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(54) Titre : COMPOSITION ANTIPARASITAIRE, PROCEDE DE FABRICATION ET MODE D'UTILISATION
(54) Title: PARASITICIDAL COMPOSITION AND METHODS FOR ITS MAKING AND USE

(57) Abrégé/Abstract:
A liquid phase composition of a pyrethroid in concentrations greater than 50 % w/w that may be used as a basis for other pyrethroid containing formulations in physical phases other than the liquid phase is described. A method of treatment utilizing the composition on domestic mammals is also described.
Parasiticidal Composition and Methods for its Making and Use

A liquid phase composition of a pyrethroid in concentrations greater than 50 % w/w that may be used as a basis for other pyrethroid containing formulations in physical phases other than the liquid phase is described. A method of treatment utilizing the composition on domestic mammals is also described.
PARASITICIDAL COMPOSITION AND
METHODS FOR ITS MAKING AND USE

This invention relates in general to a composition for controlling ectoparasites. More particularly this invention relates to such a composition employing a pyrethroid in concentrations greater than 50% w/w.

Ectoparasites such as ticks and fleas are often found on domesticated animals, such as dogs. Ectoparasites will feed off their animal host and are a constant source of irritation to the animal. It is therefore desirable to control such infestations. By control, it is meant that, desirably, all parasites on the host are killed. Control of tick infestation on all mammals, especially household pets, has recently assumed greater importance than at any other recent time because of the discovery that certain tick species may carry the micro-organism responsible for the transmission of Lyme disease to humans.

While there are known compositions and methods for controlling ectoparasites, many of them are systemic products. That is, they are products containing active parasiticides that enter the bloodstream of the animal in order to create the insecticidal effect. Systemic insecticides are generally less desirable if suitable alternatives exist. They have shown some efficacy against fleas, but have generally not been useful in controlling ticks. Because systemic products, even if topically applied, must enter into the host bloodstream, they are more likely to be toxic to the host. In addition, systemic products that are not applied
topically can be difficult to administer. They may require injection equipment or involve the difficult task of getting an animal to swallow oral formulations.

Liquid compositions containing up to 50% w/w of a pyrethroid are known as are methods for applying said formulations topically. See for example, U.K. Pat. 2,088,212 to Kieran & Townsend, hereafter referred to as '212. However, known compositions do not encompass the formulation of liquid compositions containing greater than 50% by weight/weight of pyrethroid, like those of the instant invention. It is surprising that such concentrated formulations do not cause irritation and toxicity. It would be anticipated that highly concentrated solutions of a pyrethroid, when applied to the skin, would be absorbed into the host and result in systemic toxicity. The present invention encompasses a topical formulation of greater than 50% w/w of a pyrethroid that is non-irritating and non-toxic to the host animal as well as a method of controlling ectoparasites utilizing such a formulation.

It is believed that one reason why the prior art does not teach the use of such highly concentrated pyrethroid formulations is because of the solvent systems heretofore employed. For example, U. K. Patent No. 2,088,212 teaches the dissolution of solid pyrethroids into liquid formulations by using undesirable, irritating, organic solvents such as xylene, toluene, and cyclohexanone. It teaches the use of one of these solvents in conjunction with alkyl glycol ethers. It also teaches the use of combinations of the three organic solvents in conjunction with a glycol. The referenced U. K. patent does not teach the use of glycols without adding undesirable, irritating, organic solvents. Those skilled in the art would not expect that the weak solvent power of the glycols could be compatible with commercial production methods. When the active ingredients according to the present invention are formulated in an alkyl glycol ether solvent, the resulting liquid formulation
can then be used as an ingredient in formulating other topical compositions.

Concentrations of more than 50% make topical application of the composition more convenient than ever before. The higher the concentration, the smaller the dose for effective ectoparasite control. Such small doses can be applied without the treated animal being made aware thus easing administration. Formulations containing more than 50% w/w of a pyrethroid thus obtain many advantages not taught by the prior art of using formulations with maximum concentrations of up to 50%.

