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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 7969-57. Review of Resubmitted Data from Developmental Toxicity and Ophthalmology. Study No.: Reg. No. BASF: 88/0493, October 1988, MRID No. 409505-01, and Study No. Reg. No. BASF: 88/0492, MRID No.: 408595-02

Tox. Chem. No.: 323C.
Project No.: 9-0647
Record No.: 237776.

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Registration Division (H7505C)

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CONCLUSIONS:

All of these submitted studies were either supplementary or inadequate because they were not submitted in sufficient detail for full evaluation. However, the studies were sufficient to indicate a new probable NOEL for developmental toxicity (pseudohermaphroditism as chacterized by decreased anal-genital distance) of 15 mg/kg/day, and eye effects (precataract findings) with a LEL of about 7.5 mg/kg/day. Previously the lowest NOEL for developmental toxicity was 80 mg/kg/day, and for eye effects was > 2000 ppm or about 100 mg/kg/day.

It is recommended that the DERs be submitted to the registrant for their information.

INTRODUCTION:

In a covering letter (MRID No. 409505-00) from BASF to the Registration Division, dated December 28, 1988, BASF submitted toxicity data under the requirements of P 86-5, but did not accept the need to do so. Included in the package were data on the toxic effects of Vinclozolin designated MRID No. 409505-01

(summary data on developmental toxicity), and MRID No. 409505-02 (summary data from the ophthalmology).

Under MRID No. 409505-01, were summaries of 4 developmental toxicity studies, which were reviewed in one DER, and one developmental toxicity study from Japan which was reviewed in another DER. Under MRID No. 409505-02, were summaries of 2 ophthalmological studies reviewed in one DER, and one ophthalmological study from Japan reviewed in another DER. Enclosed are the DER's associated with the studies under these MRID Numbers 409505-01 and 409505-02.

The four developmental studies were conducted in response to a study in Japan under Japanese guidelines for BASF Japan (K Takehara, M Itabashi, T Inoue and M Tajima, "Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration", conducted by Nippon Institute for Biological Science, 2221-1 Shin-machi, Ohme-shi, Tokyo 198, December 1979 for BASF Japan. This study from Japan differed from EPA guideline studies essentially in that the test material was administered in the diet, and from gd 0 through 21, 11 days longer than OPP requirements of gd 6 through 15. The four new studies were also conducted for a longer dosing period, 6 through 19, but by gavage.

DATA REVIEWED:

(1) Studies Contained Under MRID No. 409505-01:
(a)
J Hellwig. First Preliminary Results of Several Prenatal Toxicology Studies with Reg. No. 258 Vinclozolin) in Rats After Oral Administration; Project No.:34R0165/84084, 34R0165/84085, 34R0165/84086, 92R0165/84088. October, 1988.

ABSTRACT of the Preliminary Studies Conducted to Validate the Japanese Developmental Toxicity Study:

Vinclozolin was administered orally by gavage (vehicle not specified) to 25 rats/group at 0, 15, 50, and 150 mg/kg/day in study 4 (34R0165/84084), at 0, 50, 100, 200 mg/kg/day in study 5 (34R0165/84085), at 0, 200, 400 mg/kg/day in study 6 (34R0165/84086), and to 10 rats/group at 0, 600, and 1000 mg/kg/day in study 8 (92R0165/84088) from gestational day (gd) 6 through 19. At gd 20 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Maternal toxicity was demonstrated at 600 and 1000 mg/kg/day by the statistically significant increase in absolute and relative adrenal and liver weight in study 8, the only study where organ weights were determined. No histology was conducted on the organs, but other studies have demonstrated lipid accumulation in the adrenals, and centrilobular cloudiness of the liver. Statistically significant increases and decreases occurred in the body weight gain and in food consumption with no apparent dose

relatedness in any of the studies. The relative efficiency of food utilization was too variable to be definitive.

Statistically significant male and female fetal body weight decrements occurred at 1000 mg/kg/day in study 8. These weight decrements are considered test material related.

A statistically significant increase occurred in pseudohermaphroditism among male fetuses. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. The anal-genital distance in male fetuses was statistically significantly decreased at 50 mg/kg/day and higher in study 4, 6, and 8. The anal-genital distance was not determined in study 5. The response was dose related. These results are consistent with hormonal effects from the test material.

Soft tissue examination of fetuses indicated that increased incidence occurred in dilated renal pelvis and hydroureter at 400 mg/kg/day in study 6. At higher dose levels in study 8, the incidence of dilated renal pelvis and hydroureter was nominally increased. The failure of the dilated renal pelvis, and hydroureter to be significantly increased in study 8 was attributed to the fewer litters used (7, 5, and 8 in controls, 600, and 1000 mg/kg/day). However, although these effects appear to be real, there is doubt about the NOEL for these renal effects.

Skeletal examination of fetuses indicated increased incidence of accessory 14th rib at 400 mg/kg/day in study 6, and in fetuses and litters at 600, and 1000 mg/kg/day in study 8. These effects on the 14th rib are not definitive, and require historical control data to aid in the interpretation of the effects. Preliminary evaluation suggest a dose related increase in 14th ribs.

No other dose related effects were reported, but it was reported that evaluation of the fetuses for visceral and skeletal effects was not complete.

Summary:
Doses Administered: In study 4 - 0, 15, 50, and 150 mg/kg/day, in study 5 - 0, 50, 100, and 200 mg/kg/day, in study 6 - 0, 200, and 400 mg/kg/day, and in study 8 - 0, 600, and 1000 mg/kg/day.

Developmental Toxicity:
NOEL: 15 mg/kg/day.
LEL: 50 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, hydroureter, and accessory 14th rib may have occurred at 400 mg/kg/day and higher.

Maternal Toxicity:
NOEL: < 600 mg/kg/day.
LEL: < 600 mg/kg/day for increases in absolute and relative adrenal and liver weight (neither were weighed at lower dose

levels).

Core classification: Supplementary because it is a preliminary study series which results in insufficient experimental detail for complete evaluation.

(b)
K Takehara, M Itasbashi, T Inoue, and M Tajima. Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration. Reg. No. BASF: 88/0493, No project No., December, 1979.

ABSTRACT of the Developmental Toxicity Study from Japan:

Vinclozolin was administered orally in the feed to 19-20 rats/group at 0, 300, 1500, and 7500 ppm from gestational day (gd) 0 through 21. At gd 21 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Treatment related decreases in the maternal weight gain may have occurred at the MDT, but statistically significant decreases occurred only at the HDT. Food consumption was also decreased at the HDT, but the relative efficiency of food utilization was also depressed at the HDT before gd 10. Water consumption was statistically significant increased on gd 16 and nominally increased at gd 17 at the HDT. The treatment relatedness of these increases could not be determined.

The only organ weights obtained were for the adrenal, pituitary, brain,and ovary. The left adrenal weight was statistically significantly increased at all dose levels, but the right adrenal weight was nominally elevated at LDT and statistically significantly elevated at higher dose levels. These dose related adrenal weight increases at all dose levels were supported by gross swelling of the adenal noted at necropsy. The pituitary weights were statistically significantly decreased at the HDT, but the brain weight was unaffected. Statistically significant increases occurred in the weight of the ovaries in dams at the HDT, which was due to an increase in the size of corpora lutea.

Centrilobular cloudiness of the liver was noted at necropsy at the HDT.

Statistically significant decreases occurred in male and female fetal weight at the HDT.

The anal-genital distance was statistically significantly decreased at the mid dose tested (MDT) and the highest dose tested (HDT). Male fetuses externally were no different from female fetuses at the HDT. A statistically significant decrease in the anal-genital distance occurred in males at the MDT and HDT. This decreased anal-genital distance was designated pseudohermaphroditism because these males appeared to have superficially normal internal testes. The response was dose

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related. The increased size in the corpora lutea, the increased adrenal weights in dams at all dose levels, the decreased anal-genital distance in males at the MDT and HDT and in females at the HDT are consistent with the hypothesis that the test material causes secondary or primary hormonal effects.

Statistically significantly increased incidence of hypoplasia of the renal papillae, dilated renal pelvis, hydronephrosis, and hydroureter occurred in fetuses at the HDT.

Statistically significantly decreased ossification occurred at the HDT in cervical vertebrae, metacarpal bones, proximal phalanges, and metatarsal bones. Statistically significant increases occurred in left lumbar ribs in the MDT and HDT.

