID# 42581301 and 43254705), a 90 day rat feeding study (MRID# 42728801 and 42728802) corrected for dermal absorption, and two oral rat developmental studies, one by BASF in the Wistar rat (0.5% carboxymethylcellulose in water vehicle) and one by Gray et al. (1993) in the Long Evans Hooded rat (corn oil vehicle), corrected for dermal absorption.

The committee selected the oral developmental toxicity study in the Long Evans Hooded rat by E. Gray et al. (1993) as the most appropriate to provide the endpoint for intermediate term worker exposure. The endpoint was decreased anogenital distance (AGD) in male pups with an effective NOEL of 3 mg/kg/day and nipple development at 6 mg/kg/day. Since the endpoint was seen in an oral study, it would be adjusted for dermal absorption of 25%. This study was selected from among others primarily for the following reasons:

(a) The Gray et al. (1993) study is the study with the most sensitive endpoint (decreased AGD in male pups). Previously, the HED Developmental/Reproductive Peer Review Committee had chosen this study and the endpoint as the most sensitive for vinclozolin from among the available studies.

The TESC noted that the decreased AGD in the Gray study was part of a continuum of developmental effects observed in the male rat pups with increasing dose in that study. Some effects occurring at lower doses were reversible over time with cessation of dosing (anogenital distance, possibly nipple development), although hypospadias, occurring at higher doses, was not reversible. The committee considered the nipple development at 6 mg/kg/day to be an important supportive finding.

(b) Although decreased AGD was seen in the BASF oral developmental toxicity studies, it occurred at a lower dose in the Gray study than in the study by BASF. The difference between the Gray and BASF studies with regard to this endpoint may be due, at least in part, to strain differences (i.e., the Long Evans Hooded rat may be more sensitive to vinclozolin administration than the Wistar rat). In addition, different vehicles were used in the Gray and the BASF studies; different protocols and differing AGD measurement methods were used and all these factors may have contributed to the differences seen.

(c) Decreased AGD was noted in the BASF dermal studies. Although the committee would have liked to have used an endpoint for dermal exposure based on a dermal study, this approach was not favored. This was because the Gray oral developmental study provided a lower NOEL for decrease AGD than did the corresponding oral BASF study when the two were compared. Possible reasons for the differences in the results of the oral studies are discussed in point b) above. Therefore, if BASF had performed its dermal developmental study in the Long Evans Hooded rat using the procedures similar to those of the Gray study for measuring AGD, the committee would have felt more comfortable using the dermal study.

(d) The oral 90-day rat study, as suggested by the registrant, was not selected to provide the endpoint for intermediate worker exposure because the effective NOEL and LOEL from the Gray study was lower and the endpoint (decreased AGD) was considered to be the most sensitive endpoint.

Note: 90-day feeding: NOEL = 4.4 mg/kg/day and the LOEL = 24 mg/kg/day for increased adrenal weight, etc.  
Gray oral developmental: Effective NOEL = 3 mg/kg/day is based on decreased AGD in male pups and an increase in male nipple development at 6 mg/kg/day

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Long Term Occupational or Residential (Several Months to Lifetime)

The LTL Committee recommended that a dermal equivalent be calculated from the 2-year oral studies in the rat (83-1a, 83-2b) and the percentage dermal absorption studies (85-3) for Intermediate and Long Term Occupational or Residential Exposure.



It was recommended that the oral NOEL from the 2-year study in rats (study used as the basis for the RfD) be corrected for percentage dermal absorption at the dermal exposure level for humans. The percentage dermal absorption should be taken from Table 1 at the level of human exposure. If chronic human exposure is less than 0.10 mg/kg/day, the Toxicology Branch-1 should be consulted for an appropriate percentage dermal absorption figure.

The chronic oral studies are those used to set the RfD and are described below.

Study Selected - Guideline No.: (83-1a), (83-3b) and (85-3).

MRID#: 43254702, 43254703 and 42824309.

Summary: Two studies are necessary to determine a NOEL and LOEL. The two studies are a 2-year chronic study in the rat (MRID# 43254702) to obtain the NOEL and an oncogenicity study in the rat (MRID# 43254703) to obtain the LEL.

