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Received for review November 30, 1981. Accepted March 22, 1982. Presented in part as paper 73, Division of Pesticide Chemistry, at the 182nd National Meeting of the American Chemical Society, New York, NY, Aug 1981. Supported in part by the National Institutes of Health (Grant 5 P01 ES00049).

Pyrethroid Metabolism: Comparative Fate in Rats of Tralomethrin, Tralocythrin, Deltamethrin, and (1*R*,α*S*)-*cis*-Cypermethrin

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The insecticides tralomethrin and tralocythrin, (*S*)-α-cyano-3-phenoxybenzyl *cis*-(1*R*,3*R*,1′*R* or *S*)-3-(1,2-dibromo-2,2-dihaloethyl)-2,2-dimethylcyclopropanecarboxylates, were compared with deltamethrin and (1*R*,α*S*)-*cis*-cypermethrin relative to their distribution, excretion, metabolic fate, and tissue residues following oral administration to male rats. Tralomethrin and tralocythrin are not normally detected in treated animals or their excreta since they undergo rapid and essentially complete debromination to form deltamethrin and (1*R*,α*S*)-*cis*-cypermethrin, respectively. Deltamethrin and cypermethrin are then hydroxylated at the 2′, 4′, and 5 positions of the alcohol moiety and the methyl group trans to the carboxylate linkage. Extensive ester cleavage reactions for deltamethrin and cypermethrin and further metabolism of the cleavage products yield the expected series of alcohols and carboxylic acids and their glucuronide, glycine, and sulfate conjugates. The cyano fragment is retained several days in the stomach and skin. Toxicity studies with mice provide evidence that intracerebrally administered tralomethrin and tralocythrin may be activated by debromination in the brain.

Tralomethrin and tralocythrin (proposed common names) are potent pyrethroids (Roussel-Uclaf, 1978) that differ from the established deltamethrin and cypermethrin in having 3-tetrahaloethyl substituents instead of 3-dihalovinyl groups (Figure 1). The 1*R*,α*S*-cis configuration confers the highest insecticidal potency, and esters with the *R* and *S* configurations at the 1′ center of the 3 side chain are comparable in activity (Ackermann et al., 1980). Tralomethrin and tralocythrin are rapidly converted to deltamethrin and cypermethrin, respectively, in insects (Ruzo et al., 1981) and on irradiation with light (Ruzo and Casida, 1981).

The present study compares the distribution and metabolism of tralomethrin and tralocythrin in rats with those known for deltamethrin and cypermethrin in rats and mice (Crawford et al., 1981; Hutson et al., 1981; Ruzo et al., 1978, 1979).

MATERIALS AND METHODS

Chemicals. Tralomethrin, tralocythrin, deltamethrin, and (1*R*,α*S*)-*cis*-cypermethrin were supplied by Roussel-Uclaf (Paris, France) as unlabeled samples and as ^{14}C-labeled compounds of 40–60 mCi/mmol labeled in separate preparations in each of the benzylic methine (alcohol-^{14}C), geminal dimethyl (acid-^{14}C), and cyano (^{14}CN) positions. Thin-layer chromatography (TLC) on silica gel (see below) with toluene–carbon tetrachloride (6:1) (two developments) was used to obtain 1′*R* (lower R_f component), 1′*S* (higher R_f component), and 1′*RS* samples of >99% radiochemical purity at the time of use (Ackermann et al., 1980; Ruzo and Casida, 1981).

Metabolites are designated as shown in Figure 1, e.g., 4′-hydroxy and *trans*-hydroxy derivatives are hydroxylated at the 4′ position of the phenoxybenzyl moiety and the methyl trans to the carboxyl group, respectively, and ITCA is 2-iminothiazolidine-4-carboxylic acid. Standard unlabeled compounds for tentative metabolite identification are previously described (Ruzo and Casida, 1981; Ruzo et al., 1978; Unai and Casida, 1977). Although not shown in Figure 1, X_4CA refers to the free acid moieties of tralomethrin and tralocythrin.

Treatment of Rats and Determination of Radiocarbon in Excreta and Tissues. Male albino Sprague-Dawley rats (160–170 g, Simonsen Laboratories, Gilroy, CA) fasted for 18 h were individually treated by stomach tube with each labeled compound dissolved in a mixture of diethyl ether (75 μL) and partially hydrogenated soybean oil (Crisco oil) (150 μL); the stomach tube was then rinsed with soybean oil (100 μL). The treated rats were held in all-glass metabolism cages (Gaughan et al., 1977) for collection of urine and feces for 7 days (all compounds) and of expired $^{14}CO_2$ for 48 h (^{14}CN-labeled compounds only) in sequential traps of 10% KOH and a monoethanolamine–methyl-Cellosolve mixture (1:2). Procedures for radiocarbon quantitation by liquid scintillation counting (LSC) are given by Ueda et al. (1975).