The partial defect and fusion of thoracic vertebrae and ribs in 1 fetus, and undersized ribs in 1 fetus which occurred at the HDT may also be related to the skeletal effects.

Summary:

Doses Administered: 0, 300, 1500, and 7500 ppm or 0, 23, 111, and 394 mg/kg/day in the feed of CD/CRJ rats.

Teratogenicity and Developmental Toxicity:
NOEL: 23 mg/kg/day.
LEL: 111 mg/kg/day for decreased anal-genital distance (pseudohermaphroditism), and left lumbar ribs. At the HDT, increased hydronephrosis and delayed ossification were noted.

Maternal Toxicity:
NOEL: < 23 mg/kg/day. Very close to the NOEL.
LEL: < 23 mg/kg/day for increases in adrenal weight. At the HDT body weight, food consumption, and relative efficiency of food utilization were decreased.

Core classification: Supplementary because it is not reported in sufficient experimental detail for complete evaluation.

(2) Studies Contained Under MRID No. 409505-02:
(a)
P Kirsch. First Preliminary Information of Ophthalmological Findings with Reg. No. 83 258 (Vinclozolin) in Rats After Oral Administration. Project No. 31S0375/88034, designated study 34, and Project No. 71S0375/88026, designated study 26. October, 1988.

ABSTRACT FOR STUDY 34:

Vinclozolin was administered in the diet to 10 rats/sex/group at 0, 300, 1000, and 3000 ppm for 82 days. Ophthalmological examinations were conducted initially on the controls and 3000 ppm dose level rats, at day 42 on the 300, and 1000 ppm dose group rats, and at day 82 on all groups of rats.

The examination was conducted with the aid of a slit lamp and a fundus camera.

Indications of precataract formation occurred at day 42 and 52. The number of animals affected had increased at the examination on day 82. Males and females exhibited striated lens at all dose levels, and 1 male exhibited a weakly visible fundus at 3000 ppm. Females exhibited bosselated lens surfaces, weakly visible fundus in 4 animals, and 1 mature cataract at 3000 ppm. These findings indicate significant precateract effects on the eye of males and females at all dose levels of Vinclozolin, and 1 cataract in a female at 3000 ppm.

Note: The study is preliminary. Thus it lacked most details required to thoroughly evaluate the reliability of the data. This evaluation is made to alert the Agency that the final report should be evaluated for eye effects, and that longer term studies may be required.

Summary:

Doses administered: 0, 300, 1000, and 3000 ppm in the diet to Wistar Chbb:THOM-SPF rats.

Ophthalmological Effects:
NOEL: < 300 ppm
LEL: < 300 ppm for precataract effects which included striations of the lens in males and females and cataracts in 1 female at 3000 ppm.

Other Systemic Effects:
Not determined.

Core classification: Supplementary due to the specialized nature of the study and insufficient detail for complete evaluation.

DISCUSSION AND ABSTRACT FOR STUDY 26:

Vinclozolin was administered in the diet to 20 rats/sex/group at 0, 150, 500, 1500, and 4500 ppm for 24 months. Ophthalmological examinations were conducted initially on the controls and the 4500 ppm dose level rats, at day 94 on males and day 87 on females in all groups. The study was still in progress at the time of reporting, but it was stated that the eyes were to be examined on other days. The examination was conducted with the aid of a slit lamp and a fundus camera.

After 94 days for males and 87 day for females mature cataracts occurred in 1 males (one sided) and in 5 females (both sided) at the 4500 ppm dose level. In addition, dose related striations of the lens, water clefts and bosselated surfaces of the lens occurred at 500 ppm and above. One female each exhibited lens striations, one-sided and both-sided at the LDT, 150 ppm.

Striations of the lens (both-sided) were noted in 1 female control animal.

The preliminary report, 97 days of a 24 month study indicated possible effects (precataract) in the eye of females at all dose levels tested, and cataracts at the 4500 ppm dose level. However, since the effect occurred in only one female at the LDT and in one female in controls, the effect at the LDT is equivocal.

Note: The study is preliminary. Thus it lacked most details required to thoroughly evaluate the reliability of the data. This evaluation is made to alert the Agency that the final report should be evaluated for eye effects, and that there may not be a NOEL for eye effects.

Summary:
Doses administered: 0, 150, 500, 1500, and 4500 ppm in the diet to Wistar Chbb:THOM-SPF rats.

Ophthalmological Effects:
NOEL: < 150 ppm
LEL: < 150 ppm for striations of the lens (precataract) in males and females. Cataracts occurred in males and females at 4500 ppm.

Other Systemic Effects:
Not determined.

Core classification: Not applicable since the report reviewed represents an interim report of an ongoing study.

(b)
Takashi Suzuki, Tadaomi Kadota, and Junshi Miyamoto. Comparative Study on the Cataractogenic Activity of Procymidone, vinchlozolin and Dichlozoline in Rats. Reg. No. BASF: 88/0492, Project No. Unknown. Date of work: 12/10/75 - 2/6/77.

ABSTRACT:

Vinchlozolin (Vinclozolin) was administered in the diet at 0, 750, 1500, 3000 ppm to 20 male Sprague Dawley rats/group, and at 5000 ppm to 10 male Sprague Dawley rats for 26 weeks. Biweekly ophthalmological examinations were conducted with a slit lamp, an ophthalmological fudoscope, and an ophthalmoscope. Cataract formation were noted at the end of the 16th week at the 3000, and 5000 ppm dose level. By the end of the study at week 26, cataracts developed at the 1500 ppm dose level. The cataracts developed in both eyes at 3000 ppm and 5000 ppm. The most frequent cataract had a snow flake appearance, but posterior, anterior, nuclear, and total cataracts also developed.

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Note: Cataracts developed in other studies in another strain of rat, Wistar Chbb:THOM-SPF, at higher dose levels. However, in this latter strain, female rats were slightly more susceptible than males, and precataract lesions developed at much lower dose levels, 150 ppm.

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Summary:

Doses administered: 0, 750, 1500, 3000, 5000 ppm in the diet to male Sprague Dawley rats.

Ophthalmological Effects:
NOEL: 750 ppm
LEL: 1500 ppm for cataract formation.

Other Systemic Effects:
Not determined.

Core classification: Supplementary, it is a specialized study with insufficient detail for complete evaluation.

Cover memo. on summaries of developmental tox and ophthalmology/ B:\VINCLOZ3.23C\CMEMTOX3.23C/ D Anderson/4/26/89.

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Primary reviewer: David G Anderson, PhD. David G Anderson 5/15/89
Section VII, Tox. Branch (H7509C).
Secondary reviewer: Marion Copley, DVM. 5/15/89
Section VII, Tox. Branch (H7509C).

DATA EVALUATION REPORT 007228

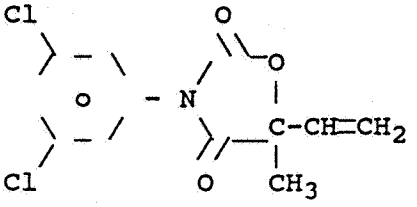
STUDY TYPE: Preliminary Report of Developmental Toxicity/ 83-3/Rat/88-0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088.

TOX. CHEM. No.: 323C

MRID No.: 409505-01

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan 50W, 50% A.I., Ronilan FL, 41% A.I.

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

TESTING FACILITY: BASF Aktiengesellshaft, Dept. Toxicology, Ludwigshafen, West Germany.

STUDY NO.: 88/0493, Project No.:34R0165/84084, 34R0165/84085, 34R0165/84086, 92R0165/84088.

REPORT TITLE: First Preliminary Results of Several Prenatal Toxicology Studies with Reg. No. 258 (Vinclozolin) in Rats After Oral Administration; Project No.:34R0165/84084, 34R0165/84085, 34R0165/84086, 92R0165/84088..

AUTHOR(S): J Hellwig, PhD

REPORT ISSUED: October, 1988.

CONCLUSIONS: This DER contains 4 studies reviewed together. The four studies or projects are referred to by the last number of the project (See Tables A, B, C, and D below).

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Preliminary Report of Developmental Toxicity/ 83-3/Rat/88-0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088. 007228

Doses Administered: In study 4 - 0, 15, 50, and 150 mg/kg/day, in study 5 - 0, 50, 100, and 200 mg/kg/day, in study 6 - 0, 200, and 400 mg/kg/day, and in study 8 - 0, 600, and 1000 mg/kg/day.

