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(54) Title: BITING MIDGES REPELLENT

(57) Abstract: The invention relates to insect repellents, in particular a repellent effective against midges of the genus Culicoides, more particularly a repellent effective against midges of the species Culicoides imicola. In one embodiment of the invention, there is provided a method for repelling midges of the genus *Culicoides* from a locus in need of protection from midges, comprising applying a midge-repellent effective amount of cyhalothrin to the locus in need of protection from midges.

BITING MIDGES REPELLENT

FIELD OF THE INVENTION

[0001] The invention relates to insect repellents, in particular a repellent effective against midges of the *Culicoides* genus, more particularly a repellent effective against midges of the *Culicoides imicola* species.

BACKGROUND OF THE INVENTION

[0002] Midges of the *Culicoides* genus are agents of dermatitis and vectors of pathogens, and considered a pest to livestock and nuisance to man. About 1400 species of *Culicoides* are known worldwide. Midges of the *culicoides* genus often bite livestock, such as horses and cattle, and in so doing, transfer pathogens which infect the livestock with diseases. For example, bluetongue in sheep and cattle, epizootic hemorrhagic disease in deer and cattle, Akabane in cattle, sheep and goats, African horse sickness, Ibaraki in cattle, and bovine ephemeral fever, can all result from infection by midge-borne viruses. While such diseases can be combated by vaccination of the population at risk of infection, vaccines are pathogen-specific. Furthermore, only a few vaccines effective against arthropod-borne diseases are known.

[0003] Alternatively, repelling the biting midges, so as to prevent bites from occurring, provides an effective means of protecting livestock against a wide range of arthropod disease vectors and does not cause development of resistance in the arthropods. Pesticides are one means of affecting such control of biting midges, by reducing their numbers. However, pesticides do not have an immediate effect. Furthermore, pesticides may be of limited application, due to environmental concerns, such as concomitant poisoning of pets or wild life, and the leaching of toxic residues into milk or meat obtained from the animals meant to be protected.

[0004] Instead of pesticides, repellents, such as diethyl toluamide (DEET), which are known to be relatively safe to mammals, can be used in order to protect them from the bites of vector harboring pathogens. Repellents can prevent the syndrome known as Sweet Itch, or *Culicoides* hypersensitivity, in horses and other farm animals. However, the time during which DEET and other repellents remain effective is only a few hours, whereas midges are active throughout the night. Furthermore, a small proportion of the animals treated may

suffer from side-effects of DEET or other repellents. There is thus a need for alternative effective means for repelling biting midges throughout the period of their activity, which means are safer to both animals and the environment.

SUMMARY OF THE INVENTION

[0005] The present invention seeks to provide a method for repelling biting midges from potential bite victims, especially mammals, wherein the method is easy to implement, safe and environmentally innocuous, and which can provide protection from midges for eight hours or more.

[0006] There is provided, in an embodiment of the invention, a method for repelling midges of the *Culicoides* genus from a locus in need of protection from such midges, comprising applying a midge-repellent effective amount of cyhalothrin to the locus in need of protection from midges.

[0007] Cyhalothrin, also known as (R,S)-α-cyano-3-phenoxybenzyl (1R, 3R, 1S, 3S)-3 -(Z-2-chloro-3,3,3,-trifluoroprop-1-enyl) – 2,2-dimethylcyclopropanecarboxylate, is a type II pyrethroid containing the α -cyano-3-phenoxybenzyl moiety, and is known in the art of a toxicant for controlling flies, lice and ticks.

[0008] It has also been reported that this compound functions as a midge toxicant (braverman et al., Medical and Veterinary Entomology 9:443 (1995)). Until the discovery of the present invention, however, it was not known that this compound, as well as preparations containing it, had a repellent effect on biting midges.

[0009] In one embodiment of the invention, the compound is mixed with a pharmaceutically or veterinarily acceptable carrier, excipient or diluent prior to application to the locus. The carrier, excipient or diluent may be water-based, in which case the compound is applied as an aqueous solution containing the active ingredient and an emulsifier or solubilizer. In an embodiment of the invention, the concentration of the compound in the carrier, excipient, or diluent is between about 0.5% (w/v) and 10% (w/v). In another embodiment the concentration is about 2% (w/v).

[0010] In addition to the carrier, excipient, or diluent, the compound may also be mixed with other pharmaceutically or veterinarily acceptable ingredients, such as emulsifiers or stabilizers, as well as other compounds known to repel midges. Thus, in an embodiment of the present invention, the mixture of oils is applied to the locus as a composition containing about 2% cyhalothrin (w/v) and 98% (w/v) of an oily base comprising maize oil and volatile silicone.

