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

MAY - 5 1993

010235

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tetramethrin; Rat General Metabolism Studies with C^{14}-Cis-Tetramethrin and C^{14}-Trans-Tetramethrin; ID #: 069003-010308; Guideline Requirement 85-1

Tox.Chem No.: 844
MRID No.: 42448901,-02
DP Barcode No.: D182564
Submission No.: S425247

TO: Napoleon Kotey, PM #52
Reregistration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D., Toxicologist
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William Dykstra 4/13/93

THRU: Roger Gardner, Section Head, Toxicologist
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Toxicology Branch I
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Roger Gardner 5-3-93

ACTION REQUESTED: In response to a DCI, the Registrant, Sumitomo Chemical Company, LTD, has submitted two rat general metabolism studies for cis-tetramethrin and trans-tetramethrin. Toxicology Branch-I (TB-I) has been requested to review these studies as part of the reregistration process for tetramethrin.

CONCLUSIONS: The rat general metabolism studies are acceptable and fulfill the Guideline Requirement 85-1 for a general metabolism study in rats.

10/35

Trans-Tetramethrin

The absorption, distribution, metabolism, and excretion of trans-tetramethrin were studied in Sprague-Dawley rats administered a single oral gavage dose of C^{14}-t-tetramethrin at 2 or 250 mg/kg, or a 14-day repeated oral dosing of 2 mg/kg unlabeled tetramethrin followed by a single dose of 2 mg/kg C^{14}-t-tetramethrin on day 15.

C^{14}-t-tetramethrin was rapidly and almost completely eliminated (95-101%) from the rats' body within 7 days of dosing. The excretion of radioactivity in the urine and feces was 42-71% and 29-58%, respectively. The highest radiolabeled residue levels were observed in the blood cells. Total residues in all tissues at day 7 postexposure accounted for <0.4% of the administered dose.

Thirty-four metabolites were detected in the feces. The major metabolite was identified as TPI-SA (1-sulfo-1,2-cyclohexanedicarboximide). Twenty-two urinary metabolites were detected as mostly alcohol and dicarboxylic acid derivatives. The major metabolites were identified as 3-OH-HPI-1 (3-hydroxy-1,2-cyclohexanedicarboximide).

The biotransformation reactions of t-tetramethrin were as follows:

(1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring, (4) oxidation at the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the tetrahydrophthalimide moiety, and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the tetrahydrophthalimide moiety.

Cis-Tetramethrin

The absorption, distribution, metabolism, and excretion of cis-tetramethrin were studied in groups of Sprague-Dawley rats administered a single oral gavage dose of 2 or 250 mg/kg [C^{14}]-c-tetramethrin, or a 14-day repeated oral dosing of 2 mg/kg unlabeled tetramethrin followed by a single oral of 2 mg/kg [C^{14}]-c-tetramethrin on day 15.

C^{14}-c-tetramethrin was rapidly and almost completely eliminated by the rats within 7 days of administration. C^{14}-labeled urine excretion was higher in the females than in the males, whereas C^{14}-labeled fecal excretion was higher in the males. Total residues in all tissues accounted for 0.5% of the administered dose.

Thirty-three metabolites were detected in the feces. The main metabolites were Unknown 34, TPI-SA, and Unknown 39. Twenty-three urinary metabolies were detected. The major metabolite was identified as 3-OH-HPI-1.

No dose-related differences in metabolic fate were observed among all groups. Fecal excretion of the parent compound was greater in the low- and high-dose groups (single oral dose groups) than in the repeated dose and control groups. No parent compound was detected in the urine. The biotransformation reactions of c-tetramethrin were proposed.

FINAL

010235

DATA EVALUATION REPORT

(1-RS, cis)-Tetramethrin

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

April 1, 1993

Principal Reviewer:	Jay Meeks, B.S.	4/1/93 Date
Independent Reviewer:	William McLellan, Ph.D.	4/1/93 Date
QA/QC Manager:	William L. McLellan for Sharon Segal, Ph.D.	4/1/93 Date

Contract Number: 68D10075
Work Assignment Number: 2-32
Clement Number: 90
Project Officer: Caroline Gordon

010235

GUIDELINE SERIES 85-1: Metabolism

EPA Reviewer: Paul Chin Ph.D. Signature: Paul Chin
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EPA Section Head: Marion Copley, D.V.M. Signature: Marion Copley
Review Section IV, Toxicology Branch I, Date: 4/7/93
Health Effects Division

R. 82.
5-3-93

DATA EVALUATION REPORT

STUDY TYPE: Metabolism

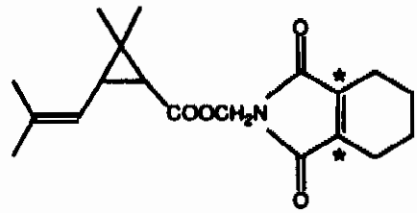
EPA IDENTIFICATION NUMBERS:

PC Code: 069003
Tox. Chem. Number: 844
MRID Number: 424489-02

TEST MATERIAL: (1 RS, cis)-tetramethrin [3,4,5,6-tetrahydrophthalimidomethyl (1RS, trans)-chrysanthemate]

SYNONYMS: cis-tetramethrin; (c-NPY); cis neopynamin

CHEMICAL STRUCTURE:



* denotes the position of the [^{14}C] label

SPONSOR: Agricultural Chemicals, Sumitomo Chemical Co., Ltd., Osaka, Japan

TESTING FACILITY: Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan

AUTHOR: Kunio Shiba

TITLE OF REPORT: Metabolism of (1RS, cis)-Tetramethrin in Rats. Study No. 2556.

DATE OF REPORT: August 6, 1992

CONCLUSIONS: The absorption, distribution, metabolism, and excretion of cis-tetramethrin were studied in groups of Sprague-Dawley rats administered a single oral gavage dose of 2 or 250 mg/kg [^{14}C]-c-tetramethrin, or a 14-day repeated oral dosing of 2 mg/kg unlabeled tetramethrin followed by a single dose of 2 mg/kg [^{14}C]-c-tetramethrin on day 15.

^{14}C-c-tetramethrin was rapidly and almost completely eliminated by the rats within 7 days of administration. ^{14}C-labeled urine excretion was higher in the females than in the males, whereas ^{14}C-labeled fecal excretion was higher in the males. The highest radiolabeled residue levels were observed in the blood cells. Total residue in all tissues accounted for 0.5% of the administered dose.

Thirty-three metabolites were detected in the feces. The main metabolites were Unknown 34, TPI-SA, and Unknown 39. Twenty-three urinary metabolites were detected. The major metabolite was identified as 3-OH-HPI-1.

No dose-related differences in metabolic fate were observed among all groups. Fecal excretion of the parent compound was greater in the low- and high-dose groups (single oral dose groups) than in the repeated dose and control groups. No parent compound was detected in the urine.

The biotransformation reactions of c-tetramethrin were as follows:

(1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring of the tetrahydrophthalimide moiety, (4) oxidation at the methyl group of the isobutenyl moiety, and (5) reduction at the 1,2-double bond and incorporation of the sulfonic acid group to the 1,2-double bond of the tetrahydrophthalimide moiety. The major metabolites were identified as sulfonate derivatives in feces and alcohol and dicarboxylic acid derivatives in the urine.

STUDY CLASSIFICATION: Acceptable. The study satisfies the requirements set forth under Guideline 85-1 (and Addendum 7) for a metabolism study in rats, and therefore, is judged to be acceptable.

A. MATERIALS

1. Test Substance

The unlabeled test material, c-tetramethrin [3,4,5,6-tetrahydrophthalimidomethyl (1RS, cis)-chrysanthemate (lot number T-9102), was a white-colored powder provided by Sumitomo Chemical Co., Ltd. The purity was determined to be 98.8%.

The radiolabeled test material, c-[Tetrahydrophthaloyl-1,2-^{14}C] tetramethrin (lot number C-91-015A), was a white powder labeled with [^{14}C] at the 1,2-double bond of the tetrahydrophthalidimide ring. It was synthesized by the Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd. The labeled preparation had a specific activity of 49.5 mCi/mmol (1.83 GBq). A radiochemical purity and chemical purity of >99% was determined.

Synthetic (unlabeled) standards, 1-hydroxy-1,2-cyclohexanedicarboximide (1-OH-HPI), 1,2-cyclohexanedicarboximide (HPI), N-(hydroxymethyl)-3,4,5,6-tetrahydrophthalimide (MTI), 2-carboxy-

3,4,5,6-tetrahydrobenzamide (THAM), 3,4,5,6-tetrahydrophthalic anhydride (TPA), were synthesized by Sumitomo Chemical Co., Ltd.

2. Test Animals

Four-to-six-week-old male and female Charles River derived-CD (Sprague-Dawley) rats were obtained from Charles River Japan, Inc. The animals were 5 weeks old at the time of first dosing for the repeated dose groups and 7 weeks old for the single dose groups. At the time of sacrifice, the groups for the single dosing and repeated dosing groups were the same age (8 weeks). The weights at sacrifice ranged from 285-332 g in males and 211-226 g in females.

B. METHODS

1. Dosing Solutions and Rationale for the Dose Selection

The nonlabeled and radiolabeled oral dosing solutions were prepared in corn oil. Dilutions of the radiolabeled material were made with nonlabeled c-tetramethrin to adjust the specific radioactivity to 4.625 MBq (125 µCi)/mg for the low; repeated, and control dose studies or 37.0 kBq (1.0 µCi)/mg for the high-dose study. The labeled material was dissolved in corn oil at 0.4 mg/ml for the low; repeated, and control groups, or suspended in corn oil at 50 mg/ml for the high-dose group.

The low dose (2 mg/kg) was selected based on an acute oral LD_{50} greater than 5000 mg/kg and a 6-month subacute toxicity study in which the no-observable effect level (NOEL) was 1500 ppm. The high dose (250 mg/kg) was selected based on a 6-month subacute toxicity study in rats in which the minimum toxicity level was 5000 ppm. Decreases in body weight gain, increases in absolute liver weights, and increases in liver-to-body weight ratios were observed in both sexes.

2. Acclimatization and Dosing

Animals were acclimated for approximately one week before the administration of the test material. Animals were housed five or less/cage in polypropylene cages with sawdust during quarantine and acclimation. Rats dosed with the ^{14}C-labeled material were housed individually in glass metabolism cages until sacrifice. The diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water were given ad libitum throughout the study. No contaminants in the food and water were reported to interfere with the study. Room temperature (23±2°C), relative humidity (55±10%), air exchanges (>10 air per hour), and a 12-hour photoperiod was established.

