Discovery and Development of Profluthrin (Fairytale®), a New Active Ingredient of Moth Proofer

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Profluthrin (Fairytale®), a newly discovered insecticide from Sumitomo Chemical Co., Ltd., provides high efficacy against fabric pests and also has relatively high vapor pressure and low mammalian toxicity, which means Profluthrin has various superior properties as an active ingredient of moth proofers. In addition, it has excellent activity against sanitary pests like flies, mosquitoes and cockroaches. Profluthrin was launched in 2004 in Japan, and several companies have adopted it for their household insecticide products. In this report we will introduce the outline of the new synthetic pyrethroid Profluthrin.

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Introduction

In previous times, when there was no knowledge regarding pest-proofing against fabric pests as seen today, the extent of worm-hole damage on clothing made of silk thread, wool and leather was tremendous. Although summer airing was known as a solution for such damage, its effect was very limited. Drawing inspiration from the phenomena whereby clothing stored in a camphor wood chest or fabrics colored in certain types of dyes tended not to be eaten by worms, the protection of fabrics has been studied actively since the end of the nineteenth century. As a result, it has been discovered that certain chemical compounds such as camphor, naphthalene and *p*-dichlorobenzene possess outstanding properties as active ingredients in moth-proofers. At Sumitomo Chemical Co., Ltd., we invented and developed empenthrin (Vaporthrin®), which proved efficacious at a dosage lower than that of conventional moth-proofers, and thus launched the product in 1983. Thanks to the dissemination of such moth-proofers, worm-hole damage has now dramatically decreased.

In response to the heightened recent trend toward the control of pests using fewer or smaller amounts of chemical agents (the so-called "inclination toward the use of less chemicals"), we have conducted an extensive search for, and research into, insecticides and moth-proofers that could offer higher levels of performance. As a result of such efforts, we have discovered a new pyrethroid called profluthrin (Fairytale®), which possesses outstanding properties as a moth-proofer while demonstrating a high degree of efficacy against nuisance pests and sanitary pests (**Fig. 1**). This paper will introduce the invention process as well as the properties of various agents; efficacy against fabric pests, nuisance pests and sanitary pests; field-application tests; physicochemical properties; manufacturing methods; and safety.

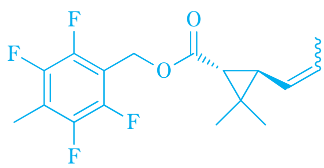


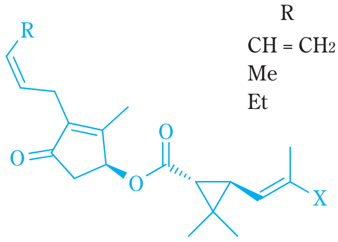
Fig. 1 Structure of profluthrin (Fairytale®)

* Present post : Osaka Works

Invention Process

A hundred years have passed since the report on the isolation of insecticidal ester — i.e. natural pyrethrin — from *Tanacetum cinerariaefolium* (a.k.a. insect flower) released by Fujitani et al. in 1909.[1)] While the natural pyrethrins demonstrate high insecticidal activity against pests, they also have low mammalian toxicity but are fast-acting, and vaporize under heat. Thus they have long been used as active ingredients in household insecticides such as mosquito coils. However, since natural pyrethrins aren't adequately stable in the presence of light and heat, their primary fields of application have been limited to indoor use.

Furthermore, while the supply of natural pyrethrins can be affected by weather because its raw materials are agricultural products, the supply of chemically synthesized pyrethrins is also difficult because the structure of the active ingredients (**Fig. 2**) is relatively complex. In order to solve these problems, research to obtain useful insecticides by modifying the structure of natural pyrethrins has been conducted over the past half-century, and thereby numerous related compounds (synthetic pyrethroids) have been invented. Consequently, synthetic pyrethroids are now used in a variety of product types, including agricultural insecticides as well as household insecticides, the latter of which was the original field of application.



R	X = Me	X = CO2Me
CH = CH2	: Pyrethrin I	: Pyrethrin II
Me	: Cinerin I	: Cinerin II
Et	: Jasmolin I	: Jasmolin II

Fig. 2 Structures of six insecticidal constituents of natural pyrethrins

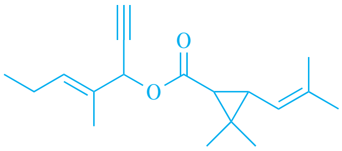
We at Sumitomo Chemical Co., Ltd. established a method for the industrial synthesis of allethrin (Pynamine®) — the first commercially successful synthetic pyrethroid — in 1953. Subsequently, we invented and developed a number of synthetic pyrethroids including *d*–tetramethrin (Neopynamin Forte®), *d*–allethrin (Pynamin Forte®), prallethrin (ETOC®), phenothrin (Sumithrin®), imiprothrin (Pralle®) and metofluthrin (Eminence®). These compounds have become widely used as household insecticides throughout the world, contributing to a more comfortable living environment.

Moth-proofers represent one of the household insecticide categories. The term "moth-proofers" is a generic one for the insect repellent products that are placed in drawers in order to prevent clothing damage from insects. Conventionally, natural oils (such as camphor) and chemical compounds with extremely high vaporization properties (such as naphthalene and *p*-dichlorobenzene) have been used as active ingredients in such moth-proofers. The reason that chemical compounds with high vaporization properties are used as active ingredients is that it is necessary to diffuse the active ingredients from moth-proofers placed in several locations throughout the drawers without using any artificial energy such as electricity and heat.

