Natural Origin Miticide

Milbemectin

MITSUI CHEMICALS AGRO, INC.

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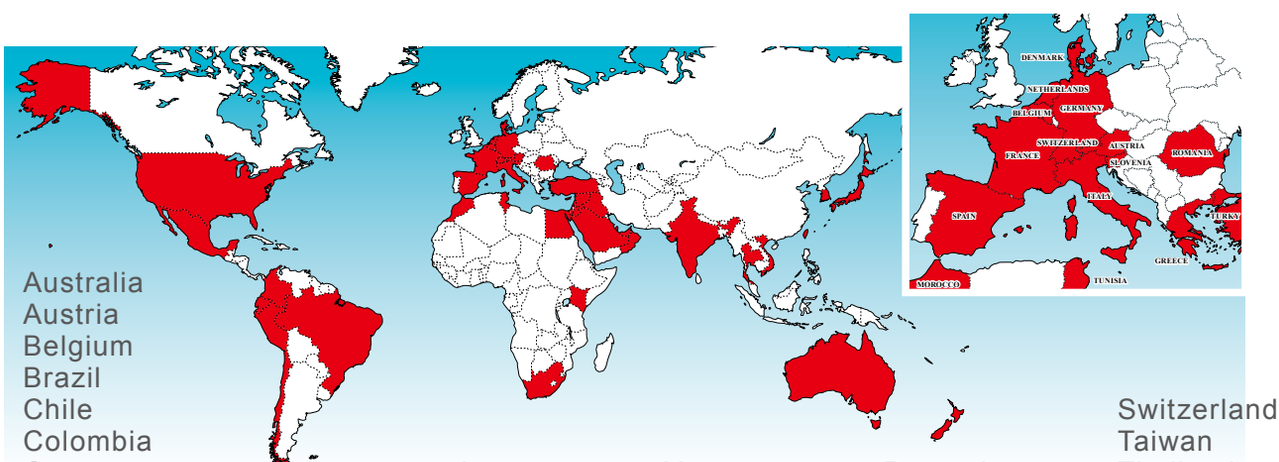
1. Introduction

- **Milbemectin** has been developed as a miticide/insecticide using Mitsui Chemical Agro's original technology together with the combined goals of environmental, crop, and worker safety.
- **Milbemectin** is a natural substance produced by fermentation of a species of *Actinomycetes* discovered in the soil of Hokkaido, Japan.
- **Milbemectin** has been recognized as a "REDUCED RISK PESTICIDE" by US-EPA (May, 2000).
- **Milbemectin** has been designated by the CTB of the Netherlands as a GNO (gewasbecshermingsmiddel van natuurlijke oorsprong) which means 'from a natural source'.
- **Milbemectin** is highly effective against a wide variety of pest mites e.g.[spider mite (*Panonychus* spp., *Tetranychus* spp., etc.) , rust mite, bud mite, broad mite, etc.], at all growth stages (ie.; egg, larva, nymph, and adult). In addition to its miticidal effect, **Milbemectin** has insecticidal activity against aphids, and some *Lepidoptera* [e.g. *Caloptilia theivora* (tea leafroller), and *Spodoptera litura* (common cutworm)], leafminer, leafhopper, whitefly, etc.
- **Milbemectin** has a unique mode of action, which is different from other conventional miticides. Thus, **Milbemectin** acts on the nervous system mediated by the inhibitory neurotransmitter, GABA. As a result, mites and insects treated with **Milbemectin** die without showing any observable actions e.g. excitation movements etc.
- **Milbemectin** has been registered for the following crops:

Apple, Asparagus, Adzuki Bean, Celery, Chard, Cherry, Citrus, Cotton, Cucumber, Eggplant, Ground cherry, Jujube, Kidney Bean, Melon, Mulukhiya, Ornamentals (Carnation, Chrysanthemum, Perennial Gypsophilla, Roses), Papaya, Parsley, Peach, Pear, Pepper, Perilla, Strawberry, Tea, Tomato, Vine, Watermelon, Yam, etc.

* Always use according to the instructions given on the label because the registration status may differ from country to country.



Australia
Austria
Belgium
Brazil
Chile
Colombia
Cyprus
Denmark
Ecuador
Egypt
France
Germany
Greece
India
Iraq
Israel
Italy
Japan
Jordan
Kenya
Korea
Lebanon
Mexico
Morocco
Netherlands
New Zealand
Oman
Peru
Qatar
Romania
Saudi Arabia
Slovenia
South Africa
Spain
Syria
Switzerland
Taiwan
Thailand
Tunisia
Turkey
U.A.E.
U.S.A.
Vietnam

2. Physical and Chemical Properties

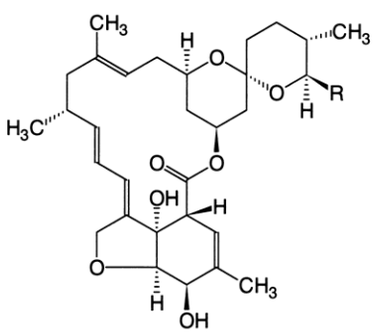
- Common name (ISO) : Milbemectin
- Code No. : CM-006, E-187, SI-8601, SI-9009
- Chemical name (IUPAC)

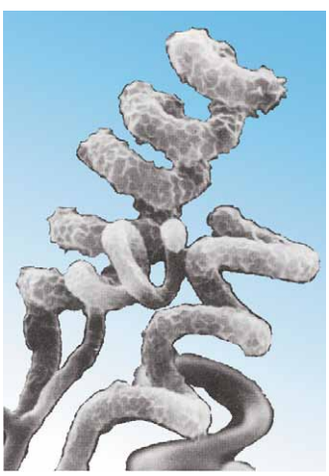
Milbemectin is a mixture of milbemycin A_3(M.A_3) and milbemycin A_4(M.A_4)
($M.A_3 \leq 30\%$, $M.A_4 \geq 70\%$)

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*,21*R*,24*S*)-21,24-dihydroxy-5',6',11,13,22-pentamethyl-3,7,19-trioxatetracyclo[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-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one

- Chemical Structure (M.A_3: R=CH_3, M.A_4: R=C_2H_5)





