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(54) Titre : ASSOCIATION INSECTICIDE CONTRE LES PUCES DES MAMMIFERES, NOTAMMENT DES CHIENS ET CHATS
(54) Title: INSECTICIDAL COMBINATION EFFECTIVE AGAINST FLEAS ON MAMMALS, PARTICULARLY CATS AND DOGS

(57) **Abrégé/Abstract:**

The present application describes a composition for long-lasting protection of small mammals against fleas comprising at least one 1-N-arylpyrazole insecticide, particularly fipronil, and at least one compound which is a chitin-synthesis inhibitor, in a fluid vehicle which is acceptable to the animal and suitable for local application to the skin.



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Abstract

The present application describes a composition for long-lasting protection of small mammals against fleas comprising at least one 1-N-arylpyrazole insecticide, particularly fipronil, and at least one compound which is a chitin-synthesis inhibitor, in a fluid vehicle which is acceptable to the animal and suitable for local application to the skin.

INSECTICIDAL COMBINATION EFFECTIVE AGAINST FLEAS ON MAMMALS, PARTICULARLY CATS AND DOGS

This is a divisional of Canadian Application No. 2,221,418, filed on March 26, 1997.

The present invention relates to an improvement to the processes for controlling mammal fleas and in particular fleas on cats and dogs. The invention also relates to a novel composition for this use, based on a synergistic combination of parasiticides which are already known. Lastly, the invention relates to the use of such already-known parasiticides for the preparation of such a composition.

A novel class of 1-N-arylpyrazole-based insecticides has been described in patents EP-A-295,217 and EP-A-352,944. The compounds of the classes defined in these patents are highly active, and one of these compounds

1-[2,6-Cl₂ 4-CF₃ phenyl]3-CN 4-[SO-CF₃]5-NH₂ pyrazole, whose common name is fipronil, has proven to be particularly effective not only against crop parasites but also against mammal ectoparasites and in particular, but not exclusively, fleas, ticks, flies and myiases.

Compounds with an ovicidal and/or larvicidal effect on the immature stages of various ectoparasites are already known, for example from patent US-A-5,439,924. Among these compounds (IGR) are featured insect growth regulator compounds which act either by blocking the development of the immature stages (eggs and larvae) into adult stages, or by inhibiting the synthesis of chitin.

Patent FR-A-2,713,889 is moreover known, which generally describes the combination of at least one compound of IGR (insect growth regulator) type, comprising compounds with juvenile hormone activity and chitin synthesis inhibitors, with at least one of three N-aryldiazole compounds, in particular fipronil, to control many harmful insects belonging to very varied orders.

The compositions may be used in very diverse forms, although the applications, for example veterinary, healthcare or plant-protection applications, for which these different forms are

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designed are not specified, nor are the parasites for which they are respectively intended.

The only application which may be thought to be veterinary is associated with the example of the manufacture of a pesticidal collar which is a slow-release formulation.

The invention proposes to improve the processes for controlling fleas in small mammals, and in particular in cats and dogs.

The object of the invention is, in particular, to use already-known parasitocides in order to prepare a composition which is highly active against the fleas of these animals.

Lastly, the object of the invention is a novel composition thus prepared and intended, in particular, to control fleas.

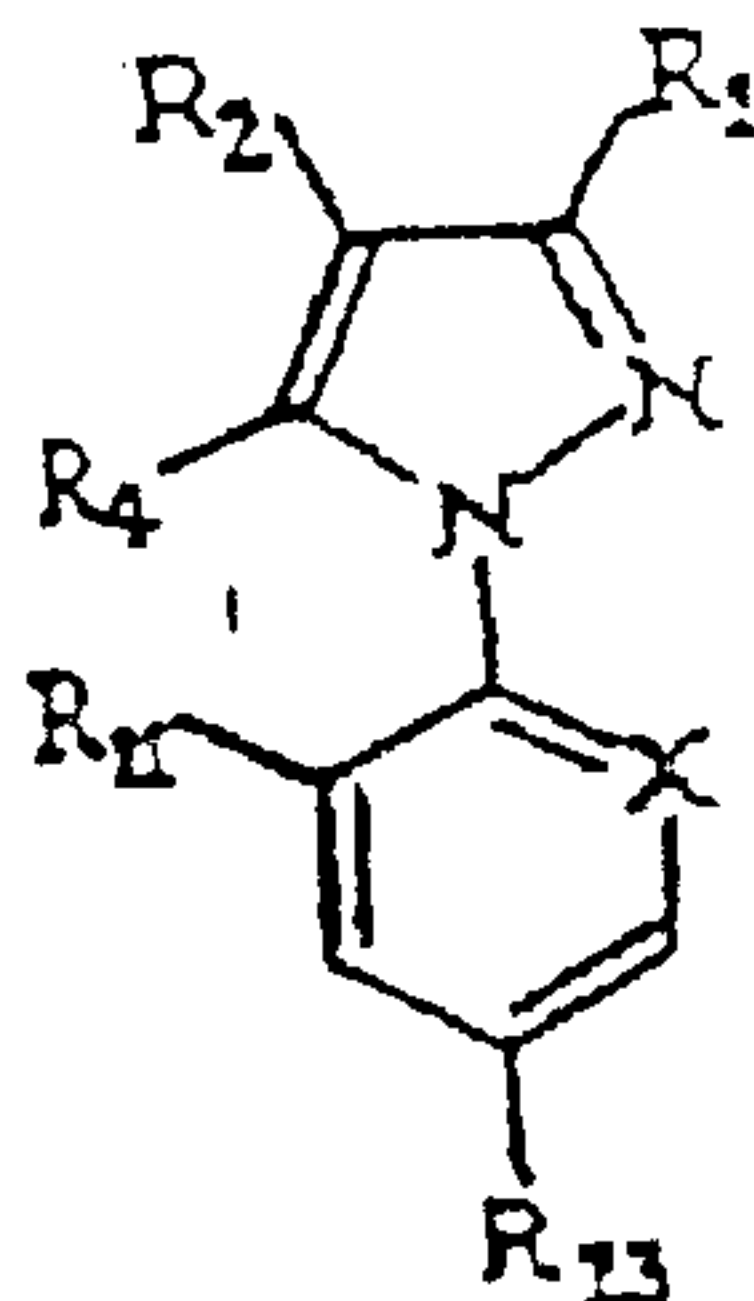
For the purposes of the present invention, the term flea is understood to refer to all the usual or accidental species of parasitic flea of the order Siphonaptera, and in particular the species Ctenocephalides, in particular C. felis and C. canis, rat fleas (Xenopsylla cheopis) and human fleas (Pulex irritans).

The very high efficacy of the process and of the composition according to the invention implies not only high immediate efficacy but also very long-lasting efficacy after the animal has been treated.

The subject of the invention is a process for controlling the fleas of small mammals, and in particular cats and dogs, over a long period, characterized in that the animal is treated by locally depositing on the skin, preferably localized over a small surface area (spot-on application), in parasitocidally effective doses and proportions, on the one hand at least one compound (A) belonging to formula (I),

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(I)

10 in which:

R_1 is CN or methyl or a halogen atom;

R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl or haloalkyl;

15 R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, $C(O)O-R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$;

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, $C(O)$ alkyl, alkoxy carbonyl or $S(O)_r-CF_3$ radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur;

R_7 represents an alkyl or haloalkyl radical;

25 R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

30 R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl;

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom, or optionally CN or NO_2 ;

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

m , n , q and r represent, independently of each other, an integer equal to 0, 1 or 2

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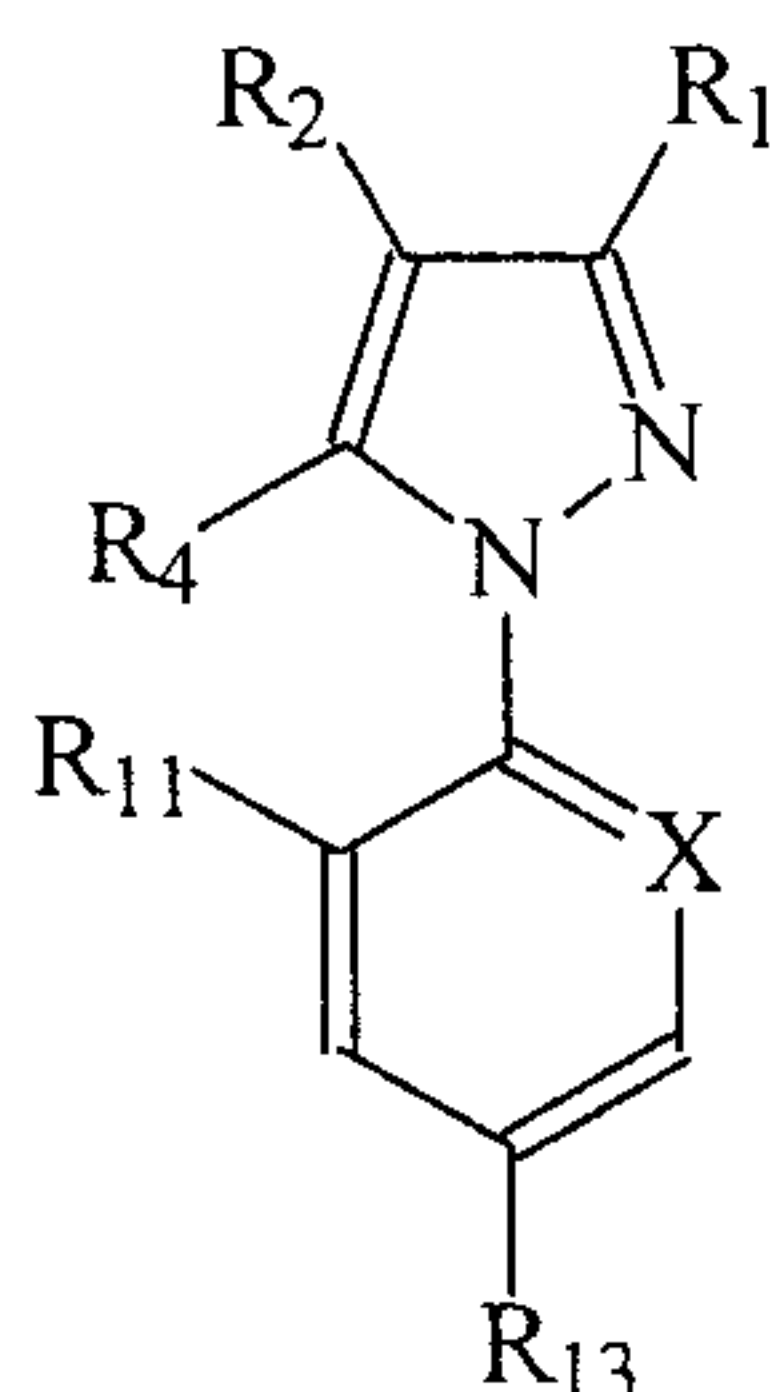
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X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R₁ is methyl, either
 5 R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N; or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl, R₁₃ is CF₃ and X is =C-Cl;

