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Development of a New Acaricide, Milbemectin

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INTRODUCTION

Milbemectin, a mixture of approximately 30% Milbemycin A_3(M. A_3) and 70% Milbemycin A_4(M. A_4) produced by *Streptomyces hygroscopicus* subsp. *aureolacrimosus*, was developed by Sankyo Co., Ltd. as a new acaricide. Milbemycins (M. A_3 and M. A_4 analogues) were discovered in 1969 during the screening of fermentation broths of various microorganisms. Although milbemycins showed an outstanding activity against various kinds of mites, the development as an acaricide was very difficult at that time of the discovery, due to the production of many structurally similar compounds and physical fragility of the producing strain. After efforts have been made to improve productivity, the strain to produce milbemectin at high yield was selected. Based on many preliminary tests, it was clarified that milbemectin has many characteristics: a high activity against broad spectrum of phytophagous mites and all developing stages of mites, high selectivity, novel mode of action, no cross-resistance with conventional acaricides and fast degradation in the environment. Furthermore, it has a suitable long-lasting efficacy and stable activity without fluctuation under the ambient temperature.

Milbemectin has been registered and marketed as an acaricide for the control of mites on tea, pear, peach, watermelon, strawberry and egg plant in Japan since 1990.

PHYSICAL AND CHEMICAL PROPERTIES

Common name: Milbemectin (ISO)
Code Number: E-187
Trade name: Milbeknock®, Koromite®

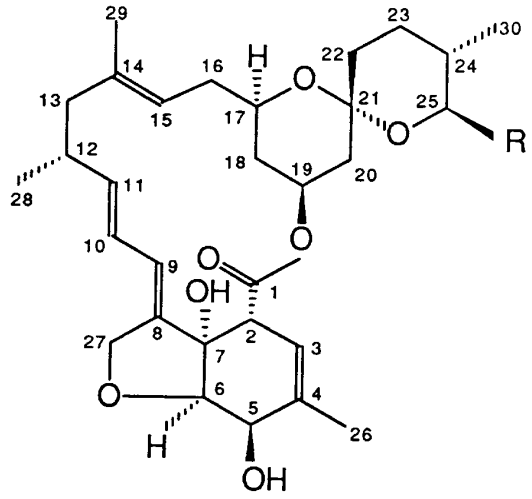
Formulation: 1% (w/w) emulsifiable concentrate

Chemical name: M. A_3, (10*E*, 14*E*, 16*E*, 22*Z*)-(1*R*, 4*S*, 5′*S*, 6*R*, 6′*R*, 8*R*, 13*R*, 20*R*, 28*R*, 13*R*, 20*R*, 21*R*, 24*S*)-21, 24-dihydroxy-5′, 6′, 11, 13, 22-pentamethyl-3, 7, 19-trioxacyclo[15, 6, 1, $1^{4,8}$, $0^{20,24}$]-pentacosa-10, 14, 16, 22-tetraene-6-spiro-2′-tetrahydropyran-2-one; M. A_4, (10*E* 14*E*, 16*E*, 22*Z*)-(1*R*, 4*S*, 5′*S*, 6*R*, 6′*R*, 8*R*, 13*R*, 20*R*, 21*R*, 24*S*)-6′-ethyl-21, 24-dihydroxy-5′, 11, 13, 22-tetramethyl-3, 7, 19-trioxacyclo[15, 6, 1, $1^{4,8}$, $0^{20,24}$]-pentacosa-10, 14, 16, 22-tetraene-6-spiro-2′-tetrahydropyran-2-one.

	M. A_3	M. A_4
Empirical formula	$C_{31}H_{44}O_7$	$C_{32}H_{46}O_7$
Molecular weight	528.68	542.71
Melting point	212–215°C	212–215°C
Water solubility	7.2 ppm (20°C)	0.88 ppm (20°C)
log K_{OW}	5.3	5.9
Vapor pressure	$<1\times10^{-10}$ mmHg (20°C)	$<1\times10^{-10}$ mmHg (20°C)
Appearance	White powder	White powder

PRODUCTION OF MILBEMECTIN

Milbemectin is a fermentation product produced by improved strain of *Streptomyces hygroscopicus* subsp. *aureolacrimosus* SANK60576. The strain was originally isolated from soil collected at Kuttian-cho in Hokkaido, Japan and the name "*Streptomyces hygroscopicus* subsp. *aureolacrimosus*" is derived from the formation of golden drops of exudate on aerial mycelium. From the cultured broth,



R : CH_3 = M.A_3

C_2H_5 = M.A_4

Fig. 1 Structure of milbemectin.

milbemectin was isolated by several steps of solvent extraction.