***Streptomyces hygroscopicus* subsp. aureolacrimosus**

	M.A_3	**M.A_4**
Molecular Formula	:$C_{31}H_{44}O_7$	$C_{32}H_{46}O_7$
CAS NO	:51596-10-2	51596-11-3
Molecular Weight	:528.68	542.71

Milbemectin

Physical State	: White Crystal (Pure Active Ingredient)			
Melting Point	: 205.2 - 208.3℃ (Pure Active Ingredient)			
Vapor Pressure	: <1.3×10^{-5}Pa at 25℃ (Pure Active Ingredient)			
Solubility/ water at 20℃	: 0.00723 g/L			
Solubility/ solvents at 25℃	: Acetone	: 203 g/L	*n*-Octanol	: 34.5 g/L
	n-Heptane	: 3.41 g/L	*o*-Xylene	: 259 g/L
	1,2-Dichloroethane	: >250 g/L	Methanol	: 251 g/L
	Ethyl acetate	: 250 g/L		

3. Characteristics of Milbemectin

1) Effective against a Range of Pests

■ *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
Tetranychus pacificus	: Pacific spider mite
Tetranychus turkestani	: Strawberry spider mite

■ *Eriophydae* (eriophyid mites)

Acaphylla theae	: Pink tea rust mite
Aculops pelekassi	: Pink citrus rust mite
Aculus schlechtendali	: Apple rust mite
Calacarus carinatus	: Purple tea mite
Epitrimerus pyri	: Pear rust mite
Eriophyes sheldoni	: Citrus bud mite
Phyllocoptruta oleivora	: Citrus rust mite

■ *Tarsonemidae* (tarsonemid mites)

Polyphagotarsonemus latus	: Broad mite
Phytnemus pallidus	: Cyclamen mite

Kanzawa spider mite

Efficacy on 4 major mite varieties

mite	stage	LC_{50}(ppm)		
		Milbemectin	A	B
Two-spotted spider mite	adult	**4.7**	14	>1000
	egg	**3.3**	290	0.8
Carmine spider mite	adult	**4.7**	17	500
	egg	**3.3**	110	0.5
Citrus red mite	adult	**0.05**	65	>500
	egg	**0.99**	380	0.5
Kanzawa spider mite	adult	**0.68**	20	>500
	egg	**1.52**	260	0.9

A, B: Reference product

Mitsui Chemicals Agro

■ Leafminers

Liriomyza trifolii	: Legume leafminer
Liriomyza sativae	: Tomato leafminer
Phyllonorycter ringoniella	: Apple leafminer

■ Whiteflies

Trialeurodes vaporariorum	: Greenhouse whitefly
Bemisia tabaci	: Sweetpotato whitefly

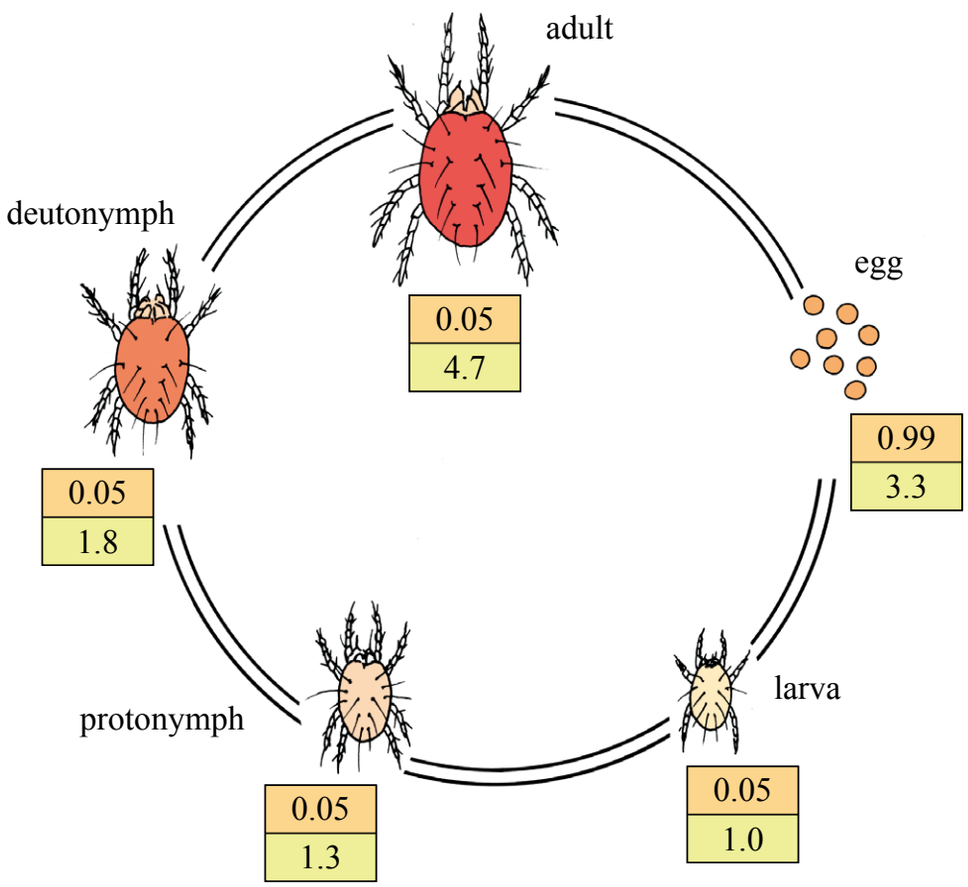
■ Aphids

Aphis citricola	: Apple aphid
Myzus persicae	: Green peach aphid
Aphis gossypii	: Cotton aphid

The reasons for this long-lasting control are as follows:

① Effective on all growth stages of mites

LC_{50} (ppm)	Citrus red mite *(Panonychus citri)*
LC_{50} (ppm)	Two-spotted spider mite *(Tetranychus urticae)*



② Suppressive effect on oviposition

With Milbemectin remaining on leaves even at levels lower than its experimentally lethal level, mites are able to survive but fail to lay eggs normally. They lay fewer eggs than untreated mites and even mites affected by other miticide. A sublethal amount of milbemectin affects the oviposition of mites, which contributes to a long-lasting effect in the field after the disappearance of milbemectin itself.

