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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. S.

Re: Expediente No. 03.067.907

Solicitud de patente de invención titulada: "COMPOSICIONES PARASITICIDAS Y MÉTODOS DE USO"

Solicitante: SCHERING PLOUGH LTD.

Ntra. Ref: P2003/000083

RESPUESTA AL OFICIO No. 0754 NOTIFICADO POR FIJACIÓN EN LISTA No. 08, DE FECHA 23 DE ENERO DE 2009.

(SEGUNDO EXAMEN DE FONDO)

CARLOS OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado sustituto de la sociedad solicitante, tal como consta en la sustitución de poder adjunta, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado** que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar esta solicitud. Para tal efecto, adjunto un recibo de pago que cubre la tasa de modificación correspondiente.

Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- Se eliminan las Reivindicaciones 1-5, 7, 10-14 y 16-17.
- La nueva Reivindicación 1 se dirige específicamente a composiciones que comprenden: una piretrina y un vehículo que puede ser d-limoneno o d-limoneno junto con éter monometílico de propileneglicol.

Valga anotar que las anteriores modificaciones en ningún momento corresponden a una ampliación de la materia originalmente revelada por la presente solicitud, por el contrario, el

Capítulo Reivindicatorio Modificado es una franca limitación de lo originalmente reclamado, cumpliendo así con lo dispuesto por el Artículo 34 de la Decisión 486.

2. a- El Examinador insiste en que las patentes US 5.236.954 (D1) y US 5.942.525 (D2) afectan la novedad y el nivel inventivo de la presente solicitud

El Examinador señala que D1 revela una composición parasiticida para aplicación tópica que comprende: una piretrina o un piretroide y un vehículo que comprende un terpeno (citronelo) y/o un éter alquil glicólico. Según el Examinador, las características esenciales de la composición de las Reivindicaciones 1 y 2 de la presente solicitud habían sido previamente divulgadas en D1, por lo que las mismas no son novedosas. Sin embargo, el Examinador establece que las Reivindicaciones 3 y 7, que presentan como característica esencial el terpeno d-limoneno, sí podrían considerarse novedosas.

Adicionalmente, el Examinador anota que el estado de la técnica más cercano es D1, el cual revela una composición empleada para el mismo propósito que la composición reivindicada, con la única diferencia que la composición divulgada en D1 no comprende limoneno. Sin embargo, el Examinador señala que D2 revela composiciones que comprenden una piretrina o piretroide y un vehículo que incluye d-limoneno, por lo que la presente invención puede resultar derivada de la información revelada en D1 en combinación con D2.

Adicionalmente, el Examinador señala que el problema de prevenir la cristalización de composiciones que contienen altas cantidades de piretrina ya había sido resuelto en el arte previo, puesto que las composiciones divulgadas en D1 no cristalizaban a bajas temperaturas, y el reemplazo de un terpeno (citronelo) por limoneno, conocido a partir de D2, resultaría obvio para el experto en la materia.

b- i) En primer lugar, y tal como lo reconoció el Examinador en su Oficio No. 754, D1 no revela composiciones que comprendan una piretrina y un vehículo, donde dicho vehículo esté constituido específicamente por d-limoneno, o por d-limoneno en combinación con éter monometílico de propilenglicol, tal como se reclama en el Capitulo Reivindicatorio Modificado. Por lo tanto, considero superada cualquier objeción dirigida a la falta de novedad de la presente invención.

ii) En cuanto al nivel inventivo de las formulaciones reivindicadas, me permito llamar nuevamente la atención al hecho que la presente invención proporciona un sistema de solventes que previene o minimiza la cristalización de piretroides o piretrinas,

particularmente de permetrina, a bajas temperaturas, constituido por d-limoneno, opcionalmente en combinación con éter monometílico de propilenglicol. De hecho, tal como se demuestra en el Capítulo Descriptivo, las composiciones de la presente invención no cristalizan a temperaturas inferiores a 20°C, aún con concentraciones de permetrina mayores al 50% (preferiblemente 65%), permitiendo así la administración tópica de pequeñas cantidades de la formulación, para control efectivo de ectoparásitos.

Como lo mencioné en mi respuesta al primer examen de fondo, el arte previo (D1 y D2) no proporciona referencia alguna acerca de la inestabilidad desventajosa de composiciones que contienen permetrina, especialmente cuando se formulaban en altas concentraciones, como al 65%. Por el contrario, la presente solicitud aborda el problema relacionado con la inestabilidad de composiciones que contienen piretroides y piretrinas, que cristalizan a temperaturas inferiores a 20°C, lo que reduce significativamente la dosis de medicamento que es finalmente administrado. La persona medianamente versada en la materia con conocimiento de D1 y D2 no hubiera estado al tanto de los problemas resueltos por la presente invención y no hubiera encontrado motivación alguna para formular una composición con el propósito específico de evitar la cristalización del ingrediente activo. La presente invención ha encontrado inesperadamente que composiciones de piretroides que comprenden un vehículo compuesto por d-limoneno, o por d-limoneno en combinación con éter monometílico de propilenglicol, previene la cristalización indeseable del principio activo.

