(10-3-94)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

#375A

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metalaxyl - Review of Additional Data to Upgrade the Core-Classification of a Rat Metabolism Study

DP Barcode No. D206107 — Submission No. S471106
EPA I.D. No. 113501 — P.C. Code No. 113501
Rereg. Case No. 0081 — Case No. 819456
CAS Registry No. 57837-19-1 — Tox. Chem. No. 375 AA

FROM: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I
Health Effects Division (7509C)
Krystyna K. Locke 9/30/94

TO: Linda Probst/Judith Loranger, PM Team No. 73
Generic Chemical Support Branch
Secial Review and Reregistration Division (7508W)

THRU: Roger Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (7509C)
Pamela M. Hurley 9/30/94
KB, 10/3/94

Section I, Toxicology Branch I/HED has completed an evaluation of the following data:

85-1 Supplemental Report on the Metabolism of Phenyl-[14C]-Metalaxyl in Rats - Identification of Major Urinary Metabolites - Amendment I; William Itterly; Ciba-Geigy Corporation, Greensboro, NC; Study No. ABR-90079; Study Completion Date: October 19, 1990. **MRID 43317301**

These data were submitted in response to the review (in 1993) of the metabolism study entitled " Characterization and Identification of Phenyl-[^{14}C]-Metalaxyl Metabolites in Rats " (No. ABR-90079; date: October 19, 1990; MRID 41664501). This study was classified as Core-Supplementary (but upgradable) for reasons stated on page 2 of the current review (attached). Since the registrant has submitted the requested information (current submission, MRID 43317301), **the classification of this study is being changed from Core-Supplementary to Core-Guideline.** This study, therefore, satisfies the requirement for § 85-1, Metabolism Studies.

Krystyna K. Locke 9/30/94

Primary Review by: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I/HED

Secondary Review by: Roger L. Gardner, Section Head
Section I, Toxicology Branch I/HED

DATA EVALUATION RECORD

STUDY TYPE: 85-1 Metabolism in Rats

EPA IDENTIFICATION NUMBERS:

MRID No. 43317301
DP Barcode No. D206107
P.C. Code No. 113501
Tox. Chem. No. 375 AA

Reregistration Case No. 0081
Submission No. S471106
Case No. 819456

TEST MATERIAL: Metalaxyl - unlabeled (tan powder, purity: 96.5%) and uniformly phenyl-labeled with ^{14}C (purity: 97.3%). Chemical name: N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester. Trade name: Ridomil

SPONSOR and **TESTING FACILITY:** Biochemistry Department, Ciba Crop Protection, Ciba-Geigy Corporation, Greensboro, NC

STUDY NUMBER: ABR-90079

TITLE OF REPORT: Supplemental Report on the Metabolism of Phenyl-[14C]-Metalaxyl in Rats - Identification of Major Urinary Metabolites - Amendment I

AUTHOR: William Itterly

STUDY COMPLETED ON: October 19, 1990

BACKGROUND

The current submission contains additional information for the already evaluated metabolism study (Report No. ABR-90072; Completion Date: October 19, 1990; MRID 41664501) in which Metalaxyl was tested as follows: Group I (1.0 mg/kg, single intravenous dose); Group II (1.0 mg/kg, single oral dose); Group III (1.0 mg/kg, repeated oral dose); and Group IV (200 mg/kg, single oral dose). Urinary and fecal metabolites in each test group were characterized and quantitated by two-dimensional TLC, using synthetic reference compounds. However, pooled urine from the Group IV females was chosen for the isolation and analytical identification (MS, NMR and IR spectroscopy) of metabolites, since it contained the largest amount of Metalaxyl and metabolites and gave the same metabolic profile as did the urine pools from other dose groups.

The already evaluated study, entitled " Characterization and Identification of Phenyl-[^{14}C]-Metalaxyl Metabolites in Rats ", had been evaluated by Toxicology Branch I/HED on April 14, 1993, but was classified as Core-Supplementary for the following reasons: (1) Two urinary metabolites, UM-23 and UM-26, accounting maximally for 23.3% and 8.3%, respectively, of the applied dose, were not identified; and (2) There was no discussion of the causes of a significant percentage (29.8) of the radioactivity remaining in the soluble fraction of the male rat urine extract in Group III. However, it was also stated in that review that the classification of " Supplementary " could be upgraded upon the receipt and acceptance of the appropriate additional information.

CURRENT SUBMISSION

Urinary Metabolites Associated with UM-23

The following metabolites were isolated from the TLC radioactive zone UM-23 and identified analytically: (1) Metabolites M_{11} and M_{12} [glucuronide conjugates and stereoisomers of previously identified Metabolite M_3 (CGA-94689, isomer A)]; (2) Metabolites M_{13} and M_{14} [glucuronide conjugates and stereoisomers of previously identified Metabolite M_4 (CGA-94689, isomer B)]; (3) Metabolite M_{15} [glucuronide conjugate of previously identified metabolite M_1 (CGA-67869)]; (4) Metabolite M_6 (CGA-62826, previously identified); and (5) Metabolite M_8 (CGA-107955, previoulsy identified). The chemical names and structures of these metabolites are in Attachment I of this review.