(1) MRID# 43254702, study report# 71S0375/88109:

In a chronic toxicity study, 20 male and 20 female Wistar rats were administered 0, 25, or 50 ppm (0, 1.2, or 2.4 mg/kg/day, respectively, for males and 0, 1.6, or 3.2 mg/kg/day, respectively, for females) of vinclozolin in their diets for 104 weeks.

No treatment-related systemic effects were observed in either sex at the dietary concentrations used in this study. Therefore, this study established a NOEL of 50 ppm for both male and female rats (2.4 and 3.2 mg/kg/day, respectively).

This study showed no evidence of carcinogenicity. The increased incidence of thymomas in male rats and benign thyroid C-cell tumors in female rats are not considered to be treatment-related.

This study and the first chronic study (MRID No. 432547-01) combined receive a classification of core - minimum, and satisfy the guideline requirements for a chronic feeding study in rodents (83-1). The classification of this study alone is supplementary upgradable. This deficiency was corrected by the first chronic study that used higher doses and established a LOEL at 150 mg/kg/day. All pertinent endpoints were evaluated; however, the study author did not calculate average severity ratings for nonneoplastic lesions nor present results of statistical analysis of incidence data.

(2) MRID# 43254703, study report# 71S0375/88105:

In a carcinogenicity toxicity study, groups of 50 male and

50 female Wistar rats were administered 0, 50, 500, or 3000 ppm (0, 2.3, 23, or 143 mg/kg/day, respectively, for males and 0, 3.0, 30, or 180 mg/kg/day, respectively, for females) of vinclozolin in their diets for 104 weeks.

Survival was not significantly affected in either male or female rats fed vinclozolin. Growth was affected throughout the study in both sexes receiving 3000 ppm; the males weighed 25% less than control and females weighed 17% less than control at termination ( $p < 0.01$  for both sexes compared with controls). Net body weight gain was reduced by 34% in males and 27% in females due in part to reduced food consumption (12 to 16% in males and 8 to 16% in females). However, since the relative efficiency of food utilization was negative in males and was reduced 85% in females at 3000 ppm from study week 52 to 102 or termination, the body weight decrement in males and females was due to toxicity and only partly due to the reduced food consumption. These findings are consistent with the body weight decrement and food efficiency calculations seen in the chronic study in rats at 1500 and 4500 ppm (MRID# 43254701).

Vinclozolin (metabolites/degradation products) competitively inhibits the androgen receptor, and has antiandrogenic activity. In addition, vinclozolin interferes with lipid metabolism and/or storage. Lesions in the testes, epididymides, accessory organs, ovary, and adrenal glands may be related to the antiandrogenicity and the effects of the test material on lipid metabolism and/or storage. Testicular lesions showing increased incidences included interstitial edema (5/50, 6/50, 7/50, 12/50\*), diffuse tubular atrophy (15/50, 14/50, 36/50\*, 45/50\*), tubular calcification (16/50, 20/50, 37/50\*, 42/50\*), cystic rete testis (3/50, 5/50, 3/50, 16/50\*), and hyperplastic rete testis (1/15, 0/50, 0/50, 13/50\*)<sup>1</sup>. There were decreases in the incidence of focal tubular atrophy (37/50, 29/50, 22/50\*, 9/50\*) and focal Leydig cell hyperplasia (36/50, 39/50, 34/50, 11/50\*). Accompanying the testicular lesions were azoospermia and oligospermia in the epididymides (13/50, 14/50, 41/50\*, 49/50\*), which occurred bilaterally in most 500- and 3000-ppm animals and degenerative lesions in accessory organs. Atrophy was noted in the seminal vesicle (3/50, 5/50, 16/50\*, 31/50\*) and coagulation gland (3/50, 5/50, 16/50\*, 30/50\*). Prostate effects included reduced secretion (4/50, 7/50, 12/50\*, 21/50\*), interstitial fibrosis (4/50, 9/50, 16/50\*, 31/50\*), and focal hyperplasia (11/50, 17/50, 25/50\*, and 20/50\*). In female rats, statistically significant increased incidences of interstitial

