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Original Article

Metabolism of Esfenvalerate in Rats and Mice and Effects of Its Isomers on Metabolic Fates of Esfenvalerate

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On single or repeated oral administration of ^{14}C-labeled esfenvalerate [(*S*)-α-cyano-3-phenoxybenzyl (*S*)-2-(4-chlorophenyl)isovalerate] to male and female rats and mice at 2.5 mg/kg or 2.5 mg/kg/day for successive 10 days, radiocarbon was rapidly and almost completely excreted into the urine and feces. ^{14}C tissue residues after single oral administration were generally very low except for in the fat in both rats and mice. Major biotransformation reactions were 1) oxidation at the 2- and 3-positions of the acid moiety and the 2′- and 4′-phenoxy positions of the alcohol moiety, 2) cleavage of ester linkage, and 3) conjugation of the resultant carboxylic acids, alcohols and phenols with glucuronic acid, sulfuric acid, glycine or taurine. Treatment of rats and mice with single or repeated oral doses of a mixture of ^{14}C-esfenvalerate and unlabeled [2*S*, α*R*]-, [2*R*, α*S*]- and [2*R*, α*R*]-isomers of fenvalerate [(*RS*)-α-cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)isovalerate] at the equal ratio revealed that the unlabeled isomers added hardly affected ^{14}C excretion profiles, ^{14}C tissue residues and amounts of metabolites of esfenvalerate, indicating that esfenvalerate behaved independently of other isomers. There were no significant differences in metabolic fates between esfenvalerate and fenvalerate except that ^{14}C fenvalerate labeled in the acid moiety showed slightly higher ^{14}C tissue residues than esfenvalerate, due to formation of cholesteryl (*R*)-2-(4-chlorophenyl)isovalerate from fenvalerate but not from esfenvalerate.

INTRODUCTION

Fenvalerate [S-5602, Sumicidin®, (*RS*)-α-cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)isovalerate] is one of the most potent pyrethroid insecticides and it has four chiral isomers due to the presence of two asymmetric carbons, which are [2*S*,α*S*]-, [2*S*,α*R*]-, [2*R*,α*S*]- and [2*R*,α*R*]-isomers abbreviated as esfenvalerate, Aβ, Bα and Bβ, respectively. Esfenvalerate having the highest insecticidal activity is under a developmental stage. Metabolic fates of racemic fenvalerate have been extensively investigated in rats, mice and dogs by using three preparations labeled with ^{14}C in the acid and alcohol moieties as well as the cyano group.[1-3] Furthermore, the *in vivo* and *in vitro* comparative metabolism studies on the four isomers of fenvalerate showed that there was a significant difference in metabolism among the four isomers.[4-8] That is, of the four isomers, only the Bα-isomer produced a lipophilic conjugate of the acid moiety with cholesterol (CPIA-cholesterol ester), which was somewhat bioaccumulative and persistent in tissues,[4,5] although the four isomers underwent almost the same metabolic fates, except for the formation of CPIA-cholesterol ester from the Bα-isomer.[8] The metabolic fate of esfenvalerate has been investigated in comparative studies of esfenvalerate and fenvalerate,[2] or of the four isomers,[4-8] but metabolism of esfenvalerate itself has never been studied sufficiently.

Pyrethroid insecticides, including fenvalerate, generally have several stereoisomers and, for instance, cypermethrin has as many as eight isomers. In several reports,[9-12] the metabolic fates of each isomer of pyrethroid insecticides are compared, but at present information regarding the interaction of the isomers of pyrethroid insecticides is not available yet. It is unknown whether the behavior of an isomer is independent of other isomers in absorption, excretion and biotransformation processes.

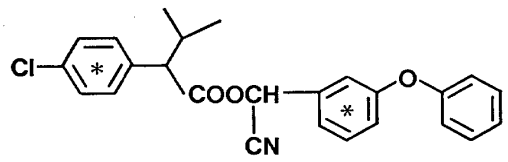
This report describes excretion profiles, tissue residues and quantification of urinary and fecal metabolites after single or 10 consecutive administration of esfenvalerate labeled with ^{14}C in the acid and alcohol moieties to rats and mice. Fenvalerate was also studied as a reference compound. Furthermore, it was investigated if the other isomers (Aβ, Bα and Bβ) have any effects on the metabolism of esfenvalerate when the labeled esfenvalerate preparation are administered concomitantly with the other unlabeled other isomers to rats and mice.

