6-1-94

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

JUN 1994 010999

JUN 1 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID# 113201: Vinclozolin, CIC DER of a 90-Day Feeding Toxicity Study and Supplementary Study.

Barcode: 193004. ToxChem No.: 323C.
Submission No.: S444317. PC No.: 113201
MRID No.: 427288-01 & -02. Case No.: 011409.

From: David G Anderson, PhD David G Anderson 5/24/94.
Toxicologist,
Section 3, Toxicology Branch-1
HED (7509C)

To: Steven Robinson/Sidney Jackson, PM 21
Fungicide and Herbicide Branch
RD (7505C)

Thru: Karen Hamernik, PhD KLH 5/26/94
Section 3 Head, Toxicology Branch-1
HED (7509C)

The 90-Day Feeding Study in Rats and a Supplement submitted in support of reregistration of vinclozolin are referenced and summarized below.

W. Mellert (March 5, 1993, Study on the Oral Toxicity of Reg. No. 83 258 (vinclozolin) in Wistar Rats: Administration in the Diet Over 3 Months. Conducted by BASF Aktiengesellschaft, Dept. Toxicology, D-W46700 Ludwigshafen/Rhein Germany, for BASF Corp., Agricultural Products. Project No. 31S0375/88034, Registration Doc. No. BASF 93/10191. MRID# 427288-01.

and

W. Mellert (March 9, 1993, Supplementary Study on the Oral Toxicity of Reg. No. 83 258 (vinclozolin) in Wistar Rats: Administration in the Diet Over 3 Months. Conducted by BASF Aktiengesellschaft, Dept. Toxicology, D-W46700 Ludwigshafen/Rhein Germany, for BASF Corp., Agricultural Products. Project No. 31S0375/88110, Registration Doc. No. BASF 93/10192 Supplementary to 31S0375/88034. MRID# 427288-02.

EXECUTIVE SUMMARY: In a subchronic oral toxicity study, vinclozolin (99.2% pure) was administered in the diet to Wistar rats (10/sex/dose) at dietary levels of 0, 300, 1000 or 30000 ppm (study no. 31S0375/88034). A supplementary study was also conducted for 90-days using dietary levels of 0 or 50 ppm (study no. 31S0375/88110). The average daily intake levels of vinclozolin were 0, 3.6, 20, 66 or 200 mg/kg/day, respectively, for males and 0, 4.4, 24, 77 or 219 mg/kg/day, respectively, for females.

At 300 ppm, females had increased incidence of enlarged and white discolored adrenal glands and acinar vacuolization in the pancreas. At 1000 ppm, males had enlarged and white discolored adrenal glands and both males and females had an increase in adrenal weights (133% of control) as well as increased hypertrophy, vacuolation, lipid storage and birefringence of the zona fasciculata. Both males and females also had an increased incidence of cloudy swelling and cell necrosis in the liver. Additional lesions observed at 1000 ppm in males included hyperplasia of the islets of Langerhans and acinar cell vacuolization in the pancreas, cystoid degeneration of the pituitary, increased testes weight (113% of control) with Leydig cell hyperplasia, decreased white blood cell count (83% of control), and decreased serum sodium (98% of control) and potassium (92% of control). Females at 1000 ppm also had increased liver weight (115% of control). At 3000 ppm, both males and females showed decreased red blood cell count (94-95% of control), decreased body weight (94% of control) and food consumption (81% and 74% of control, respectively) during the first week of exposure and increased water consumption (approximately 115% and 126% of control, respectively). Males at this dose level also showed increased liver weight (114% of control), mean corpuscular volume (104% of control) and mean corpuscular hemoglobin (103% of control) and decrease mean hemoglobin concentration (98% of control). Females at this dose level also showed hyperplasia of the islet of Langhans, bosselated structure of the lens, cataracts, increased serum total protein (110% of control), globulins (109%-116% of control) triglycerides (183% of control and cholesterol (154% of control) and decreased serum chloride (96-97% of control), hemoglobin (93% of control) and hematocrit (95% of control). **The LOEL of 300 ppm is based on the increased incidence of enlarged white discolored adrenal glands and pancreatic acinar cell vacuolization in females. The NOEL is 50 ppm.**

This study is core minimum and satisfies the guideline requirements for a 82-1 subchronic study in the rat.

FINAL

C10999

DATA EVALUATION REPORT

Vinclozolin

Study Type: Subchronic Oral Toxicity in Rats

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

April 7, 1994

Principal Reviewer _____ Date _____
Carrie Rabe, Ph.D.

Independent Reviewer William L. McLellan for Date 4/7/94
John Liccione, Ph.D.

QA/QC Manager William L. McLellan for Date 4/7/94
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 3-01
Element Number: -
Project Officer: Caroline Gordon

010999

Guideline Series 82-1: Subchronic Oral Toxicity in Rats

EPA Reviewer: Linnea Hansen, Ph.D.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Linnea J. Hansen
Date: 5/26/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Marion Copley
Date: 5/27/94

DATA EVALUATION REPORT

STUDY TYPE: Subchronic oral toxicity in rats (Guideline Series 82-1)

TEST MATERIAL: Vinclozolin

TOX. CHEM. NUMBER: 323[illegible] P.C. NUMBER: 113201

SYNONYMS: Reg. No. 83 258; number 88/3[illegible]5: code name RON

STUDY NUMBERS: (1) 31S0375/88034
(2) 31S0375/88110 (Supplementary study)

MRID NUMBERS: (1) 427288-01
(2) 427288-02 (Supplementary study)

SPONSORS: BASF Corporation
Agricultural Chemicals
Research Triangle Park, North Carolina

TESTING FACILITY: BASF Aktiengesellschaft
Department of Toxicology
Ludwigshafen/Rhein, Germany

TITLE OF REPORTS: (1) Study on the Oral Toxicity of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Administration in the Diet Over 3 Months; Project No.: 31S0375/88034

(2) Supplementary Study on the Oral Toxicity of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Administration in the Diet Over 3 Months; Project No.: 31S0375/88110; Supplementary to 31S0375/88034

AUTHOR: W. Mellert

REPORTS ISSUED: (1) Study 31S0375/88034 completed March 5, 1993
(2) Study 31S0375/88110 completed March 9, 1993

QUALITY ASSURANCE: Signed statements of Good Laboratory Practice Compliance, No Data Confidentiality, and Quality Assurance, and a list of Quality Assurance Inspections were included for both reports.

EXECUTIVE SUMMARY: In a subchronic oral toxicity study, Vinclozolin (99.2% pure) was administered in the diet to Wistar rats (10/sex/dose) at dietary

levels of 0, 300, 1,000, or 3,000 ppm (study no. 31S0375/88034). A supplementary study was also conducted for 90 days using dietary levels of 0 or 50 ppm (study no. 31SC375/88110). The average daily intake values of vinclozolin were 0, 3.6, 30, 66, or 200 mg/kg day, respectively, for males and 0, 4.4, 24, [illegible] or 210 mg/kg/day, respectively, for females.

At 300 ppm, females had an increased incidence of enlarged and white discolored adrenal glands and acinar vacuolization in the pancreas. At 1,000 ppm, males had enlarged and white discolored adrenal glands and both males and females had an increase in adrenal weights (133% of control) as well as increased hypertrophy, vacuolation, lipid storage, and birefringence of the zona fasciculata. Both males and females also had an increased incidence of cloudy swelling and single cell necrosis in the liver. Additional lesions observed at 1,000 ppm in males included hyperplasia of the islets of Langerhans and acinar cell vacuolization in the pancreas, cystoid degeneration of the pituitary, increased testes weight (113% of control) with Leydig cell hyperplasia, decreased white blood cell count (83% of control), and decreased serum sodium (98% of control) and potassium (92% of control). Females at 1,000 ppm also had increased liver weight (115% of control). At 3,000 ppm, both males and females showed decreased red blood cell count (94-95% of control), decreased body weight (94% of control) and food consumption (81% and 74% of control, respectively) during the first week of exposure and increased water consumption (approximately 115% and 126% of control, respectively). Males at this dose also showed increased liver weight (114% of control), mean corpuscular volume (104% of control), and mean corpuscular hemoglobin (103% of control), and decreased mean corpuscular hemoglobin concentration (98% of control). Females at this dose also showed hyperplasia of the islet of Langerhans, bosselated structure of the lens, cataracts, increased serum total protein (110% of control), globulins (109-116% of control), triglycerides (153% of control), and cholesterol (154% of control), and decreased serum chloride (96-97% of control), hemoglobin (93% of control), and hematocrit (95% of control). **The LOEL of 300 ppm is based on the increased incidence of enlarged and white discolored adrenal glands and pancreatic acinar cell vacuolization in females. The NOEL is 50 ppm.**

This study is core minimum and satisfies the guideline requirements for a 82-1 subchronic study in the rat.

