J. Pesticide Sci. **21**, 49-55 (1996)

Original Article

Metabolism of Imiprothrin Isomers in Rats: Absorption and Distribution

Koichi SAITO, Hideo KANEKO, Yoshitaka TOMIGAHARA, Iwao NAKATSUKA and Hirohiko YAMADA

Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Konohana-ku, Osaka 554, Japan

(Received July 13, 1995; Accepted September 29, 1995)

The absorption and distribution of imiprothrin ([2, 5-dioxo-3-(2-propynyl)-1-imidazolidinyl]methyl (1*R*)-*cis*, *trans*-chrysanthemate) were studied by dosing (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]-imiprothrin orally to male and female rats at 1 (low dose) and 200 mg/kg (high dose). ^{14}C-Concentrations in blood reached maxima within 5 hr after dosing the *trans*-isomer and decreased rapidly thereafter. In the rats treated with the *cis*-isomer, the concentrations in blood reached a lower peak within 9 hr after administration and decreased more gradually as compared with the rats given the *trans*-isomer. ^{14}C-Concentrations in tissues decreased along with the decreases in the ^{14}C-blood levels in all treatment groups, these in each tissue 72 hr after administration of the *cis*-isomer being higher than in the *trans*-isomer case. Metabolites identified in the blood were 2, 4-dioxo-1-(2-propynyl)-imidazolidine (PGH), 5-hydroxy-2, 4-dioxo-1-(2-propynyl)-imidazolidine (PGH-OH) and 2, 4-dioxo-imidazolidine (hydantoin, HYD) in the low dose groups, whereas PGH was mainly detected in the high dose groups for both *trans*- and *cis*-isomers. No parent compound was observed in any dose group. No marked sex-related differences appeared in the absorption and distribution of the *trans*- or *cis*-isomers within either dose group. These results suggest that imiprothrin is readily absorbed into the rat body, metabolized rapidly and excreted after distribution to tissues.

INTRODUCTION

Imiprothrin [S-4056F, S-41311, [2, 5-dioxo-3-(2-propynyl)-1-imidazolidinyl]methyl (1*R*)-*cis*/*trans*-chrysanthemate], a pyrethroid insecticide with strong knockdown activity, comprises two geometrical isomers [(1*R*)-*cis*- and (1*R*)-*trans*] in the ratio of 1 : 4.[1] Biotransformation and excretion of imiprothrin have been studied in rats treated orally with the *trans*- and *cis*-isomers at 1 and 200 mg/kg,[2] and both compounds were found to be almost completely eliminated from the body within 7 days. The major biotransformation reactions of imiprothrin in rats are 1) cleavage of the ester linkage, 2) cleavage of the imido methylene linkage, 3) hydroxylation of the imidazolidine ring, 4) dealkylation of the 2-propynyl group and 5) oxidation at the ω-*trans*-methyl group in the isobutenyl side chain, and almost all metabolites were established to be cleaved the ester linkage.

The present study was conducted with the objective of elucidating absorption and distribution characteristics in rats following a single oral administration of (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin.

MATERIALS AND METHODS

1. *Chemicals*

Unlabeled (1*R*)-*trans*-imiprothrin (96.9% purity) and (1*R*)-*cis*-imiprothrin (94.9% purity), (1*R*)-*trans*-[imidazolidinyl-5-^{14}C]imiprothrin (1.95 GBq/mmol) and (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin (1.95 GBq/mmol) (Fig. 1) were synthesized in our laboratory. The labeled preparations were purified as previously described.[2] The radiochemical purity of the compounds was established to be >97%.

^{14}C-Labeled standards (PGH: 2, 4-dioxo-1-(2-propynyl)-imidazolidine, PGH-OH: 5-hydroxy-2, 4-dioxo-1-(2-propynyl)-imidazolidine, and HYD: 2, 4-dioxo-imidazolidine) (Fig. 1) used in the present study were purified from urine of rats administered (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin.[2]

2. *Thin-layer Chromatography (TLC)*

TLC analysis was conducted similarly as described previously by Saito *et al.*[3] Pre-coated Silica gel 60 F_{254} chromatoplates (Art. 5715, 20×20 cm, 0.25 mm layer-thickness, E. Merck, Germany) were used for purification of ^{14}C-labeled compounds, determination of their radio-

