原　　著

Mammalian Toxicological Study of Permethrin, 3-phenoxybenzyl (±)-*cis*, *trans*-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropane-1-carboxylate. Tadaomi KADOTA, Yasuyoshi OKUNO, Hiroyuki KOHDA and Junshi MIYAMOTO (Research Department, Pesticides Division, Sumitomo Chemical Co., Ltd., Takarazuka, Hyogo, Japan) Received May. 20, 1976 *Botyu-Kagaku*, 41, 143, 1976.

25. パーメスリンの哺乳動物における毒性

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新らしいピレスロイド，パーメスリンの急性毒性，刺激並びに皮膚感受性作用および6ケ月間の亜慢性毒性を検索した．

パーメスリンの各異性体の雄マウス経口投与による LD_{50} は(+)-トランス，(+)-シス体それぞれ3100，107mg/kg であり，(−)-トランス，(−)-シス体の LD_{50} はいずれも 5000mg/kg 以上であった．(±)-シス，トランス，パーメスリン（シス/トランス比，約40/60)のマウス経口 LD_{50} は雄：650mg/kg，雌：540mg/kg，ラットでは雄：430mg/kg，雌：470mg/kg であった．一方皮下および経皮毒性はマウス，ラット共非常に弱かった．

パーメスリンのウサギの眼並びに皮膚に対する刺激作用およびモルモットにおける皮膚感受性作用はいずれも陰性であった．

パーメスリンの亜慢性毒性を明らかにするため，シス・トランス比40：60の標品を375，750，1500および3000ppm の飼料中濃度でラットに6ケ月間摂食させ，一般症状の観察，体重測定，摂食量測定，尿検査，血液検査，臨床生化学検査，病理組織学検査を実施した．

3000ppm で中毒症状の発現および肝への軽度の影響が認められた以外は各検査項目共この化合物の投与に起因する異常は見出されなかった．中毒症状は実験開始初期から発現したが6～7週後には消失した．6ケ月間の摂食後肝重量は軽度増加し，病理組織学的には軽度の肝実質細胞の腫大と脂肪変性を認めた．パーメスリンの無影響量はこの条件下において，飼料中 1500ppm，体重換算雄：92.9mg/kg/day，雌：110mg/kg/day であった．

Introduction

Permethrin, ester of 3-phenoxybenzyl alcohol with 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropane-1-carboxylic acid, is a new pyrethroidal insecticide synthesized by Elliott *et al.*[1-3] The insecticidal performances of permethrin have been reported by Tsuda *et al.*[4], indicating the compound will be of great practical use for control of insects of medical importance and agricultural plant pest. Since few toxicological informations have been available on permethrin,[3,5] the study was initiated to examine the toxicological properties of permethrin in mammals. In this paper are presented the results of testing on acute toxicity in mice and rats, eye and skin irritation in rabbits and skin sensitization in guinea pigs. Moreover, permethrin was fed to rats for consecutive 6 months to examine subchronic effect on various physiological parameters.

Materials and methods

Compounds

The following 4 isomers of permethrin, 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropane-1-carboxylic acid ester of 3-phenoxybenzyl alcohol were synthesized in this laboratory; (+)-*trans*, (+)-*cis*, (−)-*trans* and (−)-*cis*. They were all above 99% pure. In some experiments technical (±)-*cis*, *trans* permethrin (*cis*/*trans* ratio approximately 40/60, 91.3～94.6% pure) was also used.

Animals

Six-week old dd mice weighing 20～24g (male) or 18～22g (female), native Japanese strain albino male rabbits, 2.0～2.8kg, and Hartley strain male guinea pigs, 200～250g, were supplied by Nihon Dobutsu Co., Osaka. Seven-week old Sprague Dawley rats with body weight of 200～250g (male) or 170～220g (female) for the acute toxicity study were purchased from Nihon

Dobutsu Co., Osaka and 4-week old Sprague Dawley rats for the feeding study from Shizuoka Jikkendobutsu Kyodokumiai, Shizuoka. The animals were kept in an atmosphere of constant temperature (23 ± 2°C for mice and rats and 22±2°C for guinea pigs and rabbits) with relative humidity of 60 ± 10%, and had free access to water and diet (CE-2 for mice and rats, CG-3 for guinea pigs, supplied by Nihon Clea Co., Osaka) except that rabbits given 100g/day CR-1 food (Nihon Crea Co.).

