

**MENFORSAN TRIPLE ACTION
ANTI-INSECT REPELLENT
SPOT-ON**

SAFETY AND EFFECTIVENESS DOSSIER
(October 2014 - January 2016)

**INNOVATIVE TECHNOLOGY IN
PROTECTION FOR DOGS AND CATS.**

CONTENTS

- 1- GENERAL FEATURES
- 2- FLEAS, TICKS AND MOSQUITOES.
- 3- COMPOSITION.
- 4- INSTRUCTIONS FOR USE
- 5- CLINICAL TRIALS:
 - ANTI-INSECT REPELLENT SPOT-ON FOR DOGS: In vitro effectiveness trials.
 - ANTI-INSECT REPELLENT SPOT-ON FOR CATS: In vitro effectiveness trials.
 - ANTI-INSECT REPELLENT SPOT-ON FOR DOGS: In vivo effectiveness trials.
 - INSECT REPELLENT ANTI--SPOT-ON FOR CATS: In vivo effectiveness trials.
- 6- COMPARATIVE CLINICAL TRIALS WITH CURRENTLY AVAILABLE TREATMENT:
 - REPELLENT SPOT-ON FOR DOGS. (Geraniol)
 - REPELLENT SPOT-ON FOR CATS. (Geraniol)
- 7- COMPARATIVE TRIALS WITH INSECTICIDE SPOT-ON.
- 8- CLINICAL SAFETY
 - ANTI-INSECT REPELLENT SPOT-ON FOR DOGS:
Pre Clinical Trial
 - ANTI-INSECT REPELLENT SPOT-ON FOR CATS:
Pre Clinical Trial
 - ANTI-INSECT REPELLENT SPOT-ON FOR DOGS: External Irritation Trial
 - ANTI-INSECT REPELLENT SPOT-ON FOR CATS:
External Irritation Trial
- 9- STABILITY
- 10- PACKAGING

MENFORSAN NATURAL ANTI-INSECT REPELLENT SPOT-ON

1- GENERAL FEATURES

SPOT-ON FOR DOGS	Composition: 3% Geraniol, 1% Essential Lavender oil, 5% Ext HG Neem.
SPOT-ON FOR CATS	Composition: 1.5% Geraniol, 0.5% Essential Lavender oil, 5% Ext HG Neem.
Method of application	Spot-on
Usage	Fleas, ticks, mosquitoes
Duration of effectiveness	1 month *
Fragrance	Citric, very pleasant

* Under normal infestation conditions risk. In high-risk areas it may be necessary to administer the spot-on every 2 weeks.

2- FLEAS, TICKS AND MOSQUITOES

Fleas, ticks and sand fly mosquitoes are arthropod parasites and are the cause of transmission for many of the most common and frequently occurring illnesses in dogs and cats.

Arthropod	INFESTATION / RELATED ILLNESS	Main Blood borne pathogens (corresponding illnesses)
Fleas	Flea infestation / dermatitis allergy caused by fleas (FDA)	Dipylidium caninum (dipylidiosis) Bartonella hensalae (bartonellosis)
Ticks (Rhipicephalus sanguineus, Ixodes spp, Dermacentor spp, Hyalomma spp, Haemaphysalis spp and others)	Tick infestation	Babesia canis, Babesia Gibson, Babesia [Theileria] annae (piroplasmosis, babesiosis) Hepatozoon spp (hepatozoonosis) Ehrlichia canis, E.spp, Anaplasma phagocytophilum, Anaplasma platys (ehrlichiosis, anaplasmosis) Rickettsia spp (rickettsiosis) Borrelia burgdorferi sl (borreliosis = Lyme disease) Flavivirosis (e.g. tick transmitted encephalitis, Louping sickness) Acanthocheilonema [Dipetalonema] dracunculoides
Sand fly mosquitoes	Infestation by sand fly mosquitoes	Leishmania infantum (leishmaniasis)

3- COMPOSITION

The new ANTI-INSECT REPELLENT SPOT-ON FOR DOGS AND CATS are innovative products designed not only to repel fleas, ticks and mosquitoes from the bodies of dogs and cats, but also to act as an anti parasitic supplement, offering extra protection that currently available spot-on treatments do not provide.

This spot-on treatment is the result of a research project undertaken over 12 months, in order to optimize effectiveness and minimize risks for pets.

The anti parasitic spot-on's capacity has been strengthened, on the one hand by introducing two new anti parasitic ingredients, essential lavandin oil and Neem extract, and on the other, by increasing the percentage of geraniol contained. The base for the diffusion and impregnation of the active ingredients has been enhanced, with two aims. Firstly, to increase the absorption and the durability of the product on the skin and secondly to increase its viscosity, facilitating its application and avoiding spills and misapplications. The solvents used for this purpose are highly compatible for use on the skin and are commonly used in the animal health cosmetics industry.

