652C

008146

CASWELL FILE

NOV 5 1990

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP # 8F3572; Fenoxycarb - Submission of a Report Identifying the Metabolites Present in the Urine of Rats in a Previously Submitted Metabolism Study (BASF # 041/6668; MRID # 403769-04)

Tox. Chem. No.: 652C
Project No.: 0-1470
Record No.: 266233

FROM: William B. Greear, M.P.H. William B. Greear 10/11/90
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Phil Hutton/Joseph Tavano, PM Team # 17
Herbicide-Fungicide Branch
Registration Division

THRU: Marion P. Copley, D.V.M. Section Head Marion P. Copley 10/12/90
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

Conclusions: This study* is acceptable as adjunct information supporting the metabolism study in rats titled "The Metabolism of ^{14}C- labelled RO 13-5223/024 in the Rat" Maag Document # 041/6668, Project RES-MET J55. A data gap still exists for the low-and repeated-dose metabolism studies.

Requested Action:

Gerald D. Rosebery has submitted a metabolism study in rats to supplement a previous metabolism study (Maag # 041/6668) in rats.

* see DER attached

1

Reviewed by: William B. Greear, M.P.H.
Section II, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M.
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 85-1
Metabolism - Rat

TOX. CHEM NO: 652C
MRID NO.: 412414-01

TEST MATERIAL: Ro 13-5223/024

SYNONYMS: Fenoxycarb; Ethyl 2- (4-Phenoxyphenoxy) ethyl carbamate

STUDY NUMBER: RES-MKT J55; Maag Doc # 041/8088

SPONSOR: Maag Agrochemicals, Inc.

TESTING FACILITY: Metabolism Section, Dr. R. Maag AG
CH-8157 Dielsdorf, Switzerland

TITLE OF REPORT: Ro 13-5223/024: Further Identification of Polar Metabolites Observed in Rat Study Carried Out by IRI (Project No. 131863)

AUTHOR(S): A. Pryde, N. Pluss Angehrn

REPORT ISSUED: August 31, 1989

CONCLUSION: The amount of radioactivity present in the urine of males and female rats 6-72 hrs. post-dosing was 41.2% at 32.9% for males and females, respectively. The metabolites identified represented 27% and 22.5% in males and females, respectively. The major metabolites were Ro 43-4754 Ro 17-3192, Ro 16-8797, and Ro 43-4764 (males only).

Classification: Acceptable. This study together with IRI Report # 4217 (Proj # 131863), Maag #041/6668; - see HED Proj. No. 9-0911, 9-1190 and 9-1316A, satisfies a portion of the requirements for a Guideline Series 85-1 metabolism study.

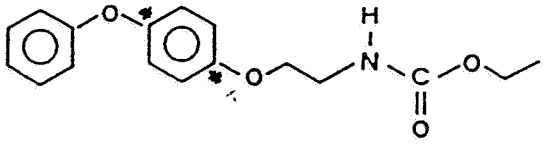
NOTE: There is still a data gap for the low-and repeated-dose metabolism studies.

Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: ^{14}C-Ro 13-5223/024, Description: position of label see below, Batch # JJ-5/98, Purity 98%, Specific Activity of 36.06 Ci/mg, contaminants: not reported.

*14_C label



2. Test animals: Species: rat, Strain: not specified, Weight: not specified, Source: not specified.

B. STUDY DESIGN:

Purpose - to isolate and identify the polar metabolites present in the urine of rats which had received a single dose of 3000 mg/kg in an earlier study (see "The Metabolism of ^{14}C- labelled Ro 13-5223/024 in the Rat"; IRI Report # 4217 (Project # 131863) Maag Document # 041/6668, MRID # 403769-04).

1. Urine Sample Collection: - All rats received 3000 mg/kg of the test substance. Urine was collected from rats at intervals specified in Table 1.

Table 1: Urine Sample Collection

Collection Interval (hrs)	Animal Numbers	
	Males	Females
0-6	41, 42, 44, 45	46-50
6-24	41, 42, 44, 45	46-50
24-48	41, 42, 44, 45	46-50
48-72	41, 42, 44, 45	46-50
72-96	41, 42, 44, 45	46-50

Urine samples containing the majority of the radioactivity were combined to give 2 samples: 300 ml from males and 400 ml from females for the interval 6-72 hours. [In study IRI Report #4217 (Proj. #131863), the radioactivity excreted in the urine during the 6-72 hours interval was 41.2% and 32.9% of the dose for males and females, respectively.]