Procedures

Acute toxicity: In acute oral and subcutaneous toxicity studies the test compound was dissolved in corn oil, and 0.1 m*l*/10g body weight and 0.5~1.0m*l*/100g body weight were administered to groups of 10 mice and rats, respectively. Some liquid compounds were applied without vehicle. In acute dermal toxicity study, the dorsal hair of animals anesthetized by diethyl ether was sheared by an electric clipper and the sheared area (1.5cm² in mice and 15cm² in rats) of 10 animals each was treated with the undiluted test compounds. The toxic symptoms and death were observed for 2 weeks, and LD_{50} was culculated according to Litchfield & Wilcoxon method.[6]

Eye and skin irritation: Eye irritation study was carrid out according to the proposed guideline of Environmental Protection Agency of United States.[7] One tenth m*l* of technical permethrin (lot 1, purity 91.3%) was instilled into left eye of eight rabbits. The rabbits were divided into two groups. At 5 minutes post-treatment the eye of the five rabbits in group I was washed with 300m*l* of distilled water for 3 minutes. The eye of 3 remaining animals (group II) was similarly washed after 24 hours. In both cases the other untreated eye was served as a control. The eyes of each animal in the test group were examined by means of an ophthalmoscope and fluorecein coloration, 1, 24, 48, 72 hours and 7 days after the application.

For skin irritation test dorsal hair of 5 rabbits was sheared and one hour thereafter, the 20cm² wide sheared area was treated with 0.5m*l* of technical permethrin (lot 1, purity 91.3%). The treated area was grossly examined 1, 4, 24 hours after the treatement and every 24 hours thereafter for 7 days.

Skin sensitization: The skin sensitization study was carried out according to the method of Landsteiner-Draize,[8] using 2,4-dinitro chlorobenzene (DNCB: Wako pure Chem. Ind. Ltd., Osaka) as the positive control. Prior to the administration hair was sheared of the abdomen of 8 animals of each test group. For the sensitization, 0.05m*l* at first and subsequently 0.1m*l*/animal of 1% or 5% corn oil solution of technical permethrin (lot M-010A-M, purity 94.6%) was injected intracutaneously 3 times a week at the interval of one or two days during the whole period of 23 days. The sensitizing administration of DNCB was conducted three times every other day with the dosage of 0.1m*l* of 0.05% corn oil solution per animal.

The challenging administration was done at the dose of 0.05m*l* of each solution 14 days after the final sensitizing administration. Animals prepared for a negative control were divided into 3 groups, each of which received 1%, 5% technical permethrin or 0.05% DNCB as the challenging material.

Macroscopic observations were made on the injection site of each animal 24 hours after the challenging administration, and then subcutaneous tissues were grossly examined.

Six month subchronic toxicity: Eighty males and 80 females rats were randomized into 5 groups, 4 each in one aluminum cage of 35×42×20cm. Groups of 16 each of males and females were fed technical permethrin (lot M-1, purity 93.3%) at the dietary concentration of 0, 375, 750, 1500 and 3000ppm for 6 months. Behavioral changes and mortality were observed every day, and body weight, food and water consumption were recorded weekly. At 3rd and 6th month of the feeding urinary sugar (Benedict method*), protein (protein error method*), ketone bodies (sodium nitroprusside method*), occult blood (orthotolidine method*), bilirubin (azobirilubin method*) and urobilinogen (Ehrich method*) were examined with 8 males and 8 females in 0 and 3000ppm groups. At the termination of the

* The reagents for the test were purchased from Ames Division, Miles-Sankyo Co., Ltd.