Geraniol

Geraniol, a monoterpenoid, is the main component in most essential rose oils, and it is also present in other species of flowers, plants and fruits, such as geraniums, lemons and oranges etc. It is a staple ingredient in a wide range of perfumes and cosmetics.

It is a powerful insect repellent and natural insecticide. It is biodegradable and, due to its diffusive capacity, its aroma is released gradually and spreads throughout the body of the animal, discouraging fleas, ticks and mosquitoes from approaching.

It is not harmful to animals or people. Only those animals which are allergic to perfumes may have a slight hypersensitive reaction and this can be easily reversed through discontinuation of the treatment.

Essential Lavender Oil (Lavandula Hybrida Oil)

This is obtained from the Lavandula Hybrida plant. It is a natural essential oil with anti parasitic properties, which acts in a similar manner to geraniol, by means of a gradual continuous release, which creates a protective barrier around the animal.

Neem Extract

This is the most important anti parasitic ingredient in the product. More than half a century ago US researchers discovered the benefits that the Neem Tree could offer and since then it has been in used in commercial products like insect repellent, both for humans and animals. Its extract contains compounds that mimic the insect's hormones, disrupting their life cycle and causing rapid death.

Neem Extract also plays a prominent role from a cosmetic point of view, because of its ability to moisturise and condition the animal's skin, which may have been affected by the action of external elements. It quickly relieves dryness of the skin and is absorbed in the superficial layers, restoring the balance of hydration.

4. INSTRUCTIONS FOR USE

REPELLENT SPOT-ON FOR DOGS: Remove the spot-on from its protective packaging. Hold the spot-on upwards and break off the top. Part the hair and apply the tip of the spot-on directly to the skin, emptying the contents completely. The spot-on should be applied at the base of the neck and tail.

REPELLANT SPOT-ON FOR CATS: Remove the spot-on from its protective packaging. Hold the spot-on upwards and break off the top. Part the hair and apply the tip of the spot-on directly to the skin, emptying the contents completely. The spot-on should be applied to the neck area.

CLINICAL TRIALS

5.1- PRODUCT EFFECTIVENESS LABORATORY TESTING

ANTI-INSECT REPELLENT SPOT-ON FOR DOGS.

5.1.1 Product Description

This ANTI-INSECT REPELLENT SPOT-ON FOR DOGS product has been developed to treat and prevent parasite infestation in dogs. The product was tested to demonstrate its effectiveness against fleas, ticks and mosquitoes. The product is owned by the Laboratorios Bilper Group.

5.1.2-Testing methods.

a) Preliminary information.

i) Identification of the active substance

The product is a spot-on of 1.5 ml.

It contains three active substances: 3% Geraniol (CAS: 106-24-1), 1% Essential Lavender Oil (CAS: 91722-69-9) and 5% HG Neem Extract (Melia azadirachta leaf extract (CAS: 90063-92 -6) 3.5%).

Trial dates: November 2014 - December 2014

ii) Anti parasitic effectiveness against fleas.

To test the effectiveness of the product, an internal control method was employed, using an olfactory chamber of four arms with a continuously circulating stream of moist air. Two arms contained the product being tested and the other two acted as a control since they contained nothing. Anti parasitic effectiveness was determined by monitoring the time fleas were present in each area.

iii) Anti parasitic effectiveness against ticks.

To test the effectiveness of the product, an internal control method was used based on the ability of ticks to climb onto and attach themselves to the surface of the body of a warm blooded, mobile host. This capability may be modified through the use of repellent products.

iv) Anti parasitic effectiveness against mosquitoes.

To test the effectiveness of the product, an internal control method was used based on a Y-shaped olfactometer with a stream of air flowing against the direction of movement of the mosquitoes. One arm contained the sample being tested and the other contained nothing. The mosquitoes chose which route to take.

Description of testing methods

i) Testing against fleas.

For this test male and female adult *Spilopsyllus cuniculi* fleas were used. The fleas were stored in glass jars in dark conditions at 4°C. The fleas were acclimatized to room temperature for about 30 minutes before testing began.

Ten fleas were introduced into the olfactometer chamber. In two of the arms of the apparatus samples of the repellent product being tested was placed and the other two were empty, acting as a control.

Every minute the number of fleas in each area and the change in this number was recorded (whether it fluctuated or not). The test lasted for 20 minutes. The same test was repeated over 5 weeks. (once a week)

The repellent effectiveness rate was determined as follows:

$I = (T - P) / (T + P)$ where T is the number of fleas observed in the areas impregnated with the product and P is the number of fleas observed in non-impregnated areas. This index ranges from -1 to 1.

The number of dead fleas was counted.

ii) Testing against ticks.

