(TXR 013598) (8-3-99) 11

[Trifloxystrobin] Chronic Oral Study 83-1(a)

EPA Reviewer: William B. Greear, MPH, DABT , Date _____
Registration Action Branch 3 (7509C)
EPA Secondary Reviewer: Stanely Gross, Ph.D. , Date _____
Registration Action Branch 3 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic/oncogenicity-feeding-rat OPPTS 870.4300 [§83-5]

DP BARCODE: D244009 SUBMISSION CODE: S538790
P.C. CODE: 129112 TOX. CHEM. NO.: N/A

TEST MATERIAL (PURITY): CGA-279202 technical (trifloxystrobin, 96.4%)

SYNONYMS: N/A

CITATION: Gerspach, R. (1997) 24-Month Carcinogenicity and Chronic Toxicity Study in Rats. Novartis Crop Protection, AG, Toxicology/Experimental Toxicology, 4332 Stein/Switzerland. Test No. 943038, Novartis Nexus Number 707-97, October 22, 1997. MRID 44496711. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., Greensboro, NC 27419

EXECUTIVE SUMMARY:

In a chronic toxicity/carcinogenicity study (MRID 44496711) CGA-27902 technical, 96.2%) was administered to 70 Tif: Raif (SPF) rats/sex/group in the diet at dose levels of 0, 50, 250 750 or 1500 ppm (M: 0, 1.95, 9.81, 29.7 or 62.2 mg/kg/day; F: 0, 2.22, 11.37, 34.5 or 72.8 mg/kg/day) for 2 years. Additionally, groups of 10 rats/sex/group were fed the same diets for 53 weeks and then sacrificed. Observations for clinical signs of toxicity, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross necropsy and histopathology were determined.

There were no compound related effects in mortality, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic (including tumors) pathology. Towards the end of the study, diarrhea was observed in several males in the 1500 ppm group. Body weights were decreased in males in the in the 750 ppm (5.2% at 51 weeks) and 1500 ppm (16.3% at 51 weeks) groups. Body weights were also decreased in females in the 750 ppm (10.8% at 51 weeks) and in the 1500 ppm (26.2% at 51 weeks) groups. Body weight gain was decreased in males by 5% (750 ppm) and 13% (1500 ppm) and in females by 10% (750 ppm) and 19% (1500 ppm) after 12 weeks. Food consumption was decreased in females in the 1500 ppm group (7.9% from week 1-

1/6

103). **The LOEL is 750 ppm (M: 29.7 mg/kg/day; F: 34.5 mg/kg/day), based on decreased body weights and body weight gain. The NOEL is 250 ppm (M: 9.81 mg/kg/day; F: 11.37 mg/kg/day).**

This chronic toxicity/carcinogenicity study in the rat is Acceptable/Guideline and does satisfy the guideline requirement for a chronic oral study (83-1a) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

COMMENTS:

There were no indications of neurotoxicity, immunotoxicity, endocrine disruption or increased sensitivity based on the age of the animal.

ADDENDUM

A. Body Weight Gain

Mean Body Weight Gain (g)					
Males	Dose Levels (ppm)				
Week No.	0	50	250	750	1500
1	51.57	52.04	53.39	53.34	51.71
12	309.5	309.6	308.6	293.7*	270.5*
26	422.1	418.7	416.9	396.6*	355.2*
39	487.7	486.1	486.4	460.4	409.7*
51	535.2	535.7	535.3	507.4	447.7*
63	586.4	590.8	585.7	545.5	495.0*
78	614.9	622.2	615.2	575.4	524.6*
91	624.5	612.1	618.1	583.6	521.0*
103	546.8	583.2	580.2	553.5	511.0*

* - Statistically significant at $p < 0.01$

Mean Body Weight Gain (g)					
Females	Dose Levels (ppm)				
Week No.	0	50	250	750	1500
1	30.88	30.11	29.76	29.44	26.92*
12	169.0	168.0	160.1	151.4*	136.7*
26	212.5	208.9	198.0	189.2*	167.1*
39	238.9	236.5	223.9	213.2*	183.8*
51	268.4	265.5	248.6	239.5*	198.0*
63	304.0	308.1	280.5	272.5*	218.2*
78	338.1	336.9	316.4	311.9	247.4*
91	361.1	360.4	336.5	329.1	264.9*
103	361.0	336.5	344.6	329.7	268.8*

* - Statistically significant at $p < 0.01$
Data extracted from table on p.52 0f 2427, Study No. 943038, MRID 44496711.

B. Miscellaneous

1. California EPA's review has an error in the Mean Body Weight Table on page 3. The value for body weight at week -1 for the 750 ppm group should be 183.8 not 183.6.

2. Dose levels selected for testing were based on the results of a 3-month toxicity study in rats (MRID 44496701). Treatment-related deaths included 1 male and 1 female at 2,000 ppm and 5 females at 8,000 ppm. Signs of clinical toxicity included hunched posture, hypoactivity, soft feces and piloerection in females at 8,000 ppm. At the end of dosing, body weight was statistically decreased in males in the 2,000 ppm group (13%) and in females in the 8,000 ppm group (20%). At the end of the recovery period, body weight was similar between the control and high-dose groups. Cholesterol was increased in males at 2,000 ppm group (28%). Glucose was increased in females at 8,000 ppm (13%) and urea was increased in females at 8,000 ppm (18%), however, the reported increase was not biologically significant. There may, however, be a possible correlation between the reported increase in glucose and the pancreatic atrophy reported in high dose females. Clinical chemistry values were comparable between the control and high-dose groups at the end of the recovery period. Relative liver weights were increased in males at 500 ppm (13%) and at 2,000 ppm (22%) and in females at 8,000 ppm (39%). At the end of the recovery period, relative liver weights were comparable. Relative heart weights were increased in females at 8,000 ppm at 14 weeks (26%) and at 18 weeks (21%). Minimal hypertrophy of the hepatocyte was increased in males in the 2,000 ppm group (5/21) and females in the 8,000 ppm group (11/21). Atrophy of the pancreas was increased in males in the 2,000 ppm group (5/21) and in females in the 2,000 ppm (2/10) and 8,000 ppm (12/21)groups. FOB and motor activity were comparable among the control and test groups. Neuropathological examination revealed no treatment-related abnormalities. The LOAEL is 2,000 ppm (127-133 mg/kg/day), based on decreased body weight in males, hypertrophy of the hepatocyte in males, and pancreatic atrophy in males and females. The NOAEL is 500 ppm (30.6-32.8 mg/kg/day).

COMMENTS:

There were no indications of neurotoxicity, immunotoxicity, endocrine disruption or increased sensitivity based on the age of the animal.

APPENDIX

A. Histopathology

Trifloxystrobin: Histological Lesions in Rats*					
	Trifloxystrobin (ppm)				
	0	100	500	2,000	8,000
Lesion	Males				
Liver-hepatocyte hypertrophy	0/20	0/10	0/10	5/21	0/0
Pancreas-atrophy	0/20	0/10	0/10	5/21	0/0
	Females				
Liver-hepatocyte hypertrophy	0/20	0/10	0/10	0/10	11/21
Pancreas-atrophy	0/20	0/10	0/10	2/10	12/21

*Incidence data for each dose level are reported as total number of affected animals/total number of animals examined microscopically.

ATTACHMENT: Attached is California's EPA review of this study which should be used as a supplement to HED's review. It contains tables on body weight, food consumption and organ weight ratios.

SignOff Date:	8/3/99
DP Barcode:	D243979
HED DOC Number:	013599
Toxicology Branch:	TOX2