The dosing regimens are listed below:

Group	Sex	mg/kg Dose Level:	Number
Single low	M	2	5
	F	2	5
Single high	M	250	5
	F	250	5
Repeated low[a]	M	2	8[b]
	F	2	8[b]
Control[c]	M	2	5[d]
	F	2	5[d]

Footnotes:

[a]Rats were given an oral dose of 2 mg/kg/day of unlabeled c-tetramethrin in corn oil at a volume of 5 ml/kg/day for 14 days followed by a single administration of 2 mg/kg/day of ^{14}C-c-tetramethrin on day 15.
[b]Three animals were designated as "spares" to be used in case a misdose occurred.
[c]A control group was treated concurrently with 5 ml/kg/day of corn oil without c-tetramethrin for 14 days and then received a single oral gavage low-dose of ^{14}C-labeled c-tetramethrin.
[d]Two animals were designated as "spares" to be used in case a misdose occurred.

The test and control materials were administered using a glass syringe equipped with a stainless steel gastric probe.

An intravenous dose of the compound was not administered because the water solubility of the compound was very low (1.83 mg/kg 25°C).

Physiological conditions and behavioral patterns of the treated animals were observed 10 minutes and 6 hours after administration of ^{14}C-labeled c-tetramethrin, and at least once daily until sacrifice in all of the dosed groups. Observations were also conducted once daily during the pretreatment period on animals dosed with the unlabeled c-tetramethrin in the repeated dose group or with corn oil in the control group.

3. Sample Collection

The urine and feces for individual rats were collected and pooled 6 hours (urine only), 1, 2, 3, 5, and 7 days after administration of the ^{14}C-labeled material and the samples were stored at -20°C until analysis. Duplicate aliquots of 0-6-hours, 6-hours-1-day, 1-2-day, 2-3-day, 3-5-day and 5-7-day urine were radioassayed by liquid scintillating counting (LSC). Each metabolism cage was washed with water to recover ^{14}C (cage-wash) and duplicate aliquots were radioassayed. Radioactivity in the cage-wash was included in the urinary excretion. The 0-2-day urine were combined for each rat and subjected to TLC analysis after concentration with a rotary evaporator in vacuo at ca.35°C.

The 0-1, 1-2, and 2-3 day fecal samples of each individual rat on each collection day were homogenized with 50-100 ml of methanol/water-9/1 and centrifuged. Residues were further extracted twice with methanol/water-9/1. The supernatants were obtained by decantation and the total volume was measured. Aliquots of the supernatant and residual precipitate were radioassayed separately.

The 3-5 and 5-7 day fecal samples were each homogenized with water and duplicate aliquots were combusted for the radioassay. The combined 0-2 day fecal extracts for each individual rat and each extract were concentrated by rotary evaporation or lyophilization and analyzed by TLC.

Expired air was not collected for this study, since in a preliminary study 0.1% of the dosed ^{14}C was expired.

On day 7 after administration of ^{14}C c-tetramethrin, the rats were euthanized and exsanguinated and major tissues and blood aliquots were removed for radioassay. Duplicate aliquots of blood as well as weighed aliquots of tissue and minced carcass were combusted for radioassay. The remaining blood was separated into blood cell and plasma by centrifugation and then radioassayed. Tissue residues were expressed as nanogram (ng) equivalents of c-tetramethrin and percentages were calculated on the basis of tissue weights. Standard conversion factors were used for estimating the percentage of distribution in blood and fat.

4. Metabolite Analysis

Thin layer chromatography (TLC) in eight different solvent systems was tested with a series of authentic standards. Three solvent systems used for separation of urinary and fecal metabolites were: A--benzene/ethyl acetate (2/1); E--benzene saturated with formic acid/ethyl acetate/diethyl ether (10/4/2); and H--ethyl acetate/acetone/water/acetic acid (4/1/1/1). Two dimensional TLC was performed with solvent system A and E for each dimension. Polar metabolites were separated with system H.

Since no significant differences were seen in the TLC chromatograms between individual rats in males and females of all dosage groups, the 0-2-day fecal and 0-2 day urinary extracts of the individual rat were pooled per sex and dose group and subjected to two-dimensional TLC analyses using solvent system A and E, then one-dimensional TLC using solvent system H.[1]

[1]This work was not conducted in compliance with GLP; however, mass spectroanalyses of the purified metabolites were once again conducted in compliance with GLP in order to confirm that mass spectrum with Non-GLP was identical to GLP and to use the purified metabolites as authentic standards for qualitative analyses of metabolites.

5. Protocol

The materials and methods used in this study followed the protocol.

C. REPORTED RESULTS

1. Clinical Observations

No clinical signs of toxicity were observed in any of the groups throughout the study.

2. Elimination and Recovery

Elimination of administered radioactivity in the urine was rapid. Under all dosing regimens, approximately 76-94% of the administered dose was recovered in the excreta within 24 hours of administration (data not shown). Table 1 summarizes the cumulative percent of the administered radioactivity eliminated in urine (8.5-32.4%) and feces (65.9-91.3%) at 7 days postexposure and the percent recovery.

When comparing sexes, the percentage of radiolabeled material excreted in the urine of the females was greater than that of the males. Data from the 0-7 day (cumulative) interval indicate that there was a 32.0, 29.2, 29.0, and 20.5% increase in urinary excretion among the females of the low-, high-, repeated, and control group, respectively, when compared to the male rats. The percentage of radiolabeled material eliminated in the feces was slightly higher in males (71-91%) than in females (66-88%).

When comparing groups, the percentage of radiolabeled material excreted in the urine was lower (9-12.0%) in the high-dose group than the low- (21-31%), repeated (23-32%) and control (26-32%) groups. However, fecal ^{14}C-excretion was greater in the high-dose group (88-91%) than the low-(66-75%), repeated (69-78%), and control (68-71%) group indicating that absorption had apparently been saturated at the high-dose level.

3. Tissue Distribution

Selected ^{14}C-tissue residues on day 7 after administration of radiolabeled tetramethrin are presented in Table 2. The residue detected in the tissues analyzed were presented in nanograms (ng) of tetramethrin equivalent per grams of tissue (same as ppb). The highest radiolabeled residue levels were observed in the blood cells, and the means for males and females, respectively were as follows: 75.7-83.9 ng/g for the low-dose group (2 mg/kg), 4980-5340 ng/g for the high dose group (250 mg/kg), 83.3-103.5 ng/g for the repeated low-dose group (2 mg/kg), and 88.4-104.5 ng/g for the corn oil pretreatment (control group). Other tissues displaying elevated levels of radiolabeled residue included the blood, hair, kidneys, liver, lungs, spleen, and thyroid. There did not appear to be any

sex- or dose-related differences in the tissues among the low-, high-, repeated, or control groups.

It was reported that in all groups, <0.5% of the administered dose were found in the tissue and blood. Data tabulating tissue levels as percent of administered dose were indicated to be in Appendix M. However, Appendix M was not included in the submission.

4. Metabolism

Fecal and urinary metabolites were identified by radioautography of two-dimensional TLC plates developed with a combination of solvent system A and E or system E and H (as described in the method section). Table 3 presents the profile of the identified and unidentified metabolites in the feces and urine (expressed as percent of the administered ^{14}C dose) for the four different dosage regimens. Refer to Table 5 and Figure 1 for chemical abbreviations and metabolic scheme.

Thirty-three metabolites were detected in the fecal extracts by radioautography of two-dimensional TLC plates developed with a combination of solvent systems A and E or systems E and H. Four polar metabolites (1-OH-5-oxo-HPA, TPI-SA, 3-OH-MTI-SA, and 1-OH-HPA), seven less polar metabolites (TPI, MTI, THAM, THPA, 3-OH-HP-1, TCDA, and the parent compound) were identified. The main fecal metabolites identified were Unknown 34 (5.80-14.82% of ^{14}C), TPI-SA (8.30-13.19%), and Unknown 39 (2.69-6.70%). Other less polar metabolites included TPI (0.02-1.09%), MTI (0.05-0.40%), THAM (0.02-0.44%), 3-OH-HPI-1 (0.01-0.36%), TCDA (0.23-0.67%), THPA (0.30-0.88%), and 1-OH-HPA (0.61-4.22%).

The amount of parent compound in the feces was greatest in the high-dose group of both sexes, intermediate in the single low-dose group, and lowest in the repeated and control group. The values of the parent compounds were as follows: 12.97% (males) and 13.70% (females) in the low-dose group; 29.73% (males) and 34.15 (females) in the high-dose group; 3.45% (males) and 3.85% (females) in the repeated dose group; and 3.06% (males) and 3.01% (females) in the control dose group. The absorption was apparently saturated at the high-dose level.

Twenty-three metabolites were detected in the urine by radioautography of two-dimensional TLC plates developed with a combination of solvent systems A and E or systems E and H. The main metabolites identified in the urine were 3-OH-HPI-1 (1.86-7.32%), TCDA (0.14-1.83%), THPA (0.23-1.51%), Unknown 30 (0.47-2.39%), 1-OH-HPA (0.32-1.51%), and 1-5-oxo-HPA (0.11-1.10%). No parent compound was detected in the urine.

Spectroanalysis was conducted to identify the major unknown metabolites. Results indicated that Unknown 30 (in urine) and Unknown 34 (in feces) were apparent derivatives of MTI and a cis-isomer of Acid

3-OH-NPY-SA, respectively. The chemical structure was not definitely determined because of the instability of these compounds.

The major biotransformation reactions of c-tetramethrin in rats were as follows:

(1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring of the 3,4,5,6-tetrahydrophthalimide moiety, (4) oxidation at the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the tetrahydrophthalimide moiety, and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the tetrahydrophthalimide moiety. The major metabolites were identified as sulfonate derivatives in feces and alcohol and dicarboxylic acid derivatives in the urine.

D. CONCLUSIONS

A single oral dose of ^{14}C-cis-tetramethrin was rapidly and almost completely eliminated from the rat's body within 7 days of administration. The following recovery values were reported: 96.3% in males and 96.6% in females of the low-dose group, 99.8% in males and 100.4% in females of the high-dose group, 100.7% in males and 101.6% in females of the repeated dose group, and 96.9% in males and 99.7% in females of the control group. Urinary ^{14}C-excretion in females of all groups were higher than in the males. The amount of radiolabeled material remaining in the tissue on day 7 was generally low with residues primarily accumulating in the blood cells. The main metabolites were sulfonate derivatives in feces, and alcohol and dicarboxylic acid derivatives in the urine.

