Discovery and Development of a Novel Pyrethroid Insecticide Momfluorothrin

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
Tatsuya Mori
Jun Oshita
Masahiro Yamada*1
Yoshito Tanaka*2
Masaji Hirota*3
Environmental Health Science Laboratory
Kaori Miyata
Miho Tabuchi

Momfluorothrin is an exciting novel pyrethroid discovered by Sumitomo Chemical Co., Ltd. Momfluorothrin exhibited excellent knockdown activity which is approximately 20-fold higher (KT_{50} (min)) against house flies and approximately 30-fold higher (KT_{50} (min)) against German cockroaches than that of Tetramethrin in aerosol formulation. In addition to this extremely high knockdown activity, it has excellent performance (freezing effect) that knocked-down insects are promptly immobilized, which other pyrethroids have not ever had. Momfluorothrin is expected to become one of our key products as a new knockdown agent for aerosol. This paper describes the discovery story, physical properties, stability, insecticidal efficacies, synthetic method and safety evaluations of Momfluorothrin.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2019.

Introduction

Natural pyrethrins, which are the active ingredients of *Chrysanthemum cinerariefolium* (pyrethrum) have excellent insecticidal activity and knockdown activity, and because of their high safety for mammals, they have been used as active ingredients in mosquito coils for a long time (**Fig. 1**). However, the stability of natural pyrethrins in sunlight and heat is insufficient, and there are problems such as the supply being controlled by the weather because agricultural products are used as raw materials. In order to solve these problems, structural modifications of natural pyrethrins have been made for more than a half-century, and a series of related compounds (pyrethroids) with a variety of characteristics have been marketed.

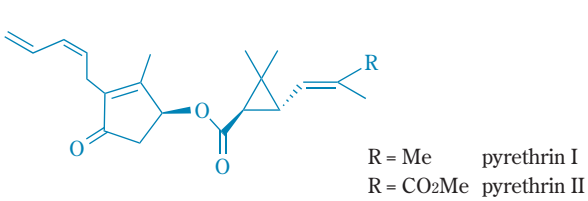


Fig. 1 Structure of pyrethrins

Sumitomo Chemical Co., Ltd. discovered a new pyrethroid, Dimefluthrin, having excellent knockdown activity for insects by modifying the alcohol part of natural pyrethrin to 4-methoxymethyl-2,3,5,6-tetrafluorobenzyl alcohol (**Fig. 2**).[1)]

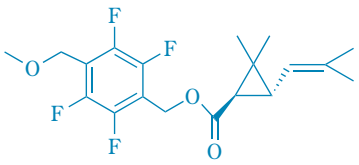


Fig. 2 Structure of Dimefluthrin

Further modifications have been continued in order to develop a new pyrethroid having excellent knockdown activity for house flies and cockroaches, and a new pyrethroid, Momfluorothrin, was discovered (**Fig. 3**).[2)]

*1 Current affiliation: Sumitomo Chemical Enviro-Agro Asia Pacific Sdn. Bhd.
*2 Current affiliation: SC Environmental Science Co., Ltd.
*3 Current affiliation: Health and Crop Sciences Sector Planning and Coordination Office

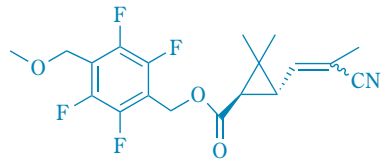


Fig. 3 Structure of Momfluorothrin

Momfluorothrin exhibited excellent knockdown activity approximately 20-fold higher (KT_{50} (min)) against house flies (*Musca domestica*) and approximately 30-fold higher (KT_{50} (min)) against German cockroaches (*Blattella germanica*) than that of Neopynamin™ (Tetramethrin in the following) which is widely used for control of pests in aerosol formulation.

In addition to this extremely high knockdown activity, it has excellent performance (freezing effect) in that knocked-down insects are promptly immobilized, which other pyrethroids have not ever had.

In this paper, we will report the story of the discovery, physical properties, stability, insecticidal efficacies, synthetic method and safety evaluations of Momfluorothrin.

Story of the Discovery

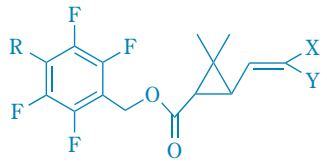
Mosquito coils, fan vaporizers, liquid vaporizers, aerosols, fumigants, and baits are typical formulations for household insecticides.

To respond to the recent trend toward controlling 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 that could offer higher levels of performance.

As a result of such efforts, we discovered Dimefluthrin. This compound also has excellent thermal stability and is an agent generally applicable to volatile heating devices, and it has been launched mainly in China and Southeast Asia, which are major markets.

Next, we continued further research for making progress in reduction of chemicals in the field of aerosols while maintaining the basic structure of Dimefluthrin.

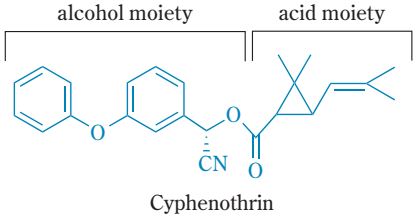
Here, we took into consideration that one substituent of the double bond in the acid part of Pyrethrin II is a methoxycarbonyl group and that there was room for structural change in this part. Thus, we carried out structural development based on synthesis of ester compounds formed from cyclopropanecarboxylic acids that have various substituents on the double bond and 2,3,5,6-tetrafluorobenzyl alcohols (**Fig. 4**).



R, X, Y = various functional groups

Fig. 4 Structure of 2,3,5,6-tetrafluorobenzylesters

At this time, we also focused on the fact that while existing pyrethroids contain compounds having a cyano group in the alcohol part (**Fig. 5**), no commercial pyrethroids have a cyano group in the acid part.



