

PATENT SPECIFICATION

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(54) METHOD FOR INSECTICIDE USE

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1. a company incorporated in England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns the new use of known compounds and formulations containing them.

Flies of the order Diptera are a source of concern in animal husbandry as troublesome pests of many domestic animals. Apart from infesting animal wounds with eggs which mature in the flesh, they transmit a variety of infectious diseases by biting the animals, and can cause weight loss and decrease in milk yield.

A variety of insecticides have been shown to be active against such flies, and some found commercial application in preventing or limiting irritation of the animals. Such preparations have included DDT, pyrethrins, methoxychlor and diazinon, but all known remedies have at least one of the drawbacks of little or no repellent action on the flies, low insecticidal activity, and poor residual effects. A repellent effect of an insecticide is of particular importance in minimising or preventing the fly from attaching itself to the host thus decreasing the annoyance to the animal and the risk of infestation.

Pyrethrins in particular are recognised to have no commercial potential as repellents for biting flies and have further found little commercial application in the control of other arthropod ectoparasites of mammals such as cattle ticks, cattle and sheep lice, sheep keds, and sheep scab. Amongst the synthetic pyrethroid analogues of the pyrethrins the compound bioresmethrin (2-benzyl-4-furylmethyl *d-trans* chrysanthemate) is known to be outstanding as a kill insecticide as measured by for example results obtained upon topical application of the compound to adult houseflies (*Musca domestica*) but has been found to have only limited knock-down

activity against these flies compared with that of pyrethrins.

The compound, 3 - phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate, and its optical and geometrical isomers, (hereinafter referred to as the compounds of formula I) are known to have insecticidal activity against a variety of insects including *Musca domestica* but have been found to be significantly less active against these flies both as regards knock-down and upon topical application than bioresmethrin.

It has now been found that the compounds of formula (I) provide, for domestic animals, a remarkable protective effect against attack by insects of the order Diptera, and that this effect includes a high repellent effect, an excellent insecticidal effect, and long residual protection of the host animals against infestation when the compounds of formula (I) are used at substantially lower doses than have hitherto been used for pyrethrins. In particular the compounds are very effective in protecting cattle and other domestic mammals against the stable fly (*Stomoxys calcitrans*), the horn fly (*Haematobia irritans*) and the buffalo fly (*Lyperosia exigua*).

The compounds of formula (I) may be used in the protection of a variety of animals against Diptera, including cattle, sheep, horses, and other ungulate domestic mammals.

Pests which may be controlled by the use of compounds of formula (I) include Simuliidae (e.g. *Simulium* sp.), Tabanidae (e.g. *Tabanus* sp.), Muscidae (e.g. *Stomoxys calcitrans*, *Glossina* sp., *Lyperosia* sp., *Haematobia* sp., and *Hydrotaea* sp.), Calliphoridae (e.g. *Lucilia* sp., *Chrysomya* sp., *Calliphora* sp. and *Callitroga* sp.) and Oestridae (e.g. *Hypoderma bovis*, *H. lineatum*, and *Dermatobia hominis*).

The compounds of formula (I) may be used for protecting an animal against Diptera infestations by application of the compounds themselves or in a diluted form in known fashion, as a dip, a spray, a foam, a dust, a paste or grease, or a pour-on formulation. Dips are not applied *per se*, but the animals

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immersed in a dipping bath containing the dip wash. Sprays may be applied by hand or by means of a spray race or arch or automatic treadle. Dusts may be distributed over the animals by means of a powder gun or incorporated in perforated bags attached to trees or rubbing bars. Pastes and greases may be applied manually or distributed over the surface of an inert material against which animals rub and transfer the material to their skins. Pour-on formulations are dispensed as a unit of liquid of small volume onto the backs of animals such that all or most of the liquid is retained on the animals.

The compounds of formula (I) may be formulated either as formulations ready for use on the animals or as formulations requiring further dilution prior to application, but both types of formulations comprise a compound of formula (I) in intimate admixture with one or more carriers or diluents. The carriers may be liquid, solid or gaseous or comprise mixtures of such substances, and the compound of formula (I) may be present in a concentration of from 0.025 to 99% w/v depending upon whether the formulation requires further dilution.