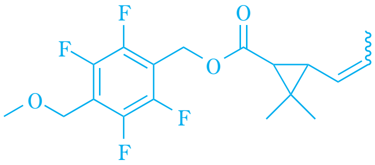
However, although the standard pyrethroid possesses high insecticidal activity against insects that cause worm-hole damage in clothes (fabric pests) such as *Tinea translucens, Tineola bisselliella* and *Attagenus unicolor*, its vaporization property is low. It simply doesn't show any practical efficacy when used in moth-proofers. Therefore, at Sumitomo Chemical Co., Ltd., we conducted research pertaining to the structural modification of pyrethroid with focus on its vaporization properties. As a result we have discovered the chemical compound called empenthrin (Vaporthrin®), which possesses vaporization property at ambient temperature while demonstrating high activity against fabric pests (**Fig. 3**). Due to the special features listed below, empenthrin is also applied in areas in which conventional moth-proofers could not be applied:

- It not only has an insect repellent effect but also has high insecticidal and egg-hatching inhibition effects;
- It demonstrates efficacies at significantly lower doses compared to conventional moth-proofers;
- It can be used in combination with conventional moth-proofers;
- It is almost completely odorless.

Meanwhile, we at Sumitomo Chemical Co., Ltd., in the course of inventing a novel pyrethroid chemical compound called metofluthrin (SumiOne®) (**Fig. 3**), which demonstrates outstanding pest-control activity against mosquitoes, have discovered that some of the chemical compound group — called norchrysanthemic acid esters — possess excellent insect repellent activity under the condition of vaporization at ambient temper-



Empenthrin



Metofluthrin

Fig. 3 Structures of empenthrin (Vaporthrin®) and metofluthrin (SumiOne®)

ature.[2)] Paying attention to the high vaporization property of norchrysanthemic acid esters at ambient temperature as well as their outstanding insecticidal activity, we decided to also evaluate this chemical compound group as moth-proofers. Consequently, it was discovered that profluthrin (Fairytale®) possesses outstanding properties as an active ingredient for use in moth-proofers.

Manufacturing Method

As shown in **Fig. 4**, profluthrin can be produced through the reaction between a norchrysanthemic acid ester derivative and 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol. More specifically, a condensation reaction between acid halide (X = halogen) and alcohol, a dehydration reaction between carboxylic acid (X = OH) and alcohol, and transesterification between carboxylate ester (X = OR) and alcohol can be listed as manufacturing methods.

By studying those reactions and various intermediate manufacturing methods over a wide range, we have established the industrial manufacturing method by which to effectively produce profluthrin.

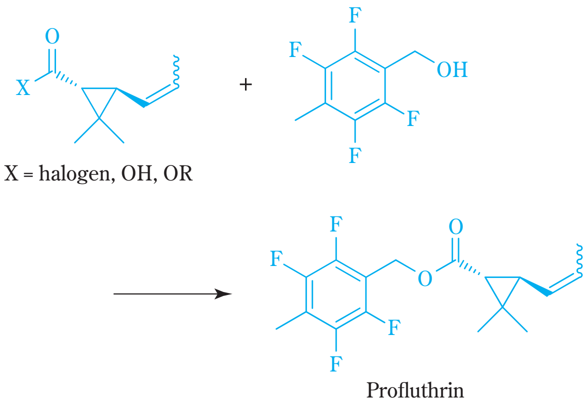


Fig. 4 Synthetic route to profluthrin

Efficacy

1. Basic Efficacy against Fabric Pests

We investigated the basic insecticidal efficacy of profluthrin against typical fabric pests such as *Tinea translucens*, *Tineola bisselliella* and *Attagenus unicolor* that can cause worm-hole damage in clothing.

(1) Lethal Effects on Fabric Pests

The lethal effect of profluthrin against fabric pests was investigated by a topical application method and compared to that of *EZ*-empenthrin.

The lethal effects of profluthrin on *Tineola bisselliella, Tinea translucens* and *Attagenus unicolor* larvae were as follows, respectively: approximately four times greater, more than five times greater and approximately eight times greater than that of *EZ*-empenthrin. From these results we can see that profluthrin possesses high lethal effect against the larvae of various types of fabric pests (**Table 1**).

Table 1 Efficacy of profluthrin against fabric pests by topical application method (LD50 [μg/larva])

	Profluthrin	*EZ*-Empenthrin
Tineola bisselliella	0.055	0.23
Tinea translucens	0.061	0.34
Attagenus unicolor	0.23	1.8

(2) Vapor Action on Fabric Pests

To investigate the vapor action of profluthrin against fabric pests, a small-space test was conducted using a cup with a capacity of approximately 1 L (**Fig. 5**). The result was then compared to *EZ*-empenthrin.

