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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: EPA ID 113201; Vinclozolin, Contractor DERs on Two Rat/Chronic Studies (MRID# 43254701 & 43254702), Two Oncogenicity Studies in the Rat and Mouse (MRID# 43254703 & 43254704) and a Supplementary 2- Generation Reproduction Study (MRID# 432547-05).

Barcode: D222842.
Submission No.: S468567.
MRID No.: 43254701, 43254702,
43254703, 43254704
& 43254705.

ToxChem No.: 323C.
PC No.: 113201.
Case No.: 819455.
Rereg. Case No.: 2740.
CAS Reg No.: 50471-44-8.

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Thru: Karen Hamernik, PhD
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Karen Hamernik 2/9/96

CONCLUSIONS:

Below are the Executive Summaries for MRID# 43254701, 43254802, 43254703, 43254704 and 43254705, submitted in support of the reregistration of vinclozolin. All studies are acceptable or in combination are acceptable for Guideline 83-1a, 83-2a, 83-2b. The 2 dose level 2-generation study on reproduction is an unnecessary study, since the previous study was classified acceptable (MRID# 42581301 & 42581302) for Guideline 83-4. However, the study was reviewed and the Executive Summary is included below.

Table of D222842 submissions, adequacy and guideline fulfillment		
Report MRID#	Acceptability	Guideline# Fulfillment
43254701 and 43254702	Acceptable together	83-1a
43254703	Acceptable	83-2a
43254704	Acceptable	83-2b
43254705	Acceptable with 42581301	83-4, confirms acceptability of 42581301, but unnecessary.

(1) Chronic/Rat MRID# 43254701:

Mellert, W. (1994) Chronic Toxicity Study with Reg. No. 83 258 - Vinclozolin in Rats Administration in the Diet for 24 months. Study conducted by BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen/ Rhein, FRG, study no. 71S0375/88026, BASF no. 94/10287, May 3, 1994. MRID# 43254701. Unpublished report submitted to USEPA, OPP.

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID# 43254701), groups of 20 male and 20 female Wistar rats were administered 0, 150, 500, 1500, or 4500 ppm (0, 7, 23, 71, or 221 mg/kg/day, respectively, for males and 0, 9, 29, 88, or 257 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 markedly reduced in both sexes fed the test material. During the second year of treatment with 4500 ppm, male and female rats weighed 17-33% and 14-30%, respectively, less than controls. At termination body weight gain was reduced by about 45% in both sexes receiving 4500 ppm, due in part to reduced food consumption. At termination and 1500 ppm, body weight gain in females was 76% ($p < 0.01$) and in males 82% ($p > 0.05$, N.S.) of control values. The overall relative efficiency of food utilization from week 52 to 102 in males and females showed a biologically significant dose related decrease at 1500 and 4500 ppm. In control, 1500 and 4500 ppm, respectively, the values for males are 4.1,

-0.03 and -3.3 and for females the values are 6.9, 4.5 and -0.2. Water consumption for week 0-102 was increased at 4500 ppm and at 1500 ppm for week 0-13 in males and females.

Organ weight changes in male and female rats fed 4500 ppm of the test material included statistically significant increases in absolute and relative liver and adrenal weights. Increases in absolute and relative testes weights occurred at all doses, but relative weights were statistically significant only at 4500 ppm.

At various times during treatment bilateral lesions such as cataracts, bosselated structures in the lens, bulbiform thickening of the lens, and focal opacity were seen in both sexes receiving doses \geq 500 ppm and in males at all dose levels. Serous fluid accumulation in the anterior chamber of the eyes was noted in males and females at 4500 ppm.

