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(54) Title: DINOTEFURAN LIQUID FLEA AND TICK TREATMENT

(57) Abstract: There is provided in accordance with an embodiment of the disclosure a spray-on composition for the treatment and prevention of insect or arachnid infestation on a mammal comprising between 0.1% and 1.0% by weight dinotefuran. There is also provided in accordance with an embodiment of the disclosure a method for treatment of an animal at risk of insect or arachnid infestation comprising topically administering to the coat of the animal a composition comprising between 1 and 50 mg dinotefuran per kilogram of animal weight. Optionally, topically administering includes spraying on a majority of the area of the coat of the animal.

WO 2017/187435 A1

DINOTEFURAN LIQUID FLEA AND TICK TREATMENT

RELATED APPLICATIONS

[0001] The present application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application 62/326,756 filed on April 24, 2016, the disclosure of which is incorporated herein by reference.

FIELD

[0002] Embodiments of the invention relate to compositions comprising dinotefuran and methods of treatment of infestation using them.

BACKGROUND

[0003] Dogs, cats and other household pets may become infested by ectoparasites (surface dwelling parasites) known as fleas and ticks. Common fleas which affect pets include the cat flea (Ctenocephalides felis) and the dog flea (Ctenocephalides canis). Fleas tend to feed on the blood of pets causing discomfort to the animal. Fleas may also bite humans, causing irritation and potentially causing allergic reactions.

[0004] Rhipicephalus sanguineus, the brown dog tick, is a tick commonly found on dogs in a household setting. It has been implicated in causing diseases such as babesiosis and ehrlichiosis in dogs and diseases such as Rocky Mountain spotted fever in humans.

[0005] Other insects can be harmful to humans and mammals, such as flies.

SUMMARY

[0006] An aspect of an embodiment of the invention relates to compositions comprising dinotefuran, known chemically as 1-Methyl-2-nitro-3-((tetrahydrofuran-3-yl)methyl)guanidine. The compositions are optionally in liquid form and may be used to cure and/or prevent insect and/or arachnid infestations in animals, including, but not limited to, cats and dogs. According to an embodiment of the invention, compositions comprise between 0.1% and 1% by weight of active dinotefuran in the composition.

[0007] Dinotefuran is a nicotinic acetylcholine receptor inhibitor which acts to disrupt nervous systems of insects. Dinotefuran-comprising compositions have been disclosed in WO 2014/060960, incorporated herein by reference.

[0008] According to an embodiment of the invention, the compositions are topically applied to animals being treated. Optionally topical application may be spraying on the hair/fur of the animal. The compositions may be applied to the fur of a majority of the surface of an animal until the fur is wet.

[0009] Embodiments of the invention relate to compositions comprising dinotefuran in low doses, relative to previously known dinotefuran-containing compositions. Compositions according to embodiments of the invention are advantageous in that they have been shown to provide long-lasting, highly effective protection against fleas and ticks when applied to animals. Even after multiple washing of the animals after administration of the compositions, the compositions remain effective to prevent future infestation of the animals for a month subsequent to administration. Compositions according to embodiments of the invention have been shown to be effective and safe in treating young animals including puppies and kittens.

[0010] In the discussion unless otherwise stated, adjectives such as "substantially" and "about" modifying a condition or relationship characteristic of a feature or features of an embodiment of the invention, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended. Unless otherwise indicated, the word "or" in the specification and claims is considered to be the inclusive "or" rather than the exclusive or, and indicates at least one of, or any combination of items it conjoins.

[0011] This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF FIGURES

[0012] Non-limiting examples of embodiments of the disclosure are described below with reference to figures attached hereto that are listed following this paragraph. Identical structures, elements or parts that appear in more than one figure are generally labeled with a same numeral in all the figures in which they appear. Dimensions of components and features shown in the figures are chosen for convenience and clarity of presentation and are not necessarily shown to scale.

[0013] Fig. 1 shows a data table of flea and tick counts for animals treated with a dinotefuran spray composition in accordance with an embodiment of the disclosure;

[0014] Fig. 2A shows a data plot showing mean flea counts over a 30-day course of treatment with a dinotefuran spray composition in accordance with an embodiment of the disclosure; and

[0015] Fig. 2A shows a data plot showing mean tick counts over a 30-day course of treatment with a dinotefuran spray composition in accordance with an embodiment of the disclosure.

DETAILED DESCRIPTION

[0016] In the detailed description below, compositions according to embodiments of the invention, methods of their manufacture, and methods of treatment comprising using the compositions for treatment of flea and tick infestation are described.

[0017] Example 1A – Manufacture of dinotefuran compositions.

[0018] Dinotefuran compositions are manufactured by combining the ingredients listed in table 1.