Una vez más, una persona medianamente versada en la materia, siguiendo las enseñanzas del arte previo citado por el Examinador, no hubiera estado motivada a formular un vehículo que evitara la cristalización de la permetrina, y aún menos, a usar d-limoneno como el ingrediente clave que produce el efecto de estabilidad deseado. Aunque D1 se refiere a composiciones que contienen permetrina en cantidades mayores al 50%, esta referencia no contiene mención alguna a las desventajas de la cristalización de este principio activo cuando se encuentra en formulaciones líquidas. **D1 no proporciona sugerencia alguna acerca de como prevenir la cristalización de la permetrina**. De otra parte, las enseñanzas de D2 solamente proporcionan enseñanzas que sugieren la formulación de permetrina en cantidades inferiores al 50% (p.ej. 45%), utilizando únicamente solventes oleosos, medio en que el fenómeno de cristalización no se presenta. Adicionalmente, aunque D2 enseña el uso de d-limoneno, dicha referencia en ningún momento aplica este componente como agente estabilizante para formulaciones altamente concentradas como lo aplica la presente invención, **D2 utiliza D-limoneno solamente como fragancia**.

En conclusión, dado que D1 no proporciona información acerca de la inestabilidad en las composiciones de interés (cristalización en soluciones concentradas), y D2 usa solventes oleosos

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(que no tienen dicha desventaja de estabilidad) y D-limoneno solamente como fragancia, no hay motivación alguna en el arte previo para combinar las divulgaciones de D1 y D2, específicamente buscando superar el fenómeno de cristalización identificado en la presente solicitud.

iii) Ahora bien, en relación con los argumentos específicos del Examinador en respuesta a mi memorial al primer examen de fondo, me permito anotar lo siguiente:

- La Tabla 1 del Capítulo Descriptivo demuestra que las formulaciones sugeridas en el arte previo (es decir, que no incluyen d-limoneno) y que solo incluyen un éter alquil glicólico, tal como dipropilenglicol monometil éter (usado en D1), solidifican a 15°C. Esto es, las composiciones del arte previo sí cristalizan a bajas temperaturas. Por el contrario, las composiciones de la presente invención que comprenden d-limoneno, no cristalizan, aún a la temperatura más baja de 15°C. Adicionalmente, debo llamar respetuosamente la atención del Examinador al hecho que D1 solo sugiere el empleo de éter monometílico de dipropilenglicol, no de éter monometílico de propilenglicol, presente en las composiciones reclamadas en la nueva Reivindicación 1, el cual proporciona menor número de cristales a baja temperatura (Tabla 2).
- El arte previo no sugiere el uso de vehículos que incluyan una mezcla de d-limoneno y un éter alquil glicólico, con el propósito específico de mejorar la solubilidad de una alta concentración de permetrina. De hecho, D2 revela el uso de d-limoneno como fragancia y el empleo de cantidades reducidas de principio activo.
- Nada en el arte previo enseña o siquiera sugiere que las mezclas de d-limoneno y éter monometílico de propilenglicol resultarían en soluciones con mejores propiedades de disolución para la permetrina, en comparación con los solventes independientes.
- Los resultados de los Ejemplos 3A-3D, demuestran claramente que la permetrina presenta la mayor solubilidad en d-limoneno. En orden de solubilidad decreciente, los solventes evaluados fueron: (1) d-limoneno; (2) éter monometílico de propilenglicol; (3) éter monometílico de dipropilenglicol (sugerido en D1); (4) éter monometílico de dietilenglicol; y (5) 2-metil-2,4-pentandiol (hexilenglicol). Por lo tanto, la afirmación del Examinador que la solubilidad de la permetrina en d-limoneno no es diferente en comparación con otros solvente o mezclas de solventes, es evidentemente equivocada.

De acuerdo con lo anterior, debo subrayar enfáticamente que las composiciones de la presente invención, tal y como se reclaman en el Capitulo Reivindicatorio Modificado, presentan efectos sorprendentes e inesperados que demuestran su altura inventiva.

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3. Para terminar, deseo poner bajo su conocimiento el hecho que en relación con la invención de la presente solicitud además de la Oficina Mexicana, también ha sido otorgado el privilegio de patente por parte de oficinas de patente en China, Nueva Zelanda, Perú, Filipinas, Rusia, Singapur, Taiwán, Ucrania, Estados Unidos y SurAfrica.

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, éstas sí corresponden a un fuerte indicio sobre el cumplimiento de los requisitos de patentabilidad, puesto que los requisitos de novedad y nivel inventivo son requisitos universales y objetivos.