Topical compositions can be formulated to take a variety of physical states. They can be a mixture of liquids or a solid active agent can be dissolved in solution. Alternatively, the active agent may be carried in a suspension or emulsion. The suspensions can be water or oil based sols, gels, or ointments. Emulsion carriers contain both aqueous and oily components and can take the form of creams, lotions, or ointments.

In addition, topical administration is further made convenient if the active agent insecticide is contained in an optimal composition. An optimal composition has the following characteristics. The active agent comprises more than 50% of the active agent so that the smallest effective dose may be achieved. During application and while on the host, the carrier components of the formulation facilitate delivery, adsorption on the hair and distribution of the active agent to the parasite. The carrier may inhibit absorption of the active agent into the host and thus avoid systemic toxicity. In the optimal composition, the carrier may also comprise ingredients that soothe or prevent irritation as well as merely employing solvents that are non-irritating.

The choice of carrier can also be varied to optimize frequency of dosing according to particular environmental conditions. For example, oily carriers resist washing.
Formulations comprised of oily carriers reduce dosing frequency for hosts exposed to rain and water. Formulations comprised of aqueous carriers are more suited to dry environs. If the host is in dry environs the aqueous formulation is less likely to be washed off and the required frequency of dosing remains low.

Formulations with pyrethroid concentrations in excess of 50% w/w can be packaged in a single dose package. For example, a single 1 cc dose of a liquid formulation comprised of permethrin and 35% 2-(2-methoxyethoxy)ethanol can be packaged in a collapsible 1 cc tube. Because, the formulation avoids the use of strong organic solvents like xylene, cyclohexanone, and toluene, there is greater choice of tube material. Single dose containers make storage and disposal more convenient for animal owners.

Multiple dose liquid formulations can be packaged in photoresistant containers of more than 1 cc capacity. The high concentration composition also decreases container size requirements for multiple dose containers as well as the container size requirements for single dose containers for larger animals. Again, the smaller container sizes are more conveniently stored and disposed.

It has been discovered that a composition including a pyrethroid in concentrations greater than 50% and up to 85% can be prepared and that said highly concentrated composition is effective for topical application for control of ectoparasites such as fleas and ticks, on animals, especially canines, while remaining non-toxic and non-irritating to the host.

In one aspect of the invention the pyrethroid used is permethrin. The composition preferably comprises 65% permethrin in a carrier, preferably the solvent carrier 2-(2-methoxyethoxy)ethanol. The composition may include other inert ingredients such as perfumes, skin conditioners or coat sheeners. A preferred composition is in a pourable form so
that it can be easily applied to the fur and skin of host animals. The preferred composition is non-irritating to the host skin, coat, and fur and is also not systemically toxic to the host.

The present invention is a composition for controlling ectoparasites that can be found on animals and methods for preparing and using the composition. Generally, the composition comprises pyrethroid and a carrier.

Pyrethroids are a class of chemicals, that have shown efficacy against ectoparasites. Suitable pyrethroids include permethrin, cypermethrin, cyhalothrin, deltamethrin, flumethrin and fenvalerate. The most preferred pyrethroid for use in this invention is permethrin. Permethrin has a technical name of 3-(phen-oxyphenyl)-methyl-(1RS)-cis,trans-3-2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate and a formula of:

\[
\text{Cl} \quad \text{O} \\
\text{Cl} \\
\text{C} \quad \text{CH}_3 \quad \text{CH}_3
\]

[Ar denotes a phenyl group]

Permethrin has a molecular weight of 391.29 grams/mole and technical permethrin comprises from about 25 to 80% cis and about 20-75% trans isomers by weight. In the insecticidal composition of the invention, technical permethrin is suitable and it preferably has a minimum amount of the trans isomer of about 45% by weight and a minimum amount of cis isomer of about 35% by weight.
Any carrier that can deliver a pyrethroid, preferably perme-thrin, is a suitable carrier substance to comprise the pyrethroid composition so long as the carrier is also not irritating to the host's skin and not systemically toxic to the host and allows distribution to and absorption by the target parasite. Some suitable liquid carriers include most alcohols, aromatic petroleum products, corn oil, eucalyptus oil, dimethyl glycol, glycol ether, and 2-(2-methoxybutoxy)-ethanol and 2-(2-methoxyethoxy)ethanol. The compound 2-(2-methoxyethoxy)ethanol is the preferred liquid carrier for use in the insecticidal composition of the present invention.