Dusts may be prepared by intimate admixture of the chosen compound with a powdered solid inert carrier for example suitable clays, kaolin, talc, mica, starch and diatomaceous earths.

Sprays of a compound of formula (I) may comprise a solution in an organic solvent (e.g. those listed below) or an emulsion in water (dip wash or spray wash prepared in the field from an emulsifiable concentrate (otherwise known as a water miscible oil) which may also be used for dipping purposes. The concentrate preferably comprises a mixture of the active ingredient, an organic solvent and one or more emulsifiers. Solvents may be present in wide limits but preferably in an amount of from 20 to 60% w/v of the composition and may be selected from kerosene, ketones, alkanols, xylene, aromatic naphtha, and other solvents known in the formulating art. The concentration of emulsifiers may be varied within wide limits but preferably in the range of 5 to 25% w/v and are conveniently non-ionic surface active agents including polyoxy-alkylene esters of alkyl phenols and polyoxy-ethylene derivatives of hexitol anhydrides.

Dip washes may be prepared not only from emulsifiable concentrates but also from wettable powders comprising a compound of formula I in intimate admixture with a dispersing agent and one or more surface active agents.

Greases (or ointments) may be prepared from vegetable oils, synthetic esters of fatty acids or wool fat together with an inert base such as soft paraffin. A compound of formula (I) is preferably distributed uniformly through the mixture in solution or suspension. Greases

may also be made from emulsifiable concentrates by diluting them with an ointment base.

Pastes are also semi-solid preparations in which a compound of formula (I) may be present as an uniform dispersion in a suitable base such as soft or liquid paraffin or made on a non-greasy basis with glycerin, mucilage or a suitable soap. As greases and pastes are usually applied without further dilution they should contain the appropriate percentage of the compound of formula (I) required for treatment.

Aerosol sprays may be prepared as a simple solution of the active ingredient in the aerosol propellant and co-solvent such as halogenated alkanes and the solvents referred to above, respectively. Pour-on formulations may be made as a solution or suspension of a compound of formula I in a liquid medium which also contains a viscous oil to minimize spreading of the formulation on the surface of the animals.

The concentration of the compound of formula (I) to be applied to an animal will vary according to the isomer chosen, the nature of the formulation and the likely infestation, but in general 0.025% to 1% w/v of the compound should be present in the applied formulation. For the control of biting flies, a weekly application by standard techniques of a solution or emulsion of 0.025 to 0.05% w/v has been found to provide satisfactory control. If the compound is to be applied at longer intervals then a concentration of 0.05 to 0.1% w/v is desirable. It will be understood that the amount of the compound deposited on an animal will vary according to the method of application, size of the animal, concentration of the compound in the applied formulation and the nature of the formulation.

Dusts, greases, pastes and aerosol formulations are usually applied in a random fashion as described above and concentrations of 0.5 to 1.0% w/v of a compound of formula (I) in the applied formulation may be used.

In one aspect therefore the present invention provides a method of treating a domestic mammal for the prevention or minimisation of infestation by insects of the order Diptera which comprises application to the mammal of a non-toxic, infestation prevention or minimisation effective amount of compound 3-phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl)cyclopropane - 1 - carboxylate or of a formulation comprising said compound in intimate admixture with a carrier or diluent therefor.

The following Example illustrates the present invention and the manner in which it may be carried out but should not be construed as in any way constituting a limitation thereof. In the Example and Reference Examples, compound Ia refers to 3 - phen-

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oxybenzyl ($\pm$)*cis* - *trans* - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl)cyclopropane - 1 - carb-
oxylate. Other compounds of formula I in-
clude the (+)*trans*, (+)*cis*, ($\pm$)*trans* and
the ($\pm$)*cis* isomers. These compounds may be
made according to the description in Dutch
Patent Specification No. 7307130.

Example 1

Control of *S. calcitrans*

Groups of two matched Friesian steers
were sprayed, each with one litre of com-
pound Ia at 0.01%, 0.025% and 0.050%
w/v. The pairs were exposed almost daily in a
fly chamber after treatment to approximately
100 starved *S. calcitrans*. The numbers of
flies landing on the steers was counted over a
7 minute observation period. Counts at 1 and
2 minutes after treatment were discarded and
an average taken for the group over the 3—7
minute period.