Urine was analyzed directly by LSC. Feces (0–24-h wet or fresh samples) were extracted with cold ether (10 mL/g)

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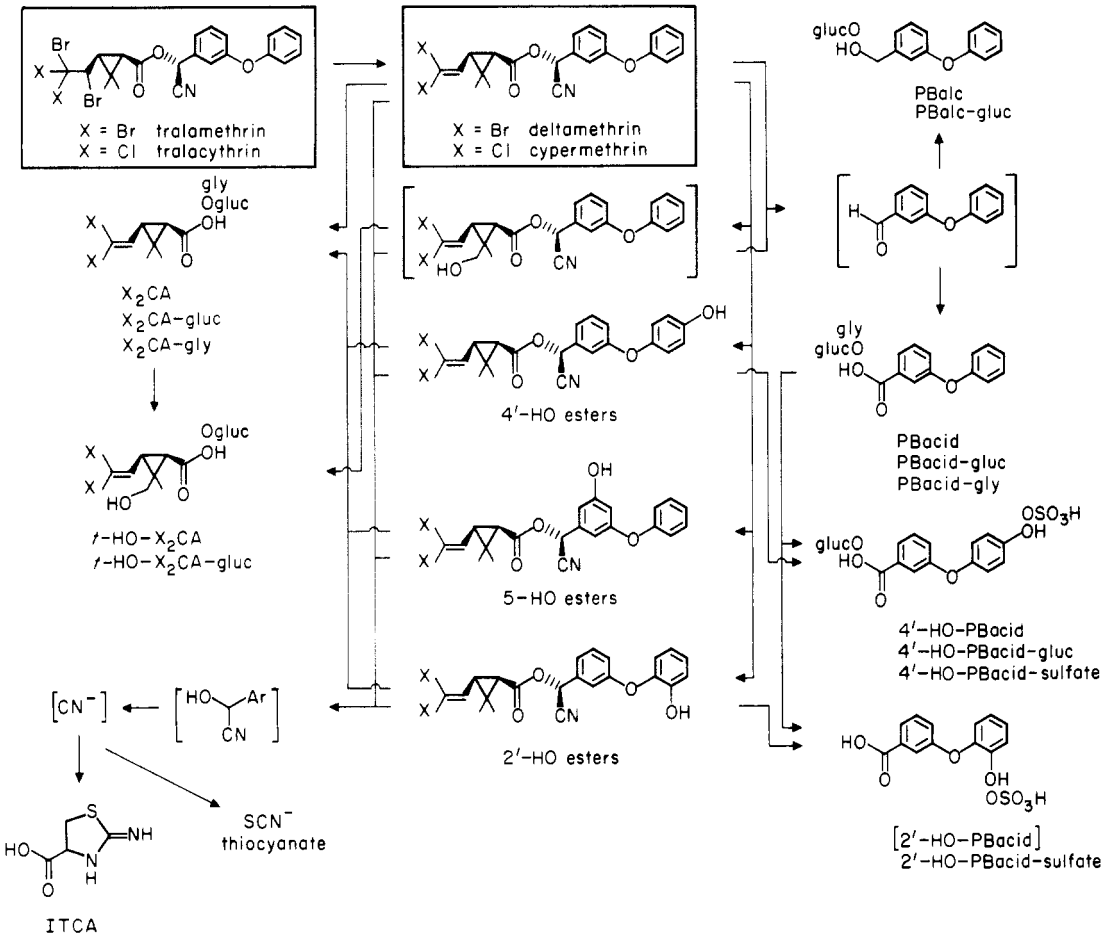

Figure 1. Metabolic pathways in rats for tralomethrin, tralocythrin, deltamethrin, and (1*R*,α*S*)-*cis*-cypermethrin. Tralomethrin and tralocythrin are proposed common names of Roussel-Uclaf. Conjugates are designated as gluc for glucuronides and gly for glycine conjugates. Glucuronides of dihydroxy compounds are arbitrarily indicated with the conjugating moiety at the carboxylic acid position. Compounds shown in brackets although not detected are likely intermediates to identified metabolites. Cyanohydrin and aldehyde intermediates to benzoic acid derivatives are often omitted. Ar = 3-phenoxyphenyl.

by homogenization with a Polytron homogenizer and then reextracted with methanol. Later feces samples (1–7 days) were extracted directly with methanol (10 mL/g) and then soaked overnight in a second portion of methanol. The radiocarbon contents of the ether and combined methanol extracts were determined by LSC and of the unextractable residues by combustion and then LSC (Gaughan et al., 1977). Excreted radiocarbon is expressed as percent of the recovered dose.

