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Chemical:	**Pyrethrins**
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Memo Date:	**04/18/88**
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12/26/2001

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

APR 18 1988

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PC 069001

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA File Symbol 52563-R: Pyrethrins. Toxicology Branch response to the inquiry from John W. Kennedy consultant to the U.S. Pyrethrum Culture concerning registration of dried pyrethrum flowers grown in the USA and shipped to refineries for processing to pesticide products.

TOX CHEM No.: 715
TOX PROJECT No.: 8-0400
Record No.: 187933

FROM: John Doherty 4/14/88
Toxicology Branch
Hazard Evaluation DIvision (TS-769)

TO: Phil Hutton
Product Manager #17
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/14/88 4/18/88

Mr. John W. Kennedy, consultant for the U.S. Pyrethrum Culture, has submitted a collection of published articles from the general literature regarding various aspects of pyrethrum toxicity, metabolism and chemistry. Mr. Kennedy is requesting that the information be used in support of the registration of their product dried chrysanthemum flowers containing pyrethrin grown in the USA. These flowers will be packaged and shipped to manufacturers where they will be processed into refined pyrethrin and formulated into pesticide products. Mr. Kennedy asserts that most of the data developed on pyrethrins is "public" and can be used to support the registration of pyrethrins grown in America as well as elsewhere.

Toxicology Branch Response

1. TB has surveyed the information provided by the U.S. Pyrethrum Culture and notes that most of the information has already been made available to the Agency. Most of these studies would have to be classified as either SUPPLEMENTARY or INVALID according to the current guidelines for toxicity testing because of incomplete data submissions or the study designs are not consistent with current standards.

2. The formal toxicity data base for pyrethrins is in the process of being updated and newer studies using current guidelines for toxicity testing are being provided by the Pyrethrin Joint Venture/Chemical Specialties Manufacturers Association (PJV/CSMA) in response to a DATA-CALL-IN notice previously issued by Registration DIvision of OPP. These studies are being conducted with a blend of pyrethrin plus stabilizers and solvent that was previously agreed upon between Toxicology Branch (TB) and PJV/CSMA group (refer to memo from J. Doherty July 15, 1986 for EPA Id. No.: 069001).

TB expects that these studies if found to be acceptable to the Agency will be used to support the registrations and tolerances for pyrethrins. The U.S. Pyrethrum Culture group may not be able to use these studies to support the registration of their product without prior compensation to the PJV/CSMA group. Such proprietary concerns are not the responsibility of TB.

3. TB noted that a paper on the metabolism of radiolabelled pyrethrins I and II and allethrin (refer to DER attached) was included. This paper described the synthesis of ^{3}H and ^{14}C labelled pyrethrin I and II and proposed pathways for their metabolism based on identification of urinary and fecal metabolites. This study has been assigned SUPPLEMENTARY classification but provides information that is considered useful to the overall problem of the metabolism of pyrethrins.

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Reviewed by: J.D. Doherty 4/14/88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: E.R. Budd
Section II, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: General Metabolism: Rats and MIce TOX CHEM No.: 715

ACCESSION NO.: Not Provided MRID NO.: Not provided

TEST MATERIAL: Radiolabelled (^3H and ^{14}C) pyrethrins (I and II) and allethrin.

SYNONYMS: N/A

STUDY NUMBER(S): None provided (journal publication)

SPONSOR: None

TESTING FACILITY: University of California, Division of Entomology Berkeley, California

TITLE OF REPORT: "Metabolic Fate of Pyrethrin I and Pyrethrin II and Allethrin Administered Orally to Rats.

AUTHOR(S): M. Elliott, N.J. Janes, E.C. Kimmel and J.E. Casida

REPORT ISSUED: In Journal of Agriculture and Food Chemistry 20(2) 300-313 (1972).

CONCLUSIONS:

The publication reports on the synthesis of radiolabelled pyrethrins I and II and allethrin and how these were metabolized by rats and mice. The methods used for the analysis and identification of the metabolites were extensively described and several metabolites identified. See review.

Classification: CORE-SUPPLEMENTARY. The data are presented in a publication form and no original data are included.

Special Review Criteria (40 CFR 154.7): N/A.