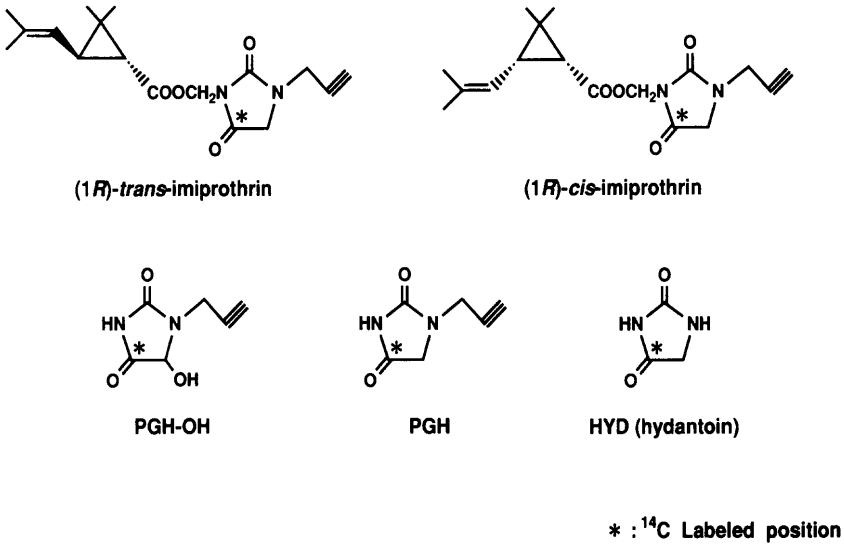

Fig. 1 Chemical structures of ^{14}C-labeled (1*R*)-*trans*- and (1*R*)-*cis*-imiprothrin, and their metabolites.

chemical purity and analysis of metabolites in blood. The following solvent systems were used in the present study: (A) *n*-butanol/acetic acid/water (6/1/1, v/v); (B) ethyl acetate/ethanol/water (7/2/1, v/v); and (C) benzene/ethyl acetate (4/1, v/v). Radioactive metabolites on TLC plates were detected by X-ray films (SB-5, Kodak, U.S.A.) exposed for about one week at 4°C and then developed with a Model M6B processor (Kodak).

3. *Treatment of Animals and Sample Collection*

SD male and female rats (male 225–259 g, female 164–196 g) were purchased from Charles River Japan Inc. (Kanagawa, Japan) at 6 weeks of age and acclimatized for 1 week before use. Animals were given pellet diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and water *ad libitum* throughtout the study.

For determination of ^{14}C-levels in blood, groups of five males and five females were given a single oral dose of (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin at 1 (low dose) or 200 mg/kg (high dose). Corn oil was used as the vehicle and given at 5 ml/kg. Blood samples were collected with a capillary from the retro orbital plexus under anesthesia with diethyl ether 1, 3, 5, 7, 9, 12, 24, 48, 72 and 144 hr (only animals in the high dose group at 144 hr) after administration, and being immediately placed into heparinized tubes.

For the examination of ^{14}C-tissue distribution, groups of three males and three females were given a single oral dose of (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]-imiprothrin at 1 (low dose) or 200 mg/kg (high dose) as described above. The animals were then sacrificed by collection of blood from the abdominal aorta under anesthesia with diethyl ether 0.5, 3, 18 and 72 hr after administration of the low dose, and 1, 6, 24 and 72 hr after administration of the high dose. Fifteen (female) or fourteen (male) organs/tissues except gastrointestinal tracts were immediately removed for assessment. The collected blood was immediately placed into heparinized tubes, and separated into blood cells and plasma by centrifugation.

4. *Radioanalysis*

Radioanalysis was carried out similarly as described previously by Yoshino *et al.*[4] Radioactivity in blood extracts was quantified by liquid scintillation counting (LSC) with a Tri-Carb® 2500TR Liquid Scintillation Counter (Packard, U.S.A.) using Emulsifier Scintillator 299™ (Packard) as the scintillator. Samples of whole blood, blood cells, plasma, organs/tissues and unextractable blood residues were combusted with a Tri-Carb® 307 Sample Oxidizer (Packard) or a Tri-Carb® 306 Sample Oxidizer (Packard) followed by LSC. Carbo-sorb® CO_2 and Permafluor® E (Packard) were used as the $^{14}CO_2$ absorbent and the scintillator, respectively.