Developmental Toxicity:
NOEL: 15 mg/kg/day.
LEL: 50 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, hydroureter, and accessory 14th rib may have occurred at 400 mg/kg/day and higher.

Maternal Toxicity:
NOEL: < 600 mg/kg/day.
LEL: < 600 mg/kg/day for increases in absolute and relative adrenal and liver weight. Organ weights were not determined at lower dose levels.

Core classification: Supplementary because it is a preliminary study series which results in insufficient experimental detail for complete evaluation.

A. MATERIALS:

1. Test compound:Vinclozolin, Description was NOT SPECIFIED Batch # 173, Purity 99.6%.

2. Test animals: Species:Rats, Strain: Chbb:THOM-SPF Wistar, Age:NOT SPECIFIED, Weight: 200-250 g, Source: NOT SPECIFIED.

B. STUDY DESIGN: The submitted report of the study indicated that the material and methods could be found in the protocols of 9/15/87, 12/30/87, 3/24/88, and 5/20/88 for the 4 respective studies. These protocols could not be found in the package submitted with the reports.

1. Animal Assignment - Animals were assigned a method NOT SPECIFIED to the groups.

2. Test Substance Administration: Test substance was administered by gavage, but the vehicle was NOT SPECIFIED. Total volume of the dose was NOT SPECIFIED. Dates of administration were NOT SPECIFIED, but were administered on gestational day (gd) 6 through 19. Test material was administered orally, but no other details were given of the route, vehicle, or volume. Doses were given longer than required by the guidelines. Guidelines require administration of the doses, gestational day (gd) 6-15. The dose levels and the number of animals used per group in the

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Preliminary Report of Developmental Toxicity/ 83-3/Rat/88-0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088.

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four studies are given in Tables A, B, C, and D.

Table A.

Groups used for Project Number 34R0165/84084. Hereafter designated Study 4.

Test group	Dose mg/kg/ day	Volume of Doses ml/kg/day	Number of Females
1. Cont.	vehicle ?	?	25
2. Low (LDT)	15	?	25
3. Mid (MDT)	50	?	25
4. High(HDT)	150	?	25

Table B.

Groups used for Project Number 34R0165/84085. Hereafter designated Study 5.

Test group	Dose mg/kg/ day	Volume of Doses ml/kg/day	Number of Females
1. Cont.	vehicle ?	?	25
2. Low (LDT)	50	?	25
3. Mid (MDT)	100	?	25
4. High(HDT)	200	?	25

Table C.

Groups used for Project Number 34R0165/84086. Hereafter designated Study 6.

Test group	Dose mg/kg/ day	Volume of Doses ml/kg/day	Number of Females
1. Cont.	vehicle ?	?	25
2. Low (LDT)	200	?	25
3. High(HDT)	400	?	25

Preliminary Report of Developmental Toxicity/ 83-3/Rat/88-0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088.

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Table D.

Groups used for Project Number 92R0165/84088. Hereafter designated Study 3.

Test group	Dose mg/kg/ day	Volume of Doses ml/kg/day	Number of Females
1. Cont.	vehicle ?	?	10
2. Low (LDT)	600	?	10
3. High(HDT)	1000	?	10

3. Analysis of Dosing Solutions: No stability studies, or analyses of dosing suspensions were submitted.

4. Food and Water: - The food source was **NOT SPECIFIED.** The water source and purity water was **NOT SPECIFIED.** Whether or not they were supplied ad libitum was **NOT SPECIFIED.**

5. Statistics - **NOT SPECIFIED.**
All tests were reported at the 5% and 1% level of significance.

6. Quality assurance was not signed because the study is preliminary. The study however was conducted under the EPA GLP, which will be verified in the final report.

7. History - These four studies were conducted in response to a study in Japan under Japanese guidelines for BASF Japan (K Takehara, M Itabashi, T Inoue and M Tajima, "Teratogenicicy Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration", conducted by Nippon Institute for Biological Science, 2221-1 Shin-machi, Ohme-shi, Tokyo 198, December 1979 for BASF Japan. This study from Japan differed from EPA guideline studies essentially in that the test material was administered in the diet, and from gd 0 through 21, 11 days longer than OPP requirements of gd 6 through 15. The four new studies were also conducted for a longer dosing period, 6 through 19, but by gavage. These four studies demonstrated effects on the anal-genital distance in males, and verify the study results from Japan.

As a result, BASF conducted preliminary studies to validate the effects. This preliminary validation is reported in a series of studies designated by an overall study number of 88/0493 or Registration Number BASF: 88/0493, and four individual studies within the study number 88/0493 designated (34R0165/84084)

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(34R0165/84085), (34R0165/84086), (92R0165/84088). The studies are preliminary, and therefore are not reported in the detail necessary for a guideline study. Although all are supplementary, they probably contain valid information, and indicate that the effects noted in the Japanese study were valid.

The results of these four preliminary studies are the subject of this DER.

C. METHODS AND RESULTS: The numbered tables were copied from study report submitted.

1. Observations - Animals were inspected daily for signs of toxicity and mortality.

Results - Toxicity - Unsteady gate was observed in a total of 7/10 animals by the end of gestation; 4/10 animals on gd 11 and 12, and 2/10 animals on gd 14 and 13 at the 1000 mg/kg/day dose level. These effects disappeared after gd 14. Piloerection was observed in 2/10 animals, and urine stained fur in 1/10 animals at 1000 mg/kg/day. No other adverse observations were reported.

Mortality (Survival) - No unscheduled deaths were reported.

2. Body Weight - They were weighed on gd 0, 1, 3, 6, 8, 10, 13, 15, 17, 19, and 20. The body weight gain was determined between successive weighings.

Results - Body weights and body weight gain were variable but none appeared to demonstrate a dose related decrement or elevation. Statistically significant increases and decreases were noted, but no treatment related responses were noted even at 1000 mg/kg/day. Body weight gain was statistically significantly decreased on gd 8 to 10, but statistically significantly increased of gd 13 to 15 at 1000 mg/kg/day (Table 003 of study 8). On the other gestational days the body weights and weight gains alternated between nominally elevated and nominally decreased. At lower dose levels, statistically significant body weight gain elevations and decrements occurred but due to the inconsistencies and failure to exhibit body weight gain decrements at 1000 mg/kg/day, they probably were not dose related. No dose related body weight gain change occurred gd 0-6, 6-19, 19-20, or 0-20 (Table 004 of study 8).

3. Food consumption - Food consumption was determined and mean daily intake was calculated. Efficiency was NOT SPECIFIED.

Food consumption was determined gd 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10, 10 to 13, 13 to 15, 15 to 17, 17 to 19, and 19 to 20.

Results - Food consumption was comparable to control values on the last one-half of the gestational days. On gd 6 to 8 (88% of

controls), 8 to 10 (64% of controls), and 10 to 13 (70% of controls) at 1000 mg/kg/day, food consumption was statistically significantly decreased. However, preliminary observations of the food consumption and body weight gain patterns did not indicate any dose related effects.

Relative efficiency of food utilization was not calculated because preliminary calculations indicated that the results were too variable.

4. Blood was collected - The method of collection was NOT SPECIFIED. Blood was collected on gd 20. When a percent change is reported in parentheses, it refers to percent of control values.

The CHECKED (X) parameters were examined.

a. Hematology -

X Hematocrit (HCT)*	Total plasma protein (TP)
X Hemoglobin (HGB)*	Leukocyte differential count
X Leukocyte count (WBC)*	X Mean corpuscular HGB (MCH)
X Erythrocyte count (RBC)*	X Mean corpuscular HGB conc.(MCHC)
X Platelet count*	X Mean corpuscular volume (MCV)
Thromboplastin time	

Results - Platelets were statistically significantly depressed at 150 mg/kg/day (92%) in study 4. The white blood cell count was statistically significantly depressed at 200 mg/kg/day in study 5, and statistically significantly elevated at 1000 mg/kg/day in study 8. There were no statistically significant differences in study 6. None of the effects showed any dose relationship or consistency, and thus, these effects did not appeared to be test material related.