No dose-related differences in metabolic fate was observed among all groups. Fecal excretion of the parent compound was greater in the low- and high-dose groups (single oral dose groups) than in the repeated-dose and control groups.

The main metabolic reaction was determined by the study author to be as follows: (1) cleavage of the ester linkage, (2) cleavage of the -imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring of the 3,4,5,6-tetrahydrophthalimide moiety, (4) reduction at the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety, and (5) incorporation of the sulfonic acid group to the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety.

E. QUALITY ASSURANCE MEASURES

A Quality assurance statement for the study was signed on August 8, 1992.

The statement of Good Laboratory Practices compliance for the study was signed by the study director on August 8, 1992.

F. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study adequately described the absorption and distribution of ^{14}C-c-tetramethrin. The test material was rapidly eliminated in the feces and urine for all dose groups. Recovery of ^{14}C labeled c-tetramethrin was high (96.3%-101.6%). Individual animal data were adequately presented to support means and standard deviations. Results of thin layer chromatography and mass spectrometry accurately supported identification of metabolite.

It was reported in a previous study that the main metabolites from the alcohol moiety of (1RS, cis)-tetramethrin in rats were 3-OH-HPI, 2- and 4-OH-HPI.[2] However, in the present study, sulfonic and acid derivatives were newly found metabolites. According to the study author the reason for this difference appears to be that identification of the metabolites was not carried out extensively in the previous studies and that many polar metabolites remained unknown.

The metabolic pathway of radiolabeled t-tetramethrin (Study No. 2556) and c-tetramethrin are comparable with most of the material being rapidly eliminated in the urine and feces. The amount of radiolabeled material remaining in the tissue was low with most of the residues accumulating in the blood cells.

The following deficiencies were noted in the final report.

- The statistical analyses, as described in the text, could not be supported when data were compared among groups.
- A portion of the study report was not provided for review (Appendix M-N).

These deficiencies neither comprise the interpretation of the data nor the adequacy of the study.

G. REFERENCES

Kaneko, H., et al., J. Pesticide Sci., 6, 425-435 (1981).

Miyamoto, J., et al., Agric. Bio. Chem., 32, 628-630 (1968).

Silver. I.S., et al., Xenobiotica, 19, 509-519 (1989).

[2] J. Miyamoto et al., H.Kaneko et al., and I. Silver et al.

GUIDELINE SERIES 85-1: Metabolism

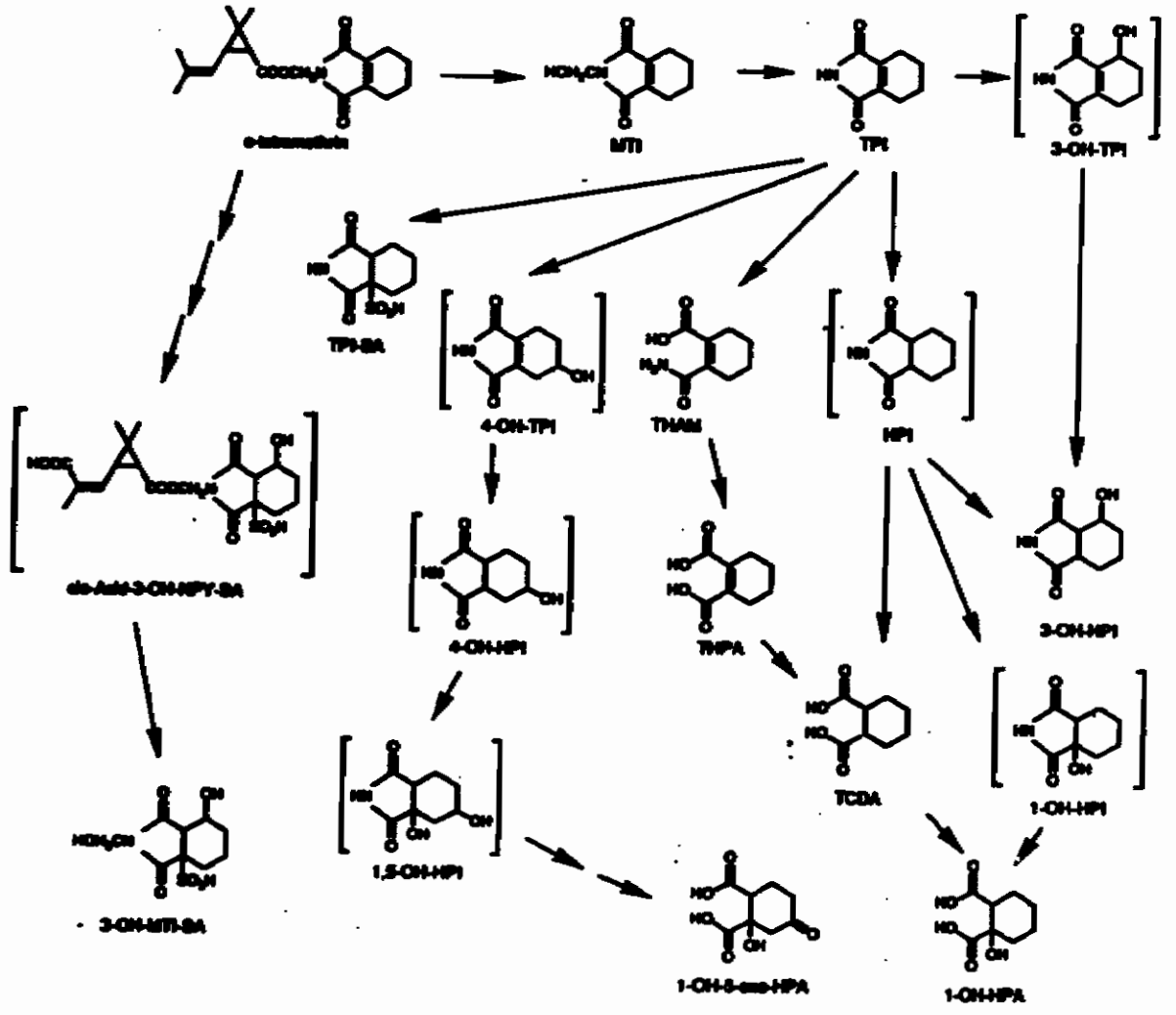


FIGURE 1. Proposed Metabolic Pathway of 1 RS cis-Tetramethrin in Rats (refer to Table 5 for the chemical names of the metabolites)

Source: Figure 1, p. 79

Table 1. Cumulative (Day 0-7) ^{14}C-Excretion In Feces and Urine (Expressed as % of Administered Radioactivity) After Administration of A Single Oral Dose of (1RS, cis) Tetramethrin in Rats[a]

	Dose Level (mg/kg)			
Parameter	2	250	2[b]	2[c]
Male				
Feces	75.4±1.51	91.3±1.71	77.7±2.36	71.3±2.22
Urine	20.9±0.37	8.5±1.13	23.0±2.36	25.3±2.64
Total	96.3±1.52	99.8±0.76	100.7±0.25	96.9±0.90
Female				
Feces	65.9±4.12	88.4±3.22	69.2±3.61	67.5±1.00
Urine	30.7±2.00	12.0±2.50	32.4±2.83	32.2±0.66
Total	96.6±4.64	100.4±2.53	101.6±1.02	99.7±0.94

[a]Data show the mean values ± S.D. of five rats.

[b]Animals were treated for 14 consecutive days with 2 mg/kg of the unlabeled material prior to the single dose of the labeled material.
[c]Animals were treated for 14 consecutive days with 5 mL/kg of corn oil prior to the single dose of the labeled material.

Source: Tables 3-1 through 3-4, pp. 58-61.

Table 2

Selected ^{14}C-Tissue Residues in Male and Female Rats on Day 7 After A Single Oral Administration of (1RS, cis) Tetramethrin

	PPB (ng tetramethrin equivalents/ g tissue)							
	2 mg/kg		250 mg/kg (10^2 mg equivalent)		2 mg/kg[a]		2 mg/kg[b]	
Tissue	Male	Female	Male	Female	Male	Female	Male	Female
Blood Cell	75.7±13.34	85.9±9.50	49.8±8.85	53.4±7.66	83.3±12.42	103.5±17.42	88.4±15.47	104.5±23.27
Blood	42.1±4.84	50.4±4.83	24.1±5.45	28.2±5.33	39.3±4.79	43.1±13.75	51.8±2.40	56.5±9.65
Hair	6.8±3.73	145.6±162.92	14.6±10.72	40.2±60.89	4.7±1.51	7.2±3.49	6.7±4.51	12.4±6.84
Kidney	15.8±1.71	16.6±1.19	6.8±2.64	7.7±2.22	16.8±2.09	18.2±2.57	19.0±1.36	16.9±3.48
Liver	11.4±1.89	9.1±0.94	4.6±0.68	4.6±1.31	12.4±1.73	11.5±1.69	14.0±1.59	11.3±2.85
Lung	8.5±1.39	10.1±0.37	3.8±0.99	5.6±0.72	7.9±0.56	11.9±1.64	10.5±1.71	13.2±6.14
Skin	7.5±2.15	17.3±14.62	5.0±2.81[e]	7.4±4.87	5.7±2.52	10.6±1.41	9.0±1.94	7.5±1.31
Spleen	9.1±1.17	12.7±3.85	4.4±1.52	5.1±2.41	8.9±1.22	11.4±2.28	11.3±2.74	13.8±2.36
Thyroid	13.2±1.26[d]	22.3± 3.36[e]	<17.0	16.3±5.85[f]	12.7±4.21	22.3±10.62	13.7±1.03[c]	47.9±6.78

[a]Radiolabeled material was administered after 14 consecutive days of dosing with nonlabeled c-tetramethrin at 2 mg/kg/day.
[b]Radiolabeled material was administered after 14 consecutive days of dosing with corn oil at 5 ml/kg/day.
[c]Figure represents mean values ± S.D. of two rats.
[d]Figure represents mean values ± S.D. of three rats.
[e]Figure represents mean value ± S.D. of four rats.
[f]Below the detection limit

Source: Tables 4-1 through 4-4, pp. 62-65.