MATERIALS AND METHODS

1. Chemicals

^{14}C-Labeled esfenvalerate and fenvalerate used in this study are listed in Table 1. "^{14}C-alc" and "^{14}C-acid" represent the labeled positions of the phenoxy phenyl and the chlorophenyl ring, respectively. *Esfenvalerate represents ^{14}C-esfenvalerate containing the other three unlabeled isomers (Aβ, Bα and Bβ) at the equal ratio. Their radiochemical purities were more than 99%, determined by TLC. The preparation of unlabeled authentic standards used in this study was reported previously.[1,2,4]

Table 1 Labeled positions and specific activities of ^{14}C-labeled preparations of esfenvalerate, *esfenvalerate[a] and fenvalerate.



* ^{14}C labeled position

Specific activity (mCi/mmol)					
Esfenvalerate		*Esfenvalerate		Fenvalerate	
acid	alcohol	acid	alcohol	acid	alcohol
34.9	35.5	34.9	33.5	34.5	34.0

[a] *esfenvalerate; ^{14}C-esfenvalerate containing 3 unlabeled isomers [(2*S*, α*R*), (2*R*, α*S*) and (2*R*, α*R*)] at the equal ratio.

2. TLC

Precoated silica gel $60F_{254}$ chromatoplates (20×20 cm, 0.25 mm layer thickness, Merck) were used for both analysis and separation of metabolites. The solvent systems used were A) *n*-hexane–toluene–acetic acid (3/15/2, two developments), B) benzene saturated with formic acid–diethyl ether (10/3, two developments), C) 1-butanol–acetic acid–water (6/1/1), and D) petroleum ether–diethyl ether–acetic acid (90/10/1).

Rf values for authentic standards of various metabolites were reported previously.[1,4] The unlabeled standards were detected under ultraviolet light.

3. Radioanalysis and Autoradiography

Liquid scintillation counting (LSC), combustion analysis and TLC autoradiography were performed as reported previously.[13]

4. Treatment of Animals

Six week old Charles River (CD)-derived Sprague-Dawley rats and ddY mice were obtained from Charles River, Japan and Shizuoka Laboratory Animal Center, Shizuoka, Japan, respectively, and were acclimatized for about 7 days prior to use.

These animals were supplied with a diet (CE-2, Clea Japan Inc., Japan) and water *ad libitum* during the experiment.

4.1 Single dose group

Each of the labeled preparations was dissolved in corn oil prior to administration. Both sexes of five SD rats and five ddY mice received a single oral dose of each of ^{14}C-acid- or ^{14}C-alc-esfenvalerate and *esfenvalerate at 2.5 mg/kg (10 mg/kg fenvalerate equivalent). Similarly ^{14}C-acid- or ^{14}C-alc-fenvalerate was orally given to the animals at 10 mg/kg. The administered volume was 5 ml/kg throughout

this study.

4.2 Ten consecutive dose group

Both sexes of five ddY mice at the age of 7 weeks old received daily a single oral dose of ^{14}C-acid-esfenvalerate, *esfenvalerate or fenvalerate at the rates of 2.5, 2.5 or 10 mg/kg/day, respectively for consecutive 10 days.

The treated rats and mice were kept in all-glass metabolism cages (Metabolica CO-2®, Sugiyamagen Iriki Co., Ltd., Tokyo, Japan), and the urine and feces were collected separately for 7 days (single dose groups) or for 16 days (10 consecutive dose groups). Expired air was not trapped because in a previous test no $^{14}CO_2$ was exhaled in the expired air.[1] The treated animals were sacrificed 7 days after a single oral dose or 7 days after the last shot of 10 consecutive doses and major tissues were excised to determine total radiocarbon by combustion and LSC. Tissue residue levels were given as parts per billion equivalents (ppb) of the administered ^{14}C-labeled preparations based on wet tissue weight.