feeding all surviving animals were starved for 24 hours and under ethyl ether anesthetization blood was withdrawn from abdominal aorta for hematological and clinical biochemical examinations. Hematological examination on all animals in control and 2 highest dose groups were carried out with erythrocyte count, leucocyte count, platelet count and hemoglobin content with a microcell counter (TOA Electric Co. Ltd., type II), and hematocrit value and sedimentation rate by the standard technique. Serum was subjected to clinical biochemical examination including sodium, potassium, calcium, total protein, glucose, blood urea nitrogen, uric acid, bilirubin, cholesterol, alkaline phosphatase, transaminase (GOT and GPT), cholinesterase, leucine aminopeptidase and lactic dehydrogenase by use of a Technicon autoanalyzer SMA 60/12 or type II except for leucine aminopeptidase (*p*-dimethylaminobenzaldehyde method[9]) and lactic dehydrogenase (dinitrophenylhydrazine method[10]).

Immediately after blood sampling every tissue and organ were grossly observed and major organs were dissected out to weigh. Also the following tissues were subjected to histopathological examinations by fixation with 10% formalin, followed by double staining with Hematoxyline and Eosin: brain, eye, spinal cord, trachea, lung, heart, spleen, bone marrow, lymph node, thymus, esophagus, stomach, small and large intestine, salivary gland, liver, pancreas, kidney, urinary bladder, testis or ovary, prostate or uterus, pituitary, thyroid and adrenal.

Mean and standard errors were calculated and the results were statistically analyzed by t-test.

Results and Discussions

Acute toxicity: Acute oral LD_{50} values of each isomer and racemic mixtures of permethrin in male mice are summarized in Table 1. The toxic symptoms such as hypersensitivity, tremor and then mortor ataxia were observed except that the symptoms were shown in neither (−)-*trans* nor (−)-*cis* isomers at the dosage level of 5000mg/kg. The onset of symptoms with (+)-*cis* isomer and the racemic mixtures were observed 30 to 60 minutes and 2 to 3 hours post-treatment, respectively, and in the case of (+)-*trans* isomer 4 to 5 hours after administration. The toxic symptoms in surviving animals disappered within 24 hours. Among the materials tested, (+)-*cis* isomer was more toxic than other isomers and racemic mixtures. On the basis of LD_{50} values of (±)-*trans* and (±)-*cis* isomers, the theoretical LD_{50} value of the racemic mixtures was calculated according to the method of Finney[11]. As indicated in Table 1, the actual LD_{50} values of racemic mixtures agree well with the calculated ones except that of permethrin containing 75% of (±)-*trans* isomer. These findings suggest no potentiating effects of one isomer against another.

Acute oral, subcutaneous and dermal toxicity

Table 1. Acute oral toxicity of isomer and racemic mixtures of Permethrin in male mice.

Compound	LD_{50}, mg/kg	
	Experimental	calculated
Permethrin, (+)-*trans*	3100 (2440-3940)[a]	—
(+)-*cis*	107 (86- 134)	—
(−)-*trans*	>5000[b]	—
(−)-*cis*	>5000[b]	—
(±)-*trans*	>5000[b]	6200
(±)-*cis*	265 (217- 323)	214
racemic[c] (*trans/cis*=25/75)	310 (263- 366)	348
racemic (*trans/cis*=50/50)	470 (405- 545)	510
racemic (*trans/cis*=75/25)	1620 (1290-2020)	943

[a] Figures in the parenthese indicate 95% confidence limit.
[b] No death was shown at this dosage level.
[c] These were prepared by mixing (±)-*trans* isomer with -*cis* isomer.

Table 2. Acute toxicities of technical Permethrin administered by various routes to mice and rats.