Quality Assurance Statement: None provided. Study is circa 1970 and is a published literature citation.

REVIEW

In this experiment both radiolabelled (with ^{3}H and ^{14}C) and unlabelled pyrethrin I and pyrethrin II were utilized. The unlabelled pyrethrins I and II were made by "reconstitution from the acid and alcohol moieties isolated from the natural esters" The radiolabelled Compounds were prepared by methods developed over a span of several years by Dr. J.E. Casida and his colleagues. ^{3}H was generally used to label the pyrethrins in the alcohol moiety and ^{14}C was used to label the cyclopropane carboxy groups.

The rats (male, Sprague-Dawley young adult) were dosed for either tracer studies with low dose (1-5 mg/kg) to determine the isotope content of the urine and other factors of metabolic and pharmacokinetics. In another set of experiments designed to collect large quantities of metabolites, the pyrethrins were given orally for a total of 1.10 g of pyrethrin I and 2.4 g of pyrethrin II. In still another set of experiments, male mice were dosed with 1-5 mg/kg of the $1^{4}C$ pyrethrins and the ^{14}C content of the urine and expired air were monitored. The test materials were dissolved in DMSO and administered via stomach tube.

The paper described the various methods and procedures used to isolate the urinary and fecal metabolites, enzymatic cleavage of conjugates, the radioactivity balance studies and chromatography systems and spectroscopy used in analysis of the metabolic pathways.

The proposed metabolic scheme or pathway for pyrethrins I and II is shown in Figures 2 (xeroxed from the study report). The initial step in this metabolic scheme appears to be oxidation of the vinyl side chain to a carboxylic group. This is followed by oxidation of side chain of the alcoholic side chain to form first an epoxide and subsequently diol which are in turn conjugated. The metabolic pathway for allethrin in rats was also studied and is shown in Figure 3 (xeroxed from the study report). The initial step in the metabolism of allethrin is apparently the same for pyrethrins I and II. It is noted that esteratic cleavage of these chemicals is apparently not a major route of metabolism. Table I (xeroxed from the study report) shows the distribution of the radioactivity among the metabolites in the urine and feces.

One problem that must be resolved regarding this study concerns the actual chemical synthetized (both radiolabelled and unlabelled). For example, are these chemicals the same stereo-specific isomers as the natural pyrethrins. If they are, the method(s) of proving the identity must be provided.

