SumiLarv™ 0.5G

TECHNICAL BROCHURE

SUMITOMO CHEMICAL

Contents

Product Information

SumiLarv™ 0.5G is a granule formulation containing 0.5% w/w pyriproxyfen. SumiLarv 0.5G prevents mosquito pupae from developing into flying adult mosquitoes which can later bite humans. SumiLarv 0.5G has been developed by Sumitomo Chemical Co., Ltd.

Product Profile

- Active ingredient: pyriproxyfen
- Residual efficacy: repeat treatment every 4 – 6 weeks
- Target vectors: *Aedes spp., Anopheles spp.,* and *Culex spp*.
- Formulation type: granule
- Dosage: 2-10g/ 1000 litres
- Treatment method: SumiLarv 0.5G may be applied by spoon (1 teaspoonful = approximately 2.0 g), or by hand using granule spreaders or suitably adapted knapsack blowers

Key Features:

- Effective at very low dose rates.
- Active against mosquito species - *Aedes, Culex,* and *Anopheles*.
- Long duration of activity under field conditions.
- Useful in resistance prevention or resistance management programmes.
- Low mammalian toxicity.
- Unique mode of action.

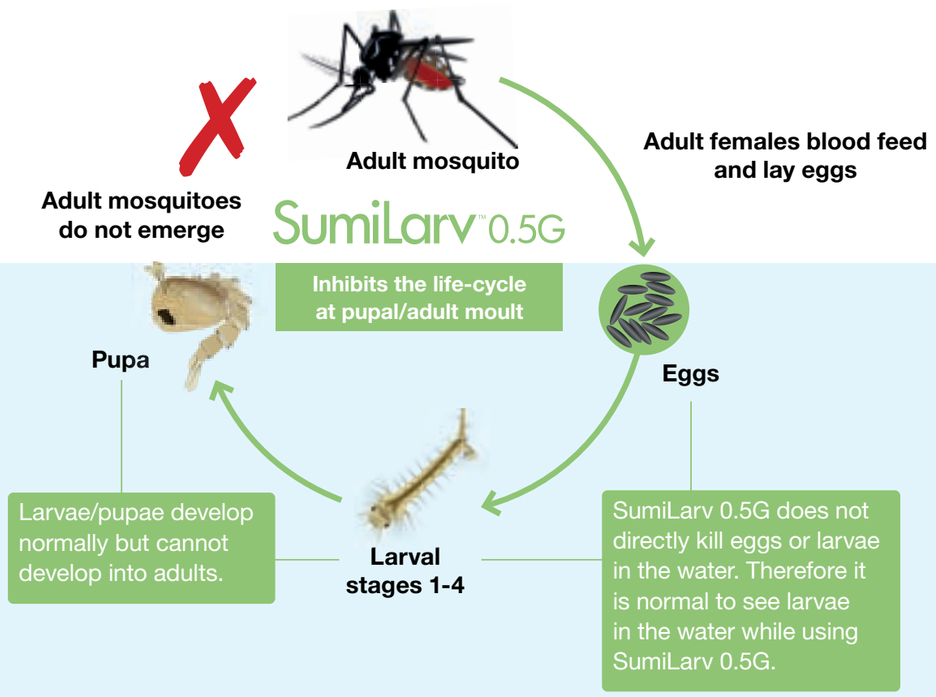
SumiLarv™ 0.5G (pyriproxyfen): Mode of Action

SumiLarv 0.5G is a novel mosquito larval control product based on the insect growth regulator (IGR) pyriproxyfen. Pyriproxyfen was invented and developed by Sumitomo Chemical Co., Ltd. and has a unique mode of action that is insect-specific, stage-specific, and not neurotoxic.

Pyriproxyfen does not directly kill mosquito larvae, but prevents adult emergence.
The late 4th larval stage and pupae just after pupation are the most susceptible to pyriproxyfen (Y.Kono et al., Medical Entomology & Zoology, 48(2), 85-89, 1997). Since pyriproxyfen does not kill larvae after treatment, users need to adjust to the concept that although larvae can still be seen following an application of SumiLarv 0.5G, mortality will normally occur at the pupal/ adult moult thus preventing the emergence of adult mosquitoes. For this reason, evaluation of pyriproxyfen is determined by measuring adult emergence inhibition.