For this test male and female nymphs of the *Ixodes ricinus* L. species, which had been stored in a glass flask in conditions of 90% humidity at 25°C, were used.

2 glass spheres, which had been heated to 38-40°C beforehand, were suspended in a glass case, both in movement, and filter paper was stuck to them so that the parasites could cling to the surface if they were to enter. The 2 spheres were placed 1 metre apart.

One area was impregnated with the repellent product being tested beforehand and the other acted as a control.

20 ticks were introduced and their behaviour was observed, to see whether or not they attached themselves the filter attached to the surface of the sphere. The test took 30 minutes and was repeated weekly over 5 weeks.

iii) Test against mosquitoes.

For this test 10 sand fly mosquitoes, which had been stored in a glass bottle at room

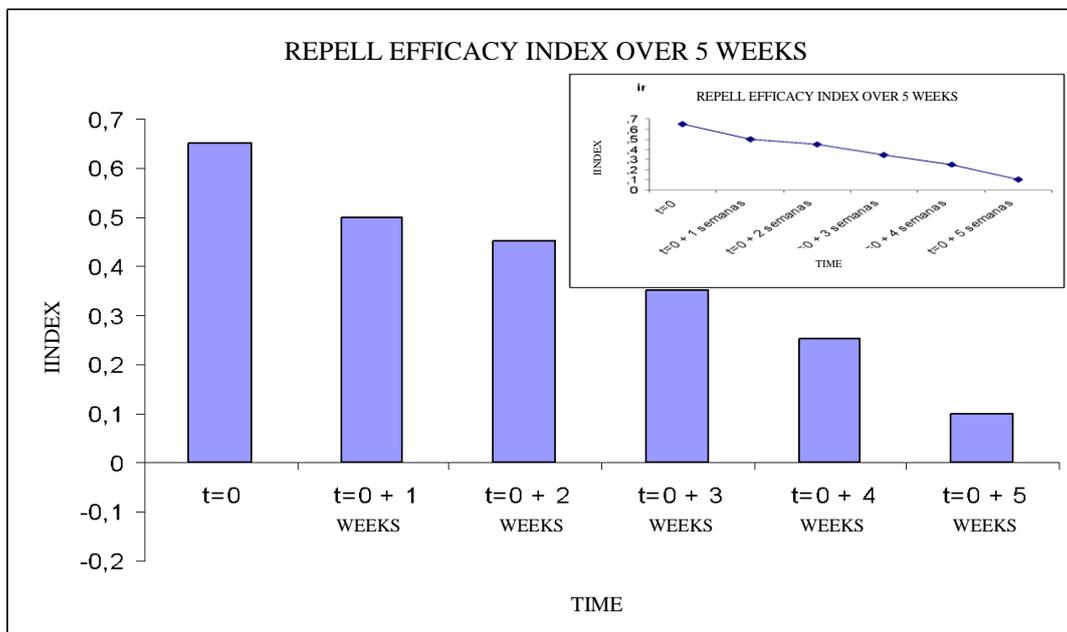
temperature of 25°C, were used.

The mosquitoes were introduced into the Y-shaped olfactometer one by one. One arm contained filter paper with a sample of the repellent being tested; the other arm contained nothing and served as a control.

The mosquito's behaviour on arriving at the decision-making area of the olfactometer was observed. They had two choices of route: the path leading to the area impregnated with the sample or the path to the control zone. Mosquitoes that fell by the wayside in the decision-making area were considered to not be repelled. The test was repeated over 5 weeks.

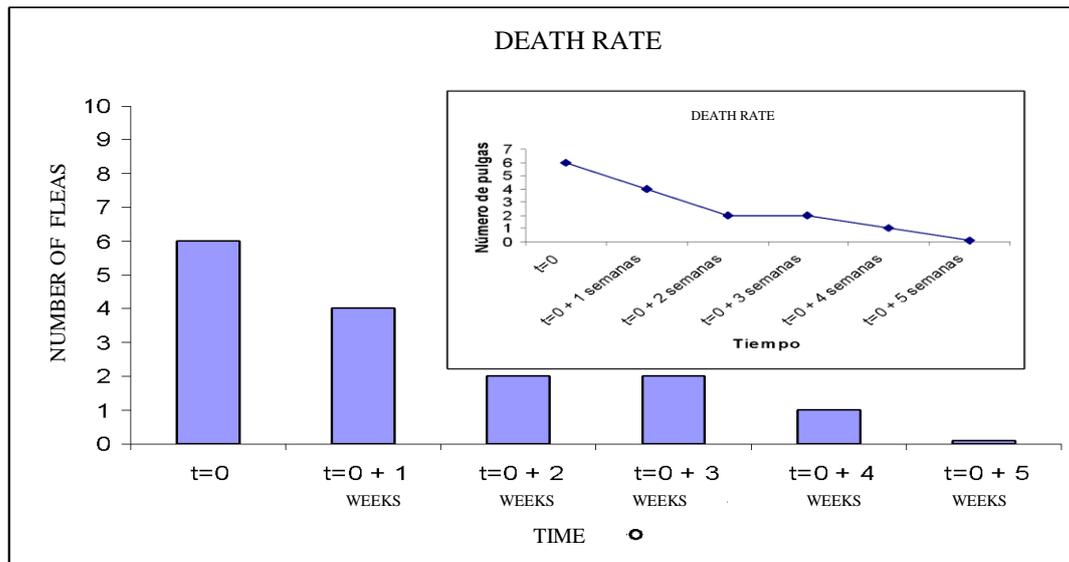
5.1.3- Results.