Cyphenothrin

Fig. 5 Structure of CN containing pyrethroid

As a result, Momfluorothrin, which has a cyano group substituted for one methyl group of the isobutenyl group in Dimefluthrin, was discovered to have excellent performance as an active ingredient of aerosol formulations for house flies and cockroaches.

Physical Properties and Stability

1. Physicochemical Properties

The physicochemical properties of Momfluorothrin are given in **Table 1**. Momfluorothrin is a pale yellow crystalline solid soluble in organic solvents such as acetone and ethyl acetate, but hardly soluble in water. The vapor pressure is 1.390×10^{-6} Pa (25 °C), which is low similar to that of Tetramethrin, which is a solid pyrethroid. In order to improve the ease of its handling, Momfluorothrin is sold as Sumifreeze™, which is a liquid formulation (Manufacturing Use Product (MUP)) premixed with a solvent.

Table 1 Physicochemical property of Momfluorothrin

Molecular Formula	$C_{19}H_{19}F_4NO_3$
Molecular Weight	385.35
Physical State	Crystalline solid
Color	Pale yellow
Odor	Odorless
Relative density	1.3660 (20.4 °C)
Vapor Pressure	1.390×10^{-6} Pa (25 °C)
Melting point	63.95–73.30 °C (pure active ingredient)
Partition Coefficient (*n*–octanol/water):	LogPow = 2.88–2.99 (25 °C)
Solubility in Water	0.933 ± 0.0916 mg/L (20 °C) (pure active ingredient)
Solubility (other)	Methanol: 67–80 g/L (20 °C) Acetone: > 250 g/L (20 °C) Ethyl acetate: > 250 g/L (20 °C) *n*–Heptane: < 10 g/L (20 °C) *n*–Octanol: < 10 g/L (20 °C) *p*–Xylene: > 250 g/L (20 °C)

2. Stability

The results of storage stability tests conducted at 40 ± 2 °C/75 ± 5% RH for six months and at 25 ± 2 °C/60 ± 5% RH for three years indicate that Momfluorothrin is stable. In addition, it is stable in the MUP formulation, which was confirmed by both accelerated and long-term storage stability tests. It is also stable in various solvents (**Table 2**), and because it is an ester compound, there is a possibility that transesterification reactions may occur in the presence of alcohol, depending on the conditions. Therefore, it is necessary to handle it with caution in the presence of lower alcohols such as ethanol and isopropanol.

In an accelerated stability tests in basic aqueous solutions, Momfluorothrin was decomposed (**Table 3**). Although it is stable in both acidic and neutral conditions, because it is an ester compound, there is a possibility that hydrolysis may occur under conditions different from those used in the tests above. Therefore, it is necessary to handle it with caution under aqueous conditions.

In photostability tests under xenon light and sunlight conditions, Momfluorothrin was confirmed to have higher stability than that of Tetramethrin. Thus, Momfluorothrin is expected to be used in products requiring longer residual effect in indoor and outdoor use (**Table 4**).

Use in aerosol formulations is envisioned for Momfluorothrin. In aerosol formulations, the use of an active ingredient in combination with other insecticides is common; therefore, compatibility with other active ingredients was confirmed by accelerated storage stability testing. The results show that each of the active ingredients in tested combinations was stable (**Table 5**).

Table 2 Stability in various organic solvents (Momfluorothrin: 0.3 ~ 1.0% w/v)

	Recovery rate* (%)
Exxsol D80	100.1
Isopropanol	100.0
Isopropyl myristate	100.1
Propylene glycol monomethyl ether	99.6

*: Momfluorothrin content of the samples stored at –5 °C as 100%
Storage condition: 40 °C, 1 month

Table 3 Stability in various pH buffer solutions mixed with acetonitrile (Momfluorothrin: 0.2% w/v, Acetonitrile/pH buffer solution = 3 : 2)

pH	Recovery rate* (%)
9.6	84.0
6.8	101.7
2.2	102.0

*: Initial Momfluorothrin content as 100%
Storage condition: 40 °C, 1 month

Table 4 Photostabilty of Momfluorothrin on petri dish

	Recovery rate (%)	
	Xenon light*	Sunlight*
Momfluorothrin	95.6	83.3
Tetramethrin	36.1	17.8

*: Accumulated illumination: 1.01×10^6 lx · h

Table 5 Stability of Momfluorothrin mixed with other insecticides in Exxsol D80 (Momfluorothrin: 0.05%, Insecticide: 0.1% (w/v))

Insecticide	Recovery rate* (%, Momfluorothrin/insecticide)
Permethrin	100.1/100.3
Phenothrin	99.5/99.8
Cyphenothrin	100.1/99.7
d-Resmethrin	100.1/100.1

*: Insecticide content of the samples stored at –5 °C as 100%
Storage condition: 40 °C, 1 month

Insecticidal Efficacy

1. Basic Efficacy

The knockdown activity of Momfluorothrin was compared with Neopynamin Forte™ (*d*-Tetramethrin in the following), which is a typical aerosol knockdown agent, for three representative insect pests (common house mosquito, house fly, German cockroach). The KT_{50} (time to 50% insect knockdown) for common house mosquitoes (*Culex pipiens pallens*) was extremely short at ≤ 0.7 minutes for Momfluorothrin in an oil solution spray at 0.0063%, and the relative potency was eight times or greater than that of *d*-Tetramethrin (**Table 6**). Likewise, superior efficacy was shown, with the KT_{50} for house flies (*Musca domestica*) being 1.8 minutes for the oil solution spray at 0.0063%, eight times better than that of *d*-Tetramethrin (**Table 7**) and KT_{50} for adult German cockroaches (*Blattella germanica*) being 0.58 minutes in a 0.010% oil solution spray, 20 times better than that of *d*-tetramethrin (**Table 8**). In other words, Momfluorothrin rapidly exhibits efficacy in low amounts for all these typical sanitary insect pests (mosquitoes, house flies and cockroaches), and is clearly greatly superior to *d*-Tetramethrin.