[0019] Table 1:

Component	Function	CAS number
Dinotefuran	Active	165252-70-0
Isopropyl Alcohol	Solvent	67-63-0
Polyvinylpyrrolidone (PVP)	Film-forming agent	9003-39-8
Armid® FMPC	Co-solvent	4394-85-8 and 108-32-7
Butylated Hydroxytoluene (BHT)	Stabilizer	128-37-0

[0020] The solvent blend Armid® FMPC is manufactured by Akzo Nobel (www.akzonobel.com) and is based on a blend of morpholine derivative with propylene carbonate. Armid® FMPC is a commercially available material comprising N-formyl morpholine (80.0% by weight) and Propylene carbonate (20.0% by weight), and is highly soluble in many other solvents such as water, propylene glycol, xylene, vegetable oil and mineral oil.

[0021] Additional dinotefuran spray-on compositions:

[0022] Alternate dinotefuran compositions according to embodiments of the invention may be prepared as described in Example 1A, with modifications as described in the following section. Compositions were prepared using the excipients in weight percent described in Table 2 below:

[0023] Table 2:

Component	Comp 1	Comp 2	Comp 3	Comp 4	Comp 5
Dinotefuran	0.25	0.1	0.5	0.75	1.0
Isopropyl Alcohol	until 100	until 100	until 100	until 100	until 100
Polyvinylpyrrolidone (PVP)	2.5	2.5	0	5	0
Armid® FMPC	2	0	5	5	5
Butylated Hydroxytoluene (BHT)	0.001	0.001	0	0.001	0

[0024] As shown in Table 2, compositions according to embodiments of the invention may comprise between 0.1% and 1% dinotefuran by weight. Preferred compositions according to embodiments of the invention comprise between 0.20% and 0.30% by weight dinotefuran. Preferred compositions according to embodiments of the invention comprise 0.25% by weight dinotefuran.

[0025] Alternate dinotefuran compositions according to embodiments of the invention were prepared with other solvents other than isopropyl alcohol. Other alcohols may be used in addition to or instead of isopropyl alcohol. Exemplary alcohols which may be used include alone or in combination comprise: ethanol, methanol, 1-propanol, 1,3-propanediol, benzyl alcohol, n-butanol, isobutanol, tert-amyl alcohol and 2-butanol. Table 3 lists dinotefuran compositions comprising other solvents:

[0026] Table 3:

Component	Comp 6	Comp 7	Comp 8	Comp 9	Comp 10
Dinotefuran	1.0	1.0	1.0	1.0	1.0
Solvent	Benzyl alcohol until 100	Ethanol until 100	Methanol until 100	Isobutanol until 100	2-butanol until 100

Polyvinylpyrrolidone (PVP)	2.5	2.5	5	2.5	5
Armid® FMPC	0	0	2	0	2
Butylated Hydroxytoluene (BHT)	0.001	0.001	0.001	0.001	0.001

[0027] Amounts of alcohol in dinotefuran compositions according to embodiments of the invention may be used to ensure that compositions are sprayable using a pump spray bottle and that active ingredients may be dissolved in the compositions. Amount of alcohol in dinotefuran compositions may range from 50% to 98%, according to embodiments of the invention. Amount of alcohol in dinotefuran compositions may range from 90% to 96%, according to embodiments of the invention.

[0028] PVP is an alcohol-soluble polymer which in the compositions described herein, assists in adhering dinotefuran to the coat of the animal to which the compositions are being administered. In compositions according to embodiment of the invention, PVP acts as a film-forming polymer, as it assists in a film being formed on the coat of an animal after evaporation of the alcohol solvent from compositions. Other polymers suitable for use in compositions according to embodiments of the invention include, but are not limited to: polyurethane resins, cellulose acetate butyrate resins, cellulose acetate propionate resins and polyamide resin.

[0029] Amounts of film-forming polymer in dinotefuran compositions according to embodiments of the invention may be used to ensure that compositions are sprayable using a pump spray bottle and that active ingredients adhere to the coats of animals being treated. Amount of film-forming polymer in dinotefuran compositions may range from 1% to 10% according to embodiments of the invention. Amount of film-forming polymer in dinotefuran compositions may range from 2% to 5% according to embodiments of the invention. Compositions according to embodiments of the invention having varied amounts of film-forming polymer are described in Table 4.

[0030] Table 4:

Component	Comp 11	Comp 12	Comp 13	Comp 14	Comp 15
Dinotefuran	1.0	1.0	1.0	1.0	1.0
Ethanol	until 100	until 100	until 100	until 100	until 100

PVP	5	0	1	2.5	10
Armid® FMPC	5	5	5	5	2
Butylated Hydroxytoluene (BHT)	0.001	0.001	0.001	0.001	0.001

[0031] Armid® FMPC, as mentioned above, acts as a co-solvent to assist dissolution of dinotefuran in compositions according to embodiments of the invention. In addition to or in place of Armid® FMPC, other co-solvents may be used to assist in dissolution of dinotefuran in compositions. For example, isophorone, a cyclic ketone, and methylpyrrolidone may be used. Other combinations of N-formyl morpholine and propylene carbonate may be used as solvents in ratios other than those in Armid® FMPC such as, but not limited to, 95:5, 90:10, 75:25 and 70:30.

