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I SOUCITUD DE:
Patente de Invención, Patente de Modelo de Utilidad.

Lnj Capitulo I. [11] CapItulo II.
2 Nombre: CHEMINOVANS IDENTIFICACION

SO CITANTE DirecciOn: P.O. Box 9, DK-7620 Lemvig, Dinamarca C.C. 0 NIT 0
(TI) Nacionalidad a Domicilia: Dinamarca
Lugar de Constitución: Dinamarca C.E. 0 Otro 0

TelØfono: Fax: Cual_______
E-mail Ncsmero

3 Nombre: JUAN PABLO CADENA SARMIENTO IDENTIFICACION

RE RESENTANTE Direcciôn: Cra. 7 No. 71-21 Torre B- Piso 4, C.C. NIT 0
0 ODERADO Bogota, Colombia.

C.E. [=1 Otro 0

TelØfono: 744-2200 Fax: 742-2200

E-mail: Cual Nu. mero 80.410.337 TP 5792
4 Nombre: Marten PEDERSEN, Henette Sie WOLDUM.

I NTOR (ES) Dlrecclón: Sejbjerg 55, DK-7620 Lemvig, Dinamarca; Moldevej 1.1, DK-7100 Vejie, (72) Dinamarca (Respectivamente).
Naclonailclad o Domlcffio: Dinamarca (Respectivamente).
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6 to (54): COMBINACION SINRGICA DE PESTICIDA AGONISTA DE CLORURO DEPENDIENTE DE
GLUTAMATO V GABA V POR LO MENOS UNA VITAMINA E1 N1ACINAIL 0 DERIVAbOS DE
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7 Clasificacion Intemaclonal (51):

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EP 09-03-2006 06388016.5
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10 ANEXOS

Comprobante de pago de la tasa de presentación de la soilcitud. $ 501.000
Documento que acredita la existencia y representaciôn legal cuando el solicftante sea persona juridica. Poderes, si fuere el caso. Fotocopla autenticada
Documento de cesión del inventor al solicitante o a su causante.

0 Declaraciones.
Copia de la solicitud intemacional. (Resumen, descpción, reMndicaciones, dibujos)
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12 So!icto la concesiOn de la patente

NOMBRE JUAN PABLO CADENA SARMIENTO

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Instrucciones para la presentación de los anexos, ver reverso de esta pÆgina.

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NOTIFICATION OF THE RECORDING

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Rlgensgade 11
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1. The fóilowi indications appeared on record concerning:
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PEDERSEN, Morten, I I I III I I III I I I DK
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2. The Lnrnati ani Bureau hereby notifies the ipplicant that the following change has concerning:

0 the person (J the name the address [3 the nationality 0 the residence
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PEDERSEN, orten DK DK.
Sejbjerg 55 1
DK-7620 Lem Telephone No.
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3. Further observ lions, if necessary:

4. A copy of thisotilication has been sent to;
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13 September 2007 (13.09.2007) WO 2007/101447 A3
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C9, CR, CU, CZ, DE, DX, DM, DZ, BC, BE, EG, E, Fr, (23, GD, GE, GIl, GM, GT, TIN, ER, HE, ID, IL I, IS,
3?, KB, KG, KM, KN, KP, KR, KZ, LA, LC, LK, L, LS, IT, LU, LY, MA, MD, MG, MX, MN, MW, MX, MY MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN TR, TI’, TZ, UA, UG, US, UZ, VC, YN, ZA, ZM, ZW.

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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, Ti, TM), European (AT, BE, BG, CH, CY, CZ, DE, DX, BE, B, Fl,

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Declaration under Rule 4.17:

ant (for all designated States except US): CREMI- - as to applicant’s entitlement to applyfor and be grantsd a A/S [DK/DKI; P.O. Box 9, DK-7620 Lenivig (DK). patent (Rule 4.17(11))
rs; and
rs/Applicants (for US only): PEDERSEN,
[DK/DK]; Frejasvej 125, DK-7620 Lemvig (DK).
LJM, Renrlette Sle [DK/DKI; GI. Aalborgvej 107,
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1316 KØbenhavn K (DK). 31 January

Ignated States (unless otherwise indicated, for every Fortwo-letter codes and other abbreviations, refer to the
ofnational protection available): AE, AG, AL, AM, ance Notes on Codes andAbbreviations" appearing at the
AU, AZ, BA, BB, BO, BR, BW, BY, BZ, CA, CH, CN, ning ofeach regular Issue ofthe PCT Gazette.