Mean fly counts

	Days post treatment	0.01%	0.025%	0.05%
25	PRE	27.1	>24.1	25.4
	1	10.9	4.6	5.9
	2	—	4.9	—
	4	10.7	5.2	4.7
	5	17.1	8.4	5.5
30	6	16.5	7.2	6.0
	7	13.4	8.1	8.0
	8	13.1	10.7	6.7
	11	8.3	8.6	7.0
	12	16.6	13.1	7.6
35	13	14.7	10.8	14.3
	14	25.0	15.6	11.7
	15	—	18.2	13.4
	18	—	12.2	11.7
	19	—	17.7	17.1
40	20	—	20.1	15.1
	21	—	—	17.5

Flies feeding in quantity were first noted at
5 days 0.01%, 14 days 0.025% and 13 days
0.05%. Protection afforded by 0.025% and
0.05% treatment appear similar; both are
superior to the 0.01% treatment.

Flies were collected after exposure and
retained for 24 hours to observe mortality:—

0.01% engorged flies—
50% at 6 days, 0% thereafter
unengorged flies—
100% at 1 day, decrease to 0%
at 13 days
0.025% engorged flies—
100% to 8 days decrease to
20% at 19 days
unengorged flies—
100% to 8 days decrease to
80% at 19 days

0.05% engorged flies—

100% to 6 days, 50% at 7
and 8 days, 100% at 11 and
12 days, decrease to 14% at
14 days

unengorged flies—

100% to 18 days, 62% at 21
days.

The control of unengorged flies is superior
to that of engorged flies. An increase in con-
centration gives an increase in length of
control.

Reference Example 2

Miscible Oil Formulation

Compound Ia	21% w/w	
Trimethyl Benzenes (Aromasol H)	67% "	75
Alkyl Phenol Ethylene Oxide condensate of 8—12 mol. Ethylene Oxide	4% "	80
Calcium Dodecyl Benzene Sulphonate	8% "	

("Aromasol" is a Trade Mark).

Reference Example 3

Dust Formulation

Compound Ia	1% w/w	
Talc	99% "	85

Reference Example 4

Wettable Powder Formulation

Compound Ia	20% w/w	90
Diatomaceous Earth	74% "	
Sodium Salt Naphthalene Sulphonic Acid	5% "	
Alkyl Phenol Ethylene Oxide Condensate 2—12 mol.	1% "	95

Reference Example 5

Pour-On Formulation

Compound Ia	20% w/w	
Trimethyl Benzenes	20% "	100
Vegetable Oil	60% "	

Reference Example 6

Containers

Each of the formulations of Reference
Examples 2 to 5 were packed in sealed con-
tainers, each container labelled with indica-
tions of the suitability of its contents to con-
trol a Diptera infestation of a domestic
mammal.

WHAT WE CLAIM IS:—

1. A method of treating a domestic mam-
mal for the prevention or minimisation of in-
festation by insects of the order Diptera which
comprises application to the mammal of a
non-toxic, infestation prevention or minimisa-
tion effective amount of a compound 3 -

oxybenzyl ($\pm$)*cis* - *trans* - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl)cyclopropane - 1 - carbonylate. Other compounds of formula I include the (+)*trans*, (+)*cis*, ($\pm$)*trans* and the ($\pm$)*cis* isomers. These compounds may be made according to the description in Dutch Patent Specification No. 7307130.

Example 1

Control of *S. calcitrans*

Groups of two matched Friesian steers were sprayed, each with one litre of compound Ia at 0.01%, 0.025% and 0.050% w/v. The pairs were exposed almost daily in a fly chamber after treatment to approximately 100 starved *S. calcitrans*. The numbers of flies landing on the steers was counted over a 7 minute observation period. Counts at 1 and 2 minutes after treatment were discarded and an average taken for the group over the 3-7 minute period.

Mean fly counts

Days post treatment	0.01%	0.025%	0.05%
25 PRE	27.1	>24.1	25.4
1	10.9	4.6	5.9
2	—	4.9	—
4	10.7	5.2	4.7
5	17.1	8.4	5.5
30 6	16.5	7.2	6.0
7	13.4	8.1	8.0
8	13.1	10.7	6.7
11	8.3	8.6	7.0
12	16.6	13.1	7.6
35 13	14.7	10.8	14.3
14	25.0	15.6	11.7
15	—	18.2	13.4
18	—	12.2	11.7
19	—	17.7	17.1
40 20	—	20.1	15.1
21	—	—	17.5

Flies feeding in quantity were first noted at 5 days 0.01%, 14 days 0.025% and 13 days 0.05%. Protection afforded by 0.025% and 0.05% treatment appear similar; both are superior to the 0.01% treatment.