Urinary Metabolites Associated with UM-26

The TLC radioactive zone UM-26, which was referred to in the original report (MRID 41664501) as a "metabolite", turned out to be not a metabolite, but the material associated with the origin of the chromatographic plate. It was a mixture of polar components containing endogenous natural products, salts and metabolites aggregated together.

Aqueous Soluble Residue Following Enzyme Hydrolysis

The following reasons were given for the 29.8% of sample radioactivity remaining in the aqueous phase of the Group III male rat urine after enzyme hydrolysis (β-glucuronidase and aryl sulfatase) and solvent (ethyl acetate) partition: (1) Enzyme reactions were probably inadvertently conducted at conditions less than optimal for the enzyme, resulting in the reduced amount of the (ethyl acetate-extractable) free metabolites formed; and/or (2) pH-Dependent solvent partition of the hydrolyzate was probably inadvertently performed at a pH not ideal to extract the free metabolites. According to the current submission, the bulk of

the metabolism data supported the presence of the glucuronide and sulfate conjugates for all dose groups and both sexes. It is, therefore, unlikely that only the (low-dose) Group III male rats would exhibit unique metabolism products which differred from the biotransformation products identified in the male and female rats from Groups I, II and IV. In other words, in the case of the Group III males, the inadvertent faulty methodology was most likely responsible for the high radioactivity in the aqueous phase of the urinary extracts. Toxicology Branch I/HED agrees with this explanation.

Core-Classification of Study

Since the registrant has submitted additional and satisfactory information (current submission, MRID 43317301), in respose to the original review of this study (No. ABR-90079, MRID 416645-01; HED Document No. 010164), **the classification of this study is being changed from Core-Supplementary to Core- Guideline.** This study, therefore, satisfies the requirement for § 85-1, Metabolism Studies.

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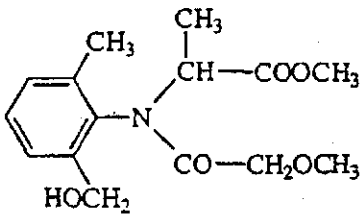
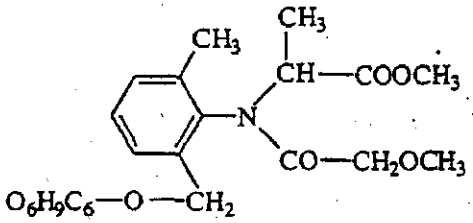
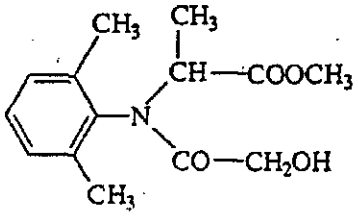
Attachment I



CGA-94689 Isomer B
mw = 295

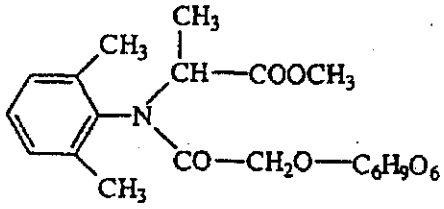


CGA-94689 B Glucuronide
mw = 471

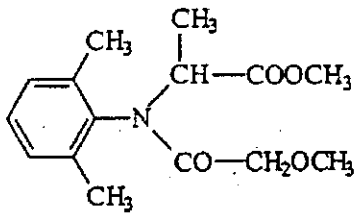


CGA-67869
mw = 265

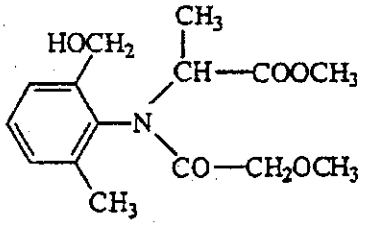
N-(2,6-dimethylphenyl)-N-(hydroxyacetyl) alanine methyl ester



CGA-67869 Glucuronide
mw = 441

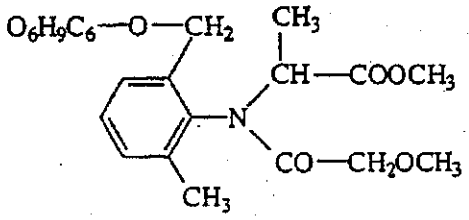


Metalaxyl
mw = 279

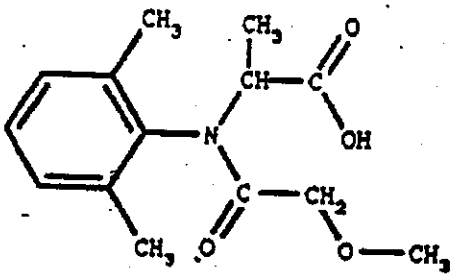


CGA-94689 Isomer A
mw = 295

N-[(2-hydroxymethyl)-6-methylphenyl]-N-(methoxy acetyl) alanine methyl ester

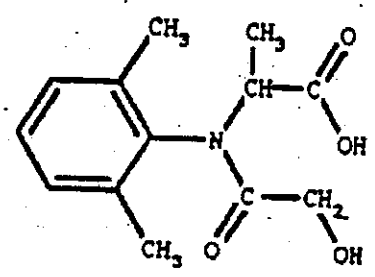


CGA-94689 A Glucuronide
mw = 471



CGA-62826

N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine



CGA-107955

N-(2,6-dimethylphenyl)-N-(hydroxyacetyl) alanine

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