5. Necropsy of Mothers and Fetal Examinations: Dams were sacrificed on gd 20. Pregnant uteruses were weighed and subtracted from the weight of the dam. The corpora lutea, the number of viable fetuses, dead fetuses, resorptions, and implantation sites were counted. Fetal weights were determined and malformations and variations were determined. The anal-genital distance was determined in fetuses from study 4, 6, and 8. Fetuses were stated to be examined according to the FIFRA guidelines, but no other description of the methods used was presented.

a. Gross pathology on Mothers - No dose related effects were reported.

b. Results on Mothers - The carcass weight of dams, and the gravid uterus was not statistically significantly different from control values. Absolute and relative liver weights (Abs. 133-147% of control values) and adrenal weights (Abs. 220-280% of control values) were statistically significantly elevated at 600

and 1000 mg/kg/day in study 8 (Table 009 and 010 of study 8). Organ weights were not determined at lower dose levels in the other studies.

Reproduction data and corpora luteal counts, implantation loss, and post-implantation loss did not differ from control values.

c. Results of the Fetal Examination - The fetal anal-genital distances are reported in Table 1-012 of study 4, Table 1-012 of study 6, and Table 1-014 of study 8. The anal-genital distance was not determined in study 5. A statistically significant dose related decrease occurred in male fetuses at 50 mg/kg/day and higher, and in the anal-genital index at 150 mg/kg/day and higher. The method of calculation of the index was not explained but it was stated to be a method taken from the literature, reference not given. The male fetuses in the 1000 mg/kg/day dose group looked like females, but on examination of the placement and appearance of the male gonads, they appeared to be superficially normal. On this basis the phenomenon was considered to be pseudohermaphroditism. No comment was made with regard to female fetuses, which may have been affected.

Fetal weights are statistically significantly depressed only at 1000 mg/kg/day in study 8 (Table 1-015). Early, late, and total resorptions did not differ from control values. The number of live male and females fetuses did not differ from control values.

On soft tissue examination, the incidence of dilated renal pelvis and hydroureter in fetuses and hydroureter in litters were each statistically significantly elevated at 400 mg/kg/day in study 6 (Table 017 of study 6). At the higher dose levels in study 8, statistically significant increases occurred only in hydroureter in fetuses at 600 and 1000 mg/kg/day, but dilated renal pelvis was nominally elevated at 1000 mg/kg/day (Table 1-019 of study 8). However these results may not have been based on sufficient numbers of litters to give definitive results. These results were based on litters from 7, 5, and 8 dams in controls, 600, and 1000 mg/kg/day dose groups, respectively.
Lower dose level groups contained 24 litters. In study 6 with 24 litters, statistically significant increases were seen in hydroureter, and dilated renal pelvis in fetuses. The LEL for this effect should be considered 400 mg/kg/day and NOEL should be considered 200 mg/kg/day.

On skeletal examination, the incidence of fetuses with accessory 14th rib is statistically significant increased, and the incidence in litters is nominally increased at 400 mg/kg/day in study 6 (Table 1-020 of study 6). The accessory 14th rib was statistically significantly increased at the 600 and 1000 mg/kg/day dose level in litters in study 8 (Table 022 of study 8). Other parameters were statistically significantly increased in fetuses, but in litters incidence was decreased, and probably not compound related. Even the increased incidence of 14th rib

may not be treatment related because at the higher incidence noted in the controls of study 5, and the marginal increase seen in study 6 and 8. Thus the apparent effects on the 14th rib are equivocal. Statistically significant increases occurred in ossification of the sternebrae in fetuses at 1000 mg/kg/day in study 8 (Table 024 of study 8).

D. DISCUSSION AND ABSTRACT:

Vinclozolin was administered orally by gavage (vehicle not specified) to 25 rats/group at 0, 15, 50, and 150 mg/kg/day in study 4 (34R0165/84084), at 0, 50, 100, 200 mg/kg/day in study 5 (34R0165/84085), at 0, 200, 400 mg/kg/day in study 6 (34R0165/84086), and to 10 rats/group at 0, 600, and 1000 mg/kg/day in study 8 (92R0165/84088) from gestational day (gd) 6 through 19. At gd 20 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Maternal toxicity was demonstrated at 600 and 1000 mg/kg/day by the statistically significant increase in absolute and relative adrenal and liver weight in study 8, the only study where organ weights were determined. No histology was conducted on the organs, but other studies have demonstrated lipid accumulation in the adrenals, and centrilobular cloudiness of the liver. Statistically significant increases and decreases occurred in the body weight gain and in food consumption with no apparent dose relatedness in any of the studies. The relative efficiency of food utilization was too variable to be definitive.

Statistically significant male and female fetal body weight decrements occurred at 1000 mg/kg/day in study 8. These weight decrements are considered test material related.

A statistically significant increase occurred in pseudohermaphroditism among male fetuses. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. The anal-genital distance in male fetuses was statistically significantly decreased at 50 mg/kg/day and higher in study 4, 6, and 8. The anal-genital distance was not determined in study 5. The response was dose related. These results are consistent with hormonal effects from the test material.

Soft tissue examination of fetuses indicated that increased incidence occurred in dilated renal pelvis and hydroureter at 400 mg/kg/day in study 6. At higher dose levels in study 8, the incidence of dilated renal pelvis and hydroureter was nominally increased. The failure of the dilated renal pelvis, and hydroureter to be significantly increased in study 8 was attributed to the fewer litters used (7, 5, and 8 in controls, 600, and 1000 mg/kg/day). However, although these effects appear to be real, there is doubt about the NOEL for these renal effects.

Preliminary Report of Developmental Toxicity/ 83-3/Rat/88-0493, Project #: 34R0165/84084, 34R0165/84085, 34R0165/84086, and 92R0165/84088.

007228

Skeletal examination of fetuses indicated increased incidence of accessory 14th rib at 400 mg/kg/day in study 6 and in fetuses and litters at 600, and 1000 mg/kg/day in study 8. These effects on the 14th rib are not definitive, and require historical control data to aid in the interpretation of the effects. Preliminary evaluation suggest a dose related increase in 14th ribs.

No other dose related effects were reported, but it was reported that evaluation of the fetuses for visceral and skeletal effects was not complete.

Summary:

Four preliminary studies were conducted in rats to determined the potential of Vinclozolin to cause developmental effects. In the combined studies doses were administered by gavage at 0, 15, 50, 100, 150, 200, 400, 600, 1000 mg/kg/day from gestational day 6 to 19. Maternal toxicity was demonstrated at 600 and 1000 mg/kg/day by the statistically significant increase in absolute and relative adrenal and liver weight at 600, and 1000 mg/kg/day, the only dose levels where organ weights were determined. No histology was conducted on the organs, but other studies have demonstrated lipid accumulation in the adrenals, and centrilobular cloudiness of the liver. No dose related body weight effects occurred in dams. A dose related statistically significant increase occurred in pseudohermaphroditism among male fetuses at the 50 mg/kg/day dose level and above. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. At higher dose levels renal and skeletal effects were noted at 400 mg/kg/day. No effects were noted at 15 mg/kg/day.

DER for Developmental Toxicity/88/0493/34R0165/84084/84085/ 84086/84088/ B:\VINCLOZ3.23C\DDEV4COM.BIN/D Anderson/4/18/89.

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Vinclozolin Toxicology Reviews

Page _____ is not included in this copy.

Pages 18 through 30 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary reviewer: David G Anderson, PhD. David G Anderson 5/15/89
Section VII, Tox. Branch (H7509C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 5/16/89
Section VII, Tox. Branch (H7509C).

007228

DATA EVALUATION REPORT

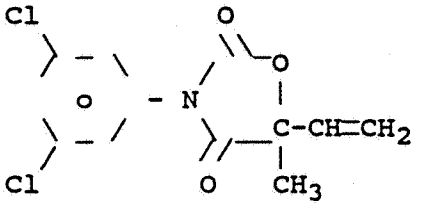
STUDY TYPE: Developmental Toxicity Study (83-3)/Rat/No study #/Study under Reg Doc # BASF:88/0493.

TOX. CHEM. No.: 323C

MRID No.: 409505-01

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan 50W, 50% A.I., Ronilan FL, 41% A.I.

SPONSOR: BASF Japan Ltd.

TESTING FACILITY: Nippon Institute for Biological Science, 222-1 Shin-machi, Ohme-shi, Tokyo 198, Japan.

STUDY NO.: Reg. No. BASF:88/0493, Project No.:Unknown.