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Vinclozolin

Formula: 3-(3,5-Dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidin-2,4-dione

Lot number: N 183 (used in both the main and addendum studies)

Purity: 99.2%

Physical property: Not reported

Stability: Not reported; however, when mixed with feed, less than a 7% loss occurred following storage for 32 days at room temperature (see below)

2. Rationale for Dose Selection

The doses used in the current study were selected based on the results of one 4-week[1] study, two 3-month[2,3] studies, and one chronic[4] feeding study in Sprague-Dawley rats conducted approximately 20 years previously. The 4-week study showed dose-dependent whitish discoloration of the adrenal cortex (macroscopically), increases in ascorbic acid content of the adrenals, increases in absolute and relative liver and adrenal weights, and decreases in hemoglobin, hematocrit, erythrocytes (blood effects in females only), and hepatic glycogen (males only) at 900 ppm (lowest dose tested) and above. At the highest dose tested in the 4-week study (15,000 ppm), the relative testes weight was also increased. The 3-month studies showed transient decreases in erythrocytes and hematocrit at 300 ppm, no effects at 150 or 450 ppm, and dose-dependent decreases in erythrocytes and hematocrit, increases in absolute and relative liver weights and absolute adrenal weights, whitish discoloration of the adrenals, and increased lipid incorporation in the adrenal cortex at 1,000 and 2,000 ppm. The chronic feeding study showed no effects at ≤486 ppm and decreases in body weight and food consumption and increases in urinary ascorbic acid and 17-ketosteroid content at 1,458 ppm and 4,374 ppm. No carcinogenicity was reported in the chronic study. These studies were not provided for review.

3. Test Article Analyses for Purity and Stability

The purity of the test material was not verified by the testing facility. However, the sponsor identified the purity of the lot sent to the testing facility as 99.2% pure.

---

[1]Report on the supplementary toxicological investigation of 3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidin-2,4-dione in a 4-week feeding study in rats; BASF Aktiengesellschaft, June 10, 1975

[2]Report on the investigation of 3-(3,5-dichloro-phenyl)-5-methyl-5-vinyl-1,3-oxazolidin-2,4-dione in a 3-month feeding study in rats; BASF Aktiengesellschaft, April 3, 1974

[3]Report: 3-Month toxicity of an oxazolidine derivative, Batch 83 258 - called "OXA" for short - in Sprague-Dawley rats after dietary administration; Prof. Dr. Deuschner, Laboratory of Pharmacology and Toxicology, Hamburg, FRG, May 20, 1975

[4]Report: Chronic oral toxicity of oxazolidine derivative, Batch 83 258 - called for short "OXA" - in the Sprague-Dawley rat; Prof. Dr. F. Deuschner, Hamburg, FRG, December 15, 1977 (Reviewed by HED, Doc #s 244 and 4994)

Test diets were prepared by mixing appropriate amounts of vinclozolin with rat feed to form a concentrated premix. Dietary levels were prepared by mixing the premix with appropriate amounts of feed. Fresh diets were prepared each week.

Measurement of the homogeneity, stability, and actual concentration of the test material in the diets was conducted by the facility's analytical chemistry laboratory using gas chromatography (method 184; details not specified). Measurements for homogeneity and stability were conducted using diets containing vinclozolin that were prepared for other studies (53S0375/88025 and 71S0375/88026). Homogeneity analyses from studies 53S0375/88025 and 71S0375/88026 showed variation between dietary samples of less than 10% at 100 or 150 ppm and less than 13% at 4,500 or 5,000 ppm. Stability of the test material in the diet was measured using a sample of 50-ppm diet from study 53S0375/88025. Less than a 7% loss of test material was observed following storage for 32 days at room temperature.

The actual concentration of the test material in the diets offered to the rats was measured twice (once at the beginning and once at the end of each study). All individual measurements were within 10% of target. The average measured concentrations at each test level were as follows:

TABLE 1. ACHIEVED DIETARY CONCENTRATIONS

Nominal Concentration (ppm)	Measured Concentration (ppm)
50[a]	46.0 ± 0.4
300[b]	289 ± 7
1,000[b]	941 ± 29
3,000[b]	2,925 ± 87

[a]Mean ± S.D., data from study 53S0375 88113, p232
[b]Mean ± S.D., data from study 53S0375 88034, p287-288

4. Animals

Wistar rats (Chbb:Thom, SPF) for both studies were received from Dr. Karl Thomae, Biberach/Riss, Germany. The rats were 32-34 days old upon arrival and were caged individually in stainless steel wire cages. The animal room was operated on a 12-hour light/dark cycle, and temperature and relative humidity were maintained between 20°C and 24°C and 30% and 70%, respectively.

Rats were acclimated for 8-10 days prior to exposure to test material. During the acclimation period, rats considered to be free of any clinical signs of disease were randomly assigned to the following treatment groups (10/sex/dose) based on body weight such that groups of the same sex had similar mean body weights:

TABLE 2. STUDY DESIGN

Dietary Level (ppm)	Number of Animals Males	Females
Study 31S0375/88110		
0	10	10
50	10	10
Study 31S0375/88034		
0	10	10
300	10	10
1,000	10	10
3,000	10	10

At the time of the first exposure to test diets, the rats were approximately 6 weeks old. The males ranged in weight from 199 to 226 g in study 31S0375/88034 and from 173 to 189 g in study 31S0375/88110. Females ranged in weight from 148 to 178 g in study 31S0375/88034 and from 138 to 154 g in study 31S0375/88110. The rats were uniquely identified through the use of ear tattoos. Feed (Kliba maintenance diet rat/mouse/hamster, GLP 343 meal) and water were provided ad libitum throughout the acclimation and study periods.

5. Statistical Analyses

Body weight, hematology, clinical chemistry, and organ weight data were analyzed using a one-way analysis of variance. If the result was significant ($p \leq 0.05$), Dunnett's test was used to analyze for differences between the control and treated groups. Urinalysis data for each parameter were compared against benchmark levels. Animals at each dose were then divided into two groups depending how their urinalysis data compared to the benchmark values. Chi square analysis was then used to determine whether the distribution of animals in the two groups at any given dose was different from the distribution of the controls in the two groups. No rationale was provided for the use of the benchmark levels that were selected.

6. General Observations

(a) Mortality/moribundity/survival

Animals were observed twice daily on weekdays for mortality/moribundity. On weekends and holidays, animals were observed once daily.

Results - All animals survived until study termination.

(b) Clinical observations

Animals were observed twice daily on weekdays for overt adverse clinical signs. On weekends and holidays, animals were observed once daily. In addition, physical examinations for adverse clinical signs were made weekly.

Results - During week 1 of the study, all males and females at the highest dose tested showed some deterioration in their general health status (not further explained in the study report) and decreased food consumption.

(c) Body weights/food consumption/feed efficiency/water consumption/test article intake

Body weights--Individual body weights were determined weekly throughout the study.

Results - Body weights of both males and females at the highest dose tested were decreased 6% compared to controls after 7 days of exposure (Table 3). This decrease corresponded to decreased food consumption (see below). Thereafter, body weights at all doses were not significantly different from controls. No effects on total body weight gain were observed.

Food consumption--Individual food consumption values were determined weekly.

Results - Both males and females at 3,000 ppm showed a statistically significant decrease in food consumption during the first week of the study (Table 4). Thereafter, food consumption at all doses was comparable to controls. The transient nature of the effect on food consumption indicates that the effect may have reflected adjustment of the animals to the taste of the compound.

Feed efficiency--Feed efficiency values were determined weekly.

Results - Feed efficiency was not affected by consumption of vinclozolin.