It is surprising to find that the insecticidal composition of the present invention comprising such a high percentage of the active ingredient, a pyrethroid, is effective against ectoparasites while remaining non-irritating and non-toxic to the host. A composition of the insecticidal composition having such a high concentration of active ingredient also allows for small, easily applied, and yet effective doses. No special expertise is required to apply the treatment so animal owners may do so without the assistance of a veterinarian.

Other inert ingredients can be added to the present composition and can include up to 15% w/w of the total composition and can include spreading agents, synergists, attractants, repellents, adhesion promoters, surface active agents, stabilizers, skin conditioners, perfumes, coat sheeners and coloring agents.

Suitable spreading agents are liquids which distribute themselves particularly readily on the skin. Dipropylene glycol monomethylether is a particularly suitable spreading agent for inclusion within the compositions of the present invention. Isopropyl myristate is within the compositions of the present invention. Isopropyl myristate is another
Suitable spreading agents are liquids which distribute themselves particularly readily on the skin. Dipropylene glycol monomethylether is a particularly suitable spreading agent for inclusion within the compositions of the present invention. Isopropyl myristate is within the compositions of the present invention. Isopropyl myristate is another commonly used spreading agent. The desirable properties of spreading agents, sometimes referred to as spreading oils, are generally well known to those skilled in the art. Attractants include pheromones such as 2,6-dichlorophenol. Repellents include citronellol, diethyl toluimidide, dimethyl phthalate, and the like.

Of the other inert ingredients that can be utilized with the present invention there are the adhesion promoters. Adhesion promoters include carboxymethyl-cellulose, methylcellulose and other cellulose derivatives and starch derivatives, polyacrylates, alginates gelatin, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, copolymers of methyl vinyl ether and maleic anhydride, polyethylene glycols, paraffins, oils, waxes and hydrogenated castor oil, colloidal silicic acid or mixtures of the substances mentioned.

The compositions of the present invention do not normally contain surface active agents; however these may be included if desired. Surface-active agents (comprising emulsifiers and wetting agents) include: 1. anionic surface active agents, such as Sodium lauryl sulfate, fatty alcohol ethersulfates and monoethanolamine salts of mono-/di-alkylpolyglycol ether orthophosphoric acid esters, 2. cationic surface active agents, such as cetyltrimethyl-ammonium chloride, 3. amphophilic surface-active agents, such as Di-sodium-N-lauryl-amino-dipropionate or lecithin, and 4. non-ionic surface active agents, for example, polyoxyethylene castor oil, polyoxyethylated sorbitane monoleate, sorbitan monostearate, ethyl alcohol, glycerol monostearate, polyoxyethylene stearate and alkylphenol polyglycol ethers.
For preventing chemical degradation which occurs in the case of some active compounds, stabilizers may also be used and include, for example, antioxidants, such as tocopherols, butyl-hydroxyanisole, butylhydroxytoluene and carbodiimides, e.g. 2,2-6,6-tetraisopropylidiphenylcarbo-diimide) and scavengers such as epi-chlorhydrin. Coloring agents include conventional dyes which are soluble in the carrier of the present invention, such as Sudan red or Oil Golden Yellow.

In order to prepare the insecticidal composition of the present invention, a pyrethroid is heated to 65-80 degrees Centigrade until any crystals present are liquefied. The liquid is then mixed until uniform. A liquid carrier solvent is placed into a separate unheated vessel. The permethrin is then added to the vessel. The permethrin and carrier solvent are then mixed to uniformity. Additives may also be included in the vessel and mixed into the formulation. The additives comprise traditional pharmaceutical additives like skin conditioners, perfumes, coat sheeners, and spreading agents.

In the preferred embodiment of this invention, permethrin is heated to about 65 degrees centigrade. The carrier 2-(2-methoxyethoxy)ethanol is placed in a clean tank and the permethrin added and mixed until uniform. After the permethrin has been formulated into this simple liquid mixture, the mixture may serve as a starting point for the formulation of topical preparations in other physical states. For instance, gelling agents may be added to create topical preparations in the form of gels and sols. Gases may be added to create topical preparations that can be delivered as aerosols. Other formulating agents may be added to the liquid mixture to create ointments and pastes.