A) Anti parasitic effectiveness against fleas.



Index = I	0<I<1
If I<0,20	Not repellent
If 0,20<I<0,25	Moderately effective
If 0,25<I<0,35	Good effectiveness
If I>0,35	Very good effectiveness

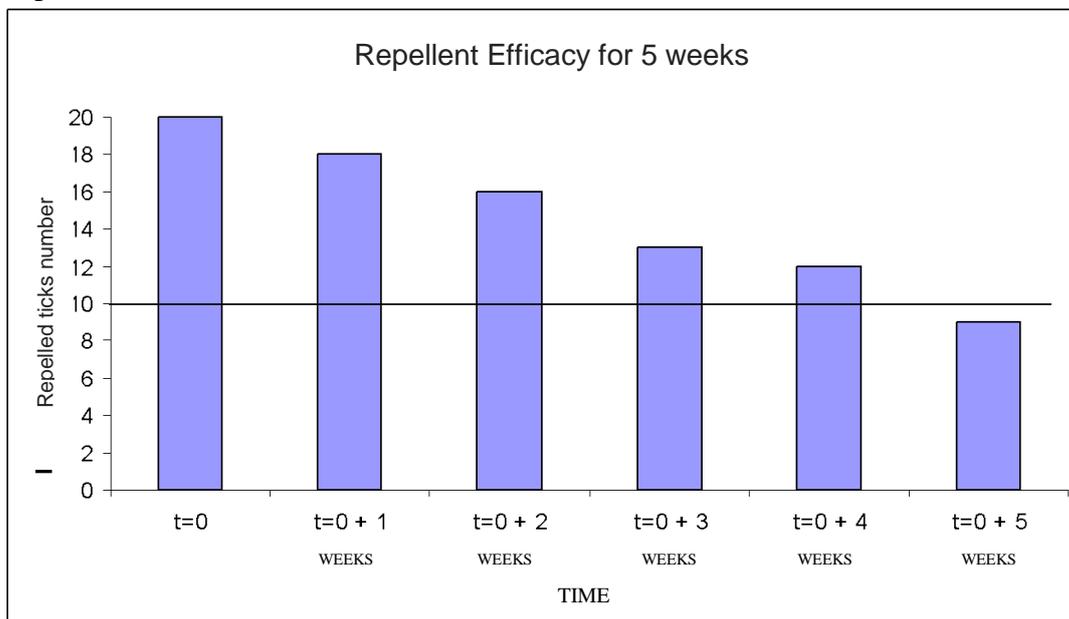
During the testing period, the motionless (dead) fleas were counted weekly.



It was found that the ANTI-INSECT REPELLENT SPOT-ON FOR DOGS provided an excellent repellent effect during the first 4 weeks of testing. The mortality data also showed considerable insecticidal effect during the first days of treatment.

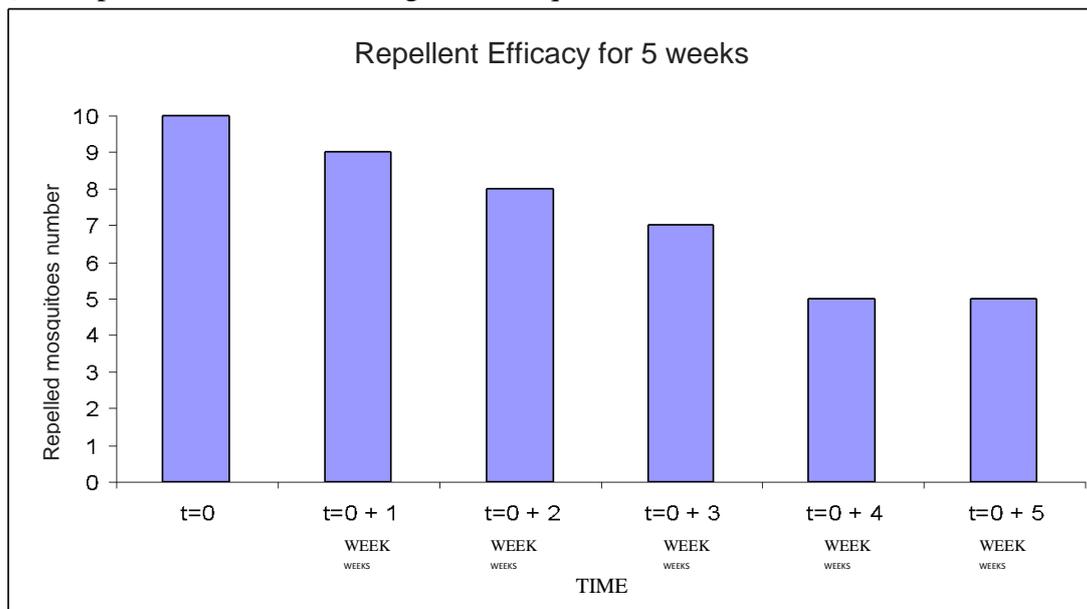
b) Anti parasitic effectiveness against ticks.