SYNERGISTIC COMBINATIONOF GLUTAMATE-AND GABA-GATED CHLORIDE AGONISTPESTICIDE ONE OF VITAMIN B, NIACIN, OR DERIVATIVES THEREOF

stract: Presented are pesticidal compositions comprising at least one pesticide selected among Glutamate- or GAB channel agonist pesticides and at least one synergist which is selected among Vitamin E, Niacin and derivatives binations of these compounds show a synergistic effect allowing a composition to be prepared comprising a lesser ide, while still controlling the harmful pests.

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INTERNATIONAL SEARCH REPORT 1International application No I PCT/DK2007/050030
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(71) Applicant (for all designated States except US): CREM-INIOVA Ai [DKIDKI; P.O. Box 9, DK-7620 Lemvfg (DX).

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3?, KB, KG, KM, Kt’l, Xl’, KR, KZ, LA, LC, LXI 14 LS, LT, LU, LY, MA, MD, MG, MX MN, MW MX, M MZ, NA, NO, NI, NO, NZ, OM, P0, PR, PL, PT, 1(0, RS RU, SC, SD, SE, SO, 5K, SL, SM, SV, SY, TI, TM, T1, TR, ’IT, 1Z UA, UG, US, liz, VC, VN, ZA, ZM, ZW

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Inventors and Declaration under Rule 4.17:

Inventors/Applicants (for US only): PEDERSEN, -. as to applicant’s entitlement to applyfor and be gr4nted a Morten [DK/DK]; Frejasvej 125, DX-7620 Lemvig (DX). patent (Rule 4.17(U))
WOLDUM, Henriette Sin (DK/DK]; 01. Aalborgvej 107,
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D1C4316 KØbenhavn K (DX).

Fortwo-Iettercodes and other abbreviations, refertot "Grid- Designated States (unless otherwise Indicated, for every ance Notes on Codes andAbbreviations" appearing at: begin- kind ofnational protection available): AE, AG, AL, AM, ning ofeach regular Issue ofthe PCT Gazette.

Title: PESTICIDAL COMPOSITIONS

Abstract: Presented are pesticidal compositions comprising at least one pesticide selected among Glutamate- or BA-gated ride channel agonist pesticides and at least one synergist which is selected among Vitamin Band Niacin. The comb nations of
compounds show a synergistic effect allowing a composition to be prepared composing a lesser amount of past: ide, while controlling the harmful pests.

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PESTICIDAL COI4P0S1TX014S

Field ofthe Invention
The present invention relates to pesticidal. compositions In general. Inpatticular, the present
5 invention relates to a method of obtaining a pesticidal composition containing a pesticide
and a synergist, a method ofreducing the amount ofpesticide in a posticidal composition while maintaining the pettcidal effect, a method for controlling harmful pests on plants, a method for controlling harmful pests in or on animals including humans, a method for ob-taining reduced application ofa pesticide while maintaining the pesticidal effect, and a
10 method for obtaining reduced dose rates of a pesticide while maintaining the pesticidal ef-
fect The pesticide used in the pesticidal composition is selected among Glutamate- or GAI3A-gated chloride channel agonist pesticides

Background
5 Pesticidal active compounds whose targets are insects and other axtbropods and nematodes
usually have a neurological effect on such pests Their pesticidal target sites are defined as the specific biochemical or physiological sites within an organism that pesticide compounds interact ’with to create a toxic effect Among neurological target sites are acetyicholi-nesterase enzyme, voltage-gated sodium channels, Glutamate- and GABA-gated chloride
0 channels and nicotinic acetylcholine, receptors. The actions ofpesticides at these sites are
diverse and range from enzyme inhibition, to receptor agonisni (stimulation), receptor an-
tagomsin (llockagc), and ion channel modulation Glutamate and gamma-aminobulyrie
acid (GABA) are inhibitory neurotransmitters that elicit the influx ofchloride ions into cen-
tral neurons through chloride channels.
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In United States patent -110. US 4,560,677 synergistic compositions are disclosed comprising .. avermectins or mllbeniyems and a s$ergistselected among agricultural spray oils

The use ofVitamin B compounds and.Niacin compounds as dietary supplements and as an-
3(tloxidants is well known. However other functions have been described as well Vitamin B
used as an agent to increase the resistance In plants against pests and pathogens is known
from United States att no.. US 5,004493. In German patent application no. DR 4437945
Al it is suggested to use Vitamin B to protect plants against injury from other pesticides
(i