5. *Analysis of Metabolites in Blood*

For the ^{14}C-tissue distribution study, blood was extracted three times with five-fold volumes of methanol containing 0.01% of unlabeled imiprothrin (*cis*/*trans* = 1 : 4). The extracts were concentrated *in vacuo*, and the metabolites in the extracts were identified by TLC co-chromatography under solvent systems A, B and C using ^{14}C-labeled standards according to the previously described method.[2, 5] Quantification of metabolites in blood was conducted by TLC with solvent system A. Individual radioactive areas on silica gel plates were scraped and radioactivity determined by LSC as described previously.[3]

RESULTS

1. ^{14}C-Concentration in Blood

^{14}C-Concentrations in blood in male and female rats treated with single oral administrations of ^{14}C-labeled (1*R*)-*trans*- and (1*R*)-*cis*-isomers at 1 mg/kg (low dose) or 200 mg/kg (high dose) are shown in Fig. 2. The maximum time (T_{max}, hr), maximum concentration (C_{max}, ppm) and the biological half-lives ($T_{1/2}$, hr) from 12 to 24 hr are shown in Table 1.

For the low dose group given the *trans*-isomer, the maximum concentration occurred at 3 hr in males and females (0.43 and 0.47 ppm, respectively), declined gradually to 9 hr after administration, and then rapidly thereafter. The biological half-lives from 12 to 24 hr after administration were calculated to be about 6.4 hr in both males and females. For the low dose group given the *cis*-isomer, the peak concentration occurred 5 and 9 hr after administration in males and 1 and 7 hr after administration in females (the maxima of 0.29 ppm in males and 0.30 ppm in females) and then decreased. The biological half-lives from 12 to 24 hr after administration were about 11.8 and 9.1 hr in males and females, respectively.

For the high dose group given the *trans*-isomer, the peak ^{14}C-concentration in blood occurred at 5 hr (123 ppm in males and 110 ppm in females) and high levels were then maintained until 12 hr after administration, followed by rapid decrease. The biological half-lives calculated from values between 12 and 24 hr were about 6.5 and 6.7 hr in males and females, respectively. For the high dose group treated with the *cis*-isomer, the concentration reached a peak 9 hr after administration (82 ppm in males and 89 ppm in females) and then decreased relatively gradually. The biological half-lives calculated from the values between 12 and 24 hr after administration were about 8.1 and 7.2 hr in males and females, respectively.

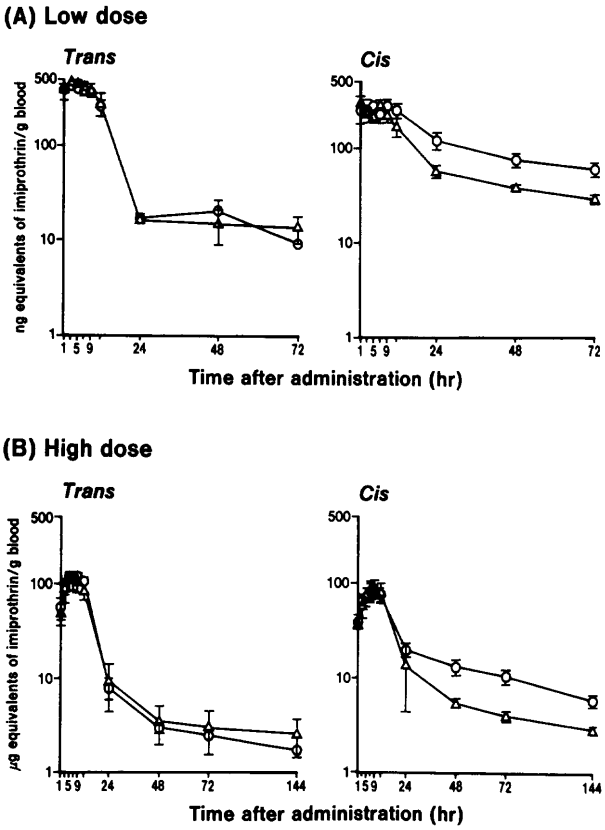

Fig. 2 ^{14}C-Blood levels after a single oral administration of ^{14}C-labeled (1*R*)-*trans*- or (1*R*)-*cis*-imiprothrin to male (○) or female (△) rats at 1 (low dose) or 200 mg/kg (high dose).
The data are expressed as the mean±S.D. of five animals.

2. Metabolites in Blood

The concentrations of the metabolites in blood for *trans*- and *cis*-isomers are shown in Tables 2 and 3, respectively. The parent compound was not observed in any treatment group. The major metabolites in the low dose group given the *trans*-isomer were PGH-OH, PGH and HYD. The maximum concentration of PGH-OH was found at 3 hr in males and 0.5 hr in females (147 and 137 ppb, respectively). The concentration of PGH reached a miximum 0.5 hr after administration in both males and in females (175 and 199 ppb, respectively). The concentration of HYD reached a maximum 3 hr after administration in males and 0.5 or 3 hr after administration in females (49 and 39 ppb, respectively). The

Table 1 Maximum times (T_{max}), maximum cocentrations (C_{max}) and biological half-lives ($T_{1/2}$) of ^{14}C in blood after single oral administrations of (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 1 (low dose) and 200 mg/kg (high dose).

