Discovery and Development of a Novel Pyrethroid Insecticide 'Metofluthrin (SumiOne®, Eminence®)'

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Metofluthrin (SumiOne®, Eminence®) is an exciting novel pyrethroid discovered by Sumitomo Chemical Co., Ltd. It was registered in Japan in January 2005 and has now been under worldwide development for environmental health use. Metofluthrin has extremely high knockdown activity against various insect pests especially mosquitoes, as well as relatively high volatility and low mammalian toxicity. This is applicable to not only existing formulations and devices such as a mosquito coil and a liquid vaporizer, but also various new type products such as a fan vaporizer, a paper emanator and a resin emanator. It is noted that knockdown activity of Metofluthrin is more than 40 times higher than that of *d*-allethrin against southern house mosquitoes in a mosquito coil formulation. This paper describes the discovery story, insecticidal efficacies in various formulations, synthetic methods and safety evaluations of Metofluthrin.

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Introduction

In the past and in the present, the mosquito has been one of the insects most troublesome to mankind, and malaria, which is transmitted by the Anopheles mosquito is still a threat to people particularly in the various African countries. The intermediate for West Nile fever, which appeared in New York City in 1999 is the house mosquito (*Culex pipiens*), but and at present, more than 100 people in the United States lose their lives to it annually. Besides Japanese encephalitis due to *Culex tritaeniorhynchus* and filariasis in dogs due to *Culex pipiens* in Japan, the Asian tiger mosquito (*Aedes albopictus*), which is normally seen here has potential for being a vector for dengue fever. Furthermore, recent investigations have suggested that the areas inhabited by the mosquitoes which have potential of disease transmission are expanding because of global warming.

At present, the main devices used for mosquito protection are mosquito coils, electric mosquito mats and liquid vaporizers, but all of these are methods that vaporize insecticides into the air using heating by means of fire or electricity to kill the insects. Pyrethroids are main active ingredients for these devices. In addition to their insecticidal effects, pyrethroids are superior in what is called "knockdown effect," where noxious insects are rapidly paralyzed and cannot suck blood, and with their high level of safety for humans, they are widely used for controlling mosquitoes. However, high temperature heat sources have been necessary for vaporizing the active ingredients, up to now, and this has limited the situation for use of these methods.

As a result of making progress in research and development at Sumitomo Chemical targeting the development of groundbreaking pyrethroids that have abundant vaporizing action and are superior in all aspects to conventional products in terms of the capability to control noxious insects, we have found and developed Metofluthrin (SumiOne®, Eminence®) (**Fig. 1**), which achieves these goals. If Metofluthrin is used, the agent is vaporized at room temperature, and mos-

quitoes can be controlled. We can expect the development of a variety of uses and applications, such as equipment for insect control in outdoor and portable applications in addition to battery operated fan type mosquito controllers.

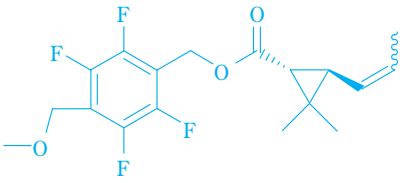


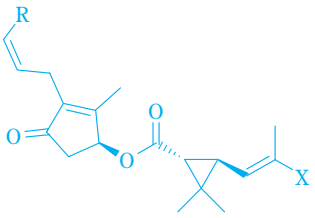
Fig. 1 Structure of Metofluthrin (SumiOne®, Eminence®) (E : Z ≒ 1 : 8)

This agent exhibits effects several times to several tens of times greater than existing agents for the control of various species of mosquitoes, and it is an extremely practical insecticidal component. In this paper, we will report on the discovery story of Metofluthrin, the characteristics of various formulations, the effects on mosquitoes, practical testing, physical and chemical properties, manufacturing methods and safety.

Discovery

1. Research Background

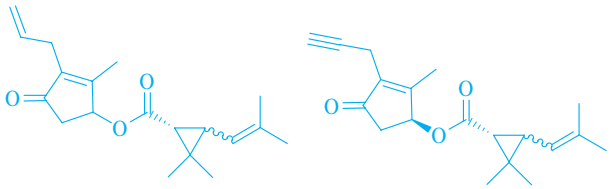
Natural pyrethrins, which are the insecticidal components of pyrethrums, contain six insecticidal components, and they have superior insecticidal action and are fast-acting (knockdown action) on insects. Since they have a high degree of safety for mammals, they have been used for a long time as insecticides for the control of major household insect pests (**Fig. 2**). However, natural pyrethrins have a low stability in light and oxygen, and the applications are mainly limited to the indoors. To solve these problems, there has been more than half of a century of research on modifying the structures of natural pyrethrins, and a large number of related compounds (pyrethroids) with a variety of characteristics have been discovered. As a result, pyrethroids are currently used widely not only as insecticides for indoor use but also in agricultural use. In addition, some types of pyrethroids are particularly superior in terms of the action that causes rapid paralysis of insects, and they are widely used as the active ingredients in mosquito coils and electric devices for eliminating mosquitoes.



R	X = Me	X = CO_2Me
$CH=CH_2$	: Pyrethrin I	: Pyrethrin II
Me	: Cinerin I	: Cinerin II
Et	: Jasmolin I	: Jasmolin II

Fig. 2 Structures of six insecticidal components of natural pyrethrins

In the field of household insecticides, Sumitomo Chemical has developed and marketed a large number of pyrethroids, such as Pynamin Forte® and ETOC® for the active ingredients in mosquito coils and electric devices for eliminating mosquitoes (**Fig. 3**). In recent years, we have focused on new types of devices for eliminating mosquitoes that do not use heat sources, such as fan type mosquito controllers, with the goal of reducing the risk of fires and burns due to inappropriate use of devices and further improving portability and convenience. However, insecticides that can be used in new types of devices for eliminating mosquitoes must have the property of exhibiting their effects without heating (room temperature vaporization). Therefore, we started the investigative research for new pyrethroids that have both action that exceeds that of Pynamin Forte® and ETOC® for mosquitoes and abundant vapor activity.