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as a safener compound) PCT publication,110. WO 2004/95926-A2 describes the use of
35 antioxidants in treatment of plants and plantpropagation material to improve plant health
and yield The use ofVitamin E(acetate) as a stabilizer In veterinary formulations coinpris-

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mg avermectins is known front United States patent no US 6,340672, PCT publication no
WO 2005/37294-Al and Brazihan patent publication no BR P1-0102125 The latter dis-close the use of a nutritive composition comprising Iverniectin and vitamin for the treat-ment ofparasites in farm animals, which composition further comprises e g mineral salts,
5 ammo acidsand vitamins. In PCT publication no WO 2000/50009-Al compositions are
disclosed wherein a.pbannacologlcally active compound is encapsulated. in liposomes; the active compound is selected among e.g. avcnnectms, nnlbemycins and Plperazme and the compositions may further comprise nutrients such as vitamins 0.9. Vitamin E

10 An insecticidal composition must satisi’ a range ofrequirements to be viable on the mar-
ket One such requirement ofthe pesticidal composition is the ability to be selective in bio-logic action and have low toxicity and a high margin ofsafety to humans, crops, economic animals, aquatic organisms and birds Another requirement is the dsire that the compost-tion Should be environmental-friendly in that there Should be demonstrably low impacts on
15 the environment, Further, there should be none or little insect resistance to such compounds
or combinations, Also, there is a need for Improved compositions which are not only more effective against particular pests, but which are also versatile and can be used to combat a wide spectrum ofpests

0 There is an increasing demand and need for pesticidal compositions, winch can be used
against pests afflicting beneficial crops as well as animals, including humans or their envi-roment, and which are effective at low application rates ofthe pesticide The present in-vention is directed towards such pesticidal compositions in which the pesticide can be ap-

plied in a low application rate or a low dose rate Thus, the environment is favoured as the
5 total amount of pesticide applied to a field for a certain pesticidal effect to be obtained is
lowered. As the pesticide is the most expensive component In a pesticidal composition, also the cost for producing the peSticidal composition is low,

Descripton ofthe invention
0

It has now surprisingly been found that by combining Glutamate- or GABA-gated chloride channel agonist pesticides (A) with at least one synergist (U) which is selected among Vi-tamin B compounds and Niacin compounds an enhanced pesticidal activity of the chloride channel agonist pesticides is observed when used for the control ofharmful pests, i.e. a syn-
5 ergistac interaction between the chloride channel agonist pesticides and the compound(s) B
is observed

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According to a first aspect ofthe invention a method of obtaining a pesticidal composition containing a pesticide and a synergist is disclosed, said composition having an actual pesti-cidal effect higher than the awn of pesticidal effects of each ofthe pesticide and the syner-gist when taken alone, comprising the step ofreplacing a part of the amount of pesticide, which is, selected among glutamate- or GAHA-gated chloride channel agonist pesticides, by a synergistic amount of a synergist selected among Vitamin B compounds and Niacin com-pounds. The pesticidal compostion obtained according to this aspect is more environ-mental-friendly than a traditional composition containing, the same pesticide since less pes-ticide is used to obtain a pesticidal effect.

According to a second aspect, a method ofreducing the amount of pesticide in a pesticidal composition while maintaining a similar pesticidal effect is disclosed. The method com-prises the step ofreplacing a part ofthe amount of pesticide, which is selected among glu-tamate- or GABA-gated chloride channel agonist pesticides, by a synergistic amount of a synergist selected among Vitamin B compounds and Niacin compounds. As the pesticide generally is the most expensive part ofthe pesticidal composition, the method ofthe present aspect benefits from that by providing a less expensive pesticidal compositon.

20 In a third aspect, the present invention provides a method for controlling harmful pests on
plants. The method involves applying to a plant to be treated a composition containing a pesticide and a synergist, said composition having an actual pesticidal effect higher than the sum ofpesticidal effects of each ofthe pesticide and the synergist when administered alone, wherein ’a part of the amount of pesticide, which is selected among glutamate- or GABA-
25 gated chloride channel agonist pesticides, is replaced by a synergistic amount of a synergist
selected among Vitamin E compounds and Niacin compounds In this aspect ofthe inven-tion a less expensive pesticidal compostion may applied to a plant to obtain a satisfactory pesticidal effect.