[0011] In an embodiment of the invention, the locus to which the compound is applied is a human being. In another embodiment of the invention, the locus is a domesticated animal. In a further embodiment of the invention, the locus is a cow. In another embodiment of the invention the locus is a horse. In another embodiment of the invention the locus is a sheep. In yet another embodiment of the invention the locus is a goat.

[0012] In another embodiment of the invention, the locus may be protected by applying cyhalothrin to a garment covering the locus or in close proximity to the locus.

[0013] In another embodiment of the invention, the midges are selected from the group consisting of *Culicoides imicola* (an afro-asiatic species), *Culicoides schultzei* complex, *C. obsoletus* complex and *C. pulicaris complex*.

[0014] In a further embodiment of the invention, the midges are of the *Culicoides imicola* species.

[0015] The present invention also relates to a repellent effective against midges of the *Culicoides* genus, comprising cyhalothrin and a pharmaceutically or veterinarily acceptable carrier, excipient or diluent.

[0016] The present invention also relates to the use of cyhalothrin in the preparation of a biting midge repellent, and to cyhalothrin for use as a biting midge repellent.

BRIEF DESCRIPTION OF THE DRAWING

[0017] The present invention will be understood and appreciated more fully from the following detailed description, taken in conduction with the drawing in which:

[0018] FIG. 1 shows the number of *Culicoides imicola* caught in traps fitted with bed nets which were treated with different midge repellents.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0019] As stated, the present invention provides a method for repelling midges of the *Culicoides* genus from a locus in need of protection from such midges, comprising applying a midge-repellent effective amount of the compound cyhalothrin to the locus in need of protection from such midges.

[0020] There are several advantages to using cyhalothrin as a biting midge repellent. One such advantage is that this mixture is not harmful to other mammals, unlike some pesticides, and in fact, one preparation usable in the practice of the present invention (a formulation commercially available under the name Coopertix®, Cylotox® and Cylofly® containing about 2%(w/v) cyhalothrin and about 98% (w/v) inactive ingredients (maize oil and volatile silicone) is known as a toxicant effective against houseflies, lice and ticks but safe and effective for use with mammals

[0021] Another advantage is that it has been found that cyhalothrin is effective as a midge repellent for a period in excess of 8 hours. Since midges are generally active at nighttime, the long-lasting efficacy of the compound as a midge repellent enables protection of the locus (e.g., a domestic animal) from midge bites for an entire night, utilizing a single application of the repellent. The animals can thus be provided with protection from pathogens transmitted by biting midges and the dermatitis syndrome caused by such bites is thus prevented.

[0022] The cyhalothrin is applied in an embodiment of the invention to the locus to be protected in a diluted form. For example, cyhalothrin may be mixed with a diluent (such as toluene, animal or vegetable oil, or inorganic oil) or a mixture of diluents, and, optionally, a stabilizing agent or emulsifier prior to application to the locus. Such diluents, stabilizing agents and emulsifiers are well-known in the art and will be readily appreciated by skilled artisans. Cyhalothrin has low solubility in water, and therefore if application of cyhalothrin in the form of a water-based solution is desired, additional agents known in the art, such as emulsifiers, must be added to water to effect solubilization of the cyhalothrin. The preparation containing the cyhalothrin may also contain other compounds which have

midge-repellent properties. As will readily be appreciated by the skilled artisan, the cyhalothrin may be applied in the form of other pharmaceutically and veterinarily acceptable formulations, containing various combinations of carriers, excipients and diluents, said formulations being designed for the application of active compounds to the exterior of mammals. Such formulations are well known in the art, and are not discussed here for the sake brevity. In an embodiment of the invention the formulation contains about 2% (w/v) cyhalothrin and about 98% inert ingredients.

[0023] The way in which the midge repellent is applied to the locus will depend on the formulation employed. Thus, for example, liquid formulations of low viscosity may be applied to the locus by spraying, e.g. spraying as a liquid stream or as droplets. More viscous formulations may be applied by spreading the formulation across the locus of application.

[0024] The cyhalothrin presented in the formulation is in an amount of at least 0.5% (w/v), preferably at least 2%(w/v).

EXAMPLES

Example 1

Experimental Procedures

[0025] The following procedure was used to demonstrate the efficacy of cyhalothrin as a midge repellent. Rounded pieces of polyester bed nets, each of size 0.34 m^2, containing 14 holes per square inch, each hole of diameter ~1.3 mm, were weighed. Some of the nets were than immersed in a solution containing an active ingredient (Coopertix® solution containing cyhalothrin, a solution containing 15 wt.% DEET, or a neem oil-based solution containing 4.5 wt.% azadirachtin) for 30 minutes, dried for another 30 minutes, and fixed on the bottom of suction traps of the kind described by DuToit, Onderstekpoort Journal of Veterinary Sience and Animal Industry, 19 (1944), 7-16: The nets which were not immersed in the solution were similarly mounted and served as controls. The amount of preparation absorbed was calculated as g/m^2 net, according the W.H.O. method described by Schreck & Self (World Health Organization document WHO/VBC/85.914).