Animal	Route	Sex	LD_{50}, mg/kg
Mouse	Oral	Male	650 (520- 813)[a]
		Female	540 (489- 597)
	Subcutaneous	Male	> 10,000[b]
		Female	ca. 10,000[c]
	Dermal	Male	> 2,500[d]
		Female	> 2,500[d]
Rat	Oral	Male	430 (355- 520)
		Female	470 (379- 583)
	Subcutaneous	Male	7,800 (6270-9710)
		Female	6,600 (5160-8450)
	Dermal	Male	> 2,500[d]
		Female	> 2,500[d]

[a] Figures in the parenthese indicate 95% confidence limit.
[b] Mortality at 10,000 mg/kg was 20%.
[c] Mortality at 10,000 mg/kg was 50%.
[d] No symptoms were observed by this dosage level.

of (±)-*cis, trans* technical permethrin in mice and rats were tested. The results are shown in Table 2. Together with the toxic symptoms described above, fibrillation and salivation were also noted in rats. By both oral and subcutaneous administration permethrin was slightly less toxic in rats than in mice, and dermally 2500mg/kg of the compound caused no symptoms of intoxication. The formation of granulation tissues including oily substance was observed in the subcutaneous tissues of mice and rats by subcutaneous treatment. The mass of granulation tissue observed at the doses above 1000mg/kg increased proportionally to the dosage levels of the test material. The sex difference was not found in either species by any administration route.

When oral toxicity in mice of permethrin is compared with other pyrethroidal insecticides[5], it is similarly toxic to natural pyrethrin mixture, allethrin and resmethrin. The previous investigation in this laboratory indicates that oral LD_{50} of permethrin in rats is a little above 5000mg/kg[6], although minimum toxic dose was similar in both experiments. The reason for the discrepancy has not been investigated.

Eye and skin irritation: No particular changes were found during 21-day observation period in cornea, iris and conjunctiva of rabbits eye treated with technical permethrin. Nothing abnormal was observed in the skin of rabbits treated with the compound, either.

Skin sensitization: Guinea pigs showed no skin sensitization effects by intracutaneous sensitization and challenging of permethrin. By contrast DNCB showed diffuse hyperemia and swelling, together with blood-spot and hyperemia in the subcutaneous tissues.

Six month subchronic toxicity: Symptoms of intoxication such as hypersensitivity and tremor were observed in most males and 4 to 5 females of 3000ppm group during early period of feeding. The symptoms were more clearly seen in the morning and disappeared in the evening. The toxic signs became less severe after 4 to 5 weeks, and disappeared around 6 to 7 weeks. No death was noted in any group during feeding period.

Fig. 1 shows mean body weight of rats during the feeding period. Body weight curve of any treated group was comparable to the control.

The results of food and water consumption revealed no distinct difference among any groups. Intake of permethrin during the feeding period was calculated from food consumption, and the results are indicated in Table 3.

No significant differences between 3000ppm and control groups were observed in urinalysis at 3rd

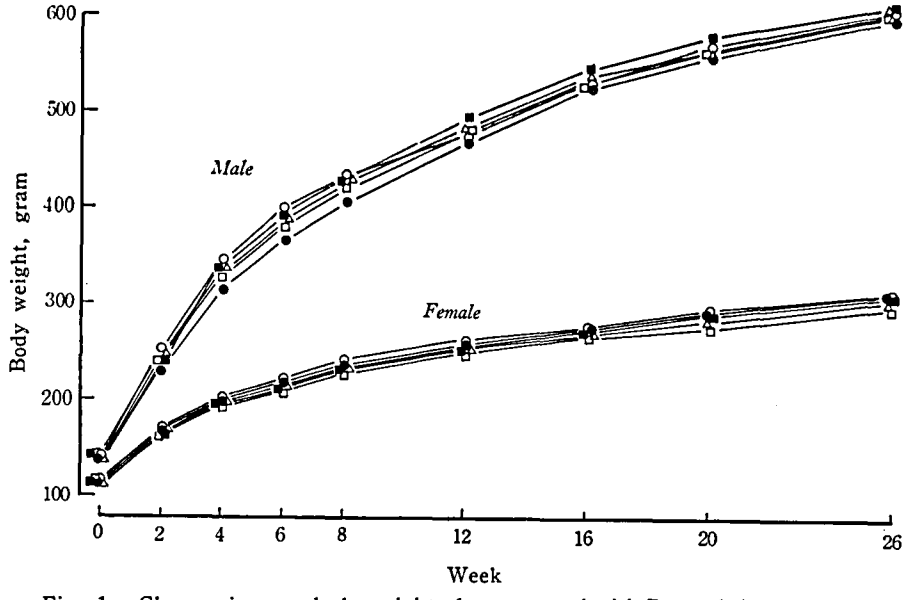

Fig. 1. Changes in mean body weight of rats treated with Permethrin for 6 months
○ Control ● 375 ppm □ 750 ppm ■ 1,500 ppm △ 3,000 ppm

Table 3. Intake of Permethrin during 6 month feeding period.