4. Según todo lo anterior, considero que las objeciones interpuestas por el Examinador en cuanto a novedad y nivel inventivo de la solicitud han sido superadas, cumpliendo a cabalidad con lo dispuesto por la Decisión 486; en consecuencia, solicito respetuosamente que se proceda con la concesión del privilegio de patente.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295
Anexos:

- Capítulo Reivindicatorio Modificado.
- Recibo de pago correspondiente a la tasa de modificación.
- Sustitución de poder legalizada


DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA
NOTARÍA
46
EL ANTERIOR ESCRITO DIRIGIDO A
FUE PRESENTADO PERSONALMENTE
ANTE EL SUSTRITO NOTARIO CUARENTA
Y SEIS DE BOGOTÁ, D.C. POR:
Con C.C.
Y ADEMÁS DECLARÓ QUE
ES CIERTO Y QUE
PUESTA POR EL
EL DECLARANTE
HOY:
2 1 ABR 2009
NOTARIA CUARENTA Y SEIS
REPUBLICA DE COLOMBIA
REPUBLICA DE COLOMBIA
MARIA EUGENIA ROJAS DE URUETA
NOTARIA
Notaría 46 - Bogotá. D.C.

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CAPITULO REIVINDICATORIO MODIFICADO
(Segundo Examen de Fondo)

1. Una composición parasiticida para aplicación tópica a un animal que comprende un piretroide ó una piretrina y un vehículo, en donde dicho vehículo comprende d-limoneno ó una mezcla de d-limoneno y propilenglicol monometil eter.

2. La composición de la Reivindicación 1, en la cual dicho piretroide es permetrina.

3. La composición de la Reivindicación 2, en donde dicha permetrina está presente en una cantidad mayor al 50% en peso de la composición total.

4. La composición de la Reivindicación 3, donde dicha permetrina está presente en una cantidad del 65% en peso de la composición total.

5. La composición de la Reivindicación 1, donde dicho vehículo está presente en una cantidad del 30% al 70% en peso de dicha composición.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 03-067907- -00008-0000

Fecha: 2009-04-21 16:19:17 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 29,968
FECHA : ABRIL 21 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800251	20/04/2009	1,776,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	111,000.00
		TOTAL : $	111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

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Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 03.067.907
Solicitud de patente de invención titulada: "COMPOSICIONES PARASITICIDAS Y MÉTODOS DE USO"
Solicitante: SCHERING PLOUGH LTD.
Ntra. Ref: P2003/000083

SUSTITUCIÓN DE PODER

J. IAN RAISBECK LLINAS, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **CARLOS R. OLARTE**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá, y portador de Tarjeta Profesional de Abogado No. 74.295 expedida por el Consejo Superior de la Judicatura, para que sea el quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

J. IAN RAISBECK
C.C. No. 79.376.996 de Bogotá
T.P. 135.799 del C. S. de la J.

DILIGENCIA DE PRESENTACIÓN PERSONAL Y RECONOCIMIENTO DE CONTENIDO Y FIRMA

NOTARÍA 46

EL ANTERIOR ESCRITO DIRIGIDO A Industria y Comercio

FUE PRESENTADO PERSONALMENTE ANTE EL SUSCRITO NOTARIO CUARENTA Y SEIS DE BOGOTÁ D.C. POR

Con C.C.

Y ADEMÁS DECLARÓ QUE EL CONTENIDO DEL ANTERIOR DOCUMENTO ES CIERTO Y QUE LA FIRMA QUE LO AUTORIZA FUE PUESTA POR EL.

EL DECLARANTE:

HUELLA

HOY: 21 ABR 2009

MARÍA EUGENIA ROJAS DE URUETA
NOTARIA CUARENTA Y SEIS
REPÚBLICA DE COLOMBIA

NOTARÍA CUARENTA Y SEIS

REPÚBLICA DE COLOMBIA
MARÍA EUGENIA ROJAS DE URUETA
NOTARIA
Notaría 46 - Bogotá D.C.

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US005236954A

United States Patent [19]

Gladney et al.

[11] Patent Number: 5,236,954

[45] Date of Patent: Aug. 17, 1993

[54] PARASITICIDAL COMPOSITION AND METHODS FOR ITS MAKING AND USE

[75] Inventors: Julie G. Gladney, McKinney, Tex.; David S. Seymour, Kansas City; Jack I. Shugart, Gurnee, Ill.; Robert G. Pennington, Rayville, Mo.

[73] Assignee: Pitman-Moore, Inc., Mundelein, Ill.

[21] Appl. No.: 707,629

[22] Filed: May 30, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 487,913, Mar. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/215; A61K 31/275

[52] U.S. Cl. 514/531; 514/521

[58] Field of Search 514/521, 531

[56] References Cited

U.S. PATENT DOCUMENTS

2,074,188	3/1937	Rippert	514/72
4,404,223	9/1983	Matthewson	424/305
4,595,579	6/1986	Broadbent	514/65
4,607,050	8/1986	Kieran et al.	514/531
4,731,378	3/1988	Naik et al.	514/331
4,904,464	2/1991	Albanese	514/65

FOREIGN PATENT DOCUMENTS

0045424	2/1982	European Pat. Off. .	
0061208	9/1982	European Pat. Off. .	
2436028	2/1976	Fed. Rep. of Germany	514/72
2002635	2/1979	United Kingdom .	
2088212	6/1982	United Kingdom	514/65

Primary Examiner—Allen J. Robinson

Attorney, Agent, or Firm—Wendell Ray Guffey; Penny R. Slicer

[57] 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 mammal is also described. The composition can be applied as a small dose to a localized region of the animal's body which is then delivered to relatively all of the animal's body surface by migration of the pyrethroid.