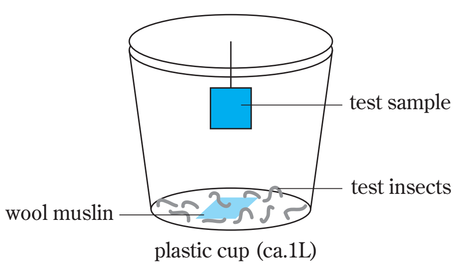


Fig. 5 Vapor action test method

Profluthrin demonstrated efficacy against *Tineola bisselliella* and *Tinea translucens* larvae by a factor of approximately four times greater than that of *EZ*-empenthrin. It also showed high efficacy against *Attagenus unicolor* larvae which was approximately eight times greater than that of *EZ*-empenthrin (**Table 2**). It has therefore been revealed that profluthrin possesses high vapor action against the larvae of fabric pests.

Table 2 Efficacy of profluthrin against fabric pests by vapor action test method (LD_{50} [μg/cup])

	Profluthrin	*EZ*-Empenthrin
Tineola bisselliella	2.6	11
Tinea translucens	6.3	25
Attagenus unicolor	11	93

2. Practical Efficacy against Fabric Pests

When using profluthrin as an active ingredient for moth-proofing products, such products will be used in carton cases, drawers and wardrobes that contain clothing. Therefore, several efficacy tests were conducted in such practical conditions.

(1) Egg-Hatching Inhibition Effect in a Drawer Test

The practical efficacy of each test sample was evaluated, assuming usage in carton cases and drawers, through the following procedure: Filter papers impregnated with agent were placed in a carton case containing clothes (with an approximate capacity of 50 L); and the effect of the test sample on *Tineola bisselliella* eggs was observed each time a specific time interval had passed (**Fig. 6**).

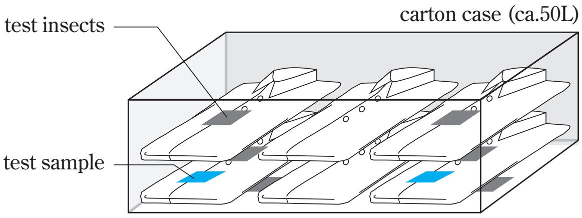


Fig. 6 Drawer test method against fabric pests

Profluthrin demonstrated high efficacy (egg-hatching inhibition effect and lethal effect on newly hatched larvae) against *Tineola bisselliella* eggs under a dosage of 20 mg during the period from one to six months after the initiation of the test. This result was nearly equivalent to that of a fivefold quantity of *EZ*-empenthrin and significantly greater than that of 80 g of *p*-dichlorobenzene (**Fig. 7**).

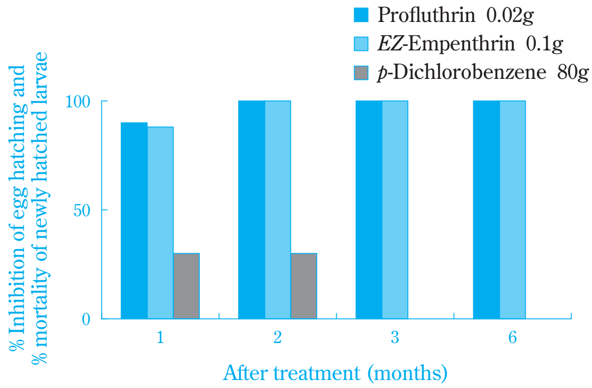


Fig. 7 Practical efficacy of profluthrin against common clothes moth (*Tineola bisselliella*) in a drawer test

(2) Egg-Hatching Inhibition Effect in a Wardrobe Test

Assuming the use in wardrobes, the practical efficacy of each agent against *Tineola bisselliella* was evaluated using a wardrobe (**Fig. 8**).

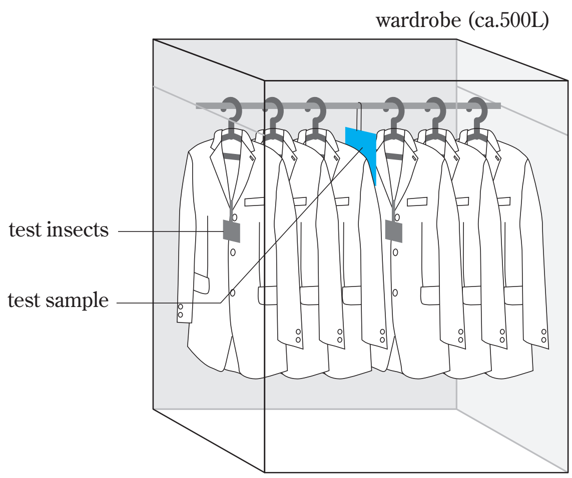


Fig. 8 Wardrobe test method

Profluthrin demonstrated pest-control rates of 100% (egg-hatching inhibition and lethal rate of newly hatched larvae) against *Tineola bisselliella* eggs under a dosage of 0.1g during the period from one to six months after the initiation of the test.

This result was equivalent to that of a fivefold quantity of *EZ*-empenthrin. On the contrary, *p*-dichlorobenzene did not show sufficient efficacy during the period from

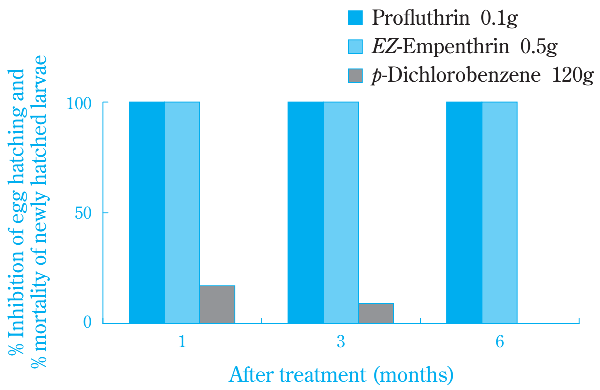


Fig. 9 Practical efficacy of profluthrin against common clothes moth (*Tineola bisselliella*) in a wardrobe test

the initiation of the test until six months after the test, even with a dosage of 120 g (**Fig. 9**).