Microscopically, several lesions were statistically significantly increased in the testes, such as increased tubular calcification at all dose levels and diffuse tubular atrophy at \geq 500 ppm, and accessory organs. There was a significant decrease in the incidence of focal Leydig cell hyperplasia at \geq 1500, and statistically significant increase in hyperplastic rete testes at 4500 ppm. Microscopic lesions were noted in the epididymis (notably reduced size or atrophy and azoospermia/oligospermia at doses \geq 500 ppm), seminal vesicle (reduced size or atrophy at doses \geq 1500 ppm), coagulation gland (atrophy at doses \geq 1500 ppm), and prostate (reduced size or reduced secretion at doses \geq 500 ppm). In addition, interstitial fibrosis was a notable lesion in the prostate, showing a dose-related increase in incidence and severity at all dose levels (perhaps indicative past inflammatory damage or cellular replacement). In female rats, a statistically significant increase in the incidence of interstitial lipidosis in the ovaries occurred at all doses. Test material related atrophy of skeletal muscle fibers was significant in males and females at 4500 ppm. Vinclozolin inhibits androgen receptor binding and interferes with lipid metabolism and possibly steroidogenesis; therefore, the lesions in the testes, male accessory organs and ovaries may be related to a hormonal imbalance due to excessive stimulation by luteinizing hormone (LH) or by interference with aspects of lipid/cholesterol metabolism/storage. In addition, the muscle atrophy and body weight gain reduction seen may be due in part to the inhibition of androgen receptors on muscles.

Increased incidences of lesions were seen at one or more dose levels in the liver of both sexes (cellular hypertrophy, single cell necrosis, and eosinophilic foci (1500 and 4500 ppm), kidney of male

rats (urothelial hyperplasia, ≥ 500 ppm; renal pelvis calcification, 4500 ppm), lungs of both sexes (foam cell aggregates, 4500 ppm), pancreas of both sexes (vacuolated acinar cells, ≥ 500 ppm), skeletal muscle of both sexes (focal fiber atrophy, 4500 ppm), and adrenal gland of both sexes (lipidosis, ≥ 500 ppm for males and ≥ 1500 ppm for females, extracortical nodules, 4500 ppm).

Incidences of lesions showing significant decreases were clear cell foci in the liver (male and female, 4500 ppm), basophilic foci in the liver (females, 4500 ppm), interstitial nephritis (females, 4500 ppm), cystic degeneration of the adrenal cortex (females, ≥ 500 ppm), myocardial fibrosis (male, 4500 ppm; females, ≥ 1500 ppm), glandular cysts in mammary tissue (females, ≥ 1500 ppm), focal hyperplasia of the pituitary (males, ≥ 500 ppm), interstitial edema in the testes (males, ≥ 1500 ppm), and acinar concretions in the prostate (males, 4500 ppm).

Several clinical chemistry values were biologically and statistically significantly changed (increased liver SGGT and other parameters)(serum triglycerides were consistently reduced in males and cholesterol was increased in females) in males and females mostly at 4500 ppm.

The LOEL for systemic toxicity is 150 ppm (7 mg/kg/day for males and 9 mg/kg/day for females) based on bilateral lenticular degeneration of the eyes, seminiferous tubular calcification in the testes, and interstitial fibrosis in the prostate of male rats and interstitial cell lipidosis in the ovaries of female rats. There is no corresponding NOEL, because the lowest dose tested is the LOEL.