28 Claims, No Drawings

PARASITICIDAL COMPOSITION AND METHODS FOR ITS MAKING AND USE

This is a continuation-in part of U.S. patent application Ser. No. 07/487,913, filed on Mar. 5, 1990 and now abandoned which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

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% by weight of the total composition.

Ectoparasidic arthropods such as ticks, flies and fleas are often found on mammals, such as humans and a variety of animals. Ectoparasites will feed off their mammal host and are a constant source of irritation to the host. It is therefore desirable to control such infestations. By control, it is meant that, desirably, about 80% by weight of all parasites on the host are killed or repelled. Control of tick infestation on all mammals, especially household pets, has recently assumed greater importance than at an other recent time because of the discovery that certain tick species may carry the microorganism 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 host in order to create the insecticidal effect. Systemic insecticides are generally less desirable if suitable alternatives exist. 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% by weight 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. However, known compositions do not encompass the formulation of liquid compositions containing pyrethroid in an amount greater than 50% by weight of the total composition, 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, or would cause severe skin irritation. The present invention encompasses a topical formulation of greater than 50% by weight of a pyrethroid that is non-irritating and non-toxic to the host animal. The present invention also encompasses a method of controlling ectoparasites wherein the total formulation can be applied as a small dose to one or more localized regions on the skin of the hosts. The concentrated formulation applied in this manner spreads over relatively all of the body surface of the host and effectively controls ectoparasites.

Although applicant does not wish to be bound by theory or speculation, 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 other undesirable and irritating components. 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% by weight make topical application of the composition more convenient and more aesthetic than ever before. The higher the concentration, the smaller the dose for effective ectoparasite control. A small dose can be applied to a relatively small region of the skin, thus preventing the host from being covered with solvent. This formula and method of application is particularly useful for treating domestic animals, because the animal will not drip solvent or feel sticky when petting immediately after application. Such small doses can be applied without the treated animal being made aware thus easing administration. Although the composition is applied as one or more small doses to a localized region on the animal, the pyrethroid translocates to effectively control ectoparasite infestation over relatively all of the animal. Formulations containing more than 50% by weight of a pyrethroid thus obtain many advantages not taught by the prior art of using formulations with maximum concentrations of up to 50% by weight of the total formulation.

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, or may be as a microencapsulation and carried in a suspension. 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. 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% by weight of the formulation so that the smallest effective dose may be achieved. Although the mechanism is not fully known, it is thought that during application and while on the host, either or both the carrier components and the active agent of the formulation facilitates distribution of the agent over the surface of the animal and to the parasite. The carrier may also facilitate migration of the pyrethroid component to cover relatively all of the animal body surface for effective ectoparasite control. 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% by weight can be packaged in a single dose package. For example, a single 1 cubic centimeter (cc) dose of a liquid formulation comprised of permethrin and 35% 2-(2-methoxy-ethoxy)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 containers, possibly 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.

SUMMARY OF THE INVENTION

It has been discovered that a composition including a pyrethroid in concentrations greater than 50% and up to 95% by weight of the total composition can be prepared and that said highly concentrated composition is effective for topical application for control of ectoparasites such as fleas, flies, and ticks on some mammals, while remaining non-toxic and non-irritating to the host.

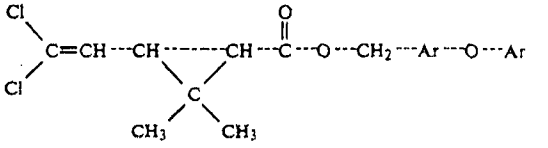
In one aspect of the invention the pyrethroid used is permethrin. The composition preferably comprises 65% by weight permethrin in a carrier, preferably the solvent carrier 2-(2-methoxyethoxy)ethanol. The composition may include other inert ingredients such as perfumes, skin conditioners or coat sheeners. A preferred composition is in a pourable form so that it can be easily applied to the fur or 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.

Another aspect of this invention encompasses a method for administering an effective amount of pyrethroid to control ectoparasite infestation over the entire body surface of the host. A composition comprising a pyrethroid, preferably permethrin, in an amount ranging from above 50% and up to 95% by weight is applied as one or more small doses to one or more localized regions on the host. Although the exact mechanism is not known, it is thought that the pyrethroid component translocates by migration to cover relatively all of the mammal's body surface within a short period of time. The concentrated dose thus effectively controls ectoparasite infestation over the entire body surface of the host.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a composition for controlling ectoparasites that can be found on mammals and to 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, phenothrin, cypermethrin, cyhalothrin, lambda cyhalothrin, cyfluthrin, cyphenothrin, tralomethrin, tralocythrin, deltamethrin, sluvalinate fluvinate, 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:



[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 tran isomer of about 45% by weight and a minimum amount of cis isomer of about 35% by weight.

In the formulation of an ectoparasiticide composition according to the instant invention the concentration of permethrin is from above 50% up to about 95% (by weight) with a preferred range of 60–70% (by weight) and a most preferred range of 65–70% (by weight). The remaining portion of the composition is a carrier substance.