5. Analysis of Excreta

Each of the 0–2 day (single oral dose) and 0–4, 4–8 and 8–11 day (consecutive dose) urine was directly subjected to radioanalysis.

Each of the 0–2 day (single oral dose) and 0–4, 4–8 and 8–11 day (consecutive dose) feces was homogenized three times with acetone–water (9/1) by using an Excel Auto Homogenizer (Nihon Seiki, Tokyo, Japan), the homogenates were filtered, and then the extracts and residues were radioassayed. The acetone extracts were each combined and then subjected to TLC analysis after concentration with a rotary evaporator at 30–40°C. The 3–7 day (single oral dose) and 11–16 day (consecutive dose group) feces were homogenized with water by a Polytron® (Kinematica, Switzerland) and aliquots of the homogenates were combusted prior to LSC.

6. Analysis of Metabolites in Excreta

The acetone extracts of feces, urine and conjugated metabolites were analyzed in the same manner as reported previously.[1-4]

RESULTS

1. ^{14}C Excretion

Single oral administration of ^{14}C-acid- or ^{14}C-alc-esfenvalerate, *esfenvalerate or fenvalerate to both sexes of rats and mice at 2.5 and/or 10 mg/kg resulted in rapid and almost complete elimination of radiocarbon from the animal body into the urine and feces. Mice excreted radiocarbon into the urine to a larger extent than rats. Total recoveries of ^{14}C in rats for esfenvalerate, *esfenvalerate and fenvalerate were 98–101% (20–39% into the urine and 59–79% into the feces) for the ^{14}C-acid-preparations and 95–101% (24–35% into the urine and 61–71% into the feces) for the ^{14}C-alc-preparations, and in mice 97–103% (35–52% into the urine and 46–64% into the feces) for the ^{14}C-acid-preparations and 95–102% (49–60% into the urine and 42–49% into the feces) of the ^{14}C-alc-preparations (Table 2). Distribution of ^{14}C excreted into the urine and feces of rats and mice treated with esfenvalerate was very similar to those with *esfenvalerate and fenvalerate. No significant differences between both sexes were observed in the excretion patterns of esfenvalerate, *esfenvalerate and fenvalerate.

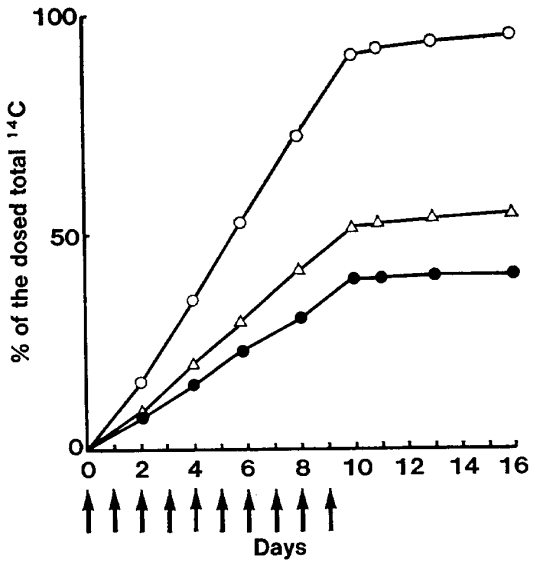


Fig. 1 ^{14}C recovery during a period of 10 consecutive oral administration of ^{14}C-acid-esfenvalerate to male ddY mice at 2.5 mg/kg/day and subsequent 7 days.

○, total ^{14}C; ●, ^{14}C in feces; △, ^{14}C in urine ; ↑, dose of ^{14}C-acid-esfenvalerate.

Table 2 ^{14}C recovery during 7 days after single oral administration of each of ^{14}C-acid- or ^{14}C-alc-esfenvalerate, *esfenvalerate or fenvalerate to SD rats and ddY mice at 2.5 to 10 mg/kg.