(3) Oviposition Inhibition Effect on Fabric Pests

Worm-hole damage can be caused by the larvae of fabric pests through the following process: The adults of *Tinea translucens, Tineola bisselliella* and *Attagenus unicolor* fly into houses, enter drawers and wardrobes, lay eggs on clothing, and finally the hatched larvae feed on fabrics. For this reason the insecticidal activity against such larvae and egg-hatching inhibition effect on eggs laid on clothes were conventionally considered important evaluation criteria. However, it can be assumed that it is also important to prevent the adults of fabric pests from coming into contact with clothing and/or laying eggs in order to prevent worm-hole damage. Therefore, the oviposition inhibition effect of profluthrin on those adults was evaluated in a 28m^3 test chamber using a wardrobe with a capacity of approximately 700 L (**Fig. 10**).

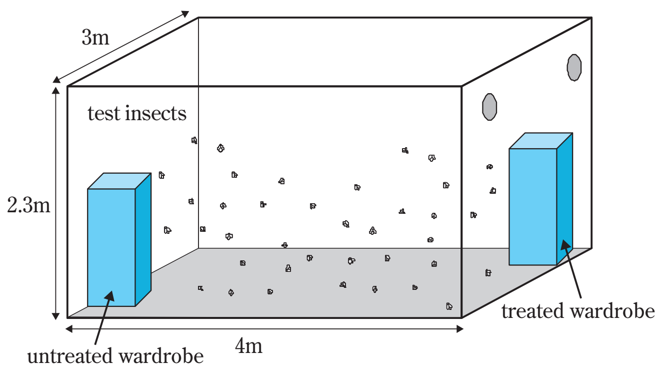


Fig. 10 Large chamber test method for inhibitory activity of oviposition

Filter papers impregnated with test samples were placed in a wardrobe containing clothes and fabrics. Two wardrobes — one containing impregnated filter paper and the other containing no such filter paper — were placed in two separated areas of the testing chamber, which were respectively called the treated section and the untreated section. The test insects (adults) were then released into the chamber. After a specified time period the number of eggs laid on the clothing and fabrics were counted. As a result, profluthrin demonstrated a high oviposition inhibition effect on *Tineola bisselliella* and *Tinea translucens* adults in the filter paper impregnated with 100 mg of profluthrin, which was one-fifth the quantity of *EZ*-empenthrin (**Fig. 11**).

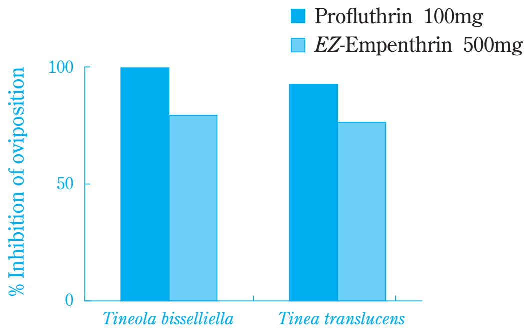


Fig. 11 Practical efficacy of profluthrin against fabric pests in a large chamber test

Profluthrin shows an oviposition inhibition effect that is different from any other conventional moth-proofer. Moreover, it is significant due to the fact that this effect is expressed immediately after the placement of the agent-impregnated paper.

3. Efficacy against Sanitary Pests and Nuisance Pests

Profluthrin possesses high efficacy not only against fabric pests but also sanitary pests (houseflies, mosquitoes, cockroaches) and nuisance pests (moth flies, fruit flies).

(1) Lethal Effects on Sanitary Pests

The lethal effect of profluthrin against various sanitary pests was investigated by a topical application method and compared with that of *EZ*-empenthrin. Profluthrin showed a high lethal effect on the adults of *Culex pipiens pallens*, *Culex pipiens molestus* and *Aedes albopictus*, and its relative insecticidal activity was approximately ten to twenty times greater than that of *EZ*-

empenthrin. However, the lethal effect of profluthrin against *Musca domestica* adults was nearly equal to that of *EZ*-empenthrin, while its lethal effect against *Blattella germanica* adults was slightly greater than that of *EZ*-empenthrin (**Table 3**).

Table 3 Efficacy of profluthrin against sanitary pests by topical application method (LD_{50} [μg/female adult])

	Profluthrin	*EZ*-Empenthrin
Culex pipiens pallens	0.014	0.16
Culex pipiens molestus	0.0036	0.065
Aedes albopictus	0.0063	0.078
Musca domestica	0.18	0.24
Blattella germanica	6.1	9.3

(2) Efficacy against Mosquitoes in a Glass Chamber Test

The knockdown effects of profluthrin against various species of mosquitoes were observed in a glass chamber with a capacity of 0.34 m^3 and compared to those of *EZ*-empenthrin (**Fig. 12**). The following procedures were undertaken to observe the knockdown effects: A piece of filter paper impregnated with each test sample was suspended from the ceiling of the chamber. The test insects (adults) were then released into the chamber. The number of knocked-down insects was counted each time the specified time interval had elapsed, and the time required for knocking down half of the test insects (KT_{50}) was measured (**Table 4**).