REPORT TITLE: Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration.

AUTHOR(S): K Takehara, M Itasbashi, T Inoue, and M Tajima.

REPORT ISSUED: December, 1979.

CONCLUSIONS:
Doses Administered: 0, 300, 1500, and 7500 ppm or 0, 23, 111, and 394 mg/kg/day in the feed of CD/CRJ rats.

Teratogenicity and Developmental Toxicity:
NOEL: 23 mg/kg/day.
LEL: 111 mg/kg/day for decreased anal-genital distance (pseudohermaphroditism), and left lumbar ribs. At the HDT, increased hydronephrosis and delayed ossification were noted.

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Developmental Toxicity Study (83-3)/Rat/No study #/Study under Reg Doc # BASF:88/0493.

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Maternal Toxicity:
NOEL: < 23 mg/kg/day. Very close to the NOEL.
LEL: < 23 mg/kg/day for increases in adrenal weight. At the HDT body weight, food consumption, and relative efficiency of food utilization were decreased.

Core classification: Supplementary because it is not reported in sufficient experimental detail for complete evaluation.

A. MATERIALS:

1. Test compound:Vinclozolin, Technical, Description white powder, Batch # lot No. 83 258 173, Purity 92.8%.

2. Test animals: Species:Rats, Strain: CD/CRJ, Age: seven weeks, Weight: 216-223 g average among groups, Source: Charles River Japan.

3. Environmental: Test animals were acclimatized for 2 weeks. The animal room was a barrier type system. Humidity: 68 ± 10%. Temperature: 23 ± 1 degrees C. Light:dark = 12:12.

B. STUDY DESIGN:

1. Animal Assignment - The method of animals assignment to groups was NOT SPECIFIED.

2. Test Substance Administration: Test substance was administered in the feed. Dates of administration were on gestational day (gd): NOT SPECIFIED. The study was conducted from August 23 to October 4, 1979. Test material administered was administered orally in the feed at 0, 300, 1500 and 7500 ppm from gestational day (gd) 0 to 21 to groups of 19 to 22 presumed pregnant rats.

Test group	Dose mg/kg/ day	Dose ppm	Number of Females
1. Cont.	0	0	22
2. Low (LDT)	23	300	19
3. Mid (MDT)	111	1500	22
4. High(HDT)	394	7500	22

3. Analysis of Dosing Solutions: No stability studies, or analyses of dosing suspensions were submitted, but the report claimed they were conducted by BASF AG. (West Germany).

4. Food and Water: - The food was CRF-1 from Oriental Yeast Co.

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Ldt., the water was from the tap, both were supplied ad libitum.
5. Statistics - NOT SPECIFIED except inter-group relations were tested by the t-test. All tests were reported at the 5% and 1% level of significance.

5. Quality assurance statements were not submitted with this study.

C. METHODS AND RESULTS: The numbered Tables were copied from study report submitted.

1. Observations - Animals were inspected daily for signs of toxicity and mortality.

Results - Toxicity - At HDT, several effects were observed which are indicated below. Decreased fecal excretion was noted in all rats from gd 2 to the end of the study. Piloerection and reddish-brown stained hair around the nostrils were seen from gd 9 to the end of the study. Transient ptosis, decreased responsiveness to stimuli, and bradypnea occurred in 4 animals after gd 11. Reddish urine was excreted by 1 rat. No noteworthy effects were observed in other groups.

Mortality (Survival) - All rats survived to terminal sacrifice.

2. Body Weight - They were weighed daily. The body weight gain was not determined in the submitted report.

Results - A statistically significant depression in body weights occurred on gd 2 (94% of control) to gd 21 (73% of control) at the HDT, and gd 10 (96% of control) at the MDT (Table 3). Body weight loss occurred from gd 2 through gd 5 (-1 to -4 g), and again at gd 7 (-2 g). The initial body weight of the HDT group was higher (103%) than controls. Body weights in the 1500 ppm dose group did not differ statistically significantly from control values before and after gd 10, but they were nominally depressed. Body weight gain did not differ appreciably from controls after gd 15, although the body weight was statistically significantly depressed for most of the dosing period at the HDT. These weight effects appeared to be test material related.

3. Food consumption - Food consumption was determined and mean daily intake of test material was calculated. Efficiency was NOT SPECIFIED. The relative food efficiency was calculated, however, for this DER.

Food consumption was determined gd 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10, 10 to 13, 13 to 15, 15 to 17, 17 to 19, 19 to 20, and 20 to 21.

Results - Food consumption was generally comparable to control values. However, food consumption was statistically significantly

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increased on gd 0 to 1 (113% of control values), dg 16 to 17, and gd 19 to 20 at the LDT, statistically significantly decreased on gd 0 to 4 (88% of controls) at the MDT, and on all gestational days (37% - 70% of controls) at the HDT (Table 1).

Relative efficiency of food utilization was calculated from the body weight gains and the food consumption/animal (See table A). The data indicated that the relative food efficiency was decreased for the first 10 gestational days, but after gd 10 relative food efficiency could not be distinguished from control values.

Table A.

The relative efficiency of food utilization as calculated from the submitted report [(body weight gain)(g)/(g food consumed during period of the weight gain)] = Relative Efficiency

Study day (Post-coital)	Group Control	300 ppm	1500 ppm	7500 ppm
0 to 1	0.067	0.29	0.067	- 1.43
1 to 2	0.29	0.26	0.00	- 0.43
2 to 3	0.37	0.29	0.13	- 0.29
3 to 4	0.16	0.16	0.25	- 0.57
4 to 5	0.21	0.20	0.18	- 0.11
5 to 6	0.20	0.24	0.26	0.10
6 to 7	0.15	0.20	0.26	- 0.18
7 to 8	0.30	0.20	0.16	0.17
8 to 9	0.25	0.29	0.25	0.09
9 to 10	0.35	0.29	0.25	0.09
Means from day 0 to 10	0.24	0.21	0.18	- 0.26
10 to 11	0.29	0.24	0.38	0.25
11 to 12	0.23	0.23	0.20	0.23
12 to 13	0.22	0.22	0.22	0.21
13 to 14	0.24	0.14	0.32	0.23
14 to 15	0.32	0.29	0.32	0.36
15 to 16	0.41	0.43	0.38	0.47
16 to 17	0.48	0.54	0.56	0.50
17 to 18	0.56	0.56	0.56	0.38
18 to 19	0.62	0.58	0.54	0.47
19 to 20	0.65	0.55	0.52	0.64
20 to 21	0.33	0.27	0.17	0.00
Means from day 0 to 21	0.40	0.37	0.38	0.34
Overall mean	6.70/21 = 0.32	6.11/21 = 0.29	5.98/21 = 0.28	1.88/21 = 0.09

4. Water Consumption - Water consumption was determined daily (Table 2). Significant increases over control values occurred on

gd 16 (121%), 17 (114%)and 20 (117%). These decreases in water consumption are expressed because a possible relationship to the adrenal effects in dams and the hydronephosis seen in some fetuses. Other statistically significant changes occurred but none were dose related.

5. Necropsy of Mothers and Fetal Examinations: Dams were sacrificed by exsanguination after anesthesia between 9:30 and 10:30 AM on gd 21. Organ weights were determined. Placentae and fetuses were weighed. The corpora lutea, the number of viable fetuses, dead fetuses, resorption, and implantation sites were counted. One third of the fetuses were fixed in Bouin's solution and the head and the abdomen were examined for anomalies by the method of Wilson. Two thirds of the fetuses were examined for skeletal anomalies with the aid of alizarin staining. The anal-genital distance was measured with a micrometer after fixation in Bouin's.

a. Results from Determination of Maternal Organ Weights - Six animals were randomly selected from each group for adrenal, pituitary, and brain weights determination (Table 5). The organ weights in only 6 animals were determined, and thus, the significance of the weight difference is in doubt. However, adrenal weights were increased at all dose levels, dose related. The right adrenal weights were statistically significantly increased at all dose levels, but the left adrenal weight was nominally increased at the LDT (112% of control values). These adrenal weight increases were supported by gross observations of mild adrenal swelling. Pituitary weights were statistically significantly depressed at the HDT (78% of control). Brain weights did not differ from control values. The ovary weights were statistically significantly increased (143% of control) at the HDT (Table 6). The ovarian weight increase came from the increased size of the corpora lutea (Table 6).

b. Results from Maternal Gross pathology - Mild swelling of the adrenals were noted in 1 rat at the LDT, 7 rats in the MDT, and 17 rats at the HDT. Centrilobular cloudiness of the liver was noted at the HDT. Pronounced yellowing of the corpora lutea was seen at the HDT. Mild to moderate hydronephrosis was seen in the right kidney in 1 rat each at the MDT, and HDT.

c. Results from Maternal Examination - Reproduction data on corpora luteal counts and implantation sites did not differ from controls. Early, mid, and total resorption appeared to increase at the HDT, but the values were not statistically significant. Mortality of embryos or fetuses were 225% of control values at the HDT, but they apparently were not statistically significant (Table 7).

d. Results from Fetal Examination - The results from the fetal weight determinations are reported in Table 7. Males and female

fetal body weights were statistically significantly decreased (75% of control values for males and females) at the HDT, and the placentae from HDT male fetuses were statistically significantly depressed (86% of control, $p < 0.01$)(Table 7).

