(TXR 013599) (8-3-99)

[Trifloxystrobin] Carcinogenicity Study 83-2(b)

EPA Reviewer: W. Greear, MPH, DABT , Date _____
Toxicology Branch II (7509C)
EPA Secondary Reviewer: A.P. Bearden Ph.D. , Date _____
Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity - feeding - mouse
OPPTS 870.3200 [§83-2b]

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

TEST MATERIAL (PURITY): CGA-279202 (96.2%, trifloxystrobin)

SYNONYMS: N/A

CITATION: Gerspach, R. (1997) 18-Month Carcinogenicity Study in Mice. Toxicology/Experimental Toxicology, Novartis Crop Protection, AG, 4332 Stein, Switzerland. Test No. 943039, Novartis Nexus No. 705-97, October 22, 1997. MRID 44496705. Unpublished.

SPONSOR: Novartis Crop Protection, Greensboro, NC 27419

EXECUTIVE SUMMARY:

In a carcinogenicity toxicity study (MRID 44496705), CGA-279202 (96.2%, Batch No. P.405009 was administered to 70 Tif: MAGf (SPF) mice/sex/dose in the diet at dose levels of 0, 30, 300, 1000 or 2000 ppm (M:0, 3.90, 39.4, 131.1 or 274 mg/kg/day; F: 0, 3.51, 35.7, 124.1 or 246 mg/kg/day) for 18 months. Additional groups of 10 mice/sex were fed the test diets for a period of 52 weeks and then sacrificed. Observations for clinical signs of toxicity, mortality, hematology, organ weights, gross necropsy and histopathology were determined.

There were no compound related effects on mortality or clinical signs of toxicity. Body weights were decreased for females in the 300 ppm (10% at 43 weeks), 1000 ppm (7% at 43 weeks) and 2000 ppm (11% at 43 weeks). Body weight gain was decreased in females in the 300 ppm (21% at 43 weeks), 1000 ppm (16% at 43 weeks) and 2000 ppm (20% at 43 weeks). Mean liver weights were increased in males in the 2000 ppm group at 39 weeks (49%) and 79 weeks (22%), and in females in the 2000 ppm group (5%) at 79 weeks. Mean relative liver weights were increased in males in the 2000 ppm group at 39 weeks (27%) and 79 weeks (25%), and in females in the 2000 ppm group at 39 weeks (14%) and 79 weeks (12%). There was an increase in fatty change in the liver of male mice at 2000 ppm (48/60; control 41/60). Single cell necrosis of the liver was increased in males in the 1000 ppm (17/60; control 7/60) and 2000 ppm (26/60) groups and in females in the 2000 ppm group (17/60; control 7/60). Necrosis of the liver was also increased in

females in the 2000 ppm group (10/60; control 3/60). Hepatocellular hypertrophy was increased in females in the 1000 ppm (15/60; control 9/60) and 2000 ppm (26/60) groups. Chronic reactive hyperplasia of the mesenteric lymph node was increased in females in the 1000 ppm (17/47; control 9/44) and 2000 ppm (17/47) groups. There was an increase in systemic malignant lymphoma with statistical significance (trend test) in the bone marrow, kidneys, and lacrimal gland in males in the 2000 ppm group and in the ovaries and salivary gland of females in the 2000 ppm group. The LOAEL is 300 ppm (35.7 mg/kg/day) in females based on decreases in body weight and body weight gain. The NOAEL is 30 ppm (3.51 mg/kg/day).

[The LOAEL in males is 1000 ppm (131.1 mg/kg/day) based on liver pathology. The NOAEL is 300 ppm (39.4 mg/kg/day)].

At the doses tested, there was a treatment related increase in tumor incidence (malignant lymphoma). Dosing was considered adequate based on decreases in body weight and body weight gain in females and liver pathology in both sexes.

This carcinogenicity study in the mouse is acceptable, and the study does satisfy the guideline requirement for a carcinogenicity study (83-2b) in the mouse.

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 in Females

Body Weight Gain (g)					
Females	Dose Level (ppm)				
Week	0	30	300	1000	2000
1	1.246	1.385	1.879*	0.930	1.144
13	11.61	11.09	10.73	10.07*	10.02*
27	19.90	18.78	17.77	15.80*	15.46*
43	24.58	22.26	19.49*	20.71*	19.56*
55	25.71	23.65	22.79	22.39*	20.94*
67	26.00	24.13	22.30*	24.26*	21.31*
78	23.85	21.99	20.61	23.31	21.28

* - Statistically significant at $p < 0.01$ (Jonckheere)

B. FATTY CHANGE IN THE LIVER OF MALE MICE

It is noted that there was a significant (trend test) increase in fatty change in the liver of male mice in the 2000 ppm group. The incidence of fatty change was: 41/60, 40/60, 44/60, 46/60 and 48/60 in the control, 30, 300, 1000 and 2000 ppm groups, respectively.

C. MISCELLANEOUS

1. The Table "Liver Histology-Non Neoplastic", page 6 of California EPA's review, should include a section for liver necrosis at 39 weeks. There should be 1, 0, 0, 0 and 1 animals with necrosis in the 0, 30, 300, 1000 and 2000 ppm dose groups.

ATTACHMENT: California EPA's review is attached and should be used in conjunction with HED's review. It provides tables on body weight, food consumption liver weights (absolute, relative), non-neoplastic pathology and neoplastic pathology.

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