Pynamin forte® ETOC®

Fig. 3 Notable pyrethroids containing cyclopentenolones

2. Discovery of Lead Compound

We focused on norchrysanthemic acid in the design of the compound (**Fig. 4**). In naming conventions, compounds with one methyl group removed are called "nor" plus the compound name, and in this paper, we have called the compound where a methyl group on the double bond has been removed in chrysanthemic

acid "norchrysanthemic acid." Historically, there is a description of norchrysanthemic acid being obtained through thermal decomposition of a pyrethrin II hydrolysis product by Staudinger in 1924.[1] In the 1970's, Sumitomo Chemical and the group of Elliott et al. independently discovered several norchrysanthemates,[2, 3] and it became clear that the insecticidal action of these was comparable to the corresponding chrysanthemates. Thus, even though the fact that norchrysanthemates exhibit a high insecticidal action comparable to chrysanthemates has been known for a long time, there had been almost no focus on norchrysanthemates up to this point. We can assume that this is because characteristics counterbalancing the difficulty in synthesizing norchrysanthemic acid could not be discovered. However, if we focus on norchrysanthemates from the standpoint of vaporization, their molecular weight is lower than the corresponding chrysanthemates, and they can be assumed to have suitable chemical features for exhibiting room temperature vapor activity.

Chrysanthemic Acid (Natural)　　Norchrysanthemic Acid

Fig. 4 Structures of acid moieties

Therefore, we synthesized several compounds where existing chrysanthemates were transformed into norchrysanthemates and measured their vapor action at room temperatures (**Fig. 5**). However, these compounds did not show remarkable action on mosquitoes in the room temperature vapor action that will be described later.

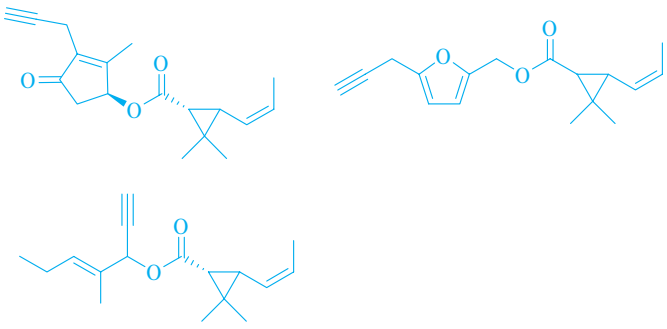
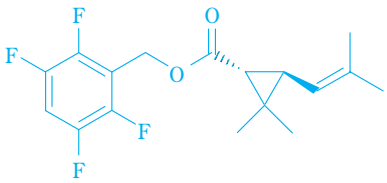
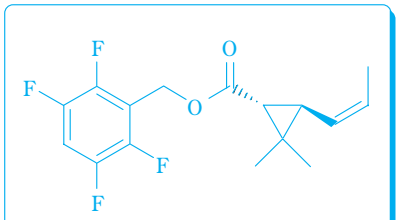


Fig. 5 Known norchrysanthemates

Furthermore, when we expanded the range of our investigation and screened various alcohol esters, we found that the 2,3,5,6-tetrafluorobenzyl alcohol derivative **2** exhibited a comparatively high vapor activity at room temperature (**Fig. 6**). This vapor activity did not meet out desired targets, but compared with the corresponding chrysanthemate **1**, we found that it clearly exhibited a higher knockdown efficacy. Based on these results, we selected 2,3,5,6-tetrafluorobenzyl norchrysanthemate **2** as the lead compound and introduced various substituents at the fourth position on the benzene ring.



Chrysanthemate (1)
KT_{50} = 79 min



Norchrysanthemate (2)
KT_{50} = 55 min

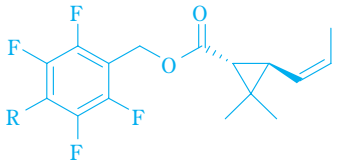
Lead Compound

Fig. 6 Knockdown efficacy of 2,3,5,6-tetrafluorobenzyl chrysanthemate and norchrysanthemate

3. Discovery of Metofluthrin

The basic insecticidal efficacy for *Culex pipiens pallens* of the fourth position substituents is given in **Table 1**. All of the compounds exhibit higher basic efficacy than the unsubstituted compound **2**. Looking at this from the standpoint of the size of the substituent, the peak activity was between the ethyl group and the propyl group. In addition, a substituent containing unsaturated bonds (**7**) and a substituent containing an oxygen atom (**8**) exhibited efficacy equal to or greater than compounds **5** and **6**. In particular, compound **9**, where a methoxymethyl group was introduced, exhibited an extremely high basic efficacy 25 times that of the allethrin.

Table 1 Lethal efficacy of tetrafluorobenzyl derivatives against *Culex pipiens pallens*

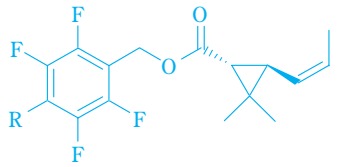


Compound	R	R.T.*
2	H	30
3	F	100
4	Me	200
5	Et	490
6	*n*-Pr	250
7	allyl	500
8	OMe	360
9	CH_2OMe	2500
d-allethrin (standard)		100

* Relative toxicity (R.T.) based on LD_{50} by the topical application method

From these compounds, we selected compounds **4**, **8** and **9** with the methyl group, methoxy group and methoxymethyl group as R substituents, taking into consideration their molecular weight, basic efficacy, ease of synthesis and other physical and chemical properties. The results are shown in **Table 2**.

Table 2 Knockdown efficacy of tetrafluorobenzyl derivatives against *Culex pipiens pallens*



Compound	R	KT_{50} (min)[a)]	KD% [b)]
2	H	55	60
4	Me	38	94
8	OMe	52	70
9	CH_2OMe	27	100

a) Large chamber cage method by a non-heating formulation
KT_{50} : time for 50% knockdown calculated by the probit method
b) Percentages of knockdown mosquitoes afer 60 min

As is clear from a look at Table 2, the methoxymethyl derivative (**9**) exhibits a higher level of knockdown action than the other compounds in room temperature vaporization tests. Based on these results we selected the methoxymethyl derivative (Metofluthrin) for the potent new pyrethroids with high vapor activity for mosquitoes.[4a, b)]

Physical Properties and Stability

1. Physical and Chemical Properties

The physical and chemical properties of Metofluthrin are given in **Table 3**. Metofluthrin is a pale yellow transparent oily liquid, and it can be dissolved in almost all organic solvents, but it is insoluble in water. The vapor pressure at 25°C is 1.96×10^{-3} Pa, and this is higher than known pyrethroid insecticides. The kinetic viscosity is 19.3 mm^2/s (20°C), and this can be thought of as an easily handled level.