Repelled ticks number



These results confirm the excellent repellent effectiveness of the product against ticks during the first 4 weeks of the testing period.

c) Anti parasitic effectiveness against mosquitoes.



It was demonstrated that the repellent effect of the product in vitro against mosquitoes was optimal over the 5-week duration of the testing period.

5.1.4- Conclusion

Taking into account the overall test results of effectiveness, it may be concluded that under laboratory conditions the ANTI-INSECT REPELLENT SPOT-ON FOR DOGS product has an excellent degree of repellent effectiveness against fleas, ticks and mosquitoes over a 4-week period.

5.2- PRODUCT EFFECTIVENESS LABORATORY TESTING:

ANTI INSECT REPELLENT SPOT-ON FOR CATS.

5.2.1- Product Description

This ANTI-INSECT REPELLENT SPOT-ON CAT product has been developed to treat and prevent parasites infestations in cats. The product was tested to demonstrate its effectiveness against fleas, ticks and mosquitoes. The product is owned by Laboratorios Bilper Group.

5.2.2- Testing methods.

a) Preliminary information.

i) Identification of the active substance

The product is a spot-on of 1.5 ml.

It contains three active substances: 1.5% Geraniol (CAS: 106-24-1), 0.5% Essential Lavender oil (CAS: 91722-69-9) and 5% HG Neem Extract (Melia Azadirachta leaf extract (CAS: 90063-92-6) 3.5%).

Trial dates: November 2014 - December 2014

ii) Anti parasitic effectiveness against fleas.

To test the effectiveness of the product, an internal control method was employed, using an olfactory chamber with four arms and a continuously circulating stream of moist air. Two arms contained the product being tested and the other two acted as a control since they contained nothing. Anti parasitic effectiveness was determined by monitoring the time fleas were present in each area.

iii) Anti parasitic effectiveness against ticks.

To test the effectiveness of the product, an internal control method was used based on the ability of ticks to climb onto and attach themselves to the surface of the body of a warm blooded, mobile host. This capability may be modified through the use of repellent products.

iv) Anti parasitic effectiveness against mosquitoes.

To test the effectiveness of the product, an internal reference method was used based on a Y-shaped olfactometer with a stream of air flowing against the direction of mosquitoes. One arm contained the sample being assessed and the other contained nothing. The mosquitoes chose which route to take.

Description of the test methods

i) Testing against fleas.

For this test male and female *Spilopsyllus cuniculi* adult fleas were used. The fleas were stored in glass jars in dark conditions at 4°C. The fleas were acclimatized to room temperature for about 30 minutes before testing began.

Ten fleas were introduced into the olfactometer chamber. In two of the arms of the apparatus samples of the repellent product to be tested were placed and the other two were empty, acting as a control.

Every minute the number of fleas in each area and the change in this was recorded (whether it fluctuated or not). The test lasted for 20 minutes. The same test was repeated for 5 weeks (once a week).

Repellent effectiveness rate was determined as follows:

$I = (T - P) / (T + P)$ where T is the number of fleas observed in the areas impregnated with the product and P is the number of fleas observed non-impregnated areas.

The number of dead fleas was counted.

ii) Testing against ticks.

For this test male and female nymphs of the *Ixodes ricinus* L tick species, which had been stored in a glass flask in conditions of 90% humidity at 25°C, were used.

Two hanging glass spheres, previously heated to 38-40°C, were placed in a glass case,

both in movement, and filter paper was stuck to them so that the parasites could cling to the surface if they were to enter. The 2 spheres were placed 1 metre apart.

One area was previously impregnated with the repellent product being tested and the other acted as a control.

20 ticks were introduced and their behaviour was observed, to see whether or not they passed through the filter attached to the surface of the spheres. The test took 30 minutes and was repeated weekly over 5 weeks.