External hermaphroditism was noted in all male fetuses or 123 males of 246 male and female fetuses at the HDT (Table 8). On superficial examination, internal genitalia were found not to differ from controls. The fetal anal-genital distances are reported in Table 9. The perineal or anal-genital distance was decreased at 1500 ppm (MDT) and above (Table 9). The perineal distance was statistically significantly decreased (89% of controls, $p < 0.01$) in female fetuses at the HDT.

Fetal renal problems were evident at the HDT only. Hypoplasia of the renal papillae was increased from 2/72 in controls to 4/71 at the HDT. There were 3/71 incidences of dilated renal pelvis, and hydronephrosis was statistically significantly increased (15/71) at the HDT (Table 10).

Statistically significantly decreased ossification occurred at the HDT in cervical vertebrae, metacarpal bones, proximal phalanges, and metatarsal bones. Statistically significant increases occurred in left lumbar ribs in the MDT and HDT (Table 11).

Additional possible treatment related effects were noted at the HDT, such as partial defect and fusion of thoracic vertebrae and ribs in 1 fetus, and undersized ribs in 1 fetus.

D. DISCUSSION AND ABSTRACT:

Vinclozolin was administered orally in the feed to 19-20 rats/group at 0, 300, 1500, and 7500 ppm from gestational day (gd) 0 through 21. At gd 21 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Treatment related decreases in the maternal weight gain may have occurred at the MDT, but statistically significant decreases occurred only at the HDT. Food consumption was also decreased at the HDT, but the relative efficiency of food utilization was also depressed at the HDT before gd 10. Water consumption was statistically significantly increased on gd 16 and nominally increased at gd 17 at the HDT. The treatment relatedness of these increases could not be determined.

The only organ weights obtained were for the adrenal, pituitary, brain, and ovary. The left adrenal weight was statistically significantly increased at all dose levels, but the right adrenal weight was nominally elevated at LDT and statistically significantly elevated at higher dose levels. These dose related adrenal weight increases at all dose levels were supported by gross swelling of the adenal noted at necropsy. The pituitary weights were statistically significantly decreased at the HDT, but the brain weight was unaffected. Statistically significant increases occurred in the weight of the ovaries in

dams at the HDT, which was due to an increase in the size of corpora lutea.

Centrilobular cloudiness of the liver was noted at necropsy at the HDT.

Statistically significant decreases occurred in male and female fetal weight at the HDT.

The anal-genital distance was statistically significantly decreased at the mid dose tested (MDT) and the highest dose tested (HDT). Male fetuses were no different externally from female fetuses at the HDT. A statistically significant decrease in the anal-genital distance occurred in males at the MDT and HDT. This decreased anal-genital distance was designated pseudohermaphroditism because these males appeared to have superficially normal internal testes. The response was dose related. The increased size in the corpora lutea, the increased adrenal weights in dams at all dose levels, the decreased anal-genital distance in males at the MDT and HDT and in females at the HDT are consistent with the hypothesis that the test material causes secondary or primary hormonal effects.

Statistically significantly increased incidence of hypoplasia of the renal papillae, dilated renal pelvis, hydronephrosis, and hydroureter occurred in fetuses at the HDT.

Statistically significantly decreased ossification occurred at the HDT in cervical vertebrae, metacarpal bones, proximal phalanges, and metatarsal bones. Statistically significant increases occurred in left lumbar ribs in the MDT and HDT.

The partial defect and fusion of thoracic vertebrae and ribs in 1 fetus, and undersized ribs in 1 fetus which occurred at the HDT may also be related to the skeletal effects.

DER for Developmental Toxicity, Japan/no study no./
B:\vincloz3.23C\DDEVRAT.JAP/D Anderson/4/17/89.

Vinclozolin Toxicology review 5/31/89

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Pages 38 through 48 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary reviewer: David G Anderson, PhD. David G Anderson 5/15/89
Section 2, Tox. Branch 1 (IRS) (H7509C).
Secondary reviewer: Marion P Copley DVM. Marion P. Copley 5/16/89
Section 2, Tox. Branch 1 (IRS) (H7509C).

007228

DATA EVALUATION REPORT

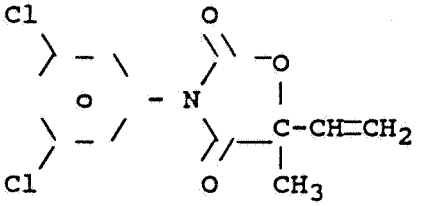
STUDY TYPE: Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 88/0492/Project # 31S0375/88034 and 71S0375/88026. (Project 31S0375/88034 is referred to as study 34 and project 71S0375/88026 is referred to as study 26.

TOX. CHEM. No.: 323C

MRID No.: 409505-02

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan 50W, 50% A.I., Ronilan FL, 41% A.I.

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

TESTING FACILITY: BASF Aktiengesellschaft, Dept. of Toxicology, Ludwigshafen, West Germany.

STUDY NO.: Reg. No. BASF:88/0492, Project No.: 31S0375/88034, and 71S0375/88026, (Interim report).

REPORT TITLE: First Preliminary Information of Ophthalmological Findings with Reg. No. 83 258 (Vinclozolin) in Rats After Oral Administration.

AUTHOR(S): P Kirsch.

REPORT ISSUED: October, 1988.

CONCLUSIONS:

Study 34 or Project No. 31S0375/88034:
Doses administered: 0, 300, 1000, and 3000 ppm in the diet to

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Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 88/0492/Project # 31S0375/88034 and 71S0375/88026. 007228

Wistar Chbb:THOM-SPF rats.

Ophthalmological Effects:
NOEL: < 300 ppm
LEL: < 300 ppm for precataract effects which included striations of the lens in males and females and cataracts in 1 female at 3000 ppm.

Other Systemic Effects:
Not determined.

Core classification: Supplementary due to the specialized nature of the study and insufficient detail for complete evaluation.

Study 26 or Project No. 71S0375/88026 (Interim report):

Doses administered: 0, 150, 500, 1500, and 4500 ppm in the diet to Wistar Chbb:THOM-SPF rats.

Ophthalmological Effects:
NOEL: < 150 ppm
LEL: < 150 ppm for striations of the lens (precataract) in males and females. Cataracts occurred in males and females at 4500 ppm.

Other Systemic Effects:
Not determined.

Core classification: Not applcable since the report reviewed represents an interim report of an ongoing study.

A. MATERIALS:

1. Test compound:Vinclozolin, Technical, Description white powder, Batch No. N 183, Purity 99.2%.

2. Test animals: Species:Rats, Strain: Chbb:THOM-SPF, Age: NOT SPECIFIED, Weight: males 150-230, and females 120-190 ; average among groups, Source: NOT SPECIFIED.

3. Environmental: Test animals were acclimatized for NOT SPECIFIED. Humidity: NOT SPECIFIED. Temperature: NOT SPECIFIED. Light:dark = NOT SPECIFIED.

B. STUDY DESIGN:

1. Animal Assignment - The method of animal assignment to groups was NOT SPECIFIED.

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Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 88/0492/Project # 31S0375/88034 and 71S0375/88026.