[0026] The diameter of each rounded piece of net measured 66 cm, to enable overlap the 53 cm diameter bottom of the suction light traps. The nets were stretched and fixed with

a rubber band under the bottom entrance of each of the four suction light traps. The mesh size permitted free entrance of the *C. imicola* to the trap. Traps fitted with impregnated nets were operated for 12 hours from late afternoon until morning, for four nights, with trap catches sorted hourly and counted during the hours of operation. *Culicoides* were trapped only during the nine hours of darkness during each of these 12-hour periods.

[0027] The suction light traps were placed at the horse stable at the Kimron Veterinary Institute at Bet Dagan, Israel. This site is known from many years of suction light trappings to attract almost pure *C. imicola* samples, which have repeatedly been found to breed in the damp horse manure under the water troughs of the horses. The traps were fitted with mercury vapor lamps, which in combination with the horses in the stable served as the main attractants for *C. imicola*.

[0028] Two of the four nets, namely untreated (negative control) and impregnated with 15 wt% DEET (positive control), served as controls. The location of the four traps fitted with bed nets of the various treatments were randomized for four nights in a latin-square design. Analyses of variance tests were performed with the general linear model (GLM) of the Statistical Analysis System (SAS Institute, 1982), followed by Student-Newman-Keuls (SNK) test for the separation of means.

Experimental Results

[0029] Figure 1 summarizes the results of these experiments (averaged over all nights). As can be seen in Figure 1, significant differences (probability $P < 0.0001$) between the numbers of midges caught in each of the nets were observed. The untreated control trap caught significantly ($P < 0.05$) more *C .imicola* than the DEET, neem or cyhalothrin treated traps during the first three hours of operation. During the fourth hour of operation, the neem (Ag-100) and DEET treated traps caught significantly ($P<0.05$) fewer midges than the untreated trap, but the cyhalothrin treated trap caught significantly ($P<0.05$) fewer midges than even the DEET – and neem-treated traps. Overall, cyhalothrin was the only preparation that exerted a repellent effect throughout the night.

[0030] It will be appreciated by persons skilled in the art that the present invention is not restricted to the embodiments which have been particularly described hereinabove, but that many modifications and variations thereof may be made, without departing from the

spirit of the invention or its scope as defined in the preceding description and in the appended claims.

What is claimed is:

1. A method for repelling midges of the *Culicoides* genus from a locus in need of protection from midges, comprising applying a midge-repellent effective amount of cyhalothrin to said locus in need of protection from midges.

2. A method according to claim 1 wherein said cyhalothrin is mixed with pharmaceutically or veterinarily acceptable carrier, excipient or diluent prior to application to the locus.

3. A method according to claim 2, wherein the carrier is oil-based.

4. A method according to claim 3, wherein said carrier further comprises at least one additional component selected from the group of emulsifiers and stabilizers.

5. A method according to claim 2, wherein said cyhalothrin is applied as an aqueous solution containing an emulsifier or stabilizer.

6. A method according to claim 2, wherein said cyhalothrin is applied to the locus as a composition containing about 0.5-10% cyhalothrin (w/v).

7. A method according to claim 6, wherein said cyhalothrin is applied as a composition containing about 2% cyhalothrin (w/v) and about 98% inert ingredients comprising maize and volatile silicone.

8. A method according to claim 2, wherein the concentration of said cyhalothrin in the carrier, excipient or diluent is between about 0.5% and 10% (w/v).

9. A method according to claim 8, wherein the concentration of said cyhalothrin in the carrier, excipient or diluent is about 2% (w/v).

10. A method according to claim 1, wherein the locus to which said cyhalothrin is applied is a human being.

11. A method according to claim 1, wherein the locus to which said cyhalothrin is applied is a domesticated animal.

12. A method according to claim 11, wherein said locus is a cow.

13. A method according to claim 11, wherein said locus is a horse.

14. A method according to claim 11, wherein said locus is a sheep.

15. A method according to claim 11, wherein said locus is a goat.

16. A method according to claim 1, wherein the midges are selected from the group consisting of *Culicoids imicola, C. obsoletus* complex, *C. pulicaris* complex and the *C. schulzei* complex.

17. A method according to claim 16, wherein the midges are of the *Culicoides imicola* species.

18. A method according to claim 1, wherein the locus is protected by applying said cyhalothrin to a garment covering the locus or in close proximity to said locus.