Application of SumiLarv 0.5G to the aquatic larval habitat reduces the emergence of adult mosquitoes which in turn reduces biting rates and transmission. Pyriproxyfen has received U.S. EPA (United States Environmental Protection Agency) status as a reduced risk insecticide and an organophosphate alternative and is recognized by the WHO for treatment of potable water against mosquitoes (Sullivan, J.J. & Goh, K.S., Journal Pesticide Science, 33(4) 339-350, 2008)

Mosquito Lifecycle



Application Rates

SumiLarv 0.5G is available as a 0.5% sand based granular formulation. SumiLarv 0.5G may be applied by spoon and by hand using granule spreaders or suitably adapted knapsack blowers.

Usage

The choice of dose rate will depend on the level of pollution/organic matter in the water. The lowest dose will give a long duration of efficacy when applied in clean drinking water in vessels stored around houses. The highest dose rate should be used in septic tanks or ditches where levels of organic pollution are high.

Practical Example of Correct Application
The lowest dose (for clean drinking water):
2g SumiLarv 0.5G/1000 litres
The highest dose (for non-drinking water):
10g SumiLarv 0.5G/1000 litres

2g SumiLarv 0.5G/1000 litres is equivalent to 10 ppb a.i. 10g SumiLarv 0.5G/1000 litres is equivalent to 50 ppb a.i. Calculate the approximate volume of water to be treated. Target water volume (m^3) = Surface area (m^2) x average depth (m).

Frequency of Application

The required frequency of application will depend on three factors: dose rate, degree of pollution of water treated and dilution (caused by rainfall or removal and replacement of water in storage containers). Generally, repeat treatment every 4-6 weeks. Wherever possible the larval control team should determine the correct dose rate and from time to time, remove any pupae and take them back to the laboratory to determine if adult emergence takes place. If a significant proportion of pupae emerge then it is time to re-treat.
Note: the presence of actively swimming larvae or pupae after a SumiLarv 0.5G treatment is normal and should not be taken as an indication of failure. SumiLarv 0.5G does not act until the pupal stage. When treating ditches/pools etc. try to ensure that the granules are distributed as evenly as possible over the area. The treatment of water containers requires only a few granules with the dose applied being based on the volume of the container. It is normal that householders will remove and replenish water in these containers regularly. This is however not a problem since studies have shown that when applied according to label recommendations, SumiLarv 0.5G continues to work even when significant amounts of water are regularly removed and replaced with fresh water (Vythlingam et al., Journal of American Mosquito Control, 21(3)296-300, 2005).

Information for Householders
After application to water storage jars, householders should be instructed not to completely empty and wash out their containers, as the granules will then be lost. In addition, householders should be advised that SumiLarv 0.5G treatments will not taint water, and will have no adverse effects on water quality. The success of such treatments relies on an efficient campaign to identify and treat every container. Householders should also be encouraged to remove unused pots, tyres and any other items in which water can collect in the vicinity of their house which could act as mosquito breeding sites.