Any carrier that can deliver a pyrethroid, preferably permethrin, 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 contact with or 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. A particularly effective method of application consist of applying the composition to one or more localized regions of the host, such as by applying a small spot of the composition on an animal at the region between its shoulder blades. It is believed that the pyrethroid component translocates within a relatively short period of time to effectively cover the entire surface of the host's body. No special expertise is required to apply the treatment so animal owners may do so without the assistance of a health care professional and without special equipment.

Other inert ingredients can be added to the present composition and can include spreading agent, synergists, attractants, repellents, adhesion promoters, surface active agents, stabilizers, skin conditioners, perfumes, coat sheeners and coloring agents. Additional

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 4× 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.

What is claimed is:

1. A parasiticidal composition for topical application to mammals comprising a pyrethroid in a carrier, wherein said carrier is an alkyl glycol ether and said pyrethroid is present in an amount greater than 50% and up to about 95% by weight of the total composition.

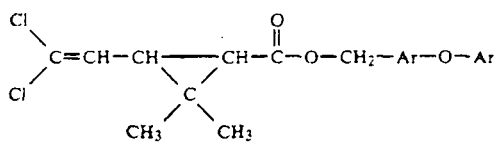
2. A composition according to claim 1, wherein said carrier is present in an amount ranging from 5% to about 50% by weight of the total composition.

3. A composition according to claim 2 wherein said alkyl glycol ether is selected from the group consisting of 2-(2-butoxyethoxy) ethanol and 2-(2-methoxyethoxy)ethanol.

4. A composition according to claim 1 wherein said pyrethroid is dissolved in said carrier.

5. A composition according to claim 1, wherein said pyrethroid is selected from the group consisting of permethrin, phenothrin, deltamethrin, cypermethrin, cyhalothrin, lambda cyhalothrin, flumethrin, cyfluthrin, cyphenothrin, sluvalinate fluvinate, tralomethrin, tralocythrin, and fenvalerate.

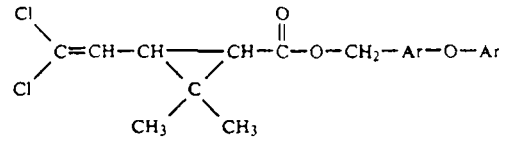
6. A composition according to claim 5, wherein said permethrin is selected from the group consisting of compositions of the formula:



and stereo isomers thereof, Ar is a phenyl group.

7. A composition according to claim 1, wherein said pyrethroid is present in an amount of about 65% by weight of the total composition.

8. A composition according to claim 7, wherein said pyrethroid is a permethrin selected from the group consisting of compositions of the formula:



and stereo-isomers thereof, Ar is a phenyl group.

9. A composition according to claim 7, wherein said alkyl glycol ether is present in an amount of about 35% by weight of the total composition.

10. A composition according to claim 9, wherein said alkyl glycol ether is selected from the group consisting of: 2-(2-butoxyethoxy) ethanol, 2-(2-methoxyethoxy)ethanol and mixtures thereof.

11. A method of non-systemically controlling ectoparasite infestation on mammalian hosts comprising topically applying a parasiticidal composition to a localized external region on the mammal, said parasiticidal composition comprising a pyrethroid in a carrier said pyrethroid present in an amount greater than 50% and up to about 95% by weight of the total composition.

12. A method according to claim 11, wherein said method comprises applying said composition to one or more external localized region on the mammal, said composition comprising a pyrethroid in an alkyl glycol ether carrier.

13. A method according to claim 11 wherein said applying step comprises topically applying a parasiticidal composition on said mammal, said composition comprising a pyrethroid in a carrier wherein said carrier is selected from the group consisting of 2-(2-butoxyethoxy) ethanol and 2-(2-methoxyethoxy)ethanol.

14. A method according to claim 11, wherein said applying step comprises topically applying said parasiticidal composition to a localized external region on a mammal, said mammal selected from the group consisting of humans, dogs, cattle, giraffes and horses.

15. A method according to claim 14, wherein said applying step comprises topically applying said parasiticidal composition to a localized external region on a mammal, said mammal being a dog.

16. A method according to claim 11, wherein said applying step comprises topically applying 33.3 milligrams of said parasiticidal composition on the mammal per kilogram of said mammal's body weight.

17. A method according to claim 11 wherein said method of applying said composition to one or more localized external regions on the mammal is effective as a method for administering the pyrethroid component onto relatively all of the mammal's body surface.

18. A method according to claim 15 wherein said method of applying said composition to one or more localized external regions on the mammal comprises applying the composition to one or more regions each ranging from one to four cubic centimeters in size.

19. A method according to claim 17 wherein said method comprises applying said composition to one localized external region on the mammal.

20. A method according to claim 17 wherein said method comprises applying said composition to two localized external regions on the mammal.

21. A method according to claim 18 wherein said method of applying said composition to a localized external region on the mammal comprises applying said composition to a localized external region on the mammal as a spot.