2. Test Substance Administration: The test substance was administered in a manner NOT SPECIFIED. Dates of administration were NOT SPECIFIED. The study was conducted from July 15 - October 17/18, 1988 for study 34; and July 1, 1988 - July 3-5, 1990 for males, and July 8, 1988 - July 10-12, 1990 for females in study 26. Test material was administered orally in the diet at 0, 300, 1000, and 3000 ppm for 82 days to 10 rats/sex/group in study 34 (Table A); and at 0, 150, 500, 1500, and 4500 ppm for 24 months to 20 rats/sex/group in study 26 (Table B).

Table A.
Dose levels and number of animals used in Study 34 (Project No. 31S0375/88034). Ophthalmological examination conducted initially on control and HDT animals.

Test group	Approx. Dose mg/kg/day	Dose ppm	Number of Males/ Females	Ophthalmological examination conducted on day
1. Cont.	0	0	10/10	42 - 82
2. Low (LDT)	15	300	10/10	- 52 82
3. Mid (MDT)	50	1000	10/10	- 52 82
4. High(HDT)	150	3000	10/10	42 - 82

Table B.
Dose levels and number of animals used in Study 26 [Project No. 71S0375/88026 (Interim Report)]. Ophthalmological examination conducted initially on control and HDT animals.

Test group	Approx. Dose mg/kg/day	Dose ppm	Number of Males/ Females	Ophthalmological examination conducted on day *	
				Males	Females
1. Cont.	0	0	20/20	94	87
2. Low (LDT)	7.5	150	20/20	94	87
3. Mid1 (MDT1)	25	500	20/20	94	87
4. Mid2 (MDT2)	75	1500	20/20	94	87
5. High (HDT)	225	4500	20/20	94	87

* Ophthalmological examinations are planned for other days of this 24 month study.

4. Analysis of Dosing Solutions: No stability studies, or analyses of dosing suspensions were submitted.

5. Food and Water: - NOT SPECIFIED.

6. Statistics - NOT SPECIFIED.

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7. Quality assurance statements were not submitted with these preliminary studies.

STUDY 34

METHODS AND RESULTS: The numbered Tables were copied from study report submitted.

1. Only ophthalmological examinations were reported on these animals. The eyes were examined using the hand-held slit lamp and the fundus camera.

Results - Initially remainders of the pupillary membrane and corneal stipplings were detected. These were considered to be spontaneous findings without pathological relevance. The frequency was not stated, but they were apparently not considered sufficiently significant to be recorded.

At day 42 and 52 no significant changes could be detected with the naked eye, however with the hand-held slit lamp striations were visible on the lens. This finding was observed in 1 male at 1000 and 2 males at 3000 ppm. This finding was noted in 1 female at 300 ppm, and in 6 females at 1000 ppm, and 4 females at 3000 ppm. Clearly visible Y-suture lines were visible in males, 3 at 1000 ppm and 3000 ppm, and in females, 3 and 2 females at 1000 ppm and 3000 ppm, respectively. The fundus was weakly visible in 3 females at 3000 ppm. In the remaining animals the fundus was clearly visible (Tables 001 and 002). These findings were stated to possibly represent the first stage of cataract formation.

On day 72, the first mature cataract was visible to the naked eye in 1 female from the 3000 ppm dose group (Table 004).

On day 82, all animals exhibited similar qualitative findings to those exhibited on day 42 and 52. The number of animals with these lesions increased from day 42 and 52 to day 82 (Table 003 and 004), although comparisons are difficult because of the different examination days at the HDT. Animals were examined on day 42 at the 0, and 3000 ppm dose levels, and on day 52 at the 300 and 1000 ppm dose levels. All animals in all groups were examined on day 82. However, males and females exhibited striations on the lens at all dose levels, and 1 male exhibited a weakly visible fundus at 3000 ppm, and 1 male at 1000 ppm, and 6 females at 3000 ppm exhibited bosselated lens surfaces (a rounded eminence on a surface)(Tables 003 and 004). A weakly visible fundus was observed in 1 male, and in 4 females at 3000 ppm. Mature cataracts were observed (both-sided) in female at 3000 ppm (Table 003 and 004). These findings indicate significant effects on the eye of males and females (precataract) at all dose levels of Vinclozolin, and 1 cataract in a female at 3000 ppm.

Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 88/0492/Project # 31S0375/88034 and 71S0375/88026. 007228

STUDY 26:

METHODS AND RESULTS: The numbered Tables were copied from study report submitted.

1. Only ophthalmological examinationswere reported on these animals.

Results - Initially remainders of the pupillary membrane and corneal stipplings were detected. These were considered to be spontaneous findings without pathological relevance. The frequency was not stated, but they were apparently not considered sufficiently significant to be recorded.

After 94 days for males and 87 day for females mature cataracts occurred in 1 males (one sided) and in 5 females (both sided) at the 4500 ppm dose level (Table 005 and 006). In addition, there were dose related occurrences of striations of the lens, water clefts and bosselated surfaces of the lens at 500 ppm and above. One female each exhibited lens striations, one-sided and both-sided at the LDT, 150 ppm. Striations of the lens (both-sided) were noted in 1 female control animal.

The preliminary report, 97 days of a 24 month study indicated possible effects (precataract) in the eye of females at all dose levels tested, and cataracts at the 3000 ppm dose level. However, since the effect occurred in only one female at the LDT and in one female in controls, the effect at the LDT is equivocal.

DISCUSSION AND ABSTRACT FOR STUDY 34:

Vinclozolin was administered in the diet to 10 rats/sex/group at 0, 300, 1000, and 3000 ppm for 82 days. Ophthalmological examinations were conducted initially on the controls and 3000 ppm dose level rats, at day 42 on the 300, and 1000 ppm dose group rats, and at day 82 on all groups of rats. The examination was conducted with the aid of a slit lamp and a fundus camera.

Indications of precataract formation occurred at day 42 and 52. The number of animals affected had increased at the examination on day 82. Males and females exhibited striated lens at all dose levels, and 1 male exhibited a weakly visible fundus at 3000 ppm. Females exhibited bosselated lens surfaces, weakly visible fundus in 4 animals, and 1 mature cataract at 3000 ppm. These findings indicate significant precateract effects on the eye of males and females at all dose levels of Vinclozolin, and 1 cataract in a female at 3000 ppm.

Note: The study is preliminary. Thus it lacked most details required to thoroughly evaluate the reliability of the data. This evaluation is made to alert the Agency that the final report

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should be evaluated for eye effects, and that longer term studies may be required.

DISCUSSION AND ABSTRACT FOR STUDY 26:

Vinclozolin was administered in the diet to 20 rats/sex/group at 0, 150, 500, 1500, and 4500 ppm for 24 months. Ophthalmological examinations were conducted initially on the controls and the 4500 ppm dose level rats, at day 94 on males and day 87 on females in all groups. The study was still in progress at the time of reporting, but it was stated that the eyes were to be examined on other days. The examination was conducted with the aid of a slit lamp and a fundus camera.

After 94 days for males and 87 day for females mature cataracts occurred in 1 males (one sided) and in 5 females (both sided) at the 4500 ppm dose level. In addition, dose related striations of the lens, water clefts and bosselated surfaces of the lens occurred at 500 ppm and above. One female each exhibited lens striations, one-sided and both-sided at the LDT, 150 ppm. Striations of the lens (both-sided) were noted in 1 female control animal.

The preliminary report, 97 days of a 24 month study indicated possible effects (precataract) in the eye of females at all dose levels tested, and cataracts at the 4500 ppm dose level. However, since the effect occurred in only one female at the LDT and in one female in controls, the effect at the LDT is equivocal.

Note: The study is preliminary. Thus it lacked most details required to thoroughly evaluate the reliability of the data. This evaluation is made to alert the Agency that the final report should be evaluated for eye effects, and that there may not be a NOEL for eye effects.

Prelim. ophthalmological study/b:\VICHLOZ3.23C\DOPHRAT.PRE/D Anderson/4/25/89.

Vinclozolin toxicology review - 5/31/89

Page _____ is not included in this copy.

Pages 55 through 60 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

X FIFRA registration data.

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_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary reviewer: David G Anderson, PhD. David G Anderson 5/15/89
Section 2, Tox. Branch 1 (IRS) (H7509C).
Secondary reviewer: Marion P Copley DVM. Marion P Copley 5/16/89
Section 2, Tox. Branch 1 (IRS) (H7509C).