Dose	T_{max}, hr (C_{max} ppm)				$T_{1/2}$, hr (12–24 hr)			
	Trans		*Cis*		*Trans*		*Cis*	
	M	F	M	F	M	F	M	F
Low	3 (0.43)	3 (0.47)	5 (0.29) 9 (0.29)[a)]	1 (0.30) 7 (0.29)[a)]	6.4	6.4	11.8	9.1
High	5 (123)	5 (110)	7 (82) 9 (82)	9 (89)	6.5	6.7	8.1	7.2

[a)] Two peaks were observed.
M : male, F : female.

Table 2 Concentrations of metabolites in blood after single oral administrations of (1*R*)-*trans*-[imidazolidinyl-5-^{14}C]-imiprothrin to rats at 1 (low dose) and 200 mg/kg (high dose).

Metabolite	Low dose (ppb)								High dose (ppm)							
	0.5 hr		3 hr		18 hr		72 hr		1 hr		6 hr		24 hr		72 hr	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PGH-OH	78	137	147	132	N.D.[a)]	7	N.D.	N.D.	3	2	2	6	1	1	0	N.D.
PGH	175	199	99	113	N.D.	4	N.D.	N.D.	40	16	61	54	3	2	0	N.D.
HYD	48	39	49	39	N.D.	N.D.	N.D.	N.D.	4	2	3	2	1	N.D.	0	N.D.
Unidentified	62	59	90	82	8	9	4	4	14	7	19	19	4	3	1	1
Unextractable	10	14	16	9	9	1	4	2	1	1	3	3	2	2	1	1
Total	375	447	401	375	17	21	8	6	63	27	89	84	11	8	2	2

[a)] Not detected. M : male, F : female.

Table 3 Concentrations of metabolites in blood after single oral administrations of (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 1 (low dose) and 200 mg/kg (high dose).

Metabolite	Low dose (ppb)								High dose (ppm)							
	0.5 hr		3 hr		18 hr		72 hr		1 hr		6 hr		24 hr		72 hr	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PGH-OH	42	43	63	60	3	2	0	N.D.[a)]	2	1	7	2	N.D.	1	N.D.	0
PGH	81	81	45	41	3	N.D.	1	N.D.	14	17	23	37	N.D.	2	N.D.	0
HYD	42	69	27	49	N.D.	N.D.	N.D.	N.D.	2	2	5	2	N.D.	N.D.	N.D.	N.D.
Unidentified	70	91	59	108	5	6	2	5	7	10	23	11	N.D.	4	N.D.	1
Unextractable	30	22	71	53	72	45	35	27	3	2	8	3	N.D.	5	N.D.	3
Total	266	307	264	311	83	52	38	32	28	32	66	57	N.D.	11	N.D.	4

[a)] Not detected. M : male, F : female.

Table 4 ^{14}C-Concentrations in tissues after a single oral administration of (1*R*)-*trans*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 1 mg/kg (high dose).