and, on the other hand at least one compound
 (B), of IGR (insect growth regulator) type, in a fluid
 10 vehicle which is acceptable to the animal and suitable for local application on the skin.

The present divisional application is directed to a composition for long-lasting protection of small mammals against fleas comprising at least one
 15 compound (A) of the formula (I)



(I)

in which:

R₁ is CN or methyl or a halogen atom;

R₂ is S(O)_nR₃ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

30 R₃ is alkyl or haloalkyl;

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_mR₇, C(O)R₇ or C(O)O-R₇, alkyl, haloalkyl or OR₈ or a radical -N=C(R₉)(R₁₀);

R₅ and R₆ independently represent the hydrogen
 35 atom; an alkyl radical, haloalkyl, C(O) alkyl, or alkoxy carbonyl; S(O)_rCF₃; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;

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R₇ represents an alkyl or haloalkyl radical;

R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

5 R₉ represents an alkyl radical or a hydrogen atom;

R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups selected from OH, -O-alkyl, -S-alkyl, cyano and alkyl;

10 R₁₁ and R₁₂ represent, independently of one another, a hydrogen or halogen atom, or optionally CN or NO₂;

R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group;

15 m, n, q and r represent, independently of one another, an integer equal to 0, 1 or 2;

X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring;

20 provided that, when R₁ is methyl, then R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N; or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl, R₁₃ is CF₃ and X is =C-Cl;

25 and at least one compound (B) which is a chitin-synthesis inhibitor, in a fluid vehicle which is acceptable to the animal and suitable for local application to the skin.

Preferably, in formula (I):

R₁ is CN or methyl

30 R₂ is S(O)_nR₃

R₃ is alkyl or haloalkyl

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_mR₇, C(O)R₇, alkyl, haloalkyl or OR₈ or a radical -N=C(R₉) (R₁₀)

35 R₅ and R₆ independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl or S(O)_r-CF₃ radical; where R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur

R₇ represents an alkyl or haloalkyl radical

R₈ represents an alkyl or haloalkyl radical or a hydrogen atom

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R₉ represents an alkyl radical or a hydrogen atom

R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl

R₁₁ and R₁₂ represent, independently of each other, a hydrogen or halogen atom

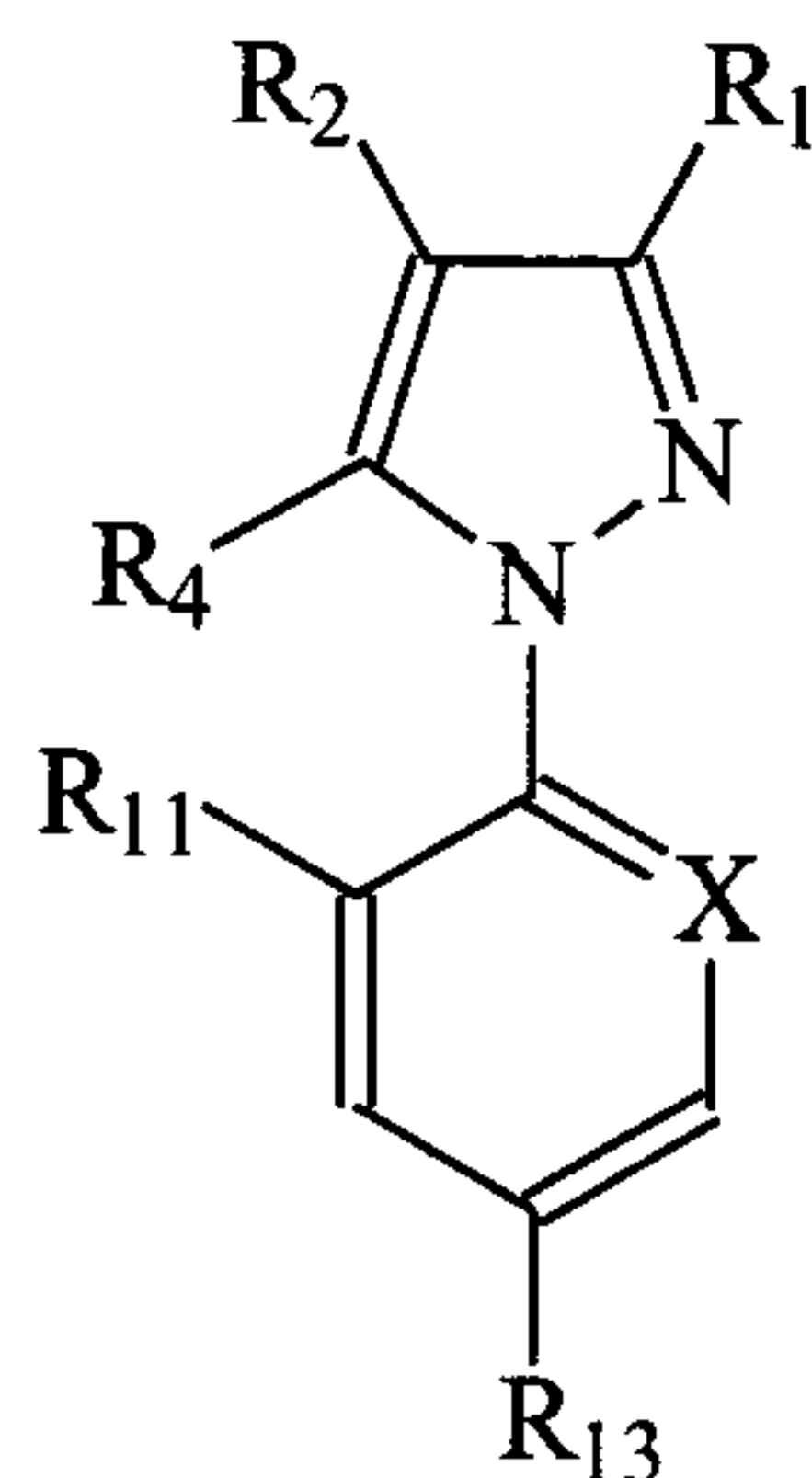
R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

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According to one aspect of the present invention,
there is provided a spot-on composition for protection of a
small mammal against ectoparasites for a duration of at
least one month, comprising at least one compound (A) of the
5 formula (I)



(I)

in which:

R₁ is CN or methyl or a halogen atom;

15 R₂ is S(O)_nR₃ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R₃ is alkyl or haloalkyl;

R₄ represents a hydrogen or halogen atom; or a
radical NR₅R₆, S(O)_mR₇, C(O)R₇ or C(O)O-R₇, alkyl, haloalkyl
or OR₈ or a radical -N=C(R₉)(R₁₀);

20 R₅ and R₆ independently represent a hydrogen atom;
an alkyl radical, haloalkyl, C(O) alkyl, or alkoxycarbonyl;
S(O)_rCF₃; or R₅ and R₆ may together form a divalent alkylene
radical which may be interrupted by one or two divalent
hetero atoms;

25 R₇ represents an alkyl or haloalkyl radical;

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R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

R₉ represents an alkyl radical or a hydrogen atom;

R₁₀ represents a phenyl or heteroaryl group, which
5 is unsubstituted or substituted with at least one halogen atom or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R₁₁ and R₁₂ represent, independently of one another, a hydrogen or halogen atom, or CN or NO₂;

R₁₃ represents a halogen atom or a haloalkyl,
10 haloalkoxy, S(O)_qCF₃ or SF₅ group;

m, n, q and r represent, independently of one another, an integer equal to 0, 1 or 2; and

X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the
15 carbon atom forming part of the aromatic ring;