TABLE 3. Distribution of Metabolites in Urine and Feces (Expressed as Percent of Administered Dose) Within 2 days After Oral Administration of (1RS, cis) Tetramethrin[a]

	2 mg/kg (single oral)				250 mg/kg (single oral)				2 mg/kg (single oral[b])				2 mg/kg (single oral[b])			
	Male		Female		Male		Female		Male		Female		Male		Female	
Metabolites	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine
Unknown-1	0.02	--	0.06	--	0.02	--	0.01	--	0.01	--	0.03	--	0.03	--	0.02	--
c-MPT (Parent)	12.97	--	13.70	--	29.73	--	34.15	--	3.45	--	3.85	--	3.06	--	3.01	--
Unknown-2	0.19	--	0.16	--	0.53	--	0.61	--	0.02	--	0.07	--	0.04	--	0.03	--
Unknown-3	0.06	--	0.05	--	0.09	--	0.60	--	0.02	--	0.03	--	0.03	--	0.03	--
Unknown-4	0.06	--	0.09	--	0.16	--	0.32	--	0.04	--	0.08	--	0.04	--	0.02	--
TPI	0.25	0.06	0.18	0.13	0.61	0.02	1.09	0.04	0.05	0.05	0.08	0.06	0.02	0.09	0.08	0.12
Unknown-5	0.10	--	0.07	--	0.10	--	0.12	--	0.06	--	0.07	--	0.04	--	0.08	--
MTI	0.12	--	0.08	--	0.29	--	0.40	--	0.07	--	0.07	--	0.06	--	0.05	--
Unknown-7	--	0.06	--	0.15	--	0.05	--	0.00	--	0.10	--	0.17	--	0.17	--	0.36
Unknown-8	--	0.01	--	0.03	--	0.00	--	0.00	--	0.02	--	0.05	--	0.03	--	0.07
Unknown-9	0.07	--	0.04	--	0.09	--	0.12	--	0.06	--	0.07	--	0.05	--	0.08	--
Unknown-10	0.13	--	0.10	--	0.29	--	0.27	--	0.15	--	0.12	--	0.11	--	0.16	--
Unknown-11	--	0.34	--	0.48	--	0.13	--	0.18	--	0.23	--	0.40	--	0.12	--	0.25
Unknown-12	--	0.21	--	0.30	--	0.11	--	0.13	--	0.15	--	0.27	--	0.11	--	0.12
3-OH-MPI-2	--	0.38	--	0.52	--	0.13	--	0.12	--	0.18	--	0.29	--	0.15	--	0.35
3-OH-MPI-1	0.19	3.77	0.11	7.32	0.36	1.86	0.16	2.24	0.02	3.77	0.02	6.89	0.01	4.26	0.03	5.69
Unknown-13	--	0.48	--	0.74	--	0.33	--	0.37	--	0.51	--	0.73	--	0.95	--	0.89
Unknown-14	--	0.31	--	0.58	--	0.25	--	0.28	--	0.41	--	0.53	--	0.52	--	0.84
Unknown-15	--	0.37	--	0.60	--	0.15	--	0.22	--	0.35	--	0.53	--	0.50	--	0.60
TCDA	0.38	0.36	0.23	0.65	0.64	0.14	0.67	0.31	0.29	0.81	0.30	1.83	0.37	0.95	0.35	1.37
THPA	0.51	0.76	0.30	1.51	0.88	0.23	0.63	0.32	0.60	0.65	0.69	1.04	0.71	0.68	0.59	1.24
Unknown-18	0.04	--	0.04	--	0.14	--	0.12	--	0.01	--	0.01	--	0.00	--	0.00	--
Unknown-19	0.05	--	0.03	--	0.07	--	0.10	--	0.00	--	0.00	--	0.00	--	0.01	--
Unknown-20	0.07	--	0.05	--	0.17	--	0.28	--	0.01	--	0.03	--	0.07	--	0.01	--
TMAM	0.10	--	0.08	--	0.44	--	0.43	--	0.04	--	0.11	--	0.06	--	0.02	--
Unknown-22	0.39	--	0.08	--	0.38	--	0.27	--	0.39	--	0.56	--	0.43	--	0.54	--
Unknown-25	--	0.70	--	1.22	--	0.31	--	0.66	--	0.75	--	0.86	--	0.61	--	0.81
Unknown-26	--	0.82	--	0.83	--	0.24	--	0.41	--	0.79	--	1.11	--	0.73	--	0.93
Unknown-27	--	0.91	--	1.06	--	0.32	--	0.58	--	0.87	--	1.09	--	1.17	--	1.49
Unknown-28	0.52	--	0.46	--	0.52	--	0.77	--	0.76	--	0.63	--	0.70	--	0.47	--
Unknown-29	0.64	--	0.49	--	0.94	--	1.96	--	0.91	--	1.65	--	0.90	--	1.36	--
Unknown-30	2.34	1.28	2.41	1.53	2.53	0.47	2.19	0.69	3.05	1.71	3.68	2.39	3.25	1.97	3.66	2.32
1-OH-BPA	0.89	0.77	1.01	1.51	4.22	0.32	2.85	0.54	1.27	1.00	1.07	1.08	0.67	0.97	0.61	1.47
Unknown-32	--	0.67	--	0.90	--	0.32	--	0.57	--	1.02	--	1.27	--	0.83	--	1.14
Unknown-33	--	0.72	--	0.96	--	0.29	--	0.33	--	0.86	--	1.11	--	1.17	--	1.07
Unknown-34	12.82	--	10.02	--	10.06	--	5.80	--	14.19	--	14.82	--	12.90	--	13.58	--
TPI-SA	11.05	0.89	10.18	1.05	8.30	0.28	8.77	0.63	13.19	1.01	12.09	1.25	12.65	0.95	12.31	1.03

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TABLE 3 (Continued)

	2 mg/kg (single oral)				250 mg/kg (single oral)				2 mg/kg (single oral[b])				2 mg/kg (single oral[c])			
	Male		Female		Male		Female		Male		Female		Male		Female	
Metabolites	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine
Unknown-35	--	0.35	--	0.34	--	0.11	--	0.12	--	0.32	--	0.41	--	0.39	--	0.47
Unknown-36	--	0.94	--	1.24	--	0.34	--	0.49	--	1.53	--	2.27	--	1.08	--	1.33
Unknown-37	3.10	--	1.81	--	4.84	--	4.72	--	2.45	--	1.75	--	2.37	--	1.54	--
3-OH-MTI-SA	3.97	--	2.45	--	4.11	--	4.24	--	2.82	--	3.96	--	5.57	--	5.31	--
Unknown-39	4.72	--	5.52	--	2.69	--	6.70	--	6.10	--	4.17	--	3.10	--	3.69	--
Unknown-40	--	--	--	--	--	--	--	--	0.06	--	0.06	--	0.06	--	0.07	--
Unknown-41	--	--	--	--	--	--	--	--	0.00	--	0.01	--	0.01	--	0.02	--
Unknown-42	--	--	--	--	--	--	--	--	0.00	--	0.01	--	0.01	--	0.02	--
Unknown-43	--	--	--	--	--	--	--	--	0.01	--	0.06	--	0.02	--	0.05	--
Unknown-44	--	--	--	--	--	--	--	--	0.36	--	0.17	--	0.21	--	0.26	--
1-OH-5-α-HPA	1.64	1.10	0.62	0.86	1.15	0.15	0.73	0.11	1.45	0.56	0.88	0.79	1.45	0.36	1.16	0.62
Others	6.81	4.17	4.22	5.40	9.30	1.72	3.92	2.36	7.73	4.83	4.84	5.38	5.97	6.10	4.86	6.74
Water Extract	7.34	--	6.47	--	4.32	--	2.91	--	11.16	--	7.86	--	11.47	--	8.43	--
Unextract.	4.40	--	2.95	--	2.90	--	1.81	--	6.39	--	4.83	--	4.63	--	4.61	--
Total	74.34	20.26	64.08	29.91	90.87	8.28	87.72	11.68	77.20	22.47	68.72	31.84	71.09	24.84	67.11	31.32

[a]Values given as percentage of administered dose
[b]Radiolabeled material was administered after 14 consecutive days of dosing with nonlabeled α-tetramethrin at 2 mg/kg/day.
[c]Radiolabeled material was administered after 14 consecutive days of dosing with corn oil at 5 ml/kg/day.

Source: Tables 5-1 through 5-4, pp. 66-69

Table 4

Summary of Radioactive Metabolites in Urine and Fecal Extracts

Group	% of Total Administered Radioactivity							
	Low		High		Repeated		Control	
	M	F	M	F	M	F	M	F
Total Excreted ^{14}C	96.3	96.6	99.8	100.4	100.7	101.6	96.9	99.7
Metabolites								
g-NFY (Parent)	13.0	13.7	29.7	34.2	3.5	3.9	3.1	3.0
TPI	0.3	0.3	0.6	1.1	0.1	0.1	0.1	0.2
MTI	0.1	0.1	0.3	0.4	0.1	0.1	0.1	0.1
THAM	0.1	0.1	0.4	0.4	0.0	0.1	0.1	0.0
TCDA	0.7	0.9	0.8	1.0	1.1	2.1	1.3	1.7
THPA	1.3	1.6	1.1	1.0	1.3	1.7	1.4	1.8
3-OH-HPI-1	4.0	7.4	2.2	2.4	3.8	6.9	4.3	5.7
3-OH-HPI-2	0.3	0.1	0.1	0.1	0.2	0.3	0.2	0.4
1-OH-5-oxo-HPA	2.8	1.5	1.3	0.8	2.0	1.7	1.8	1.8
1-OH-HPA	1.7	2.5	4.5	3.4	2.3	2.2	1.6	2.1
TPI-SA	11.9	11.2	8.6	9.4	14.2	13.3	13.6	13.3
3-OH-MTI-SA	4.0	2.5	4.1	4.2	2.8	4.0	5.6	5.3
Identified Metabolites	40.2	42.5	53.7	58.4	31.4	36.4	33.2	35.4
Unknown Metabolites	42.7	42.0	38.3	36.3	50.7	51.5	46.6	50.0
Water Extract	7.3	6.5	4.8	2.9	11.2	7.9	11.5	8.4
Unextractable	4.4	3.0	2.9	1.8	6.4	4.8	4.6	4.6
Total	94.6	94.0	99.2	99.4	99.7	100.6	95.9	98.4

The data show the summed amounts of the 37 metabolites.