Tissue	^{14}C-Concentration (ppb)							
	0.5 hr		3 hr		18 hr		72 hr	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal	262±116.6	419±346.9	251±95.3	272±60.0	21±5.4	29±7.8	12±2.0	12±3.4
Blood	375±89.8	447±399.0	401±46.4	375±75.6	17±0.8	21±5.3	8±1.1	6±0.7
Blood cells	315±72.6	382±347.7	346±41.7	317±73.0	13±0.9	17±4.3	9±0.6	7±0.4
Plasma	427±106.0	524±477.6	454±40.8	429±84.7	20±1.5	24±6.4	7±1.2	5±0.9
Bone	159±44.7	195±175.1	165±29.2	154±31.2	14±2.7	18±3.6	10±0.4	7±1.2
Bone marrow	313±61.6	368±319.9	325±31.9	296±61.9	22±2.5	28±5.7	8±0.9	7±0.6
Brain	157±26.7	228±211.2	171±9.3	158±30.6	9±0.7	15±4.2	2±0.4	2±0.4
Fat	63±29.3	259±247.3	89±62.6	56±26.3	6±1.9	6±1.1	5±1.6	5±3.1
Heart	267±62.7	404±320.6	276±34.7	242±40.1	27±28.9	14±4.2	6±0.9	5±1.2
Kidney	570±151.0	848±637.7	768±54.5	619±99.5	34±2.4	46±14.7	16±3.2	16±2.0
Liver	425±69.3	505±394.6	337±23.4	309±38.3	45±31.1	66±13.5	25±0.7	23±4.1
Lung	269±71.1	380±286.6	259±20.3	261±17.0	15±1.5	18±3.3	8±2.1	7±1.3
Muscle	259±58.5	375±311.0	266±21.0	255±58.7	9±0.5	16±4.4	6±0.5	6±1.5
Pancreas	283±95.4	446±229.1	246±22.9	182±13.7	15±0.7	21±6.6	7±2.0	7±1.5
Skin and hair	229±58.5	307±271.7	269±47.2	256±55.0	54±20.4	112±35.6	16±2.8	45±12.8
Spleen	285±65.7	438±308.8	283±23.9	235±37.7	15±1.3	19±5.1	9±1.5	8±1.8
Testis	161±36.8	—	271±5.1	—	11±1.2	—	5±0.7	—
Ovary	—	495±313.5	—	227±17.1	—	26±1.8	—	9±1.5
Uterus	—	447±299.4	—	240±28.0	—	26±3.4	—	9±1.9

Data are expressed as the means±S.D. of three animals.

major metabolites in the low dose group given the *cis*-isomer were PGH-OH, PGH, and HYD as in the group given the *trans*-isomer. The concentration of PGH-OH reached a maximum 3 hr after administration in both males and in females (63 and 60 ppb, respectively). The concentration of PGH reached a maximum 0.5 hr after administration in both sexes (81 ppb) while that of HYD reached a maximum 0.5 hr after administration in both male and female rats (42 and 69 ppb, respectively).

The main metabolite for the high dose group given the

Table 5 ^{14}C-Concentrations in tissues after a single oral administration of (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 1 mg/kg (low dose).

Tissue	^{14}C-Concentration (ppb)							
	0.5 hr		3 hr		18 hr		72 hr	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal	331±123.9	309±14.2	165±25.4	200±16.9	52±11.3	27±18.1	29±2.9	30±3.8
Blood	266±90.3	307±12.1	264±47.3	311±17.3	83±19.2	52±18.1	38±2.5	32±4.5
Blood cells	198±67.0	238±11.7	195±32.7	215±47.5	50±11.4	32±10.6	31±2.1	26±3.3
Plasma	294±115.0	360±36.6	337±48.1	374±27.6	115±30.2	73±27.2	43±2.1	36±5.2
Bone	102±43.2	116±11.2	120±26.6	127±15.7	53±10.7	35±11.3	33±4.9	30±3.9
Bone marrow	194±65.7	231±16.4	182±24.3	229±22.9	67±11.6	54±16.4	27±3.0	29±4.7
Brain	87±32.9	105±4.6	91±17.8	112±15.9	8±1.8	7±1.5	4±0.6	5±2.5
Fat	34±10.2	64±22.5	33±7.6	44±2.2	14±3.0	9±4.5	10±0.5	9±1.6
Heart	225±45.0	255±8.1	144±26.4	202±28.4	29±6.1	20±6.6	18±1.1	17±2.3
Kidney	837±194.8	853±96.8	518±91.8	641±36.8	90±17.2	64±21.0	47±7.0	45±6.5
Liver	801±258.3	683±65.5	403±37.0	484±80.8	195±53.5	143±39.8	70±3.0	73±12.4
Lung	254±89.3	265±9.7	162±23.9	172±62.8	46±8.4	37±11.5	26±4.4	25±3.2
Muscle	175±67.1	225±9.6	135±21.4	192±43.9	21±5.8	15±2.7	14±0.5	14±3.4
Pancreas	305±131.7	245±26.9	145±18.9	178±11.8	41±8.8	31±10.2	18±3.4	17±2.7
Skin and hair	172±62.6	199±6.0	156±28.8	189±31.0	52±10.7	30±6.6	40±3.2	37±7.6
Spleen	264±90.8	240±9.4	149±23.5	184±21.4	41±6.4	27±7.4	21±2.9	22±2.3
Testis	104±42.6	—	140±22.6	—	21±5.0	—	11±1.0	—
Ovary	—	246±19.4	—	219±39.9	—	43±16.2	—	30±5.3
Uterus	—	224±17.4	—	201±6.2	—	33±6.6	—	35±6.9

Data are expressed as the means±S.D. of three animals.