007228

DATA EVALUATION REPORT

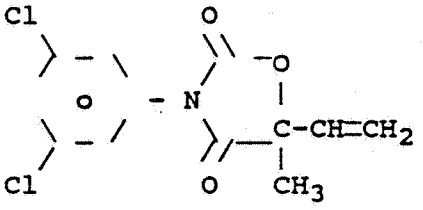
STUDY TYPE: Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 88/0492/No study #/From Japan.

TOX. CHEM. No.: 323C

MRID No.: 409505-02

TEST MATERIAL: Vinchlozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one]. Note that pesticide name as used differs from the usual name Vinclozolin, however, the chemical names are identical.

STRUCTURE:



SYNONYMS: Ronilan 50W, 50% A.I., Ronilan FL, 41% A.I.

SPONSOR: BASF Japan.

TESTING FACILITY: Biochemical Toxicology Laboratory, pesticides Division, Japan.

STUDY NO.: Reg. No. BASF:88/0492, Project No.:Unknown.

REPORT TITLE: Comparative Study on the Cataractogenic Activity of Procymidone, vinchlozolin and Dichlozoline in Rats.

AUTHOR(S): Takashi Suzuki, Tadaomi Kadota, and Junshi Miyamoto.

REPORT ISSUED: Date of work: 12/10/75 - 2/6/77.

CONCLUSIONS:

Doses administered: 0, 750, 1500, 3000, 5000 ppm in the diet to male Sprague Dawley rats.

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007228

Ophthalmological Effects:
NOEL: 750 ppm
LEL: 1500 ppm for cataract formation.

Other Systemic Effects:
Not determined.

Core classification: Supplementary, it is a specialized study with insufficient detail for complete evaluation.

A. MATERIALS:

1. Test compound: Vinchlozolin (Vinclozolin), Technical, Description NOT SPECIFIED, Reg. No. 83258, Purity 95.0%, supplied by Badische Anilin und Soda Fabrik AG..

2. Test animals: Species:Rats, Strain: Sprague Dawley, Age: 5 weeks, Weight: NOT SPECIFIED. Source: Shizuoka Agricultural Cooperative Association for Experimental animals. Acclimatized 1 week.

3. Environmental: Test animals were acclimatized for 1 week. Humidity: 60 ± 10%. Temperature: 24 ± degrees C. Light:dark = NOT SPECIFIED. Animals caged 5/cage.

B. STUDY DESIGN:

1. Animal Assignment - The method of animals assignment to groups was NOT SPECIFIED.

2. Test Substance Administration: Test substance was administered in the diet at 0, 750, 1500, and 3000 ppm to 20 male rats/group, and at 5000 ppm to 10 male rat/group for 6 months (Table A). The test material was administered sometime between December 10, 1975 and February 6, 1977.

Table A.
Dose levels and number of male animals used.

Test group	Approx. Dose mg/kg/day	Dose ppm	Number of Males	Ophthalmological examination conducted biweekly for 26 weeks on all animals.
1. Cont.	0	0	20/0	all
2. Low (LDT)	37.5	750	20/0	all
3. Mid1 (MDT1)	75	1500	20/0	all
4. Mid2 (MDT2)	150	3000	20/0	all
5. High (HDT)	250	5000	10/0	all

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3. Analysis of Dosing Solutions: No stability studies, or analyses of dosing suspensions were submitted.

4. Food and Water: - Food - CE-2 type, Clea Japan Inc., Osaka. The animals were allowed free access to food and water.

5. Statistics - NOT SPECIFIED.

6. Quality assurance statements were not submitted with these preliminary studies.

C. METHODS AND RESULTS: The numbered Tables were copied from study report submitted.

1. Conduct: The ophthalmolcgical examinations were carried out using an ophthalmoscope (Varinofocal, Riester Co., West Germany), a slit lamp (KOWA SL type, Kowa Kogyo Co., Tokyo) and an ophthalmological fudoscope (KOWA KC-2 type, Kowa Kogyo Co., Tokyo). Any abnormalities observed at the end of the study were confirmed by Prof. Sho Ogata, MD, Department of Ophthalmology, Ichikawa Hospital, Tokyo Dental College. Mydrin-P (Santen Pharmaceutical Co., Osaka) was administered to the eyes of the animals and they were anesthetized with diethylether prior to the examination.

2. Only ophthalmological examination were reported on these animals.

Results - Male rats feed vinchlozolin developed cataracts after 16 weeks at 3000 ppm. Later, cataracts developed in both eyes at 3000, and 5000 ppm. The incidence by the end of the study at 26 weeks was 11%, 50%, and 67% at the 1500, 3000, and 5000 ppm dose levels, respectively. The cataracts formed were snow flake in appearance, and the highest incidence was posterior polar cataract. Other cataract types at lower incidence were anterior polar, nuclear, and total cataracts.

DISCUSSION AND ABSTRACT:

Vinchlozolin (Vinclozolin) was administered in the diet at 0, 750, 1500, 3000 ppm to 20 male Sprague Dawley rats/group, and at 5000 ppm to 10 male Sprague Dawley rats for 26 weeks. Biweekly ophthalmological examinations were conducted with a slit lamp, an ophthalmological fudoscope, and an ophthalmoscope. Cataract formation were noted at the end of the 16th week at the 3000, and 5000 ppm dose level. By the end of the study at week 26, cataracts developed at the 1500 ppm dose level. The cataracts developed in both eyes at 3000 ppm and 5000 ppm. The most

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Preliminary Ophthalmological Studies/rat/Reg Doc # BASF: 007228
88/0492/No study #/From Japan.

frequent cataract had a snow flake appearance, but posterior, anterior, nuclear, and total cataracts also developed.

Note: Cataracts developed in other studies in another strain of rat, Chbb:THOM-SPF, at higher dose levels. However, in this latter strain, female rats were slightly more susceptible than males, and precataract lesions developed at much lower dose levels, 150 ppm.

Japanese ophthalmological study/b:\VICHLOZ3.23C\DOPHRAT.JAP/D Anderson/4/25/89.

Table 1. Time course onset of cataract in rats treated with procymidone, dichlozoline and vinchlozolin for 6 months

Week	Incidence of cataract*						
	Compounds and their dietary concentration (ppm)						
	Control	Procymi-done	Dichlo-zcline	vinchlozolin			
	0	5,000	5,000	750	1,500	3,000	5,000
0	0/20	0/10	0/10	0/20	0/20	0/20	0/10
2	0/20	0/10	0/10	0/20	0/20	0/20	0/10
4	0/20	0/10	0/10	0/20	0/19	0/20	0/10
6	0/10	0/10	3/10	0/20	0/19	0/20	0/10
8	0/10	0/10	8/10	0/20	0/19	0/19	0/10
10	0/20	0/10	10/10	0/20	0/19	0/19	0/9
12	0/20	0/10	10/10	0/20	0/19	0/19	0/9
14	0/20	0/10	10/10	0/20	0/19	0/19	0/9
16	0/20	0/10	10/10	0/20	0/19	2/19	1/9
18	0/20	0/10	10/10	0/20	0/19	2/19	3/9
20	0/20	0/10	10/10	0/20	0/19	7/19	4/9
22	0/20	0/10	10/10	0/20	0/19	9/19	4/9
24	0/20	0/10	10/10	0/19	0/19	9/19	5/9
26	0/20	0/10	10/10	0/19	2/18	9/18	6/9

* number of animals with cataract/ number of animals examined

One rat of 750 ppm-, 2 of 1,500 ppm-, 2 of 3,000 ppm-, and 1 of 5,000 ppm-vinchlozolin-treated groups were dead during the course of feeding, probably due to pneumonia, as revealed by necropsy.

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Table 2. Occurence of cataract in left, right or both eyes by feeding vinchlozolin or dichlozoline to rats for 6 months

Compound	Dietary concentration (ppm)	Incidence of cataract*		
		One eye only		Both eyes
		Left	Right	
Vinchlozolin	1,500	1/18	1/18	0/18
	3,000	0/18	0/18	9/18
	5,000	0/9	0/9	6/9
Dichlozoline	5,000	0/10	0/10	10/10

* number of rats with cataract/ number of rats examined

Table 3. Site of opacity in the lens from rats treated with vinchlozolin for 6 months

Dietary concentration	No. of rats with cataract	No. of eyes with cataract			
		Site of opacity in lens			
		Anterior	Nuclear	Posterior	Total
750	0	0	0	0	0
1,500	2	1	0	1	0
3,000	9	1	5	11	1

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