Small Scale Usage

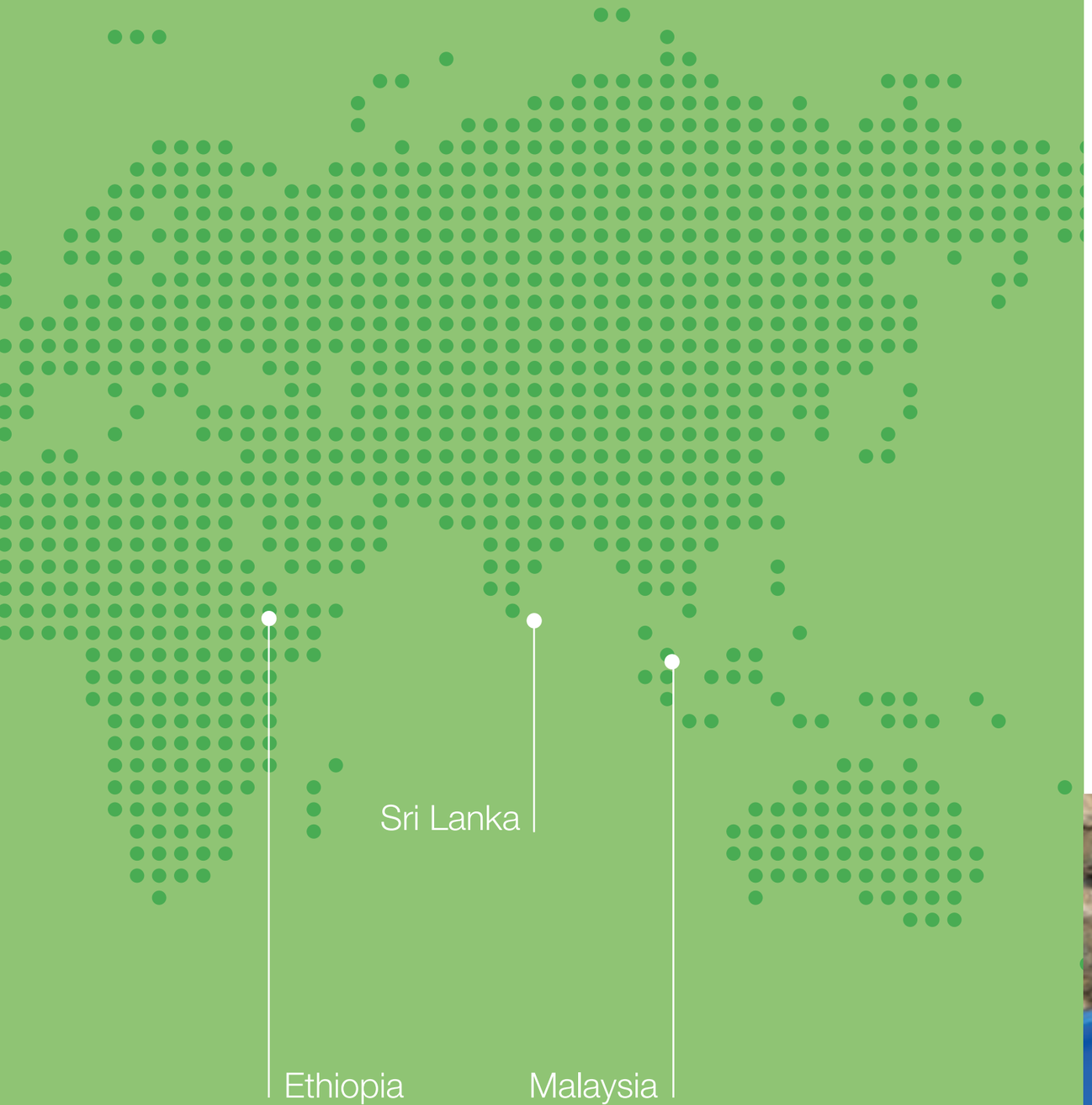
Water type	SumiLarv 0.5G (g/1000 L)	mg a.i./litre	Dose in ppb
Clean drinking water	2 g	0.01	10
Dirty water	10 g	0.05	50

Large Scale Usage

Depth of water (cm)	SumiLarv 0.5G (kg/ha)*
10	2-10
20	4-20
30	6-30
50	10-50

*Dose selected should be based on water quality, see above

SumiLarv™ 0.5G - Field Trials



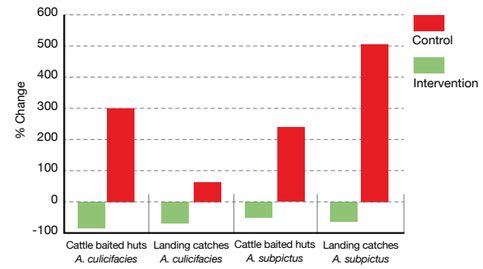
Sri Lanka Field Trial

1. Hand dug gem pits and river bed pools in Sri Lanka are a problem as they create breeding sites for *Anopheles culicifacies* and *Anopheles subpictus*. A small scale field trial was conducted to evaluate a dose rate of 2g SumiLarv 0.5G/1000 litres equivalent to 10 ppb a.i. in gem pits and river bed pools.This dose rate inhibited adult emergence for between 60-140 days. It was recommended that SumiLarv 0.5G would only require application twice a year whereas temephos would require 12 applications and hence considerable cost savings could be made. (Yapabandara, A. & Curtis, CF., Acta Tropica, 81, 211-223, 2002).