Dietary level ppm	Compound ingested mg/kg body weight/day	
	Male	Female
375	22.5	27.5
750	46.0	52.3
1,500	92.9	110
3,000	185	221

and 6th month.

The results of hematological examination are shown in Table 4. Although there were some statistically significant differences between control and treated groups, they were within the range of normal physiological fluctuation, and feeding of permethrin at 1500 and 3000ppm did not adversely affect hematological profiles. In clinical biochemical examination statistically significant differences were observed in several of the items examined. (Tables 5 and 6) However, the changes were not corelated with the dosage of the compound.

Weight of 10 major organs at the termination of feeding and its ratio to body weight are shown in Tables 7, 8, 9 and 10, respectively. Liver weight as well as its body weight ratio was significantly higher at the highest 3000ppm group. Although some other changes were sporadically observed, they were not dose-related, and therefore presumed not to be attributable to the administration of the compound. At the necropsy, there were no abnormal gross findings except that liver of the rats in 3000ppm group was slightly enlarged. Twenty-five organs and tissues of rats in control, 1500ppm and 3000ppm groups were microscopically examined. The summarized results are shown in Table 11. There were no abnormal histopathological findings related to permethrin administration except that a slight hypertrophy (megalocytic changes) of liver parenchymal cells and slight fatty changes were observed in 3000ppm group. However, these changes were not accompained by alteration of liver function as exemplified by clinical biochemistry. The change is not specifically found in permethrin, since similar adverse effects have often been observed by subacute administration of other pyrethroidal compounds[5].

Summary

Mammalian toxicological properties of a new

synthetic pyrethroidal insecticide, permethrin were examined and the following results were obtained.

Oral LD_{50} values of (+)-*cis* and (+)-*trans* permethrin to male mice were 107mg/kg and 3100mg/kg, respectively, whereas (−)-*trans* and (−)-*cis* isomers were both very lowtoxic. Acute toxicity of (±)-*cis*, *trans* technical permethrin with *cis/trans* ratio of approxmately 40/60 on mice and rats was examined by several administration routes. Oral LD_{50} values in mice was 650mg/kg in male and 540mg/kg in female, and in male and female rats are 430mg/kg and 470mg/kg, respectively. Subcutaneous and dermal toxicity of permethrin in both species were very low as compared with the oral toxicity.

Permethrin caused neither eye and skin irritation nor skin sensitizing effects.

Six month feeding study of permethrin at the dietary concentration of 0, 375, 750, 1500 and 3000ppm in rats revealed that the no effect level is 1500ppm in diet or 92.9mg/kg/day for males and 110mg/kg/day for females. At the higher level (3000ppm) toxic symptoms were observed at the early stages of feeding, together with a slight increase of liver weight and a slight hypertrophy of hepatoparenchymal cells after 6 months.

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Table 4. Hematological changes of rats treated with Permethrin for 6 months.

Items	Unit	Hematological values at various dietary levels indicated[a)]					
		Male			Female		
		Control	1,500ppm	3,000ppm	Control	1,500ppm	3,000ppm
Hematocrit	%	48.8±0.32	46.1±0.57**	48.3±0.65	43.8±0.46	45.8±0.56**	43.3±0.40
Hemoglobin	g/dl	15.0±0.07	14.2±0.11**	14.7±0.16	14.0±0.13	14.0±0.14	13.8±0.10
Erythrocyte	$\times 10^4/mm^3$	899 ±10.4	888 ±8.61	919 ±11.0	821 ±9.34	811 ±11.8	813 ±8.36
Platelet	$\times 10^4/mm^3$	86.7±9.27	—	80.9±4.53	78.7±5.87	—	74.8±4.23
Leukocyte	$\times 10^2/mm^3$	127 ±4.47	94.6±3.90**	130 ±5.45	71.1±4.34	66.4±3.39	84.9±5 02**
Sedimentation	mm/hr	0.57±0.10	0.34±0.07	0.79±0.24	0.41±0.16	0.26±0.03	0.48±0.22