2. Isolation/Identification Methodology

The radioactivity content of each sample was determined by liquid scintillation counting (LSC) and radio-high performance liquid chromatography (radio-HPLC). The methods used in the separation and identification of the polar metabolites can be found in the flow charts for males (see Figure 1) and females (see Figure 8). It was determined that a large portion of radioactivity (males 37.9%, females 29.4%) present in the urine appeared to be present as conjugates. Therefore, the samples were evaporated to dryness and then 160/200 ml of 0.1 M Sodium acetate buffer pH 5.0 and 300/400 mg of sulfatase were added. The solution was incubated at 37°C for 18 hours. After incubation, the solution was adjusted to a pH of 9.0 with 1 N sodium hydroxide and extracted twice with ethyl acetate. The radioactive content in the aqueous and organic phase was determined by LSC. The organic phase underwent radio-thin layer chromatograph (radio-TLC) and radio-HPLC. The ethyl acetate extracts at pH 3 and 9 were obtained from males (containing 12.9% of the dose, respectively), evaporated to dryness and redissolved in the HPLC mobile phase. Three fractions were collected and each fraction was evaporated to remove acetonitrile. The residual aqueous phases were extracted with ethyl acetate and filtered through sodium sulphate. Quantitative recovery of the radioactivity present in the ethyl acetate phase was confirmed by LSC. Then the ethyl acetate phase was evaporated to dryness and the residues underwent radio-gas chromatography (GC)/GC-mass spectrometry (MS) analysis.

C. RESULTS:

The radioactivity recovered from urine of the high dose during 6-72 hrs. post-dosing was determined to be 41.2% and 32.9%* in males and females, respectively. Radio-TLC and radio-HPLC of urine showed that the most radioactivity was present as polar compounds which were on the origin of the TLC plate or eluting at the beginning of the HPLC chromatogram. A large portion of the radioactivity (females 29.4%, males 37.9%) was believed to be conjugates. The results of the radio-TLC and radio-HPLC of the organic extracts are provided in Tables 2 and 3 attached. The major metabolite present in the urine was Ro 16-8797 (males of 16.1%, females 14.7%) which was mostly conjugated with sulphate (males 13.2%, females 13.7%). Eighteen metabolites were identified in the urine of male rats by radio-GC/GC-MS analysis. They were: Ro 43-4756 (4.0%), Ro 43-4764 (2.5%), Ro 17-3192 (4.4) and 14 other in trace amounts - Ro 1-1086, Ro 1-1374, Ro 43-4757, Ro 43-4758, Ro 43-9571, Ro 43-4759, Ro 43-4760, Ro 17-3193, Ro 43-4761, Ro 43-4763, Ro 43-4765, Ro 43-4766, Ro 43-4767 and Ro 43-4768. In females, Ro 43-4756, Ro 17-3192 and Ro 16-8797 were found at levels of 2.4, 5.4 and 14.4% in the urine, respectively. The

* - of the dose administered

structures of the major metabolites can be found in Table 4 (attached). One metabolite in males, Ro 43-4764, at a level of 2.5% was not found in the urine of females. No parent compound was detected. The metabolites identified represented 27% and 22.5% of the dose administered in males and females, respectively.

Quality assurance was provided and a statement dated August 31, 1989 was submitted with the study.

D. DISCUSSION:

This study acts as a supplement to a metabolism study (Maag document #041/6668). The amount of radioactivity present in the urine of rats receiving a single 3000 mg/kg oral dose of the test material during 6-72 hours post-dosing was determined to be 41.2% and 32.9% in males and females, respectively. The metabolites identified represented 27% and 22.5% of the dose administered. The major metabolites in rats were Ro 16-8797 (males 16.1%; females 14.7%) which was present primarily in conjugated form (males 13.2%; females 13.7%). Eighteen metabolites were identified in male urine (refer to RESULTS section). No parent compound was identified in urine. One metabolite present in males, Ro 43-4764, was not identified in female urine.

DEFICIENCIES: Individual animal data should have been recorded (not pooled data). It is unknown whether the presence of Ro 43-4764 was characteristic of all males, or simply due to the differential metabolism of only 1 male.

TC652C/Mary/Disk #3

Fenoxycarb toxicology review

Page _____ is not included in this copy.

Pages 6 through 11 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