2. A further study was conducted in eight villages in Sri Lanka where there were many shallow pits dug by gem miners that fill with water. These become breeding places for the main malaria vector *Anopheles culicifacies* and the second most important *An.subpictus*. The villages were divided into 4 villages with high malaria transmission and 4 with lower transmission.

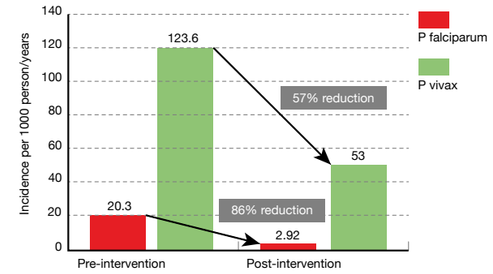
   Two villages were selected from each as intervention areas treated with SumiLarv 0.5G at 0.01mg a.i./litre (10 ppb) and the remaining villages acted as untreated controls. There was a substantial impact on the population of the two main mosquito vectors compared to the control villages, Fig.1. There was also a reduction of 86% in the incidence of Plasmodium falciparum malaria (Fig. 2). (Yapabandara, A. et al., Acta Tropica, 80:265-276, 2001).

Figure 1



Impact of SumiLarv 0.5G on adult mosquito populations using two trapping methods

Figure 2



Comparison of malaria incidence pre and post intervention

Ethiopia Field Simulation

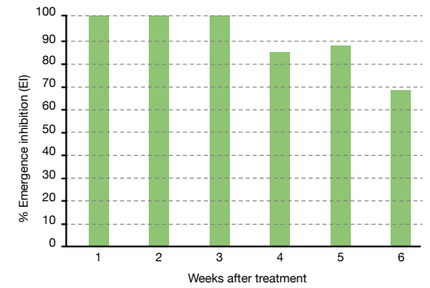
Anopheles stephensi is a highly competent Asian urban malaria vector that now poses serious challenges to malaria control and elimination efforts in Africa following its invasion and dramatic continuing expansion across the continent. This species has been associated with an increase in malaria cases in Djibouti - the first country in Africa to be invaded (Faulde et al. Acta Trop 139, 39–43 (2014)) and more recently in Ethiopia (Emiru et al. Nat. Med. 29, 3203–3211 (2023)).

A study was carried out by Jimma University to evaluate the efficacy of SumiLarv 0.5G against the local multi resistant population of *An. stephensi* in Awash Sebat Kilo town, Eastern Ethiopia.
Four plastic containers filled with 100 litres of tap water were treated with 0.2 g SumiLarv 0.5G.
For controls, two plastic containers containing 100 litres of tap water were used.

Mosquito larvae were collected from the field and reared in an insectary. Batches of 20-25 third to fourth instar larvae from the insectary were introduced to each container every week. Half of the water in each container was replaced weekly to mimic normal water usage.

Results show that SumiLarv 0.5G achieved > 80% emergence inhibition of the local multi resistant population of *An. stephensi* for 5 weeks.
See Fig. 3.

Figure 3



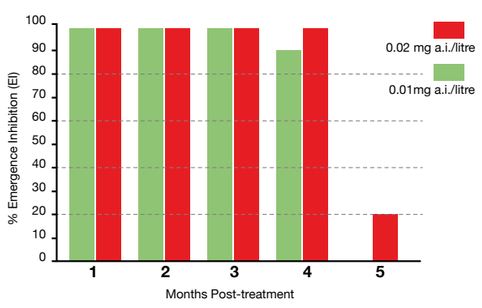
Evaluation of SumiLarv 0.5G against *An. stephensi* - Ethiopia

Malaysia Field Simulation

Trials were conducted in Malaysia against *Aedes aegypti* using 60 litre earthenware storage jars. To simulate actual usage 20% of the water was replaced every 2 weeks. Two dose rates of SumiLarv 0.5G were used - 0.01 and 0.02 mg a.i./litre (10 and 20 ppb). Inhibition of emergence of adult mosquitoes was achieved for 4 months at both dose rates.