Tissue samples at 7 days were analyzed by combustion as previously described (Gaughan et al., 1977) to determine total residues (unidentified compounds) as parts per billion (ppb) equivalents of the administered compound based on tissue wet weights.

In separate studies, rats and male albino mice (18–22 g, Simonsen) were treated with the pyrethroid in soybean oil (as above with ether for solubilization) administered orally, intraperitoneally (ip), or dermally to obtain feces or tissue samples for analysis.

Metabolite Analysis and Chromatography. *Cochromatography and Derivatization.* Compounds retaining the ester linkage were recognized by their identical TLC positions with the three labeled preparations and identified according to the procedures previously reported (Ruzo et al., 1978, 1979). Unconjugated metabolites were subjected to direct cochromatography with authentic standards from synthesis, usually with confirmation of structure by appropriate derivatization (methylation of phenols and carboxylic acids with diazomethane; conversion of thiocyanate to *p*-nitrobenzyl thiocyanate) and degradation procedures (acid and base hydrolysis). Conjugates were subjected to direct cochromatography when standards were available. They were also cleaved by appropriate enzymes, acid, and base and then cochromatographed with the cleavage products with and without methylation as previously described (Gaughan et al., 1977; Ruzo et al., 1978, 1979).

Chromatography. TLC utilized precoated silica gel 60 F254 chromatoplates with 0.25-mm gel thickness (EM Laboratories, Elmsford, NY) and the following solvent systems: A, butanol–acetic acid–water (6:1:1); B, toluene (saturated with formic acid)–ether (10:3), two developments; C, toluene–ethyl acetate (6:1); D, hexane–ether (1:1); E, toluene–carbon tetrachloride (1:1), two developments; F, hexane–ether (4:1), three developments. Procedures for visualization of unlabeled standards, radioautography, and cochromatography are given by Ueda et al. (1975), Gaughan et al. (1977), Ruzo et al. (1978), and Hutson et al. (1981).

Urinary and Fecal Metabolites. For separation and quantitation of urinary metabolites an aliquot (50 μL) was subjected directly to two-dimensional TLC (A × B), radioautography, and LSC. For identification individual ^{14}C-labeled metabolites isolated in the A × B system were extracted from the appropriate gel regions with methanol. Metabolites in feces extracts were tentatively identified by two-dimensional cochromatography in neutral solvent systems (C × D and E × F) (for esters) and one-dimensional cochromatography using an acidic solvent system (B) (for other metabolites). Solvent system E × F sepa-

Table I. Radiocarbon in the Urine, Feces, and Carbon Dioxide of Male Rats Up to Seven Days after Oral Administration of Tralomethrin and Deltamethrin, Each ^{14}C Labeled in the Acid, Alcohol, and Cyano Moieties

	acid-^{14}C label		alcohol-^{14}C label		^{14}CN label	
sample analyzed	tralo-methrin	delta-methrin	tralo-methrin	delta-methrin	tralo-methrin	delta-methrin
Administered Dose, Milligrams per Kilogram Tralomethrin or Deltamethrin Equivalent						
	0.30	0.29	0.32	0.32	0.32	0.49
Percent of Administered Dose						
urine						
0-1 day	45.8	46.3	34.2	49.0	4.2	3.9
1-3 days	10.1	9.4	6.4	14.1	3.1	5.2
3-5 days	2.2	3.3	1.3	1.5	3.1	6.7
5-7 days	1.6	1.8	0.7	0.6	2.1	7.3
feces						
ether-methanol extract						
0-1 day	27.6	27.5	44.0	28.0	27.5	2.5
1-3 days	3.3	3.1	2.9			4.2
3-5 days	0.6	0.5	0.3	1.0	1.5	2.7
5-7 days	0.5	0.2	0.2	0.5	0.7	3.5
unextractable, 0-7 days	7.2	6.9	8.6	3.1	35.7	8.9
carcass and tissues, 7 days	1.1	1.0	1.4	2.2	22.0	55.0
CO_2, 0-2 days					0.1	0.1