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<sup>1</sup> \* = statistically significantly different from control,  $p < 0.05$ , for the control, low, mid or high dose levels, respectively.

lipidosis in the ovaries occurred at all doses (2/50, 15/49\*, 35/50\*, 43/50\*). There was also a dose-related increase in the severity of this lesion. Adrenal cortical lesions occurred in both sexes with incidences reaching statistical significance at 500 and 3000 ppm. Lipidosis occurred in males (1/50, 2/50, 33/50\*, 50/50\*) and females (0/50, 3/50, 12/50\*, 50/50\*) as did extra cortical nodules (males: 25/50, 32/50, 21/50, 40/50\*; females: 19/50, 24/50, 40/50\*, 45/50\*). The occurrence of lipogenic pigment did not show an increase in incidence, which was very high in all groups, but an increase in the severity rating at 3000 ppm was noted for both sexes. There was a decrease in the incidence of cystic degeneration in the adrenal cortex of female rats (50/50, 48/50, 49/50, 13/50\*).

Liver cellular hypertrophy was not seen in either male or female controls, but the incidence was increased in treated male (0/50, 2/50, 12/50\*, 44/50\*) and female rats (0/50, 0/50, 11/50\*, 44/50\*). Eosinophilic foci, which were not seen in male control and in only one female control, showed a significantly increased incidence at all doses in males (0/50, 15/50\*, 33/50\*, 38/50\*) and at the high dose in females (1/50, 0/50, 5/50, 38/50\*). Basophilic and clear cell foci showed dose related decreases. The incidence of biliary cysts was increased in males (4/50, 5/50, 11/50\*, 15/50\*) and females (8/50, 10/50, 20/50\*, 36/50\*). Foam cell aggregates in the lungs also showed a significantly increased incidence in male rats at all doses (14/50, 27/50\*, 24/50\*, 40/50\*). The incidence of lenticular degeneration was significantly increased in female rats at all doses (9/50, 23/50\*, 49/50\*, 50/50\*) and at the two highest doses in male rats (11/50, 15/50, 39/50\*, 50/50\*). This lesion occurred bilaterally in almost all animals receiving 500 and 3000 ppm of the test material. In addition, lenticular calcification (males: 0/50, 1/50, 4/50, 46/50\*; females: 0/50, 0/50, 12/50\*, 48/50\*) occurred in almost all high-dose animals.

Other organs showing dose related and statistically significant increased incidences of lesions at one or more doses are the pancreas of both sexes (vacuolated acinar cells, 500 and 3000 ppm, skeletal muscle (focal fiber atrophy: 3000 ppm in males, dose-related increase in females), and iliac lymph nodes in males (pigment storage: 500 and 3000 ppm).

Lesions showing statistically significant decreased incidences were basophilic foci (males and females, 500 and 500 ppm) in the liver, clear cell foci in the liver (males 3000 ppm; females, 3000 ppm), myocardial fibrosis (males, 3000 ppm; females, all doses), and cystic degeneration of the adrenal cortex (females, 3000 ppm).

The LOEL for systemic toxicity is 50 ppm ( 2.3 mg/kg/day for males and 3 mg/kg/day for females) based on eosinophilic foci in the liver and foam cell aggregates in the lung of male rats and

lenticular degeneration of the eyes and interstitial cell lipodosis in the ovaries of female rats. There is no corresponding NOEL, because the lowest dose tested is the LOEL.