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TABLE 5. Chemical Names and Abbreviations of Tetramethrin Isomers Identified in Urine and Feces

Metabolite Code	Chemical Name
c-NPY (Parent)	3,4,5,6-tetrahydrophthalimidomethyl (1RS, cis)-chrysanthemate
MTI	N- (hydroxymethyl)-3 4,5,6-tetrahydrophthalimide
THPA	3,4,5,6-tetrahydrophthalic acid
TPI	3,4,5,6-tetrahydrophthalimide
TPA	3,4,5,6-tetrahydrophthalic anhydride
THAM	2-carboxy-3,4,5,6-tetrahydrobenzamide
HPI	1,2-cyclohexanedicarboximide
TCDA	trans-1,2-cyclohexanedicarboxylic acid
1-OH-HPI	1-hydroxy-1,2-cyclohexanedicarboximide
3-OH-HPI-1	3-hydroxy-1,2-cyclohexanedicarboximide
3-OH-HPI-2	3-hydroxy-1,2-cyclohexanedicarboximide
1-OH-HPA	1-hydroxy-1,2-cyclohexanedicarboxylic acid
1-OH-5-o-HPA	1-hydroxy-5-oxo-1,2-cyclohexanedicarboxylic acid
TPI-SA	1-sulfo-1,2-cyclohexanedicarboximide
Acid-NPY-SA	1-sulfo-1,2-cyclohexanedicarboximidomethyl (1RS, trans) -3-(2'-E-carboxy-1'-propenyl)-2,2-dimethyl-1-cyclopropane-carboxylate
Acid-3-OH-NPY-SA	3-hydroxy-1-sulfo-1,2-cyclohexanedicarboximidomethyl (1RS, trans)-3-(2'-E-carboxy-1'-propenyl)-2,2-dimethyl-1-cyclopropanecarboxylate
3-OH-MTI-SA	N-(hydroxymethyl)-3-hydroxy-1-sulfo-1,2-cyclohexanedicarboximide

Source: Table I, p. 56

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FINAL

010235

DATA EVALUATION REPORT

(1-RS, trans)-Tetramethrin

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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9300 Lee Highway
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April 1, 1993

Principal Reviewer:	Jay Meeks Jay Meeks, B.S.	3/31/93 Date
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QA/QC Manager:	William McLellan for Sharon Segal, Ph.D.	March 31, 1993 Date

Contract Number: 68D10075
Work Assignment Number: 2-32
Clement Number: 91
Project Officer: Caroline Gordon

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GUIDELINE SERIES 85-1: Metabolism

EPA Reviewer: Paul Chin, Ph.D. Signature: Paul Chin
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Health Effects Division

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Review Section IV, Toxicology Branch I, Date: 4/7/93
Health Effects Division

R. H.
5-3-93

DATA EVALUATION REPORT

STUDY TYPE: Metabolism in rats

EPA IDENTIFICATION NUMBERS:

P.C. Code: 069003

Tox. Chem. Number: 844

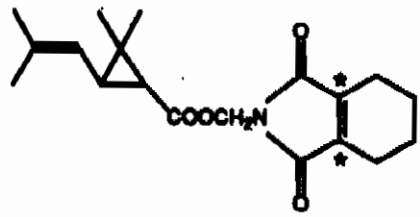
MRID Number: 424489-01

Study Number: 2556

TEST MATERIAL: 3,4,5,6-Tetrahydrophthalimidomethyl (1RS, trans)-chrysanthemate

SYNONYMS: t-Tetramethrin; (t-NPY)

CHEMICAL STRUCTURE:



* denotes the position of the [^{14}C] label

SPONSOR: Agricultural Chemicals, Sumitomo Chemical Co., Ltd.

TESTING FACILITY: Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan

AUTHOR: Kunio Shiba

TITLE OF REPORT: Metabolism of (1RS, trans)-Tetramethrin in Rats. Study No. 2556.

DATE OF REPORT: August 5, 1992

CONCLUSIONS: The absorption, distribution, metabolism, and excretion of trans-tetramethrin were studied in Sprague-Dawley rats administered a single oral gavage dose of ^{14}C-t-tetramethrin at 2 or 250 mg/kg, or a 14-day repeated oral dosing of 2 mg/kg unlabeled tetramethrin followed by a single dose of 2 mg/kg ^{14}C-t-tetramethrin on day 15.

^{14}C-t-tetramethrin was rapidly and almost completely eliminated (95-101%) from the rats' body within 7 days of dosing. The excretion of radioactivity in the urine and feces was 42-71% and 29-58%, respectively. The highest radiolabeled residue levels were observed in the blood cells. Total residues in all tissues at day 7 postexposure accounted for <0.4% of the administered dose.

Thirty-four metabolites were detected in the feces. The major metabolite was identified as TPI-SA (1-sulfo-1,2-cyclohexanedicarboximide). Twenty-two urinary metabolites were detected as mostly alcohol and dicarboxylic acid derivatives. The major metabolite was identified as 3-OH-HPI-1 (3-hydroxy-1,2-cyclohexanedicarboximide).

The biotransformation reactions of t-tetramethrin were as follows:

(1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring, (4) oxidation at the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the tetrahydrophthalimide moiety, and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the tetrahydrophthalimide moiety.

STUDY CLASSIFICATION: Acceptable. The study satisfies the requirements set forth under Guideline Series 85-1 (and Addendum 7) for a metabolism study in rats and, therefore, is judged to be acceptable.

A. MATERIALS

1. Test Substance

The unlabeled test material (lot number T-9101) was a white-colored powder provided by Sumitomo Chemical Co., Ltd. The test material was purified by Ricerca, Inc., and the purity was determined to be 98.1%.

The radiolabeled t-(tetrahydrophthaloyl-1,2-^{14}C) tetramethrin (lot number C-91-005A) was labeled with [^{14}C] on the aromatic ring. It was synthesized by the Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd. The labeled preparation had a specific activity of 49.5 mCi/mmol (1.83 GBq). A radiochemical purity of >99% was determined.

Synthetic (unlabeled) standards, 1-hydroxy-1,2-cyclohexane-dicarboximide (1-OH-HPI), 1,2-cyclohexanedicarboximide (HPI), N-(hydroxymethyl)-3,4,5,6-tetrahydrophthalimide (MTI), 2-carboxy-3,4,5,6-tetrahydro-benzamide (THAM), 3,4,5,6-tetrahydrophthalic anhydride (TPA) were also

synthesized by Sumitomo Chemical Co., Ltd.

2. Test Animals

Four-to-six-week old male and female Charles River Sprague-Dawley rats were obtained from Charles River Japan, Inc. The group mean weights of male rats ranged from 236 g to 261 g and the group mean weights of female rats ranged from 167 g to 212 g at the time of the radiolabeled dosing of t-tetramethrin.

B. METHODS

1. Dosing Solutions and Rationale for the Dose Selection

The nonlabeled and radiolabeled oral dosing solutions were prepared in corn oil. Dilutions of the radiolabeled material were made with nonlabeled t-tetramethrin to adjust the specific radioactivity to 4.625 MBq (125 µCi)/mg for the low-, repeated-, and control-dose studies or 27.0 kBq (1.0 µCi)/mg for the high-dose study. The labeled material was dissolved in corn oil at 0.4 mg/ml for the low-, repeated- and control- groups, or suspended in corn oil at 50 mg/ml for the high-dose group.

The low dose (2 mg/kg) was selected based on an acute oral LD_{50} greater than 5000 mg/kg and a 6-month subacute toxicity study in which the no-observable effect level (NOEL) was 1500 ppm. The high dose (250 mg/kg) was selected based on a 6-month subacute toxicity study in rats in which the minimum toxicity level was 5000 ppm. Decreases in body weight gain, increases in absolute liver weights, and increases in liver-to-body weight ratios were observed in both sexes.

2. Acclimatization and Dosing

Animals were acclimatized for approximately one week before the administration of the test material. Animals were housed five or less/cage in polypropylene cages with sawdust during quarantine and acclimation. Rats dosed with the ^{14}C-labeled material were housed individually in glass metabolism cages until sacrifice. The diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water were given ad libitum throughout the study. No contaminants in the food and water were reported to interfere with the study. Room temperature (23±2°C), relative humidity (55±10%), air exchanges (>10 air per hour), and a 12-hour photoperiod was maintained.

The dosing regimens are listed below:

Group	Sex	Dose Level: mg/kg	Number of Animals
Single low	M	2	5
	F	2	5
Single high	M	250	5
	F	250	5
Repeated low[a]	M	2	8[b]
	F	2	8[b]
Control[c]	M	2	5[d]
	F	2	5[d]

Footnotes:

[a]Rats were given an oral dose of 2 mg/kg/day of unlabeled _t_-tetramethrin in corn oil at a dose level of 5 ml/kg/day for 14 days followed by a single administration of 2 mg/kg/day of ^{14}C-_t_-tetramethrin on day 15.
[b]Three animals were designated as "spares" to be used in case a misdose occurred.
[c]A control group was treated concurrently with 5 ml/kg/day of corn oil without the added _t_-tetramethrin for 14 days and 3/5 per sex were then given a single oral dose of 2 mg/kg ^{14}C-tetramethrin.
[d]Two animals were designated as "spares" to be used in case a misdose occurred.

The test and control materials were administered using a glass syringe equipped with a stainless steel gastric probe.

An intravenous dose of the compound was not administered because the water solubility of the compound was very low (1.83 mg/kg; 25°C).

Physiological conditions and behavioral patterns of the treated animals were observed 10 minutes and 6 hours after administration of ^{14}C-labeled _t_-tetramethrin, and at least once daily until sacrifice for all dose groups. Similar observations were also conducted once daily during the pretreatment period on animals dosed with the unlabeled _t_-tetramethrin in the repeated dose group or with corn oil in the control group.

3. Sample Collection

The urine and feces for individual rats were collected and pooled 6 hours (urine only), 1, 2, 3, 5, and 7 days after administration of the ^{14}C-labeled material and stored at -20°C until analysis. Duplicate aliquots of 0-6- hr,6 hr-1- day, 1-2- day and 2-3- day urine and the 5- and 7- day samples were radioassayed by liquid scintillation counting (LSC). Each metabolism cage was washed with water to recover ^{14}C (cage wash), and the duplicate aliquots were radioassayed. Radioactivity in the cage wash was included in the urinary excretion. The 0-2- day urine samples were combined for each rat and subjected to TLC analysis after concentration by a rotary evaporator _in vacuo_ at 35°C.