Table 3 Physical and chemical property of Metofluthrin

Molecular formula	$C_{18}H_{20}F_4O_3$
Molecular weight	360.34
Appearance	Pale yellow transparent liquid
Odor	Slightly characteristic odor
Specific gravity (d_4^{20})	1.21
Vapor pressure	1.96×10^{-3} Pa (25°C) (Gas saturation method)
Viscosity	19.3 mm^2/s (20°C)
Flashing point	178°C (Cleveland open method)
Distribution coefficient	logP=5.64 (Ambient shake flask method)
Solubility	Water : 0.73mg/L (20°C Saturated solution method)
	Soluble in following solvents
	Acetonitrile, Dimethyl sulfoxide, Methanol, Ethanol, Acetone, Hexane

Thermal analysis thermogravimetry : Weight loss by vaporization was observed from 91.8°C.
Differential thermal analysis : Fluctuation by vaporization with decomposition was observed at 202.7°C.

2. Stability

Metofluthrin is stable for six months at 50°C, and it was not observed to be affected by humidity. In addition, it was stable when stored for three years at room temperature (**Table 4**).

It was stable in various general purpose solvents (**Table 5**). However, since it is an ester compound, there is a possibility that ester exchange reactions will occur depending on the conditions when an alcohol is present, and discretion is necessary when handling in lower alkyl alcohols, such as methanol, ethanol and propylene glycol.

When we investigated the stability in various solid carriers, it was unstable in Fubasami® M Clay, but it exhibited a recovery rate of 90% or greater in other carriers (**Table 6**).

In addition, Metofluthrin is stable in acidic or alkaline aqueous solutions (**Table 7**), but since it is an

ester compound, it is hydrolyzed somewhat in alkaline aqueous solutions, so caution is necessary for handling in these media.

Table 4 Stability of Metofluthrin

Storage conditions	25°C 60% RH[a] In the dark		40°C 75% RH[a] In the dark		25°C 60% RH[a] In the dark	
Storage period	12 months		6 months		36 months	
Container	Epoxy resin-lined can	Plastic (PP[b]) bottle	Epoxy resin-lined can	Plastic (PP[b]) bottle	Epoxy resin-lined can	Plastic (PP[b]) bottle
Content	Stable	Stable	Stable	Stable	Stable	Stable

Storage conditions	50°C In the dark	25°C 100% RH[a] In the dark
Storage period	6 months	3 months
Container	Brown glass bottle with airtight stopper	Brown glass bottle with airtight stopper
Content	Stable	Stable

a) Relative humidity
b) polypropylene

Table 5 Stability of Metofluthrin in various solvents (1%w/v)

Solvent	Recovery rate (%)*
Acetone	100.8
Methanol	99.2
Ethanol	100.6
2-Propanol	99.5
Kerosene (Isopar® M)	99.6
Isopropyl myristate	99.6
Alkyl benzene	99.7
Propylene glycol	97.3

* Recovery rate of the sample which was stored at –5°C expressed as 100%
Storage condition : 60°C, 1 month

Table 6 Stability of Metofluthrin in various carriers (1%w/w)

Carrier	Recovery rate* (%)
Radiolite® #200	100.0
Tokusil® GU-N	100.2
Kyokuho Talc	96.9
Escalon #100	90.5
Bentnite Fuji	90.9
Fubasami M Clay	22.9

* Recovery rate of the sample which was stored at –5°C expressed as 100%
Storage condition : 60°C, 1 month

Metofluthrin is more stable than *d*-allethrin and prallethrin, which are used in heated and unheated vaporization fields, in the sun, and this shows that it is suitable for use in outdoor applications (**Table 8**).

Table 7 Stability of Metofluthrin in water* (25°C)

pH	Recovery rate (%)		
	6 days	14 days	30 days
2	99.6	100.0	100.0
7	100.0	100.0	100.0
10	100.0	99.5	99.3

* 0.2%(w/v) Acetonitrile/Water Solution

Table 8 Photostability of Metofluthrin

Compound	Recovery rate* (%)
Metofluthrin	98.2
empenthrin	82.7
d-allethrin	6.9
prallethrin	11.2

* Initial recovery rate is expressed as 100%

Test condition
Test Sample : Filter paper (Φ5.5cm) with 20mg of compound was put on a glass petri dish with quartz cover. Slit was sealed with Teflon tape
Temperature : 15°C (ave.) [10°C (min.)–22°C (max.)]
Accumulated illumination: 7.56×10^5 lx · h (6h.×2days in the sunlight)

Efficacy and Formulation

1. Insecticidal Activity

The lethal efficacy (topical application) of Metofluthrin for medically important pests is given in **Table 9**.

The LD_{50} value of Metofluthrin for common house mosquito (*Culex pipiens pallens*) adults was 0.0015μg/female adult, and the relative lethal effica-

Table 9 Lethal efficacy of Metofluthrin against sanitary pests*

Compound	*Culex pipiens*	*Aedes albopictus*	*Musca domestica*	*Blattella germanica*
Metofluthrin	0.0015	0.00047	0.24	1.3
d-allethrin	0.038	0.023	0.21	2.9
prallethrin	0.0056	0.0050	0.13	0.59
d-tetramethrin	0.0096	0.0036	0.28	7.8
permethrin	0.0028	0.0012	0.013	1.5

* LD_{50}(μg/female adult) by topical application method

cy of Metofluthrin was approximately 25 times *d*-allethrin and approximately four times prallethrin. In addition, it had approximately two times the efficacy of permethrin, which is a representative killing agent. The LD_{50} value of Metofluthrin for Asian tiger mosquito (*Aedes albopictus*) adults was 0.00047μg/female adult, and the relative lethal efficacy of Metofluthrin was approximately 50 times *d*-allethrin, approximately 10 times prallethrin and approximately four times permethrin. The lethal efficacy of Metofluthrin for adults of the southern house mosquito (*Culex quinquefasciatus*) from Southeast Asia was 33.3 to 78.8 times that of *d*-allethrin for the four strains from Indonesia, Thailand, Vietnam and Malaysia.[5)]

On the other hand, the lethal efficacy against adult house flies (*Musca domestica*) is about the same as *d*-allethrin and approximately 0.5 that of prallethrin. In addition, the efficacy against female adult German cockroaches (*Blattella germanica*) is approximately two times that of *d*-allethrin and approximately 0.5 that of prallethrin. From the results mentioned above, we can see that Metofluthrin in particular has an extremely high lethal efficacy for mosquitoes.