Water consumption--Water consumption was determined 1 day/week, starting during the third week of the main study. Water consumption was not measured in the addendum study.

Results - At the highest dose tested (3,000 ppm), females showed significantly greater water consumption than controls on several occasions (Table 5; statistical analyses performed by reviewers). Water consumption of the high-dose females averaged 126% (range, 107-146%) of controls over the period in which it was measured. Water consumption of high-dose males averaged 115% (range, 106-121%) of controls during this period, but this increase was not statistically significant. The increases in water consumption in both sexes are considered to be treatment-related

TABLE 3. Body Weight Data (Mean ± S.D.) for Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

Interval	Study No. 31S0375/88110-- Body Weight Data by Dietary Level (ppm)		Study No. 31S0375/88034-- Body Weight Data by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
			Males			
Day 7	234.3 ± 7.0	237.6 ± 8.3 (101)	259.8 ± 8.7	260.9 ± 10.0 (100)	269.9 ± 9.2 (104)	244.8 ± 9.0** (94)
Day 35	365.3 ± 18.0	367.9 ± 20.2 (101)	382.3 ± 17.7	381.8 ± 23.9 (100)	399.9 ± 23.7 (105)	370.5 ± 18.9 (97)
Day 63	437.6 ± 24.6	436.1 ± 27.5 (100)	447.6 ± 21.6	441.6 ± 27.9 (99)	471.5 ± 32.9 (105)	433.4 ± 22.6 (97)
Day 91	488.5 ± 33.6	480.4 ± 32.9 (98)	472.8 ± 25.4	471.7 ± 38.0 (100)	506.9 ± 33.3* (107)	454.6 ± 25.1 (96)
			Females			
Day 7	168.8 ± 8.0	171.7 ± 8.5 (102)	185.7 ± 9.5	188.6 ± 8.5 (103)	186.4 ± 5.3 (101)	173.0 ± 7.0* (94)
Day 35	214.9 ± 14.5	216.8 ± 14.9 (101)	234.2 ± 11.9	244.9 ± 15.8 (105)	228.8 ± 13.4 (98)	238.4 ± 14.6 (102)
Day 63	244.9 ± 19.8	246.9 ± 15.1 (101)	258.5 ± 12.8	269.2 ± 19.3 (104)	259.3 ± 17.9 (100)	266.1 ± 15.0 (103)
Day 91	271.5 ± 18.8	270.5 ± 16.4 (100)	288.2 ± 15.3	279.0 ± 17.8 (97)	266.6 ± 17.7 (93)	273.2 ± 17.7 (95)

[a]Data extracted from Study No. 31S0375/88034, Tables 9-12, and Study No. 31S0375/88110, Tables 5-8.
[b]Numbers in parentheses indicate of percent control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

TABLE 4 Food Consumption Data (Mean ± S.D.) for Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

Interval	Study No. 31S0375/88110 Food Consumption Data by Dietary Level (ppm)		Study No. 31S0375/88034 Food Consumption Data by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
			Males			
Day 7	25.7 ± 1.2	26.8 ± 1.5 (104)	24.9 ± 1.1	25.3 ± 1.0 (102)	26.3 ± 1.2 (106)*	20.1 ± 1.0 (81)**
35	27.4 ± 1.6	27.4 ± 1.9 (100)	26.1 ± 1.2	25.9 ± 2.0 (99)	27.3 ± 2.1 (105)	25.7 ± 1.4 (98)
63	27.0 ± 1.5	26.4 ± 1.5 (98)	25.8 ± 1.7	25.5 ± 2.0 (99)	28.0 ± 1.9 (109)*	25.5 ± 1.3 (99)
91	26.5 ± 1.8	25.8 ± 2.2 (97)	23.8 ± 1.2	24.7 ± 1.7 (104)	26.7 ± 0.8 (112)**	24.9 ± 1.4 (105)
			Females			
Day 7	19.3 ± 0.9	19.9 ± 1.1 (103)	17.8 ± 1.3	18.9 ± 0.7 (106)	18.2 ± 1.2 (102)	13.1 ± 1.3 (74)**
35	18.4 ± 1.1	19.7 ± 1.5 (107)	19.2 ± 1.0	19.9 ± 1.4 (104)	17.9 ± 1.2 (93)	18.6 ± 1.6 (97)
63	19.2 ± 0.7	20.0 ± 1.4 (104)	19.2 ± 1.6	19.4 ± 1.5 (101)	18.8 ± 1.4 (98)	18.2 ± 1.1 (95)
91	19.4 ± 0.9	20.3 ± 1.4 (105)	18.1 ± 1.0	19.0 ± 1.1 (105)	18.3 ± 1.6 (101)	17.3 ± 1.1 (96)

[a]Data extracted from Study No. 31S0375/88034, Tables 1-4, and Study No. 31S0375/88110, Tables 1-4.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

C109:9

TABLE 3. Water Consumption Data for Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

Interval	Water Consumption Data (Mean ± S.D.) by Dietary Level (ppm)			
	0	300	1,000	3,000
		Males		
Day 15	28.9 ± 3.7	28.4 ± 3.5 (98)	31.9 ± 5.1 (110)	33.4 ± 3.8 (116)
22	38.5 ± 4.0	37.1 ± 5.1 (96)	39.7 ± 3.7 (103)	43.5 ± 4.2 (113)
36	27.3 ± 3.1	26.3 ± 5.6 (96)	28.3 ± 6.1 (104)	32.7 ± 3.6 (120)
58	28.2 ± 4.7	24.6 ± 4.5 (87)	28.8 ± 4.1 (102)	29.5 ± 4.8 (105)
92	35.5 ± 3.4	34.8 ± 6.3 (98)	35.7 ± 6.6 (101)	40.5 ± 4.2 (114)
		Females		
Day 15	22.2 ± 3.8	24.9 ± 5.5 (112)	18.4 ± 6.1 (83)	32.5 ± 11.2* (146)
22	27.4 ± 5.2	30.4 ± 2.9 (111)	27.9 ± 4.5 (102)	35.2 ± 9.0 (128)
36	21.2 ± 5.6	22.5 ± 8.3 (106)	18.2 ± 8.6 (86)	27.6 ± 6.0 (130)
58	25.5 ± 5.7	26.4 ± 4.8 (104)	25.2 ± 5.8 (99)	27.3 ± 5.3 (107)
92	28.5 ± 3.8	30.7 ± 3.0 (108)	30.1 ± 6.6 (106)	36.7 ± 6.6** (129)

[a] Data extracted from Study No. 3130375/88034, Tables 5-8.
[b] Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$ using an analysis of variance and Scheffe's test as calculated by the reviewers.
** Significantly different from control values, $p \leq 0.01$ using an analysis of variance and Scheffe's test as calculated by the reviewers.

because the effects were sustained over the duration of the study.

Test article intake--Test article intake (mg vinclozolin/kg body weight/day) was calculated weekly. These values were calculated using the weekly body weight and food consumption values and the nominal dietary concentrations of vinclozolin.

Results - The approximate average daily intake values of vinclozolin for rats receiving diets containing 0, 30, 300, [illegible] or 3,000 ppm were [illegible] 3.6, 21, 66, or 200 mg/kg/day, respectively, for males and 0, [illegible], 24, 77, or 219 mg/kg/day, respectively, for females.

Ophthalmoscopic examinations

Eye examinations were conducted using an ophthalmoscope after dilation of the pupils with a mydriatic agent. In study [illegible]375/88034, eye examinations were conducted in control and [illegible]-ppm animals prior to the first exposure to vinclozolin and again at study days 42 and 91. Eye examinations in the 300- and [illegible],000-ppm animals were conducted at study days 21 and 91, but not prior to exposure. In study 41S0375/88110, eye examinations were conducted in all rats prior to first exposure to vinclozolin and at study days 42 and 91.