The insecticidal composition of the present invention is suitable for use on mammals, preferably domesticated companion animals such as dogs. Because it is so surprisingly non-toxic, it may be used on puppies as well as adult animals. It is also useful on a variety of domestic animals.
except that its use is not recommended for cats. It is also effective against a variety of parasites including ticks, fleas, keds, and mites.

The composition according to the present invention is particularly useful for horses and other large mammals because the doses required are much smaller as compared to the pyrethroid compositions of 50% or lesser concentrations taught by the prior art. The insecticidal composition of this invention is useful for the control of insect and ascarine ectoparasites such as fleas, ticks, keds, and mites. Its most preferred use is for the control of ticks and fleas on dogs.

The composition may be applied to the host animal by any conventional method for the localized application of compositions, for example by dropping a small volume of liquid composition on the animal's body. One advantage of the use of a highly concentrated composition is that only a small volume is necessary. While the necessary amount of the composition of the present invention needed to be applied for effective insecticidal activity depends upon the size of the animal and the precise concentration and delivery capabilities of the particular composition, a 1 ml volume of the preferred liquid composition has been found to be effective on dogs weighing less than 15 kg. A 1-2 milliliter volume of the preferred 65% w/w permethrin delivers 65-130 mg permethrin. On dogs larger than 15 kg, it has been found to be effective to apply 1 ml of 65% permethrin composition between the shoulder blades in conjunction with another 1 ml at the tailhead.

The method for applying the preferred embodiment of the invention, its efficacy, as well as the absence of toxicity and irritation, is illustrated, by way of example only, by the following in-vivo experiments:
Twenty dogs were selected according to health and their ability to maintain parasite infestations and divided into four groups of five dogs each. The condition of each animal was checked daily.

On day 0, three groups of five dogs were treated with a dosage of a liquid formulation consisting of 65% w/w permethrin and 35% w/w 2-(2-methoxyethoxy)ethanol, and the other group of five dogs was left untreated. Treatments were applied to the skin by parting the hair in each treatment location. Treatment locations were between the shoulder blades and at the tailhead. Each treatment location received 1 milliliter of the formulation. Treatment groups are defined in Table 1 entitled Experimental Design.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental Design</strong></td>
</tr>
<tr>
<td>Group 1: Five dogs of various weights - untreated</td>
</tr>
<tr>
<td>Group 2: Five dogs less than 33 lbs receiving 1 treatment between the shoulder blades.</td>
</tr>
<tr>
<td>Group 3: Five dogs less than 33 lbs receiving treatment between the shoulder blades and at the tailhead.</td>
</tr>
<tr>
<td>Group 4: Five dogs over 33 lbs receiving treatment between the shoulder blades and at the tailhead.</td>
</tr>
</tbody>
</table>

Infestations

One hundred unfed, adult fleas and 50 unfed, adult brown dog ticks were applied to each dog on the days specified in the following Activity Schedule. At each infestation the unfed, adult parasites were placed along the dorsal midline of each dog from its head to the base of its tail.
Parasite Counts

Counts were made of the live fleas and ticks remaining on each dog on the days specified in the following Activity Schedule given in Table 1. Tick records indicate the location, sex, and stage of engorgement of each live, attached tick.

The untreated dogs were counted first, and the examiners wore gloves during the examination. The examination table was washed and the examiners changed gloves following the examination of each treated group. Examinations were conducted according to the activity schedule shown in Table 2.