[0032] Compositions according to embodiments of the invention may be free of a co-solvent. Alternatively, compositions may comprise between 0% and 20% co-solvent.

[0033] Compositions according to embodiments of the invention comprising alternate co-solvents in varying amounts (or no co-solvents) are described in Table 5:

[0034] Table 5:

Component	Comp 16	Comp 17	Comp 18	Comp 19	Comp 20
Dinotefuran	0.25	0.25	0.25	1.0	0.25
Isopropanol	until 100	until 100	until 100	until 100	until 100
PVP	2	2	2	2	2
Co-solvent	Armid 0	N-methyl-2-pyrrolidone 2	Armid 2	Armid 5	Armid 15
Butylated Hydroxytoluene (BHT)	0.001	0.001	0.001	0.001	0.001

[0035] BHT is used in small quantities in compositions according to embodiments of the invention. BHT acts as a stabilizer/ preservative. Alternative stabilizer may be used. A preferred amount of stabilizer is between 0.0001% and 0.01% by weight.

[0036] Compositions according to embodiments of the invention may comprise an insect growth regulator (IGR). An IGR is a compound which targets parasites during juvenile stages such as eggs and/or larvae. The IGR may be a hormonal mimetic or a chitin synthesis inhibitor. The IGR may comprise azadirachtin, hydroprene, triflumuron, pyriproxyfen and/or methoprene. The composition may comprise between 0.1% and 10% IGR. Compositions comprising insect growth regulator are described in table 6.

[0037] Table 6:

Component	Comp 21	Comp 22	Comp 23	Comp 24	Comp 25
Dinotefuran	0.25	0.3	0.25	0.35	0.3
Isopropanol	until 100	until 100	until 100	until 100	until 100
PVP	2.5	5	5	2.5	5
Armid® FMPC	2	0	1	1	0
IGR	Methoprene 0.1	Methoprene 1	Pyriproxyfen 0.1	Pyriproxyfen 1	Methoprene 5
BHT	0.001	0.001	0.001	0.001	0.001

[0038] Synergists can be used in compositions comprising dinotefuran according to embodiments of the invention. A synergist which may be used is piperonyl butoxide (PBO). Other synergists include piperonyl sulfoxide and sesoxane. Synergists may be present in concentrations of up to 5% by weight. Synergist compositions are prepared in accordance with Table 7.

[0039] Table 7:

Component	Comp 26	Comp 27	Comp 28	Comp 29	Comp 30
Dinotefuran	0.25	0.3	0.3	0.25	0.2
Isopropanol	until 100	until 100	until 100	until 100	until 100
PVP	2.5	5	2.5	5	2.5
Armid® FMPC	0	1	2	4	4
PBO	2	1	0.1	0.5	5
BHT	0.001	0.001	0.001	0.001	0.001

[0040] Compositions according to embodiments of the invention may comprise flumethrin. Flumethrin may be present in the composition as an additional insecticide to act synergetically with dinotefuran. According to an embodiment of the invention, the ratio between dinotefuran

(by weight) is between 4:1 and 2:1. According to an embodiment of the invention, the ratio between dinotefuran (by weight) is between 40:1 and 10:1, preferably between 30:1 and 15:1.

[0041] Example 1B: Stability testing of Dinotefuran Compositions

[0042] Compositions described in Example A were prepared and stored in a sealed spray bottle comprising 420 milliliters (ml), at 25° Celsius (C) at 60% relative humidity. Bottle content and dinotefuran concentration were tested soon after bottling and further tested at 12, 24 and 36 months after bottling. The results indicate that the bottle content and dinotefuran concentration remained constant with a variation of less than 2% between initial observation and 36 months post-bottling.

[0043] Example 2A: Use of Dinotefuran Composition on Animals for Prevention and Treatment of Flea and Tick Infestation

[0044] The studies performed in the following examples were based on EMEA/CVMP/EWP/005 "Guideline for the Testing and Evaluation of the Efficacy of Antiparasitic Substances for the Treatment and Prevention of Tick and Flea Infestation in Dogs and Cats", OPPTS 870.7200 “Companion Animal Safety”; and was performed with the approach to the OECD Principles of Good Laboratory Practice Directive 2004/10/EC and US FDA Good Laboratory Practice Regulations, 21 CFR Part 58.

[0045] The following compositions were tested on animals: a Placebo composition and a composition having 0.25% by weight dinotefuran.