In addition, this study showed Leydig cell tumors (almost all benign) in male rats at incidences of 23/50, 25/50, 47/50\*, and 49/50\* and prostate adenomas with incidences of 0/50, 3/50, 7/50\*, and 5/50\* (controls, 50, 500, and 3000 ppm, respectively). There was no increase in the total number of treated male rats developing neoplasms compared with the controls. Adrenal cortical adenomas/carcinomas developed in 1/50, 2/50, 1/50 and 22/50\* female rats; benign sex cord tumors (unilateral and bilateral) developed in 4/50, 7/49, 10/50, 29/50\*; and adenocarcinomas of the uterus developed in 1/50, 0/39, 1/31, and 7/50\*. The adrenal cortical tumor was malignant in one high-dose rat. The development of the Leydig cell tumors are probably due indirectly to the antiandrogenic activity of vinclozolin, which disrupts the feedback mechanism for luteinizing hormone (LH), resulting in over stimulation of the Leydig cells by LH and not to a direct effect of the test material on the testes. The development of prostate, adrenal cortical, ovarian, and uterine tumors may also be related to a hormonal imbalance. The maximum tolerated dose was exceeded in animals receiving 3000 ppm as evidenced by a significant reduction in growth, decreased relative food efficiency and induction of numerous nonneoplastic lesions. However, the development of Leydig cell, adrenal cortical, and ovarian tumors is probably not due to the excessive toxicity, but to a hormonal imbalance.

Comments about studies and/or endpoint: The NOEL from the above two oral studies is 1.2 mg/kg/day based on the discussion under the RfD and Basis, below. The committee indicated that the oral dose level of 1.2 mg/kg/day in the chronic study (MRID# 43254702) should form the basis of calculating an acceptable dermal dose level for human exposure by the method discussed under Dermal Absorption Studies (see Table 1 for values for calculating human dermal exposure and MOE calculations).

A risk assessment using this endpoint is required.

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Cancer Classification and Basis: In a meeting on the carcinogenic potential of vinclozolin, the CPRC (April 17, 1996 meeting) classified vinclozolin as a "B2", but recommended that a MOE be used in the risk assessment. The bases for the category "B2" classification was the statistically significant increase in benign tumors of testicular Leydig cells and prostate at the 2 highest dose levels tested and benign ovarian sex chord tumors

(marginally significant at the mid-dose), all of which may be relevant to humans. Other tumors occurred at excessive dose levels. The CPRC in considering the endocrine mode of action, especially for the testicular Leydig cell tumors, believed that a nonlinear extrapolation and a MOE would adequately protect humans.

No dose related tumors were noted in mice at MTD (MRID# 43254704).

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The Selected Endpoint for the Nonlinear Extrapolation and MOE:

The TESC recommended that the epididymal weight from a 2-generation reproduction studies (MRID# 42581301 and 43254705) with a NOEL/LOEL = 4.9/30 mg/kg/day be used as the endpoint for the MOE based on the evidence that androgen deprivation (antiandrogen effects) results in both testicular Leydig cell tumors and epididymal weight decrease. Since other tumors were mostly benign, they also would be regulated based on the same endpoint as the testicular Leydig cell tumors.

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RfD and Basis: The chronic RfD = 0.012 mg/kg/day, including an uncertainty factor (UF) of 10 for interspecies variation and 10 for intraspecies variation for total UF of 100. This value is based on a NOEL of 25 ppm (1.2 mg/kg/day in males and 1.6 mg/kg/day in female rats) in a second 2-year study in rats (MRID# 43254702) and a LEL of 50 ppm (2.3 mg/kg/day for males and 3.0 mg/kg/day for females) based on eosinophilic liver foci and lung foam cell aggregates in males and eye lenticular degeneration and ovarian interstitial cell lipidosis in females in an initial carcinogenicity study in rats (MRID# 43254703).

NOEL for Critical study: 1.2 mg/kg/day in males.

Study type - Guideline No.: Second chronic oral 2-year toxicity study (MRID# 43254702) (Guideline no. 83-1) and a 2-year carcinogenicity study in rats (MRID# 43254703) (Guideline no. 83-2).

MRID#: 43254702 and 43254703. The Executive summaries of these two studies are presented under the previous section on Long Term Occupational and Residential Exposure.