0 In a fourth aspect ofthe invention a method for controlling harmful pests in or on animals
including humans is provided. The ’method comprises administrating to an animal or a hu-man in need thereof a pharmaceutical or veterinary effective amount of a composition con-taining a pesticide and a synergist, said composition having an actual pesticidal effect higher than the sum of pesticidal effects of each of the pesticide and the synergist when
5 administered alone, wherein a part ofthe amount ofpesticide, which is selected among glu-
tamate- or GABA-gated chloride channel agonist pesticides, is replaced by a synergistic

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amount of a synergist selected among Vitamin E compounds and Niacin compounds. As pesticides generally are alien to the human or animal body they should be used in a small amount to avoid any side effects. According to this aspect a method is provided for effec-tive treatment of animals or humans suffering from a disease emanating from pests using a
5 minimum ofpesticide.

According to a fifth aspect ofthe present invention a method for obtaining a reduced appli-cation rate of a pesticide is deviced. The method comprises the steps of providing a pesti-cidal composition containing a pesticide, which is selected among glutamate- or GABA-
1 0 gated chloride channel agonist pesticides, and an synergistic mount of a synergist selected
among Vitamin E compounds and Niacin compounds, and applying the pesticidal composi-tion to a plant in an amount sufficient for controlling harmful pest. The application rate is generally measured as the amount of active ingredient, i.e. pesticide, applied to a certain area, such as hectare or acre. According to this aspect of the invention the environment
15 benefits from the application of a minor amount of pesticide while the harmful pests are
still controlled. Further, by lowering the application rate, the pre-harvest interval (I’m) rec-ommended for use in benificial crops, i.e. the time between the last pesticide application and harvest of the treated crops, is lowered, and thus providing improved protection ofthe crops against harmful! pests as close to the time of harvest as possible without increasing
0 undesired residual effects cause by the applied pesticide and/or possible breakdown prod-
ucts thereof,

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According to a sixth aspect ofthe invention, a method for obtaining reduced dose rate of a pesticide is provided. More specifically, the method involves the steps ofproviding a pesti-cidal composition containing a pesticide, which is selected among glutamate- or GABA-gated chloride channel agonist pesticides, and an synergistic mount of a synergist selected among Vitamin E compounds and Niacin compounds, administering the pesticidal compo-sition to an animal or a human in need thereof in a pharmaceutical or veterinary effective amount sufficient for controlling harmful pest. The dose rate is generally measured as the amount ofpesticide administrated per weight ofthe animal or human in need of a treatment. This aspect provides a method in which a less amount ofpesticide can be used for control-ling harmful pest. Further, by lowering the dose rate, undesired residual effects cause by the applied pestice and/or possible breakdown products thereofis reduced.

Generally, the compositions are active against all or individual stages ofdevelopment ofthe pests and against normally sensitive species and resistant species, i.e. species that have de-

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veloped resistance against the pesticides (A). The compositions may also be useful for con-trolling pests tliat"bavepràven to be uneffected by the ’pesticides (A) either completely or
 ’ requiring unacceptable high doses to provide adequate col.’

5 In an aspect of the invention it relates to a pcsticidal composition comprising at least one
compoind A which is selected among Glutamate- or GABA-gated chloride channel agonist pesticides and at least one compound B which is selected among Vitamin E compounds and
Niacin,ompounds, wherein the compounds A and B are present in a synergistically effec-
tive amount
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The invention also relates to a kit comprising (i) a first composition comprising at least one
pesticide selected among glutamate- or. GABA-gated chloride channel agonist pesticides
WWI and (11) a second composition comprising a synergistic amount of a synergist selected
among Vitamin E compounds and Niacin compounds. In this connection the term "a kit" Is
15 intended to mean a collection of at least two items intended for coordinated use i.e. for use
as mixture’ or for a specified consecutive use. The components ofthe kit may be provided...’.
in one package, or It may be provided in separate packages, Further the kit usually coni-
prises written instruction for the intended itso .. H