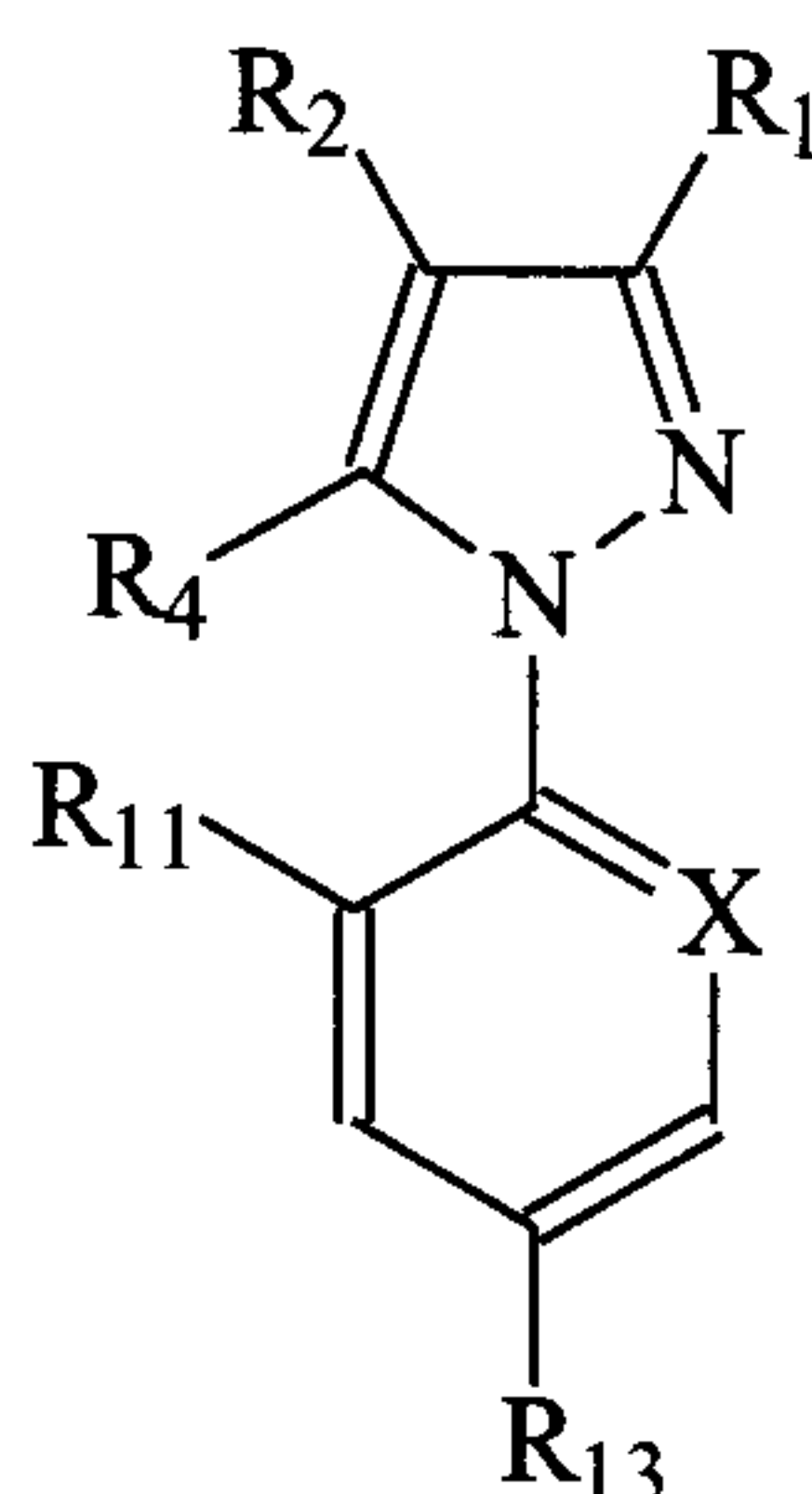
provided that, when R₁ is methyl, then
R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N;
or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl,
R₁₃ is CF₃ and X is =C-Cl;

20 and at least one compound (B) which is a chitin-synthesis inhibitor, in a fluid vehicle which is acceptable to the animal and for local application to the skin.

According to another aspect of the present invention, there is provided use of at least one
25 compound (A) of formula (I)

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(I)

in which:

R₁ is CN or methyl or a halogen atom;

10 R₂ is S(O)_nR₃ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R₃ is alkyl or haloalkyl;

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_mR₇, C(O)R₇ or C(O)O-R₇, alkyl, haloalkyl
15 or OR₈ or a radical -N=C(R₉)(R₁₀);

R₅ and R₆ independently represent a hydrogen atom; an alkyl radical, haloalkyl, C(O) alkyl, or alkoxycarbonyl; S(O)_rCF₃; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent
20 hetero atoms;

R₇ represents an alkyl or haloalkyl radical;

R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

R₉ represents an alkyl radical or a hydrogen atom;

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R₁₀ represents a phenyl or heteroaryl group, which is unsubstituted or substituted with at least one halogen atom or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R₁₁ and R₁₂ represent, independently of one another,
5 a hydrogen or halogen atom, or CN or NO₂;

R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group;

m, n, q and r represent, independently of one another, an integer equal to 0, 1 or 2;

10 X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valence positions of the carbon atom forming part of the aromatic ring;

on the condition that, when R₁ is methyl, then R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N;
15 or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl, R₁₃ is CF₃ and X is =C-Cl;

and of at least one compound (B) which is a chitin-synthesis inhibitor,

in the preparation of a spot-on composition for
20 local application to the skin, for protection against ectoparasites on a small mammal for a duration of at least one month.

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According to another aspect, the present invention relates to a kit comprising the spot-on composition as defined herein, wherein said kit comprises separately, in the same packaging, at least one container containing the
5 compound (A) and at least one container containing the compound (B), and written instructions specifying that the compounds contained in the containers are to be used alternatively, at an interval of at least one month.

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X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R₁ is methyl, then
 5 R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N.

Compounds of formula (I) in which R₁ is CN will be selected most particularly. Compounds in which R₂ is S(O)_nR₃, preferably with n = 1, R₃ preferably being CF₃
 10 or alkyl, for example methyl or ethyl, or alternatively n = 0, R₃ preferably being CF₃, as well as those in which X = C-R₁₂, R₁₂ being a halogen atom, will also be selected. Compounds in which R₁₁ is a halogen atom and those in which R₁₃ is haloalkyl, preferably CF₃, are
 15 also preferred. Within the context of the present invention, compounds which combine two or more of these characteristics will advantageously be selected.

A preferred class of compounds of formula (I) consists of compounds such that R₁ is CN, R₃ is
 20 haloalkyl, R₄ is NH₂, R₁₁ and R₁₂ are, independently of each other, a halogen atom, and/or R₁₃ is haloalkyl.

In these compounds, R₃ preferably represents CF₃ or ethyl.

The alkyl radicals in the definition of the
 25 compounds of formula (I) generally comprise from 1 to 6 carbon atoms. The ring formed by the divalent alkylene radical representing R₅ and R₆, as well as the nitrogen atom to which R₅ and R₆ are attached, is generally a 5-, 6- or 7-membered ring.

30 A compound of formula (I) which is most particularly preferred in the invention is 1-[2,6-Cl₂ 4-CF₃phenyl]3-CN 4-[SO-CF₃] 5-NH₂ pyrazole, the common name of which is fipronil.

The two compounds which differ from the above
 35 by the following characteristics:

- | | |
|-----------|----------------------------------|
| 1- n = 0, | R ₃ = CF ₃ |
| 2- n = 1, | R ₃ = ethyl. |

may also be mentioned.

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Among the compounds (B), mention may be made in particular of compounds which mimic juvenile hormones, in particular:

5 azadirachtin - Agridyne
 diofenolan (Ciba Geigy)
 fenoxycarb (Ciba Geigy)
 hydroprene (Sandoz)
 kinoprene (Sandoz)
 methoprene (Sandoz)
 10 pyriproxyfen (Sumitomo/Mgk)
 tetrahydroazadirachtin (Agridyne)
 4-chloro-2-(2-chloro-2-methylpropyl)-5-(6-iodo-3-pyridylmethoxy)pyridizin-3(2H)-one
 15 and chitin-synthesis inhibitors, in particular:
 chlorfluazuron (Ishihara Sangyo)
 cyromazine (Ciba Geigy)
 diflubenzuron (Solvay Duphar)
 fluazuron (Ciba Geigy)
 20 flucycloxuron (Solvay Duphar)
 flufenoxuron (Cyanamid)
 hexaflumuron (Dow Elanco)
 lufenuron (Ciba Geigy)
 tebufenozide (Rohm & Haas)
 25 teflubenzuron (Cyanamid)
 triflumuron (Bayer)

these compounds being defined by their international common name (The Pesticide Manual, 10th edition, 1994, Ed. Clive Tomlin, Great Britain).

30 As chitin-synthesis inhibitors, mention may also be made of compounds such as 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenyl)urea, 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)urea and
 35 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoromethyl)phenyl)urea.

Novaluron (Isagro, Italian company) may also be mentioned as a compound (B).

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The preferred compounds (B) are methoprenes, pyriproxyfens, hydroprene, cyromazine, lufenuron and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenyl)urea.

5 Another preferred compound (B) is again novalluron.

It is preferable for the administration of the two types of compound to be concomitant and preferably simultaneous.

10 It is preferable for the treatment according to the invention to be carried out every two or, preferably, every three months on cats and dogs.