The 0-1-, 1-2-, and 2-3- day fecal samples of each individual rat on each collection day were homogenized with 50-100 ml of methanol/water-9/1 and then centrifuged. Residues were further extracted twice with methanol/water-9/1. The supernatants were obtained by decantation and the total volume was recorded. Aliquots of the

supernatant and residual precipitate were radioassayed separately. The 3-5- and 5-7- day fecal samples were each homogenized with water and duplicate aliquots were combusted for the radioassay. The combined 0-2 day fecal extracts for individual rats were concentrated by rotary evaporation or lyphiliza- tion and analyzed by TLC.

Expired air was not collected for this study, since in a preliminary study <0.1% of the dosed ^{14}C t-tetramethrin was expired.

On day 7 after administration of ^{14}C t-tetramethrin, rats were euthanized and exsanquinated and major tissues and blood aliquots were removed for radioassay. Duplicate aliquots of blood as well as weighed aliquots of tissues and minced carcass were combusted for radioassay. The remaining blood was separated into blood cell and plasma by centrifugation and then radioassayed. Tissue residues were expressed as nanograms (ng) equivalents of t-tetramethrin and percentages were calculated on the basis of tissue weights. Standard conversion factors were used for estimating the percentage of distribution in blood and fat.

4. Metabolite Analysis

Thin layer chromatography (TLC) in eight different solvent systems was tested with a series of authentic standards. Three solvent systems used for separation of urinary and fecal metabolites were: A-- benzene/ethyl acetate (2/1); E-- benzene saturated with formic acid/ethyl acetate/ diethyl ether (10/4/2); and H-- ethyl acetate/acetone/water/acetic acid (4/1/1/1). Two dimensional TLC was performed with solvent system A and E for each dimension. Polar metabolites were separated with system H. Since no significant dose-related difference in qualitative analysis was found among individual rat composites, the 0-2- day urine and the 0-2-day fecal extracts of the individual rats were pooled per sex and dose group for quantitative analysis of the metabolites. For positive identification of metabolites by spectroanalysis, insufficient amounts were available in the high-dose group. Therefore, an additional group of rats, seven males and five females (reported in Appendix D, p. 141), were given 250 mg/kg/day of t-tetramethrin for four consecutive days. Most of the metabolites were purified by silica gel column chromatography, high performance liquid chromatography (HPLC), and TLC.[1]

5. Protocol

The materials and methods used in this study were adequately described.

[1]This work was not conducted in compliance with GLP; however, mass spectromalyses of the purified metabolites were once again conducted in compliance with GLP in order to confirm that mass spectrum with Non-GLP was identical with GLP and to use the purified metabolites as authentic standards for qualitative analyses of metabolites.

C. REPORTED RESULTS

1. Clinical Observations

No clinical signs of toxicity were observed in dosed groups throughout the study.

2. Elimination and Recovery

Elimination of administered radioactivity in the urine and feces was rapid. Under all dosing regimens, approximately 82-93% of the administered dose was recovered in the excreta within 24 hours post administration (data not shown). Table 1 summarizes the percent of the administered radioactivity eliminated in urine (42-71%) and feces (29-58%) at 7 days post exposure and the percent recovery.

Female rats excreted a greater percent of the administered dose in the urine than in the feces when compared to the males. Data from the 0-7- day (cumulative) interval indicate that there was a 26.8, 26.2, and 12.4% increase in urinary excretion among females of the low-, high-, and repeated- dose group, respectively, when compared to male rats. Repeated dosing of the unlabeled test material tended to increase the percent of a ^{14}C-labeled radioactivity excreted in the urine compared to either male or female rats administered a single oral dose of 2 mg/kg ^{14}C-tetramethrin. Predosing for 14 days with corn oil prior to a single 2 mg/kg oral dose of ^{14}C-tetramethrin tended to increase the percentage of the radioactivity found in the urine.

3. Tissue Distribution

Selected ^{14}C-tissue residues on 7 day after administration of radiolabeled tetramethrin along with the percentages of ^{14}C-distributed in the blood are presented in Table 2. The residue detected in the tissue analyzed were presented in nanograms (ng) of tetramethrin equivalent per grams of tissue. The highest radiolabeled residue levels were observed in the blood cells, and the ranges were as follows: 34.8-45.7 ng/g for the low-dose group (2 mg/kg), 53.9-56.7 ng/g for the repeated dose group, 47.3-60.7 ng/g for the corn oil pretreated group, and 8090-9970 ng/g for the high dose group (250 mg/kg). Additionally, radiolabeled residue levels in the hair and thyroid were higher than other examined tissues for all groups. Other tissues displaying elevated levels of radiolabeled residue included the blood, kidneys, liver, lungs, spleen, and skin.

As shown in Table 2, total residues in all tissues at day 7 postexposure, however, accounted for only <0.4% of the administered dose in any of the dosage groups. Average total residues were higher in rats treated for 14 days with 2 mg/kg of unlabeled $\underline{t}$-tetramethrin (0.35%) than average total residues in both the low- (0.23%) and high- (0.28%) single ^{14}C-labeled dose. Radiolabled $\underline{t}$-tetramethrin accumulated more in the blood than in any other evaluated tissue.

4. Metabolism

Table 3 presents the amount (% of the administered ^{14}C) of the pooled (day 0-2) fecal and urinary metabolites. Thirty-four metabolites were detected in fecal extracts by radioautography of two-dimensional TLC plates developed with a combination of solvent systems A and E or developed with systems E and H. (Refer to Table 5 and Figure 1 for chemical abbreviations and metabolic scheme, respectively.) Five polar metabolites, all sulfonate derivatives, nine less polar metabolites, and the parent compound were identified. The major metabolite, TPI-SA (1-sulfo-1,2 cyclohexane dicarboximide), is the result of ester cleavage of the chrysanthemate side chain (Figure 1) with formation of the imine (TPI) and sulfonation at the 1 position of the ring. Sulfonated products are accompanied by reduction at the 1,2- double bond (Figure 1) without ester cleavage. This occurred after hydroxylation of the methyl group (of the isobutenyl moiety of the chrysanthemate side chain) to the alcohol (Alc-NPY) and oxidation of the alcohol to the acid. The fecal metabolites were identified as Acid-3-OH-NPY, and its sulfonated derivatives, Acid-3-OH-NPY-SA and 3-OH-MTI-SA (after cleavage of the ester linkage). The less polar fecal metabolites, which are minor, include TPI (0.04-0.95%), MTI (0.03-0.44%), THAM (0.05-0.65%), TCDA (0.16-1.21%), THPA (0.14-0.74%), 3-OH-HPI-1 (0.14-0.42%), 1-OH-HPA (0.19-0.74%), and 1-OH-5-oxo-HPA (0.41-1.06%). The highest percent of the less polar metabolites were found in the high-dose groups (250 mg/kg). These non-sulfonated compounds shown in the metabolic scheme (Figure 1) are the result of ester cleavage and hydroxylation of the cyclohexane ring and cleavage of the imine linkage. The amount of t-NPY (parent) in the feces was considerably less in females than males (4.8% versus 23.2% in the 2 mg/kg-group and 10.26% versus 20.75% in 250-mg/kg-group).

Twenty-two urinary metabolites were detected. The major metabolite was 3-OH-HPI-1 resulting from ester cleavage and ring hydroxylation. Minor amounts of the sulfate conjugates TPI-SA and Acid-NPY-SA were found in the urine. However, no unchanged t-NPY (parent) was found in the urine. Other urinary metabolites were various alcohols and dicarboxylic acids resulting from imide bond cleavage and oxidation or hydroxylation. The metabolites include 3-OH-HPI-1 (11.01-23.12%), THPA (1.69-3.24%), Acid-NPY-SA (1.75-4.18%), 1-OH-HPA (1.31-2.57%), Unknown-10 (2.13-5.12%), and Unknown-25 (2.20-4.15%). Other metabolites identified in the urine included TPI (0.18-0.40%), TCDA (0.87-1.74%), 1-OH-5-oxo-HPA (0.00-2.54%) and TPI-SA (0.14-1.24%).

A summary of the radioactive metabolites in the combined urine and fecal extractions is presented in Table 4. Identification of the metabolites was determined by TLC cochromatography. Table 5 presents names of the metabolites found in the urine and/or feces. The parent compound (t-NPY) values were highest in both sexes of the low- and high-dose groups, and lower in the repeated and control groups. The values were as follows: 23.21 (males) and 4.76% (females) in the low-dose group; 20.75 (males) and 10.26% (females) in the high-dose group; 0.66 (males)

and 1.20% (females) in the repeated dose group; and 1.80 (males) and 2.17% (females) in the control group.

As presented by the study author, the major biotransformation reactions of t-tetramethrin in rats were as follows:

(1) cleavage of the ester linkage, (2) cleavage of the -imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring of the 3,4,5,6-tetrahydrophthalimide moiety, (4) oxidation at the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety, and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety. The main metabolites were sulfonate derivatives in feces and alcohol derivatives from the 3,4,5,6-tetrahydrophthalimide moiety in urine.

D. STUDY AUTHOR'S CONCLUSIONS

The study author concluded that at all tested dose levels, ^{14}C-tetramethrin was rapidly and almost completely eliminated from the rat's body within 7 days of administration. Radiolabeled residues on day 7 postexposure were generally low with residues primarily accumulating in the blood cells. The main metabolites were sulfonate derivatives in feces, and alcohol and dicarboxylic acid derivatives postcleavage of the imino bond in urine. Some sex-related differences in metabolism were noted. Females showed higher radiolabel levels in blood, blood cells, kidneys, and spleen of the low- dose group and in blood of the high dose group than males. Urinary excretion of radiolabel was higher in the females than in the males of the low-, high-, and repeated dose groups. Spectroanalysis and chromatography adequately reflected the identity of the metabolite characterization.

No marked difference in metabolic fate was observed among all dosed groups. A higher percentage of the administered dose was excreted in the feces of the low- and high dose- groups (single oral dose groups) than in the repeated and control dose groups.

The main metabolic reactions were determined by the study author to be as follows: (1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexane ring of the 3,4,5,6-tetrahydrophthalimide moiety, (4) oxidation at the methyl of the isobutenyl group in the chrysanthemic acid, (5) reduction at the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety, and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide moiety.

E. QUALITY ASSURANCE MEASURES

A Quality assurance statement for the study was signed on August 5, 1992.

The statement of Good Laboratory Practices compliance for the study was signed by the study director on August 5, 1992.

