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(TXR 013599) (8-3-99)

[CGA-279202-Trifloxystrobin/1997] [Metabolism 870.7485]

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Data Evaluation Record

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

MRID number: 44496822 Submission: S538790

DP Barcode: D244009 P.C. Code: 129112

Laboratory Project Ids: PR 12/97, Novartis Report No. 712-97
Test materials: CGA-279202 Technical (unlabeled, >99% a.i., batch No. AMS 759/101); [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 (radiochemical purity >97 to >99%, >99%, respectively)

Synonym: Trifloxystrobin

Citation: Thanei, P. (1996): The Metabolism of [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 in the Rat. Animal Metabolism, Novartis Crop Protection AG, Basle, Switzerland. Report Date: November 14, 1997. MRID# 44496822. Unpublished.

Sponsor: Novartis Crop Protection, Inc.

Executive Summary:

In a rat metabolism study (MRID # 44496822), urine, feces, and bile that were recovered from the previous CGA-279202 pharmacokinetics study (MRID 44496821) were pooled by group and sex, subjected to methods involving solvent extractions, chemical purification (LC and HPLC), quantification (HPLC), and metabolites characterization (MS and NMR), and the information was used to elucidate and propose a metabolic pathway. Samples from two additional dosed groups were also included. In group B2, male and female rats were administered 0.5 mg/kg [Trifluormethyl-Phenyl-(U)-^{14}C]CGA-279202 and urine (0-48 hrs) and fecal (0-72 hrs) samples were collected. A second female group (G4a) was also added to replace the high dose bile-duct cannulated group G4 whose total 42 hours excretion (including bile) of radiolabel was relatively low (54.8 % of the administered dose). Overall, the metabolite profiles were different among the urine, feces and bile. The urinary metabolite pattern was complex and was dependent on sex and position of label, only slightly dependent on dose, but was independent of pretreatment with non-radiolabeled CGA-279202. The fecal pattern, on the other hand, was qualitatively independent of dose, sex, position of label, or pretreatment despite some quantitative variations. The biliary

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metabolite pattern was complex with some qualitative and quantitative sex- and dose-dependent variations (e.g., larger number of metabolites in males than females). Based on the identified structures of more than 30 metabolites, schemes of metabolic pathways were proposed (copies attached) with the following major reaction types: 1) Hydrolysis of the methyl ester to the corresponding acid (e.g., CGA 321113). 2) O-Demethylation of the methoxyimino group to the hydroxyimino derivative(s) (e.g., NOA 405637). 3) Oxidation of the methyl side chain to the primary alcohol (e.g., MET 2U) with further partial oxidation to the corresponding carboxylic acid (e.g., MET 13U). The metabolism of the methyl side chain to a primary alcohol was more pronounced in female than in male rats resulting in various sex specific major urinary metabolites. There were other minor reaction types including chain shortening by oxidative decarboxylation of the glyoxyl moiety to a benzoic acid amide (MET 13U), hydrolysis of the hydroxyimino group to a ketone (MET 5U) followed by oxidative decarboxylation to a benzoic acid derivative (MET 4U), oxidation of the hydroxyimino group to a nitro group (MET 3U), and hydroxylations of the phenyl rings. In addition, nearly 10% of the administered dose was accounted for by cleavage between the glyoxyl-phenyl and the trifluoromethyl-phenyl moieties with further metabolism by one or more of the above described reactions to yield several one phenyl ring metabolites including *ortho*-phthalic acid and *meta*-trifluoromethyl benzoic acid, among others. It should be noted that the majority of the metabolites were formed by more than one the above mentioned reactions. Most of the bile metabolites were hydroxylated and conjugated to glucuronic and, to a lesser extent, sulfuric acid which, after hydrolysis by gut micro flora, were hypothesized to ultimately get eliminated via feces or, after enterohepatic circulation and further transformation, via urine. Of the administered low and high dose, about 4 - 7% and 31 - 47%, respectively, were excreted in the feces as unchanged CGA-279202, reflecting the variant degree of absorption as a function of dose. In conclusion, the major metabolic pathways of CGA-279202 and the excretion patterns were influenced more by the sex of the animals than by the dose level or the repeated administration of the chemical.

The assigned chemical structures and related chemistry data were not verified by this US-EPA reviewer due to time constraints and other competing priorities in addition to the lack of extensive background training in the interpretation of NMR and Mass Spectrometry data by the reviewer; henceforth, these assignments are considered the responsibility of the Registrant.

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/

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HED Comments

The attached CALEPA review dated June 5, 1998 was limited to an executive summary of MRID 44496822 which the CALEPA considered a "Supplemental Information." Due to the fact that this study utilized the same samples from the previous study (MRID 44496821) there has been no need to repeat the description of the protocol and the study design which were adequately summarized in the CALEPA review (refer to attachment with DER dated February 16, 1999). The USEPA reviewer recommends referring to that CALEPA review and the DER of 2/16/99 for additional information which, when combined with this document, should be used in place of a DER prepared by HED staff or Contractors. While the CALEPA reviewer considered this study (MRID 44496822) "supplemental information," the HED reviewer regards the study **acceptable** (guideline). The following material which was copied from the subject MRID 44496822 is also attached as additional and useful information to be included as part of this evaluation record:

- Summary Table of dosing groups, treatment, and sampling time of pooled specimens used for metabolite analysis and characterization (reproduced from page 22 of 353 of MRID 44496822).

- Table 5 entitled, "Quantitative distribution of urinary metabolite fractions of male and female rats after oral administration of CGA 279202 in % of dose (Groups B1, C1, D1, B2, and D2)" (reproduced from page 67 of 353 of MRID 44496822).

- Table 6 entitled, "Quantitative distribution of urinary metabolite fractions of bile-cannulated male and female rats after oral administration of CGA 279202 in % of dose (Groups G1, G2, G3, and G4a)" (reproduced from page 68 of 353 of MRID 44496822).

- Table 7 entitled, "Quantitative distribution of fecal metabolite fractions of male and female rats after oral administration of CGA 279202 in % of dose (Groups B1, C1, D1, B2, and D2)" (reproduced from page 69 of 353 of MRID 44496822).

- Table 8 entitled, "Quantitative distribution of fecal metabolite fractions of bile-cannulated male and female rats after oral administration of CGA 279202 in % of dose (Groups G1, G2, G3, and G4a)" (reproduced from page 70 of 353 of MRID 44496822).

- Table 9 entitled , "Quantitative distribution of biliary metabolite fractions of male and female rats after oral administration of CGA 279202 in % of dose (Groups G1, G2, G3, and G4a)" (reproduced from page 71 of 353 of MRID 44496822).

- Figure 34 entitled, "Proposed metabolic pathways of CGA 279202 in the rat" (reproduced from pages 109-111 of 353 of MRID 44496822).

Attachment: **CALEPA Toxicology Study Evaluation Report dated 6/5/98 (Record # 160219).**

SignOff Date:	8/3/99
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