[0046] Cats and dogs were used for testing efficacy of the compositions as compared with Placebo. Composition and Placebo were administered using a pump spray dispenser, dispensing 1.2 ml per pump. The animals were coated until the fur was damp to thoroughly wet. Administration amounts of Comp 1 in pumps per kilogram (kg) bodyweight, ml of composition per kg, milligram (mg) of composition per kg, and mg of active dinotefuran per kg are detailed as follows in Table 8:

[0047] Table 8:

Type of animal	Pumps per kilogram	ml/kg	g/kg (composition)	mg/kg (dinotefuran)
Short-haired animals	2	2.4	1.9	4.7
Long-haired or dense-coat animals	5	6.0	4.7	12

[0048] Animals used in the study were all short- haired animals. Animals were divided into two groups, treatment group and placebo group. The treatment group consisted of 6 adult dogs and 6 adult cats. The placebo group consisted of 2 adult dogs and 2 adult cats.

[0049] Flea and ticks in the treatment and placebo groups were counted by visual observation shortly before administration and at the following intervals following administration: 24 hours, 72 hours, 10 days (prior to reinfestation) 20 days and 30 days. Visual observation for parasitic counting was performed by the same veterinarian for all animals.

[0050] Animals were also observed for clinical observations daily by a veterinarian to detect: changes in skin and fur, eyes and mucous membranes, respiratory system, circulatory system, autonomic and central nervous system, somatomotor activity, and behavior pattern. Particular attention was directed to observations of central nervous system signs (seizures, tremors, salivation), vomiting and diarrhea. All animals were individually weighed at initiation and at the end of the study.

[0051] On day 1, animals in the treatment and placebo groups were administered treatment or placebo respectively. Animals were re-infested 10 days after treatment with 50 fleas and 50 ticks each, to test the long-lasting effects of the compositions. Animals were washed once daily with water.

[0052] The efficacy of treatment was calculated as percent efficacy compared with the original flea or tick count, and was calculated according to the formula: ((mean of original flea or tick count - mean flea or tick count after treatment) / mean of original flea or tick count) x 100%. Because animals were re-infested with 50 fleas after the counting at 10 days, the original flea or tick count was counted differently during the first 10 days compared to later counting days, at days 20 and 30. Up to and including the first 10 days, the original flea or tick count was the count of fleas or tick prior to treatment. Following day 10, at days 20 and 30, the original flea or tick counts was set at 50, is accordance with the number of re-infested fleas and ticks.

[0053] Fig. 1 shows a data table of flea and tick counts for the dinotefuran spray treatment group in a combined group of dogs and cats (n=12; 6 dogs and 6 cats).

[0054] Fig. 2A shows a data plot showing mean flea counts in the combined group over the 30-day course of the study The efficacy for the treatment group was at 100% after 72 hours, 10 days, and 20 days and at 99.6% after 30 days.

[0055] Fig. 2B shows mean tick counts in the same combined group of dogs and cats as in Fig. 2B (n=12; 6 dogs and 6 cats). The efficacy for the treatment group was at 100% (free of ticks) at days 3 and 10, 99.6% at day 20 and 97% at day 30.

[0056] As mentioned above, animals were re-infested at day 10 with 50 ticks and 50 fleas each. Nevertheless, the long-lasting effect of treatment prevented the fleas and ticks from remaining on the animals. This is evident from the counts at 20 and 30 days post-treatment, in which flea and tick counts were lower than at the initiation of the treatment despite the re-infestation.

[0057] No adverse reactions were found in any of the animals treated from the treatment group. The effect lasted long although the animals were washed during the trial, indicating that the tested compositions were an effective, waterproof treatment.

[0058] With respect to the Placebo group (n=4; 2 dogs and 2 cats; not shown), dogs and cats were treated with placebo as described. The number of fleas on dogs and cats in the placebo group was not significantly reduced through the 30-day course of the study. The number of ticks decreased somewhat over the course of the study, perhaps due to the daily washing (or a result of data jitter due to small sample size), but remained substantially higher than the number of ticks in the experimental group treated with the dinotefuran spray up to day 20, after which the tick count converged.

[0059] Example 2B: Safety of Dinotefuran Composition in Animals

[0060] The compositions comprising between 0.25% and 1% dinotefuran were administered to 6 dogs in a 5-fold dosage compared to the dosages administered in Example 2A (12 ml/kg) to test the safety of the active ingredient. 5-fold administration was performed by spraying on animals until wet, waiting until the animals dried, then spraying again until wet, waiting again until the animals and repeating until appropriate 5-fold amount was reached.

[0061] Dogs were weighted at the start and end of a 14 day trial. Dogs were administered Comp 1, topically, at day 0. Six dogs were tested, and of the 6 dogs, 2 were puppies. Dogs were tested according to the following parameters: changes in skin and fur, eyes and mucous membranes, respiratory system, circulatory system, autonomic and central nervous system, somatomotor activity, and behavior pattern. Particular attention was directed to observations of central nervous system signs (seizures, tremors, salivation), vomiting and diarrhea. The dog initial weight, ending weight (30 days after administration) were measured. The examinations took place on days 1, 2 and every alternate day until day 14.