Animal	^{14}C-compound	Dosage (mg/kg)	Sex	% of dosed ^{14}C					
				Acid-labeled preparation			Alc-labeled preparation		
				Total	(Urine / Feces)		Total	(Urine / Feces)	
Rat[a)]	Esfenvalerate	2.5	Male	98.5±3.1	(27.3± 9.5/71.2± 8.9)		95.0±3.0	(24.1± 5.5/70.9± 7.1)	
			Female	98.6±0.8	(31.5± 9.6/67.1± 9.1)		98.7±1.9	(33.0±13.6/65.7±15.0)	
	*Esfenvalerate	2.5	Male	99.4±1.5	(20.0± 3.4/79.4± 4.0)		94.8±0.8	(29.4± 0.8/65.4± 2.1)	
			Female	100.0±0.8	(36.1±11.2/63.9±10.4)		100.6±1.0	(34.8± 7.4/65.8± 6.7)	
	Fenvalerate	10	Male	101.3±2.4	(29.0± 8.2/72.3±10.0)		95.8±1.5	(34.9±18.9/60.9±17.8)	
			Female	97.5±1.2	(39.0±10.8/58.5±11.8)		99.9±3.2	(32.5± 9.1/67.4±11.7)	
Mouse[b)]									
	Esfenvalerate	2.5	Male	101.4	(37.9	/63.5)	97.5	(52.4	/45.1)
			Female	98.8	(48.9	/49.9)	99.6	(51.0	/48.6)
	*Esfenvalerate	2.5	Male	98.0	(41.4	/56.6)	96.3	(52.8	/43.5)
			Female	96.7	(35.4	/61.3)	95.3	(49.7	/45.6)
	Fenvalerate	10	Male	102.7	(51.5	/51.2)	97.5	(49.2	/48.3)
			Female	97.1	(50.8	/46.3)	101.7	(59.6	/42.1)

[a)] Figures represent mean values±standard deviation of five rats.
[b)] Figures represent sum total of values of five mice.

Table 3 ^{14}C recovery after 10 consecutive oral administration of ^{14}C acid-labeled preparations to male and female ddY mice at 2.5 to 10 mg/kg/day.

^{14}C-compound	Dosage (mg/kg/day)	Sex	^{14}C recovery (%)		
			Total	Urine	Feces
Esfenvalerate	2.5	Male	98.5	45.5	53.0
		Female	94.4	54.1	40.3
*Esfenvalerate	2.5	Male	92.8	52.0	40.8
		Female	91.3	48.4	42.9
Fenvalerate	10	Male	96.4	48.9	47.5
		Female	97.6	56.5	41.1

Treatment of both sexes of mice with 10 consecutive oral doses of ^{14}C-acid-esfenvalerate, *esfenvalerate or fenvalerate for 10 days resulted in rapid and almost complete excretion (Fig. 1) and there were no significant differences observed in the excretion patterns among esfenvalerate, *esfenvalerate and fenvalerate (Table 3).

2. Tissue Residues

Table 4 shows ^{14}C residue levels in the tissues of male rats and mice 7 days after single oral administration of each of ^{14}C-labeled preparations of esfenvalerate, *esfenvalerate and fenvalerate. Tissue residue levels in all groups were very low although the fat for both the ^{14}C-acid- and ^{14}C-alc-preparations showed slightly higher residue levels than other tissues. No apparent sex differences were observed in the ^{14}C tissue residue levels (data on females not shown).

With respect to the ^{14}C-alc-preparations, esfenvalerate showed almost the same tissue residues as *esfenvalerate, and fenvalerate gave approximately 4 times higher ^{14}C residues than esfenvalerate or *esfenvalerate, indicating that there was no substantial difference in tissue residues among esfenvalerate, *esfenvalerate and fenvalerate, because the dosage of fenvalerate was four times higher than that of esfenvalerate or *esfenvalerate.

With respect to the ^{14}C-acid-preparations, the ^{14}C tissue residues were generally higher in mice than in rats, and esfenvalerate and *esfenvalerate gave almost the same tissue residues in both animals, whereas fenvalerate gave slightly higher ^{14}C tissue residue, particularly in the adrenal, liver, mesenteric lymph node and spleen of mice compared with esfenvalerate and *esfenvalerate.