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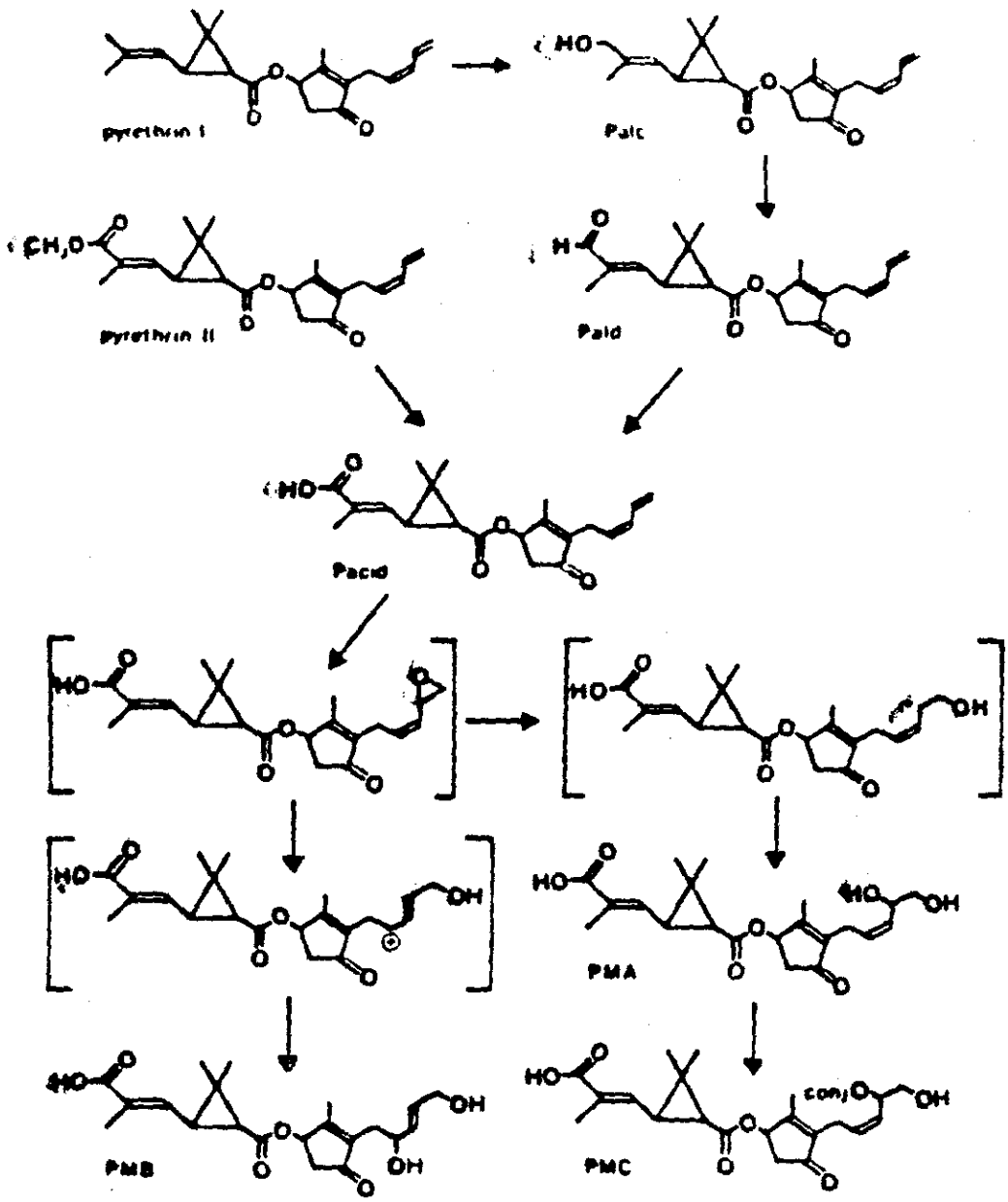


Figure 2. Tentative metabolic pathway for pyrethrins I and II in rats

the products were dissolved in deuterochloroform and filtered through a cottonwool plug into a nmr tube. After determining the nmr spectrum, the sample was subdivided for further analysis, particularly by ms, as described below.

Enzymatic Cleavage of Conjugates. The possibility that some of the metabolites of pyrethrin I occur in the urine as conjugates was tested by attempting to cleave them enzymatically with glusulase. An aliquot of the urine from rats given pyrethrin I [PyI-^{14}C(O)O-acid] was evaporated to dry-