[0062] A similar trial was performed in cats, rabbits and ferrets.

[0063] All animals passed the clinical observations satisfactorily. None of the animals showed signs of adverse reactions to the composition, indicating that the composition is safe, even if administered in a 5-fold excess dose. All of the dogs gained weight over the course of the trial, indicating that the composition is safe and does not cause weight loss in animals. Even puppies

(having initial weight of about 0.5 kg at start of study) did not show adverse effects after administration.

[0064] Blood was sampled from all of the animals tested before administration and after 15 days. Blood samples were tested for levels of urea, creatinine, alkaline phosphatase, alanine amino transferase, aspartate amino transferase and total bilirubin. Blood was taken by venipuncture from v. cephalica antebrachii. All animal showed no significant changes in blood levels between starting the trial and after 15 days.

[0065] This study indicates that the dinotefuran compositions are safe for use and even accidental overdose 5 times the tested dosage will not negatively impact animals, including 4 types of mammals tested.

[0066] Example 2C:

[0067] Testing on horses:

[0068] Compositions comprising between 0.2% and 1% by weight dinotefuran were sprayed on to horses effected with myiasis larvae infestation. Horses were cured from the myiasis infestation after topical administration. No side effects were evident after administration.

[0069] Methods of treatment:

[0070] Methods of treatment according to embodiments of the invention, comprise administering compositions described above to an animal in need thereof. According to an embodiment of the invention, the animal is a mammal. The mammal may be a dog, a cat, a ferret, a rabbit or a rodent. The rodent may be a rat, mouse, hamster, guinea pig, gerbil or chinchilla. The mammal may be a horse, a cow, a sheep or a pig.

[0071] The amounts of composition administered and dinotefuran administered per kg for short-haired and long-haired animals according to embodiments of the invention are tabulated below in table 9. The specific gravity of the compositions described in the tables below is about 0.79 g/ml :

[0072] Table 9, short haired animals:

Composition	Animal	ml composition per kg animal	grams composition per kg animal	mg dinotefuran per kg animal
Comp 2	Short Hair	2.4	1.9	1.9
Comp 1	Short Hair	2.4	1.9	4.7
Comp 5	Short Hair	2.4	1.9	19
Comp 2	Long Hair	6	4.7	4.7

Comp 1	Long Hair	6	4.7	12
Comp 5	Long Hair	6	4.7	47

[0073] According to an embodiment of the invention, methods of treatment comprise spraying the composition onto a majority of the surface area of an animal. According to an embodiment of the invention, the composition is sprayed on the entire coat of the animal, excluding the eye, mouth and nose area.

[0074] In the description and claims of the present application, each of the verbs, "comprise," "include" and "have," and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb.

[0075] Descriptions of embodiments of the invention in the present application are provided by way of example and are not intended to limit the scope of the invention. The described embodiments comprise different features, not all of which are required in all embodiments of the invention. Some embodiments utilize only some of the features or possible combinations of the features. Variations of embodiments of the invention that are described, and embodiments of the invention comprising different combinations of features noted in the described embodiments, will occur to persons of the art. The scope of the invention is limited only by the claims.

CLAIMS

1. A spray-on composition for the treatment and prevention of insect or arachnid infestation on a mammal comprising between 0.1% and 1.0% by weight dinotefuran.
2. The composition according to claim 1 further comprising a solvent.
3. The composition according to claim 1 or 2 wherein the solvent comprises one or more than one of: isopropyl alcohol, ethanol, methanol, 1-propanol, 1,3-propanediol, benzyl alcohol, n-butanol, isobutanol, tert-amyl alcohol, and 2-butanol.
4. The composition according to claim 3 wherein the solvent comprises isopropyl alcohol.
5. The composition according to any one of the previous claims wherein composition further comprises at least one film forming agent.
6. The composition according to claim 5, wherein the film-forming agent is selected from the group consisting of: polyvinylpyrrolidone, polyurethane resins, cellulose acetate butyrate resins, cellulose acetate propionate resins and polyamide resin.
7. The composition according to claim 5 or 6 wherein the film-forming agent is present in the composition in a concentration of 1% to 20% by weight.
8. The composition according to claim 7 wherein the film-forming agent comprises polyvinylpyrrolidone.
9. The composition according to any one of the previous claims further comprising a co-solvent.
10. The composition according to claim 9 wherein the co-solvent comprises N-formyl morpholine and propylene carbonate.
11. The composition according to claim 9 or 10 wherein the co-solvent is present in the compositions in an amount between 0.1% and 20% by weight.
12. The composition according to any one of the previous claims comprising between 0.2% and 0.5% by weight dinotefuran.
13. The composition according to claim 12 comprising 0.25% by weight dinotefuran.
14. The composition according to any one of the previous claims further comprising an insect growth regulator.
15. The composition according to claim 14 wherein the insect growth regulator comprises at least one of a hormonal mimetic or a chitin synthesis inhibitor.