a) Average of 16 rats. The mean ± standard error is given.
** $p < 0.01$

Table 5. Biochemical changes of male rats treated with Permethrin for 6 months.

Items	Unit	Biochemical values at various dietary levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Sodium	meq/l	140 ±0.56	143 ±0.65**	141 ±0.31	142 ±0.53	139 ±0.90
Potassium	meq/l	5.65±0.08	5.37±0.09*	5.28±0.09**	5.21±0.12**	5.51±0.08
Calcium	meq/l	9.52±0.09	9.72±0.06	9.47±0.08	9.49±0.15	9.60±0.10
Total protein	g/dl	6.67±0.09	6.82±0.07	6.69±0.06	6.67±0.08	6.68±0.10
Albumin	g/dl	2.95±0.03	3.06±0.04*	2.97±0.04	2.95±0.06	3.03±0.07
Glucose	mg/dl	131 ±2.67	133 ±2.94	133 ±4.80	150 ±3.77**	131 ±4.13
Uric acid	mg/dl	2.16±0.09	2.47±0.06**	2.40±0.04*	2.36±0.15	2.34±0.07
Bilirubin	mg/dl	0.32±0.02	0.37±0.01*	0.36±0.02	0.24±0.02**	0.35±0.02
Blood urea-N	mg/dl	15.8±0.48	18.5±0.61**	15.8±0.33	15.7±0.40	17.0±0.60
Cholesterol	mg/dl	79.7±4.67	—	—	91.9±5.57	96.5±5.11*
ALP	I U/l	78.5±4.09	80.9±4.38	73.6±3.96	81.1±4.15	80.1±4.21
GOT	I U/l	206 ±10.0	203 ±6.28	203 ±7.43	167 ±6.79**	192 ±6.71
GPT	I U/l	23.5±1.14	16.4±0.77**	14.0±1.25**	16.1±0.92**	22.2±1.40
LAP	G-R U/ml	134 ±6.02	—	—	—	123 ±5.89
CH-E	GSH m. mol.	4.60±0.21	4.56±0.24	5.17±0.31	4.90±0.25	4.31±0.19
LDH	LDH U/ml	1790±36.7	—	—	—	1620±57.9

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$
ALP: Alkaline phosphatase, GOT: Glutamic oxaloacetic transaminase,
GPT: Glutamic pyruvic transaminase, LAP: Leucine aminopeptidase, CH-E: Cholinesterase,
LDH: Lactic dehydrogenase.

Table 6. Biochemical changes of female rats treated with Permethrin for 6 months.