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United States Patent [19]

Pennington et al.

[11] **Patent Number: 5,942,525**

[45] **Date of Patent: *Aug. 24, 1999**

[54] **SPOT TREATMENT OF ANIMALS WITH PYRIPROXYFEN AND AN INSECTICIDE**

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[73] Assignee: **Ecto Development Corporation**, Excelsior Springs, Mo.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/796,593**

[22] Filed: **Feb. 7, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/438,950, May 11, 1995, abandoned.

[51] **Int. Cl.**[6] **A01N 43/40**; A01N 53/00

[52] **U.S. Cl.** **514/345**; 514/531

[58] **Field of Search** 514/345, 521, 514/531

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,178,384	12/1979	Ensing	424/305
4,764,529	8/1988	Naik et al.	514/531
4,780,459	10/1988	Matthewson	514/136
4,826,874	5/1989	Bonin et al.	514/521
4,879,292	11/1989	Nishida et al.	514/241
5,057,527	10/1991	Alig et al.	514/345
5,236,954	8/1993	Gladney et al.	514/531
5,266,324	11/1993	Stendel et al.	424/411
5,286,749	2/1994	Kieran et al.	514/531
5,310,557	5/1994	Brandt et al.	424/411

FOREIGN PATENT DOCUMENTS

0 576 267 A1	6/1993	European Pat. Off. .

OTHER PUBLICATIONS

Introduction of Vitellogenin Synthese in *Locusta migratoria*by the Juvenile Hormone Analog, Pyriproxyfen, Gordon C. Edwards, Ralph P. Braun, and Gerard R. Wyatt, published in the J. Insect Physiol, vol. 39,No. 7, pp. 609–614, 1993.

Worthing et al, The Pesticide Manual, 9th Ed. (1991) pp. 662–663.

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[57] **ABSTRACT**

A method for treating animals to rid the animal's body of ectoparasites such as fleas and ticks comprising applying a spot treatment of a composition to the exterior surface of the animal's body containing a growth regulating effective amount of pyriproxyfen or derivatives thereof and an insecticide.

5 Claims, No Drawings

SPOT TREATMENT OF ANIMALS WITH PYRIPROXYFEN AND AN INSECTICIDE

CROSS REFERENCE TO RELATED APPLICATION

The present application is a continuation of U.S. application for patent Ser. No. 08/438,950 filed May 11, 1995 on SPOT TREATMENT OF ANIMALS WITH PYRIPROXYFEN AND INSECTICE, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to the general field of controlling insect pests with chemical agents and in particular to the spot treatment of animals with an insect growth regulator.

Parasitic infestation by fleas, ticks and the like of domestic animals, such as dogs and cats, results in considerable nuisance, pain and possible harm to the infested animals as well as the animals'owners. Such infestation also results in the transmission of disease to and between humans and domestic animals. For this reason effective control of such parasites has always been desirable and necessary.

Adult fleas generally live in the coat and surrounding environment of the host animal. They feed on the host's blood and lay their eggs in the host's coat. Many of the flea eggs do not stick to the animal, because they are not glued to the coat or skin, and so the eggs fall off the animal into the surrounding environment. Insecticides applied to the animal will generally kill the adult fleas on the animal, but are not generally effective in killing the egg or pupated stages of the fleas because these stages are not normally on the animal. Except where an insecticide has an extremely long effective or residual life, use of such insecticides generally does not prevent re-infestation at the time when the eggs released by fleas prior to or during treatment subsequently hatch, mature through a pupa stage and return to the animal as adults.

Active compounds which inhibit the growth of parasites, such as fleas, have been developed and are applied to the host animal. It is believed by applicants that these compounds either contaminate the eggs or are incorporated into the eggs and thereby effect growth of the eggs and pupae and also thereby prevent eggs and pupated stages of the parasites from developing into adults. In this manner the fleas are prevented from subsequently breeding and re-infestation. Pyriproxyfen or 2-1-methyl-2-(4-phenoxyphenoxy) ethoxy pyridine is a known insect growth regulator, as are insect growth regulators (IGRs) such as lufenuron, diflubenzuron, methoprene and fenoxycarb. U.S. Pat. No. 5,266,324 discloses use of pyriproxyfen in collars for domesticated animals. Applicant understands that formulations containing pyriproxyfen at concentrations of approximately 0.125% by weight have been applied to dogs and cats as a whole body spray or dip to prevent the hatching or maturation of flea eggs and larvae.

Application methods other than collars are desirable because many pet owners consider the collars unsightly and ineffective. Further, such collars often annoy the pets to which they are secured. Application of the active compound through dips or sprays is often undesirable in that such treatments, particularly dips, are difficult to administer and often result in considerable stress to the treated animals. Further, such applications require relatively large amounts of solvent and in the case of dips often result in the waste of considerable excess material.