Results - In study number 41S0375 88034, a dose-related increase was observed in the incidence of striations of the lens in both males and females (Tables 6a and 6b) at 300 ppm and above. In addition, females at [illegible],000 ppm had an increased incidence of vesiculated structure of the lens and two females at this dose had cataracts. In study number 41S0375 88110, no increase in the incidence of any ophthalmologic findings was observed. However, the incidence of striations of the lens was very high in the controls in this study. The study author presented data from several other studies examining the effects of vinclozolin in Wistar rats (study numbers 71S0375 88026, 71S0375/88109, 71S0375 88105, 31S0375/88150, and 39S0375/88116). These studies substantiated the findings reported above. The study author concluded that striations of the lens were a spontaneous lesion in Wistar rats that was accelerated by exposure to vinclozolin. The author also concluded that neither striations nor bosselated structure of the lens were precursors for the formation of cataracts but that vinclozolin was a cataractogenic agent in rats.

Clinical Pathology

Hematological and blood chemistry analyses were performed on all rats in study 41S 375 88034 on study days 42 and 91. In study [illegible] 71S0375 88110, hematological analyses were performed on study days [illegible] and clinical chemistry determinations were performed on study [illegible] and [illegible]. Animals were not fasted before collection of samples

TABLE 6.1 Incidence of Ophthalmologic Findings in Male Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b,c,d]

	Study No. 51503/5/88110 Incidence by Dietary Level (ppm)		Study No. 51503/5/88034 Incidence by Dietary Level (ppm)			
	0	50	0	500	1,000	5,000
			Males			
Striation of lens						
day 42, 52, or 44						
one side	1 (10)	5 (50)	0 (0)	0 (0)	1 (10)	1 (10)
both sides	8 (80)	6 (60)	0 (0)	0 (0)	0 (0)	1 (10)
day 82 or 91						
one side	0 (0)	1 (10)	0 (0)	0 (0)	2 (20)	1 (10)
both sides	9 (90)	9 (90)	0 (0)	1 (10)	6 (60)	9 (90)
Bosselated structure of lens						
day 42, 52, or 44						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
day 82 or 91						
one side	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cataracts						
day 42, 52, or 44						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
day 82 or 91						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Data extracted from Study No. 51503/5/88034, pp. 303-304
[b] Numbers in parentheses indicate percent incidence.
[c] The exams were performed on either day 42 or 52 and day 82 for Study No. 51503/5/88034, and on days 44 and 91 for Study No. 51503/5/88110.
[d] N = 10

TABLE 6b. Incidence of Ophthalmologic Findings in Female Rats Fed Technical Thiacloprid in the Diet for 1 Month[a,b,c,d]

	Study No. 3150375/88110 Incidence by Dietary Level (ppm)		Study No. 3150375/88034 Incidence by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
Striation of lens						
day 42, 52, or 44						
one side	2 (20)	0 (0)	0 (0)	1 (10)	0 (0)	1 (10)
both sides	5 (50)	6 (60)	0 (0)	0 (0)	6 (60)	3 (30)
day 82 or 91						
one side	4 (40)	2 (20)	0 (0)	0 (0)	2 (20)	1 (10)
both sides	6 (60)	6 (60)	0 (0)	3 (30)	8 (80)	8 (80)
Bosselated structure of lens						
day 42, 52, or 44						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
day 82 or 91						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)[e]
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (40)
Cataracts						
day 42, 52, or 44						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
day 82 or 91						
one side	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)[f]
both sides	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)

[a]Data extracted from Study No. 3150375/88034, pp. 303-304
[b]Numbers in parentheses indicate percent incidence.
[c]The exams were performed on either day 42 or day 52 and on day 82 for Study No. 3150375/88034, and on days 44 and 91 for Study No. 3150375/88110.
[d]N = 10
[e]This value was listed as 2/10 in the summary table; however, only one animal had this finding in the individual data.
[f]Cataract was observed on day 91.

from the retroorbital venous plexus. Urinalysis was performed in study 31S0375/88034 on study days 39 and 81. Urine was collected overnight in metabolism cages. Urinalysis was not performed in study 31S0375/88119.

a. Hematology

The parameters marked with an "X" below were examined.

X Hematocrit (HCT)*	X Leukocyte differential count*
X Hemoglobin (HGB)*	X Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	X Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*	X Mean corpuscular volume (MCV)
X Platelet count*	X Thromboplastin time*
X Reticulocyte count (RETIC)	

* Recommended by Subdivision F (November 1984) Guidelines

Results - There were statistically significant decreases in white blood cell count in males at 1,000 (83% of control) and 3,000 (73-81% of control) ppm (Table 7a). The decreases were primarily due to decreases in polymorphonuclear neutrophils and lymphocytes. Similar effects were not observed in females (Table 7b). The study author suggested that the decrease in white blood cell count may have been associated with altered corticosteroid levels associated with lesions of the adrenal gland (see pathology data below). This comment was based on the observation that decreases in lymphocytes frequently accompany increases in corticosteroid levels; however, serum corticosteroid levels were not measured in this study.

In addition, at the highest dose tested, small but statistically significant decreases in red blood cell count (94-95% of control) were observed in both males and females. In addition, there were small but statistically significant increases in mean corpuscular volume (103-104% of control) and mean corpuscular hemoglobin (103% of control) and significant decreases in mean corpuscular hemoglobin concentration (98% of control) in males at this dose and small but statistically significant decreases in hemoglobin (93% of control) and hematocrit (95% of control) in females at this dose. The study authors suggested that the slight hematological effects were treatment-related because they were consistent with the results of some other studies.

b Blood (clinical) chemistry

Blood chemistry analyses included the parameters marked with an "X" below

TABLE 7a Selected Hematological Data (Mean ± S.D.) for Male Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

	Study No. 31S0375/88110 Hematological Data by Dietary Level (ppm)		Study No. 31S0375/88034 Hematological Data by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
Red blood cells (tera/L)						
day 46 or 50	7.50 ± 0.30	7.39 ± 0.44 (99)	8.18 ± 0.55	8.28 ± 0.38 (101)	7.96 ± 0.31 (97)	7.65 ± 0.23* (94)
87 or 92	8.24 ± 0.35	8.46 ± 0.32 (103)	8.50 ± 0.36	8.49 ± 0.36 (100)	8.20 ± 0.44 (96)	8.09 ± 0.25* (95)
Hemoglobin (mmol/L)						
day 46 or 50	8.28 ± 0.15	8.16 ± 0.28 (99)	9.84 ± 0.52	9.90 ± 0.44 (101)	9.69 ± 0.28 (98)	9.52 ± 0.36 (97)
87 or 92	8.39 ± 0.25	8.69 ± 0.40 (104)	10.18 ± 0.39	10.14 ± 0.32 (100)	9.94 ± 0.39 (98)	9.84 ± 0.32 (97)
Hematocrit (%)						
day 46 or 50	0.41 ± 0.01	0.40 ± 0.01 (98)	0.40 ± 0.02	0.40 ± 0.02 (100)	0.40 ± 0.02 (100)	0.39 ± 0.02 (98)
87 or 92	0.42 ± 0.01	0.44 ± 0.03 (105)	0.41 ± 0.01	0.41 ± 0.01 (100)	0.40 ± 0.02 (98)	0.40 ± 0.02 (98)
Mean cell volume (fL)						
day 46 or 50	54.10 ± 1.80	54.70 ± 2.50 (101)	48.98 ± 0.99	48.57 ± 1.43 (99)	49.97 ± 1.58 (102)	51.15 ± 0.79** (104)
87 or 92	51.40 ± 1.80	51.40 ± 1.70 (100)	47.98 ± 0.97	47.69 ± 1.57 (99)	48.82 ± 1.10 (102)	49.65 ± 1.01** (103)
MCH (fmol)						
day 46 or 50	1.10 ± 0.03	1.11 ± 0.04 (101)	1.20 ± 0.03	1.19 ± 0.03 (99)	1.22 ± 0.03 (102)	1.24 ± 0.02** (103)
87 or 92	1.02 ± 0.04	1.03 ± 0.03 (101)	1.20 ± 0.03	1.19 ± 0.04 (99)	1.21 ± 0.03 (101)	1.21 ± 0.02 (101)
MCHC (mmol/L)						
day 46 or 50	20.40 ± 0.20	20.20 ± 0.45 (99)	24.55 ± 0.34	24.57 ± 0.28 (100)	24.34 ± 0.36 (99)	24.28 ± 0.30 (99)
87 or 92	19.83 ± 0.17	19.96 ± 0.38 (101)	24.94 ± 0.45	25.04 ± 0.25 (100)	24.81 ± 0.36 (99)	24.43 ± 0.38* (98)
White blood cells (giga/L)						
day 46 or 50	6.74 ± 1.04	6.83 ± 1.05 (101)	8.55 ± 1.17	7.93 ± 0.98 (93)	8.67 ± 1.03 (101)	6.99 ± 1.82* (82)
87 or 92	5.45 ± 1.17	5.49 ± 1.11 (101)	8.23 ± 1.50	7.13 ± 1.29 (87)	6.80 ± 1.14* (83)	5.97 ± 0.98** (73)
Polymorphonuclear neutrophils (giga/L)						
day 46 or 50	0.52 ± 0.25	0.48 ± 0.27 (92)	0.89 ± 0.38	0.80 ± 0.39 (90)	0.81 ± 0.25 (91)	0.64 ± 0.17 (72)
87 or 92	0.44 ± 0.19	0.53 ± 0.22 (120)	0.84 ± 0.28	0.62 ± 0.24 (74)	0.61 ± 0.38 (73)	0.48 ± 0.22* (57)
Lymphocytes (giga/L)						
day 46 or 50	5.69 ± 0.80	5.77 ± 0.96 (101)	7.25 ± 0.98	6.85 ± 1.22 (94)	7.49 ± 1.04 (103)	6.07 ± 1.71 (84)
87 or 92	4.34 ± 0.87	4.46 ± 0.95 (103)	7.11 ± 1.48	6.22 ± 1.22 (87)	5.99 ± 1.20 (84)	5.31 ± 0.97* (75)