TABLE 2

<table>
<thead>
<tr>
<th>Day</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14</td>
<td>Begin preconditioning dogs</td>
</tr>
<tr>
<td>-4</td>
<td>Infest w/ticks</td>
</tr>
<tr>
<td>20</td>
<td>Infest w/fleas</td>
</tr>
<tr>
<td>0</td>
<td>Count fleas and ticks.</td>
</tr>
<tr>
<td></td>
<td>Select dogs, weigh</td>
</tr>
<tr>
<td>1</td>
<td>Assign to groups, and treat</td>
</tr>
<tr>
<td>2</td>
<td>Count fleas</td>
</tr>
<tr>
<td>3</td>
<td>Count fleas and ticks, remove ticks, reinfest w/ticks</td>
</tr>
<tr>
<td>25</td>
<td>Reinfest w/fleas</td>
</tr>
<tr>
<td>6</td>
<td>Count fleas and ticks, remove ticks</td>
</tr>
<tr>
<td>7</td>
<td>Reinfest w/ticks</td>
</tr>
<tr>
<td>10</td>
<td>Reinfest w/fleas</td>
</tr>
<tr>
<td>13</td>
<td>Count fleas and ticks, remove ticks</td>
</tr>
<tr>
<td>14</td>
<td>Reinfest w/ticks</td>
</tr>
<tr>
<td>19</td>
<td>Reinfest w/fleas</td>
</tr>
<tr>
<td>20</td>
<td>Count fleas and ticks, remove ticks</td>
</tr>
<tr>
<td>21</td>
<td>Reinfest w/ticks</td>
</tr>
<tr>
<td>22</td>
<td>Reinfest w/fleas</td>
</tr>
<tr>
<td>25</td>
<td>Count fleas and ticks, remove ticks</td>
</tr>
<tr>
<td>26</td>
<td>Reinfest w/ticks</td>
</tr>
<tr>
<td>31</td>
<td>Reinfest w/fleas</td>
</tr>
<tr>
<td>34</td>
<td>Count fleas and ticks</td>
</tr>
<tr>
<td>35</td>
<td>Count fleas and ticks</td>
</tr>
</tbody>
</table>
Evaluation
The following parameters were used for tabulating results:
(1) Visual counts of fleas (ticks) on host; and (2) Percent control of fleas (ticks) on host =

RESULTS:

Fleas
The three treatments with the preferred composition were performed similarly throughout the study with percent control ranging from 70 to 89 on Day 1, 87 to 100 on Day 2, 92 to 100 on Day 3, 99 to 100 on Day 7, 97 to 100 on Day 14, 99 to 100 on Day 21, 93 to 95 on Day 28 and 63 to 89 on Day 35. Group 3 (dogs weighing less than 33 pounds and treated with 1 cc. between the shoulder blades and 1 cc. at the tailhead) had noticeably higher control figures at Days 1 and 2 than Group 2 (dogs weighing less than 33 pounds and treated with 1 cc. between the shoulder blades only) and Group 4 (dogs weighing more than 33 pounds and treated with 1 cc. between the shoulder blades and 1 cc. at the tailhead). Group 3 reached 89 and 100 percent control of Days 1 and 2 respectively whereas Group 2 reached 75 and 90 percent control and Group 4 reached 70 and 92 percent control on Days 1 and 2. Also, from Day 3 through Day 28, Group 3 was slightly higher (one to eight percentage points) in percent control than Group 2 and Group 4.
A summary of flea counts and percent control of fleas is presented in Table 3.

### TABLE 3

Flea counts and percent control of fleas:
Groups defined in Text, p. 12.

<table>
<thead>
<tr>
<th>TIME</th>
<th>TIME</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>less than</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shld.</td>
</tr>
<tr>
<td>10</td>
<td>Day -1</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Fleas</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>75</td>
</tr>
<tr>
<td>15</td>
<td>Day 1</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>Day 2</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>93</td>
</tr>
<tr>
<td>15</td>
<td>Day 3</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>Day 4</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>97</td>
</tr>
<tr>
<td>20</td>
<td>Day 5</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>99</td>
</tr>
<tr>
<td>25</td>
<td>Day 6</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>94</td>
</tr>
<tr>
<td>25</td>
<td>Day 7</td>
<td>Fleas</td>
</tr>
<tr>
<td></td>
<td>% Control</td>
<td>63</td>
</tr>
</tbody>
</table>

(a. Shld. denotes that the treatment site was between the shoulder blades.)
(b. Shld./Tail denotes that treatments were at two sites, one between the shoulders and the other at the tail head.)