Table 6 ^{14}C-Concentrations in tissues after a single oral administration of (1*R*)-*trans*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 200 mg/kg (high dose).

Tissue	^{14}C-Concentration (ppm)							
	1 hr		6 hr		24 hr		72 hr	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal	59±20.7	37±17.0	73±8.1	69±22.6	23±25.1	9±2.4	2±0.5	3±1.5
Blood	63±21.1	27±8.9	89±24.4	84±3.8	11±5.9	8±2.9	2±0.2	2±0.1
Blood cells	50±18.9	25±1.0	71±18.7	68±4.6	10±4.6	7±2.0	3±0.3	3±0.1
Plasma	71±26.3	37±3.0	103±28.4	95±2.3	13±7.4	8±3.5	1±0.3	1±0.1
Bone	27±9.3	16±6.5	38±10.8	38±7.5	7±2.7	4±1.7	2±0.3	1±0.1
Bone marrow	50±19.3	33±11.9	79±20.4	84±12.3	10±5.5	7±3.1	1±0.3	1±0.1
Brain	42±17.4	28±11.6	71±22.0	71±2.8	8±4.6	6±2.6	0±0.2	1±0.3
Fat	14±1.2	24±30.2	13±1.6	16±5.0	1±0.7	1±0.6	1±0.2	1±0.7
Heart	56±21.5	29±4.2	75±17.7	73±3.9	12±11.4	5±2.6	1±0.2	2±1.0
Kidney	101±42.3	54±9.2	114±23.3	107±8.7	20±9.6	15±5.5	2±0.5	5±2.2
Liver	73±23.5	40±7.0	82±14.2	79±3.8	21±11.2	12±2.9	4±0.7	7±3.6
Lung	59±20.7	28±5.0	75±10.8	72±2.9	14±12.4	6±2.7	1±0.2	2±1.4
Muscle	54±18.4	37±17.0	77±21.2	76±1.4	8±5.2	6±2.8	1±0.1	1±1.1
Pancreas	81±36.6	66±79.0	58±11.1	74±20.1	10±6.3	6±2.4	1±0.3	2±1.0
Skin and hair	43±17.6	29±11.5	71±14.4	60±0.6	15±2.7	21±13.0	5±1.6	5±3.9
Spleen	66±6.0	51±44.5	69±13.7	72±8.8	11±6.1	6±2.5	1±0.4	2±1.0
Testis	45±18.0	—	82±22.5	—	10±5.7	—	1±0.1	—
Ovary	—	49±34.1	—	73±3.0	—	7±3.1	—	3±1.4
Uterus	—	44±22.1	—	74±7.0	—	7±3.0	—	3±2.4

Data are expressed as the means±S.D. of three animals.

trans-isomer was PGH, the maximum concentration occurring 6 hr after administration in both males and females (61 and 54 ppm, respectively). The main metabolite in the group treated with the *cis*-isomer was also PGH, its concentration reaching a maximum 6 hr after administration in both males and females (23 and 37 ppm, respectively).

3. ^{14}C-Concentrations in Tissues

^{14}C-Concentrations in selected organ/tissue samples are shown in Tables 4 to 7. For the low dose group given the *trans*-isomer, the concentration reached a maximum 0.5–3 hr after administration in all samples of both sexes (Table 4). The concentrations decreased rapidly in the tissues along with the decrease in blood

Table 7 ^{14}C-Concentrations in tissues after a single oral administration of (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin to rats at 200 mg/kg (high dose).