[a]Data extracted from Study No. 31S0375/88034, Tables 23-24 and 29-30, and Study No. 31S0375/88110, Tables 25-26 and 31-32.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.
* Significantly different from control values, $p \leq 0.05$ using an analysis of variance and Scheffe's test as calculated by the reviewers.

TABLE 7b. Selected Hematological Data (Mean ± S.D.) for Female Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

	Study No. 31503/5/88110 Hematological Data by Dietary Level (ppm)		Study No. 31503/5/88034 Hematological Data by Dietary Level (ppm)			
	0	50	0	100	1,000	3,000
Red blood cells (tera/L)						
day 46 or 50	7.08 ± 0.26	7.04 ± 0.35 (99)	7.54 ± 0.21	7.68 ± 0.25 (102)	7.60 ± 0.30 (101)	7.26 ± 0.29 (96)
87 or 92	8.15 ± 0.25	8.09 ± 0.36 (99)	7.87 ± 0.26	7.88 ± 0.26 (100)	7.71 ± 0.15 (98)	7.42 ± 0.17** (94)
Hemoglobin (mmol/L)						
day 46 or 50	8.03 ± 0.23	8.02 ± 0.33 (100)	9.13 ± 0.24	9.47 ± 0.25*(104)	9.24 ± 0.28 (101)	8.84 ± 0.29 (97)
87 or 92	8.59 ± 0.21	8.56 ± 0.38 (100)	9.62 ± 0.34	9.67 ± 0.26 (101)	9.46 ± 0.23 (98)	8.97 ± 0.19** (93)
Hematocrit (%)						
day 46 or 50	0.39 ± 0.01	0.39 ± 0.02 (100)	0.38 ± 0.01	0.39 ± 0.01*(103)	0.38 ± 0.01 (100)	0.36 ± 0.01 (95)
87 or 92	0.43 ± 0.01	0.43 ± 0.02 (100)	0.39 ± 0.02	0.40 ± 0.01 (103)	0.38 ± 0.01 (97)	0.37 ± 0.01** (95)
Mean cell volume (fL)						
day 46 or 50	55.30 ± 1.30	55.90 ± 0.70 (101)	49.78 ± 0.72	50.69 ± 0.68 (102)	49.96 ± 0.54 (100)	50.03 ± 1.09 (101)
87 or 92	52.80 ± 1.10	53.10 ± 0.90 (101)	49.37 ± 0.69	50.06 ± 0.69 (101)	49.28 ± 0.84 (100)	49.17 ± 1.10 (100)
MCH (fmol)						
day 46 or 50	1.13 ± 0.03	1.14 ± 0.02 (101)	1.21 ± 0.01	1.23 ± 0.03 (102)	1.22 ± 0.02 (101)	1.22 ± 0.03 (101)
87 or 92	1.05 ± 0.02	1.06 ± 0.03 (101)	1.22 ± 0.02	1.23 ± 0.03 (101)	1.23 ± 0.02 (101)	1.21 ± 0.03 (99)
MCHC (mmol/L)						
day 46 or 50	20.47 ± 0.23	20.37 ± 0.25 (100)	24.30 ± 0.44	24.31 ± 0.45 (100)	24.30 ± 0.38 (100)	24.31 ± 0.33 (100)
87 or 92	19.94 ± 0.33	19.88 ± 0.52 (100)	24.71 ± 0.40	24.48 ± 0.30 (99)	24.85 ± 0.16 (101)	24.57 ± 0.44 (99)
White blood cells (giga/L)						
day 46 or 50	4.17 ± 1.00	3.87 ± 0.69 (93)	4.77 ± 1.12	4.82 ± 0.88 (101)	4.38 ± 1.03 (92)	4.68 ± 1.10 (98)
87 or 92	3.58 ± 0.81	3.10 ± 0.66 (87)	4.71 ± 1.65	4.59 ± 1.16 (97)	4.11 ± 1.09 (87)	4.44 ± 0.91 (94)
Polymorphonuclear neutrophils (giga/L)						
day 46 or 50	0.51 ± 0.14	0.48 ± 0.25 (94)	0.78 ± 0.18	0.58 ± 0.24 (74)	0.59 ± 0.22 (76)	0.44 ± 0.22* (56)
87 or 92	0.43 ± 0.17	0.39 ± 0.19 (91)	0.70 ± 0.35	0.51 ± 0.31 (73)	0.43 ± 0.24 (61)	0.38 ± 0.19 (54)
Lymphocytes (giga/L)						
day 46 or 50	3.28 ± 0.84	3.07 ± 0.67 (94)	3.78 ± 1.05	4.06 ± 0.80 (107)	3.56 ± 0.82 (94)	4.03 ± 1.13 (107)
87 or 92	2.71 ± 0.80	2.35 ± 0.57 (87)	3.75 ± 1.36	3.89 ± 1.14 (104)	3.52 ± 0.80 (94)	3.87 ± 0.81 (103)

[a]Data extracted from Study No. 31503/5/88034, tables 29 28 and 33 34, and Study No. 31503/5/88110, tables 27-28 and 35 36.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.
• Significantly different from control values, $p \leq 0.05$ using an analysis of variance and Scheffe's test as calculated by the reviewers.

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
X Sodium*	X Blood creatinine*
X Phosphate*	X Blood urea nitrogen*
X Potassium*	X Globulin
	X Total protein*
Enzymes	X Glucose*
	X Total bilirubin*
X Alkaline phosphatase (ALP)	X Triglycerides
X Serum alanine aminotransferase (SGPT)*	X Cholesterol
X Serum aspartate aminotransferase (SGOT)*	
X Gamma glutamyltransferase	

* Recommended by Subdivision F (November 1984) Guidelines

Results - Small but statistically significant decreases in sodium and potassium were observed in males at 1,000 and 3,000 ppm at study termination (Table 8a). A statistically significant decrease in chloride was observed in females at 3,000 ppm (Table 8b) at 1.5 and 3 months. These changes were suggested by the study author to be the result of altered serum corticosteroid levels.

Statistically significant increases in total protein, globulins, triglycerides, and cholesterol were observed in females at 3,000 ppm. The underlying pathology leading to these changes was unclear, but the study author concluded that these changes were treatment related. In addition, alkaline phosphatase activity was significantly decreased in both males and females at 3,000 ppm at study termination. However, this effect was not considered to be biologically significant.

c) Urinalysis

Urinalysis included the parameters marked with an "X" below.

X Appearance	X Sediment (microscopic)	X Bilirubin
Volume	X Protein	X Blood
Specific gravity	X Glucose	X Urobilinogen
X pH	X Ketones	X Nitrites

Results - No treatment-related effects were observed.