Items	Unit	Biochemical values at various dietary levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Sodinm	meq/l	141 ±0.27	141 ±0.35	141 ±0.35	142 ±0.36*	141 ±0.41
Potassium	meq/l	4.95±0.07	4.60±0.08**	5.08±0.07	4.37±0.10**	4.64±0.09*
Calcium	meq/l	9.96±0.10	10.2±0.11	10.1±0.07	10.1±0.07	10.2±0.08
Total protein	g/dl	7.20±0.08	7.13±0.11	7.14±0.06	7.08±0.05	7.13±0.07
Albumin	g/dl	3.97±0.07	4.08±0.10	4.05±0.06	4.18±0.21	3.87±0.06
Glucose	mg/dl	121 ±2.41	124 ±3.38	121 ±5.63	132 ±4.80	121 ±2.64
Uric acid	mg/dl	2.23±0.06	2.26±0.05	2.46±0.05	2.33±0.06	2.20±0.04
Bilirubin	mg/dl	0.39±0.01	0.56±0.01**	0.40±0.01	0.38±0.01	0.21±0.02**
Blood urea-N	mg/dl	16.0±0.46	16.5±0.40	16.8±0.77	16.7±0.45	15.6±0.38
Cholesterol	mg/dl	75.6±3.11	—	—	93.5±3.83**	88.2±3.21**
ALP	I U/l	41.9±6.21	38.1±3.03	24.5±2.57*	26.8±2.17*	36.4±2.44
GOT	I U/l	190 ±8.81	182 ±6.81	178 ±4.37	174 ±5.90	181 ±5.31
GPT	I U/l	15.6±1.19	19.4±2.48	17.4±1.65	16.3±2.47	13.3±0.93
LAP	G-R U/ml	84.8±2.25	—	—	—	80.1±3.03
CH-E	GSH m. mol.	9.98±0.64	9.26±0.52	9.35±0.53	9.21±0.51	8.31±0.30*
LDH	LDH U/ml	1650±57.9	—	—	—	1560±57.2

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$
ALP: Alkaline phosphatase, GOT: Glutamic oxaloacetic transaminase,
GPT: Glutamic pyruvic transaminase, LAP: Leucine aminopeptidase, CH-E: Cholinesterase,
LDH: Lactic dehydrogenase.

Table 7. Organ weights of male rats treated with Permethrin for 6 months.

Items	Unit	Organ weights at various dietary levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Body weight	g	604 ±10.3	598 ±17.6	607 ±13.3	615 ±16.7	605 ±11.5
Brain	g	2.06±0.02	1.99±0.02	2.06±0.02	2.00±0.02	2.08±0.03
Lung	g	2.26±0.16	2.01±0.06	1.89±0.07	1.99±0.14	2.11±0.10
Heart	g	1.58±0.04	1.49±0.06	1.60±0.04	1.53±0.05	1.68±0.07
Spleen	g	0.82±0.06	0.72±0.04	0.74±0.02	0.74±0.02	0.73±0.03
Thymus	g	0.32±0.03	0.34±0.02	0.39±0.03	0.34±0.02	0.42±0.04
Liver	g	14.7±0.46	14.3±0.66	14.4±0.40	15.6±0.53	18.1±0.51**
Kidney	g	3.05±0.06	3.00±0.10	3.20±0.07	3.27±0.10	3.44±0.06**
Testis	g	3.59±0.08	3.44±0.10	3.57±0.07	3.71±0.10	3.44±0.12
Adrenal	mg	64.1±2.88	58.5±2.24	58.1±2.08	55.8±1.98*	72.1±2.77*

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$

Table 8. Organ weights of femals rats treated with Permethrin for 6 months.

Items	Unit	Organ weights at various dietary levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Body weight	g	314 ±8.69	309 ±9.12	296 ±7.86	310 ±7.93	307 ±7.82
Brain	g	1.89±0.02	1.78±0.03*	1.87±0.02	1.83±0.03	1.93±0.02
Lung	g	1.39±0.05	1.37±0.05	1.41±0.04	1.47±0.04	1.43±0.04
Heart	g	0.93±0.03	0.96±0.04	0.91±0.03	0.91±0.02	0.94±0.02
Spleen	g	0.52±0.03	0.50±0.02	0.49±0.02	0.48±0.01	0.47±0.02
Thymus	g	0.27±0.03	0.22±0.01	0.23±0.02	0.25±0.02	0.24±0.01
Liver	g	6.93±0.23	6.80±0.25	6.79±0.25	7.20±0.29	8.30±0.20**
Kidney	g	1.69±0.04	1.66±0.05	1.67±0.07	1.63±0.03	1.69±0.04
Ovary	mg	81.8±4.93	78.1±16.6	75.0±4.29	86.4±5.68	74.2±5.68
Adrenal	mg	79.2±2.17	67.8±2.55**	65.8±3.78**	69.3±2.21**	74.3±2.81

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$

Table 9. Relative organ weights of male rats treated with Permethrin for 6 months.