Preferably, the treatment is carried out so as to administer to the animal a dose of from 0.1 to 40 and in particular from 1 to 20 mg/kg of derivative (A) and a dose of from 0.1 to 40 and in particular 1 to 30 mg/kg of compound (B).

The preferred doses are from 5 to 15 mg/kg for compound (A) and from 0.5 to 15 mg/kg for the preferred compounds (B), or 10 to 20 mg/kg for the other compounds (B).

In another embodiment of the process according to the invention, compounds (A) and (B) may be applied in a distinct and separate manner over time. In this case, it is preferred to alternate the applications with an interval, for example of one month between two applications, the first application preferably being made with compound (A).

It is understood that the dosage values which are thus indicated are average values which may vary within a wide range, since, in practice, a formulation having defined doses of compound (A) of 1-N-phenylpyrazole-type derivative and of compound (B) will be administered to animals having relatively different weights. Consequently, the doses actually applied are often smaller or larger by a factor which may be up to 2, 3 or 4 relative to the preferred dose, without entailing any toxic risk for the animal in the case of an overdose, and while at the same time

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retaining real efficacy, possibly of shorter duration, in the case of an underdose.

The object of this process is non-therapeutic and relates in particular to the cleaning of animal hairs and skin by elimination of the parasites which are present, as well as their residues and dejections. The treated animals thus have hair which is more pleasant to look at and to feel.

The invention also relates to such a process for therapeutic purposes, which is intended to treat and prevent parasitoses having pathogenic consequences.

In accordance with the present invention, the process described above may also be used to control ectoparasites, in particular ticks.

The subject of the invention is also a composition, in particular one for controlling fleas on small mammals, characterized in that it includes, on the one hand, at least one compound (A) of formula (I) as defined above, and, on the other hand, at least one compound (B) defined above, in doses and proportions which have parasitocidal efficacy on fleas, in a fluid vehicle which is acceptable for the animal and convenient for local application to the skin, preferably localized over a small surface area.

Preferably, in formula (I);
 R_1 is CN or methyl
 R_2 is $S(O)_nR_3$
 R_3 is alkyl or haloalkyl
 R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, $C(O)alkyl$ or $S(O)_r-CF_3$ radical; where R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur

R_7 represents an alkyl or haloalkyl radical

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom

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R₉ represents an alkyl radical or a hydrogen atom

R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl

R₁₁ and R₁₂ represent, independently of each other, a hydrogen or halogen atom

R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R₁ is methyl, then R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N.

Compounds of formula (I) in which R₁ is CN will be selected most particularly. Compounds in which R₂ is S(O)_nR₃, preferably with n = 1, R₃ preferably being CF₃ or alkyl, for example methyl or ethyl, or alternatively n = 0, R₃ preferably being CF₃, as well as those in which X = C-R₁₂, R₁₂ being a halogen atom, will also be selected. Compounds in which R₁₁ is a halogen atom and those in which R₁₃ is haloalkyl, preferably CF₃, are also preferred. Within the context of the present invention, compounds which combine two or more of these characteristics will advantageously be selected.

A preferred class of compounds of formula (I) consists of compounds such that R₁ is CN, R₃ is haloalkyl, R₄ is NH₂, R₁₁ and R₁₂ are, independently of each other, a halogen atom, and/or R₁₃ is haloalkyl.

In these compounds, R₃ preferably represents CF₃ or ethyl.

A compound of formula (I) which is most particularly preferred in the invention is 1-[2,6-Cl₂ 4-CF₃phenyl]3-CN 4-[SO-CF₃] 5-NH₂ pyrazole.

The two compounds which differ from the above by the following characteristics:

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1- n = 0, R₃ = CF₃
2- n = 1, R₃ = ethyl

may also be mentioned.

The compounds of formula (I) may be prepared
5 according to one or other of the processes described in
patent applications WO-A-87/3781, 93/6089, 94/21606 or
European patent application EP-A-0,295,117, or any
other process which falls within the competence of a
specialist skilled in the art of chemical synthesis.
10 For the chemical preparation of the products of the
invention, a person skilled in the art is considered as
having at his disposal, inter alia, all of the contents
of "Chemical Abstracts" and the documents cited
therein.

15 Among the compounds of IGR type listed above,
methoprenes, pyriproxyfens, hydroprene, cyromazine,
lufenuron and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-
(trifluoromethyl)phenylurea are preferred.

Novaluron is also preferred.

20 The proportions, by weight, of compounds of
formula (I) and of compound (B) are preferably between
80/20 and 20/80.

The fluid vehicle may be simple or complex and
it is adapted to the route and mode of administration
25 selected.

The compositions for spot-on application can
advantageously comprise:

b) a crystallization inhibitor, in particular
one which is present in a proportion of from 1 to 20%
30 (W/V), preferably from 5 to 15%, this inhibitor
satisfying the test according to which:

0.3 ml of a solution A comprising 10% (W/V) of the
compound of formula (I) in the solvent defined in c)
below, along with 10% of this inhibitor, are deposited
35 on a glass slide at 20°C for 24 hours, after which it
is observed with the naked eye that there are few or no
crystals, in particular fewer than 10 crystals, prefer-
ably 0 crystals on the glass slide,

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c) an organic solvent having a dielectric constant of between 10 and 35, preferably of between 20 and 30, the content of this solvent c) in the overall composition preferably representing the difference to
5 make the composition up to 100%,

d) an organic cosolvent having a boiling point of below 100°C, preferably of below 80°C, and having a dielectric constant of between 10 and 40, preferably of between 20 and 30; this cosolvent may advantageously be
10 present in the composition in a d)/c) weight/weight (W/W) ratio of between 1/15 and 1/2. The solvent is volatile, so as to serve in particular as a drying promoter, and is miscible with water and/or with the solvent c).

15 Although this is not preferred, the composition for spot-on application may optionally comprise water, in particular in a proportion of from 0 to 30% (volume per unit volume, V/V), in particular from 0 to 5%.

The composition for spot-on application may
20 also comprise an antioxidant intended to inhibit air-oxidation, this agent being present in particular in a proportion of from 0.005 to 1% (W/V), preferably from 0.01 to 0.05%.

The compositions according to the invention
25 intended for pets, in particular cats and dogs, are generally applied by being deposited onto the skin ("spot-on" or "pour-on" application); this is generally a localized application over a surface area of less than 10 cm², especially of between 5 and 10 cm², in
30 particular at two points and preferably localized between the animal's shoulders. Once deposited, the composition diffuses, in particular over the animal's entire body, and then dries without crystallizing or modifying the appearance (in particular absence of any
35 whitish deposit or dusty appearance) or the feel of the fur.

The compositions for spot-on application according to the invention are particularly advantageous owing to their efficacy, their speed of

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action and the pleasant appearance of the animal's fur after application and drying.

As organic solvent c) which can be used in the invention, mention may be made in particular of:

5 acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene
10 glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, in particular N-methylpyrrolidone, diethylene glycol monoethyl ether, ethylene glycol and diethyl phthalate, or a mixture of at least two of these solvents.

15 As crystallization inhibitor b) which can be used in the invention, mention may be made in particular of:

- polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, poly-
20 ethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters; lecithin, sodium carboxymethylcellulose, acrylic derivatives such as methacrylates and the like,

- anionic surfactants such as alkaline
25 stearates, in particular sodium, potassium or ammonium stearate; calcium stearate; triethanolamine stearate; sodium abietate; alkyl sulphates, in particular sodium lauryl sulphate and sodium cetyl sulphate; sodium dodecylbenzenesulphonate, sodium
30 dioctylsulphosuccinate; fatty acids, in particular those derived from coconut oil,

- cationic surfactants such as water-soluble quaternary ammonium salts of formula $N^+R'R''R'''R''''Y^-$ in which the radicals R are optionally hydroxylated hydro-
35 carbon radicals and Y^- is an anion of a strong acid such as the halide, sulphate and sulphonate anions; cetyltrimethylammonium bromide is among the cationic surfactants which can be used,

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- amine salts of formula $N^+R'R''R'''$ in which the radicals R are optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is among the cationic surfactants which can be used,

5 - nonionic surfactants such as optionally polyoxyethylenated sorbitan esters, in particular polysorbate 80, polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters,
10 polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, copolymers of ethylene oxide and propylene oxide,

- amphoteric surfactants such as substituted lauryl compounds of betaine,

15 or preferably a mixture of at least two of these crystallization inhibitors.

In a particularly preferred manner, a crystallization inhibitor couple, namely the combination of a film-forming agent of polymeric type
20 and a surfactant, will be used. These agents will be chosen in particular from the compounds mentioned as crystallization inhibitor b).

Among the film-forming agents of polymeric type which are particularly advantageous, mention may be
25 made of:

- the various grades of polyvinylpyrrolidone,
- polyvinyl alcohols, and
- copolymers of vinyl acetate and vinylpyrrolidone.

30 As regards the surfactants, mention will be made most particularly of nonionic surfactants, preferably polyoxyethylenated sorbitan esters and in particular the various grades of polysorbate, for example polysorbate 80.

35 The film-forming agent and the surfactant may be incorporated, in particular, in similar or identical amounts within the limit of the total amounts of crystallization inhibitor mentioned elsewhere.

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The couple thus produced ensures the objectives of absence of crystallization on the hairs and maintenance of the cosmetic appearance of the coat in a noteworthy manner, that is to say without any tendency
5 towards stickiness or to a sticky appearance, despite the high concentration of active material.