Tissue	^{14}C-Concentration (ppm)							
	1 hr		6 hr		24 hr		72 hr	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal	29±13.1	51±24.0	60±9.5	60.2±28.0	11±1.2	10±2.3	5±1.3	2±0.7
Blood	28±11.1	32±1.2	66±12.6	56.5±20.3	16±1.9	11±3.1	7±1.3	4±0.8
Blood cells	20±8.5	22±1.4	52±9.7	43.9±16.7	9±1.3	8±1.5	6±0.5	4±0.6
Plasma	33±13.4	38±2.6	80±15.3	66.8±24.2	21±2.2	13±4.2	7±1.6	4±0.9
Bone	12±6.3	12±0.7	31±5.8	20.1±9.0	10±0.2	5±1.4	7±1.3	3±0.7
Bone marrow	22±10.0	25±1.4	58±11.3	49.6±18.5	13±0.9	10±2.9	5±1.2	3±1.1
Brain	17±10.3	28±4.7	48±10.9	46.1±19.0	3±1.0	5±1.4	1±0.2	0±0.0
Fat	5±1.6	50±66.0	11±0.7	27.0±30.8	3±0.7	2±0.6	2±0.6	0±0.2
Heart	26±7.4	50±9.0	55±16.7	52.2±19.3	7±1.0	7±2.2	3±0.9	1±0.3
Kidney	77±46.6	66±13.2	108±10.3	90.2±31.8	21±3.4	19±7.0	7±1.5	3±0.6
Liver	69±18.6	95±27.3	90±22.3	83.3±41.1	37±3.6	21±8.0	14±2.9	4±1.6
Lung	27±5.8	48±34.6	63±21.9	63.7±19.4	10±1.4	8±2.4	5±1.1	1±0.6
Muscle	21±9.4	26±6.5	55±8.0	49.2±18.1	6±1.0	6±1.7	3±0.3	1±0.2
Pancreas	35±19.9	43±23.5	51±9.9	114.2±89.8	10±1.9	8±2.9	4±0.9	1±0.4
Skin and hair	21±8.6	23±1.9	47±9.7	46.2±16.1	14±2.1	27±3.7	10±2.2	9±1.9
Spleen	28±13.9	30±11.5	54±10.2	69.5±40.0	9±1.1	7±2.3	4±1.0	1±0.4
Testis	15±6.2	—	56±11.2	—	5±1.1	—	2±0.4	—
Ovary	—	40±15.6	—	54.0±11.5	—	9±2.8	—	2±0.6
Uterus	—	39±14.8	—	56.1±22.0	—	8±2.8	—	2±0.5

Data are expressed as the means±S.D. of three animals.

levels. The concentrations at 72 hr were 45 ppb or less in all samples. For the low dose group given the *cis*-isomer, the concentration also reached a maximum 0.5–3 hr after administration in all samples of both sexes (Table 5). The concentrations in both males and females decreased more gradually as compared with the *trans*-isomer case, but values 72 hr after administration were less than 73 ppb in all samples.

For the high dose group given the *trans*-isomer, the maximum concentration occurred 1–6 hr after administration in all samples of both sexes (Table 6). The concentration decreased along with the decrease in the blood levels. The concentrations 72 hr after administration were 7 ppm or less in all samples. For the high dose group treated with the *cis*-isomer, the concentration reached a maximum 1–6 hr after administration in all tissues in both sexes (Table 7). The concentration then decreased with that in the blood, values at 72 hr being less than 14 ppm in all samples.

DISCUSSION

In our previous rat metabolism study of imiprothrin,[2] radiocarbon was almost completely eliminated from male and female rats given a single oral dose of (1*R*)-*trans*- or (1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin at 1 or 200 mg/kg within 7 days. In addition, ^{14}C-tissue residues on the 7th day after administration were generally low in all treated rats. The main excretion route was urine, and more than 89 and 83% of dosed radiocarbon was excreted into urine from the *trans*- and *cis*-isomers, respectively. Moreover, parent compounds were observed only in the feces, and the amounts were very low (less than 2.3% of dose), suggesting that almost all of the dosed compounds was absorbed, although no bile excretion study was conducted. In the present study, ^{14}C-blood levels become rapidly elevated in rats treated with the *trans*- and *cis*-isomers, indicating rapid and complete absorption of imiprothrin.

The time-courses of the ^{14}C-blood levels were similar for males and females for each dose while ^{14}C-blood levels of males were slightly higher than those of females 24–144 hr after dosing of the *cis*-isomer, showing no marked sex-related differences in absorption of imiprothrin isomers. However, ^{14}C-blood levels with the *cis*-isomer decreased more gradually than with the *trans*-isomer in line with the previous studies of other pyrethroids such as tetramethrin,[6] cyphenothrin[7] and phenothrin.[7] In our previous metabolism study,[2] urinary excretion of the *trans*-isomer was slightly higher than that of the *cis*-isomer, and the amounts of urinary ester type cleaved metabolites (PGH-OH, HYD and PGH) for the *trans*-isomer was larger than those for the *cis*-isomer. In addition, ester metabolites (*ω*-*trans*-carboxylic acid-type metabolites) clearly appeared in the urine of rats treated with the *cis*-isomer. These results may be mainly due to a difference in esterase hydrolysis activity between *trans*- and *cis*-isomers, which is well-known to occur with many pyrethroids.[5, 7–11] In the present study, the major imiprothrin metabolites in blood were ester cleavaged type metabolites, and therefore, we

conclude that the *cis*-isomer is metabolized slowly and retained longer than the *trans*-isomer.