35 **Ticks**

Control of attached ticks on Day 3 was 70 percent in Group 2, 59 percent in Group 3 and 49 percent in Group 4. Groups 2 and 3 were similar in control (96-100 percent control) of post-treatment tick infestation through Day 21. Group 4
stayed at 90 percent control from Day 7 to 14 then increased to 98 percent control on Day 21. By Days 28 and 35 the tick control figures for all three groups were falling slightly to 88-96 percent on Day 28 and 84 to 92 percent on Day 35.

Tick counts and percent control are summarized in Table 4.

<table>
<thead>
<tr>
<th>TIME</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>15 Day -1</td>
<td>Ticks 131</td>
</tr>
<tr>
<td></td>
<td>Ticks 63</td>
</tr>
<tr>
<td></td>
<td>% Control 70</td>
</tr>
<tr>
<td>20 Day 7</td>
<td>Ticks 110</td>
</tr>
<tr>
<td></td>
<td>% Control 96</td>
</tr>
<tr>
<td>25 Day 14</td>
<td>Ticks 119</td>
</tr>
<tr>
<td></td>
<td>% Control 99.1</td>
</tr>
<tr>
<td>25 Day 21</td>
<td>Ticks 183</td>
</tr>
<tr>
<td></td>
<td>% Control 99.5</td>
</tr>
<tr>
<td>25 Day 28</td>
<td>Ticks 203</td>
</tr>
<tr>
<td></td>
<td>% Control 88</td>
</tr>
<tr>
<td>25 Day 35</td>
<td>Ticks 193</td>
</tr>
<tr>
<td></td>
<td>% Control 92</td>
</tr>
</tbody>
</table>

(a. Shld. denotes treatment site was between the shoulder blades.)

(b. Shld./Tail denotes that treatments were at two sites, one between the shoulders and the other at the tailhead.)

Adverse Reaction

No adverse reactions occurred. An oily residue was evident in the hair surrounding the sites treated with the invented formulation, but no skin irritation, dermatitis, or hair loss occurred.
EXPERIMENT II.

Permethrin toxicity studies have been completed in numerous species, including rats, mice, rabbits, dogs, cats, cattle, poultry, swine and horses. This study documents the safety of the invention embodiment consisting of 65% permethrin and 35% 2-(2-methoxyethoxy) ethanol on dogs.

Experimental Design

Five dogs were randomly assigned to each treatment group; two dogs served as untreated controls. All dogs were mixed breed, six months to one year of age and 15 to 25 pounds in weight.

Complete chemistry profiles were completed on each of 12 dogs prior to initiation of the study. Dogs were examined by a veterinarian and judged to be healthy prior to the treatment phase.

Treatment Regime

The two treatments consisted of 1 cc or 4cc of 50% permethrin in 2-(2-methoxyethoxy) ethanol. Each dog was individually treated by administering the indicated amount of material (1cc or 4cc) to the shoulder blade area using a 1cc eyedropper.

Dogs were observed for any signs of adverse reactions, including, but not limited to diarrhea, vomiting, salivation, excessive lacrimation, muscle fasciculations, hyperactivity, depression or anorexia. Dogs were noted as being normal if no signs were observable and the dog appeared similar to pre-treatment observations and untreated dogs. Observations were noted immediately at the time of treatment, at two, four, six and eight hours after treatment and daily thereafter for four days. The treatment and observation process was repeated on days 7 through 11 and again on days 14-18, resulting in three treatments and three weeks of observations.

Results

No adverse reactions were noted in any dog at any time during the course of this study. All dogs exhibited normal behavior.
Food and water consumption remained normal throughout the study.

Conclusion

No adverse reactions were noted after dogs were repeatedly treated with the preferred formulation (permethrin formulated as a ready-to-use spot-on topical applicant). Additionally, this formulation exhibits a wide margin of safety, with no acute toxicological reactions at 4X the effective dose. This study demonstrates that the most preferred formulation is safe for use on dogs even when applied at several times the recommended dose.
CLAIMS:

1. A topically applied composition for controlling an ectoparasite on a non-human domestic mammal, which comprises: a non-toxic, non-irritating quantity, but greater than 50% w/w of a pyrethroid, in a carrier that is non-irritating and non-systemically toxic to the animal and allows distribution and absorption by the ectoparasite.