This study showed some evidence of carcinogenicity probably involving a hormonal imbalance. Leydig cell tumors (mostly benign) occurred in male rats at ≥ 500 ppm. Hepatocellular carcinomas at incidences of 0/20, 0/20, 1/20, 1/20, 9/20*¹ occurred in controls, 150, 500, 1500, and 4500 ppm, respectively. In addition, the total number of 4500-ppm male rats with malignant tumors at any site (13/20 vs. 3/20) was significantly increased. Females had significantly increased incidences of adrenal cortical tumors (0/20, 0/20, 0/20, 1/20, 6/20*), benign sex cord tumors in the ovaries (0/20, 0/20, 2/20, 4/20*, 10/20*), and all ovarian tumors combined (4/20, 3/20, 4/20, 7/20, 11/20*). However, there was a dose related decrease in the incidence of pituitary adenomas in females rats (14/20, 12/20, 12/20, 6/18*, 5/20**) and mammary fibroadenomas (5/20, 5/9, 3/10, 6/9, 1/18). The development of the Leydig cell tumors may be due indirectly to the antiandrogenic activity of vinclozolin, which disrupts the feedback mechanism for luteinizing hormone (LH), resulting in overstimulation of the Leydig cells by LH and not to a direct effect of the test material on the testes. The development of adrenal cortical and ovarian tumors may also be related to a hormonal imbalance or interference with aspects of lipid metabolism/storage. The maximum tolerated dose was clearly exceeded in animals receiving 4500 ppm and possibly at 1500 ppm as evidenced by marked reduction in growth and induction of numerous nonneoplastic lesions and the decreased efficiency seen in males and females at dose levels ≥ 1500 ppm. However, the development of Leydig cell, adrenal cortical, and ovarian tumors is probably not due to the excessive toxicity, but to a hormonal imbalance or interference with aspects of lipid metabolism/storage. Except for one male rat in the 1500-ppm group, hepatocellular carcinomas developed only in male rats fed 4500 ppm. The lack of adenomas either accompanying or preceding the hepatocellular carcinomas suggests that the development of hepatocellular carcinomas is not an indirect effect of hepatocellular toxicity. However, the induction of hepatocellular carcinomas was not confirmed in the carcinogenicity study (MRID No. 432547-03) where male rats fed 3000 ppm for 104 weeks did not develop hepatocellular carcinomas at a significantly increased incidence.

Core Classification: Acceptable. This study (MRID# 43254701) and the supplementary study using lower doses (MRID# 43254702) combined are acceptable for a Guideline (83-1) study for

¹ * & ** = statistical significance at $p \leq 0.05$ & 0.01 , respectively.

chronic toxicity in the rat. Toxic effects and a NOEL are shown only when the two studies are combined.

(2) Second Chronic/Rat MRID# 43254702:

Mellert, W. (1994) Second Chronic Toxicity Study with Reg. No. 83 258 - Vinclozolin in Rats Administration in the Diet for 24 months. Study conducted by BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen/Rhein, FRG, study no. 71S375/88109, BASF no. 94/10288, May 4, 1994. Unpublished report submitted to USEPA, OPP. MRID# 43254702

EXECUTIVE SUMMARY: 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 or present results of statistical analysis of incidence data.

(3) Oncogenicity in the Rat MRID# 43254703:

Mellert, W. (May 2, 1994) Toxicology Study Report: Carcinogenicity Study With No. 83 258 - Vinclozolin in Wistar Rats Administration in the Diet for 24 Months. Laboratory name BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen/ Rhein, FRG, study no. 71S0375/88105, BASF No. 94/10279, May 2, 1994. MRID# 43254703. Unpublished report submitted to USEPA, OPP.

EXECUTIVE SUMMARY: In a carcinogenicity toxicity study (MRID# 43254703), 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 in part 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).

The absolute and relative weights of the testes were slightly decreased at 50 ppm and significantly increased ($p < 0.01$) at 500 ppm (168 and 163%, respectively) and 3000 ppm (188 and 244%, respectively). Absolute and relative weights of the epididymides were depressed at all doses. The adrenal glands weights were elevated at all doses, but were significant ($p < 0.01$) at 3000 ppm (191 and 262%, respectively). In female rats, organ weights did not show a clear dose-response or the effects were not biologically or statistically significant, except for the liver weights and the relative weight of the ovaries. The absolute (129%) and relative weights (156%) of the liver were increased ($p < 0.01$) at 3000 ppm compared with the control group. The absolute (123 to 156%) and relative weights (121 to 190%) of the ovaries were increased at all three doses compared with the control group, but only relative weight at 3000 ppm was significant ($p < 0.01$).