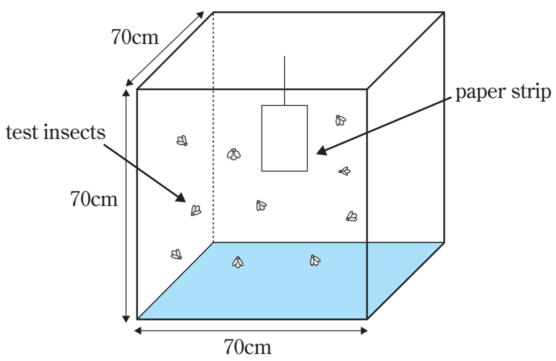


Fig. 12 Glass chamber test method

Profluthrin, vaporizing under ambient temperature, demonstrated excellent fast-acting efficacy against the adults of *Culex pipiens molestus* and *Aedes albopictus*. It also showed a knockdown effect greater than that of *EZ*-empenthrin with just one-fourth the dose.

(3) Efficacy against Nuisance Pests by Vapor Action Test

To investigate the vapor action of profluthrin against nuisance pests, the vapor action test was conducted in a small space under ambient temperature and compared to the vapor action of *EZ*-empenthrin. Adults were released into a 200 mL plastic cup, the top of which was covered with a net in order to prevent the insects from directly coming into contact with the treated surface. The cup was then placed upside down on the treated aluminum plate. Lastly, the number of knocked-down insects was counted each time the specified time interval had elapsed (**Fig. 13**).

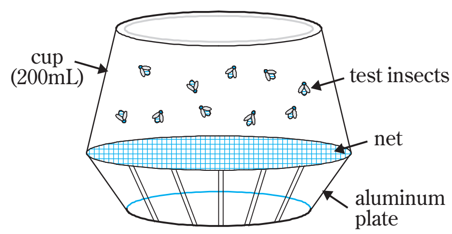


Fig. 13 Vapor action test method against nuisance pests

Table 5 Efficacy of profluthrin against nuisance pests by vapor action test method (KT_{50} [min])

	Profluthrin	*EZ*-Empenthrin
Clogmia albipunctata (2mg/m^2)	64.2	124.3
Drosophila melanogaster (10mg/m^2)	47.5	105.4

Table 4 Efficacy of profluthrin against mosquitoes in a glass chamber test (KT_{50} [min])

	Profluthrin			*EZ*-Empenthrin		
Amount A.I.	25mg	50mg	100mg	25mg	50mg	100mg
Culex pipiens pallens	11.7	10.6	7.1	20.1	18.6	14.4
Culex pipiens molestus	8.1	6.6	5.4	14.7	11.4	10.6
Aedes albopictus	4.4	4.2	3.0	9.2	6.4	7.4

Profluthrin showed excellent knockdown effects on *Clogmia albipunctata* and *Drosophilamelanogaster* adults, which were much greater than those for the equivalent amount of *EZ*-empenthrin (**Table 5**).

Physical Properties and Stability

1. Physicochemical Properties

Table 6 shows the physicochemical properties of profluthrin. Profluthrin is a slightly yellow to pale yellow transparent liquid (**Fig. 14**). While it is soluble in most organic solvents, it is insoluble in water. Because profluthrin's viscosity is 14.1 mPa · s (20°C), it is assumed to be easy to handle. Its vapor pressure is 10.3 mPa (25°C), which is remarkably high for a pyrethroid. Of all the over-the-counter pyrethroids, the vapor pressure of profluthrin is second only to empenthrin (**Fig. 15**).

Table 6 Physicochemical property of profluthrin

Molecular Formula	$C_{17}H_{18}F_4O_2$
Molecular Weight	330.32
Appearance	Pale yellow to light yellow clear liquid
Odor	Slightly characteristic odor
Density	1.19g/mL (17.5°C)
Vapor Pressure	10.3mPa (25°C)
Viscosity	14.1mPa · s (20°C)
Flashing Point	158°C (Cleveland open method)
Distribution Coefficient	logP = 5.9
Solubility	Water : 0.16mg/L (20°C) Soluble in following solvents Acetonitrile, Dimethyl sulfoxide, Methanol, Ethanol, Acetone, Hexane, Isopropyl myristate, Kerosene (*n*-Paraffin)

Fig. 14 Aspect of profluthrin

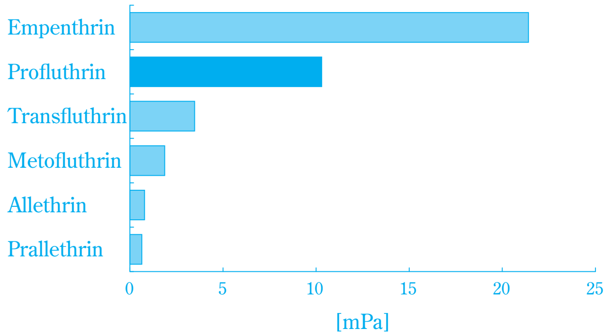


Fig. 15 Vapor pressures of some pyrethroids (Vapor pressures were measured by the method of Donovan[3].)