2. A composition according to claim 1, in which the carrier is a liquid selected from the group comprising alkyl glycol ethers.

3. A composition according to claim 2, in which the liquid solvent is selected from the group consisting of 2-(2-butoxyethoxy)ethanol and 2-(2-methoxyethoxy)ethanol.

4. A composition according to any one of claims 1 to 3, which is a solution of the pyrethroid dissolved in the carrier.

5. A composition according to any one of claims 1 to 4, wherein the pyrethroid is selected from the group consisting of permethrin, phenothrin, deltamethrin, cypermethrin, cyhalothrin, flumethrin, cyfluthrin, cyphenothrin, tralomethrin, tralocythrin and fenvalerate.

6. A topically applied composition for controlling an ectoparasite infestation on a non-human domestic mammalian host, which comprises a permethrin selected from the group comprising compositions of the formula:

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{Cl} & \quad \text{C} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{C} \quad \text{O} \quad \text{CH}_2 \quad \text{Ar} \quad \text{O} \quad \text{Ar} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
(in which Ar denotes a phenyl group) and stereo-isomers thereof, in a non-irritating, non-toxic quantity comprising greater than 50% w/w in a carrier that is non-irritating and non-systemically toxic to the host and allows distribution and absorption by the ectoparasite.

7. A method of controlling ectoparasite infestation on a non-human domestic mammalian host, which comprises:

applying to a localized region of the skin of the host a composition comprising greater than 50% w/w of a pyrethroid and a carrier that is non-irritating and non-systemically toxic to the host and allows distribution and absorption by the ectoparasite.

8. A method according to claim 7 in which a major portion of the formulation is selected from the group consisting of 2-(2-butoxyethoxy)ethanol and 2-(2-methoxyethoxy)ethanol.

9. A method according to claim 7 or 8, wherein the host is selected from the group consisting of dogs and horses.

10. A method according to claim 8 wherein the applying step comprises applying a dose of more than 33.3 mg per kilogram host body weight.

11. A parasiticidal composition for topical application to non-human domestic mammals comprising a pyrethroid and a carrier, wherein the carrier is an alkyl glycol ether and the pyrethroid is present in an amount greater than 50% and up to about 85% by weight of the total composition.

12. A composition according to claim 11, wherein the carrier is present in an amount ranging from 15% to about 50% by weight of the total composition.
13. A composition according to claim 11 or 12, wherein the pyrethroid is selected from the following: permethrin, phenothrin, deltamethrin, cypermethrin, cyhalothrin, flumethrin, cyfluthrin, cyphenothrin, tralomethrin, tralocythrin and fenvalerate.

14. A composition according to claim 13, wherein the permethrin is selected from the group comprising compositions of the formula:

\[
\begin{align*}
\text{Cl} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{C} \quad \text{O} \quad \text{CH}_2 \quad \text{Ar} \quad \text{O} \quad \text{Ar} \\
\text{Cl} & \quad \text{C} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

(in which Ar denotes a phenyl group) and stereo-isomers thereof.

15. A composition according to any one of claims 11 to 14, wherein the alkyl glycol ether is selected from 2-(2-butoxyethoxy)ethanol, 2-(2-methoxyethoxy)ethanol and mixtures thereof.

16. A composition according to any one of claims 11 to 15, wherein the pyrethroid is dissolved in said carrier.

17. A composition according to claim 11, wherein the pyrethroid is present in an amount of about 65% by weight of the total composition.

18. A composition according to claim 17, wherein the pyrethroid is a permethrin selected from the group comprising
compositions of the formula:

(Cl denotes a phenyl group) and stereo-isomers thereof.

19. A composition according to claim 17 or 18, wherein the alkyl glycol ether is present in an amount of about 35% by weight of the total composition.

20. A composition according to claim 19, wherein the alkyl glycol ether is selected from the following: 2-(2-butoxyethoxy)ethanol, 2-(2-methoxyethoxy)ethanol and mixtures thereof.