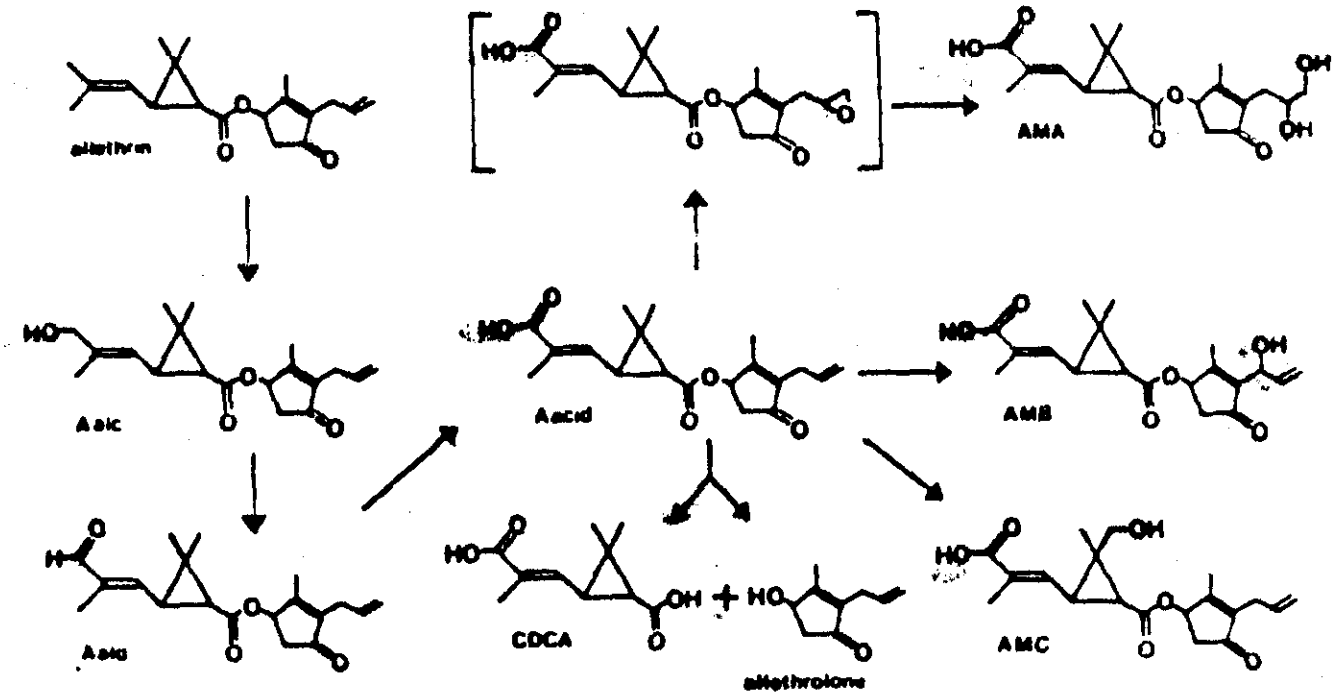
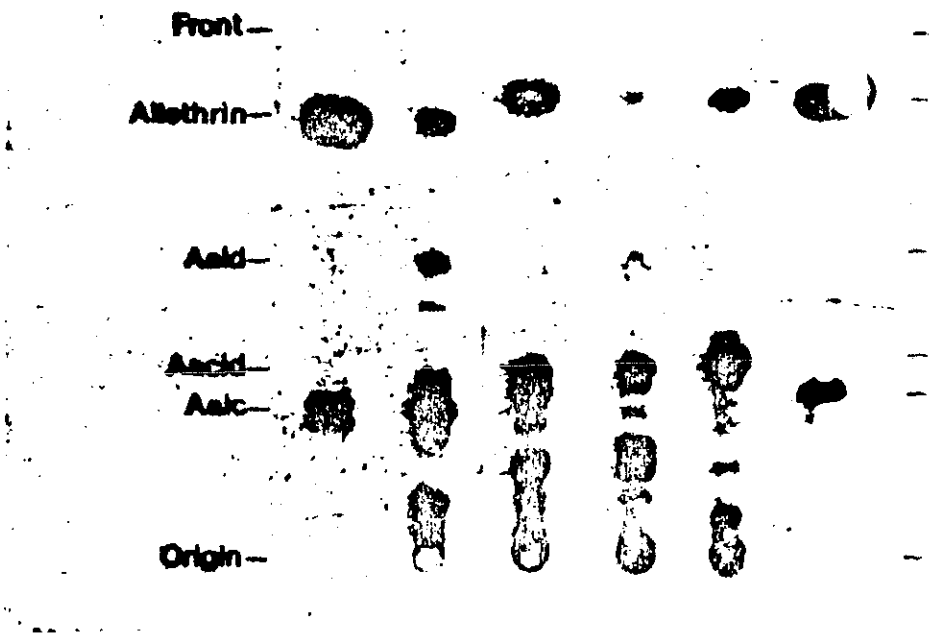


Figure 3. Tentative metabolic pathway for allethrin in rats

sional tlc, the chromatoplates were developed with benzene, air-dried, and then developed with the BFE1 solvent system. For two-dimensional tlc, the chromatoplates were developed with benzene and then with the EMBF solvent system in the first direction, followed by the EBMF solvent system in the second direction. All products obtained from various enzyme preparations were compared by one-dimensional tlc. In addition, two-dimensional cochromatography was used to compare the metabolites of pyrethrins I and II from the rat liver microsome–NADPH enzyme system with those in the urine of rats treated orally with pyrethrins I or II.

Radioactivity Balance Studies. The metabolism cages, the methods for collecting the urine, feces, and expired CO_2, and for combusting feces, to determine their respective ^{14}C and