2

(TXR 013599) (8-3-99)

[CGA-279202-Trifloxystrobin/1996] [Metabolism 870.7485]

Reviewed by: Ghazi A. Dannan, Ph.D. _____ Date:_____
Registration Branch III (7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. _____ Date:_____
Senior Scientist, Registration Branch III (7509C)

Data Evaluation Record

Study type: Metabolism and Pharmacokinetics - rat; OPPTS 870.7485 [(§85-1)]

MRID number: 44496821 Submission: S538790

DP Barcode: D244009 P.C. Code: 129112

Laboratory Project Ids: PR 13/96, Novartis Report No. 692-97
Test materials: CGA-279202 Technical (unlabeled, 99.7% a.i.); [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 (radiochemical purity >97 to >99%, >99%, respectively)

Synonym: Trifloxystrobin

Citation: Muller, T. (1996): The Absorption, Distribution, and Excretion of [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 in the Rat. Animal Metabolism, Product Safety Division, Novartis Crop Protection AG, Basle, Switzerland. Report Date: August 29, 1996. MRID# 44496821. Unpublished.

Sponsor: Novartis Crop Protection, Inc.

Executive Summary:

In a metabolism study (MRID # 44496821), several groups of male and female rats were administered by gavage [Glyoxyl-Phenyl-(U)-^{14}C]CGA-279202 and another group (D2) was gavaged with [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202. In Groups B1 and D1 (5/sex/group), urine and feces were collected up to 7 days post-dosing with 0.5 or 100 mg/kg of the test material , respectively. For group C1, urine and feces were also collected for 7 days after administering 0.5 mg/kg of [Glyoxyl-Phenyl-(U)-^{14}C]CGA-279202 to 5 animals/sex that were pretreated for 14 days with 0.5 mg/kg of unlabeled CGA-279202 (technical, 99.7% a.i.). In group D2, 5 rats/sex were dosed with 100 mg/kg of [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 and urine and feces were collected up to 7 days. In tissue pharmacokinetics study, 12 rats/sex were dosed with either 0.5 mg/kg (male group F1 and female group F5) or with 100 mg/kg (male group F2 and female group F6) and tissue samples were analyzed at 4 time points based upon preliminary pharmacokinetics data from the previous groups. In bile duct cannulated studies, Glyoxyl-Phenyl-(U)-^{14}C]CGA-279202 was administered to groups G1 (6 males) and G3

1/4

(5 females) at 0.5 mg/kg or to groups G2 (6 males) and G4 (4 females) at 100 mg/kg.

Of the administered single or repeated low dose, 56% (males) and 65% (females) was absorbed (based on total recovery from urine, bile, and tissues), with 41 and 47% being in the bile of males and females, respectively. In the high dose group males and females, the degree of absorption was 41% and 27%, while the bile content was 35% and 19%, respectively. The extent of excretion in the urine and feces of the low dose groups was, respectively, 19% and 79% in the males and 35-42% and 56-63% in the females, with little or no alteration in the extent of excretion following pretreatment with unlabeled test material (group C1 vs. group B1). In the high dose groups, the urinary and fecal excretions were, respectively, 10-12% and 82-84% in males and 27% and 64-66% in females, with little or no influence from the labeling site (group D1 vs. group D2). Very little or no radioactivity was detected in the expired air with the largest amount found in group D2 (0.05-0.08% of the administered dose). At 7 days post-dosing, 91.2-98.9% of the administered dose was recovered in the urine and feces, in addition to a total tissue/carcass content of 0.3-0.5%. The bile-duct cannulated animals (groups G1-G4) had lower total recoveries (54.8-83.4%) in their excreta and bile during the study period of 42-48 hours. The tissues with the highest residues were blood, liver, and kidneys with concentrations ranging from 1 to 2 ppm in the high dose groups D1 and D2. Most of the examined tissues had somewhat higher residue levels in the females than in the males (by up to 2-fold). The radioactivity in the blood was associated mainly with the red blood cells with a marked sex difference being noted for the calculated RBC/Plasma ratios (Male/Female: 4.4/18.2 in group D1 and 10.5/16.5 in group D2). The half lives for the depletion of radiolabel from the tissues ranged from 13 to 42 hours with the exception of the spleen (68 hours) and blood (82 hours) of the high-dose females in group F6. The times to maximal (t_{max}) and half maximal ($t_{max/2}$) blood concentrations were 12-24 hours and 23-67 hours, respectively. In general, there was little or no effect of the dose level, sex of the animal, or the site of label on t_{max} while clearance (approximated by $t_{max/2}$) was faster among the females than the males (23, 44, and 52 hours in females vs. 48, 50, and 67 hours in males of groups B1, D1, and D2, respectively). Bioavailability, represented by the area under the curves were somewhat higher among the males than the females of groups B1($AUC_{0\text{-}96hr}$ 3.8 vs. 2.3 mg.hr.kg^{-1}) and D1 ($AUC_{0\text{-}48hr}$ 335 vs. 214 mg.hr.kg^{-1}).

Classification: This study is classified as **acceptable** (guideline) and satisfies the data requirement (OPPTS 870.7485; OPP §85-1) for a metabolism study in rats.

Compliance: Signed and dated statements of GLP, Quality Assurance, and No Data Confidentiality were provided. Attachment: CALEPA Toxicology Study Evaluation Report dated 6/5/

HED Comments

The CALEPA review dated June 5, 1998 is attached and RAB III recommends using this document in place of a DER prepared by HED staff or Contractors. The HED reviewer concurs with the CALEPA reviewer that the report is complete and the study is acceptable. However, there were some typos or errors in the CALEPA review (generally of little or no consequence on the conclusions) which are shown with a strikeout and a handwritten correction made by the HED reviewer with his initials "GAD". The following also specifies the source in the subject MRID from which the Tables of the CALEPA review were obtained:

- Table of page 4 of CALEPA review entitled, "Absorption of Oral Dose (% of dose)" was reproduced from summary Table of page 37 of 122 of the subject MRID. The abbreviation n.a. in the Table means not applicable.

- Table of page 5 of CALEPA review entitled, "Excretion of Radiolabel (% of dose)" was reproduced from summary Table of page 39 of 122 of the subject MRID. The abbreviation n.a. in the Table means not applicable.

- Table of page 6 of CALEPA review entitled, "Tissue Residues 7 Days After Administration" was reproduced from summary Table of page 42 of 122 of the subject MRID.

- Top Table of page 7 of CALEPA review entitled, "Depletion of Residual Radioactivity: Halflife (hours)" was reproduced from summary Table of page 41 of 122 of the subject MRID. The abbreviation n.a. in the Table means not applicable.

- Second Table of page 7 of CALEPA review entitled, "Blood Kinetics" was reproduced from summary Table of page 36 of 122 of the subject MRID. The abbreviation n.a. in the Table means not applicable.

Attachment: **CALEPA Toxicology Study Evaluation Report dated 6/5/98 (Record # 160253).**

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