(Days After Treatment)

		0	10
Milbemectin (10 ppm)	Mortality(%)	100	7.9
	Eggs/Survivor	–	0.4
Untreated	Mortality(%)	0	0
	Eggs/Survivor	–	7.53

Tetranychus urticae

3) Toxicity to Mammals

● Milbemectin Technical

Acute oral LD_{50}	(rat)	: 762 (M), 456 (F) mg/kg bw
Acute dermal LD_{50}	(rat)	: > 5000 mg/kg bw (M/F)
Acute inhalation LC_{50}	(rat)	: 1.90 (M), 2.80 (F) mg bw/L (4 hour exposure)
Eye irritation	(rabbit)	: May cause slight eye irritation
Skin irritation and sensitization	(rabbit)	: Negative
Subchronic toxicity (13 weeks)	NOEL(rat)	: 375 ppm (M)
	(dog)	: 3 mg/kg bw/day (M/F)
Chronic/Carcinogenicity		: No carcinogenicity was observed
(24 months)	NOEL(rat)	: 150 ppm (M/F)
(12 months)	NOEL(dog)	: 3 mg/kg bw/day (M/F)
Mutagenicity		: No mutagenicity was observed
Teratogenicity	NOEL(rat)	: No teratogenicity was observed
Reproduction	NOEL(rat)	: 200 ppm (parental and offspring)
Proposed ADI (EU)		: 0.03 mg/kg bw/day

● Milbemectin formulation (1%EC)

Acute oral LD_{50}	(rat)	: 5200 (M), 5300 (F) mg/kg
Acute dermal LD_{50}	(rat)	: > 2000 mg/kg
Acute inhalation LC_{50} (4-hour)	(rat)	: > 6.75 mg/L (M/F)
Eye irritation	(rabbit)	: May cause slight eye irritation
Skin irritation	(rabbit)	: May cause slight skin irritation
Skin sensitization	(guinea pig)	: Negative

4) Ecotoxicity (1%EC)

Fish toxicity LC_{50} (96-hour)	(rainbow trout)	: 0.45 mg formulation/L
Daphnia magna acute toxicity EC_{50} (48-hour)		: 0.42 mg formulation/L
Algal growth inhibition E_bC_{50} (5-day)		: 33 mg formulation/L
Avian toxicity LD_{50} (14-day)	(mallard duck)	: > 2250 mg formulation/kg
Bee toxicity oral LD_{50} (48-hour)	(honey bee)	: > 100 μg formulation/bee
Bee toxicity contact LD_{50} (48-hour)	(honey bee)	: 4.23 μg formulation/bee
Earthworm acute toxicity LC_{50} (14-day)		: > 1250 mg formulation/kg dry soil

5) Selective (less impact) to beneficial insects

Milbemectin does not have a significant impact on beneficial insects. :

■Effects on the ground beetle *Poecilus cupreus*

Treatment	Application rate (g a.i./ha)	% mortality of beetles after 14 days	Mean number of fly pupae consumed /surviving beetle
Untreated		0	3.30
Milbemectin 1% EC	27.9	0	3.50
Reference product	300	100	–

■Effects on the aphid parasitoid *Aphidius rhopalosiphi*

Treatment	Application rate (g a.i./ha)	% mortality of wasps after 48h	Abbott-corrected % mortality	Mean fecundity (mummies/ female, n=15)
Untreated		3	–	16
Milbemectin 1% EC	9.3	7	4	21
Milbemectin 1% EC	27.9	13	10	14
Reference product	85.2	100	100	–

■Effects on the foliar-active predatory bug *Orius Laevigatus*

Treatment	Application rate (g a.i./ha)	Abbott-corrected % mortality	Mean number of eggs laid / female / day	Mean number of viable eggs / female / day
Untreated		–	7.7	6.9
Milbemectin 1% EC	9.3	0	8.1	7.0
Milbemectin 1% EC	27.9	3	9.9	7.6
Reference product	360	100	–	–

6) Pre-Harvest Interval

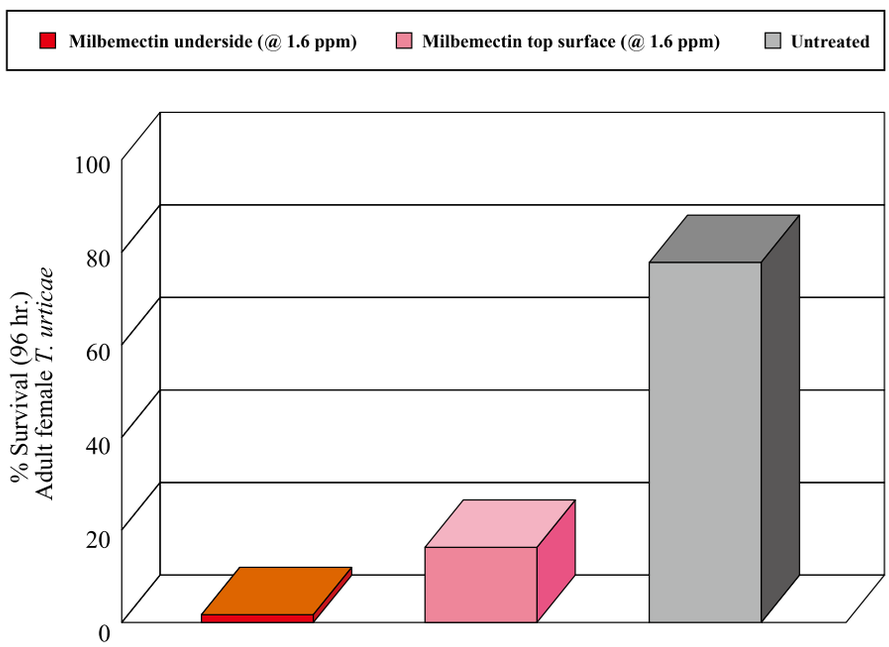
The pre-harvest interval of Milbemectin 1% EC is relatively short. Growers find this to be an advantage over other products, should crops require treatment close to harvest.