As cosolvent d), mention may be made in particular of: absolute ethanol, isopropanol, methanol.

As antioxidant, standard agents are used in
10 particular, such as: butylhydroxyanisole, butylhydroxytoluene, ascorbic acid, sodium metabisulphite, propyl gallate and sodium thiosulphate, or a mixture of not more than two of these agents.

The compositions for spot-on application
15 according to the invention are usually prepared by simple mixing of the constituents as defined earlier; advantageously, to begin with, the active material is mixed in the main solvent and the other ingredients or adjuvants are then added.

20 The volume applied may be from about 0.3 to 1 ml, preferably about 0.5 ml for cats, and from about 0.3 to 3 ml for dogs, according to the weight of the animal.

In a particularly preferred manner, the
25 composition according to the invention may be in the form of a concentrated emulsion, suspension or solution for spot-on application to a small area of the animal's skin, generally between the two shoulders (spot-on type solution). In a clearly less preferred manner, forms of
30 solution or suspension to be sprayed, forms of solution, suspension or emulsion to be poured or spread onto the animal (pour-on type solution) an oil, a cream, an ointment or any other fluid formulation for topical administration may be provided.

35 Advantageously, the ready-to-use composition contains a dose of from 0.1 to 40 mg/kg of compound (A) of formula (I) and 0.1 to 40 mg/kg of compound (B).

Preferably, a ready-to-use dosed formulation, in particular one for spot-on application, contains 1

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to 20 mg/kg, preferably 2 to 10 mg/kg of compound (A), in particular fipronil, and from 1 to 30 mg/kg, preferably 2 to 10 mg/kg, of preferred compound (B) or 10 to 20 mg/kg of other compound (B).

5 Advantageously, ready-to-use compositions dosed for 1-10, 10-20 and 20-40 kg animals respectively may be provided.

 In another embodiment, provided for separate application over time, a composition may be made in the
10 form of a kit separately combining, in the same packaging, a composition containing a compound of formula (I), in particular fipronil, and a composition containing compound (B), preferably pyriproxyfen, each of the compositions including a vehicle which allows it
15 to be applied onto the skin.

 Preferably, each of the two compositions is provided for local spot-on application and, preferably, a container containing just the dose required is provided for each application.

20 Thus, for example, a kit may contain, in a package, three containers each containing a single dose of composition of compound (A) and three containers each containing a single dose of composition of compound (B), the containers (A) being distinguished
25 from the containers (B) by markings, shapes or colours, as well as a notice specifying that the containers (A) and (B) must be used alternately with an interval, for example, of one month, and starting, for example, with a container (A).

30 The compositions according to the invention, in particular those for spot-on application, have proven to be extremely effective for the very long-lasting treatment of fleas on mammals, and in particular small mammals such as cats and dogs.

35 The discovery that the compound (A), such as fipronil, dissolves in the sebum so as to cover the entire animal and becomes concentrated in the sebaceous glands, from which it is gradually released over a very long period, is a plausible explanation of this long-

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lasting efficacy for these compositions, and could perhaps also explain the long-lasting action of the associated compound (B).

They also have a certain efficacy against other parasitic insects and, in particular, ticks, and it is understood that the application of the composition according to the invention may be extended to the treatment of ectoparasites, or even endoparasites for which the composition proves to have real utility capable of being obtained practically, according to the criteria of the veterinary art.

Thus, for example, a composition based on fipronil and fluazuron may also be used in particular against ticks.

Where appropriate, the composition according to the invention may also comprise another insecticide, and in particular imidaclopride.

The subject of the invention is also the use of at least one compound (A) of formula (I) and of at least one compound (B) of IGR type, as defined above, for the preparation of a composition as defined above.

Other advantages and characteristics of the invention will become apparent on reading the description which follows, which is given by way of non-limiting example.

The composition preparation example which follows includes, as compound (A) of formula (I), the compound known as fipronil.

By way of example to prepare a composition for local application to the skin according to the invention, the following components may advantageously be mixed together:

- a1 - compound (B) in a proportion of from 1 to 20% (percentage as a weight per unit volume W/V)
- a2 - compound (A) of formula (I), in a proportion of from 1 to 20%, preferably 5 to 15% (percentage as a weight per unit volume W/V).

By way of example, the compositions according to the invention comprise the following concentrations

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(W/V) of compounds (A) and (B) in a liquid medium comprising a representative of each of the components b, c and d. The total volume is 1 ml.

Example 1

5 fipronil 10%
 pyriproxyfen 5%

Example 2

10 fipronil 5%
 pyriproxyfen 5%

Example 3

15 fipronil 5%
 pyriproxyfen 20%

Example 4

 fipronil 10%
 methoprene 30%

Example 5

20 fipronil 10%
 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoromethyl)phenylurea 5%.

25 Cats are infested with 100 fleas each, and are
 then reinfested every 10 days. Concomitant with the
 first manifestation, they receive a local skin
 application of 0.1 ml/kg of the composition according
 to Example 1. Two months after the treatment and ten
30 days after the last infestation, no fleas are detected
 and the eggs collected are found to be non-viable.

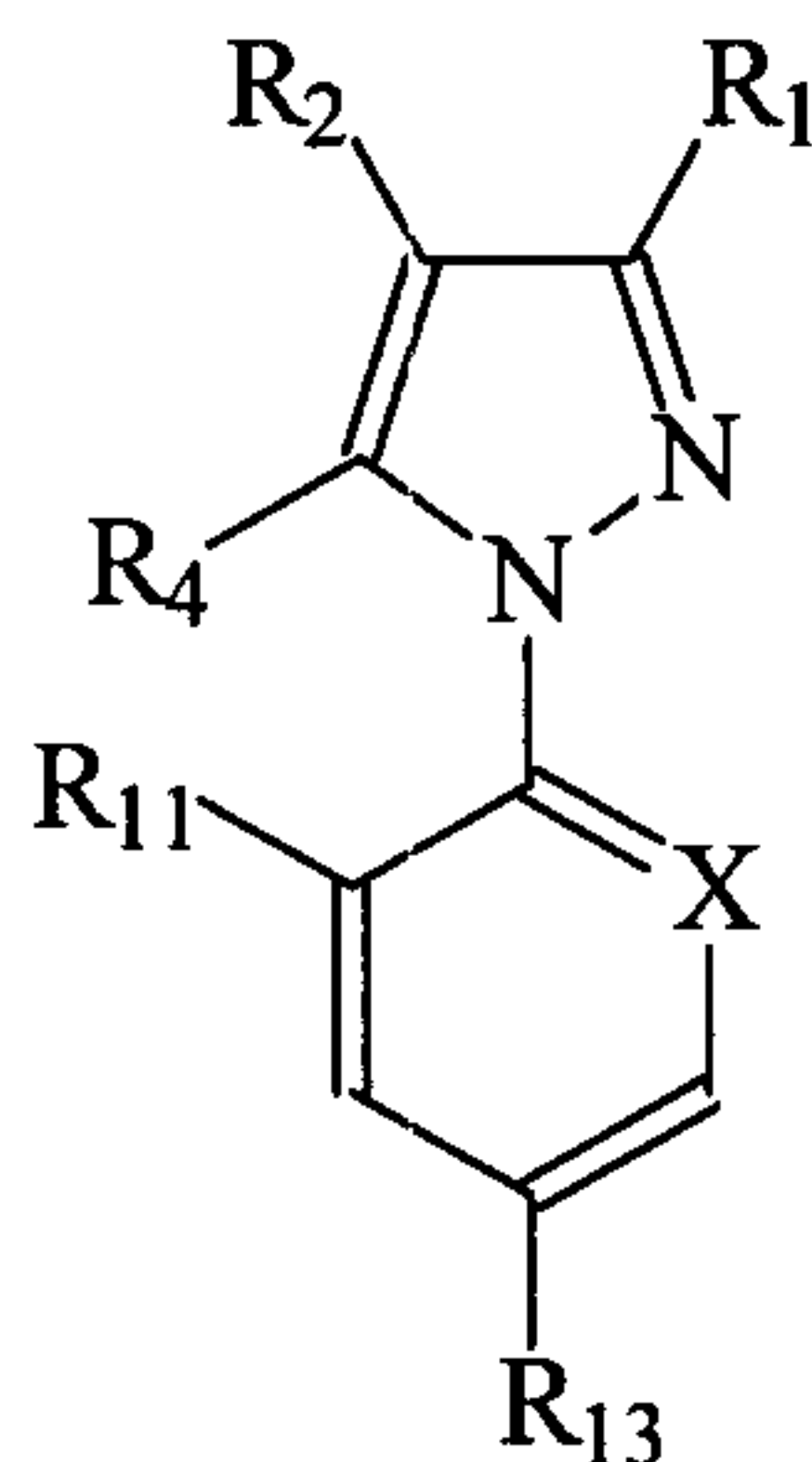
 Dogs treated according to the same procedure
 with compositions according to Examples 1 and 2 show
 the same efficacy of treatment two months after
 application of the composition.