Table 6 Knockdown efficacy of Momfluorothrin oil against *Culex pipiens pallens**1

A.I.	Conc. (%w/v)	KT_{50} (min)*2
Momfluorothrin	0.0063	≦ 0.7
d-Tetramethrin	0.050	1.5

*1: Laboratory susceptible strain
*2: Glass chamber (0.7 m × 0.7 m × 0.7 m) free flying method

Table 7 Knockdown efficacy of Momfluorothrin oil against *Musca domestica**1

A.I.	Conc. (%w/v)	KT_{50} (min)*2
Momfluorothrin	0.0063	1.8
d-Tetramethrin	0.050	1.6

*1: Laboratory susceptible strain
*2: Glass chamber (0.7 m × 0.7 m × 0.7 m) free flying method

Table 8 Knockdown efficacy of Momfluorothrin oil against *Blattella germanica**1

A.I.	Conc. (%w/v)	KT_{50} (min)*2
Momfluorothrin	0.010	0.58
d-Tetramethrin	0.20	0.62

*1: Laboratory susceptible strain
*2: CSMA direct spray method

2. Practical Efficacy of Aerosol Formulation

Momfluorothrin shows rapid biological efficacy against typical sanitary insect pests such as mosquitoes, house flies and cockroaches at low dosage. In addition, it is soluble in kerosene at a sufficient level of content to be effective, therefore, it is expected to be used in aerosol formulation, which is easy to use and capable of being sprayed to any targeted areas. Thus, we evaluated Momfluorothrin in the aerosol formulation under conditions closer to practical situations.

KT_{50} for house flies for an aerosol formulation containing 0.025% Momfluorothrin was 3.0 minutes, exhibiting superior efficacy approximately 20 times that of Tetramethrin. In addition, with treatment at a higher concentration, KT_{50} was 2 minutes or less, exhibiting extremely high knockdown activity exceeding that of Tetramethrin (**Table 9**). Furthermore, house flies that were knocked down exhibited the characteristic symptom of "instant immobilization." In addition, KT_{50} for German cockroaches in an aerosol formulation containing 0.0063% Momfluorothrin was 0.95 minutes, exhibiting an extremely high efficacy approximately 30 times that of Tetramethrin (**Table 10**).

Table 9 Knockdown efficacy of Momfluorothrin oil based aerosol against *Musca domestica**1

A.I.	Conc. (%w/w)	KT_{50} (min)*2
Momfluorothrin	0.025	3.0
	0.050	2.2
	0.075	< 2.0
Tetramethrin	0.25	5.0
	0.50	2.7

*1: Laboratory susceptible strain
*2: Peet- Grady chamber (5.8 m^3) free flying method

Table 10 Knockdown efficacy of Momfluorothrin oil based aerosol against *Blattella germanica**1

A.I.	Conc. (%w/w)	KT_{50} (min)*2
Momfluorothrin	0.0063	0.95
	0.025	0.59
Tetramethrin	0.20	1.0
	0.40	0.82

*1: Laboratory susceptible strain
*2: Direct spray cylinder method

From the above, it was clear that in evaluations of Momfluorothrin as an aerosol agent, it was extremely suitable as a formulation in aerosol formulation, exhibiting extremely high efficacy in small chemical amounts for house flies and cockroaches, which are typical sanitary insect pests.

3. Freezing Effect

In evaluations as an aerosol formulation, Momfluorothrin exhibited extremely high knockdown activity exceeding that of Tetramethrin, and furthermore, house flies that were knocked down exhibited the characteristic symptom of "instant immobilization." We defined this symptom as the "freezing effect" and, for comparison with the typical knockdown agents ETOC™ (Prallethrin in the following) and Tetramethrin, and we measured and compared the distance adult house flies could move after knockdown when treated with each of these.

As a result, house flies treated with Prallethrin and Tetramethrin moved violently for 30 cm or more after knockdown, while house flies treated with Momfluorothrin rapidly stopped moving and became still in their locations within 10 cm after knockdown (**Table 11**). From the above, the high-level freezing effect of Momfluorothrin could be thought of as a superior characteristic not found in pyrethroids up to this point. Normally, when consumers use aerosols, they spray more aerosol if the house fly does not stop moving, but with the high-level freezing effect of the aerosol agent of Momfluorothrin, the excess use of aerosol on house flies by consumers can be eliminated.

Table 11 Knockdown and freezing efficacy of Momfluorothrin oil based aerosol against *Musca domestica**1

A.I.	Conc. (%w/w)	Mean KD Time (sec)*2	MD_{50}*3 (cm)*2
Momfluorothrin	0.025	50	10
Prallethrin	0.10	65	>30
Tetramethrin	0.50	54	>30

*1: Laboratory susceptible strain
*2: Direct spray method
*3: MD_{50}: Moving distance of 50% insects

4. Efficacy of Aerosol Formulation against Various Nuisance Insect Pests

The freezing effect of Momfluorothrin, which is the symptom of instant immobilization, is extremely useful not only for controlling sanitary insect pests, but also if used for control of nuisance insect pests (wasps, hornets, centipedes, stink bugs, moth flies, fruit flies, etc.). If the effect of Momfluorothrin for particularly harmful pests (wasps, hornets, centipedes, etc.) were high, we assume that it would be more valuable for practical use.; therefore, we evaluated the efficacy of Momfluorothrin on various species of harmful pests.