2. Heated Formulations

Metofluthrin is highly efficient for various species of mosquitoes, and it is also a very suitable agent for various vaporization formulations in terms of physical properties. We carried out a detailed investigation into the leveraging of the characteristics in mosquito coils and liquid vaporizers, which are typical heated vaporization formulations for mosquitoes.

(1) Mosquito Coils

Mosquito coils, which were first invented in Japan in the 19th Century are widely used throughout the world. In Southeast Asia, in particular, they are the most popular formulation at present. To evaluate the semi-practical efficacy of Metofluthrin coils for various species of mosquitoes, we carried out efficacy evaluations using a large chamber ($28m^3$) free flying method.

The efficacy against the common house mosquito (laboratory susceptible strain), which is the main species in the temperate parts of Asia, including Japan, is given in **Table 10**. Coils containing 0.013% Metofluthrin had an efficacy somewhat exceeding that of coils containing 0.2% *d*-allethrin. On the other hand, for the most important target species in the mosquito control is southern house mosquito (laboratory susceptible strain) which is widely distributed in tropical and subtropical areas worldwide, coils containing 0.005% Metofluthrin exhibited an efficacy exceeding that of coils containing 0.2% *d*-allethrin, and the relative efficacy is estimated to exceed 40 times that of *d*-allethrin (**Table 11**).

Table 10 Knockdown efficacy of Metofluthrin coil against *Culex pipiens pallens* a)

A.I.	Conc. (% w/w)	KT_{50} (min) b)
Metofluthrin	0.013	49
	0.02	35
	0.04	22
d–allethrin	0.2	54

a) Laboratory susceptible strain
b) Large chamber ($28m^3$) free flying method

Table 11 Knockdown efficacy of Metofluthrin coil against *Culex quinquefasciatus* a)

A.I.	Conc. (% w/w)	KT_{50} (min) b)
Metofluthrin	0.01	40
	0.005	60
d–allethrin	0.2	75

a) Laboratory susceptible strain
b) Large chamber ($30m^3$) free flying method

To determine the practical effects of coils containing Metofluthrin, field tests were conducted according to the method of Yap et al.[6)] using private residences in Bogor, Indonesia. The results are shown in **Table 12**. In these tests, 95% of the mosquitoes captured were southern house mosquitoes, and coils containing 0.005% Metofluthrin exhibited an efficacy exceeding that of coils containing 0.03% transfluthrin and 0.3% *d*-allethrin. A similar test was conducted in Malaysia, and the efficacy was confirmed in practical settings where coils containing 0.005% Metofluthrin exhibited an efficacy equal to that of coils containing 0.25% *d*-allethrin.[7), 8)] In order to confirm the efficacy for field strains, eggs of southern house mosquitoes were collected in Bogor and reared in the laboratory. The semi-practical efficacy tests (large chamber free flying method) were conducted for this field strain. The results are given in **Table 13**. Field strains of mosquitoes tended to have longer times before knockdown compared with laboratory susceptible strains, and these tests were carried out by releasing the test

insects after an hour of pre-fumigation. As a result, coils containing 0.005% Metofluthrin exhibited an efficacy almost equal to that of coils containing 0.3% *d*-allethrin, and the relative efficacy can be thought of as 60 times that of *d*-allethrin, an increase in the efficacy ratio over the laboratory strains.

Table 12 Field evaluation of Metofluthrin coil in Bogor, Indonesia

A.I.	Conc. (% w/w)	Collected mosquitoes*		Reduction (%)
		Pretreatment	Treatment	
Metofluthrin	0.005	210	18	93
transfluthrin	0.03	187	26	88
d-allethrin	0.3	188	27	88
Control		256	303	

* Predominant species was *Culex quinquefasciatus*

Table 13 Knockdown efficacy of Metofluthrin coil against *Culex quinquefasciatus* (Bogor field strain)

A.I.	Conc. (% w/w)	KT_{50} (min)*
Metofluthrin	0.005	25
	0.0075	16
d–allethrin	0.3	27

* Large chamber ($28m^3$) free flying method. Releasing mosquitoes after 1hour pre-fumigation in a test chamber

(2) Liquid Vaporizer

Because of the high knockdown activity for mosquitoes, the suitable degree of vaporization and the easy solubility in various solvents, starting with kerosene, Metofluthrin is suitable for use as the active ingredient in liquid vaporizer.

With a liquid vaporizerusing prallethrin, which is a typical active ingredient, the amount vaporized does not increase after the chemical concentration goes over a certain fixed amount. However, with a liquid vaporizer with Metofluthrin as the active ingredient, we found that the vaporization amount increased proportionally to the concentration of Metofluthrin, even at high concentrations (**Table 14**). Therefore, highly concentrated chemical use is possible through the use of Metofluthrin as the active ingredient in liquid vaporizer, and furthermore, it can be assumed that a reduction in the size of liquid vaporizer will be possible through the use of thinner absorbent wicks.

Table 14 Evaporation rate of Metofluthrin and prallethrin liquid vaporizer

Concentration (%)	Evaporation rate (mg/2h)	
	Metofluthrin	prallethrin
0.2	0.5	—
0.4	0.9	—
0.8	2.1	1.5
1.6	3.7	1.5
3.2	6.7	—

The efficacy of the liquid vaporizer for the common house mosquito (laboratory susceptible strain) is given in **Table 15**. A 45ml liquid vaporizercontaining 240mg of Metofluthrin has the same efficacy as a 45ml liquid vaporizer containing 600mg of prallethrin. On the other hand, the efficacy of a Metofluthrin liquid vaporizer for southern house mosquitoes (laboratory susceptible strain) was very high at 5–6 times that of prallethrin (**Table 16**). The efficacy of Metofluthrin liquid vaporizer tested by the large chamber free flying method ($28m^3$, insects released after one hour pre-fumigation) on field strains of southern house mosquitoes from Bogor, Indonesia is given in **Table 17**. In the case of the field strain, there was an increase in the efficacy ratio with prallethrin over the laboratory susceptible strain, and the relative efficacy ratio was estimated to be over 8 times that of prallethrin.