In the blood metabolite analysis, no parent compounds were detected at any time point in either treatment group, indicating rapid biotransformation of imiprothrin isomers. For the low dose groups, levels of PGH, PGH-OH and HYD were all appreciable in the blood whereas the main metabolite in blood after high dose administration was PGH. The results are consistent with the remarkable increases in the proportions of PGH in the urine of rats treated with the high dose of both isomers in the previous study.[2)]

^{14}C-Concentrations in selected organ/tissue samples reached maxima 0.5–3 and 1–6 hr after administration in the low and high dose groups, respectively. The concentrations then decreased along with the observed decrease in the ^{14}C-levels in the blood, suggesting that imiprothrin or its metabolite(s) are easily distributed to many tissues. The fact that concentrations in tissues of rats treated with the *cis*-isomer were higher at 72 hr than those in the respective tissues of rats treated with the *trans*-isomer, indicate a more gradual decrease in line with the *cis*-isomer ^{14}C-blood levels.

In conclusion, the findings in the present study suggest that both imiprothrin isomers are readily absorbed, metabolized and rapidly distributed and excreted from rats.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Miss Tomoko Takayama, Miss Tomoko Nakanishi and Miss Kaeko Mori for their technical assistance.

REFERENCES

1) S. Senbo, T. Ito & Y. Abe: Abstr.; 3rd Annu. Meet. Jpn. Soc. Environ. Entomol. Zool., p. 46, 1991 (in Japanese)
2) K. Saito, H. Kaneko, Y. Tomigahara, I. Nakatsuka & H. Yamada: *J. Pesticide Sci.* **20**, 529 (1995)
3) K. Saito, H. Kaneko, K. Sato, A. Yoshitake & H. Yamada: *Xenobiotica* **21**, 575 (1991)
4) H. Yoshino, H. Kaneko, I. Nakatsuka & H. Yamada: *Xenobiotica* **23**, 1075 (1993)
5) K. Shiba, N. Kakuta, H. Kaneko, I. Nakatsuka, A. Yoshitake, H. Yamada & J. Miyamoto: *J. Pesticide Sci.* **13**, 557 (1988)
6) H. Kaneko, H. Okawa & J. Miyamoto: *J. Pesticide Sci.* **6**, 425 (1981)
7) H. Kaneko, M. Matsuo & J. Miyamoto: *J. Pesticide Sci.* **9**, 237 (1984)
8) H. Kaneko, H. Okawa & J. Miyamoto: *J. Pesticide Sci.* **6**, 169 (1981)
9) T. Izumi, H. Kaneko, M. Matsuo & J. Miyamoto: *J. Pesticide Sci.* **9**, 259 (1984)
10) N. Isobe, T. Suzuki, J. Nishikawa, H. Kaneko, I. Nakatsuka, A. Yoshitake & J. Miyamoto: *J. Pesticide Sci.* **17**, 27 (1992)
11) Y. Tomigahara, M. Mori, K. Shiba, N. Isobe, H. Kaneko, I. Nakatsuka & H. Yamada: *Xenobiotica* **24**, 1205 (1994)

要　　約

イミプロスリン異性体のラットにおける代謝：吸収と分布

斎藤幸一，金子秀雄，冨ヶ原祥隆
中塚　巌，山田宏彦

新規ピレスロイド系殺虫剤イミプロスリン［2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl]methyl (1*R*)-*cis*, *trans*-chrysanthemate の *trans* および *cis* 体のアルコール側 ^{14}C 標識体を雌雄ラットに 1 および 200 mg/kg の割合で 1 回経口投与した．血中の ^{14}C 濃度は *trans* 体投与群で，投与後 5 時間以内，*cis* 体投与群では投与後 9 時間以内に最高値に達し，その後，減少した．*trans* 体投与群は *cis* 体投与群に比べ最高値は高値を示したが，その減少は速やかであった．組織中の ^{14}C 濃度は血中 ^{14}C 濃度の推移とともに減少した．投与後 72 時間目の各組織中の ^{14}C 濃度は，*cis* 体投与群は *trans* 体投与群に比べ高値を示した．血液中の代謝物分析の結果，低用量群ではおもに，1）エステル結合の開裂，2）イミドメチレン結合の開裂，3）イミダゾリジン環の水酸化，4）2-プロピニル基の脱離を認めたが，高用量群ではエステル結合の開裂が主反応であった．イミプロスリンのラットにおける吸収，分布には顕著な性差は認められず，また，イミプロスリンはラットにおいて速やかに吸収，代謝，分布され，そして，体外へ排泄されることが明らかとなった．