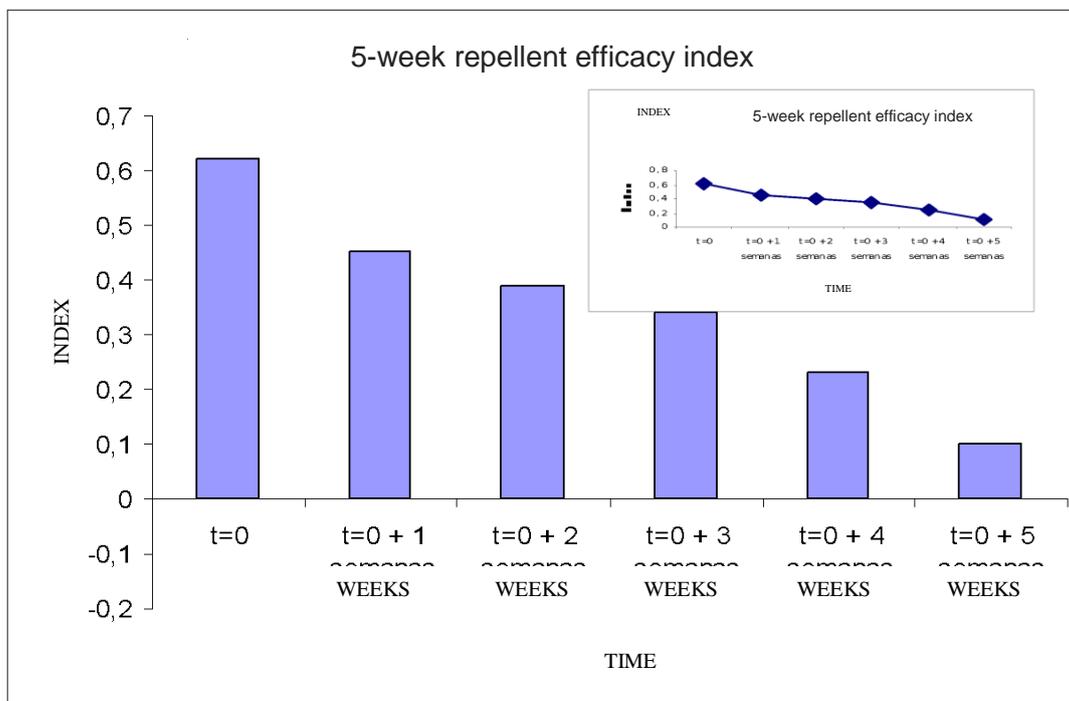
iii) Test against mosquitoes.

For this test 10 sand fly mosquitoes, which had been stored in a glass bottle at room temperature of 25°C, were used

The mosquitoes were introduced into the shaped Y olfactometer one by one. One arm contained filter paper with a sample of the repellent being tested; the other arm contained nothing and served as a control.

The mosquito's behaviour on arriving at the decision-making area of the olfactometer was observed. They had two choices of route: the path leading to the area of the impregnated sample or the path to the control area. Mosquitoes that fell by the wayside in the decision-making area were considered to not be repelled. The test was repeated over 5 weeks.

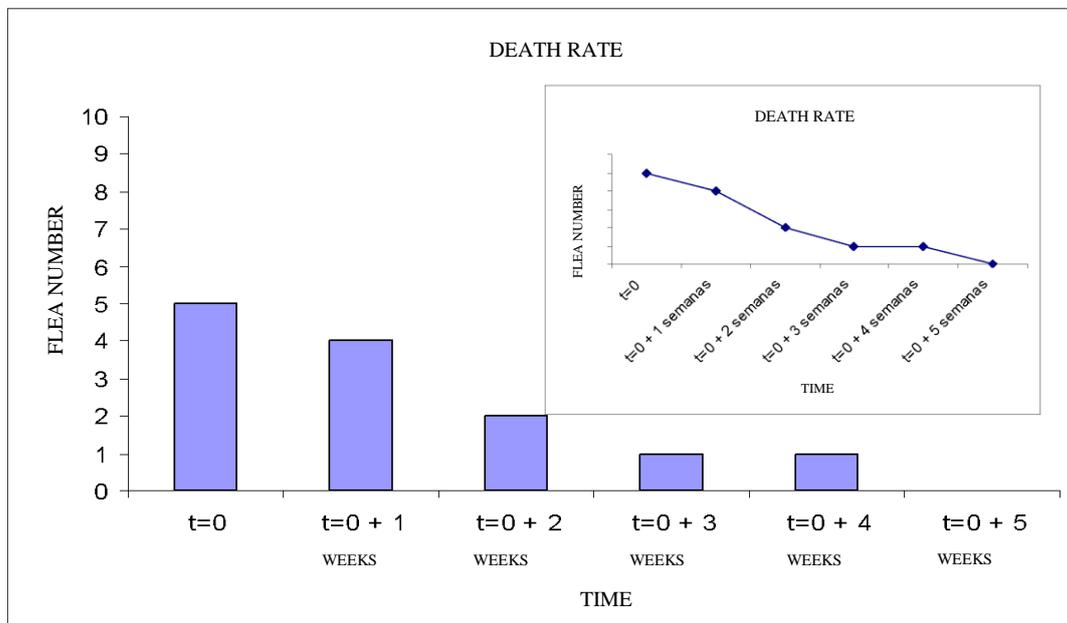
5.2.3- Results.