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CLAIMS:

1. A spot-on composition for protection of a small mammal against ectoparasites for a duration of at least one month, comprising at least one compound (A) of the
 5 formula (I)



(I)

in which:

R₁ is CN or methyl or a halogen atom;

15 R₂ is S(O)_nR₃ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R₃ is alkyl or haloalkyl;

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_mR₇, C(O)R₇ or C(O)O-R₇, alkyl, haloalkyl or OR₈ or a radical -N=C(R₉)(R₁₀);

20 R₅ and R₆ independently represent a hydrogen atom; an alkyl radical, haloalkyl, C(O) alkyl, or alkoxycarbonyl; S(O)_rCF₃; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;

25 R₇ represents an alkyl or haloalkyl radical;

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R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

R₉ represents an alkyl radical or a hydrogen atom;

R₁₀ represents a phenyl or heteroaryl group, which
5 is unsubstituted or substituted with at least one halogen atom or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R₁₁ and R₁₂ represent, independently of one another, a hydrogen or halogen atom, or CN or NO₂;

R₁₃ represents a halogen atom or a haloalkyl,
10 haloalkoxy, S(O)_qCF₃ or SF₅ group;

m, n, q and r represent, independently of one another, an integer equal to 0, 1 or 2; and

X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the
15 carbon atom forming part of the aromatic ring;

provided that, when R₁ is methyl, then
R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N;
or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl,
R₁₃ is CF₃ and X is =C-Cl;

20 and at least one compound (B) which is a chitin-synthesis inhibitor, in a fluid vehicle which is acceptable to the animal and for local application to the skin.

2. The spot-on composition according to claim 1, wherein the small mammal is a dog or a cat.

25 3. The spot-on composition according to claim 1 or 2, wherein:

R₁ is CN or methyl;

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R_2 is $S(O)_nR_3$;

R_3 is alkyl or haloalkyl;

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a
5 radical $-N=C(R_9)(R_{10})$;

R_5 and R_6 independently represent a hydrogen atom; an alkyl, haloalkyl or $C(O)$ alkyl radical; $S(O)_rCF_3$; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;

10 R_7 represents an alkyl or haloalkyl radical;

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

R_{10} represents a phenyl or heteroaryl group, which
15 is unsubstituted or substituted with at least one halogen atom or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R_{11} and R_{12} represent, independently of one another, a hydrogen or halogen atom;

R_{13} represents a halogen atom or a haloalkyl,
20 haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

m , n , q and r represent, independently of one another, an integer equal to 0, 1 or 2; and

X represents a trivalent nitrogen atom or a radical $C-R_{12}$, the other three valency positions of the
25 carbon atom forming part of the aromatic ring;

provided that, when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2 , R_{11} is Cl, R_{13} is CF_3 and X is N.

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4. The spot-on composition according to any one of claims 1 to 3, wherein the divalent hetero atom is oxygen or sulphur.

5. The spot-on composition according to any one of
5 claims 1 to 4, wherein R_1 is CN.

6. The spot-on composition according to any one of claims 1 to 5, wherein R_{13} is haloalkyl.

7. The spot-on composition according to claim 6, wherein R_{13} is CF_3 .

10 8. The spot-on composition according to any one of claims 1 to 7, wherein R_2 is $S(O)_nR_3$, n and R_3 having the definition found in claim 1.

9. The spot-on composition according to claim 8, wherein $n = 1$ and R_3 is CF_3 or an alkyl group.

15 10. The spot-on composition according to claim 9, wherein R^3 is methyl or ethyl.

11. The spot-on composition according to claim 8, wherein $n = 0$ and R_3 is CF_3 .

12. The spot-on composition according to any one of
20 claims 1 to 11, wherein X is C- R_{12} with R_{12} being a halogen atom.

13. The spot-on composition according to any one of claims 1 to 8, wherein R_1 is CN, R_3 is haloalkyl, R_4 is NH_2 , R_{11} and R_{12} are, independently of one another, a halogen atom,
25 and R_{13} is haloalkyl.

14. The spot-on composition according to claim 1, wherein the compound of formula (I) is 1-[2,6- Cl_2 4- CF_3

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phenyl]3-CN 4-[SO-CF₃]5-NH₂ pyrazole or 1-[2,6-Cl₂ 4-CF₃
phenyl]3-CN 4-[SO-C₂H₅]5-NH₂ pyrazole.

15. The spot-on composition according to claim 1,
wherein the compound of formula (I) is 1-[2,6-Cl₂ 4-CF₃
5 phenyl]3-CN 4-[SO-CF₃]5-NH₂ pyrazole.

16. The spot-on composition according to any one of
claims 1 to 15, wherein the compound (B) is:

chlorfluazuron;

cyromazine;

10 diflubenzuron;

fluazuron;

flucycloxuron;

flufenoxuron;

hexaflumuron;

15 lufenuron;

tebufenozide;

teflubenzuron;

triflumuron;

20 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-
(trifluoromethyl)) phenylurea; or 1-(2,6-difluorobenzoyl)-3-
(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)) phenylurea.

17. The spot-on composition according to claim 16,
wherein the compound (B) is:

chlorfluazuron;

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cyromazine;

diflubenzuron;

fluazuron;

flucycloxuron;

5 flufenoxuron;

hexaflumuron;

tebufenozide;

triflumuron;

10 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)) phenylurea; or 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)) phenylurea.

18. The spot-on composition according to any one of claims 1 to 15, wherein the compound (B) is lufenuron, cyromazine, or 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)) phenylurea.

19. The spot-on composition according to any one of claims 1 to 15, wherein the compound (B) is novaluron.

20. The spot-on composition according to any one of claims 1 to 19, wherein the proportions, by weight, of compounds (A) and compounds (B) are between 80/20 and 20/80.

21. The spot-on composition according to any one of claims 1 to 20, wherein the fluid vehicle and the concentration of compounds (A) and (B) are for application by a spot-on type deposit on the skin.

25 22. The spot-on composition according to any one of claims 1 to 20, wherein the fluid vehicle and the

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concentration of compounds (A) and (B) are for application by a local pour-on type deposit to the skin.

23. The spot-on composition according to claim 21, wherein the fluid vehicle and the concentration of compounds (A) and (B) are for localized application to a surface area of less than 10 cm².

24. The spot-on composition according to claim 23, wherein the surface area is between 5 and 10 cm².

25. The spot-on composition according to claim 23 or 24, wherein the application is localized at two points.

26. The spot-on composition according to any one of claims 23 to 25, wherein the application is localized between the shoulders of the small mammal.

27. The spot-on composition according to any one of claims 1 to 26, which contains a dose of from 0.1 to 40 mg/kg of compound (A) and from 0.1 to 40 mg/kg of compound (B), based on the weight of the small mammal.

28. The spot-on composition according to claim 27, which contains a dose of from 1 to 20 mg/kg of compound (A) and from 1 to 30 mg/kg of compound (B), based on the weight of the small mammal.

29. The spot-on composition according to claim 28, which contains a dose of from 2 to 10 mg/kg of compound (A) and from 2 to 20 mg/kg of compound (B), based on the weight of the small mammal.

30. The spot-on composition according to any one of claims 1 to 29, which also comprises a crystallization inhibitor (b).

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31. The spot-on composition according to claim 30, wherein the crystallization inhibitor is present in a proportion of from 1 to 20% (W/V).

32. The spot-on composition according to claim 30,
5 wherein the crystallization inhibitor is present in a proportion of from 5 to 15% (W/V).

33. The spot-on composition according to any one of claims 30 to 32, wherein the crystallization inhibitor (b) is:

- 10 - polyvinylpyrrolidone, polyvinyl alcohol, copolymer of vinyl acetate and vinylpyrrolidone, polyethylene glycol, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan ester, lecithin, sodium carboxymethyl cellulose, or an acrylic derivative;
- 15 - an anionic surfactant;
- a cationic surfactant;
- an amine salt of formula $N^+R'R''R'''$ in which the radicals R are optionally hydroxylated hydrocarbon radicals;
- a non-ionic surfactant;
- 20 - an amphoteric surfactant; or
- a mixture of at least two of these crystallization inhibitors.

34. The spot-on composition according to claim 33, wherein the acrylic derivative is a methacrylate.

25 35. The spot-on composition according to claim 33, wherein the anionic surfactant is selected from the group consisting of alkaline stearates, calcium stearate,

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triethanolamine stearate, sodium abietate, alkyl sulphates, sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate, and fatty acids.

36. The spot-on composition according to claim 35,
5 wherein the alkyl sulphates are selected from the group consisting of sodium lauryl sulphate and sodium cetyl sulphate.

37. The spot-on composition according to claim 35, wherein the fatty acids are those derived from coconut oil.

10 38. The spot-on composition according to claim 33, wherein the cationic surfactant is a water-soluble quaternary ammonium salt of formula $N^+R'R''R'''R''''$, Y^- in which the radicals R' , R'' , R''' and R'''' are optionally hydroxylated hydrocarbon radicals, and Y^- is an anion of a strong acid.

15 39. The spot-on composition according to claim 38, wherein Y^- is a halogen anion, sulphate or sulphonate.

40. The spot-on composition according to claim 33, wherein the cationic surfactant is cetyltrimethylammonium bromide.

20 41. The spot-on composition according to claim 33, wherein the amine salt is octadecylamine chlorhydrate.

42. The spot-on composition according to claim 33, wherein the non-ionic surfactant is selected from the group consisting of optionally polyoxyethylenated sorbitan esters,
25 polyoxyethylenated alkyl esters, polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, and copolymers of ethylene oxide and propylene oxide.

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43. The spot-on composition according to claim 42, wherein the sorbitan ester is Polysorbate 80.

44. The spot-on composition according to claim 33, wherein the amphoteric surfactant is a substituted lauryl
5 compound of betaine.