Vinclozolin/metabolite/degradation products competitively binds to 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 are probably related to the antiandrogenicity and the effects of the test material on the 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*). (The values in parentheses represent the incidence/number of animals studied in control, 50, 500, and 3000 ppm, respectively; the asterisk (*) denotes a statistically significant difference ($p \leq 0.05$ or $p \leq 0.01$) compared with controls.) 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*). The decreased prostatic secretion and interstitial cell fibrosis along with increased chronic inflammation, may be secondary to the antiandrogenicity of vinclozolin and the increased incidence of prostate adenoma at 500 and 3000 ppm. In female rats, statistically significant increased incidences of interstitial 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*). This increased lipid accumulation in ovaries and adrenals may be related to the interference of vinclozolin with lipid metabolism and/or storage. 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.

Lesions occurred in the pancreas of both sexes (vacuolated acinar cells, 500 and 3000 ppm, skeletal muscle (focal fiber atrophy: 3000 ppm in males, dose-related increases in females), and iliac lymph nodes in males (pigment storage: 500 and 3000 ppm).

Several lesions showed statistically significant decreased incidences at 500 and/or 3000 ppm in males and females, some of which were possibly antiandrogen related or of undetermined cause.

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 lipidosis in the ovaries of female rats. There is no corresponding NOEL, because the lowest dose tested is the LOEL.

This study showed some evidence of carcinogenicity probably involving a hormonal imbalance. Leydig cell tumors (almost all benign) occurred in male rats at incidences of 23/50, 25/50, 47/50*, and 49/50* and prostate adenomas occurred 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 and/or the effects of vinclozolin on lipid metabolism/storage. 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.

This study receives a classification of acceptable, and it satisfies the guideline requirements for a oncogenicity feeding study in rodents (83-2).

(4) Carcinogenicity Study in Mice MRID# 43254704

Mellert, W. (1994) Toxicology Study Report: Carcinogenicity Study with Reg. No. 83 258-Vinclozolin in C57BL Mice Administration in the Diet for 18 Months. Study conducted by BASF Aktiengesellschaft Crop Protection, Product Safety, Dept. of Toxicology, Ludwigshafen/Rhein, Germany, study no. 80S0375/88112, BASF no. 94/10278, May 4, 1994. MRID NO.: 43254704. Unpublished report submitted to USEPA, OPP.

EXECUTIVE SUMMARY: In a 18-month oncogenicity feeding study (MRID# 43254704), vinclozolin was administered in the diet to 50 male and 50 female C57BL/6/JICO mice per group at 0, 15, 150, 3000, or 8000 ppm. Groups of 10 animals per sex were added and sacrificed after 12 months. The doses corresponded to average doses of about 0, 2.1, 20.6, 432, and 1225 mg/kg/day for males; and to 0, 2.8, 28.5, 557, and 1411 mg/kg/day for females. Two control groups each containing 50 mice per sex for the main study and 10 mice per sex for the satellite study were maintained to obtain more historical data for this strain of mouse. The treated groups were compared to each control group and, in some cases, to the combined control groups.

Mortality at 8000 ppm was 60% in males ($p < 0.001$) and 48% in females ($p < 0.001$) when compared with combined control groups. Mortality of males and females in the 18 month study at 3000 ppm were increased significantly when compared to combined control groups but not when compared with the control group with the highest mortality and the increase in males was the same at 15, 150 and 3000 ppm and may not have been related to test material.