Additional tests with *Aedes albopictus* (Skuse) showed similar levels of efficacy. (Vythilingam, I. et. al, Journal American Mosquito Control 21 (3), 2005).

Figure 4



Evaluation of SumiLarv 0.5G against *Aedes aegypti* - Malaysia

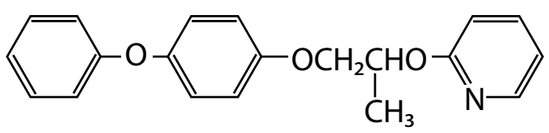
SumiLarv™ Technical Specifications

Active ingredient
ISO common name: pyriproxyfen

Chemical names:

IUPAC 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether
CA 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

Structural formula:



Empirical formula: $C_{20}H_{19}NO_3$
Relative molecular mass: 321.37 g/mol
CAS Registry number: 95737-68-1

Analysis

The analytical method for determination of pyriproxyfen as either technical grade material or formulated as SumiLarv 0.5G is based on reversed-phase HPLC with UV detection at 254 nm and internal standardization with p-benzyldiphenyl. This method has been validated by collaborative studies and was adopted by CIPAC in 2006.

Analytical methods for the determination of impurities use gas chromatography with a flame ionizing detector (GC-FID) using ethylbenzene as an internal standard, for residual solvent, and reversed-phase HPLC with external standardization, for the other impurities. Physical properties of the formulations are determined by CIPAC methods, as indicated in the specifications. The proposed specifications are in accordance with the requirements of the manual (FAO/WHO 2002).

Toxicity

The toxicity of pyriproxyfen was assessed by the WHO/FAO Joint Meeting on Pesticide Residues (FAO 1999) and the following conclusions were noted: The acute oral toxicity of pyriproxyfen is low with LD_{50} values >5000 mg/kg weight in mice, rats and dogs. The acute dermal toxicity is also low, with LD50 >2000 mg/kg body weight in mice and rats. After exposure by inhalation an LC_{50} value >1.3 mg/litre air in mice and rats was observed. Pyriproxyfen is rapidly excreted in animals, primarily in faeces, with between 88 to 96% excreted within 48hrs.

Pyriproxyfen is mildly irritating to the eye but not to the skin of rabbits. It did not sensitize the skin of Hartley strain guinea-pigs.

Pyriproxyfen was not genotoxic or carcinogenic. The acceptable daily intake (ADI) for man has been established at 0-0.1 mg a.i./ kg bw / day in a one year study of pyriproxyfen in dogs after applying a safety factor of 100. (WHO/CDS/WHOPES/2001.2)

According to the U.S. EPA while pyriproxyfen is known to produce juvenoid effects on arthropod development, this mechanism of action in target insects and some other arthropods has no relevance to any mammalian endocrine system. Pyriproxyfen is therefore not considered to possess estrogenic or endocrine disrupting properties to mammals. (Sullivan, J.J. & Goh, K.S., Journal Pesticide Science, 33(4) 339-350, 2008).

Summary
(technical grade pyriproxyfen)

Mammalian Toxicity

Acute oral LD_{50} (rat)	>5000 mg/kg
Acute dermal LD_{50} (rat)	>2000 mg/kg
Skin irritation (rabbit)	Not irritating
Eye irritation (rabbit)	Mildly irritating

Other:
Not mutagenic. Not carcinogenic in rats and mice. Not teratogenic in rats and rabbits.

Ecotoxicology

Pyriproxyfen will not adversely affect a vast majority of aquatic invertebrates and fish when applied at rates <50 ppb a.i. in mosquito control programs. In certain cases however populations of certain organisms, such as crustacea, may experience minor declines when SumiLarv 0.5G is applied at higher label dose rates. Affected populations will recover in relatively short time periods (WHO/CDS/WHOPES/2001.2).