45. The spot-on composition according to any one of claims 30 to 44, which comprises a crystallization inhibitor couple formed by a combination of a film-forming agent of polymeric type and a surfactant.

10 46. The spot-on composition according to claim 45, wherein the film-forming agent of polymeric type and the surfactant are present in close or identical quantities within the limit of the total quantities of crystallization inhibitor.

15 47. The spot-on composition according to claim 45 or 46, wherein the film-forming agent is selected from the group consisting of:

- the various grades of polyvinylpyrrolidone,
- polyvinyl alcohols, and

20 - copolymers of vinyl acetate and vinyl pyrrolidone,

and wherein the surfactant is a non-ionic surfactant.

48. The spot-on composition according to claim 47,
25 wherein the non-ionic surfactant is a polyoxyethylenated sorbitan ester.

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49. The spot-on composition according to claim 47, wherein the non-ionic surfactant is one of the various grades of polysorbate.

50. The spot-on composition according to any one of
5 claims 1 to 49, which also comprises an organic solvent (c) having a dielectric constant of between 10 and 35.

51. The spot-on composition according to claim 50, wherein the dielectric constant is between 20 and 30.

52. The spot-on composition according to claim 50 or
10 51, wherein the organic solvent has a content in the overall composition representing the complement to 100% of the composition.

53. The spot-on composition according to any one of
claims 50 to 52, wherein the organic solvent (c) is acetone,
15 acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether,
20 liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, diethylene glycol monoethyl ether, ethylene glycol, diethyl phthalate, or a mixture of at least two of these solvents.

54. The spot-on composition according to claim 53,
25 wherein the 2-pyrrolidone is N-methyl pyrrolidone.

55. The spot-on composition according to any one of
claims 50 to 53, which also comprises an organic co-solvent (d) having a boiling point below 100°C, and having a dielectric constant of between 10 and 40, which is miscible

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with water, with the solvent (c), or with both water and the solvent (c).

56. The spot-on composition according to claim 55, wherein the organic co-solvent (d) has a boiling point below 5 80°C.

57. The spot-on composition according to claim 55 or 56, wherein the dielectric constant is between 20 and 30.

58. The spot-on composition according to any one of claims 55 to 57, wherein the solvent (c) is present in a 10 co-solvent (d)/solvent (c) weight/weight (W/W) ratio of between 1/15 and 1/2.

59. The spot-on composition according to any one of claims 55 to 57, wherein the co-solvent (d) is absolute ethanol, isopropanol, or methanol.

15 60. The spot-on composition according to any one of claims 1 to 59, wherein the ectoparasites are ticks.

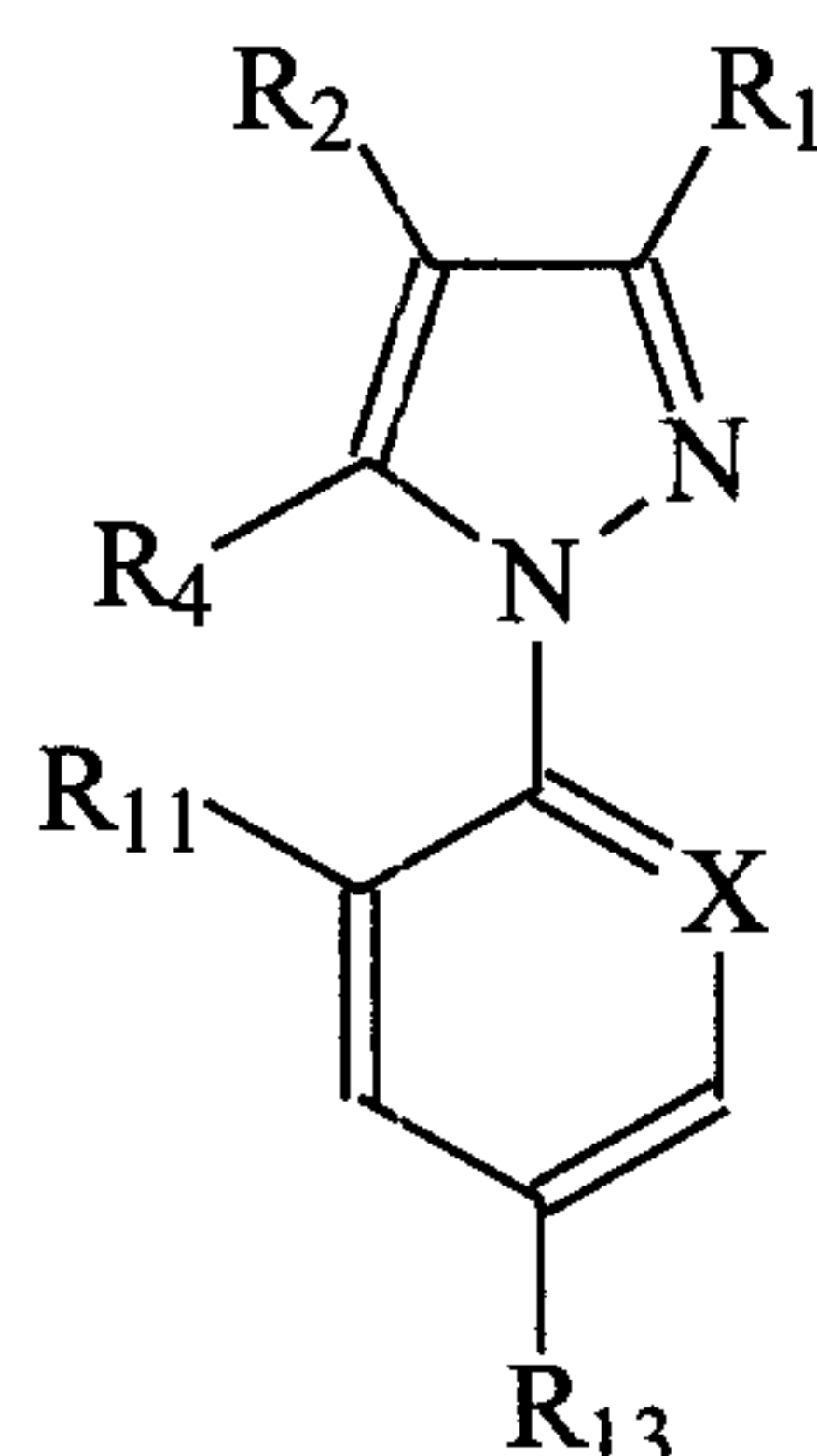
61. The spot-on composition according to any one of claims 1 to 29, which provides protection for 2 to 3 months.

62. A kit comprising the spot-on composition according 20 to any one of claims 1 to 60, wherein said kit comprises separately, in the same packaging, at least one container containing the compound (A) and at least one container containing the compound (B), and written instructions specifying that the compounds contained in the containers 25 are to be used alternatively, at an interval of at least one month.

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63. Use of at least one compound (A) of formula (I)



(I)

in which:

R_1 is CN or methyl or a halogen atom;

5 R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl or haloalkyl;

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$ or $C(O)O-R_7$, alkyl, haloalkyl
10 or OR_8 or a radical $-N=C(R_9)(R_{10})$;

R_5 and R_6 independently represent a hydrogen atom; an alkyl radical, haloalkyl, $C(O)$ alkyl, or alkoxycarbonyl; $S(O)_rCF_3$; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent
15 hetero atoms;

R_7 represents an alkyl or haloalkyl radical;

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

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R_{10} represents a phenyl or heteroaryl group, which is unsubstituted or substituted with at least one halogen atom or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R_{11} and R_{12} represent, independently of one another,
5 a hydrogen or halogen atom, or CN or NO_2 ;

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $\text{S}(\text{O})_q\text{CF}_3$ or SF_5 group;

m , n , q and r represent, independently of one another, an integer equal to 0, 1 or 2;

10 X represents a trivalent nitrogen atom or a radical $\text{C}-R_{12}$, the other three valence positions of the carbon atom forming part of the aromatic ring;

on the condition that, when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2 , R_{11} is Cl, R_{13} is CF_3 and X is N;
15 or R_2 is 4,5-dicyanoimidazol-2-yl, R_4 is Cl, R_{11} is Cl, R_{13} is CF_3 and X is $=\text{C}-\text{Cl}$;

and of at least one compound (B) which is a chitin-synthesis inhibitor,

in the preparation of a spot-on composition for
20 local application to the skin, for protection against ectoparasites on a small mammal for a duration of at least one month.

64. The use according to claim 63, wherein the small mammal is a dog or a cat.

25 65. The use according to claim 63 or 64, wherein:

R_1 is CN or methyl;

R_2 is $\text{S}(\text{O})_n\text{R}_3$;

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R_3 is alkyl or haloalkyl;

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$;

5 R_5 and R_6 independently represent a hydrogen atom; an alkyl, haloalkyl or $C(O)$ alkyl radical; $S(O)_rCF_3$; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms;

R_7 represents an alkyl or haloalkyl radical;

10 R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

R_{10} represents a phenyl or heteroaryl group unsubstituted or substituted with at least one halogen atom
15 or OH, -O-alkyl, -S-alkyl, cyano, or alkyl;

R_{11} and R_{12} represent, independently of one another, a hydrogen or halogen atom;

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

20 m , n , q and r represent, independently of one another, an integer equal to 0, 1 or 2; and

X represents a trivalent nitrogen atom or a radical $C-R_{12}$, the other three valency positions of the carbon atom forming part of the aromatic ring;

25 provided that, when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2 , R_{11} is Cl, R_{13} is CF_3 and X is N.