20 The mveittion further relates to various uses In an aspect, the invention relates to the use of
a synergist selected among vitamin B compounds and Niaem compounds for enhancing the
effect of a pesticidal composition comprising a pesticide, which is selected among gluta-
mate- Or GA-gated chloride, channel agonist pesticides. In another aspect invention
relates to the use of a synergist selected among Vitamin B compounds and Niacin corn-
____ 25 pounds for preparation of a pesticidal composition having a reduced amount of pesticide
while maintaining a similar pesticidal effect, wherein the pesticide is selected among gin-
tamatc- or GABA-gated chloride channel agonist pesticides. In yet another aspect the in-
vention relates to the use of a synergist selected among Vitamin B compounds and Niacin
compounds for reducing the application or dose rates of a pesticidal composition in the con-
30 trol ofpests while maintaining:a similar pesticidal effec; wherein the pesticide is selected .
among glutamate- or GABA-gated chloride channel agonist pesticides.. In a further aspect ’
the invention relates to the use of a pesticide selected among glutamate- or GABA-gated
chloride channel, agonist pesticides, and a sypergist selected among Vitamin E compounds’ .. and Niacin compounds, for the manufacture of a medicament for the control ofpests in or
35 on humans or animals’ or their environs, said medicament comprising a reduced amount of
pesticide while maintaining a similar pesticidal effect by replacing a part ofthe amount of

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pesticide with a synergistic amount ofthe synergist

Detailed disclosure of the invention

Glutamate- or GABA-gated chloride channel agonist pesticide compounds are a well
5 known and versatile group of compounds that are used as agrochemicals and as drugs
within both human and veterinary medicine. The compounds are known to have both insec-ticidal, acaricidal and anthelminthic effect even when applied at very low rates compared in other agrochemicals and drugs. They are equally suitable for controlling both plant pests and ecto- and endo-parasites in ariimalci and humans Their mode of action is based on
10 the interference with the passage of chloride ions through the Glutamate or GABA regu-
lated chloride ion channels, which results in uncontrolled physiological activity and subse-quent death ofthe pest. The effect is inhibitory, i.e., the compound interferes agonistically with the function ofthe Glutamate- or GABA-gated chloride channels and elicits increased chloride current into cells. The increased chloride current results in intracellular hyperpo-
15 lanzation and (neuro)inhibition via the cancellation of positively charged excitatory im-
pulses carried by sodium currents, and eventually leads to the death ofthe pest. By the term "agonist" is meant a chemical that produces a response, such as excitation or inhibition of action potentials when it binds to a specific receptor, opposed to an "antagonist" which is a chemical that, when it binds to a receptor, blocks the receptor and prevents it from respond-
20 ing.

Among the Glutamate and GABA-gated chloride channel agonist pesticides are macrocyc-
ho lactone compounds, which have a complex ring structure, and include the well known groups of avermectinsi milbeniycines and the spinosyns. The compound Piperazine and
25 salts thereof is also a known Glutamate and GABA-gated chloride channel agonist pesti-
cide. These pesticides are known not to possess a rapid knock-down-effect, e.g, signifi-cantly lower than that observed with insecticidal compounds from the group ofpyrethroids

The avermectius are a group of macrocydic lactone compounds produced by fermentation
30 of Streptomyces avermitilis and mutations thereof. The individual avermectins, either natu-
rally derived or prepared by synthetic means (e.g. Ivermectin), are usually mixtures ofup to
8 major components designated as Aia, Alb A, A2b, 1318, Bib B28, B2b in various ratios. For instance Abamectin is a mixture ofthe two closely structurally related components desig-nated BI, and Bib usually in a 80:20 ratio, whereas the active compound known as Aver-
35 sectin C further comprises additional components in addition to those in Abainectin. Aver-
mectin compounds are, for example, known from United States patents nos. 3,950,360; US

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4,310,519; US 4,378,353; US 5,288,710; US 4,427,663; Us 4,199,569; Us 5,015,630; US 5,089,480, US 5,981,500 and PCT publication no. WO 02/068442-Al.

The structure of the averniectins can be illustrated by the general formula (1), which only
5 serves an illustrative purpose:

(1)

When X represents a double bond, the substituents R1 and R2 on the C-22 and C-23 posi-tions are not present Illustrative substituents in the above formula (1) are those where Y
10 represents H or an optionally substituted sugar or aininosugar unit, R1 represents H, R2 represents H or hydroxy, R3 represents alkyl or cycloalkyl and R4 represents H or alkyl. Examples of avermectins falling within the general structure (1) are:

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Name Y -C22R1-X-C23R2 R3

Avermectin Aia OcH

HJI -CH=- CH sec-Butyl CIT3

CH3

H

Avermectin Alb OCH3-CH=CH- iso-Propyl CIT3

Avermectin A2

OCH CIT CHOH sec-Butyl CIT3

H

Averniectin A2b OCH3 CH2-CI-IOH- iso-Propyl CIT3

OH3
H

Avermectin Bia 00H3

HO,,4j

-CH=CH- sec-Butyl H

H

Avermectin Bib 00H3 -CH=CH- iso-Propyl H

I-I

Avermectin B2 -CH2-CHOH- sec-Butyl H

CH3
H

Avermectin B2b OCH3 -CH2-CH014- iso-Propyl H

OH3
H

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Ivermectin B13 0cH3 -CH2-C112- sec-Butyl H

CM 0
H

Ivermectin B23 00H3
H(!