3. Amounts of Metabolites in Excreta

Tables 5a and 5b show two examples of the amounts of metabolites in excreta after single oral administration of ^{14}C-esfenvalerate, *esfenvalerate or fenvalerate to male rats and mice at 2.5 and/or 10 mg/kg, because no apparent sex differences were observed and species differences occurred only in the case of ^{14}C-alc-preparations.[2)]

The parent compound and two ester metabolites (2′- and 4′-OH-parent compounds) were found in the feces of both animals.

From the acid moiety, CPIA in free and glucuronide forms was obtained as a major metabolite in both animals (data on mice not shown). 3-OH-CPIA in free and lactone forms, and 2,3-OH-CPIA in free, lactone and glucuronide forms were also obtained. In addition, Cl-Bacid in free and lactone forms, and Cl-BDacid anhydride were found as minor metabolites. These metabolites were detected in all treated groups of both species. The amounts of metabolites differ between the two species. Esfenvalerate differ slightly from fenvalerate in the amounts of metabolites, but esfenvalerate produced almost the same amounts of metabolites as *esfenvalerate. A trace amount of CPIA-cholesterol ester was detected only in the feces of mice treated with fenvalerate, but not in that of rats or of mice treated with esfenvalerate or *esfenvalerate.

Major metabolites from the alcohol moiety were PBacid and 4′-OH-PBacid both in free

Table 4 ^{14}C tissue residues 7 days after single oral administration of ^{14}C-acid- or ^{14}C-alc-esfenvalerate, *esfenvalerate or fenvalerate to male SD rats and ddY mice at 2.5 or 10 mg/kg.

(ng parent compound equivalent/g wet tissue)

Tissue	Rat					
	Esfenvalerate		*Esfenvalerate		Fenvalerate	
	2.5 mg/kg		2.5 mg/kg		10 mg/kg	
	Acid	Alc	Acid	Alc	Acid	Alc
Adrenal	—[a)]	—	—	—	188±104	—
Blood	—	3± 3	—	—	—	—
Fat	178±45	294±98	185±33	295±80	1318±657	1289±898
Kidney	—	5± 7	2± 0	3± 1	18± 8	—
Liver	5± 1	3± 2	5± 1	6± 1	51± 24	9± 5
Mesenteric Lymph node	27± 1	30±16	10± 7	31±12	122± 60	103± 59
Skin	17±19	10± 6	11± 7	7± 5	34± 20	42± 26
Spleen	—	2± 1	—	—	48± 17	—

Tissue	Mouse					
	Esfenvalerate		*Esfenvalerate		Fenvalerate	
	2.5 mg/kg		2.5 mg/kg		10 mg/kg	
	Acid	Alc	Acid	Alc	Acid	Alc
Adrenal	—	—	—	—	938±371	—
Blood	4± 1	3± 1	18±16	4± 1	32± 2	—
Fat	301±61	384±108	329±52	266±85	1340±297	1160±804
Kidney	—	18± 5	4± 1	35± 7	78± 13	101± 96
Liver	10± 1	8± 2	9± 2	10± 2	297± 71	16± 10
Mesenteric Lymph node	28±18	40± 42	39±21	32±21	509±315	129± 58
Skin	38±15	57± 45	64±33	55±22	175± 84	108± 73
Spleen	—	5± 4	—	—	142± 13	—

The figures show mean values ± standard deviation of five animals.

The following tissues showed generally lower residue levels: bone, brain, heart, lung, muscle and testis.

[a)] below the detection limit: depending on tissues and species (2–360 ppb).

and conjugated forms. The following were the species differences found in the metabolites from the alcohol moiety: 1) taurine conjugate of PBacid was found only in mice, and 2) 4′-OH-PBacid in free and sulfate forms occurred in greater amounts in rats than in mice. These results were similar to those obtained in the previously study.[2)] Although there was an apparent species difference in the metabolites from the alcohol moiety, esfenvalerate, *esfenvalerate and fenvalerate produced almost the same amounts of metabolites in both animals.

Table 6 shows the amounts of metabolites in the 8–11 day excreta of mice treated with 10 consecutive oral administration of ^{14}C-acid-esfenvalerate, *esfenvalerate or fenvalerate. There was no significant difference in the pattern of metabolites among 0–4, 4–8 and 8–11 day excreta (data not shown). The major metabolite was CPIA in free and glucuronide forms, and other metabolites were essentially identical to those in case of single oral administration. The amounts of metab-

Table 5a Amounts of metabolites in 0–2 day excreta after single oral administration of ^{14}C-acid-esfenvalerate, *esfenvalerate or fenvalerate to male SD rats at 2.5 or 10 mg/kg.