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66. The use according to any one of claims 63 to 65, wherein the divalent hetero atom is oxygen or sulphur.

67. The use according to any one of claims 63 to 66, wherein R_1 is CN.

5 68. The use according to any one of claims 63 to 67, wherein R_{13} is haloalkyl.

69. The use according to claim 68, wherein R_{13} is CF_3 .

70. The use according to any one of claims 63 to 69, wherein R_2 is $S(O)_nR_3$, n and R_3 having the definition found in
10 claim 63.

71. The use according to claim 70, wherein $n = 1$ and R_3 is CF_3 or an alkyl group.

72. The use according to claim 71, wherein R_3 is methyl or ethyl.

15 73. The use according to claim 70, wherein $n = 0$ and R_3 is CF_3 .

74. The use according to any one of claims 63 to 73, wherein X is C- R_{12} with R_{12} being a halogen atom.

75. The use according to any one of claims 63 to 70,
20 wherein R_1 is CN, R_3 is haloalkyl, R_4 is NH_2 , R_{11} and R_{12} are, independently of one another, a halogen atom, and R_{13} is haloalkyl.

76. The use according to claim 63, wherein the compound of formula (I) is 1-[2,6- Cl_2 4- CF_3 phenyl]3-CN
25 4-[SO- CF_3]5- NH_2 pyrazole or 1-[2,6- Cl_2 4- CF_3 phenyl]3-CN
4-[SO- C_2H_5]5- NH_2 pyrazole.

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77. The use according to claim 63, wherein the compound of formula (I) is 1-[2,6-Cl₂ 4-CF₃ phenyl]3-CN 4-[SO-CF₃]5-NH₂ pyrazole.

78. The use according to any one of claims 63 to 77,
5 wherein the compound (B) is:

chlorfluazuron;

cyromazine;

diflubenzuron;

fluazuron;

10 flucycloxuron;

flufenoxuron;

hexaflumuron;

lufenuron;

tebufenozide;

15 teflubenzuron;

triflumuron;

1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)) phenylurea; or 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)) phenylurea.

20 79. The use according to claim 78, wherein the compound (B) is:

chlorfluazuron;

cyromazine;

diflubenzuron;

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fluazuron;

flucycloxuron;

flufenoxuron;

hexaflumuron;

5 tebufenozide;

triflumuron;

1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)) phenylurea; or 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)) phenylurea.

10 80. The use according to any one of claims 63 to 77,
wherein the compound (B) is lufenuron, cyromazine, or
1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl))
phenylurea.

15 81. The use according to any one of claims 63 to 77,
wherein the compound (B) is novaluron.

82. The use according to any one of claims 63 to 80,
wherein the proportions, by weight, of compounds (A) and
compounds (B) are between 80/20 and 20/80.

20 83. The use according to any one of claims 63 to 82,
wherein the composition and the concentration of
compounds (A) and (B) are for application by a spot-on type
deposit on the skin.

25 84. The use according to any one of claims 63 to 82,
wherein the composition and the concentration of
compounds (A) and (B) are for application by a local pour-on
type deposit to the skin.

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85. The use according to claim 83, wherein the composition and the concentration of compounds (A) and (B) are for localized application to a surface area of less than 10 cm².

5 86. The use according to claim 85, wherein the surface area is between 5 and 10 cm².

87. The use according to claim 85 or 86, wherein the application is localized at two points.

88. The use according to any one of claims 85 to 87,
10 wherein the application is localized between the shoulders of the small mammal.

89. The use according to any one of claims 63 to 88, wherein the composition contains a dose of from
0.1 to 40 mg/kg of compound (A) and from 0.1 to 40 mg/kg of
15 compound (B), based on the weight of the small mammal.

90. The use according to claim 89, wherein the composition contains a dose of from 1 to 20 mg/kg of compound (A) and from 1 to 30 mg/kg of compound (B), based on the weight of the small mammal.

20 91. The use according to claim 90, wherein the composition contains a dose of from 2 to 10 mg/kg of compound (A) and from 2 to 20 mg/kg of compound (B), based on the weight of the small mammal.

92. The use according to any one of claims 63 to 91,
25 wherein the composition also comprises a crystallization inhibitor (b).

93. The use according to claim 92, wherein the crystallization inhibitor is present in a proportion of from 1 to 20% (W/V).

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94. The use according to claim 92, wherein the crystallization inhibitor is present in a proportion of from 5 to 15% (W/V).

95. The use according to any one of claims 92 to 94,
5 wherein the crystallization inhibitor (b) is:

- polyvinylpyrrolidone, polyvinyl alcohol, copolymer of vinyl acetate and vinylpyrrolidone, polyethylene glycol, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan ester, lecithin,
10 sodium carboxymethyl cellulose, or an acrylic derivative;
- an anionic surfactant;
- a cationic surfactant;
- an amine salt of formula $N^+R'R''R'''$ in which the radicals R are optionally hydroxylated hydrocarbon radicals;
- 15 - a non-ionic surfactant;
- an amphoteric surfactant;

or a mixture of at least two of these crystallization inhibitors.

96. The use according to claim 95, wherein the acrylic
20 derivative is a methacrylate.

97. The use according to claim 95, wherein the anionic surfactant is selected from the group consisting of alkaline stearate, calcium stearate, triethanolamine stearate, sodium abietate, alkyl sulphates, sodium dodecylbenzenesulphonate,
25 sodium dioctylsulphosuccinate, and fatty acids.

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98. The use according to claim 97, wherein the alkyl sulphates are selected from the group consisting of sodium lauryl sulphate and sodium cetyl sulphate.

99. The use according to claim 97, wherein the fatty
5 acids are those derived from coconut oil.

100. The use according to claim 95, wherein the cationic surfactant is a water-soluble quaternary ammonium salt of formula $N^+R'R''R'''R''''$, Y^- in which the radicals R' , R'' , R''' and R'''' are optionally hydroxylated hydrocarbon
10 radicals, and Y^- is an anion of a strong acid.

101. The use according to claim 100, wherein Y^- is a halogen anion, sulphate or sulphonate.

102. The use according to claim 95, wherein the cationic surfactant is cetyltrimethylammonium bromide.

15 103. The use according to claim 95, wherein the amine salt is octadecylamine chlorhydrate.

104. The use according to claim 95, wherein the non-ionic surfactant is selected from the group consisting of optionally polyoxyethylenated sorbitan esters,
20 polyoxyethylenated alkyl esters, polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, and copolymers of ethylene oxide and propylene oxide.

25 105. The use according to claim 104, wherein the sorbitan ester is Polysorbate 80.

106. The use according to claim 95, wherein the amphoteric surfactant is a substituted lauryl compound of betaine.

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107. The use according to any one of claims 92 to 106, which comprises a crystallization inhibitor couple formed by a combination of a film-forming agent of polymeric type and a surfactant.

5 108. The use according to claim 107, wherein the film-forming agent of polymeric type and the surfactant are present in close or identical quantities within the limit of the total quantities of crystallization inhibitor.

109. The use according to claim 107 or 108, wherein the
10 film-forming agent is selected from the group consisting of:

- the various grades of polyvinylpyrrolidone,
- polyvinyl alcohols, and
- copolymers of vinyl acetate and vinyl
pyrrolidone,

15 and wherein the surfactant is a non-ionic surfactant.

110. The use according to claim 109, wherein the non-ionic surfactant is a polyoxyethylenated sorbitan ester.

111. The use according to claim 109, wherein the non-
20 ionic surfactant is one of the various grades of polysorbate.

112. The use according to any one of claims 63 to 111, which also comprises an organic solvent (c) having a dielectric constant of between 10 and 35.

25 113. The use according to claim 112, wherein the dielectric constant is between 20 and 30.

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114. The use according to claim 112 or 113, wherein the organic solvent has a content in the overall composition representing the complement to 100% of the composition.

115. The use according to any one of claims 112 to 114,
5 wherein the organic solvent (c) is acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether,
10 monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, diethylene glycol monoethyl ether, ethylene glycol, diethyl phthalate, or a mixture of at least two of these solvents.

15 116. The use according to claim 115, wherein the 2-pyrrolidone is N-methyl pyrrolidone.

117. The use according to any one of claims 112 to 115, which also comprises an organic co-solvent (d) having a boiling point below 100°C, and having a dielectric constant
20 of between 10 and 40, which is miscible with water, with the solvent (c), or with both water and the solvent (c).

118. The use according to claim 117, wherein the organic co-solvent (d) has a boiling point below 80°C.

119. The use according to claim 117 or 118, wherein the
25 dielectric constant is between 20 and 30.

120. The use according to any one of claims 117 to 119, wherein the solvent (c) is present in a co-solvent (d)/solvent (c) weight/weight (W/W) ratio of between 1/15 and 1/2.

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121. The use according to any one of claims 117 to 119,
wherein the co-solvent (d) is absolute ethanol, isopropanol,
or methanol.

122. The use according to any one of claims 63 to 91,
5 wherein the composition provides protection
for 2 to 3 months.

123. The use according to any one of claims 63 to 122,
wherein the ectoparasites are ticks.

124. The use according to any one of claims 63 to 122,
10 wherein the ectoparasites are fleas.

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