16. The composition according to claim 14 wherein the insect growth regulator comprises at least one of azadirachtin, hydroprene, triflumuron, pyriproxyfen or methoprene.
17. The composition according to any one of claims 14, 15 or 16 wherein the insect growth regulator is present in the composition in an amount between 0.1% and 10% by weight.
18. The composition according to any one of the previous claims further comprising an additional insecticide.
19. The composition according to claim 18 wherein the additional insecticide is flumethrin.
20. The composition according to claim 19 wherein flumethrin is present in a ratio of dinotefuran to flumethrin of between 40:1 and 2:1 by weight.
21. The composition according to any one of the previous claims further comprising a synergist.
22. The composition according to claim 21 wherein the synergist is piperonyl butoxide.
23. The compositions according to claim 22 wherein piperonyl butoxide is present in an amount of between 0.1 and 5% by weight.
24. A spray bottle comprising the composition according to any one of the previous claims.
25. A method for treatment of an animal at risk of insect or arachnid infestation comprising topically administering to the coat of the animal a composition comprising between 1 and 50 mg dinotefuran per kilogram of animal weight.
26. The method according to claim 25 wherein the animal is selected from the group consisting of: dog, cat, ferret, rabbit, rat, mouse, hamster, guinea pig, gerbil, chinchilla, horse, cow, sheep and pig.
27. The method according to claim 25 or 26 wherein topically administering comprises spraying on a majority of the area of the coat of the animal.
28. The method according to any one of claims 25-27 comprising administering a dinotefuran-containing composition once in a period of 30 days.
29. The method according to any one of claims 25-28 further comprising washing the animal during the period of 30 days.
30. The method according to any one of claims 25-29 wherein the amount administered is between 1 and 20 mg dinotefuran per kilogram of animal.
31. The method according to claim 30 wherein the amount administered is between 2 and 6 mg dinotefuran per kilogram of animal.
32. The method according to claim 31 wherein the amount administered is between 4 and 5 mg dinotefuran per kilogram of animal.

33. The method according to any one of claims 25-32 wherein the composition further comprises a film-forming agent.
34. The method according to any one of claims 25-33 wherein at the time of administration, the animal suffers a flea or tick infestation.
35. The method according to any one of claims 25- 34 wherein administration comprises applying the composition to the fur of a majority of the surface of an animal until the fur is wet.

Table 1 First Study Group (Dogs and Cats) – Efficacy and Waterproof Study

ID		Weight (Kg) 19.08.15	Weight (Kg) 19.09.15	No of Pumps	Sex (M/F)	Number of Fleas/Ticks on the Animal: Initial Fleas	Initial Ticks	+24 hours Fleas	+24 hours Ticks	+72 hours Fleas	+72 hours Ticks	+10 days Fleas	+10 days Ticks	Re-infestation D10 Fleas	Re-infestation D10 Ticks	+20 days Fleas	+20 days Ticks	+30 days Fleas	+30 days Ticks
Dogs	11	11.4	12.1	23	M	4	11	1	2	0	0	0	0	50	50	0	0	1	6
	12	4.5	6.0	9	M	9	4	0	0	0	0	0	0	50	50	0	0	0	0
	13	9.7	10.3	19	M	14	2	2	0	0	0	0	0	50	50	0	2	0	5
	14	8.0	10.0	16	F	11	2	0	0	0	0	0	0	50	50	0	0	0	1
	15	7.3	9.6	15	F	4	5	0	0	0	0	0	0	50	50	0	0	0	0
	16	3.0	4.2	6	F	3	3	0	0	0	0	0	0	50	50	0	0	0	2
Cats	17	3.1	3.8	6	M	10	4	1	0	0	0	0	0	50	50	0	0	0	2
	18	5.4	6.3	11	M	8	2	0	0	0	0	0	0	50	50	0	0	0	0
	19	2.0	3.2	4	F	15	5	0	1	0	0	0	0	50	50	0	0	0	1
	20	3.1	4.0	6	F	13	3	0	0	0	0	0	0	50	50	0	0	0	0
	21	1.5	2.2	3	F	17	5	2	0	0	0	0	0	50	50	0	0	0	0
	22	0.9	1.8	2	F	4	2	0	0	0	0	0	0	50	50	0	0	1	2
Mean Fleas and ticks						9.3	4	0.5	0.3	0	0	0	0	50	50	0	0.2	0.2	1.6
"Solpreme Spray" Efficacy (%)								95	94	100	100	100	100			100	100	100	97