Table 15 Knockdown efficacy of Metofluthrin liquid vaporizer[a] against *Culex pipiens pallens*[b]

A.I.	A.I. mg/45ml	KT_{50} (min)[c]
Metofluthrin	120	>90
	240	70
	480	48
prallethrin	600	74

a) 60 day use formulation
b) Laboratory susceptible strain
c) Large chamber ($28m^3$) cage method

Table 16 Knockdown efficacy of Metofluthrin liquid vaporizer[a] against *Culex quinquefasciatus*[b]

A.I.	A.I. mg/45ml	Evaporation rate (mg/h)	KT_{50} (min)[c]
Metofluthrin	120	0.17	35
	180	0.22	25
	240	0.35	21
prallethrin	600	1.01	35

a) 60 day use formulation
b) Laboratory susceptible strain
c) Large chamber ($28m^3$) free flying method

Table 17 Knockdown efficacy of Metofluthrin liquid vaporizer[a] against *Culex quinquefasciatus* (Bogor field strain)

A.I.	A.I. mg/45ml	Evaporation rate (mg/h)	KT_{50} (min)[b]
Metofluthrin	30	0.080	30
	60	0.13	12
prallethrin	300	0.66	31

a) 30 day use formulation

b) Large chamber ($28m^3$) free flying method. Releasing mosquitoes after 1hour pre-heating in the test chamber

3. Non-heated Formulation

One of the major characteristics of Metofluthrin is its having room temperature vapor action not seen in the existing pyrethroids *d*-allethrin and prallethrin. We will describe a fan type formulation[7] where a motor turns a fan and the active ingredient is vaporized by the airflow from it at room temperature and a no-fan vaporizing formulation that is used by vaporization of the active ingredient held in a paper, resin or other carrier without heating and without any motive force.

(1) Fan Type Formulation

Mosquito control mats, liquid vaporizer and other formulations exhibit their effects by vaporizing the active ingredient through heating. However, since these heaters require a comparatively large amount of electric power, there has been a limit to use with normal batteries.

On the other hand, the active ingredient in a fan vaparizer is vaporized by the airflow from a fan at room temperature, but the power required to turn the fan is much smaller than that for heating, so it is possible to use them with normal batteries for the power.

Therefore, fan vaporizers have the merit of making it possible to carry them around without thinking about the availability of electrical outlets and have made it possible to use them outdoors.

Since these fan vaporizers have revolutionary performance, sales are growing each year, and within them, they may possess the possibilities for greatly realigning the map of the influence of various formulations in the noxious insect prevention market.

With the goal of getting a grasp on the basic activity of Metofluthrin as the active ingredient in a fan type formulation, we investigated the knockdown efficacy against the common house mosquito (laboratory susceptible strain) in a semi-practical setting with various amounts of vaporization using a disk capable of adjusting the amount of vaporization without changing the airflow (large chamber free flying method). Transfluthrin was used as the control chemical. The results are shown in **Table 18**.

Table 18 Knockdown efficacy of Metofluthrin fan vaporizer against *Culex pipiens pallens*[a]

	Evaporation rate (mg/h)	KT_{50} (min)[b]	Linear regression expression
Metofluthrin	0.09	34	$\log(KT_{50}) = -0.89 \times \log(\text{Evaporation rate}) + 0.61$
	0.18	18	
	0.26	14	
transfluthrin	0.2	38	$\log(KT_{50}) = -0.59 \times \log(\text{Evaporation rate}) + 1.17$
	0.36	29	
	0.54	21	

a) Laboratory susceptible strain

b) Large chamber ($28m^3$) free flying method

Based on the results of these tests, it was found that Metofluthrin had an efficacy of more than 3 times that of transfluthrin (**Table 19**).

Table 19 Estimated knockdown efficacy of Metofluthrin and transfluthrin fan vaporizer against *Culex pipiens pallens*[a]

	KT_{50}[b]	
	20min	30min
Metofluthrin (mg/h)	0.17	0.11
transfluthrin (mg/h)	0.61	0.31

a) Laboratory susceptible strain

b) Large chamber ($28m^3$) free flying method

Therefore, when Metofluthrin is used as the active ingredient in a fan vaporizer, it is possible to make the fan device even smaller. Since one of the main merit of a fan vaporizer is its portability, the reduction in size is a condition necessary for growth in demand for fan type formulations in the future, and we can assume that Metofluthrin is the only active insecticidal ingredient that can make that possible.

We investigated the efficacy against the Asian tiger mosquito (laboratory susceptible strain) which is a representative striped mosquito (*Aedes*) in Japan using a test fan vaporizer and the large chamber free flying method. The results are shown in **Table 20**. In comparisons of the efficacy based on the amount of vaporization, we found that Metofluthrin exhibited an efficacy approximately five times that of transfluthrin.

Table 20 Knockdown efficacy of Metofluthrin fan vaporizer against *Aedes albopictus*[a)]

A.I.	Evaporation rate (mg/h)	KT_{50} (min)[b)]
Metofluthrin	0.090	40
	0.28	>60
transfluthrin	0.39	55
	0.50	55

a) Laboratory susceptible strain
b) Large chamber ($28m^3$) free flying method

A carrier containing 160mg of Metofluthrin was loaded into the test fan vaporizer (using two AA alkaline batteries, with battery replacement after 332 hours), and we carried out residual effectiveness tests (large chamber free flying method) over 637 hours of operation. As a result, the fan type noxious insect control agent that used Metofluthrin as the active ingredient exhibited knockdown activity during the test period that was generally the same or greater than a commercial 60 day liquid vaporizer (**Fig. 7**).

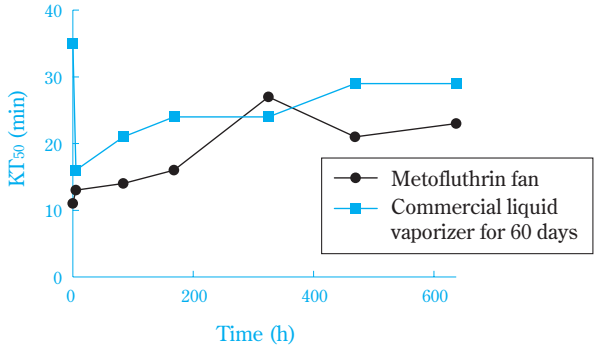


Fig. 7 Knockdown efficacy of Metofluthrin fan vaporizer against *Culex pipiens pallens* (susceptible strain)

With the 60 day liquid vaporizer the immediacy just after starting it up was somewhat insufficient, but the fan type device using Metofluthrin exhibited immediate effects after it was started.

(2) Ambient Vaporization Formulations

Natural vaporization agents, where the active ingredient is held in paper or resin, and it is vaporized without heating or use of power are easy to use, so there are particular expectations for new developments in the field of mosquito control. Insecticides that can be used in formulations for this purpose must possess the characteristics of room temperature vapor action, high level activity a high degree of safety for mammals, and Metofluthrin meets all of these features.