A) Anti parasitic effectiveness against fleas.

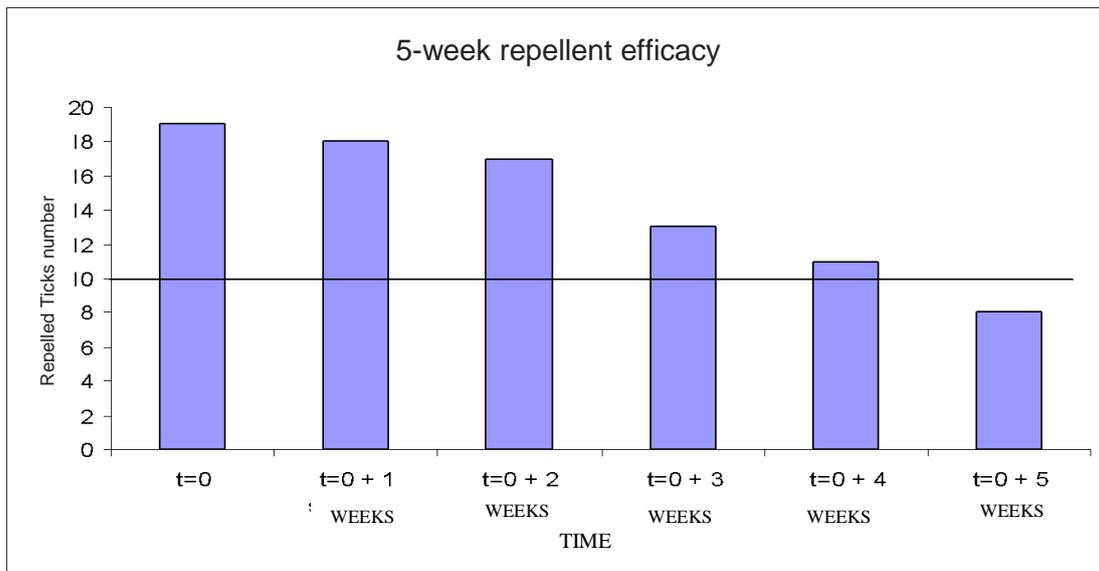
Index = I	$0 < I < 1$
If $I < 0.20$	Not repellent
If $0.20 < I < 0.25$	Moderately effective
If $0.25 < I < 0.35$	Good effectiveness
If $I > 0,35$	Very good effectiveness

During the testing period, the motionless (dead) fleas were counted weekly.



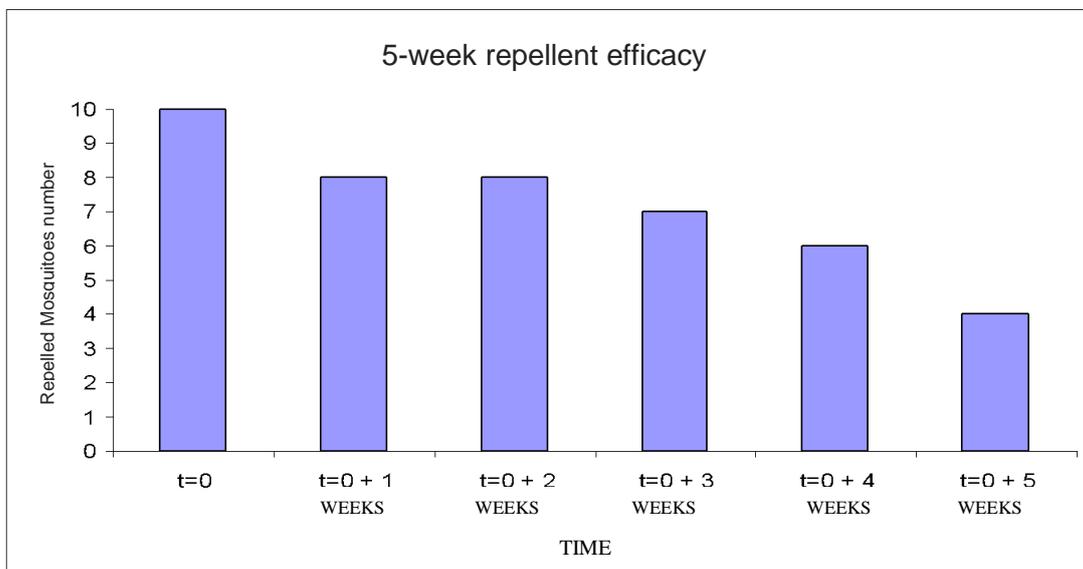
It was found that ANTI-INSECT REPELLENT SPOT-ON FOR DOGS provided an excellent repellent effect during the first 4 weeks of testing. The mortality data also showed considerable insecticidal effect during the first days of treatment.

b) Anti parasitic effectiveness against ticks.