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating animals to rid the animal's body of ectoparasites and to prevent eggs that are laid by the parasites from maturing into adults even when the eggs fall off the animal that has been treated. The method comprises applying to a selected portion of the exterior surface of the animal's body, especially a single or dual spot dosage, a composition containing a growth regulating effective amount of pyriproxyfen or derivatives thereof, so as to provide sustained control of parasites for approximately 90 to 120 days by killing parasite eggs directly, by preventing eggs from developing into larvae or pupae and/or by preventing pupae from maturing into adults. In a preferred embodiment of the invention a general insecticide, especially a pyrethroid, is incorporated in the composition to kill parasitic adult stages of the ectoparasites especially those present on the animal at time of treatment or those that transfer to the animal from another source. The present invention has been found to be especially effective against ectoparasitic insects such as fleas and certain arachnids such as ticks.

OBJECTS AND ADVANTAGES OF THE INVENTION

Therefore, it is an object of this invention to provide a method for controlling parasite insects such as fleas and arachnids such as ticks from animals; to provide such a method comprising the spot application of a growth regulating effective amount of pyriproxyfen to the infected animal; to provide such a method which further comprises the spot application of an insecticidal effective quantity of a pyrethroid in combination with the pyriproxyfen; to provide such a method which is convenient to apply and reduces the stress on the animal treated; to provide such a method that does not require use of a collar or other fixed carrier; to provide such a method that provides sustained and long lasting parasite control for approximately 90 to 120 days; and to provide such a method which is relatively inexpensive and particularly well adapted for its intend purpose thereof.

DETAILED DESCRIPTION OF THE INVENTION

As required, detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely exemplary of the invention, which may be embodied in various forms. Therefore, specific composition and functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the present invention in virtually any appropriately detailed structure.

For the purpose of this application the term ectoparasites should be deemed to include parasitic insects such as fleas and mosquitos, parasitic arachnids such as ticks and related pests and parasites of warm-blooded animals.

The present invention is directed to a method for treating animals, especially mammals such as dogs, cats and livestock, to control parasitic insects such as fleas and arachnids such as ticks and other insect pests through the application of a formulation comprising an insect growth regulating effective concentration of pyriproxyfen and the composition itself. Pyriproxyfen 2-(1-methyl-2-(4-phenoxyphenoxy)-ethoxy)-pyridine has a chemical formula of:

EXAMPLE I

Flea/Tick Treatment Efficacy Study

The efficacy of a treatment of dogs with a formulation in accordance with the present invention identified as Formulation A, having 45% by weight permethrin and 5% by weight pyriproxyfen, was studied in comparison to the efficacy of a treatment with a formulation comprising 65% by weight permethrin and no pyriproxyfen which is commercially available under the trademark ExSpot and identified as Formulation B and also in comparison to a control group of animals that were treated with nothing. The following groupings of test animals, three dogs per group, were used in the study:

- Group A1: Dogs weighing less than 33 pounds and treated with one 1.5 ml spot application (shoulder) of the Formulation A in accordance with the present invention.
- Group A2: Dogs weighing more than 33 pounds and treated with two 1.5 ml spot applications (shoulder and in front of tail) of the Formulation A.
- Group B1: Dogs weighing less than 33 pounds and treated with one 1 ml spot application (shoulder) of Formulation B.
- Group B2: Dogs weighing more than 33 pounds and treated with two 1 ml spot applications (shoulder and front of tail) of Formulation B.
- Group C1: Dogs weighing less than 33 pounds and untreated.
- Group C2: Dogs weighing more than 33 pounds and untreated.

Prior to infestation, all the dogs were combed to remove fleas and ticks were removed by hand. On Test Day—1, each dog was infested with approximately 100 unfed adult fleas and approximately 50 unfed adult ticks. On Test Day 0, the dogs were treated as follows: the dogs in Test Group A1 received a spot application comprising 1.5 ml of Formulation A applied at the skin level between the shoulder blades; the dogs in Test Group A2 received separate 1.5 ml doses of Formulation A at skin level between the shoulder blades and on the back directly above the head of the tail; the dogs in Test Group B1 received 1.0 ml of Formulation B at the skin level between the shoulder blades; the dogs in Test Group B2 received separate 1.0 ml doses of Formulation B between the shoulder blades and on the back directly above the head of the tail; and the dogs in Test Groups C1and C2 were not treated.

Each dog was reinfested with approximately 100 unfed adult fleas and approximately 50 unfed adult ticks on Test Days 10, 17 and 24 (away from the sites of application for each formulation). On test days 1–3, 11–13, 18–20 and 25–27 hand body counts were conducted to determine the number of live fleas and ticks and formulation efficacies. On Test Days 45 and 90 each dog in Test Groups A1and A2 and C1and C2 was infested with approximately 150–200 unfed adult fleas (away from the sites of the formulation application).

Flea ova collections were made on the fourth day following each of these infestations. Approximately 100 ova (if available) were collected from each dog on these days. The ova were observed for larval hatch at approximately 72 hours post-collection. A flea growth medium was added to the dishes containing the larva and adult flea counts were made at 21, 28 and 35 days following collection to determine how many, if any, larva matured to adults. One dog from each of groups A1, A2, C1and C2 was then infested again at Test Day 119 with follow-up ova collection on Test Day 122.