First of all, we investigated formulations using paper as the carrier. There is an old Japanese toy called "Denguri" where folded paper, is opened to form a variety of shapes. A hint was taken from this toy for the design of the shape of the ambient vaporization formulation with a paper carrier. In this paper we will call this formulation the "Denguri formulation." When the denguri formulation is used, designs in a variety of shapes are possible, and it is possible to obtain the maximum surface area by using it fully open. On the other hand, the merit is of being folded into a small shape when not being used.

To get a grasp on the sustained release performance of Metofluthrin in the denguri formulation, we measured the residual amount of Metofluthrin in the denguri formulation over time with a paper denguri formulation (**Fig. 8**) containing 200mg of Metofluthrin kept under conditions where the airflow was approximagely 0.6m/s (temperature: approximately 26°C, relative humidity: approximately 60%) at the center of the denguri formulation. The results are shown in **Fig. 9**.

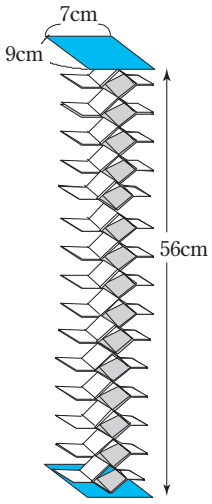


Fig. 8 Metofluthrin Denguri paper strip

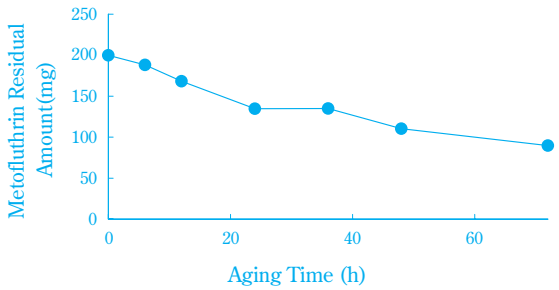


Fig. 9 Residual amount of Metofluthrin in Denguri paper strip

From these results, it was determined that the Metofluthrin vaporized from the denguri formulation in an almost fixed proportion.

To confirm the efficacy of the denguri formulation in a practical setting, practical tests were conducted with use at a home in Malaysia. The testing was carried out according to the methods of Yap et al.[6] The results are shown in **Fig. 10**. A denguri formulation containing 100mg of Metofluthrin exhibited high level preventative effects exceeding those of coil formulations containing 0.25% *d*-allethrin on southern house mosquitoes.[8), 9)]

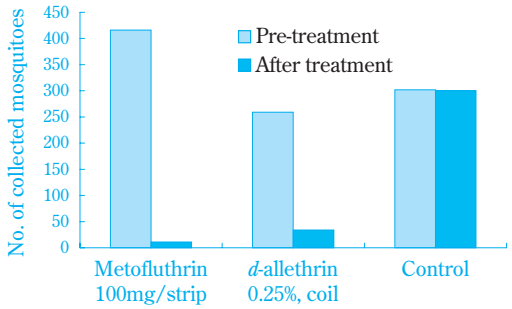
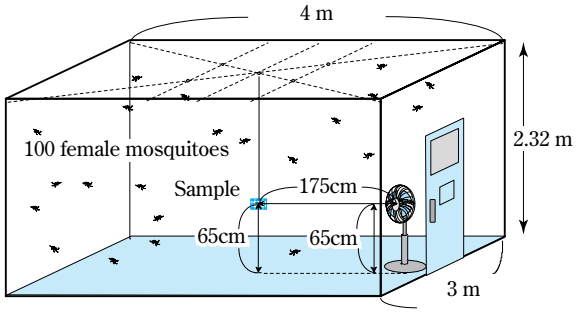


Fig. 10 Field efficacy of Metofluthrin Denguri paper strip against night biting indoor mosquitoes (*Culex quinquefasciatus*) in Malaysia

Practical tests using a similar denguri formulation were conducted on Lombok Island in Indonesia and in Japan. In a house on Lombok Island, a denguri formulation impregnated with 200mg of Metofluthrin exhibited repellent effects of 80% or greater on southern house mosquitoes and anopheles mosquitoes over a period of four weeks.[10] In addition, in outdoor conditions on Lombok Island, it exhibited superior repellant effects on southern house mosquitoes as well as *Anopheles balabaciensis* and *An. sundaicus*, which are vector mosquitoes for malaria.[11] On the other hand, the denguri formulation impregnated with 200mg of Metofluthrin exhibited almost complete repellent activity on Asian tiger mosquitoes.[12] From these results, we were able to confirm that the denguri formulation exhibited sufficient effects in practical settings.

Next, we will describe resin formulations.

Resins have superior durability and processing characteristics to paper, and they are suitable as the carriers for the active ingredients for natural vaporization formulations used indoors all along and in the severe usage environment of the outdoor use. We carried out residual effectiveness tests on two polyolefin resin formulations (8cm × 11cm × 0.5cm, 12.3g) molded into lattice shapes and containing approximately 4.4% Metofluthrin (**Fig. 11**).



(Test Conditions)
Ambient Temperature : About 30°C
Relative Humidity : About 60%
Wind Velocity : About 0.5m/s at the test sample

Fig. 11 Test method of Metofluthrin resin formulation

As a result, we determined that a resin formulation containing Metofluthrin exhibited stable efficacy over a period of at least eight weeks (**Fig. 12**).

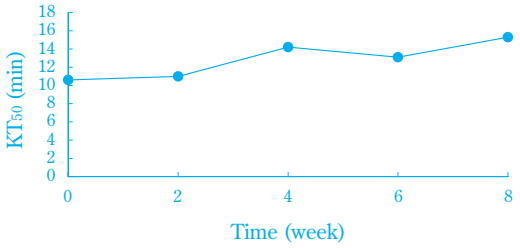


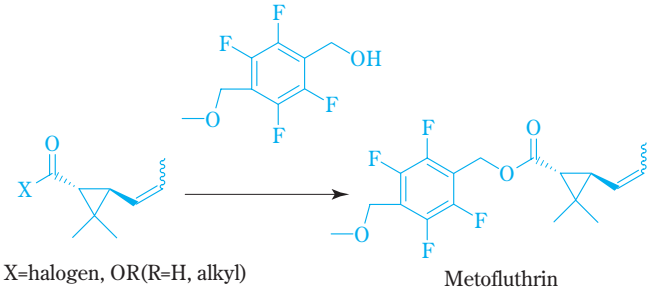
Fig. 12 Knockdown efficacy of Metofluthrin resin formulation