As a result, the KT_{90} (time to 90% knockdown) for paper wasps (*Polistes rothneyi*) was 45 seconds, exhibiting an efficacy three times or greater than that of *d*-tetramethrin (**Table 12**). Furthermore, after knockdown, paper wasps were confirmed to rapidly stop moving because of the freezing effect of Momfluorothrin. The KT_{90} of an aerosol agent containing 0.050% Momfluorothrin for centipedes (*Scolopendra* sp.) was 3.6 minutes, a large improvement over *d*-Tetramethrin (**Table 13**).

Table 12 Knockdown efficacy of Momfluorothrin oil based aerosol against Paper wasp, *Polistes rothneyi*

A.I.	Conc. (%w/w)	KT_{50} (sec)*	KT_{90} (sec)*
Momfluorothrin	0.10	29	45
d-Tetramethrin	0.30	39	75

*: Direct spray cylinder method

Table 13 Knockdown efficacy of Momfluorothrin oil based aerosol against Centipede, *Scolopendra* sp.

A.I.	Conc. (%w/w)	KT_{50} (min)*	KT_{90} (min)*
Momfluorothrin	0.050	1.7	3.6
d-Tetramethrin	0.50	2.7	6.8

*: Direct spray cylinder method

In addition, the KT_{50} for stink bugs (*Plautia stali*), for which knockdown required time with existing pyrethroids, was 2 minutes or less with an aerosol agent containing 0.050% Momfluorothrin, exhibiting extremely superior knockdown activity. The KT_{50} for moth flies (*Telmatoscopus albipunctatus*) and fruit flies (*Drosophila melanogaster*) of an aerosol agent containing 0.025% Momfluorothrin was 1 minute or less, exhibiting sufficiently practical efficacy at a low concentration (**Table 14**).

Table 14 Knockdown efficacy of Momfluorothrin against various nuisance pests (KT_{50} (min)*)

	Momfluorothrin		*d*-Tetramethrin	
A.I. Concentration (%w/w)	0.025%	0.050%	0.25%	0.50%
Plautia stali	2.6	1.8	7.5	2.7
Telmatoscopus albipunctatus	< 0.40	—	< 0.40	—
Drosophila melanogaster	0.64	0.48	—	0.67

*: Direct spray cylinder method

As per the above, Momfluorothrin not only has extremely high-level effects for sanitary insect pests, but also exhibits high knockdown activity and the freezing effect for various nuisance insect pests and exhibits an extremely high effectiveness for harmful pests such as wasps, hornets and centipedes, so it can be thought of as especially useful for practical use.

Preparation

As is shown in **Fig. 6**, Momfluorothrin can be manufactured by reacting a 3-(2-cyano-1-propenyl)-2, 2-cyclopropanecarboxylic acid derivative with 4-methoxymethyl-2,3,5,6-tetrafluorobenzyl alcohol. For example, condensation reaction of acid halide (X = halogen) and alcohol, dehydration reaction of carboxylic acid (X = OH) and alcohol, and ester exchange reaction with alcohol can be cited. After wide-ranging investigations, a manufacturing method for Momfluorothrin with high productivity was established.