BIOLOGICAL ACTIVITY

Milbemectin exhibited quite high activities on various phytophagous mites, such as *Tetranychidae* and *Eriophydae* (Table 1).

It is noteworthy that milbemectin is equally effective against all developmental stages (egg, larva, nymph and adult) of mites at quite low dosages. The acaricidal activity of milbemectin was not influenced by the ambient temperature, with the result that milbemectin can be used for the control of mites all the year round without fluctuation in its efficacy.

Cross-resistance with conventional acaricides is a serious problem. From various laboratory and field trials it became clear that milbemectin is potent against various strains resistant to conventional acaricides, because milbemectin is a new class of compound and has a unique mode of action different from conventional acaricides. Milbemectin has long-lasting efficacy against *Teranychidae*, regardless of rapid degradation of milbemectin on plants. This is why at levels of milbemectin on the leaves lower than its experimentally lethal dose, mites are able to survive, but normally fail to lay eggs. That is to say, a sublethal amount of milbemectin affects the reproduction of mites, and this contributes to a long lasting efficacy in the field after the disappearance of milbemectin itself.

Table 1 Target mites and insects.

	Scientific name	Common name
Mites	*Tetranychidae*	Spider mites
	Panonychus citri	Citrus red mite
	Panonychus ulmi	European red mite
	Tetranychus cinnabarinus	Carmine spider mite
	Tetranychus kanzawai	Kanzawa spider mite
	Tetranychus urticae	Two-spotted spider mite
	Eriophydae	Eriophyid mites
	Acphylla theae	Pink tea rust mite
	Aculops pelekassi	Pink citrus rust mite
	Aculus schlechtendali	Apple rust mite
	Calacarus carinatus	Purple tea mite
	Epitimerus pyri	Pear rust mite
	Tarsonemidae	Tarsomid mites
	Polyphagotarsonemus latus	Broad mite
Insects	*Myzus persicae*	Green peach aphid
	Toxoptera aurantii	Black citrus aphid
	Thrips palmi	Thrips
	Spodoptera litura	Common cutworm
	Caloptilia theivora	Tea leafroller

Table 2 Toxicity of milbemectin.

Toxicity test	Animal	Administration route	LD-50 (mg/kg)[a] or NOEL (mg/kg/day)[b]
Acute	Rat	Oral	♂: 762[a] ♀: 456[a]
		Dermal	♂, ♀: >5000[a]
		Inhalation	♂: 1.90 (mg/*l*) ♀: 2.80 (mg/*l*)
	Mouse	Oral	♂: 324[a] ♀: 313[a]
Irritation	Rabbit	Eye	No irritation
Chronic (2 years)	Rat	Oral (in diet)	♂: 6.81[b] ♀: 8.77[b]

Mutagenecity test: negative.
Teratogenecity test (rabbit): negative.

TOXICOLOGICAL STUDY

The safety data of milbemectin on animals are summarized in Table 2.

METABOLISM STUDY

The metabolism and degradation of milbemectin in rats, plants, soils and fish were studied along with its leaching and bioconcentration in fish. M.A_3 and M.A_4 labeled with ^{14}C were prepared by biosynthesis using sodium propanoate-1-^{14}C as a precursor and those with ^{3}H were prepared by synthesis.

Milbemectin was readily degradable in the environment and the feature of biological and non-biological degradations was oxidative. Milbemectin applied on plants degraded at half life less than 1 day and was metabolized to give polar compounds along with volatile products. In soils, milbemectin was not mobile by leaching nor translocated into the aerial part of the plants, and decomposed by aerobic soil-microorganisms. Although milbemectin was highly lipophilic, the bioconcentration factor in carp was very low due to the rapid metabolism. Also, milbemectin was metabolized in rats to give a number of polar metabolites and then rapidly excreted.

In conclusion, milbemectin is a typical agrochemical with low impact on the environment.