Table II. Radiocarbon in the Urine, Feces, and Carbon Dioxide of Male Rats Up to Seven Days after Oral Administration of Tralocythrin and Cypermethrin, Each ^{14}C Labeled in the Acid, Alcohol, and Cyano Moieties

	acid-^{14}C label		alcohol-^{14}C label		^{14}CN label	
sample analyzed	tralo-cythrin	cyper-methrin	tralo-cythrin	cyper-methrin	tralo-cythrin	cyper-methrin
Administered Dose, Milligrams per Kilogram Tralocythrin or Cypermethrin Equivalent						
	0.21	0.13	0.19	0.12	0.51	0.67
Percent of Administered Dose						
urine						
0-1 day	45.5	36.5	42.9	53.5	3.8	6.8
1-3 days	11.6	12.7	10.2	7.6	3.1	7.9
3-5 days	2.1	1.6	2.2	1.2	3.1	7.2
5-7 days	1.2	0.7	1.0	0.6	2.1	4.7
feces						
ether-methanol extract						
0-1 day	25.6	34.4	24.6	25.5	29.0	23.0
1-3 days	1.8	6.9	1.6	3.4		9.2
3-5 days	0.2	0.7	0.2	0.8	0.5	2.2
5-7 days	0.3	0.2	0.3	0.2		1.0
unextractable, 0-7 days	11.2	4.9	15.0	3.9	36.3	10.0
carcass plus tissues, 7 days	0.5	1.4	2.0	3.3	22.0	27.1
CO_2, 0-2 days					0.1	0.9

rates (1′*R*)- and (1′*S*)-tralomethrin and deltamethrin and in an analogous manner (1′*R*)- and (1′*S*)-tralocythrin and cypermethrin.

Intracerebral Toxicity in Mice. The test compound was administered intracerebrally (ic) in 3μL of methoxytriglycol injected between the cerebrum and midbrain, with mortality determinations 24 h later (Lawrence and Casida, 1982).

RESULTS

Radiocarbon in Urine, Feces, and Carbon Dioxide of Rats after Oral Administration of ^{14}C-Labeled Tralomethrin, Tralocythrin, Deltamethrin, and Cypermethrin. Radiocarbon from the acid-^{14}C-labeled and alcohol-^{14}C-labeled preparations is rapidly excreted with similar patterns for tralomethrin and deltamethrin (Table I) and for tralocythrin and cypermethrin (Table II). These labeled preparations generally give more urinary than fecal radiocarbon and almost complete elimination from the body within 7 days. The corresponding values for individual isomers (i.e., 1′*R* or 1′*S*) of tralomethrin and tralocythrin are similar to those for the 1′*RS* mixture [for data see Tables I and II of the supplementary material (see paragraph at end of paper regarding supplementary material)]. There is one possible difference between the tetrahaloethyl and dihalovinyl compounds; i.e., the unextractable ^{14}C in feces generally appears to be slightly greater for tralomethrin and tralocythrin than for deltamethrin and cypermethrin, respectively.

The cyano fragment is eliminated more slowly, with 0.1–0.9% $^{14}CO_2$ in 48 h and 22–55% ^{14}C retention in the body after 7 days (Tables I and II). The fecal ^{14}C, and particularly the unextractable portion, is higher for tralomethrin and tralocythrin than for deltamethrin and cypermethrin, respectively.

Radiocarbon in Tissues of Rats after Oral Administration of ^{14}C-Labeled Tralomethrin, Tralocythrin, Deltamethrin, and Cypermethrin. Tissue residues (unidentified compounds) for the acid-^{14}C and alcohol-^{14}C doses are highest at 7 days for the fat (4–31 ppb) with other tissues usually below 3 ppb and without remarkable differences between any of the compounds examined for any particular tissue (Tables III and IV; see also Tables III and IV of the supplementary material). The ^{14}CN compounds generally give tissue retention except in fat at least 10-fold greater than that obtained with other labels, irrespective of the compound used, with the highest levels in skin, hair, stomach, and blood (Tables III and IV; see also Tables III