Practical tests using resin formulations were conducted in Indonesia and Vietnam. Under outdoor conditions of use in well ventilated huts that only have roofs in Indonesia (Lombok Island), resin formulations containing 1g of Metofluthrin exhibited high level spatial repellent effects on mosquitoes over 15 weeks with a distribution of four resin formulations per 5–10m^2.[13] On the other hand, in tests conducted in houses in Vietnam, resin formulations containing 1g of Metofluthrin exhibited high level spatial repellent effects on the southern house mosquito and the yellow fever mosquito (*Aedes aegypti*) for at least six

weeks, and we confirmed the practicability of this formulation.[14)]

Manufacturing Methods

Metofluthrin is an ester compound, and as is shown in **Fig. 13**, it can be produced by reacting 2,3,5,6-tetrafluoro-4-methoxymethyl benzyl alcohol and a norchrysanthemic acid derivative. We carried out a variety of investigations on production methods for various intermediates and esterification methods of which we can cite the method of condensation of the acid halide and the alcohol (X=halogen atoms), esterification by dehydration condensation of carboxylic acid (X=OH) and the alcohol, and ester exchange reactions with the carboxylate ester (X=OR: R=alkyl group) and the alcohol, and we established the industrial production method for efficiently obtaining Metofluthrin.



X=halogen, OR(R=H, alkyl)

Metofluthrin

Fig. 13 Synthetic Route to Metofluthrin

Metabolism, Pharmacology and Toxicity

1. Metabolism

We investigated the disposition in rats using [acid-^{14}C] and [alcohol-^{14}C] Metofluthrin. When the [acid-^{14}C] or [alcohol-^{14}C] Metofluthrin was administered as a single oral dose of 1mg/kg or 20mg/kg in male and female rats, it was absorbed rapidly from the gastrointestinal tract (oral absorption rate of 78% or greater), and the ^{14}C concentration in the blood reached the maximum concentration 3–8 hours after administration, rapidly disappearing afterwards. Metofluthrin undergoes ester hydrolysis, oxidation, glutathione conjugation and other metabolic reactions (**Fig. 14**), and 91.5–95.2% of the dose was excreted in the urine, feces and expired air by the second day after administration and 95.4–96.7% by the seventh day after administration. The main excretion pathway is the urine. The ^{14}C is mainly distributed to the liver, and distribution to other tissues was low. The disappearance of ^{14}C from the blood cells, bones, hair and fatty tissue was slower than for other tissues, but the remainder in these tissues 7 days after the single dose was extremely low (0.1% of the dose). There are no remarkable dosage or sex-related differences in the absorption, distribution, metabolism and excretion of Metofluthrin.

2. General Pharmacology

General pharmacological tests of Metofluthrin were

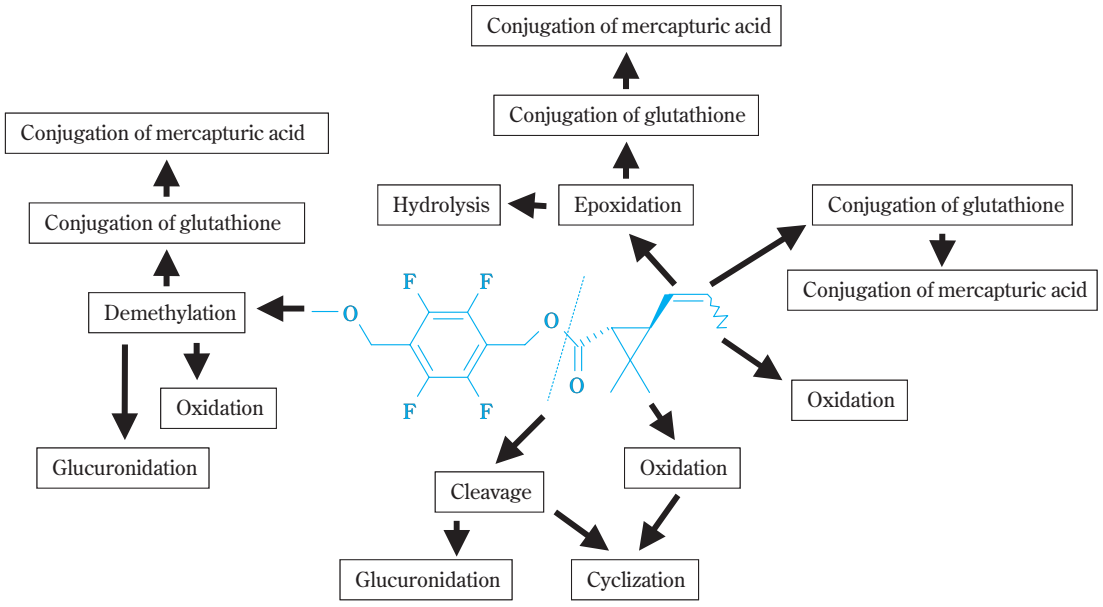


Fig. 14 Metabolic Reaction of Metofluthrin in Rats

conducted in rats, guinea pigs and dogs. For general symptoms and behaviors, tremors and twitches were observed. In terms of the central nervous system, no effects on motor activity, body temperature, hexobarbital-induced sleeping time, potentiation/antagonism for convulsion, or analgesia were found. In terms of the autonomic nervous system and smooth muscle tissue, direct contractile effect and inhibitory effect on various agonist-induced contractions were observed. In the respiratory and circulatory systems, there was an increase in heart rate, but no effects were observed on respiration, blood pressure, blood flow or electrocardiograms. In terms of water and electrolyte metabolism, no effects on urine volume or electrolyte excretion were found. In the somatic nervous system, there was an increase in contractions induced by electrical stimulation of the muscles in isolated nerve-diaphragm preparations. None of these effects were observed at low dosages, and in addition, the symptoms that appeared as general symptoms disappeared within 24 hours.

3. Toxicity

(1) Acute Toxicity

The approximate lethal dose was found to be greater than 2000mg/kg in males and to be 2000mg/kg in females in a rat acute oral toxicity study, and to be greater than 2000mg/kg in males and females in a dog acute oral toxicity study. The acute dermal LD_{50} in rats was found to be greater than 2000mg/kg for both males and females. The acute inhalation LC_{50} in rats was found to be 1960mg/m^3 for males and 1080 mg/m^3 for females (**Table 21**). On the main symptoms, hypersensitivity, tremor, clonic convulsion, salivation, ataxic gait and tip toe gait were found in rats, and neurologic symptoms such as tremor was found in dogs.

