(TXR 013599) (8-3-99) 3

[CGA 279202 Technical (trifloxystrobin)] Subchronic Oral Study (82-1)

EPA Reviewer: William B. Greear, MPH, DABT _____ _____
Toxicology Branch II (7509C) Date
EPA Secondary Reviewer: Jessica Kidwell,M.S._____ _____
Registration Action Branch 1 (7509C) Date

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity-feeding-rat
OPPTS 870.3100 [§82-1]

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

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

SYNONYMS: N/A

CITATION: Gerspach, R. (1995) 3-Month Oral Toxicity Study in Rats (Administration in Food). Short/Long-term Toxicology, Novartis Crop Protection, AG, 4332 Stein, Switzerland. Test No. 933164, Novartis Nexus No. 773-95. MRID 44496701. Unpublished.

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

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID 44496701) CGA 279202 (Batch No. KGL-4617/5, 96.2%)] was administered to 15 Tif: RAif (SPF) rats/sex/dose in the diet at dose levels of 0, 100, 500, 2,000 or 8,000 (females only) ppm (0, 6.44, 30.6 or 127 mg/kg/day (M); 0, 6.76, 32.8, 133 or 618 mg/kg/day (F)) for 3 months. Additional groups of 10 rats/sex were administered 0 and 2,000 (M) or 8,000 (F) ppm for 3 months with an additional 4 week recovery period. Survival, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, gross necropsy and histopathology including neuropathology, FOB and motor activity were determined. FOB and motor activity were examined on 15 rats/sex/group (5/sex at the end of recovery). Neuropathology was conducted on 5 rats/sex/group at 3 months.

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).**

This subchronic toxicity study is classified **ACCEPTABLE/GUIDELINE** and does satisfy the guideline requirement for a subchronic oral study (82-1) in rats. However, the study is **UNACCEPTABLE** as a series 82-7 subchronic neurotoxicity study in rats because positive control data were not submitted. The study may be upgraded upon submission of acceptable positive control data.

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.

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.

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