Table III. Radiocarbon in the Tissues of Male Rats Seven Days after Oral Administration of Tralomethrin and Deltamethrin, Each ^{14}C Labeled in the Acid, Alcohol, and Cyano Moieties

	ppb of tralomethrin or deltamethrin equiv					
	acid-^{14}C label		alcohol-^{14}C label		^{14}CN label	
sample analyzed	tralomethrin	deltamethrin	tralomethrin	deltamethrin	tralomethrin	deltamethrin
blood	1.8	1.3	1.5	2.2	107	258
bone	0.6	1.5	0.6	0.5	48	54
brain	0.9	0.6	0.1	0.2	6.7	6.8
fat	24	25	30	31	49	132
hair	3.9	2.6	1.8	1.5	201	170
heart	0.3	0.8	0.4	0.3	45	144
intestine						
large	1.3	1.4	2.3	0.7	26	28
small	2.1	2.1	1.5	1.8	58	47
kidney	1.0	2.0	1.2	0.6	67	73
liver	3.0	3.7	1.6	1.5	62	59
lung	1.2	0.9	0.6	0.3	75	336
muscle	0.6	2.0	0.5	0.3	32	38
skin plus hair	2.9	6.2	4.6	4.7	304	617
spleen	0.7	0.4	0.3	0.7	44	111
stomach	1.2	0.8	1.1	3.8	201	174
testes	0.5	0.7	0.9	1.2	38	47

Table IV. Radiocarbon in the Tissues of Male Rats Seven Days after Oral Administration of Tralocythrin and Cypermethrin, Each ^{14}C Labeled in the Acid, Alcohol, and Cyano Moieties

	ppb of tralocythrin or cypermethrin equiv					
	acid-^{14}C label		alcohol-^{14}C label		^{14}CN label	
sample analyzed	tralocythrin	cypermethrin	tralocythrin	cypermethrin	tralocythrin	cypermethrin
blood	3.8	0.9	3.4	1.7	43	145
bone	0.9	1.0	1.1	0.5	23	77
brain	0.3	0.7	0.5	0.2	3	10
fat	23	4	18	9	34	89
hair	1.8	0.3	1.6	0.3	222	1987
heart	0.8	0.3	1.1	0.3	21	68
intestine						
large	1.4	0.6	1.3	0.6	13	16
small	1.1	0.3	2.0	0.3	15	25
kidney	1.1	0.6	2.6	0.4	21	53
liver	3.1	1.0	2.8	0.6	21	57
lung	1.1	0.5	2.2	0.6	40	62
muscle	0.4	0.3	2.2	0.1	12	40
skin plus hair	2.0	1.3	4.3	1.6	196	124
spleen	0.7	0.6	1.5	0.4	21	53
stomach	1.0	0.2	0.6	0.7	111	949
testes	0.6	0.6	1.3	0.3	20	42

and IV of the supplementary material). In rats or mice administered [^{14}CN]deltamethrin, the stomach ^{14}C retention is largely attributable to [^{14}C]thiocyanate (Ruzo et al., 1978, 1979).

Metabolites Retaining Ester Linkage in Feces of Rats. Each pyrethroid examined yields products retaining the ester linkage in the feces but not in the urine (Tables V–VIII; see also Tables VA, VB, VIA, and VIB of the supplementary material). Tralomethrin and tralocythrin are not recovered in the excreta but appear as their debrominated derivatives, deltamethrin and cypermethrin, respectively (16–34% of dose). The 2′-hydroxy and 5-hydroxy esters appear in almost equal amounts but the 4′-hydroxy compounds are most important, appearing in ~3-fold greater amount (Table VIII). No evidence is available for any dehydrobromination products of the pyrethroids.

Metabolites Derived from Ester-Cleavage Fragments in Urine and Feces of Rats. The acid-^{14}C-labeled preparations yield some fecal dihalovinyl acids (X_2CA and t-HO-X_2CA) in unconjugated form but mostly urinary glucuronides of these acids plus the X_2CA compounds free and as glycine conjugates in urine (Table V). Oxidation of the *trans*-methyl group is a significant process (~6% in all cases). Possible metabolites that are not detected are the tetrahalogenated acids (i.e., X_4CA) from direct hydrolysis and the trihalogenated acids from dehydrobromination.

The major metabolites from the alcohol-^{14}C-labeled pyrethroids (Table VI) is the sulfate conjugate of 4′-HO-PBacid (24–48%). Other compounds identified include PBalc, PBacid, and 4′-HO-PBacid (both free and as their glucuronides), the glycine conjugate of PBacid, and the sulfate conjugate of 2′-HO-PBacid. Most of the ester-cleavage products are in the urine, but some unconjugated metabolites are detected in the feces (Table VI).