- CHrCH2- iso-Propyl H

CHs 0
H

Doramectin 0CM, -CH=CH- Cyclohexyl H

OH, 0

Emamectin B13 CON, -CH=CH- sec-Butyl H

OH,

Emamectin Bib OCH, -CH=CH- iso-Propyl H

OH,
H

Eprinomectin B13 0CM,
1 -CH=CH- sec-Butyl H

OH, H
Eprinomectin Bib OCH,

H2OO

-CH=CH- iso-Propyl H

OH, H

Another avermectin is Selamectin known from United States patent no. US 5,981,500. Yet another group of avermectins are those disclosed in US patent no. 6,933,260, which are de-rivatives of the avermectins B1 having an arninosulfonyloxy substituent in the 4"-position
5 as indicated above. Avermectin compounds wherein the substituent at the 5-position in the above formula (1) is a substituted oximino group or the keto group are also known. When appropriate, the avermectins also include various salt forms thereof; e.g. Emamectin as its benzoate salt.

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The nrilbemycms differ structurally from the avermectins, mainly m the absence of the
sugar residue on the C-13 carbon Milbemycins are produced by fermentation of &repto-
myces species, which further can be altered by synthetic means (e.g. Lepmiectln) Milbe-

5 mycins include Milbemectin and Milbeniycm oxnne, the latter produced by fermentation of
the actmomycete Streptomyces hygrorcopIco aureolaenmosus, and Moxidectin, preduced
by chemical modification of the milbeniycm Nemadectin, a product of fermentation of Streptomyce cyanogriseus noncyanogenus The individual mdbemycins, either naturally derived or prepared by synthetic means, are also usually mixtures ofseveral major, compo-
10 nents For instance Milbemectin is mixture of two major components designated as A3
and A4 Milbemycins are known, for example, from United States patent nos US

3,950,360; 4547,52O,:1J5 4,9oó,75 US 5,346,918; 15 5,428,034; US 4,581,247; US
5,405,867; US 5,276,033; US 4,945105; US 4,963,582; US 4,869,901 and US 5,614,470. When appropriate; the milbeniycins also include various salt forms thereof.

15 

The spmosyns are also fennelitation products- produced by Saccharopolyspara spinosa in-eluding those synthetically derived thereofincluding various salt form. The natural spino-syns are often referred to as spinosyn A spinosyn 13, spinosyn (, spinosyn D, spinosyn B

etc.
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The structure ofthe spinosyns can be illusirated by the general formula (2A) and (2B)
I
o1.o
fig

(2A)

H1

(213) A1
wherein X and Xi represents a single or double bond or an epoixide unit, Q and QIa repre-Senis an optionally substituted sugar or ammosugar unit or H* Rj, R2, R3 and R4 represents
25 such substituents as H, alkyl, alkenyl, cycloalkyl, alkylcarbonyl, alkylamino or alkyihy-
droxylanuno with such groups optionally being substituted with e g halogen atoms, by-droxy and alkozy groups, R5 represents such groups as H, OH, alkoxy or carbonyl

Spinosyn compounds are, for example, known from United States patents nos. 5,496,931;