F. REVIEWER'S DISCUSSION AND INTERPRETATION OF RESULTS

The study adequately described the absorption and distribution of ^{14}C t-tetramethrin in rats following oral exposure. The data indicate that radiolabeled t-tetramethrin is rapidly eliminated in the feces and urine for all dosing groups. Recovery of ^{14}C labelled t-tetramethrin was high (94.4-100.4%). Individual animal data were adequately presented to support means and standard deviations.

It was reported in a previous study that main metabolites from the alcohol moiety of (1RS, trans)-tetramethrin in rats were 3-OH-HPI, 2- and 4-OH-HPI. However, sulfonic acid derivatives and ester linkage-retained metabolites were found as major metabolites in the present study. The reason for this difference appears (according to the study author) to be that identification of the metabolites was not carried out extensively in the previous study and that many polar metabolites remained unknown.

The following deficiency was noted in the final report:

- The statistical analyses, as described in the text, could not be supported when data were compared among groups.

This deficiency neither compromise the interpretations of the data nor the adequacy of the study.

TABLE 1. Cumulative (Days 0-7) ^{14}C-Excretion In Feces and Urine After A Single Oral Dose of ±-[Tetrahydrophthaloyl-1,2-^{14}C] Tetramethrin to Rats

	Dose Level (mg/kg)			
Parameter	2	250	2[a]	2[b]
Male				
Feces	53.0±3.55	57.9±5.64	38.9±5.79	38.6±2.61
Urine	42.3±4.73	43.0±5.50	62.5±3.94	59.9±4.30
Total	95.3±2.49	101.0±1.65	101.4±3.92	98.5±1.92
Female				
Feces	37.8±3.70	40.6±6.32	29.0±1.31	37.5±6.02
Urine	57.8±3.87	58.3±6.04	71.4±1.60	62.3±5.91
Total	95.6±1.62	98.9±1.57	100.4±0.79	99.9±1.35

Data show the mean values ± S.D. of five rats.

[a]Animals were treated for 14 consecutive days with 2 mg/kg of the unlabeled material prior to the single oral dose of labeled material.

[b]Animals were treated 14 consecutive days with 5 ml/kg of corn oil prior to the single dose of the labeled material.

Source: Tables 3-1 through 3-4, pp. 59-62.

Table 2. Selected ^{14}C-Tissue Residues in Male and Female Rats on the 7th Day After Single Oral Administration of t-[Tetrahydrophthalolyl-1,2-^{14}C] Tetramethrin

	PPB (ng tetramethrin equivalents/ g tissue)							
	2 mg/kg		250 mg/kg (10^2ng equivalent)		2 mg/kg[a]		2 mg/kg[b]	
Tissue	Male	Female	Male	Female	Male	Female	Male	Female
Blood Cell	34.8±2.23	45.7±4.57	80.9±18.51	99.7±23.78	53.9±5.84	56.7±4.38	47.3±6.80	60.7±18.31
Blood	16.2±2.56	23.8±2.74	38.0±5.69	50.5±10.47	25.2±4.18	29.1±3.23	23.6±1.96	25.3±0.96
Hair	43.9±18.64	50.2±55.32	73.7±117.74	17.8±12.60	18.2±3.75	40.0±29.77	55.9±65.67	20.5±17.72
Kidney	3.9±0.34	4.9±0.27	7.0±1.38	8.3±1.34	6.7±0.50	6.7±0.99	5.8±1.10	5.6±0.85
Liver	3.6±1.47	3.1±0.35	6.0±1.24	5.8±1.15	4.4±0.22	4.3±1.38	3.7±0.30	3.5±0.59
Lung	4.0±1.60	5.1±0.63	6.9±1.49	9.4±2.05	5.2±0.66	5.9±1.16	4.2±0.49	4.6±0.50
Skin	21.4±9.99	20.7±13.41	13.1±9.82	8.7±6.04	14.9±7.13	36.3±21.11	28.2±27.19	10.2±10.64
Spleen	4.0±0.51	6.1±1.05	7.7±2.08	9.6±1.96	5.8±0.63	7.1±1.62	6.0±0.58	6.4±0.57
Thyroid	18.8±6.46	57.1±29.04	22.2±9.36	58.7±24.67	29.1±7.11	68.4±20.56	15.6±2.96[c]	44.2±0.92
	Residues Expressed as Percent of Administered Dose							
Blood	0.052	0.077	0.090	0.124	0.077	0.086	0.074	0.076
Total[d]	0.224	0.232	0.271	0.294	0.369	0.339	0.321	0.214

[a]Radiolabeled material was administered after 14 consecutive day doses of nonlabeled t-tetramethrin at 2 mg/kg/day.

[b]Radiolabeled material was administered after 14 consecutive day doses of corn oil at 5 ml/kg/day.

[c]Figure represents mean values ± S.D. of two rats.

[d]Total represents the values of all tissues evaluated.

Source: Tables 4-1 through 4-4, pp. 63-66

GUIDELINE SERIES 85-1: Metabolism

TABLE 3. Distribution of Metabolites in Urine and Feces Within 2 days After Oral Administration of ξ-Tetramethrin[a]

	2 mg/kg (single oral)				250 mg/kg (single oral)				2 mg/kg (single oral[a])				2 mg/kg (single oral[b])			
	Male		Female		Male		Female		Male		Female		Male		Female	
Metabolites	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine
ξ-MFY	23.21	--	4.76	--	20.75	--	10.26	--	0.66	--	1.20	--	1.80	--	2.17	--
Unknown-29	--	--	--	--	0.09	--	0.08	--	--	--	--	--	--	--	--	--
Unknown-1	0.19	--	0.06	--	0.13	--	0.07	--	0.01	--	0.02	--	0.01	--	0.02	--
Unknown-30	--	--	--	--	0.05	--	0.03	--	--	--	--	--	--	--	--	--
TPI	0.25	0.20	0.10	0.20	0.95	0.18	0.33	0.28	0.07	0.26	0.04	0.31	0.04	0.40	0.07	0.31
Unknown-2	0.22	--	0.05	--	0.23	--	0.11	--	0.02	--	0.01	--	0.01	--	0.02	--
Unknown-3	0.13	--	0.04	--	0.03	--	0.03	--	0.01	--	0.01	--	0.01	--	0.01	--
Unknown-4	0.06	--	0.02	--	0.09	--	0.04	--	0.01	--	0.00	--	0.01	--	0.02	--
MTI	0.26	--	0.05	--	0.44	--	0.17	--	0.03	--	0.02	--	0.06	--	0.06	--
Unknown-5	--	0.21	--	0.66	--	0.24	--	0.70	--	0.45	--	0.96	--	0.53	--	1.20
Unknown-6	0.03	--	0.02	--	0.04	--	0.02	--	0.01	--	0.01	--	0.03	--	0.03	--
Unknown-7	0.04	--	0.09	--	0.06	--	0.08	--	0.04	--	0.04	--	0.07	--	0.09	--
TFAM	0.15	--	0.07	--	0.65	--	0.35	--	0.09	--	0.05	--	0.08	--	0.07	--
TCDA	0.29	0.87	0.48	0.96	0.16	1.05	0.18	1.33	1.06	1.45	0.88	1.57	0.69	1.74	1.21	1.71
THPA	0.47	1.69	0.31	2.49	0.74	1.88	0.63	2.68	0.24	2.69	0.14	2.65	0.25	3.24	0.32	2.51
Unknown-8	--	0.71	--	1.16	--	0.74	--	1.14	--	0.63	--	1.18	--	0.18	--	0.38
Unknown-9	--	0.43	--	0.70	--	0.56	--	1.53	--	0.33	--	0.63	--	0.18	--	0.42
3-OH-MPI-2	--	0.73	--	0.54	--	0.47	--	0.50	--	0.54	--	0.78	--	0.55	--	0.97
3-OH-MPI-1	0.23	13.28	0.14	16.98	0.39	13.04	0.42	15.12	0.39	15.29	0.18	23.12	0.20	11.01	0.23	12.58
Unknown-10	--	2.45	--	2.13	--	2.23	--	2.73	--	3.80	--	3.94	--	5.12	--	3.39
1-OH-5-o-MPA	0.67	1.33	0.79	2.16	1.06	0.65	0.82	0.98	0.86	2.52	0.41	0.89	0.62	2.54	0.74	0.00
Unknown-12	--	1.15	--	1.31	--	1.12	--	2.46	--	1.79	--	3.18	--	3.02	--	2.31
Unknown-14	--	0.80	--	2.07	--	0.71	--	0.57	--	3.42	--	4.19	--	3.03	--	4.00
Unknown-16	--	1.72	--	2.67	--	2.10	--	2.70	--	2.76	--	2.81	--	2.11	--	2.22
Unknown-17	--	1.59	--	2.70	--	1.49	--	3.10	--	2.78	--	2.62	--	1.38	--	3.48
Unknown-18	0.30	1.12	0.24	1.63	0.30	1.12	0.31	1.97	0.31	2.27	0.21	2.47	0.22	3.41	0.28	2.52
Acid-MFY-SA	0.62	1.75	0.54	2.71	1.63	1.90	1.11	2.94	0.61	2.66	0.48	2.45	0.77	4.18	0.53	3.60
1-OH-MPA	0.38	1.31	0.19	2.00	0.72	1.67	0.74	2.36	0.56	2.57	0.27	2.43	0.56	2.35	0.51	2.40
A-3-OH-MFY-SA	1.05	--	1.09	--	1.71	--	1.12	--	0.74	--	0.59	--	0.91	--	0.88	--
Unknown-20	--	1.31	--	1.89	--	0.91	--	1.69	--	2.42	--	2.35	--	2.02	--	1.89
Unknown-21	0.42	--	0.22	--	0.68	--	0.42	--	0.53	--	0.34	--	0.54	--	0.41	--
Unknown-22	--	0.90	--	1.21	--	1.02	--	1.25	--	1.26	--	1.26	--	2.02	--	1.96
Unknown-23	0.48	--	1.37	--	0.50	--	0.25	--	0.57	--	0.66	--	0.37	--	0.35	--
Unknown-24	--	1.18	--	2.13	--	0.72	--	1.43	--	1.37	--	1.19	--	2.19	--	1.73
TPI-SA	10.75	0.39	13.40	0.81	7.23	0.14	6.45	0.43	18.71	1.24	12.62	1.04	18.52	0.36	17.02	0.58
Unknown-25	--	2.50	--	2.28	--	4.15	--	3.70	--	2.90	--	2.23	--	1.67	--	2.20
Unknown-26	1.51	--	1.83	--	2.70	--	1.80	--	1.70	2.13	--	2.13	1.36	--	1.69	--
3-OH-MTI-SA	1.50	--	2.83	--	1.63	--	1.17	--	2.07	--	2.32	--	2.35	--	2.46	--