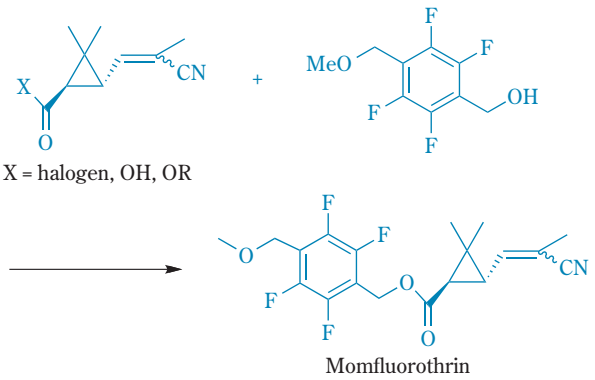


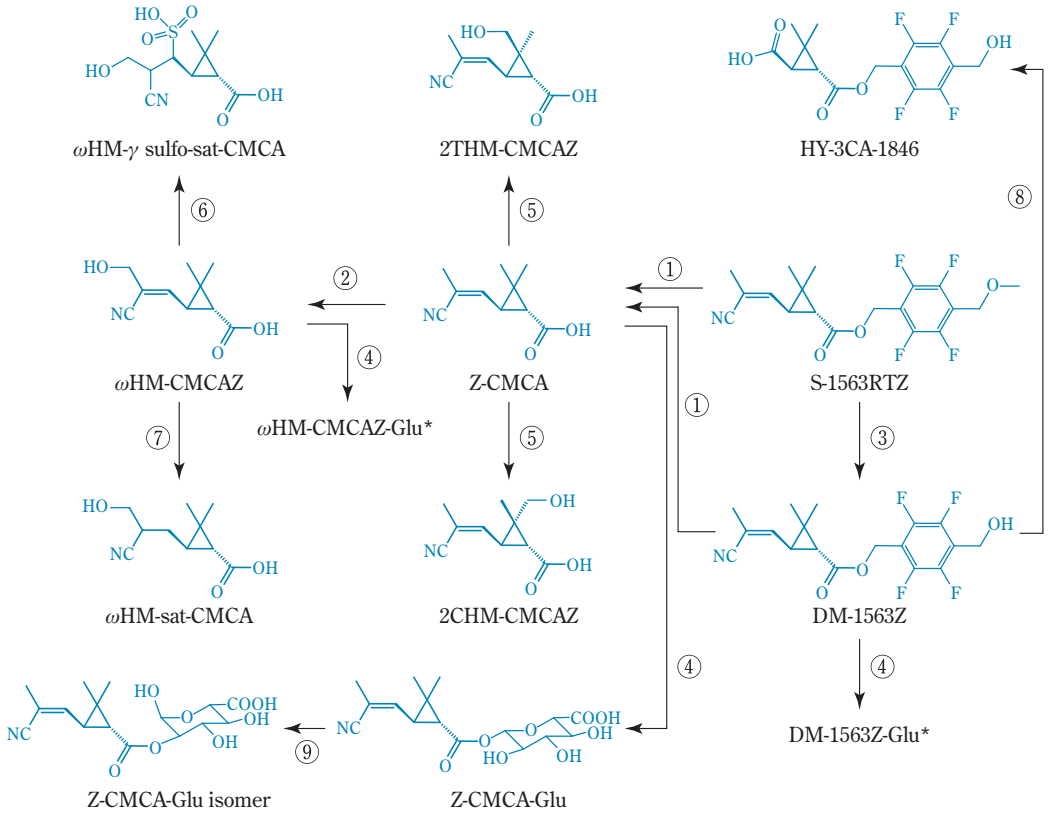
Fig. 6 Synthesis of Momfluorothrin

Metabolism, Pharmacology and Toxicity

1. Metabolism

Of the eight stereoisomers of Momfluorothrin, the major isomer RTZ and the minor isomer RTE were ^{14}C labeled, and the pharmacokinetics were investigated in male and female rats. Male and female rats were administered a single oral dose of 1 mg/kg (low-dose) and 250 mg/kg (high-dose) ^{14}C labeled Momfluorothrin RTZ. In the low dose, Momfluorothrin was rapidly absorbed in the gastrointestinal tract (90% or more oral absorption ratio), and the maximum concentration of ^{14}C in blood plasma was reached 4 - 8 hours after administration. The half-life was 10.8 - 18.5 hours and thereafter decreased over time. The ^{14}C concentration was highest in the gastrointestinal tract, liver and kidneys, and residue in the body 168 hours after administration was 0.2% of the dose in both male and female rats. The high dose showed a maximum value 4 - 8 hours after administration, and there was no remarkable difference from the low dose group in concentration transitions and distribution tendencies.

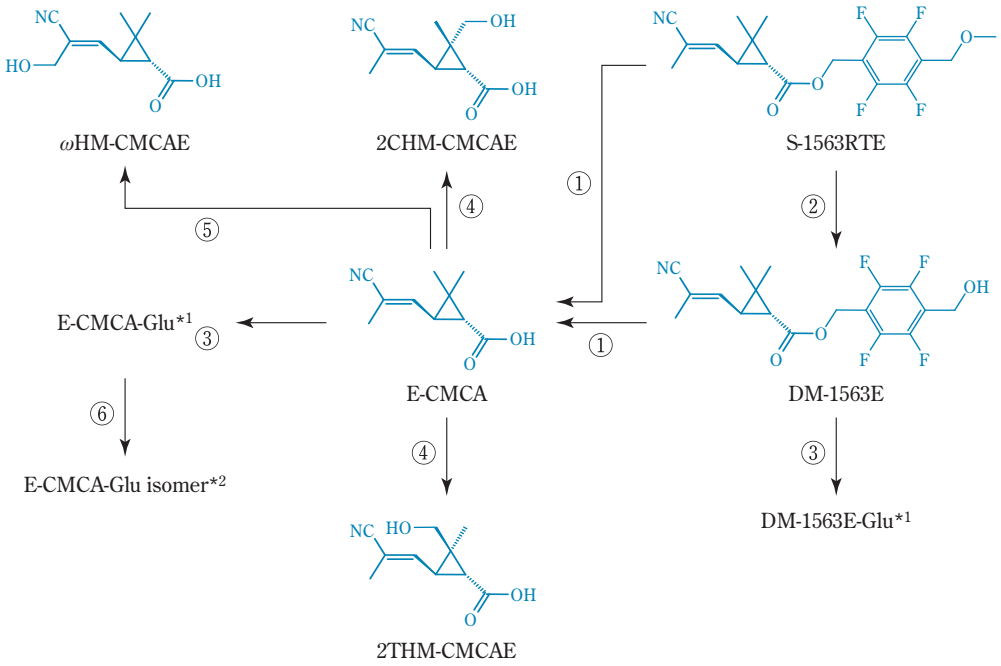
Momfluorothrin undergoes ester hydrolysis, oxidation, glucuronidation and other metabolic reactions (**Fig. 7**), and the majority (96% or greater) of the dose is excreted in the feces or urine within 48 hours after administration. There was no difference from single-dose administration even with repeated dosing, and since substantially the same pattern of transitions occurred during the period of administration for radioactivity in tissues and proportions of metabolites, it was assumed that there was almost no influence on the pharmacokinetics with repeated dosing, and there was no accumulation. S-1563RTE showed the same absorption, distribution and metabolism as S-1563RTZ, and there were no remarkable sexual differences, dosage differences, or isomeric differences (**Fig. 8**). In terms of the metabolites in the body for the alcohol side, investigations have been conducted with pharmacokinetic testing using alcohol side labeled forms of Metofluthrin, which has a similar backbone, and like the acid side labeled forms, there was rapid distribution, metabolism and excretion, and no remarkable sexual differences or dosage differences were found.[3)]



① ester cleavage ② ω-oxidation ③ demethylation ④ glucuronic acid conjugation ⑤ oxidation ⑥ addition of sulfonic acid ⑦ reduction of double bond ⑧ oxidation of double bond ⑨ isomerization of glucronide

*: Glucuronide

Fig. 7 Metabolic reaction of Momfluorothrin RTZ



① ester cleavage ② demethylation ③ glucuronic acid conjugation ④ ω-oxidation ⑤ oxidation ⑥ isomerization of glucronide

*1: Glucuronide

*2: Isomer of glucuronide

Fig. 8 Metabolic reaction of Momfluorothrin RTE

2. General Pharmacology

Increased tremors, twitching and startled reactions were found in rats, and action on the central nervous system and a shortening action on pentobarbital-induced sleeping time were found; however, no effects on locomotor activity or body temperature were found. No accompanying convulsions/antagonism or analgesic action were observed. In terms of the autonomic nervous system and smooth muscles, a single contraction action was shown in ileum isolated from guinea pigs, and inhibitory action on histamine, acetylcholine, barium chloride and serotonin-induced constriction were observed. No effects were found on the respiratory and circulatory systems in rats and dogs. In addition, increases in urine volume and urinary excretion of electrolytes were observed for water and electrolyte metabolism in rats.