● PHI (proposed to US-EPA)

Pome Fruit (Apple,pear)	7 days	Stone Fruit	14 days
Citrus	7 days	Tree Nuts	14 days
Strawberry	1 day	Cotton	20 days

7) Translaminar Activity

For the best results, Milbemectin 1% EC should be sprayed uniformly and thoroughly cover the leaf. Even though Milbemectin 1% EC is sprayed only on the top surface of the leaf, Milbemectin 1% EC also shows activity against the mite on the underside of the leaf because of a translaminar effect.



Strawberry 'Chandler' CA, USA (1995)

8) Efficacy Against Resistant Mites

Milbemectin is effective against the existing resistant mites in most cases.

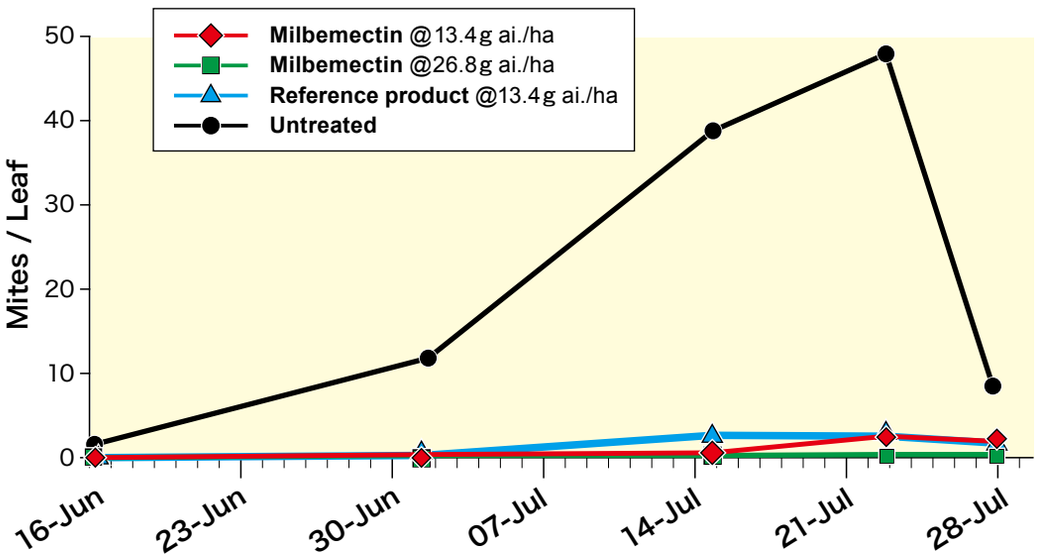
Miticide	Application rate ai. (ppm)	Mortaliry (%)							
		Tetranychus urticae				*T. kanzawai*			*T. cinna.*
		I	II	III	IV	V	VI	VII	VIII
Milbemectin	10	100	100	100	100	100	100	100	100
A	100	0	0	100	80	0	13	100	66
B	25	57	100	100	100	11	0	73	100
C	133	0	0	0	0	100	20	0	0
D	50	0	0	80	90	50	90	50	71
E	400	0	100	100	100	100	80	100	100
F	250	0	57	0	30	17	33	0	100
G	167	0	0	100	100	0	10	100	100