The ^{14}CN-labeled pyrethroids yield urinary thiocyanate and ITCA plus unidentified fecal products (Table VII).

Rapid Liberation of Deltamethrin and Cypermethrin on Treatment of Rats or Mice with Tralomethrin and Tralocythrin. Tralomethrin and tralocythrin are not detected in the feces of orally treated rats (Tables V–VIII) due to debromination either prior to excretion or during analysis. These tetrahaloethyl compounds undergo rapid debromination on addition to methanol extracts of rat feces whereas they are much more stable in comparable acetonitrile or ether extracts. On direct application to freshly excreted and mashed rat feces, (1′*S*)-tralomethrin is effectively recovered by ether extraction, i.e., 96 and 85% at 0 and 3 h after application with the remainder being deltamethrin. Some unmetabolized (1′*S*)-tralomethrin and -tralocythrin are recoverable following ip treatment of rats at 1.9 mg/kg by collecting the 0–36-h feces on dry ice and immediately extracting with cold ether, i.e., 1.6 and 0.9% of the administered dose, respectively.

(1′*S*)-Tralomethrin and -tralocythrin administered orally to mice undergo no more than 25% debromination of the material in the stomach within the first hour after dosing. Trace levels of (1′*R*)-tralomethrin appear in the liver and fat of mice 3–24 h following oral or ip treatment with this isomer and analysis by extraction and cleanup methods using acetonitrile and hexane (Marei et al., 1982). On dermal application to shaved mice, (1′*R*)-tralomethrin and -tralocythrin were >50% recoverable on extraction with ether at 0 and 1 h after treatment. (1′*R*)-Tralomethrin and -tralocythrin were almost completely debrominated when added to heparinized mouse blood and immediately extracted with ether. (1′*RS*)-Tralomethrin underwent almost complete debromination on attempted analysis of brains removed within seconds after ic treatment. Thus, a single acetonitrile extraction (3 mL) or two sequential hexane extractions (3 mL × 2) of a brain recovered ~60% of the radiocarbon of which 80% had already undergone debromination to deltamethrin. Fortification of the extracting solvents with 10 μmol of *N*-ethylmaleimide (NEM) did not alter the tralomethrin recoveries from brain.

Intracerebral Toxicity in Mice of (1′*RS*)-Tralomethrin, (1′*RS*)-Tralocythrin, Deltamethrin, and (1*R*,α*S*)-*cis*-Cypermethrin. Similar ic LD_{50} values are obtained for tralomethrin, tralocythrin, and their respective debrominated compounds (Table IX). The onset of symptoms is slightly delayed for tralomethrin compared with deltamethrin (Table X), suggesting that debromina-

Table V. ^{14}C-Labeled Compounds in the Urine and Extracts of Feces of Male Rats Seven Days after Oral Administration of Acid-^{14}C Preparations of Tralomethrin, Deltamethrin, Tralocythrin, and Cypermethrin

compound	% of administered ^{14}C in urine (and feces)			
	tralomethrin	deltamethrin	tralocythrin	cypermethrin
Products Retaining Ester Linkage				
tetrahaloethyl esters	0.0 (0.0)		0.0 (0.0)	
dihalovinyl esters				
nonhydroxylated	0.0 (22.6)	0.0 (15.9)	0.0 (20.4)	0.0 (23.1)
2′-HO	0.0 (1.2)	0.0 (4.3)	0.0 (1.1)	0.0 (2.7)
4′-HO	0.0 (2.1)	0.0 (1.4)	0.0 (3.2)	0.0 (6.5)
5-HO	0.0 (1.3)	0.0 (0.7)	0.0 (1.1)	0.0 (2.2)
Metabolites Derived from Ester-Cleavage Fragments				
X_4CA, free and conj	0.0 (0.0)		0.0 (0.0)	
X_2CA				
free	13.8 (1.2)	32.3 (1.6)	11.0 (0.7)	4.5 (3.1)
glucuronide	32.8 (0.0)	18.3 (0.0)	40.0 (0.0)	39.3 (0.0)
glycine conj	6.0 (0.0)	2.3 (0.0)	0.7 (0.0)	1.8 (0.0)
t-HO-X_2CA				
free	2.2 (1.2)	2.4 (2.4)	2.5 (0.6)	3.3 (1.3)
glucuronide	2.6 (0.0)	2.1 (0.0)	2.9 (0.0)	1.3 (0.0)
unknowns				
free	0.8 (2.1)	1.3 (5.0)	0.0 (0.3)	0.0 (0.0)
origin	1.5 (0.3)	2.1 (0.0)	3.3 (0.5)	1.3 (3.3)
total	59.7 (32.0)	60.8 (31.3)	60.4 (27.9)	51.5 (42.2)