Flies were collected after exposure and retained for 24 hours to observe mortality:—

0.01% engorged flies—

50% at 6 days, 0% thereafter
unengorged flies—
100% at 1 day, decrease to 0% at 13 days

0.025% engorged flies—

100% to 8 days decrease to 20% at 19 days
unengorged flies—
100% to 8 days decrease to 80% at 19 days

0.05% engorged flies—

100% to 6 days, 50% at 7 and 8 days, 100% at 11 and 12 days, decrease to 14% at 14 days

unengorged flies—

100% to 18 days, 62% at 21 days.

The control of unengorged flies is superior to that of engorged flies. An increase in concentration gives an increase in length of control.

Reference Example 2

Miscible Oil Formulation

Compound Ia	21% w/w	
Trimethyl Benzenes (Aromasol H)	67% "	75
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Compound Ia	20% w/w	
Diatomaceous Earth	74% "	90
Sodium Salt Naphthalene Sulphonic Acid	5% "	
Alkyl Phenol Ethylene Oxide Condensate 2-12 mol.	1% "	95

Reference Example 5

Pour-On Formulation

Compound Ia	20% w/w	
Trimethyl Benzenes	20% "	100
Vegetable Oil	60% "	

Reference Example 6

Containers

Each of the formulations of Reference Examples 2 to 5 were packed in sealed containers, each container labelled with indications of the suitability of its contents to control a Diptera infestation of a domestic mammal.

WHAT WE CLAIM IS:—

1. A method of treating a domestic mammal for the prevention or minimisation of infestation by insects of the order Diptera which comprises application to the mammal of a non-toxic, infestation prevention or minimisation effective amount of a compound 3 -



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- 5 phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate or of a formulation comprising said compound in intimate admixture with a carrier or diluent therefor.
- 10 2. A method according to claim 1 wherein the mammal is an ungulate.
- 10 3. A method according to claim 2 wherein the mammal is selected from cattle, sheep and horses.
- 15 4. A method according to any of claims 1 to 3 wherein the insects are selected from Simuliidae, Tabanidae, Muscidae, Calliphoridae and Oestridae.
- 15 5. A method according to any of claims 1 to 3 wherein the insects are selected from Tabanidae and Muscidae.
- 20 6. A method according to any of claims 1 to 3 wherein the insects are Muscidae.
- 20 7. A method according to any of claims 1 to 3 wherein the insects are selected from *Stomoxys calcitrans*, *Haematobia* sp. and *Lyperosia* sp.
- 25 8. A method according to any of claims 1 to 7 wherein a formulation as defined in claim 1 is applied to the animal.
- 30 9. A method according to claim 8 wherein the formulation contains 0.025% w/v to 1% w/v of 3 - phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate.
- 10 8 and 9 wherein the carrier or diluent in the formulation is a solid or gas.
- 35 11. A method according to claim 10 wherein the formulation contains 0.5% w/v to 1.0% w/v of 3 - phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate.
- 40 12. A method according to either of claims 8 and 9 wherein the carrier or diluent in the formulation is a liquid.
- 45 13. A method according to claim 12 wherein the formulation contains 0.025% w/v to 0.1% w/v of 3 - phenoxybenzyl - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate.
- 50 14. A method according to claim 13 wherein the formulation is reapplied to the mammal after an interval of one week.
- 55 15. A method according to any of claims 1 to 14 which comprises application to the mammal of 3 - phenoxybenzyl ($\pm$) *cis-trans* - 2,2 - dimethyl - 3 - (2,2 - dichlorovinyl) cyclopropane - 1 - carboxylate or a formulation thereof.
- 60 16. A method of treating a domestic mammal for the prevention or minimisation of infestation by insects of the order Diptera, substantially as hereinbefore described with particular reference to Example 1.
- L. D. JENKINS,
Agent for the Applicants,
Chartered Patent Agent.

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