I – VII : Location 1988, Japan

A – G : Reference products

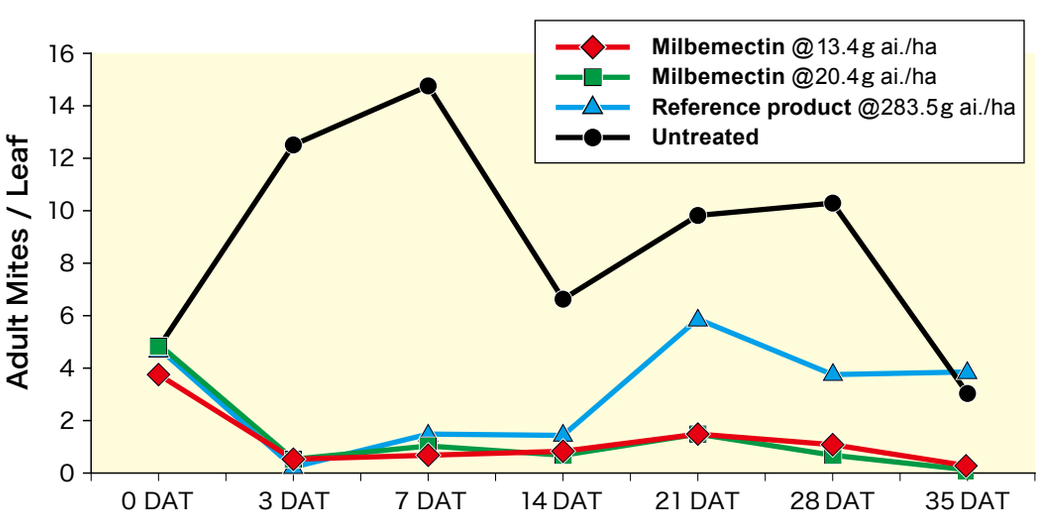
4. Efficacy

● Apple / *Panonychus ulmi*



WV,USA,1998

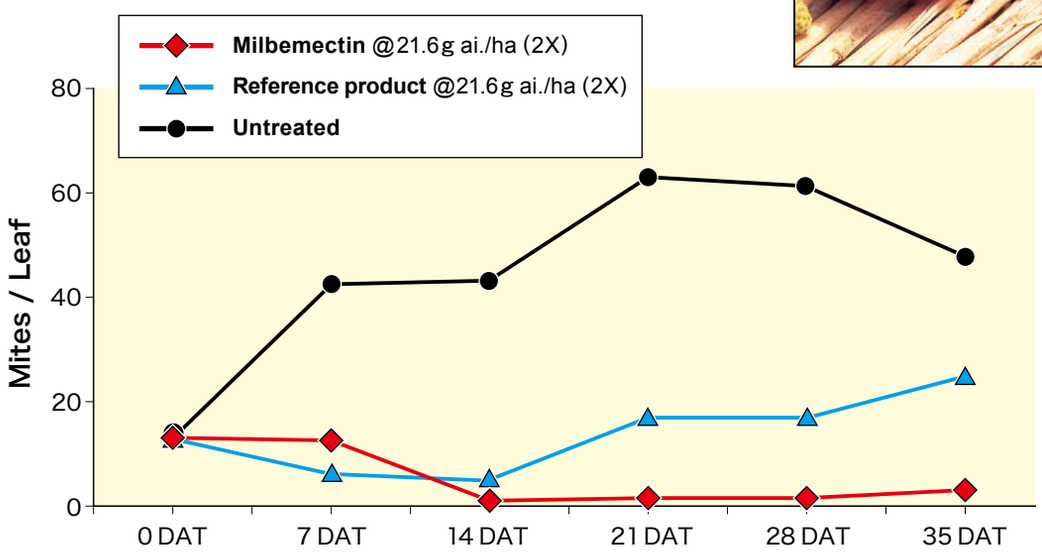
● Citrus / *Panonychus citri*



*DAT = Days after treatment

CA,USA,1999

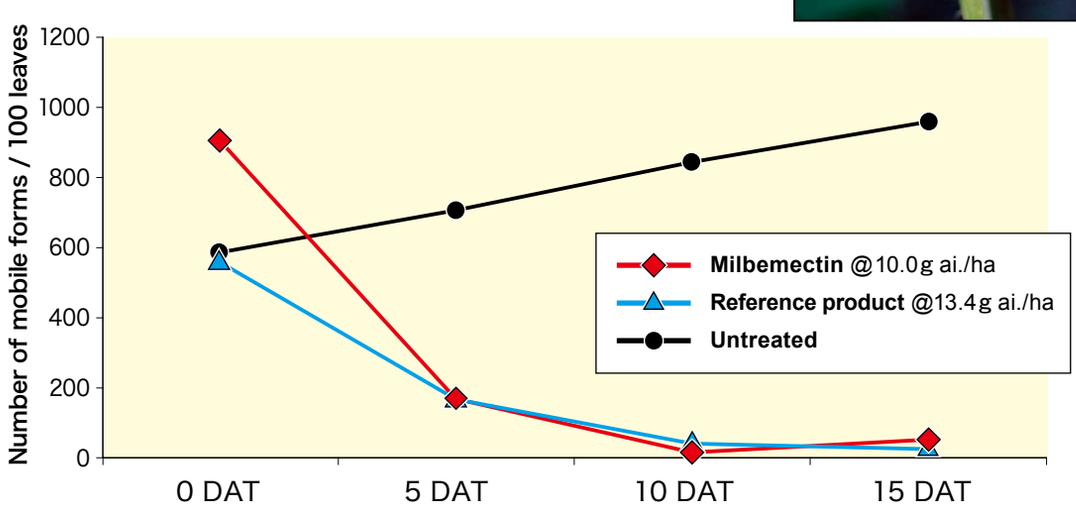
● Strawberry / *Tetranychus urticae*



Treated 7/24 and 8/3

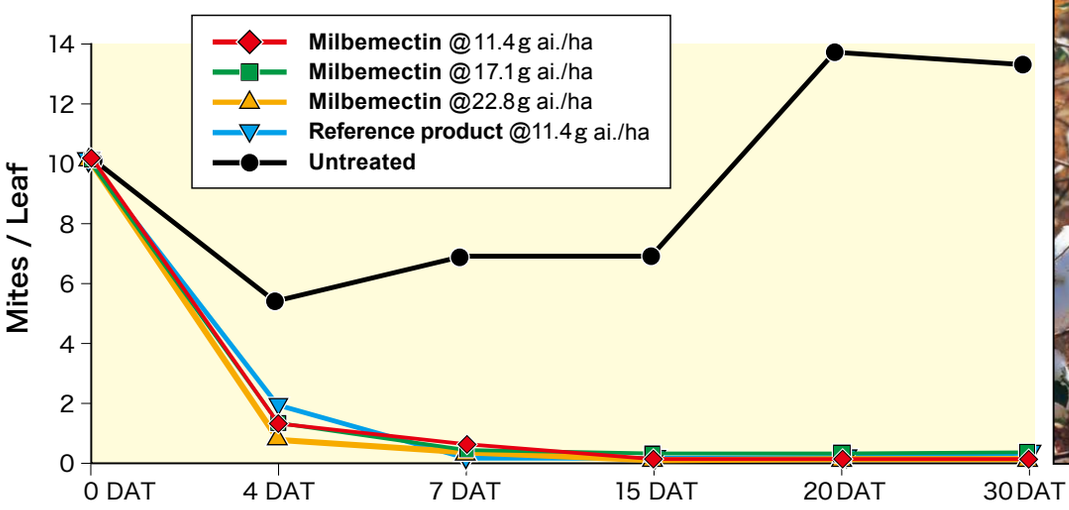
CA,USA,1998

● Tomato / *Tetranychus urticae*