2. Stability

As a result of the storage test by keeping profluthrin in a can with a resin-coated internal surface and a polyethylene container for a period of six months at a temperature of 40°C and a relative humidity of 75%, it was found that profluthrin was stable, and no obvious change was observed in its quality as compared to the quality upon initiation of the test. Although profluthrin is stable in various types of general-purpose solutions (**Table 7**), because it is an ester compound there is a possibility that transesterification may occur in the presence of alcohol, depending on the conditions. It is therefore necessary to handle it with caution in the presence of lower alcohols such as methanol, ethanol and propylene glycol.

Although profluthrin is also stable in acidic or basic solutions (**Table 8**), because it is an ester compound there is a possibility that hydrolysis may occur,

Table 7 Stability in various organic solvents

	Residual ratio on initial content (%)
Isopar® M	100.0
Exxsol® D80	100.0
Ethanol	100.0
Isopropanol	99.7
Chloroform	98.7

Table 8 Stability of profluthrin in water (2% (w/w) of profluthrin solution in acetonitrile/buffered water (3:2) was applied. Storage condition: 25°C for 1 month)

pH	Residual ratio on initial content (%)
9.6	100.0
6.9	100.0
2.2	100.0

depending on the conditions. It is therefore necessary to handle it with caution.

The photostability was evaluated using a xenon lamp. As compared to *EZ*-empenthrin, profluthrin has more stability, and neither color change (visual judgment) nor bad smell was observed (**Table 9**).

Table 9 Photostability (50mg of profluthrin/*EZ*-empenthrin dry film was applied. Dry film was exposed to xenon arc light for 168 hours. Average illumination intensity was approximately 6000 lx/h.)

	Recovery ratio (%)
Profluthrin	91.9
EZ-Empenthrin	82.2

3. Effects on Clothing Materials

In order to evaluate the effects of profluthrin on clothing materials, a contact test was conducted on various types of fabrics (non-colored), metals and colored fabrics.

(1) Effects on Fabrics

Parts of various non-colored fabrics were impregnated with appropriate amounts of profluthrin. The fabrics were then stored at a temperature of 40°C and relative humidity of 80% for a period of six months. Subsequently, color changes in fabrics were evaluated by visual judgment. However, no change was observed in any of the fabrics (**Table 10**).

Table 10 Change in color of various fabrics

Fabric material	Change in color
Wool	Not Detected
Silk	Not Detected
Nylon	Not Detected
Polyester	Not Detected
Rayon	Not Detected
Acrylic fiber	Not Detected
Acetate fiber	Not Detected

(2) Effects on Metals

Filter papers were coated with metal powders. Profluthrin-impregnated mats were wrapped with these filter papers, sealed in an air-tight container and stored at a temperature of 40°C for ten days. Subsequently, each wrap was opened in order to evaluate the color changes in the metal powders. However, no effect was observed on any type of metal powder (**Table 11**, **Fig. 16**).

Table 11 Change in color against metals

Metal	Change in color
Brass	Not Detected
Iron	Not Detected
Lead	Not Detected
Copper	Not Detected
Aluminum	Not Detected
Nickel	Not Detected
Chrome	Not Detected
Cobalt	Not Detected
Zinc	Not Detected
Tin	Not Detected

Initial	After storage under 40°C for 10 days

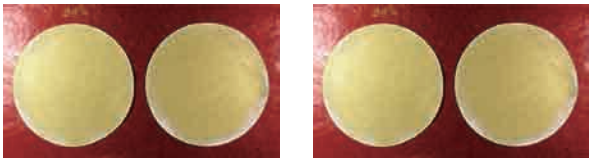


Fig. 16 Change in color against brass

(3) Effects on Dyestuffs

Parts of various colored fabrics were impregnated with appropriate amounts of profluthrin. These fabrics were then stored at a temperature of 40°C and a relative humidity of 80% for a period of six months. Subsequently, color changes in fabrics were evaluated by visual judgment. However, no change was observed in any of the fabrics (**Table 12**).

Table 12 Change in color against dyestuffs

	Base fabric	Change in color
Sumifix®, Sumifix® Supra, Sumifix® HF series dyestuffs; total 52 dyestuffs	Cotton	Not Detected
Sumilight® series dyestuffs; total 32 dyestuffs	Cotton	Not Detected
Suminol® series dyestuffs; total 36 dyestuffs	Wool	Not Detected

Based upon the above results, it can be concluded that profluthrin can be applied to a wide range of moth-proofers.

Metabolism, Pharmacology, Toxicity

1. Metabolism

The biokinetics of profluthrin in rats were investigated using ^{14}C-marked profluthrin. Low doses of 1mg/kg and high doses of 60mg/kg of ^{14}C-marked profluthrin were given as single oral administrations to male and female rats. In the low dosage, profluthrin was quickly absorbed from the alimentary tracts (oral absorption ranging from 66.4% to 72.5%), and the ^{14}C concentration in the blood plasma reached its peak from six to eight hours after administration but declined immediately after reaching the peak. Profluthrin received metabolic reactions such as ester hydrolysis, oxidation and glucuronic acid conjugation (**Fig. 17**), and most of the dosage (96% or greater) was excreted from the body within two days of administration. Urination was the primary means of excretion. Of organs and tissues (except for alimentary tracts and their contents), the ^{14}C concentration level was the highest in the livers, followed by the kidneys and the thyroid glands. Regarding both male and female rats, the persistence of profluthrin in the body 168 hours after administration was 0.3% or less of the dosage, and it was therefore assumed to have a low residual property in the tissues of the test subjects. The absorption saturation of profluthrin from the alimentary tracts was suggested in the high-dosage group. Changes in the ^{14}C concentration and the distribution tendency in the organs and tissues in the high-dosage group were similar to those of the low-dosage group. Additionally, in the high-dosage group metabolites similar to those in the low-dosage group were observed, and the percentage of excretion of the parent compound into feces increased to a slight extent.