8. Sacrifice and Pathology

All rats received a complete gross examination at the time of the scheduled sacrifice (animals were fasted 16-20 hours before sacrifice). Tissues that are marked with an "X" below were examined histologically in the control and 3,000-ppm animals in study 31S0375/88034 and in the control and 50-ppm animals in study 31S0375/88110. In addition, the pituitary, lungs, liver, kidneys,

TABLE 8.1 Selected Clinical Chemistry Data (Mean ± S.D.) for Male Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

	Study No. 3150375/88110 Clinical Chemistry Data by Dietary Level (ppm)		Study No. 3150375/88034 Clinical Chemistry Data by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
Alkaline phosphatase (μkat/L)						
day 46 or 45	6.64 ± 0.96	6.47 ± 0.68 (97)	6.63 ± 1.28	7.15 ± 1.90 (108)	6.85 ± 1.36 (103)	6.08 ± 0.87 (92)
87 or 92	4.81 ± 0.59	4.82 ± 0.55 (100)	5.48 ± 0.58	5.65 ± 0.73 (103)	5.23 ± 0.99 (95)	4.35 ± 0.56** (79)
Sodium (mmol/L)						
day 46 or 45	145.0 ± 1.7	144.5 ± 1.3 (100)	140.2 ± 3.2	139.9 ± 1.6 (100)	138.8 ± 2.0 (99)	139.4 ± 2.5 (99)
87 or 92	142.5 ± 1.8	143.1 ± 2.6 (100)	143.1 ± 2 2	142.2 ± 1.8 (99)	140.1 ± 1.6** (98)	138.9 ± 1.41** (97)
Potassium (mmol/L)						
day 46 or 45	6.44 ± 0.61	6.27 ± 0.35 (97)	6.32 ± 0.56	6.70 ± 0.51 (106)	6.47 ± 0.51 (102)	6.42 ± 0.41 (102)
87 or 92	6.55 ± 0.45	6.35 ± 0.68 (97)	7.11 ± 0.35	6.78 ± 0.53 (95)	6.54 ± 0.50* (92)	6.24 ± 0.39** (88)
Chloride (mmol/L)						
day 46 or 45	105.9 ± 1.3	105.8 ± 0.9 (100)	105.0 ± 1.4	104.7 ± 1.4 (100)	104.0 ± 1.5 (99)	104.0 ± 1.5 (99)
87 or 92	104.0 ± 0.7	104.3 ± 1.1 (100)	106.4 ± 1.5	106.5 ± 2.3 (100)	106.6 ± 0.9 (100)	104.7 ± 1.3 (98)
Total protein (g/L)						
day 46 or 45	64.57 ± 2.84	64.08 ± 3.37 (99)	68.28 ± 4.14	69.16 ± 3.73 (101)	69.46 ± 6.40 (102)	68.97 ± 3.15 (101)
87 or 92	65.75 ± 2.79	65.07 ± 4.61 (99)	71.05 ± 3.74	69.20 ± 4.98 (97)	67.38 ± 3.01 (95)	69.79 ± 2.69 (98)
Globulins (g/L)						
day 46 or 45	32.55 ± 1.79	32.12 ± 2.02 (99)	30.48 ± 1.92	32.29 ± 3.90 (106)	31.69 ± 3.95 (104)	31.69 ± 2.07 (104)
87 or 92	33.20 ± 2.03	32.34 ± 3.12 (97)	33.57 ± 2.52	32.58 ± 2.65 (97)	30.65 ± 2.70 (91)	32.68 ± 1.79 (97)
Triglycerides (mmol/L)						
day 46 or 45	2.58 ± 0.73	3.07 ± 1.41 (119)	4.07 ± 2.08	3.84 ± 2.94 (94)	3.69 ± 1.26 (91)	2.58 ± 0.63 (63)
87 or 92	3.31 ± 1.49	3.28 ± 0.95 (99)	4.73 ± 1.77	5.53 ± 2.96 (117)	5.27 ± 2.09 (111)	2.62 ± 0.82 (55)
Cholesterol (mmol/L)						
day 46 or 45	2.21 ± 0.44	2.18 ± 0.30 (99)	2.30 ± 0.33	2.63 ± 0.58 (114)	2.30 ± 0.35 (100)	2.63 ± 0.45 (114)
87 or 92	2.07 ± 0.49	2.03 ± 0.33 (98)	2.29 ± 0.40	2.52 ± 0.38 (110)	2.26 ± 0.47 (99)	2.54 ± 0.47 (111)

[a]Data extracted from Study No. 3150375/88034, Tables 43-44 and 47-50, and Study No. 3150375/88110, Tables 45-46 and 49-52.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

TABLE 8b. Selected Clinical Chemistry Data (Mean ± S.D.) for Female Rats Ingesting Vinclozolin in the Diet for 3 Months[a]

	Study No. 3150375/88110 Clinical Chemistry Data by Dietary Level (ppm)		Study No. 3150375/88034 Clinical Chemistry Data by Dietary Level (ppm)			
	0	50	0	300	1,000	3,000
Alkaline phosphatase (μkat/L)						
day 46 or 45	5.00 ± 0.53	5.57 ± 0.91 (111)	5.03 ± 0.75	5.69 ± 0.94 (113)	4.92 ± 1.19 (98)	4.46 ± 2.26 (89)
87 or 92	3.43 ± 0.49	3.85 ± 0.61 (112)	4.35 ± 1.13	4.60 ± 0.63 (106)	3.71 ± 0.73 (85)	2.81 ± 0.40** (65)
Sodium (mmol/L)						
day 46 or 45	146.7 ± 1.8	145.4 ± 1.7 (99)	139.7 ± 1.4	140.5 ± 2.6 (101)	140.8 ± 2.6 (101)	137.1 ± 2.8 (98)
87 or 92	143.3 ± 2.3	142.7 ± 1.6 (100)	140.9 ± 1.9	140.6 ± 1.5 (100)	141.0 ± 2.3 (100)	137.4 ± 1.2 (98)
Potassium (mmol/L)						
day 46 or 45	6.21 ± 0.42	5.93 ± 0.52 (95)	5.83 ± 0.73	6.28 ± 0.43 (108)	6.23 ± 0.81 (107)	6.09 ± 0.52 (104)
87 or 92	6.13 ± 0.55	5.99 ± 0.39 (98)	6.34 ± 0.75	6.35 ± 0.57 (100)	6.23 ± 0.48 (98)	5.80 ± 0.36 (91)
Chloride (mmol/L)						
day 46 or 45	109.5 ± 1.3	107.9 ± 1.0** (99)	107.8 ± 2.2	108.0 ± 1.4 (100)	106.9 ± 1.8 (99)	103.7 ± 2.9** (96)
87 or 92	106.4 ± 1.2	105.5 ± 1.1 (99)	109.1 ± 2.6	108.3 ± 1.4 (99)	108.2 ± 0.8 (99)	105.5 ± 2.1** (97)
Total protein (g/L)						
day 46 or 45	63.80 ± 3.52	64.01 ± 5.94 (100)	67.70 ± 2.98	67.84 ± 4.05 (100)	70.00 ± 3.60 (103)	74.28 ± 3.47** (110)
87 or 92	65.59 ± 2.34	65.94 ± 4.40 (101)	68.80 ± 3.92	68.87 ± 3.97 (100)	70.40 ± 3.77 (102)	72.77 ± 3.62 (106)
Globulins (g/L)						
day 46 or 45	30.46 ± 2.27	30.13 ± 3.59 (99)	28.47 ± 1.86	28.65 ± 2.70 (101)	30.33 ± 2.60 (107)	33.15 ± 1.94** (116)
87 or 92	31.59 ± 1.91	31.09 ± 2.82 (98)	28.47 ± 1.95	29.18 ± 3.18 (102)	30.46 ± 1.24 (107)	30.99 ± 1.77* (109)
Triglycerides (mmol/L)						
day 46 or 45	1.59 ± 1.30	2.00 ± 0.91 (106)	2.22 ± 1.10	1.71 ± 0.61 (77)	2.92 ± 1.89 (132)	4.06 ± 2.51* (183)
87 or 92	1.87 ± 1.43	1.84 ± 0.76 (98)	2.77 ± 0.76	3.30 ± 2.34 (119)	4.11 ± 1.78 (148)	4.14 ± 1.23 (149)
Cholesterol (mmol/L)						
day 46 or 45	2.32 ± 0.44	2.02 ± 0.30 (87)	1.99 ± 0.25	2.44 ± 0.42*(123)	2.27 ± 0.40 (114)	3.06 ± 0.40** (154)
87 or 92	2.30 ± 0.30	2.01 ± 0.28* (87)	1.96 ± 0.23	2.17 ± 0.35 (111)	2.16 ± 0.44 (110)	3.01 ± 0.46** (154)

[a]Data extracted from Study No. 3150375/88034, Tables 45-46 and 51-54, and Study No. 3150375/88110, Tables 47-48 and 53-56.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

adrenals, pancreas, testes, ovaries, and eyes were examined histopathologically in the 300- and 1,000-ppm rats. All tissues were preserved in 4% formaldehyde except the eyes, which were fixed in Zenker's solution. All tissue sections were stained with hematoxylin and eosin. The adrenals were also stained for fat using Oil-red-O. The pituitary of one male and one female each in the control and 3,000-ppm groups was also stained with Alcian blue-PAS-orange stain. Organs that are marked with an "XX" were also weighed at necropsy.