Fig. 1

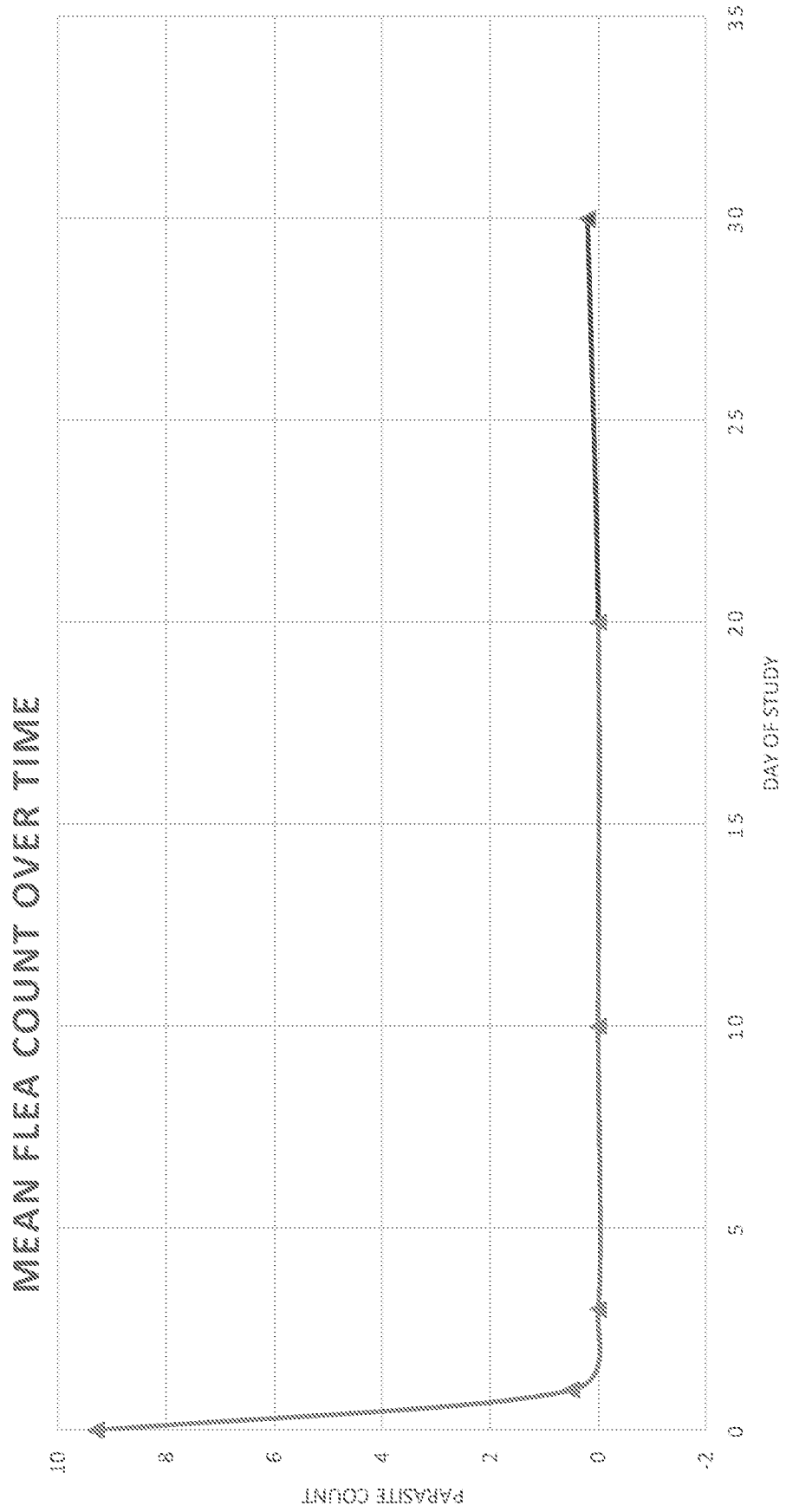

MEAN FLEA COUNT OVER TIME
PARASITE COUNT
10
8
6
4
2
0
-2
0
5
10
15
20
25
30
35
DAY OF STUDY

Fig. 2A

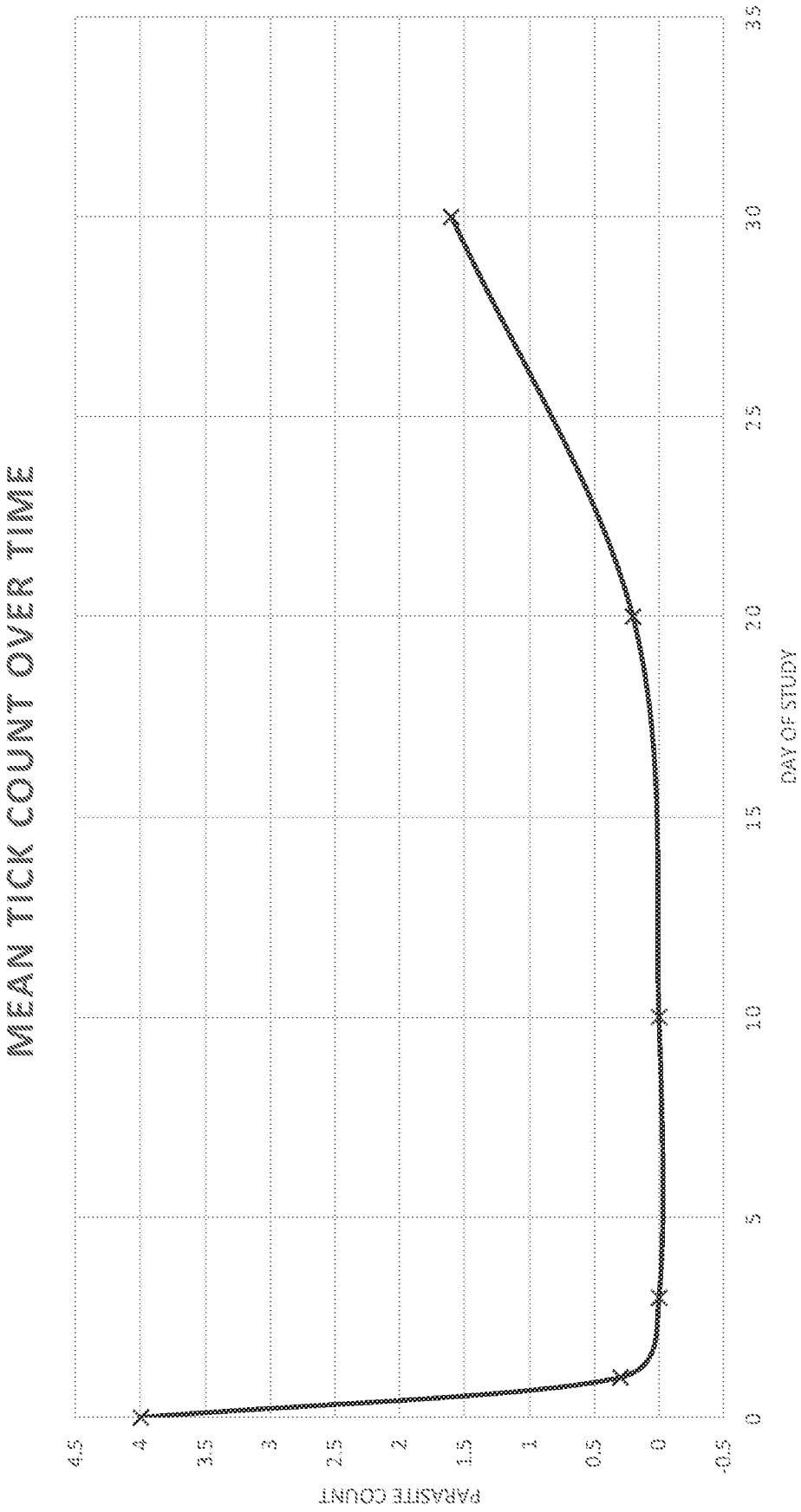

MEAN TICK COUNT OVER TIME
PARASITE COUNT
DAY OF STUDY
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
0
5
10
15
20
25
30
35

Fig. 2B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2017/050468

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2017.01) A01N 37/34, A01N 43/08, A01N 25/02, A01N 25/06, A01N 47/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2017.01) A01N 37/34, A01N 43/08, A01N 25/02, A01N 25/06, A01N 47/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: Google Patents, CAPLUS, Google Scholar
Search terms used: composition, pyrethroid insecticide, dinotefuran, insect, arachnid, film-forming agent, N-formyl morpholine, propylene carbonate, insect growth regulator, hormonal mimetic, chitin synthesis inhibitor, piperonyl butoxide.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007020304 A1 TAMARKIN DOV [IL]; FRIEDMAN DORON [IL]; EINI MEIR [IL]; FOAMIX LTD [IL] 25 Jan 2007 (2007/01/25) [0005],[0010],[0011],[0021],[0023],[0031],[0032],[0040],[0042],[0060],[0062],[0082],[0086], [0108], example 2	1-9,12-35
Y	[0005],[0042],[0060],[0108]	10,11
Y	US 2012071484 A1 REYNOLDS LOUISE [GB] 22 Mar 2012 (2012/03/22) [0014],[0024],[0025],[0038],[0040],[0041],[0043],example 4	10,11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 Jul 2017	06 Jul 2017
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer KORBAKOV Nina Telephone No. 972-2-5651757

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