The most commonly reported effect in premature decedents was erosion and ulceration of the glandular stomach (highest in the 8000 ppm group). This occurred in all groups including the controls. Increased incidences of focal necrosis, pigment storage and bile duct proliferation in the liver were seen at 3000 ppm in both sexes. These findings at the 8000 ppm dose were increased in incidence and severity; additionally, increased incidences of basophilic foci, focal hyperplasia, and cellular alterations were also reported. Decreased weight gain was seen in both sexes at all dose levels. Body weight gain in control, 15, 150, 3000 and 8000 ppm dose groups were 8.5, 5.7, 6.7, 4.8 and 1.6 for males and 7.2, 6.1, 4.0, 4.4 and 2.4 g for females, respectively. The mean body weights were significantly less than control animals from the first week of the experiment at the 8000 ppm dose. The decreased weight gain was accompanied by decreased food intake especially at the beginning of the study; however, a decrease in overall food efficiency was seen, especially at the 2 highest doses. Male and female absolute and relative liver, kidney, brain and adrenal organ weights were increased at 3000 and 8000 ppm, but the increase was frequently equivocal at 15 and 150 ppm. The absolute and relative adrenal weights were significantly ($p < 0.01$) increased in both sexes at 3000 and 8000 ppm. The absolute and relative adrenal weights were also slightly increased in males at 15 and 150 ppm; however, there was not a good dose-relationship. An increased incidence of lipoidosis in the adrenal cortex and testicular Leydig cell hyperplasia, seminal vesicle, epididymis, prostate and uterine atrophy and/or reduced size were seen at 3000 and 8000 ppm and at 8000 ppm ovarian stromal hyperplasia and absence of follicles were seen. An increase in polymorphonuclear neutrophils and monocytes, and a decrease in the percent of lymphocytes were seen at 3000 and 8000 ppm. The increases in polymorphonuclear neutrophils and monocytes may have been secondary to the stress associated the increased stomach erosions and liver necrosis noted in these groups.

These hematological changes, however, were seen primarily at 8000 ppm, are close to the normal range of values for mice. The Lowest-Effect-Level (LEL) of 150 ppm (20.6 mg/kg/day for males; 28.5 mg/kg/day for females) was based on significantly decreased mean body weight gains that were greater than 10% less than the mean body weight gain of control animals. A No-Observable-Effect-Level (NOEL) of 15 ppm (2.1 mg/kg/day for males; 2.8 mg/kg/day for females) was identified.

The incidence of hepatocellular carcinomas was significantly increased in females ($p < 0.001$) at 8000 ppm (22/50) when compared to either control group, 0/50 in control group 0 and 2/50 in control group 1). Most of the carcinomas (17/26) were observed at terminal sacrifice. Only one female developed hepatocellular carcinoma at 8000 ppm in the 12-month satellite study. In surviving males, the incidence of hepatocellular carcinomas was 3/20, $p \leq 0.05$, at 8000 ppm and 0/90 in combined controls. No additional treatment-related neoplastic findings were reported at any dose.

This study is core-guideline and satisfies the guideline requirements for a 83-2 oncogenicity feeding study in mice.

Comments by the RfD/QA Peer Review Committee:

Some members of the RfD/QA Committee objected to the NOEL of 15 ppm for males (2.1 mg/kg/day) and females (2.8 mg/kg/day) and considered that the NOEL should be 150 ppm (20.6 and 28.5 mg/kg/day for males and females, respectively) with the LEL being 3000 ppm (432 and 557 mg/kg/day for males and females, respectively) based on the failure of a good dose response at 0, 15 and 150 ppm in the body weight and body weight gain data and efficiency of food utilization. However, after acknowledging that mouse body weight gain and food efficiency data in a mouse feeding study are sometimes difficult to interpret, the committee considered that since the NOEL of 1.2 mg/kg/day from the rat studies was lower and acceptable, the NOEL in the mouse study was mute. The committee considered the matter no further.

(5) Second 2-Generation Reproduction study MRID# 43254705

Hellwig, J. (1994) Second Reproduction Study with Reg. No. 83 258 (Vinclozolin) in Rats with Continuous Dietary Administration Over 2-Generations (2 litters in Each Generation). Conducted by BASF Aktiengesellschaft, Dept. Toxicology, 6700 Ludwigshafen, Federal Republic of Germany for BASF AG. Co. Project No.: 70R0375/88119, BASF Reg.# 94/10280.; Dated May 2, 1994. MRID# 43254705. Unpublished report submitted to USEPA, OPP.

EXECUTIVE SUMMARY: In a 2-generation study on reproduction (MRID# 43254705) (1994), doses were administered in the diet at 0, 20 or 40 ppm of vinclozolin (technical, 99.2%) (Approximately 0, 2.0 or 4.1 mg/kg/day) to 25 Wistar rats per sex per group through the P0, F1 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). The study was specifically conducted to demonstrate a clear NOEL for epididymal weights.

No dose related or biologically significant effects were demonstrated on offspring or