19. A biting midge repellent for repelling midges of the *Culicoides* genus comprising cyhalothrin.

20. A formulation for controlling or repelling midges of the *Culicoides* genus, comprising cyhalothrin and a pharmaceutically or veterinarily acceptable carrier, excipient or diluent.

21. The use of a cyhalothrin in the preparation of a biting midge repellent for repelling midges of the *Culicoides* genus, substantially as described in the specification.

22. A method according to any one of claims 1 to 18, substantially as hereinbefore described.

23. A kit comprising cyhalothrin for the repelling midges of the *Culicoides* genus.

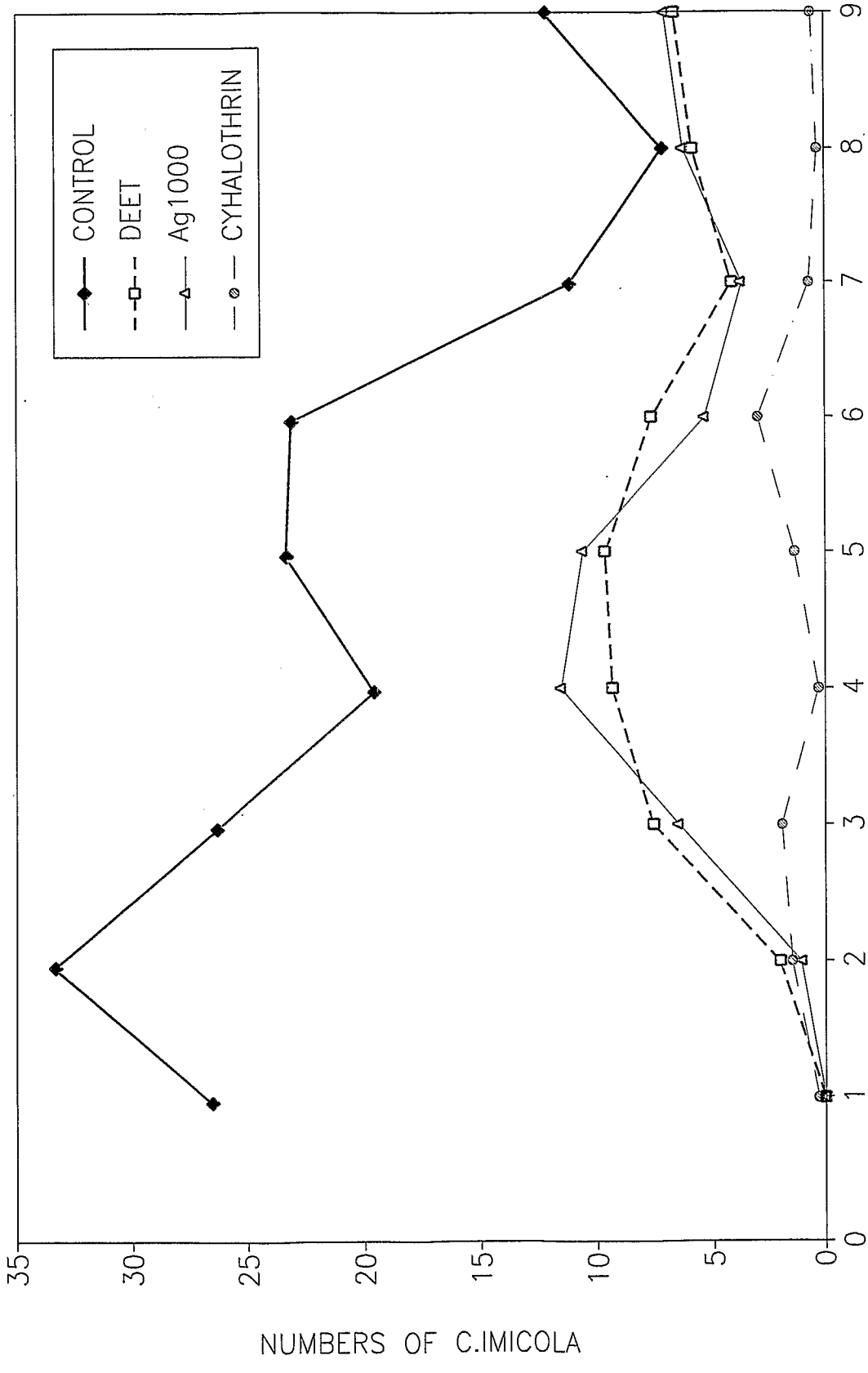
CONTROL
DEET
Ag1000
CYHALOTHRIN
NUMBERS OF C.IMICOLA
NIGHT HOURS
0
5
10
15
20
25
30
35
0
1
2
3
4
5
6
7
8
9

FIG.1