Items	Unit	Ratio of organ weight to body weight at various levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Brain	$\times 10^{-2}$	0.34±0.01	0.34±0.01	0.34±0.01	0.31±0.02	0.34±0.01
Lung	$\times 10^{-2}$	0.38±0.03	0.34±0.01	0.31±0.01	0.30±0.03*	0.35±0.01
Heart	$\times 10^{-2}$	0.26±0.01	0.25±0.01	0.26±0.01	0.24±0.02	0.28±0.01
Spleen	$\times 10^{-2}$	0.14±0.01	0.12±0.00	0.12±0.00	0.11±0.01	0.12±0.00
Thymus	$\times 10^{-2}$	0.05±0.01	0.06±0.00	0.06±0.00	0.05±0.00	0.07±0.01
Liver	$\times 10^{-2}$	2.42±0.04	2.38±0.04	2.37±0.04	2.37±0.16	2.99±0.05**
Kidney	$\times 10^{-2}$	0.51±0.01	0.50±0.01	0.53±0.01	0.50±0.04	0.57±0.01**
Testis	$\times 10^{-2}$	0.60±0.02	0.58±0.02	0.59±0.01	0.58±0.04	0.57±0.02
Adrenal	$\times 10^{-5}$	10.7±0.52	9.80±0.24	9.62±0.39	9.09±0.27	11.9±0.47*

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$

Table 10. Relative organ weights of female rats treated with Permethrin for 6 months.

Items	Unit	Ratio of organ weight to body weight at various levels indicated[a)]				
		Control	375 ppm	750 ppm	1,500 ppm	3,000 ppm
Brain	$\times 10^{-2}$	0.61±0.02	0.58±0.02	0.64±0.01	0.60±0.02	0.64±0.01
Lung	$\times 10^{-2}$	0.45±0.02	0.45±0.02	0.48±0.02	0.48±0.01	0.47±0.01
Heart	$\times 10^{-2}$	0.30±0.01	0.31±0.01	0.31±0.01	0.29±0.00	0.31±0.01
Spleen	$\times 10^{-2}$	0.17±0.01	0.16±0.01	0.16±0.00	0.15±0.00	0.15±0.00
Thymus	$\times 10^{-2}$	0.09±0.01	0.07±0.00	0.08±0.01	0.08±0.00	0.08±0.00
Liver	$\times 10^{-2}$	2.19±0.04	2.20±0.05	2.29±0.05	2.32±0.07	2.71±0.03**
Kidney	$\times 10^{-2}$	0.54±0.01	0.54±0.01	0.56±0.01	0.53±0.01	0.55±0.01
Ovary	$\times 10^{-5}$	26.0±1.37	26.1±6.23	25.5±1.51	27.9±2.13	24.2±1.72
Adrenal	$\times 10^{-5}$	25.4±0.92	22.0±0.79*	22.3±1.13*	22.4±0.50**	24.2±0.81

a) Average of 16 rats. The mean ± standard error is given.
* $p<0.05$, ** $p<0.01$

Table 11. Histopathological findings of rats treated with Permethrin for 6 months.

Organ	Findings	Control		1,500 ppm		3,000 ppm	
		Male	Female	Male	Female	Male	Female
Lung	Pneumonia and abscess	3/16	2/16	3/16	2/16	2/16	2/16
Liver	Slight fatty changes of parenchymal cells	0/16	0/16	0/16	0/16	2/16	3/16
	Slight megalocytic changes of parenchymal cells	0/16	0/16	0/16	0/16	6/16	7/16
Pancreas	Slight cell infiltration in stromal area	3/16	2/16	0/16	3/16	0/16	2/16
Kidney	Slight cell infiltration in interstitial tissue	3/16	0/16	2/16	0/16	4/16	0/16

No remarkable changes were observed histopathologically in the following organs and tissues: brain, eye, spinal cord, trachea, heart, spleen, bone marrow, lymph node, thymus, esophagus, stomach, small and large intestine, salivary gland, urinary bladder, testis or ovary, prostate or uterus, pituitary, thyroid and adrenal.