3. Toxicity

(1) Acute Toxicity

The approximate lethal dose for oral administration in both male and female rats was 2000 mg/kg, and in dogs 1000 mg/kg for males and greater than 1000 mg/kg for females. For percutaneous administration, it was greater than 2000 mg/kg for both male and female rats, and for inhalation exposure in rats, it exceeded 2030 mg/m^3 for males and was 2030 mg/m^3 for females (**Table 15**). The primary symptoms observed per oral administration and inhalation exposure in rats were salivation, clonic convulsions, tremors, urinary incontinence, tiptoe gait, etc., and no appreciable changes were found with percutaneous administration. With oral administration in dogs, vomiting, salivation, watery feces and drowsiness were observed.

(2) Subacute and Chronic Toxicity

Momfluorothrin primarily affects the liver, and increases in the weight of the liver, changes in blood biochemical parameters and hepatocellular hypertrophy in histopathology were observed. Proliferation of the smooth endoplasmic reticulum were observed in electron microscopy. Additionally, lipofuscin-like brown pigment deposition in the liver and kidneys and acinar cell hypertrophy in the submandibular gland were observed and in chronic toxicity studies, follicular cell hypertrophy in the thyroid was observed, while with inhalation exposure, tremors, ataxic gait and muscle stress or hypersensitivity were observed. In dogs, an increased tendency of liver weight, hepatocellular hypertrophy and changes in blood biochemical parameters were observed (**Table 16**).

(3) Reproductive and Developmental Toxicity

There were no effects observed on reproduction or the next generation in the results of investigations into the effects on fertility and early embryonic development up to implantation in rats, effects on embryo and fetal development in rats and rabbits, or effects on

Table 15 Acute toxicity of Momfluorothrin-approximate lethal dose

	Oral (mg/kg)		Dermal (mg/kg)		Inhalation (mg/m^3)	
	Male	Female	Male	Female	Male	Female
Rat	2000	2000	> 2000	> 2000	> 2030	2030
Dog	1000	> 1000	NE	NE	NE	NE

NE: not examined

Table 16 Subacute and chronic toxicity of Momfluorothrin

Species	Duration	Route	Dose	NOAEL/NOAEC
Rat	90 days	Oral (in diet)	300, 1000, 3000, 6000 (ppm)	M: 300 ppm (23.0 mg/kg/d) F: 300 ppm (24.8 mg/kg/d)
Rat	52 weeks	Oral (in diet)	200, 500, 1500, 3000 (ppm)	M: 500 ppm (27.4 mg/kg/d) F: 200 ppm (12.4 mg/kg/d)
Rat	28 days	Inhalation (nose only)	50, 150, 300 (mg/m^3)	MF: 62.2 mg/m^3
Rat	28 days	Dermal	100, 300, 1000 (mg/kg/d)	MF: 1000 mg/kg/d
Dog	90 days	Oral (capsule)	50, 200, 600 (mg/kg/d)	MF: 200 mg/kg/d
Dog	1 year	Oral (capsule)	50, 200, 400 (mg/kg/d)	MF: 25 md/kg/d

M: Male, F: Female

pre- and postnatal development or maternal function. In two-generation reproductive studies in rats, delays in sexual maturity that can be thought of as being related to growth retardation were seen, but there was no effect on ability to reproduce or ability to nurse in either generation (**Table 17**).

(4) Skin Sensitization

The results of skin sensitization studies (maximization) in guinea pigs were negative.

(5) Skin and Eye Irritation

There was no irritation to the skin of rabbits, and there was minimal irritation to the eyes of rabbits. It was considered that there is a washing effect.

(6) Genotoxicity

Reverse mutation tests using *Salmonella typhimurium* and *Escherichia coli* were negative. *In vitro* chromosomal aberration tests using Chinese hamster lung cells were mildly positive under conditions of metabolic activity. However, micronucleus tests using rat bone marrow cells, which are higher tier test, and *in vivo* unscheduled DNA synthesis (UDS) were negative, and it was concluded that there is no genotoxicity (**Table 18**).

Table 17 Developmental and reproductive toxicity of Momfluorothrin

Species	Study	Route/duration	Dose (mg/kg/d)	NOAEL (mg/kg/d)	
Rat	Fertility & early embryonic develop. to implantation	Oral (gavage) Male: 2 weeks before mating to termination, Female: 2 weeks before mating to day 7 of gestation	10, 40, 150	P: Systemic	MF: 40
				P: Repro.	MF: 150
				Dev.	150
Rat	Embryo- fetal develop.	Oral (gavage) Days 6-19 of gestation	10, 25, 75	Mat.: Systemic	25
				Mat.: Repro.	75
				Dev.	75
Rabbit	Embryo- fetal develop.	Oral (gavage) Days 6-27 of gestation	100, 200, 1000	Mat.: Systemic	100
				Mat.: Repro.	1000
				Dev.	1000
Rat	Pre- & postnatal develop.	Oral (gavage) Day 6 of gestation to day 20 of lactation	10, 25, 75	Mat.: Systemic	25
				Mat.: Repro.	75
				Dev.	75
Rat	2- generation	Oral (capsule) P: 10 weeks before mating to F1 weaning, F1: from weaning to F2 weaning	200, 500, 1500 (ppm)	P	MF: 200 ppm M: 11.6, F: 14.7
				F1	MF: 200 ppm M: 11.6, F: 14.7
				Repro.	MF: 500 ppm M: 32.1, F: 35.5