(2) Subacute and Chronic Toxicity

In the results of subacute and chronic toxicity studies, it was clear that Metofluthrin has some effects on the nervous system and the liver (**Table 22**).

Effects on the nervous system were found in both rats and dogs. In rats, tremors were found in the oral administration study, and tremors, hypersensitivity, ataxic gait, tip toe gait, lateral position and clonic convulsion were found in the inhalation exposure study. In the dog study, tremors were found. These neurologic symptoms were observed with the highest frequency through the first week after the commencement of dosing in rats and in the second or fourth weeks or later in dogs. It is well known that Pyrethroids generally affect on the nervous system and that the symptoms such as tremors are observed with the administration of pyrethroids.[15] Therefore, neurological symptoms observed with Metofluthrin was considered to be symptoms common to pyrethroids. There were no histopathological changes

Table 21 Acute Toxicity of Metofluthrin

Species	Administration route	Dose	Approximate Lethal Dose
Rat	Oral	1000, 1500, 2000 mg/kg	Male : >2000 mg/kg Female : 2000 mg/kg
Rat	Dermal	2000 mg/kg	Male & Female : > 2000 mg/kg
Rat	Inhalation	507, 1080, 1960 mg/m^3	Male : 1960 mg/m^3 Female : 1080 mg/m^3
Dog	Oral	200, 600, 2000 mg/kg	Male & Female : > 2000 mg/kg

Table 22 Subacute and Chronic Toxicity of Metofluthrin

Species	Administration route and duration	Dose	NOAEL
Rat	Oral (in diet), 1 month	300, 1000, 3000 ppm	Male : 300ppm (28.6 mg/kg/day) Female : 300ppm (29.0 mg/kg/day)
Rat	Inhalation, 4 weeks	9.84, 50.6, 98.7, 196 mg/m^3	Male & Female : 98.7 mg/m^3
Dog	Oral (capsule), 90 days	10, 30, 100 mg/kg/day	Male : 10 mg/kg/day Female : 30 mg/kg/day
Rat	Oral (in diet), 6 months	100, 300, 1000, 3000 ppm	Male : 300ppm (16.0 mg/kg/day) Female : 300ppm (19.0 mg/kg/day)

in either the central nerves (brain and spinal cord) or the peripheral nerves, and recovery from the symptoms was confirmed.

The effects on the liver were an increase in the liver weight and hepatocellular hypertrophy in rats. These changes are similar to those observed in induction of drug-metabolizing enzymes after administration of some chemicals [16)–18)]. As a result of metabolism tests, Metofluthrin is primarily metabolized by metabolic enzymes in the liver. Therefore, it was thought that the induction of metabolic enzymes was observed as an adaptive response in related to metabolism in the liver. Furthermore, hepatocellular vacuolation (accumulation of fat) was observed in rats, and in blood biochemistry, high levels for the total cholesterol and phospholipids were found, clearly indicating that there were effects of Metofluthrin on the fat metabolism. In addition, in blood biochemistry, high values for total protein, albumin and β-globulin were found, indicating effects of Metofluthrin on the protein metabolism in the liver. Moreover, recovery from all of the changes was confirmed.

(3) Reproductive and Developmental Toxicity

In terms of reproductive and developmental toxicity, there were no effects on reproduction or the next generation in the results of studies on the effects on fertility and early embryonic development to implantation in rats, effects on embryo-fetal development in rats and rabbits, or effects on pre- and postnatal development, including maternal function in rats (**Table 23**).

(4) Antigenicity

The results of both skin sensitization (Maximization Test) and active systemic anaphylaxis tests using guinea pigs were negative.

(5) Irritation

In the results of skin and eye irritation tests in rabbits, we determined that there was a mild irritation to the skin and no irritating to the eyes.

(6) Mutagenicity

The results of a reverse mutation test using *Salmonella typhimurium* and *E. coli*, an *in vitro* chromosomal aberration test using Chinese hamster lung cells and a micronucleus test using mouse bone marrow were all negative (**Table 24**).

Table 24 Mutagenicity of Metofluthrin

Study	Study design	Results
Reverse mutation (Ames test)	*S. typhimurium* : TA100, TA98, TA1535 and TA1537 *E. coli* : WP2*uvr*A –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 : 50 – 110 μg/mL +S9 mix : 150 – 250 μg/mL	Negative
Micronucleus	Mouse (CD-1, 8-week old) 12.5, 25, 50 mg/kg (single oral administration)	Negative

Table 23 Developmental and Reproductive Toxicity of Metofluthrin

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 7 of gestation	Male : 5, 10, 20 Female : 10, 20, 40	Parental	Systemic NOAEL Male & Female : 20 Reproductive NOAEL Male : 20 Female : 40
				Developmental	Male : 20 Female : 40
Effects on embryo-fetal development	Rat	Oral (gavage) Days 6-19 of gestation	5, 15, 30	Maternal	Systemic NOAEL : 15 Reproductive NOAEL : 30
				Developmental	30
	Rabbit	Oral (gavage) Days 6-27 of gestation	25, 125, 250	Maternal	Systemic NOAEL : 25 Reproductive NOAEL : 250
				Developmental	250
Effects on pre- and postnatal development, including maternal function	Rat	Oral (gavage) Day 6 of gestation to day 20 of lactation	5, 15, 30	Maternal	Systemic NOAEL : 15 Reproductive NOAEL : 30
				Developmental	30

(7) Fish Toxicity

An exposure test was conducted for 96 hours using carp (*Cyprinus carpio*) under flow-through conditions. The 96 hour LC_{50} value was 3.06μg/L.

Conclusion

Sumitomo Chemical has discovered and marketed more than 20 pyrethroids with diversified characteristics over a half century or more, and these pyrethroids have made a large contribution to our household, public health and agricultural chemical business. Currently pyrethroids have a indispensable presence in assuring agricultural products, controlling diseases and noxious insects and assuring comfortable living spaces worldwide. Metofluthrin was developed by bringing together the knowledge and wisdom Sumitomo Chemical has accumulated concerning pyrethroids up to now, and there are expectations for it to become a major product for Sumitomo Chemical as an ideal mosquito control agent both in Japan and overseas.

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