2. General Pharmacology

A general pharmacology test for profluthrin was conducted using rats, guinea pigs and dogs. Regarding general symptoms and behaviors, enhanced abnormal gait, tremors, twitches and startle responses were observed in rats to which 200 mg/kg of profluthrin was given by a single oral administration. Additionally, increased abdominal muscle tonicity was also seen in male rats.

Regarding the central nervous system, no effect was observed on spontaneous motor activity and body temperature. Further, no significant differences were observed in sleep actions, synergism and antagonism toward convulsion, and pain threshold. Thus only neurological symptoms were recognized as effects on the central nervous system; no effects were observed on the respiratory and renal/urinary systems of rats, the extirpated ileums of guinea pigs or the circulatory systems of dogs. Those actions were not seen in the lower-dosage group, and all the manifested symptoms disappeared within twenty-four hours.

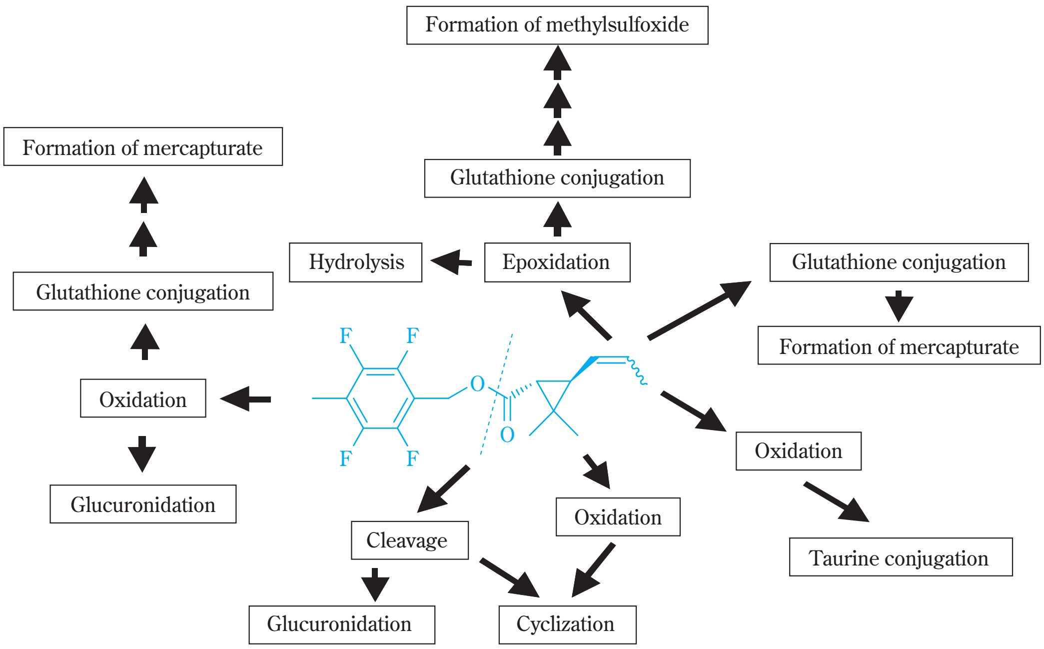


Fig. 17 Metabolic reaction of profluthrin in rats

3. Toxicity

(1) Acute Toxicity

With regard to the approximate lethal dose of profluthrin, it exceeded 2000 mg/kg in both male and female rats by a single oral administration. In male and female dogs, it exceeded 1000 mg/kg by both a single administration and four-day repeated administrations. By dermal administration, it exceeded 2000 mg/kg in both male and female rats. By inhalation exposure, it was 1990 mg/m^3 in both male and female rats (**Table 13**). The predominant symptoms observed in rats included tremors, clonic convulsions, salivations, tip-toe gait and tremor of tail, and those seen in dogs included vomiting, tremors, clonic convulsions, spasm, decease of spontaneous activity and ataxic gait.

(2) Subacute and Chronic Toxicity

As a result of subacute and chronic toxicity studies (**Table 14**), it has been found that profluthrin affects the nervous system and the liver.

It has been known that pyrethroids affect the nervous system in general and induce various clinical signs such as tremors.[4] And it has been recognized that profluthrin affects the nervous systems of rats and dogs, which is thought to be related to the pyrethroid. In rats, tremors were observed as a result of dosage by oral administration. Tremors and clonic convulsions were observed in rats from inhalation exposure. Clonic convulsions, tonic convulsion and tremors were observed in dogs from oral administration. There was no morphologic change in the central nerves (brain, spinal cord) or peripheral nerves. And clinical signs observed during administration period disappeared during the recovery period.