Digestive System	Cardiovascular/Hematologic	Neurologic
X Pancreas*	X Aorta*	X Brain*
X Salivary glands*	X Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (four levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	X Spleen*	X Eyes*
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	
X Colon*		
X Rectum*	XX Kidneys*	Glandular
XX Liver*	X Urinary bladder*	
	XX Testes*	XX Adrenals*
Respiratory	X Seminal vesicles	X Lacrimal gland
	X Prostate	X Mammary gland*
X Trachea*	Epididymides	X Thyroids*
X Lungs*	X Ovaries	X Parathyroids*
X Nasal passages*	X Uterus*	

Other

X Bone (sternum and femur)*
X Joint
X Skeletal muscle (thigh)*
X Skin
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

a) Macroscopic examination

Necropsy revealed dose-related increases in the incidence of enlargement and white discoloration of the adrenal glands in both males and females (Table 9). These effects occurred in females at doses as low as 300 ppm and in males at 1,000 ppm and above. In addition, 2 females at 3,000 ppm had cataracts in the eyes.

b) Organ weights

Dose-related increases were observed in the absolute and relative (organ-to-body) weights of the adrenals and liver in both males and females (Table 10). In addition, dose-related increases in testes weights were observed in males. Statistically significant increases in adrenal weights were observed at 1,000 ppm and above

TABLE 9. Incidence of Selected Macroscopic Findings in Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

	Study No. 31S0375/88110-- Incidence of Macroscopic Findings by Dietary Level (ppm)		Study No. 31S0375/88034-- Incidence of Macroscopic Findings by Dietary Level (ppm)			
	0	50	1	300	1,000	3,000
Males						
Eye						
Cataracts	0	0	1	0	0	0
Adrenal gland						
Enlarged	0	0	1	0	7	10
White discoloration	0	0	1	0	10	10
Females						
Eye						
Cataracts	0	0	1	0	0	2
Adrenal gland						
Enlarged	0	0	1	3	6	10
White discoloration	0	0	1	3	10	10

[a]Data extracted from Study No. 31S0375/88034, p. 343, and Study No. 31S0375/88110, p. 173.
[b]N = 10

TABLE 10. Selected Organ Weight Data in Grams (Mean ± S.D.) for Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b]

	Study No. 3150375/88110 Organ Weight Data by Dietary Level (ppm)		Study No. 3150375/88034 Organ Weight Data by Dietary Level (ppm)			
	0	50	0	500	1,000	5,000
Males						
Liver						
absolute weight	14.11 ± 2.25	13.88 ± 1.88 (98)	14.31 ± 1.91	14.61 ± 1.74 (102)	15.96 ± 1.26 (112)	16.27 ± 1.56* (114)
% body weight	3.09 ± 0.23	3.09 ± 0.26 (100)	3.17 ± 0.32	3.27 ± 0.25 (103)	3.35 ± 0.29 (106)	3.77 ± 0.26** (119)
Testes						
absolute weight	3.52 ± 0.20	3.56 ± 0.30 (101)	3.45 ± 0.21	3.70 ± 0.49 (107)	3.89 ± 0.34* (113)	4.26 ± 0.26** (123)
% body weight	0.78 ± 0.07	0.79 ± 0.05 (101)	0.77 ± 0.06	0.83 ± 0.11 (108)	0.82 ± 0.10 (106)	0.99 ± 0.09** (129)
Adrenals						
absolute weight	0.088 ± 0.016	0.086 ± 0.011 (98)	0.079 ± 0.007	0.084 ± 0.009 (106)	0.105 ± 0.015* (133)	0.180 ± 0.036** (228)
% body weight	0.019 ± 0.004	0.019 ± 0.002 (100)	0.018 ± 0.002	0.019 ± 0.003 (106)	0.022 ± 0.002 (122)	0.042 ± 0.009** (233)
Females						
Liver						
absolute weight	7.09 ± 0.56	7.31 ± 0.43 (103)	7.55 ± 0.72	7.92 ± 0.65 (105)	8.70 ± 0.89* (115)	11.66 ± 1.50** (154)
% body weight	2.88 ± 0.15	2.96 ± 0.10 (103)	2.98 ± 0.23	3.05 ± 0.15 (102)	3.50 ± 0.22** (117)	4.59 ± 0.52** (154)
Adrenals						
absolute weight	0.109 ± 0.009	0.109 ± 0.009 (100)	0.103 ± 0.011	0.119 ± 0.010 (116)	0.137 ± 0.017** (133)	0.163 ± 0.022** (158)
% body weight	0.044 ± 0.005	0.044 ± 0.003 (100)	0.041 ± 0.006	0.046 ± 0.004 (112)	0.055 ± 0.007** (134)	0.064 ± 0.009** (156)

[a]Data extracted from Study No. 3150375/88034, pp. 339-342, and Study No. 3150375/88110, pp. 169 172.
[b]Numbers in parentheses indicate percent of control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

OTC 459

in both males and females. Although no statistically significant increase in adrenal weights was observed in females at 300 ppm, the weights of the adrenals of those females with macroscopic enlargement and white discoloration (see above) were higher than those of the other females at 300 ppm. Statistically significant increases in liver weights were observed in males at 3,000 ppm and in females at 1,000 and 3,000 ppm. Statistically significant increases in testes weights were observed in males at 1,000 and 3,000 ppm.

c) Microscopic examination

Histopathologic analysis showed changes in the adrenal cortex, pituitary, testes, pancreas, and liver of treated rats (Tables 11a and 11b). The zona fasciculata of the adrenal cortex of male and female rats at 1,000 and 3,000 ppm showed increases in the incidence and severity of hypertrophy and vacuolation, and in the severity of lipid storage and birefringence. In addition, male rats at 1,000 and 3,000 ppm showed increases in the incidence and severity of cystoid degeneration in the pituitary. Additional staining of the pituitary gland in selected animals from the control and 3,000-ppm groups revealed slight increases in gonadotropin-forming and adrenocorticotropic hormone (ACTH) cells in one male at 3,000 ppm. Males at 1,000 and 3,000 ppm also showed an increase in the incidence of Leydig cell hyperplasia in the testes.

Examination of the pancreas of females at 300 ppm and above and of males at 1,000 and 3,000 ppm revealed increases in the incidence of acinar vacuolation. In males the severity increased with dose. In females the severity increased from 300 ppm to 1,000 ppm but no increase in severity was observed between 1,000 and 3,000 ppm. An increased incidence of hyperplasia of the islets of Langerhans was observed in males at 1,000 and 3,000 ppm and in females at 3,000 ppm.

Hepatic changes included increases in the incidence of cloudy swelling and single cell necrosis in both males and females at 1,000 and 3,000 ppm, single instances of acidophilic cell foci in males at 3,000 ppm and in females at 1,000 and 3,000 ppm, and mixed cell foci in a female at 1,000 ppm.

Note: The summary table for histopathological findings reported foam cell granulomas in 1 high-dose male and 3 high-dose females. These lesions were not found in the individual animal data sheets.