GUIDELINE SERIES 85-1: Metabolism

TABLE 3 (Continued)

	2 mg/kg (single oral)				250 mg/kg (single oral)				2 mg/kg (single oral[b])				2 mg/kg (single oral[c])			
	Male		Female		Male		Female		Male		Female		Male		Female	
Metabolites	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine
Unknown-28	1.43	--	1.30	--	1.13	--	1.15	--	1.98	--	1.27	--	1.62	--	1.71	--
Unknown-31	--	--	--	--	0.14	--	0.07	--	--	--	--	--	--	--	--	--
Unknown-32	--	--	0.04	--	0.04	--	0.04	--	0.03	--	--	--	--	--	--	--
Unknown-33	--	--	--	--	0.05	--	0.04	0.04	--	--	--	--	--	--	--	--
Unknown-34	--	--	--	--	0.08	--	0.06	--	--	--	--	--	--	--	--	--
Unknown-35	--	--	--	--	0.08	--	0.06	--	--	--	--	--	--	--	--	--
Unknown-36	--	--	--	--	0.04	--	0.04	--	--	--	--	--	--	--	--	--
Unknown-37	--	--	--	--	0.09	--	0.06	--	--	--	--	--	--	--	--	--
Unknown-38	--	--	--	--	0.03	--	0.06	--	--	--	--	--	--	--	--	--
Others	1.78	4.08	1.56	5.70	3.39	4.29	2.98	5.82	1.34	6.40	0.54	6.20	1.24	5.85	1.00	6.29
Unextract.	6.25	--	5.84	--	8.50	--	7.80	--	5.97	--	4.15	--	6.05	--	5.37	--
Total	52.67	41.72	37.44	57.07	56.50	42.38	39.36	57.42	38.63	61.80	28.60	70.46	38.41	59.09	37.28	61.23

[a]Values given as percentage of administered dose

[b]Radiolabeled material was administered after 14 consecutive days of dosing with nonlabeled t-tetramethrin at 2 mg/kg/day.

[c]Radiolabeled material was administered after 14 consecutive days of dosing with corn oil at 5 ml/kg/day.

Source: Tables 5-1 through 5-4, pp. 67-70

Table 4. Summary of Radioactive Metabolites in Urine and Fecal Extracts Combined[a]

	% of Total Administered Radioactivity							
	Low		High		Repeated		Control	
Dose Groups	M	F	M	F	M	F	M	F
Total Excreted ^{14}C	95.3	95.7	101.0	98.9	101.4	100.5	98.5	99.9
Metabolites								
t-NPY (Parent)	23.2	4.8	20.8	10.3	0.7	1.2	1.8	2.2
TPI	0.5	0.4	1.1	0.6	0.3	0.4	0.5	0.4
MTI	0.3	0.1	0.4	0.2	0.0	0.0	0.1	0.1
THAM	0.2	0.1	0.7	0.4	0.1	0.1	0.1	0.1
TCDA	1.2	1.4	1.2	1.5	2.5	2.5	2.5	2.9
THPA	2.2	2.8	2.6	3.3	2.9	2.8	3.5	2.8
3-OH-HPI-1	13.5	17.1	13.4	15.5	15.7	23.3	11.2	12.6
3-OH-HPI-2	0.7	0.5	0.5	0.5	0.5	0.8	0.6	1.0
1-OH-5-oxo-HPA	2.0	3.0	1.7	1.8	3.4	1.3	3.2	0.7
Acid-NPY-SA	2.4	3.3	3.5	4.1	3.3	2.9	5.0	4.1
1-OH-HPA	1.7	2.2	2.4	3.1	3.1	2.7	2.9	2.9
A-3-OH-NPY-SA	1.1	1.1	1.7	1.1	0.7	0.6	0.9	0.9
TPI-SA	11.1	14.2	7.4	6.9	20.0	13.7	18.9	17.6
3-OH-MTI-SA	1.5	2.8	1.6	1.2	2.1	2.3	2.4	2.5
Identified metabolites	61.6	53.8	59.0	50.5	55.3	54.6	53.6	50.8
Unknown metabolites	26.5	34.9	31.4	38.5	39.1	40.3	37.8	42.3
Unextractable	6.3	5.8	9.0	7.8	6.0	4.2	6.1	5.4
Total	94.4	94.5	98.9	96.8	100.4	99.1	97.5	98.5

[a]Data shows the sum of the amounts of 33 metabolites.

Source: Tables 5-1 through 5-4, pp. 67-70

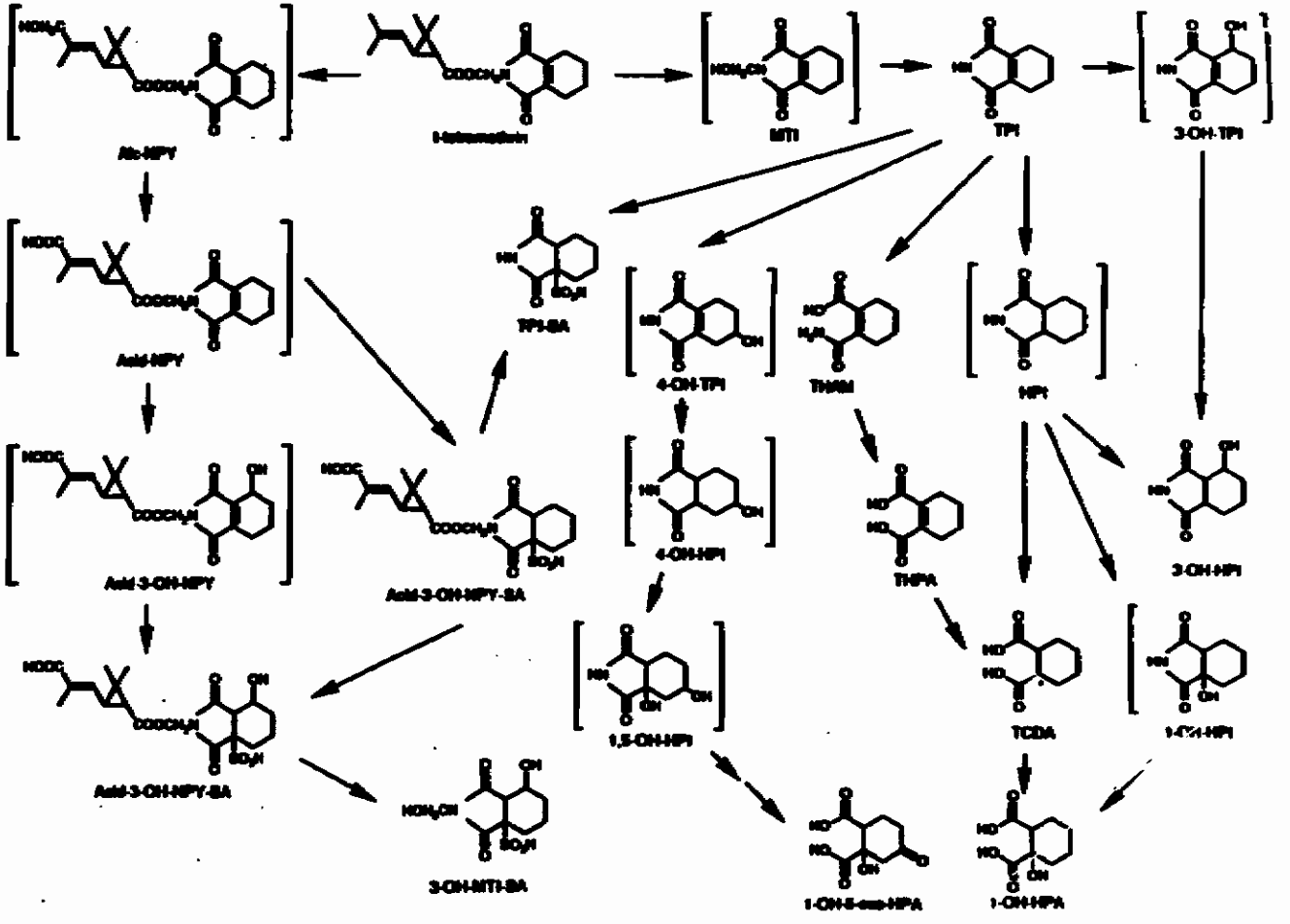
TABLE 5. Chemical Names and Abbreviations of Tetramethrin Isomers Identified in Urine and Feces

Metabolite Code	Chemical Name
*t-NPY (Parent)	3,4,5,6-tetrahydrophthalimidomethyl (1RS, trans)-chrysanthemate (Parent)
*MTI	N-(hydroxymethyl)-3,4,5,6-tetrahydrophthalimide
THPA	3,4,5,6-tetrahydrophthalic acid
TPI	3,4,5,6-tetrahydrophthalimide
*THAM	2-carboxy-3,4,5,6-tetrahydrobenzamide
TCDA	trans-1,2-cyclohexanedicarboxylic acid
3-OH-HPI-1	3-hydroxy-1,2-cyclohexanedicarboximide
**3-OH-HPI-2	3-hydroxy-1,2-cyclohexanedicarboximide
1-OH-HPA	1-hydroxy-1,2-cyclohexanedicarboxylic acid
1-OH-5-o-HPA	1-hydroxy-5-oxo-1,2-cyclohexanedicarboxylic acid
TPI-SA	1-sulfo-1,2-cyclohexanedicarboximide
Acid-NPY-SA	1-sulfo-1,2-cyclohexanedicarboximidomethyl (1RS, trans) -3-(2'-E-carboxy-1'-propenyl)-2,2-dimethyl-1-cyclopropane-carboxylate
*Acid-3-OH-NPY-SA	3-hydroxy-1-sulfo-1,2-cyclohexanedicarboximidomethyl (1RS, trans)-3-(2'-E-carboxy-1'-propenyl)-2,2-dimethyl-1-cyclopropanecarboxylate
*3-OH-MTI-SA	N-(hydroxymethyl)-3-hydroxy-1-sulfo-1,2-cyclohexanedicarboximide

* Detected in the feces only
** Detected in urine only

Source: Table I, pp. 57

FIGURE 1. Proposed Metabolic Pathway of 1 RS trans-Tetramethrin in Rats (refer to Table 5 for the chemical names of the metabolites)



Source: Figure 1, p. 73

END