Metabolite		% of dosed ^{14}C							
		Esfenvalerate		*Esfenvalerate		Fenvalerate			
		2.5 mg/kg		2.5 mg/kg		2.5 mg/kg		10 mg/kg	
		Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine
Parent compound		48.7±7.7		58.2±3.6		54.7±9.1		54.1±12.8	
4′-OH-Parent compound		5.5±1.4		4.4±0.6		2.0±0.6		3.3±0.7	
2′-OH-Parent compound		1.0±0.6		1.6±0.5		0.9±0.5		0.4±0.1	
CPIA	Free	2.8±1.3	2.8±1.9	1.9±0.8	2.4±1.3	1.5±0.6	4.3±3.1	3.1±0.7	7.9±5.2
	Glu		4.0±1.2		2.1±0.4		8.2±3.8		7.3±3.3
3-OH-CPIA	Free	0.2±0.2	1.1±0.4	0.1±0.1	1.1±0.5	<0.1	1.1±0.4	0.1±0.0	1.9±0.5
	Lactone	<0.1	3.3±1.0	<0.1	1.4±0.5	<0.1	3.8±1.2	<0.1	2.0±0.4
2,3-OH-CPIA	Free	2.4±0.9	0.6±0.2	3.3±1.4	<0.1	2.3±0.3	0.3±0.1	1.6±0.5	<0.1
	Lactone	0.5±0.2	<0.1	0.3±0.2	0.2±0.1	<0.1	0.1±0.1	<0.1	0.3±0.2
	Glu		5.0±2.3		3.5±0.5		1.9±0.5		2.5±0.8
Cl-Bacid	Free	0.4±0.2	<0.1	0.4±0.1	0.1±0.1	0.9±0.3	<0.1	1.3±0.4	0.1±0.0
	Lactone		0.2±0.1		0.2±0.1		0.2±0.0		0.2±0.0
Cl-BDacid-anhydride			3.6±1.7		2.9±1.0		2.0±0.5		1.8±0.5
Others		6.8±4.2	4.5±1.6	6.3±2.0	3.9±0.1	2.1±0.3	3.7±1.1	3.1±0.7	2.5±0.6
Unextractable ^{14}C		1.6±1.2		1.9±0.4		3.4±0.6		2.7±0.6	
Total ^{14}C		70.0±8.6	25.1±9.1	78.4±3.7	17.8±3.6	67.8±7.4	25.6±7.3	69.7±11.5	26.5±7.1

The figures show the mean values±standard deviation of five animals. Glu, glucuronide.

Table 5b Amounts of metabolites in 0–2 day excreta after single oral administration of ^{14}C-alc-esfenvalerate, *esfenvalerate or fenvalerate to male ddY mice at 2.5 or 10 mg/kg.

Metabolites		% of dosed ^{14}C					
		Esfenvalerate		*Esfenvalerate		Fenvalerate	
		2.5 mg/kg		2.5 mg/kg		10 mg/kg	
		Feces	Urine	Feces	Urine	Feces	Urine
Parent compound		30.2	0.2	31.9	0.7	35.8	0.4
4′-OH-Parent compound		4.4		3.8		2.4	
2′-OH-Parent compound		} 0.8		} 0.7		} 0.8	
PBacid	Free		3.4		3.6		2.7
	Gly		0.4		0.6		0.6
	Tau		11.2		17.3		11.7
	Glu		0.5		1.3		1.5
4′-OH-PBacid	Free	0.8	6.1	0.6	3.3	1.1	3.7
	Sul		3.1		3.3		3.1
	Glu		0.5		2.8		3.1
2′-OH-PBacid	Free		0.4		0.1		0.2
	Sul		0.3		0.6		0.3
PBacid		0.1		0.2		0.1	
Others		5.3	23.8	3.3	16.3	5.3	20.3
Unextractable ^{14}C		2.8		2.2		2.3	
Total ^{14}C		44.4	49.9	42.7	49.9	47.8	47.6

The figures show the data from five animals.
Gly, glycine conjugate; Tau, taurine conjugate; Glu, glucuronide; Sul, sulfate.