Spain, 2000

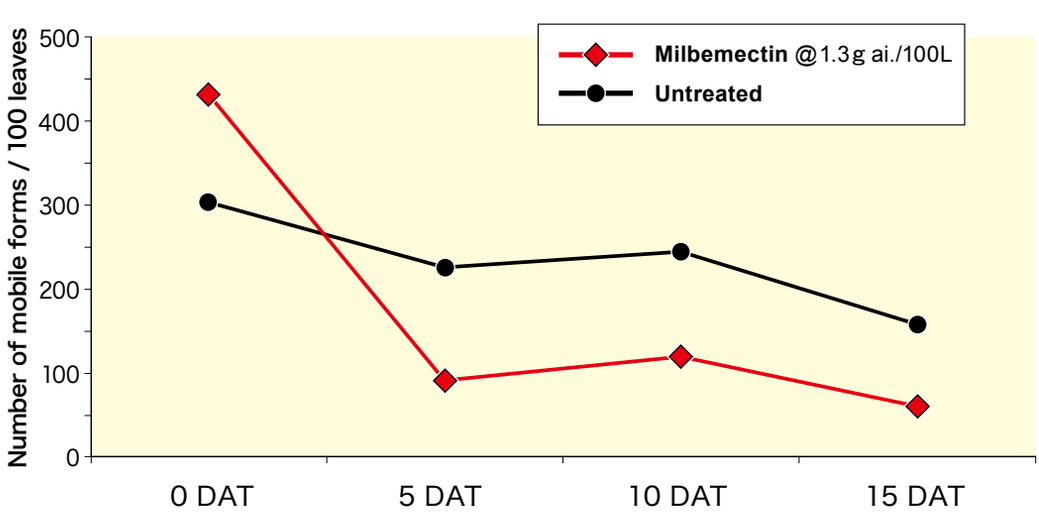
● Cotton / *Tetranychus urticae*



Treated 7/1

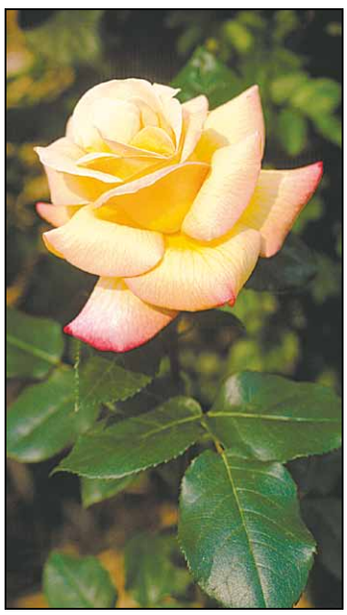
CA,USA,1998

● Carnation / *Tetranychus urticae*

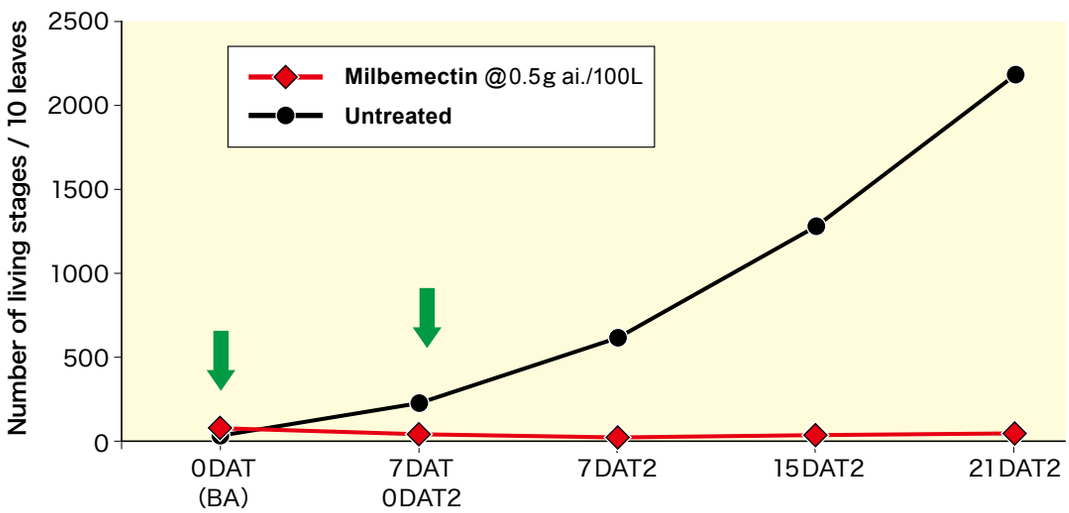


Spain, 2000

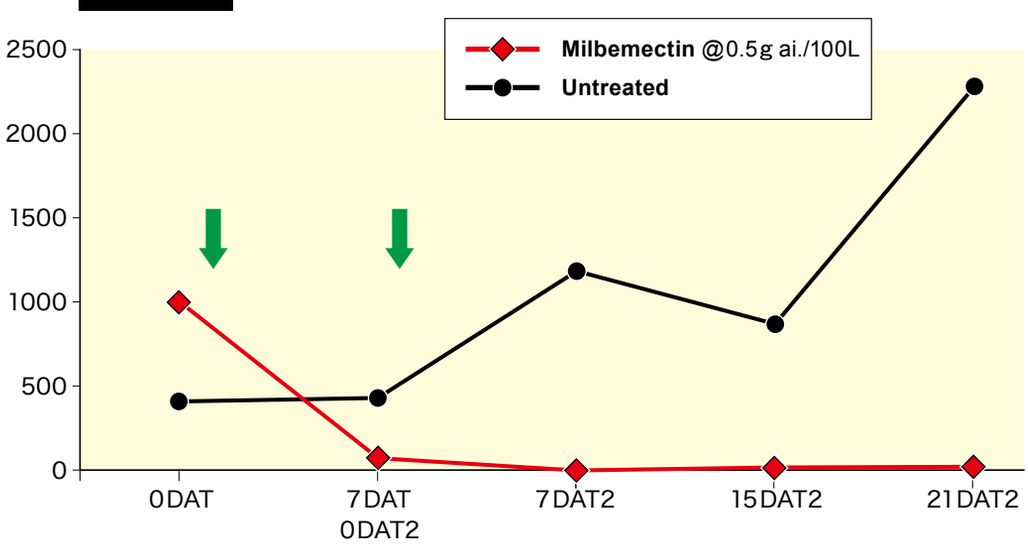
● Rose / *Tetranychus urticae*



Living stages (larvae+nymphae+adults)



Eggs



No phytotoxic symptoms were found.
No visual residue (spray deposit) was observed