Increased liver weight and diffuse hepatocyte hypertrophy were observed in rats. The results of histopathological examination were very similar to the histopathological findings[5] observed when inducing drug-metabolizing enzyme activity, which can be seen after the application of a chemical substance. Furthermore, regarding the metabolism in the liver, based upon the result of the metabolism test it can be assumed that the induction of metabolic enzymes occurred as an adaptive response, because profluthrin is metabolized mainly by the metabolic enzymes that are present in the liver. Moreover, hepatocyte vacuolation (fatty accumulation) was observed in the rat livers, and increased total cholesterol and phospholipids were seen in the clinical chemistry analysis, thereby revealing the effect on lipid metabolism. Additionally, increased total protein and albumin were observed in the clinical chemistry analysis, suggesting the effect on protein metabolism in the liver. None of the above changes were observed during the recovery period.

(3) Developmental/Reproductive Toxicity

Regarding development and reproductive toxicity, the following effects of profluthrin were studied: the effect on fertility and early embryonic development until nidation in rats; the effect on embryonic and fetal de-

Table 13 Acute toxicity of profluthrin

Species	Administration route	Dose	Approximate lethal dose
Rat	Oral	1000, 1500, 2000 mg/kg	Male & Female: >2000 mg/kg
Rat	Dermal	2000 mg/kg	Male & Female: >2000 mg/kg
Rat	Inhalation	509, 1020, 1990 mg/m^3	Male & Female: 1990 mg/m^3
Dog	Oral	250, 500, 1000 mg/kg	Male & Female: >1000 mg/kg

Table 14 Subacute and chronic toxicity of profluthrin

Species	Administration route and duration	Dose	NOAEL
Rat	Oral (in diet), 1 month	200, 1000, 5000 ppm	Male: 1000ppm (78.0 mg/kg/day) Female: 1000ppm (83.9 mg/kg/day)
Rat	Inhalation, 4 weeks	48.5, 94.0, 150, 308 mg/m^3	Male: 94.0 mg/m^3 (16.9 mg/kg/day) Female: 150 mg/m^3 (27.0 mg/kg/day)
Dog	Oral (capsule), 13 weeks	10, 50, 250, 500 mg/kg/day	Male & Female: 50 mg/kg/day
Rat	Oral (in diet), 6 months	200, 1000, 5000 ppm	Male: 200ppm (10.5 mg/kg/day) Female: 200ppm (12.8 mg/kg/day)

velopment in rats and rabbits; the effect on prenatal and postnatal development in rats; and the effect on functions of mother rats. As a result of such examinations, no effect was observed on either reproduction or offspring (**Table 15**).

(4) Skin Sensitization

The results of skin sensitization tests (maximization method) conducted on guinea pigs turned out to be negative.

(5) Skin/Eye Irritation

After skin and eye irritation testing on rabbits, no irritation was observed.

(6) Genotoxic Properties

All the results of the following tests turned out to be negative: a reverse mutation test using *Salmonella typhimurium* and *Escherichia coli*; an *in vitro* test for chromosomal aberration using Chinese hamster lung cells; and a micronucleus test using rat bone-marrow cells (**Table 16**).

(7) Fish Toxicity

An exposure test was conducted on carp for a period of ninety-six hours in running water. As a result, the ninety-six-hour LC50 value was 2.9μg/L.

Conclusion

We at Sumitomo Chemical Co., Ltd., have developed and launched more than twenty distinct pyrethroids over the past half-century. These pyrethroids have contributed greatly to the growth of our company's pesticide business and household pharmaceutical business for the prevention of epidemics. Synthetic pyrethroids are now a necessity in ensuring steady agricultural production, the prevention of epidemics, insect pest control and a more comfortable living environment throughout the world.

Table 15 Developmental and reproductive toxicity of profluthrin

Study	Species	Administration route and duration	Dose (mg/kg/day)	NOAEL (mg/kg/day)	
Effects on fertility and early embryonic development to implantation	Rat	Oral (gavage) Male: 2 weeks before mating to termination (sacrifice) Female: 2 weeks before mating to day 6 of gestation	10, 25, 75	Parental	Systemic NOAEL Male & Female: 25 Reproductive NOAEL Male & Female: 75
				Developmental	Male & Female: 75
Effects on embryo-fetal development	Rat	Oral (gavage) Days 6-17 of gestation	10, 20, 50	Maternal	Systemic NOAEL: 20 Reproductive NOAEL: 50
				Developmental	50
	Rabbit	Oral (gavage) Days 6-18 of gestation	30, 100, 300	Maternal	Systemic NOAEL: 100 Reproductive NOAEL: 300
				Developmental	300
Effects on pre- and postnatal development, including maternal function	Rat	Oral (gavage) Day 6 of gestation to day 20 of lactation	10, 20, 50	Maternal	Systemic NOAEL: 20 Reproductive NOAEL: 50
				Developmental	50

Table 16 Mutagenicity of profluthrin

Study	Study design	Results
Reverse mutation (Ames test)	*S. typhimurium*: TA100, TA98, TA1535 and TA1537 *E. coli*: WP2*uvrA* –S9 mix: 156 – 5000 μg/plate +S9 mix: 156 – 5000 μg/plate	Negative
In vitro chromosomal aberration	Chinese hamster lung cells (CHL/IU) –S9 mix: 30 – 75 μg/mL +S9 mix: 85 – 145 μg/mL	Negative
Micronucleus	Rat (9-week old) 380, 750, 1500 mg/kg (single oral administration)	Negative

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