Table 6 Amounts of metabolites in 8–11 day excreta after 10 consecutive oral doses of ^{14}C-acid-esfenvalerate, *esfenvalerate or fenvalerate to male ddY mice at 2.5 or 10 mg/kg/day.

Metabolite		% of dosed ^{14}C					
		Esfenvalerate		*Esfenvalerate		Fenvalerate	
		2.5 mg/kg		2.5 mg/kg		10 mg/kg	
		Feces	Urine	Feces	Urine	Feces	Urine
Parent compound		5.5		5.7		6.1	
CPIA-cholesterol ester						<0.1	
4′-OH-Parent compound		0.7		0.8		0.7	
2′-OH-Parent compound		0.2		0.2		<0.1	
CPIA	Free	0.3	4.7	0.3	3.5	0.3	4.5
	Glu		0.9		0.9		1.0
3-OH-CPIA	Free	0.1	0.4	<0.1	0.3	0.1	0.4
	Lactone	<0.1	1.0	<0.1	0.6	<0.1	0.9
2,3-OH-CPIA	Free	<0.1	<0.1	<0.1	<0.1	<0.1	0.2
	Lactone	<0.1	<0.1	<0.1	0.1	<0.1	<0.1
	Glu		0.4		0.2		0.3
Cl-Bacid	Free	<0.1	0.5	<0.1	0.3	<0.1	0.2
	Lactone		0.3		0.3		1.1
Cl-BDacid-anhydride			<0.1		<0.1		<0.1
Others		1.6	3.8	1.2	2.9	1.2	3.5
Unextractable ^{14}C		1.6		1.1		0.8	
Total ^{14}C		9.9	11.9	9.3	9.0	9.1	12.1

The figures show the data from five animals.
Glu, glucuronide.

olites from esfenvalerate were almost the same as those from *esfenvalerate and fenvalerate except for CPIA-cholesterol ester from fenvalerate.

DISCUSSION

In ^{14}C excretion patterns, esfenvalerate did not differ significantly from *esfenvalerate or fenvalerate. However, the radiocarbon excreted into urine of rats and mice dosed with esfenvalerate and fenvalerate was somewhat less as compared with the results obtained previously. This may be due to different vehicles (Tween 80 aqueous solution in the previous study and corn oil in the present study).[1,2,8] Corn oil seems to disturb the absorption of fenvalerate from gastrointestine to some extent.

Esfenvalerate showed less ^{14}C tissue residues for the acid-labeled preparation than fenvalerate, and this tendency was much clearer in mice than in rats. The reasons seem to be that CPIA-cholesterol ester was produced only by the Bα-isomer of fenvalerate but not by esfenvalerate[4,5] and that CPIA-cholesterol ester was somewhat bioaccumulative and persistent in tissues, particularly in the liver, spleen, adrenal and mesenteric lymph node of mice.[4,5] The previous *in vivo* studies[4,5] showed that these tissues of mice tended to retain CPIA-cholesterol ester to a larger extent than other tissues, and furthermore the previous *in vitro* studies[5,6] revealed that homogenates of mouse tissue produced CPIA-cholesterol ester to a larger extent than those of rat tissue. The findings from the present study are in agreement with the results from the previous *in vivo* and *in vitro* studies.[4-6] On the other hand, there appeared to be no significant differences in the ^{14}C tissue residues from the ^{14}C-alc-preparations because the residues were in proportion to the dosage. Similarly there was no significant difference in ^{14}C tissue residues with both the acid- and alc-labeled preparations between esfenvalerate and *esfenvalerate.