Table VI. ^{14}C-Labeled Compounds in the Urine and Extracts of Feces of Male Rats Seven Days after Oral Administration of Alcohol-^{14}C Preparations of Tralomethrin, Deltamethrin, Tralocythrin, and Cypermethrin

compound	% of administered ^{14}C in urine (and feces)			
	tralomethrin	deltamethrin	tralocythrin	cypermethrin
Products Retaining Ester Linkage				
tetrahaloethyl esters	0.0 (0.0)		0.0 (0.0)	
dihalovinyl esters				
nonhydroxylated	0.0 (34.4)	0.0 (16.5)	0.0 (17.9)	0.0 (20.8)
2′-HO	0.0 (1.6)	0.0 (0.0)	0.0 (1.0)	0.0 (0.0)
4′-HO	0.0 (3.1)	0.0 (6.2)	0.0 (2.9)	0.0 (4.1)
5-HO	0.0 (0.5)	0.0 (1.3)	0.0 (0.8)	0.0 (0.7)
Metabolites Derived from Ester-Cleavage Fragments				
PBalc				
free	2.2 (0.7)	0.0 (0.0)	0.6 (0.5)	0.0 (0.0)
glucuronide	4.3 (0.0)	4.1 (0.0)	4.8 (0.0)	15.4 (0.0)
PBacid				
free	4.7 (0.6)	3.9 (1.0)	7.2 (1.0)	4.9 (1.0)
glucuronide	0.8 (0.0)	<0.1 (0.0)	<0.1 (0.0)	<0.1 (0.0)
glycine conj	2.5 (0.0)	1.7 (0.0)	2.3 (0.0)	1.5 (0.0)
4′-HO-PBacid				
free	1.0 (1.4)	0.9 (1.9)	0.6 (1.2)	1.2 (1.8)
glucuronide	0.7 (0.0)	5.7 (0.0)	1.2 (0.0)	5.4 (0.0)
sulfate	24.3 (0.0)	47.5 (0.0)	35.2 (0.0)	28.7 (0.0)
2′-HO-PBacid				
sulfate	1.0 (0.0)	0.0 (0.0)	2.3 (0.0)	3.3 (0.0)
unknowns	1.1 (5.1)	1.4 (2.6)	2.1 (1.4)	2.5 (1.5)
total	42.6 (47.4)	65.2 (29.5)	56.3 (26.7)	62.9 (29.9)

Table VII. ^{14}C-Labeled Compounds in the Urine and Extracts of Feces of Male Rats Seven Days after Oral Administration of ^{14}CN-Labeled Preparations of Tralomethrin, Deltamethrin, Tralocythrin, and Cypermethrin

compound	% of administered ^{14}C in urine (and feces)			
	tralomethrin	deltamethrin	tralocythrin	cypermethrin
Products Retaining Ester Linkage				
tetrahaloethyl esters	0.0 (0.0)		0.0 (0.0)	
dihalovinyl esters				
nonhydroxylated	0.0 (23.5)	0.0 (4.8)	0.0 (15.7)	0.0 (24.0)
2′-HO	0.0 (0.6)	0.0 (0.4)	0.0 (1.2)	0.0 (0.5)
4′-HO	0.0 (3.1)	0.0 (2.4)	0.0 (4.2)	0.0 (8.0)
5-HO	0.0 (0.3)	0.0 (0.1)	0.0 (1.2)	0.0 (1.2)
Metabolites Derived from Ester-Cleavage Fragments				
SCN^-	11.3 (0.0)	15.3 (0.0)	10.3 (0.0)	14.3 (0.0)
ITCA	1.2 (0.0)	7.8 (0.0)	1.8 (0.0)	12.3 (0.0)
others	0.0 (2.2)	0.0 (5.2)	0.0 (7.2)	0.0 (1.7)
total	12.5 (29.7)	23.1 (12.9)	12.1 (29.5)	26.6 (35.4)