21. A method of controlling ectoparasite infestation on a non-human domestic mammal, which comprises:

  topically applying a parasiticidal composition to a localized external region on the mammal, the parasiticidal composition comprising a pyrethroid in a carrier wherein the carrier is an alkyl glycol ether and the pyrethroid is present in an amount greater than 50% and up to about 85% by weight of the total composition.

22. A method according to claim 21, wherein the composition comprises the carrier in an amount ranging from 15% to about 50% by weight of the total composition.

23. A method according to claim 21 or 22, wherein the pyrethroid is selected from the following: permethrin, phenothrin, deltamethrin, cypermethrin, cyhalothrin,
flumethrin, cyfluthrin, cyphenothrin, tralomethrin, tralocythrin and fenvalerate.

24. A method according to claim 23, wherein the pyrethroid is a permethrin selected from the group comprising compositions of the formula:

\[
\text{Cl} \quad C \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad C \quad \text{C} \quad \text{CH}_2 \quad \text{Ar} \quad \text{O} \quad \text{Ar}
\]

(in which Ar denotes a phenyl group) and stereo-isomers thereof.

25. A method according to any one of claims 21 to 24, wherein the carrier is selected from the following: 2-(2-butoxyethoxy)ethanol, 2-(2-methoxyethoxy)ethanol and mixtures thereof.

26. A method according to any one of claims 21 to 25, wherein the mammal is selected from the group consisting of dogs and horses.

27. A method of controlling ectoparasite infestation on a non-human domestic mammal, which comprises:

   topically applying a parasiticidal composition to a localized external region on the mammal, the parasiticidal composition comprising a pyrethroid in a carrier wherein the carrier is an alkyl glycol ether and the pyrethroid is present in an amount of about 65% by weight of the total composition.
28. A method according to claim 27, wherein the carrier is present in an amount of about 35% by weight of the total composition.

29. A method according to claim 28, wherein the carrier is selected from the following: 2-(2-butoxyethoxy)ethanol, 2-(2-methoxyethoxy)ethanol and mixtures thereof.

30. A method according to claim 27, 28 or 29, wherein the pyrethroid is a permethrin selected from the group comprising compositions of the formula:

\[
\begin{array}{c}
\text{Cl} \\
\text{CH}_3
\end{array}
\begin{array}{c}
\text{C} \equiv \text{CH} \quad \text{CH} \quad \text{CH} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{CH} \quad \text{C} \quad \text{O} \quad \text{CH}_2 \quad \text{Ar} \quad \text{O} \quad \text{Ar} \\
\text{Cl} \quad \text{C} \quad \text{CH}_3 \quad \text{CH}_3
\end{array}
\]

10 (in which Ar denotes a phenyl group) and stereo-isomers thereof.

31. A method according to any one of claims 27 to 30, wherein 1 milliliter of the parasiticidal composition is topically applied on the mammal and wherein the mammal weighs less than 15 kilograms.

32. A method according to any one of claims 27 to 30, wherein 33.3 milligrams of the parasiticidal composition is topically applied on the mammal per kilogram of the mammal’s body weight.

33. A composition according to any one of claims 11 to 20, which comprises only the pyrethroid and the carrier.

34. A composition according to any one of claims 11 to 20, which comprises only the pyrethroid, the carrier and at
least one non-irritating and non-toxic ingredient selected from the group consisting of spreading agents, synergists, attractants, repellents, adhesion promoters, surface active agents, stabilizers, skin conditioners, perfumes, coat sheeners and coloring agents.

35. A method according to any one of claims 21 to 32, wherein the parasiticidal composition comprises only the pyrethroid and the carrier.

36. A method according to any one of claims 21 to 32, wherein the parasiticidal composition comprises only the pyrethroid, the carrier and at least one non-irritating and non-toxic ingredient selected from the group consisting of spreading agents, synergists, attractants, repellents, adhesion promoters, surface active agents, stabilizers, skin conditioners, perfumes, coat sheeners and coloring agents.

37. A composition according to claim 1 or 6, wherein the carrier is selected from the group consisting of alcohols, corn oil, eucalyptus oil, dimethyl glycol, glycol ether, 2-(2-methoxybutoxy)ethanol and 2-(2-methoxyethoxy)ethanol.

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