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The Glutamate- or GABA-gated chloride channel agonist pesticides according to the inven-
tion may be applied in the form of a pharmacologically or agriculturally acceptable salt,
analog or combination thereof. Salts ofthe pesticides maybe prepared using standard pro-
cedures known to those skilled in the art of synthetic organic chemistry. For example, acid
5 addition salts are prepared from the free base (typically wherein the neutral form ofthe pes-
ticide has a neutral amino group) using conventional means, involving reaction with a suit-able acid. Generally, the base form ofthe drug is dissolved in an organic solvent such as al-cohols, ethers, acetonitrile and the like and the acid is added thereto. The resulting salt ei-ther precipitates or may be brought out ofsolution by addition of a less polar solvent. Suit-
10 able acids for preparing acid addition salts include both organic acids, e.g., acetic acid,
propionic acid, glycolic acid, pyruvic acid, oxalic acid, inalic acid, malonic acid, succinic acid, nialeic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, man-delic acid, methanesulfonic acid, ethanesulfonic acid, p-toluencsulfonic acid, benzenesulfo-
the acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, by-
15 drobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition
salt may be reconverted to the free base by treatment with a suitable base. Preparation of basic salts of acid moieties which may be present (e.g., carboxylic acid groups) are pre-pared in a similar manner using a pharmaceutically or agriculturally acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, mag-
20 nesiuni hydroxide, trimethylamine, or the like.

As used herein the term "Vitamin E compound" is meant to include all tocopherol and to-cotrienol derivatives and isomers, and salts and esters thereof and analogs thereof and in-elude a-tocopherol, -tocopherol, y-toeophcroi, -tocopherol, a-tocotrienol, -toeotrienol,
25 ’y-tocotrienol, 6-tocotrinol, as well as acetates and other (alkyl)esters thereof (e.g. toco-
pherol acetate, also known as tocopheryl acetate), phosphates (e.g. tocopherol phosphate disodiurn), succinates (e.g. tocopherol succinate) and optnally substituted compounds thereof as well as such analogs as e.g. alpha-tocopheryl nicotinate and Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxyiic acid). The term also includes the individual corn-
30 pounds (naturally occurring or synthetic prepared) as well as mixtures thereof. Natural Vi-
tamin E exists in eight different forms or isomers, four tocopherols and four tocotrienols as mentioned above. Synthetic Vitamin E usually marked as d,l-tocopherol or d,l tocopheiyl acetate, with 50% d-alpha tocopherol moiety and 50% 1-alpha-tocopherol moiety (often ref-ered to as tocopheryl acetate, all-rae alpha). Preferred Vitamin E compounds are tocopherol
35 and tocotrienol and esters and salts thereof such as alkylesters, succinates and phosphates;
alpha-tocopheryl nicotinate and Trolox.

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By the term "Niacin compnd" is meant nicotinic acid as well as derivatives thereofsuch as amides, esters, and hydroxyijcojj andC_aci and salts thereof and include, by example, niacinanj (nicotinamide) I50fljC
\esters (e.g. acid, IüCótiDic acid alkyl methyl- or ethylnic04Cd ester), 6-hyijro, nicotin, niceritrol, nicofinacid, acipirnox, aluminum flicoclonate nicomol, inositol hexanjacinate and oxiniacic acid. The

term also includes the individual compounds (naturally occurring or synthetic prepared) as \well as mixtures thereof. Preferred Niacin compounds are optionally hydrØxy substituted nicotinic acid and ISOthCOinJC acid and salts and C.12 aikylesters thereof, optionally hy- 10 SUbtjtued nicotinamide and isonjcotjnamjde and salts thereof:

lJsc ofmixtures of at least one Vitamin E compound and at least one Niacin compound may
applied, but is preferably used as single components with use of at least one Vitamin E
coipound solely as the component B being most preferred.
15

The Animals to be treated in accordance with the present invention includes, e.g. domestic anin\als (livestock and companion). The environs for the animals include farmyard struc-turesk dairy sheds, stables, poultry sheds, pig sties, dog and cat kennels and houses where dogs knd eats are kept. Animals on which the compositions can be applied to control pests,
20 e.g. p4hogenic endo- and ecto-parasites, include productive animals, breeding animals, zoo animal, pets as well as laboratory and experimental animals, such as mice, rats, guinea-pigs, lden hamsters, dogs, cats, cattle, horses, sheep, pigs, goats, ’camels, water buffalo, donkey rabbits, fallow deer and reindeer, fur-bearing animals such as mink, chinchilla and raccoon,\birds such as hens, geese, turkeys and ducks as well as fresh- and salt-water fish.
25 The fish include food fish, cultivated fish, aquarium fish and ornamental fish of all ages which in fresh water, sea water and pond water. The food fish and cultivated fish in-clude, for example. carp, eel, trout, whitefish, salmon, bream, roach, nuld, chub, flounder, sole, piaic4, saithe, wrasse, turbot, halibut, Japanese yellowtail (Serbia quinqueradiata), Japanese 4i (Anguilla japonica), red sea bream (Pagurus major), sea bass (Dicentrarchus