Table VIII. Parent Compounds and Metabolites Retaining the Ester Linkage in Feces of Rats Up to Seven Days after Oral Administration of Tralomethrin, Deltamethrin, Tralocythrin, and Cypermethrin, Each ^{14}C Labeled in the Acid, Alcohol, and Cyano Moieties

compound	% of administered ^{14}C in feces			
	tralomethrin	deltamethrin	tralocythrin	cypermethrin
tetrahaloethyl esters	0.0		0.0	
dihalovinyl esters				
nonhydroxylated	26.8	12.4	18.0	22.6
2'-HO	1.1	1.6	1.1	1.1
4'-HO	2.8	3.3	3.4	6.2
5-HO	0.7	0.7	1.0	1.4

Table IX. Intracerebral Toxicity in Mice of (1'*RS*)-Tralomethrin, Deltamethrin, (1'*RS*)-Tralocythrin, and (1*R*,α*S*)-*cis*-Cypermethrin

compound	LD_{50} rel to brain wt	
	μg/g	nmol/g
tralomethrin	1.6	2.4
deltamethrin	1.2	2.4
tralocythrin	2.0	3.5
cypermethrin	0.6	1.4

Table X. Time until Onset of Symptoms in Mice Treated Intracerebrally with (1'*RS*)-Tralomethrin and Deltamethrin Alone or following *N*-Ethylmaleimide

pyrethroid[a]	onset of symptoms, min[b]	
	−NEM	+NEM[c]
tralomethrin	6.4 ± 2.3	13.8 ± 3.8
deltamethrin	4.8 ± 1.5	8.6 ± 2.5

[a] LD_{50} dose (see Table IX). [b] Values are mean ± standard deviation for four mice. [c] Ic dose of 286 μg/g 5 min before pyrethroid.

tion occurs prior to poisoning. An attempt to block in vivo debromination with NEM [see Ruzo et al., (1981) for in vitro studies] and thereby further delay the onset of symptoms was unsuccessful since NEM delayed the response to deltamethrin as well (Table X).

DISCUSSION

Figure 1 shows the metabolic pathways for tralomethrin, tralocythrin, deltamethrin, and cypermethrin administered orally to rats. The results for tralomethrin are essentially the same as those for deltamethrin and the same applies for tralocythrin and cypermethrin. The findings for deltamethrin and cypermethrin in turn are in agreement with reported rat metabolism data (Crawford et al., 1981; Ruzo et al., 1978) and confirm the importance of both esteratic and oxidative processes in detoxification. Several types of evidence suggest that tralomethrin and tralocythrin undergo rapid initial debromination to deltamethrin and cypermethrin, which are then metabolized by known pathways (Casida and Ruzo, 1980; Crawford et al., 1981). Thus, tralomethrin and tralocythrin are not normally detected in feces, they do not appear as hydroxylated esters, and no X_4CA is detected in the excreta. This is reasonable in view of the ease of debromination of these pyrethroids in insects (Ruzo et al., 1981) and in other systems (Ruzo and Casida, 1981). Tralomethrin and tralocythrin are readily debrominated by tissue thiols, such as glutathione, and by nonenzymatic components in homogenates of houseflies and cabbage looper larvae (Ruzo et al., 1981) and in blood (this study).

Evolution of $^{14}CO_2$ from the compounds examined here is a minor event as is also the case for $^{14}CO_2$ from $^{14}CN^-$ as reported by Ruzo et al. (1978) and confirmed in this study. In contrast, substantial amounts of $^{14}CO_2$ were obtained from [^{14}CN]fenvalerate and also from $^{14}CN^-$ in another laboratory (Ohkawa et al., 1979), a difference possibly related to the strain of rats used.

It is interesting to note the remarkable similarities between the four compounds studied in respect to metabolism, excretion, and tissue distribution. It is apparent that bromo vs. chloro substitution has little, if any, effect on these processes and that due to rapid debromination the metabolic routes for tralomethrin and tralocythrin are essentially identical with those of their debrominated analogues.

ACKNOWLEDGMENT

We thank J. Martel of Roussel-Uclaf for the radioactive compounds and helpful discussions and our laboratory colleague L. J. Lawrence for permission to include his studies on intracerebral toxicity.

Supplementary Material Available: Six tables similar to Tables I–VI of this report but listing the findings separately for 1'*R*, 1'*S*, and 1'*RS* compounds (8 pages). Ordering information is given on any current masthead page.

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Received for review December 28, 1981. Accepted March 25, 1982. This study was supported in part by grants from the National Institutes of Health (Grant P01 ES00049) and Roussel-Uclaf (Paris, France) and a fellowship provided to E.J.W. by the Consejo Nacional de Investigaciones Cientificas y Tecnicas de la Republica Argentina.