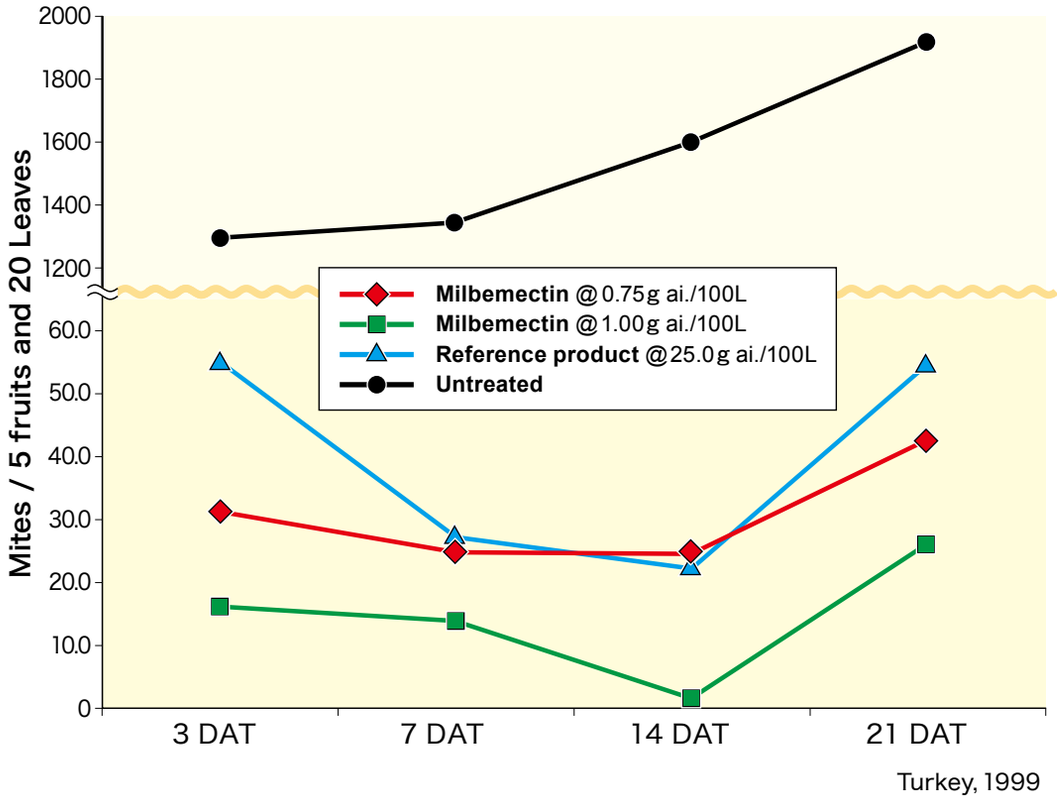
The Netherlands, 1996

Guidelines : EC Directive 91/414/EEC

BA : Before apprication

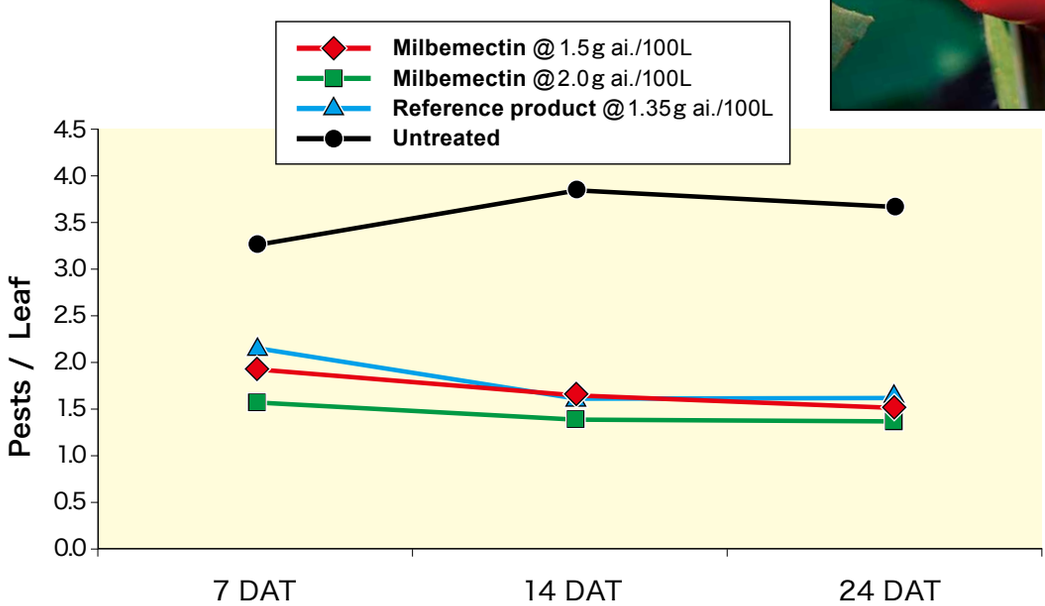
: application

● Lemon / *Phyllocoptruta oleivora*



Turkey, 1999

● Tomato / *Liriomyza huidobrensis*



Mixed with 250 ml/100L Oil

Brazil, 1999

● Review of phytotoxicity of Milbeknock on ornamentals

Test number	Year	Scientific name of ornamentals	Crop condition	Phyto-toxicity	Visible residue
910	1995	*Dracaena*	–	–	–
911	1995	*Dracaena*	–	–	–
916	1995	*Ficus*	–	–	–
917	1995	*Ficus*	–	–	–
918	1995	*Schefflera*	–	–	–
919	1995	*Schefflera*	–	–	–
924	1995	*Hedera*	–	–	–
925	1995	*Hedera*	–	–	–
928	1996	*Dracaena*	–	–	–
929	1996	*Dracaena*	–	–	–
934	1996	*Ficus*	–	–	–
935	1996	*Ficus*	–	–	–
936	1996	*Schefflera*	–	–	–
937	1996	*Schefflera*	–	–	–
940	1996	*Hedera*	–	–	–
941	1996	*Hedera*	–	–	–
912	1995	*Rosa*	–	–	–
913	1995	*Rosa*	–	–	–
914	1995	*Gerbera*	–	–	–
915	1995	*Gerdera*	–	–	–
920	1995	*Gypsophila*	–	–	–
921	1995	*Gypsophila*	–	–	–
922	1995	*Dianthus*	–	–	–
923	1995	*Dianthus*	–	–	–
926	1995	*Chrysanthemum*	–	–	–
927	1995	*Chrysanthemum*	–	–	–
930	1996	*Rosa*	–	–	–
931	1996	*Rosa*	–	–	–
932	1996	*Gerbera*	–	–	–
933	1996	*Gerdera*	–	–	–
938	1996	*Dianthus*	–	–	–
939	1996	*Dianthus*	–	–	–
942	1996	*Chrysanthemum*	–	–	–
943	1996	*Chrysanthemum*	–	–	–
810	1995	*Matricaria*	n.r	–	–
811	1995	*Mathiola*	n.r	–	–
812	1995	*Mathiola*	n.r	–	–
813	1995	*Mathiola*	n.r	–	–
814	1995	*Mathiola*	n.r	–	–
815	1995	*Mathiola*	n.r	–	–
816	1995	*Matricaria*	n.r	–	–
817	1995	*Matricaria*	n.r	–	–
818	1996	*Mathiola*	n.r	–	–
819	1996	*Mathiola*	n.r	–	–
891	1993	*Rosa*	–	n.r	–
892	1993	*Rosa*	–	n.r	–
893	1993	*Rosa*	–	n.r	–
894	1993	*Rosa*	–	n.r	–
890	1996	*Rosa*	–	n.r	–
891	1996	*Rosa*	–	n.r	–