P: Parent, Mat.: Maternal, Repro.: Reproductive toxicity, Dev.: Developmental toxicity, M: Male, F: Female, F1: Filial 1, F2: Filial 2

Table 18 Mutagenicity of Momfluorothrin

Study	Study design	Results
Reverse mutation (Ames test)	S. typhimurium: TA100, TA98, TA1535, TA1537 E. coli: WP2uvrA –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: 156–625 μg/mL (6 hours) 19.5–78.1 μg/mL (24 hours) +S9 mix: 100–140 μg/mL	Slightly positive (+S9)
Micronucleus	Rat M: 150–600 mg/kg M: 50–200 mg/kg	Negative
UDS	Rat M: 300, 600 mg/kg F: 100, 200 mg/kg	Negative

(7) Neurotoxicity

Acute and 90-day oral administration neurotoxicity studies were conducted using rats. In the acute testing, 30, 80 and 200 mg/kg dosages were implemented, and in the 200 mg/kg group, mortality and wetted or stained fur in perianal regions, tremors, salivation and straub tail were observed. The NOAEL was 80 mg/kg in both males and females. In 90-day studies (dosages of 600, 2000 and 6000 ppm), no abnormalities were observed in neurotoxicity findings (locomotor activity, FOB findings, brain weight, necropsy and histopathology in central, peripheral and autonomic nervous system), and the NOAEL for neurotoxicity in both males and females was 6000 ppm (402.32 mg/kg/d for males and 425.14 mg/kg/d for females).

(8) Immunotoxicity

In 28-day immunotoxicity studies in rats, no effects on organ weights for the adrenal glands, spleen and thymus, number of spleen cells and T cell dependent antibody response were found, and the non-toxic dose for immunotoxicity was a highest dose of 3000 ppm (241 mg/kg/d).

(9) Carcinogenicity

Carcinogenicity tests were conducted in mice and rats. While in mice high values for liver weight, hepatocellular hypertrophy and brown pigment deposition were found, there was no carcinogenicity potential. In rats, in addition to hepatocellular hypertrophy, brown pigment deposition, cystic degeneration of the liver, eosinophilic foci and cysts or biliary cysts, the incidence of hepatocellular adenoma and hepatocellular carcinoma was observed beyond historical control data, and hepatocellular tumors increased in males in the 1500 ppm or greater groups and at 3000 ppm for females. Additionally, slight chronic hypertrophy of follicular cells in the thyroid gland was observed (**Table 19**).

(10) Mode of Action of Carcinogenicity in Rats and Human Relevancy

To assess relevancy of liver tumors to humans, the mode of action (MOA) of carcinogenicity of Momfluorothrin in the liver of rats was clarified. Effects on organ weight, histopathological examinations (including proliferation index of hepatocytes), gene expression (*cyp2b*, *cyp4a*) for drug metabolizing enzymes, and enzyme activity (CYP2B, CYP4A) were examined. As a result, in addition to increases in liver weight accompanying hepatocellular hypertrophy, there was a remarkable increase in expression of *cyp2b* and an increase in CYP2B activity. An increase in the transient hepatocellular proliferative index was observed with dose dependency. There was a slight increase in *cyp4a*, and it accompanied increases in enzyme activity. In addition, recoverability was seen for all of the changes found in the liver when the drug was withdrawn.

These transitions in mitotic activity and the recoverability of effects after withdrawing the drug can be observed in enzyme induction agents.[4] CYP2B activity is increased via constitutive androstane receptors (CAR), which are receptors within the nucleus; therefore, this agent can be considered as a CAR activator like phenobarbital. Considering the fact that there is no relevance to humans from the large body of test results using phenobarbital hepatocellular tumors via CAR in rodents and epidemiological data for humans,[5)–8)] the liver tumors observed in rats can be thought of as bearing no relationship to humans. Furthermore, when the increases in the hepatocyte proliferation rate that were necessary for the carcinogenic process in rats were investigated using a primary culture of human hepatocytes and humanized mice (chimeric mouse model with human hepatocyte transplant), no increases in hepatocyte proliferative rate because of this agent were found; therefore, it is thought that this agent does not have liver carcinogenicity in

Table 19 Carcinogenicity study of Momfluorothrin

Species	Duration	Route	Dose (ppm)	NOAEL	Carcinogenic potential
Mouse	78 weeks	Oral (in diet)	600, 2500, 5500	MF: 600 ppm M: 72 mg/kg/d F: 99 mg/kg/d	Negative
Rat	104 weeks	Oral (in diet)	200, 500, 1500, 3000	MF: 500 ppm M: 23 mg/kg/d F: 28 mg/kg/d	Positive (Liver)

M: Male, F: Female

humans.[9)-11)] Based on this experimental proof, the European Chemicals Agency concluded that this agent did not need to be classified as a carcinogen. In addition, the United States Environmental Protection Agency also evaluated this agent as "Not likely to be carcinogenic to humans."

4. Behavior and Residue in the Environment

(1) Degradation in Water

In hydrolysis studies, ^{14}C labeled Momfluorothrin was stable in a buffer solution at pH 4 and 7 under dark conditions (20 °C) with a half-life of one year or greater, but at pH 9, it decomposed comparatively rapidly with a half-life of 11.7 - 12.2 days, and cleavage of the ester bonds proceeded. In addition, the half-life was 4.5 days by exposure to natural sunlight (North latitude 30 - 50° in summer), and cleavage of the ester bonds and optical isomerization proceeded.

(2) Metabolism in Soil

^{14}C labeled Momfluorothrin was rapidly degraded in aerobic soil with a half-life (20 °C) of 2.0 - 4.2 days, *via* ester bond cleavage, followed by oxidation of both benzylic positions, hydration of terminal cyano group and oxidative cleavage of propenyl group, with final mineralization to carbon dioxide or rigid adsorption on the soil.