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Acute Toxicity Endpoints

The table below summarizes the results of the acute toxicity studies on vinclozolin and the toxicity categories for the different routes of administration:

ACUTE TOXICITY VALUES - VINCLOZOLIN

Test	Result	Toxicity Category
Acute Oral LD50 in Rats MRID# 00080451 & 92194010, Study# BASF XXII/337, 90/6515, Date 2/20/73.	LD50 > 32000 mg/kg in both males and females. Acceptable	III
Acute Dermal LD50 Rats MRID# 00086339 & 921934011, Study# BASF 90/6516, Date 11/2/77.	LD50 > 2500 mg/kg in both males and females. Acceptable	III
Acute Inhalation LC50 in rats MRID# 00075474 & 92194012, Study# 90/6517, Date 4/20/79.	LC50 > 29.1 mg/l. Acceptable	IV
Primary Eye Irritation in Rabbits MRID# 00086341 & 92194013, Study# BASF 90/6518, Date 11/9/77	Slight eye irritation cleared by day 8. Acceptable	III
Primary Skin Irritation in Rabbits MRID# 00086340 & 92194014, Study# BASF 90/6519, Date 11/9/77.	Slight skin irritation cleared within 72 hours. Acceptable	IV
Skin Sensitization in Guinea Pigs MRID# 00080451 & 92194015, Study# BASF 90/6520, Date 9/7/79.	Skin sensitizer in 4/9 GP. Acceptable	Sensitizer

Memo/IES Endpoints/Vinclozolin/A:\2DTESVIN\DANDERSON/7/24/96(Edited 8/1/96; Second del & Revised 7/18/96 added 8/6/96)\*.

## APPENDIX:

Summary of Second Dermal Developmental Toxicity Study in Rats (MRID# 43703301, Study# BASF 95/10450, Lab.# 34R0375/88124, April 27, 1995).

Helwig, J (April 27, 1995) Study of Perinatal Toxicity of Reg. No. 83 258 in Wistar Rats After Dermal Application. Study No. BASF 95/10450, Lab. No. 34R0375/88124. Study conducted by BASF Aktiengesellschaft Crop Protection, Product Safety, Dept. Toxicology, D-67056 Ludwigshafen/Rhein Germany for BASF Corp. MRID# 43703301.

### Summary:

Vinclozolin was administered dermally to 24-25 pregnant Wistar rats per group at 0, 10, 20, 30 or 200 mg/kg/day in 0.5% aqueous carboxymethylcellulose-water solution. Five ml/kg was applied to the clipped backs of rats for 6 hours per day, gestational day 6 through day 20. Dams were sacrificed on day 21 rather than day 20. Blood was drawn from 5 dams per dose level for determination of Vinclozolin, M1 and M2 metabolites in dams and fetuses on gestational day 21. No maternal effects were noted, except for slightly elevated maternal body weights, but organ weights were not determined.

Serum concentrations of reg. No. 83 258 and M2 were not detected at any dose level. M1 was detected in dams with a mean value of 4.32 nmoles/g-serum (SD = 1.09) or 1.31 g/g-serum and a mean value in fetuses of 7.0 nmoles/g-serum or 2.13 g/g-serum at the 200 mg/kg/day dose level.

Anogenital distances (AGD) were determined in unfixed fetuses and were more variable than in the previous dermal developmental toxicity study (MRID# 41413001), where the AGD was determined on Bouin fixed fetuses. The mean AGD distance (standard deviation) in male fetuses is 3.3(0.30), 3.2(0.27), 3.3(0.21), 3.2(0.33) or 3.1(0.22) mm at 0, 10, 20, 30 or 200 mg/kg/day, respectively, and the index is 5.4(0.27), 5.3(0.34), 5.4(0.26), 5.4(0.35) or 5.4(0.37), respectively. Although, the AGD was nominally decreased at 200 mg/kg/day it was not statistically significant. The AGD index was neither statistically significant nor nominally reduced from control values. The registrant indicated that the difference in the 2 studies may have been due to two factors. (1) The determination of AGD in fresh fetuses rather than fixed fetuses which increased the variability of the data. (2) Due to technical problems the analytically determined dose level was 71.8% to 84.5% of the target dose level of 200 mg/kg/day. These factors may have

contributed to the lack of statistical significance of the AGD and AGD index at 200 mg/kg/day nominal dose level.

However, the study supports the NOEL of 60 mg/kg/day in the first dermal developmental toxicity study.