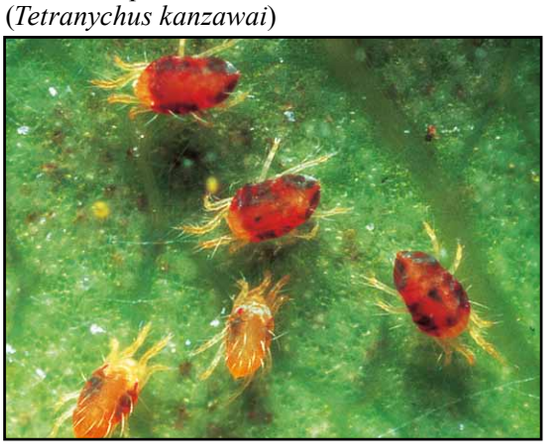
– : No abnomal growth and crop development
No phytotoxic symptoms
No visible residue

n.r (not recorded)

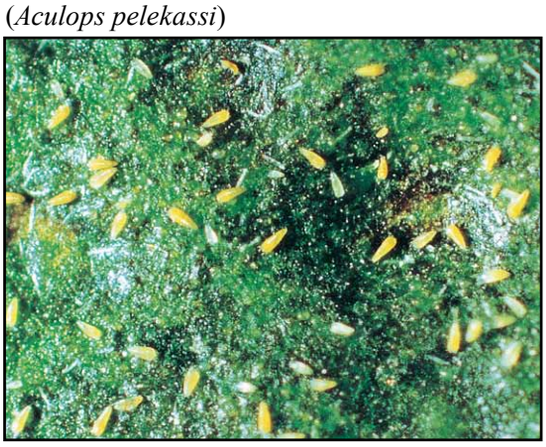
1993-1996, Netherland

Two-spotted spider mite
(*Tetranychus urticae*)

Kanzawa spider mite
(*Tetranychus kanzawai*)

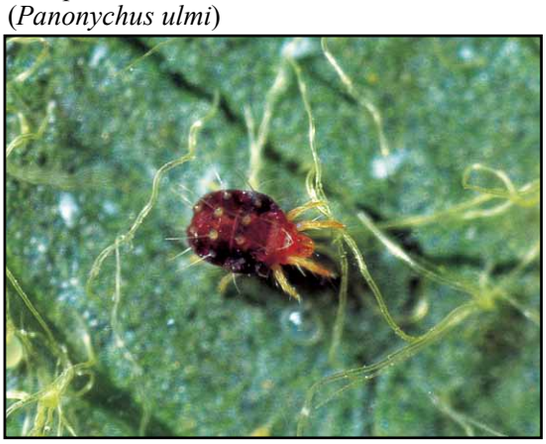


Pink citrus red mite
(*Aculops pelekassi*)



Citrus red mite
(*Panonychus citri*)

European red mite
(*Panonychus ulmi*)

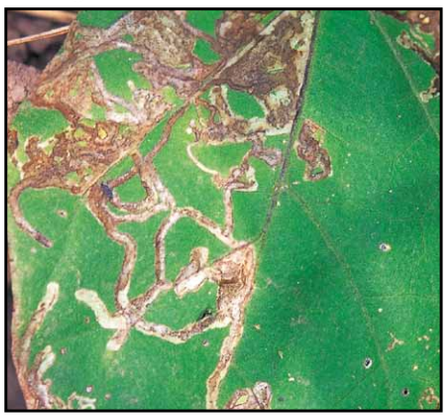


Rust mite spp.
(*Aculops lycopersici*)

Damaged leaf and stem

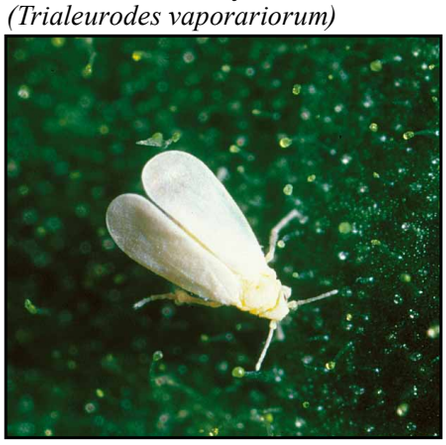
Legume leafminer
(Liriomyza trifolii)

Damaged leaf

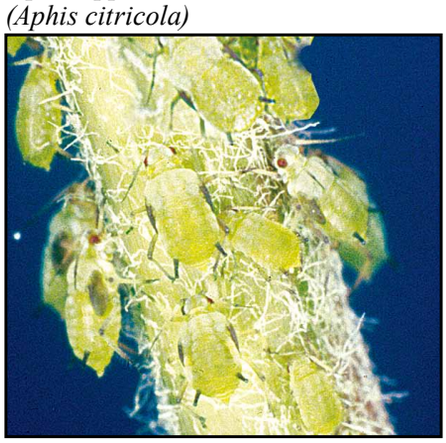


Silverleaf whitefly
(Bemisia argentifolii)

Greenhouse whitefly
(Trialeurodes vaporariorum)



Aphid spp.
(Aphis citricola)



Apple leafminer
(Phyllonorycter ringoniella)

● **Effects of Milbemectin (1%EC)** It's effective to all growth stages of pest mites, but there's a difference of effect among different growth stages of other species.

	Egg	Young Larve	Aged Larve	Pupa	Adult
Spider mite	++++	++++		—	++++
Rust mite	++++	++++		—	++++
Apple leafminer	—	+++		+++	+
Aphid	+++	++++	++++	—	++++
Whiteflie	+++	++++		++	++
Legume leafminer	++ ～ +	++++	++	+	+

++++ : Excellent
+++ : Good
++ : Fair
+ : Poor

Mitsui Chemicals Group

MITSUI CHEMICALS AGRO, INC.

Telephone; +81-3-3573-9669 Facsimile; +81-3-3573-9898

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