(3) Mobility in Soil

The soil adsorption coefficient (K_{Foc}) of Momfluorothrin corrected with the organic carbon content using the Freundlich adsorption isotherm is 1033 - 4344 mL/g, and leaching possibility to groundwater is low.

5. Effects on Non-target Species

The test results for aquatic organisms, honeybees, soil organisms and birds are summarized in **Table 20**.

(1) Effects on Aquatic Organisms

The acute toxicity values for the Momfluorothrin TG on carp, *Daphnia magna* and freshwater green algae (LC_{50}/EC_{50}/ErC_{50}) were 8.9, 7.8 and greater than 4800 µg/L, respectively.

(2) Effects on Honeybees

The acute toxicity values (LD_{50}) for oral administration and contact administration of the Momfluorothrin TG to western honeybees were greater than 5.08 and 0.21 µg per bee, respectively.

(3) Effects on Soil Organisms

The acute toxicity value (LC_{50}) of the Momfluorothrin TG on earthworms (*Eisenia fetida*) was 97.6 mg/kg.

(4) Effects on birds

The acute oral toxicity of the Momfluorothrin TG in bobwhites was low, and the LD_{50} value was greater than 2250 mg/kg.

From the above, it can be assumed that the acute toxicity of Momfluorothrin for mammals is low, and over the long-term even if there is uptake, there will be no effects on teratogenicity and fertility in the next generation. Moreover, even though there were increases in liver tumors in rats, there was no relevance to humans when the modes for carcinogenic activity were analyzed, and it was determined that this agent was not carcinogenic for humans. In addition, it can be assumed safe use is possible based on the behavior in the environment and evaluation of effects on non-target organisms.

Conclusion

Sumitomo Chemical Co., Ltd. has discovered and marketed more than 20 pyrethroids with diversified

Table 20 Ecotoxicological summary of Momfluorothrin on non-target organisms

Test species		Test type	Results
Aquatic organisms	Carp	Acute (96 hrs)	LC_{50} = 8.9 µg/L
	Daphnia magna	Acute (48 hrs)	EC_{50} = 7.8 µg/L
	Green alga*	Acute (72 hrs)	ErC_{50} > 4.8 mg/L
Honeybee	*Apis mellifera*	Acute oral (48 hrs)	LD_{50} > 5.08 µg/bee
	Apis mellifera	Acute contact (48 hrs)	LD_{50} = 0.21 µg/bee
Earthworm	*Eisenia fetida*	Acute (14 d)	LC_{50} = 97.6 mg/kg
Bird	Bobwhite quail	Acute oral	LD_{50} > 2250 mg/kg

*: *Pseudokirchneriella subcapitata*

characteristics over a half century or more, and these have made a large contribution to our agricultural, household and public health chemical business. Currently pyrethroids have an indispensable presence in assuring agricultural products, controlling diseases and noxious insects and assuring comfortable living spaces worldwide. Momfluorothrin has been developed by bringing together the knowledge and wisdom concerning pyrethroids accumulated at Sumitomo Chemical up to now, and not only does it exhibit extremely high knockdown activity, but it also has excellent performance (freezing effect) in that knocked-down insects are promptly immobilized, which other pyrethroids have not ever had, and so it is expected to become one of our key products as a new aerosol knockdown agent.

Moreover, insecticidal products containing Momfluorothrin as the active ingredient were marketed in 2014 for undesirable and harmful insects in Japan, and it received approval under the Pharmaceutical and Medical Devices Law for sanitary insect pest applications in May 2017. In addition, registration was obtained in the United States in August 2015 and in Europe in July 2017.

References

1) T. Mori *et al.*, *Jpn. J. Environ. Entomol. Zool.*, **25** (2), 81 (2014).
2) T. Mori *et al.*, *Jpn. J. Environ. Entomol. Zool.*, **28** (2), 87 (2017).
3) N. Matsuo *et al.*, SUMITOMO KAGAKU, **2005-II**, 4 (2005).
4) S. M. Cohen and L. L. Arnold, *Toxicol.Sci.*, **120**, S76 (2011).
5) C. R. Elcombe *et al.*, *Crit. Rev. Toxicol.*, **44**, 64 (2014).
6) T. Yamada *et al.*, *Toxicol. Sci.*, **142**, 137 (2014).
7) C. La Vecchia and E. Negri, *Eur. J. Cancer Prev.*, **23**, 1 (2014).
8) B. G. Lake, *Toxicol. Res.*, **7**, 697 (2018).
9) Y. Okuda *et al.*, *Toxicol. Sci.*, **158**, 412 (2017).
10) Y. Okuda *et al.*, *J. Toxicol. Sci.*, **42**, 773 (2017).
11) T. Yamada, *Toxicol. Res.*, **7**, 681 (2018).

PROFILE

Tatsuya Mori

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
Fellow, Ph. D.

Masaji Hirota

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
(Currently: Manager, Planning & Coordination Office, Health & Crop Sciences Sector)

Jun Oshita

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
Senior Research Associate, Ph. D.

Kaori Miyata

Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory, and AgroSolutions Division – International
Senior Research Associate, Ph. D.

Masahiro Yamada

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
(Currently: Sumitomo Chemical Enviro-Agro Asia Pacific Sdn. Bhd.
Product Development Manager)

Miho Tabuchi

Sumitomo Chemical Co., Ltd.
Environmental Health Science Laboratory
Senior Research Associate

Yoshito Tanaka

Sumitomo Chemical Co., Ltd.
Health & Crop Sciences Research Laboratory
(Currently: SC Environmental Science Co., Ltd.
Senior Research Associate)