On test Days 4 and 27, hair samples were collected and mixed from multiple body sites (but not the sites of the formulation application) on one randomly selected dog from each test group A1, A2, B1, B2, C1and C2. Enough hair was removed from each dog to fill a single glass test tube (20 mm ×150 mm). Each test tube was infested with approximately 15 deer tick nymphs. The mouths of the test tubes were secured with foam stoppers and the test tubes were held under high humidity conditions conducive to tick survival. Live/dead tick counts were conducted at approximately 24 and 48 hours following the test tube infestations.

The percent efficacy against adult fleas and ticks (See Table 1) was calculated after each body count as follows:

((Mean number of live fleas or ticks on untreated dogs—Mean number of live fleas or ticks on treated dogs)/Mean number of live fleas or ticks on untreated dogs)×100.

The percent of adult fleas that developed within 35 days from the actual number of ova seeded at each collection period was used to determine product efficacy (See Table 2) using the following formula:

((Percent of adult fleas in the "control" dishes—Percent of adult fleas in the "treated" dishes)/Percent of adult fleas in the "control" dishes)×100.

The percent efficacy against nymphal deer ticks (See Table 3) was calculated after each count as follows:

((Mean number of live ticks in tubes containing untreated dog hair—Mean number of live ticks in tubes containing treated dog hair)/Mean number of live ticks in tubes containing untreated dog hair)×100.

SUMMARY OF RESULTS FOR EXAMPLE 1

As shown in Table 1 below, Formulation A consistently demonstrated higher levels of efficacy against fleas on dogs weighing less than 33 pounds than did Formulation B. The only exception was on Test Day 3 when Formulation A was 90.9% effective against fleas and Formulation B was 95.5% effective. Formulation A demonstrated a longer period of high levels of efficacy against fleas than Formulation B. The efficacy of the Formulation A against fleas remained above 80% through Test Day 20, whereas the efficacy of Formulation B remained above 80% only through Test Day 13.

In general, both products were equally effective against fleas on dogs weighing more than 33 pounds. Formulation A demonstrated efficacies greater than 90% against fleas through Test Day 20 and was approximately 86% effective against fleas at Test Day 27. Formulation B demonstrated efficacies greater than 86% through Test Day 20 and was approximately 88% effective against fleas at Test Day 27.

In general, both products demonstrated excellent efficacy (100%) against ticks on the smaller dogs beginning on Test Day 11 and remained consistently high (96.8–100%) through Test Day 20. Both products demonstrated acceptable tick efficacy (approximately 80%) at Test Day 27 against ticks on the smaller dogs.

Similarly both products demonstrated excellent efficacies against ticks on the larger dogs beginning on Test Day 11. However, the efficacy of Formulation A against ticks on the larger dogs remained higher than the efficacy of Formulation B throughout the study. In particular the efficacy of Formulation A remained above 94% through Test Day 27 whereas the efficacy of Formulation B dropped to 87% and below beginning on Test Day 25.

As shown in TABLE 3, both products were highly effective against the deer tick nymph regardless of whether the hair used was removed from the smaller or larger dogs. The

general both products were equally efficacious in causing mosquito mortality and in reducing mosquito feedings.

TABLE 4

OVERALL PERCENT (%) EFFICACY AGAINST MOSQUITOES

GROUP	TEST DAY	PERCENT REDUCTION LANDINGS	PERCENT MORTALITY	PERCENT REDUCTION FEEDING
A1	5	56.0	97.2	100
B1	5	26.7	100	100
A1	14	13.5	100	91.9
B1	14	0	100	100
A1	21	14.6	100	100
B1	21	0	100	78.5
A1	28	0	51.9	90.9
B1	28	0	100	100

It is to be understood that while certain forms of the present invention have been illustrated and described herein, it is not to be limited to the specific compositions and methods described.

What is claimed and desired to be secured by Letters Patent is as follows:

1. A method of combating ectoparasites on warm-blooded animals comprising simultaneously externally applying as a spot application and without a time release carrier to said animals a growth regulating effective amount of a pour on enhanced formulation including an amount in a range from about 5% percent to about 50% by weight pyriproxyfen and an ectoparasiticidic effective amount of an ectoparasiticide for adult ectoparasites comprising permethrin in an amount in a range from about 5% to about 50% by weight wherein said enhanced formulation is effective at least over a three month period.

2. The method as disclosed in claim **1** wherein the formulation further includes about 10% by weight mineral oil.

3. The method as disclosed in claim **2** wherein the formulation further includes about 30% by weight D-Limonene.

4. A pour on external spot treatment composition without a time release carrier for use in combating ectoparasites of warm-blooded animals over at least a three month period comprising an enhanced formulation of:

(a) about 5% to about 50% by weight pyriproxyfen;

(b) about 5% to about 50% by weight permethrin;

(c) about 1% to about 30% by weight mineral oil; and

(d) about 10% to about 50% by weight D-Limonene.

5. The composition according to claim **4** having:

(a) about 5% by weight pyriproxyfen;

(b) about 45% by weight permethrin;

(c) about 10% by weight mineral oil; and

(d) about 30% by weight D-Limonene.

* * * * *