Both crustacea and aquatic insect larvae are sensitive to pyriproxyfen, although adverse effects were found to be reversible. Pyriproxyfen did not exhibit any marked effects on mayfly, dragonfly, ostracods, cladocerans, copepods, or beetles. Planktonic organisms showed no significant adverse effects resulting from 0.01 ppm treatment in experimental aquaria. Pyriproxyfen is not expected to bioconcentrate in fish under environmentally relevant conditions due to the rapid depuration (cleansing of impurities) of the parent compound from fish. (Environmental fate of pyriproxyfen, J. Sullivan, May 2000).

Pyriproxyfen was evaluated against other organisms in mosquito-breeding habitats. When applied at a rate of 0.11 kg a.i./ha to rice plots (20 times greater than required for controlling *Aedes nigromaculis* larvae), no detectable residues (<0.00005 ppm) were found after 2 days in treated water. Pyriproxyfen did not accumulate in soil, there were no residues (<0.005 ppm) after 3 days in fish (*Lepomis macrochirus rafinesque*), and the residue on rice plants declined to <0.005 ppm after 7 days. Despite slight induction of morphogenetic aberrations in Odonata (Dragonflies) at adult emergence and minor suppression of reproductive capacity of Daphnoid cladocerans and ostracods, pyriproxyfen was found to be safe to aquatic, non-target organisms, including mosquito predators. (Schaefer, C. H., Miura T. Journal of Economic Entomology 83(5) 1768-1776, 1990).

Pyriproxyfen was highly effective in inhibiting the normal development of mosquito larvae into adults in laboratory and field trials. Late fourth instar larvae were the most sensitive stage. Mortality occurred in the pupal stage and, at lower doses, resulted in the formation of abnormal adults. No long-term bioaccumulation problem was apparent following dynamic or static exposures to fish. Non-target aquatic organisms that co-exist in mosquito breeding habitats were not affected adversely by treatments which were effective against mosquitoes. In summary pyriproxyfen showed efficacy against mosquito larvae, a high degree of safety to associated non-target organisms, and chemical persistence that appear to be compatible with the environment. (Schaefer, C.H., et al., Journal of Economic Entomology, 81(6):1648-55, 1988)

Precautions

SumiLarv™ 0.5G has a very low mammalian toxicity and should not present any problems in normal usage, however as in line with any pesticide, good handling practice should be adhered to and protective clothing worn and good personal hygiene practices followed after applying the product. See label and SDS for full precautions.

Storage

SumiLarv 0.5G should be stored in a secure building that is lockable. The building should be well ventilated and dry. SumiLarv 0.5G should be stored in its original packaging, out of direct sunlight and rain.

Disposal

Dispose of contents/container appropriately in accordance with local/regional/national/international regulations.

Abbreviations: FAO: Food and Agriculture Organization, WHO: World Health Organization, HPLC: High Performance Liquid Chromatography, CIPAC: Collaborative International Pesticides Analytical Council

Abbreviations: CDS: Communicable Diseases, U.S. EPA : U.S. Environmental Protection Agency, WHOPES : WHO Pesticide Evaluation Scheme.

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SUMITOMO CHEMICAL COMPANY, LIMITED

Environmental Health Division

Tokyo Nihombashi Tower,
2-7-1 Nihonbashi, Chuo-ku, Tokyo
103-6020 Japan

Tel: +44 20 7471 3730

Email: info.scc@sumivector.com

www.sumivector.com

SUMITOMO CHEMICAL ASIA PTE LTD

3 Fraser Street, #07-28, DUO Tower,
Singapore 189352

Tel: (65) 6303 5188

Email: agrochem@sumitomo-chem.com.sg

www.sumitomo-chem-envirohealth.com

SUMITOMO CHEMICAL BRASIL Indústria Química S.A.

Environmental Health Division

Av. Paulista, 1.106 – Edifício Paulista
1100, 8º e 9º andares – Bela Vista
01310-914 – São Paulo – SP
Brasil

Tel:+55 11 3174-0355

E-mail: sacsaudeambiental@sumitomochemical.com

www.sumitomochemical.com

Z05-24 231212 LHTJ43100