3. DISCUSSION

Review of the final report and supporting data indicates that the conduct and design of the study were adequate and that the reporting of the results was (with the exception of a few minor inconsistancies) accurate. Because of the increase in lesions at the lowest dose tested (300 ppm) in the main study (TSCATS 88034), a subsequent addendum study

TABLE 11a Incidence of Selected Histopathology Findings in Male Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b,c]

	Study No. 31503?5/88110 Histopathology Findings by Dietary Level (ppm)		Study No. 31503?5/88034 Histopathology Findings by Dietary Level (ppm)			
	0	500	0	500	1,000	5,000
Adrenal cortex - zona fasciculata						
Hypertrophy	0	0	0	0	5 (1)	10 (2.4)
Vacuolation	0	0	0	0	7 (1)	10 (2.6)
Lipid storage	10 (1.3)	10 (1)	10 (1.1)	10 (1.3)	10 (1.7)	10 (3.1)
Birefringence	10 (1.4)	10 (1.3)	10 (1.2)	10 (1.1)	10 (1.6)	10 (3.6)
Pituitary						
Cystoid degeneration	0	0	5 (1)	4 (1)	9 (1.6)	10 (2.0)
Pancreas						
Acinar vacuolation	0	0	0	0	8 (1.9)	10 (3.6)
Hyperplasia of islets of Langerhorns	0	0	4 (1)	5 (1)	8 (1)	9 (1)
Testes						
Leydig cell hyperplasia	0	0	0	0	3 (1)	8 (1)
Liver						
Clear cell swelling	0	0	0	0	2 (1)	10 (1.6)
Single cell necrosis	0		0	0	3 (1)	10 (1.6)
Acidophilic cell foci	0	0	0	0	0	1 (3)
Mixed cell foci	0	0	0	0	0	0

[a]Data extracted from Study No. 31503?5/88034, pp. 344-347, and Study No. 31503?5/88110, pp. 173-175.
[b]N = 10
[c]Numbers in parentheses indicate average severity (1 = minimal, 2 = slight, 3 = moderate, and 4 = marked/severe)

TABLE 11b Incidence of Selected Histopathology Findings in Female Rats Ingesting Vinclozolin in the Diet for 3 Months[a,b,c]

	Study No. 3160375/88110 Histopathology Findings by Dietary Level (ppm)			Study No. 3160375/88034 Histopathology Findings by Dietary Level (ppm)		
	0	50	0	100	1,000	5,000
Adrenal cortex - zona fasciculata						
Hypertrophy	0	0	0	0	2 (1)	10 (2.1)
Vacuolation	0	0	0	0	6 (1)	10 (1.9)
Lipid storage	10 (1.6)	10 (1.7)	10 (1.1)	10 (1.4)	10 (2.5)	10 (3.3)
Birefringence	10 (1.8)	10 (1.9)	10 (1.1)	10 (1.3)	10 (2.3)	10 (3.6)
Pituitary						
Cystoid degeneration	0	0	1 (1)	1 (1)	2 (1)	1 (1)
Pancreas						
Acinar vacuolation	0	0	0	1 (1)	10 (2.2)	10 (1.9)
Hyperplasia of islets of Langerhorns	0	0	5 (1)	5 (1)	5 (1)	5 (1)
Liver						
Cloudy swelling	0	0	0	0	4 (1)	10 (1)
Single cell necrosis	0	0	0	0	4 (1)	10 (1)
Acidophilic cell foci	0	0	0	0	1 (2)	1 (2)
Mixed cell foci	0	0	0	0	1 (3)	0
Ovaries - luteal cell accumulation	8 (1)	9 (1)	5 (1.2)	4 (1)	5 (1)	10 (1.4)

[a]Data extracted from Study No. 3160375/88034, pp. 344-347, and Study No. 3160375/88110, pp. 173-175.
[b]N = 10
[c]Numbers in parentheses indicate average severity (1 = minimal, 2 = slight, 3 = moderate, and 4 = marked/severe).

(31S0375/88110) was initiated using 50 ppm and a control. No treatment-related effects were observed in the latter study.

The adrenal cortex, pancreas, and lens of the eye were the most sensitive target organs for vinclozolin in the Wistar rat. Macroscopic changes in the adrenal cortex were observed at doses as low as 300 ppm. At this dose, an increase in the incidence of enlarged and white discolored adrenal glands was observed in 3 of 10 females. At 1,000 ppm and above, males also showed macroscopic evidence of adrenal changes, and both males and females showed increases in adrenal weights and microscopic changes in the zona fasciculata. These microscopic changes included increases in the incidence and severity of hypertrophy and vacuolation, as well as increases in the degree of lipid storage and birefringence. Although ACTH and corticosteroid levels were not measured in this study, based on results of previous studies, it is probable that elevated levels of corticosteroids were produced.

Lesions that may be related to elevated corticosteroid levels included cystoid degeneration of the pituitary (with slight increases in gonadotropin and ACTH-forming cells), increases in testes weights with Leydig cell hyperplasia, and decreases in lymphocytes and serum levels of sodium and potassium in males at 1,000 ppm and above. Females did not show similar changes in the pituitary, lymphocyte count, or serum sodium or potassium levels, but did show decreased serum chloride and water consumption at 3,000 ppm. The pancreas showed acinar cell vacuolation in males at 1,000 and 3,000 ppm and females at 300 ppm and above, and hyperplasia of the islets of Langerhans in males at 1,000 and 3,000 ppm and in females at 3,000 ppm.

The lens of the eye showed a dose-related increase in the incidence of striations starting at 300 ppm. This is a naturally occurring lesion that increases with age, and the study author suggested that the vinclozolin accelerated the appearance of this change. No increase in the incidence of striations of the lens was observed at 50 ppm; however, the incidence of this lesion was high in both the controls and treated animals in the supplemental study precluding the determination of such a difference. The study author reported that grading the severity of this lesion was difficult because different severities were observed at various sites in a single lens. At 3,000 ppm, females also showed increases in the incidence of bosselated structure of the lens and cataracts. Neither the appearance of striations nor the occurrence of bosselated structure of the lens were predictive for cataract formation. The doses at which these effects were observed were consistent with those in other studies exposing Wistar rats to vinclozolin in the diet. Therefore, the study author concluded that vinclozolin was cataractogenic in the Wistar rat.

Treatment-related effects were also observed in the liver. At 1,000 ppm and above in both males and females there was an increase in the incidence of cloudy swelling and single cell necrosis. In addition, there was a statistically significant increase in liver weight in females at 1,000 ppm and above and in males at 3,000 ppm. Other hepatic effects observed at 3,000 ppm included increases in total protein, globulins, triglycerides, and cholesterol in females.

Slight, but possibly treatment-related hematological effects observed at 3,000 ppm included decreases in red blood cell count in both males and females, decreases in hemoglobin and hematocrit in females, and decreases in mean corpuscular hemoglobin in males. Increases in mean corpuscular volume and mean corpuscular hemoglobin were also observed in males at this dose.

The above results are consistent with those seen in the range-finding studies in Sprague-Dawley rats that were used to set doses for the current studies. It is unclear whether ophthalmological examinations were conducted in the rangefinding studies. Therefore, no conclusions may be drawn regarding the consistency of this effect between studies.

Although the study author noted an increase in the incidence of ovarian luteal cell vacuolization, it is unclear whether this effect was treatment-related because the incidence of this finding among control females in the supplemental study was also high. (See Table 15)

Taking the results of the main and addendum studies together, the NOEL for systemic effects is 50 ppm and the LOEL is 300 ppm, based on the observation of enlarged and white discoloration of the adrenals and pancreatic acinar cell vacuolation in females. Although an increase in the incidence of striations of the lens was also observed at this dose in both males and females, the toxicological significance of this finding is unclear. This study satisfies the guideline requirements for a subchronic oral toxicity study in rats but is classified as Core Minimum because of minor inconsistencies in data reporting.

3. STUDY DEFICIENCIES

-Minor inconsistencies were noted in the reporting of the data. These included reporting lung foam cell granulomas in the histopathology summary table when these lesions were not found in the individual animal data and reporting that 1 10 high-dose females had bosselated structure of the lens on one side when the individual animal data indicated that only 1/10 high-dose females had this lesion.