Major metabolic pathways of esfenvalerate were oxidation at the 2- and 3-positions of the acid moiety, and at the 2′- and 4′-positions of the alcohol moiety, ester cleavage and conjugation reactions as reported previously,[1,2] and the pathways were the same as those of fenvalerate except that CPIA-cholesterol ester was produced from the Bα-isomer of fenvalerate. Table 7 shows comparison in percentages of metabolic attacks among esfenvalerate, *esfenvalerate and fenvalerate. Esfenvalerate appeared to undergo C-2 and C-3 oxidations in rats to a slightly larger extent than fenvalerate. On the other hand, ester cleavage in rats and mice seems to occur to a smaller extent in esfenvalerate than in fen-

Table 7 Extent of metabolic attacks on esfenvalerate, *esfenvalerate or fenvalerate.

Site of attack	% of dosed ^{14}C					
	Esfenvalerate		*Esfenvalerate		Fenvalerate	
	2.5 mg/kg		2.5 mg/kg		10 mg/kg	
	Rat	Mouse	Rat	Mouse	Rat	Mouse
Acid moiety						
C-2-Oxidation	10.5	16.1	11.6	14.6	7.8	14.4
C-3-Oxidation	15.6	19.6	16.2	18.8	11.8	21.9
Alcohol moiety						
2′-Phenoxy hydroxylation	1.9	0.8	2.1	0.7	2.1	1.0
4′-Phenoxy hydroxylation	25.2	12.9	27.9	13.4	27.6	13.0
Ester cleavage[a]	27.5	32.9	24.9	30.2	33.0	39.4

The figures show the mean data from male and female animals.
The figures show the sum of oxidized metabolites at the 2- and 3-position of the acid moiety, and the 2′- and 4′-position of the alcohol moiety in 0–2 day excreta.
[a] The data show the sum of the ester-cleaved metabolites in 0–2 day excreta from the acid moiety.

valerate. Esfenvalerate showed almost the same arrays of urinary and fecal metabolites as *esfenvalerate, indicating that other unlabeled Aβ, Bα and Bβ-isomers did not have any effects on the biotransformation reaction of esfenvalerate.

There was no significant difference in the amounts of metabolites of in the 0–4, 4–8 and 8–11 day excreta of mice among esfenvalerate, *esfenvalerate and fenvalerate, implying that any isomers of fenvalerate neither induced nor inhibited the enzymes responsible for metabolism of esfenvalerate and fenvalerate, and that other unlabeled isomers hardly affected the metabolism of esfenvalerate.

From the findings in this study, it can be concluded that esfenvalerate behaved independently of other isomers in rats and mice and that esfenvalerate substantially underwent the same metabolic reactions as fenvalerate except that fenvalerate produced CPIA-cholesterol ester.

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要　　約

Esfenvalerate のラット，マウスでの代謝および他の異性体の esfenvalerate の代謝に対する影響

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^{14}C 標識 esfenvalerate [(*S*)-α-cyano-3-phenoxybenzyl (*S*)-2-(4-chlorophenyl) isovalerate] を雌雄ラットおよびマウスに 2.5 mg/kg または 2.5 mg/kg/day で 1 回経口または10日間連続経口投与を行なった．投与 ^{14}C は速やかにかつほぼ完全に尿糞中に排泄された．^{14}C 組織残留量は脂肪以外で全般的に非常に低かった．主要代謝反応は 1) 酸側の 2-,3-位とアルコール側の 2′-,4′-位の酸化，2) エステル結合の開裂および 3) グルクロン酸，硫酸，グリシンまたはタウリンとの抱合反応であった．^{14}C-esfenvalerate と fenvalerate [(*RS*)-α-cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl) isovalerate] の 3 非標識体 [(2*S*,α*S*)，(2*S*,α*R*) および (2*R*,α*R*)] との等量混合物を 1 回または連続経口投与した．^{14}C-esfenvalerate の単独投与と比べて ^{14}C 排泄率，^{14}C 組織残留量および代謝物量に差異は認められなかった．このことは esfenvalerate の体内挙動は他異性体から独立していることを示唆している．また酸側 ^{14}C 標識 fenvalerate と esfenvalerate の代謝を比較すると fenvalerate が全般的に若干高い ^{14}C 組織残留量を示した．これは fenvalerate だけから生成する cholesteryl (*R*)-2-(4-chlorophenyl) isovalerate によるもので，この生成以外には esfenvalerate と fenvalerate の生体内運命に大きな差異はなかった．