These results confirm the excellent repellent effectiveness of the product against ticks during the first 4 weeks of the testing period.

c) Anti parasitic effectiveness against mosquitoes.



It was demonstrated that the repellent effect of the product in vitro against mosquitoes was optimal over the 4-week duration of the testing period.

5.2.4- Conclusion

Taking into account the overall test results for effectiveness, it may be concluded that under laboratory conditions the ANTI-INSECT REPELLENT SPOT-ON FOR CATS product has an excellent degree of repellent effectiveness against fleas, ticks and mosquitoes over a 4-week period.

5.3- IN VIVO PRODUCT EFFECTIVENESS TESTING:

ANTI-INSECT REPELLENT SPOT-ON FOR DOGS.

5.3.1- Description of testing method.

i) Anti parasitic effectiveness against fleas.

To test the effectiveness of the product, healthy volunteered dogs (without any existing illnesses) were used and divided into two categories, according to whether or not fleas were present on the animals. The fact that fleas are more prevalent in Spain, due to higher temperatures and levels of humidity, was taken into account. These trials took place between March and September 2015, on dogs aged between 3 months and 10 years, selected from warm, humid areas.

Flea free dogs.

10 dogs were selected, with no fleas visibly apparent on their bodies: 3 Fox Terriers, 2 Basset Hounds, 3 French Cocker Spaniels and 2 Dachshunds.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of fleas on the animals was checked on a monthly basis.

Dogs with fleas.

The test was performed on 15 dogs with flea infestation of varying degrees: 2 Chihuahuas, 1 Maltese Bichon, 1 Affenpinscher, 2 Toy Poodles, 3 Yorkshire Terriers, 2 Boston Terriers, 1 Maltese Beagle and 3 Bulldogs.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).

The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

ii) Anti parasitic effectiveness against ticks.

To test the effectiveness of the product, healthy volunteered dogs (with no existing illnesses) aged between 3 months and 10 years were used and divided into two categories according to whether or not ticks were present on the animals. The trials took place between March and September 2015 on dogs selected from dry, continental areas.

Tick-free dogs.

The test was performed on 50 dogs of the following breeds:

Breed	Number	Breed	Number
Alaska Malamute	2	Old English Sheepdog	3
Belgian Shepherd	3	Doberman Pinscher	2
Catalan Shepherd	2	Beagle	2
Pointer	2	Sight hound	3
Pit Bull Terrier	1	American Stanford	2
Newfoundland	2	American Bulldog	1
German Shepherd	7	Husky	1
Rottweiler	1	Golden Retriever	1
Collie	2	Cross breeds	13

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

Presence or absence of ticks on the animals was checked on a monthly basis.

Dogs with ticks.

The test was performed on 10 dogs with tick infestation of a greater or lesser degree: 7 Cross breeds, 2 German Shepherds, 1 Yorkshire Terrier.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml applied to the specific point where the tick was adhered to the skin of the animal (t=0).

The behaviour of the ticks on the animals treated was checked every 24 hours for 7 days.

iii) Anti parasitic effectiveness against mosquitoes (sand flies).

To test the effectiveness of the product, healthy dog volunteers (with no existing illnesses) aged between 7 months and 12 years, were used. It was checked beforehand that animals involved in the trials did not have symptoms of Leishmaniasis. A blood test was performed on each of them to determine this. The trials on dogs were conducted between March and September 2015.

38 dogs were selected from high-risk areas in Spain (with endemic Leishmaniasis): Catalonia, Madrid, Andalusia and the Balearic Islands.

Autonomous Region	Breed	NUMBER
CATALONIA	German Shepherd	2
	Beagle	1
	Catalan Shepherd	2
	Cross breeds	3
MADRID	Doberman Pinscher	2
	German Shepherd	2
	Afghan Hound	1
	Yorkshire Terrier	1
	Cross breeds	7
ANDALUSIA	Golden Retriever	2
	Collie	1
	German Shepherd	2
	Cross breeds	7
THE BALEARIC ISLANDS	Snauzer	1
	German Shepherd	1
	Cross breeds	3

Guidelines for standardized monthly preventive treatment were provided:

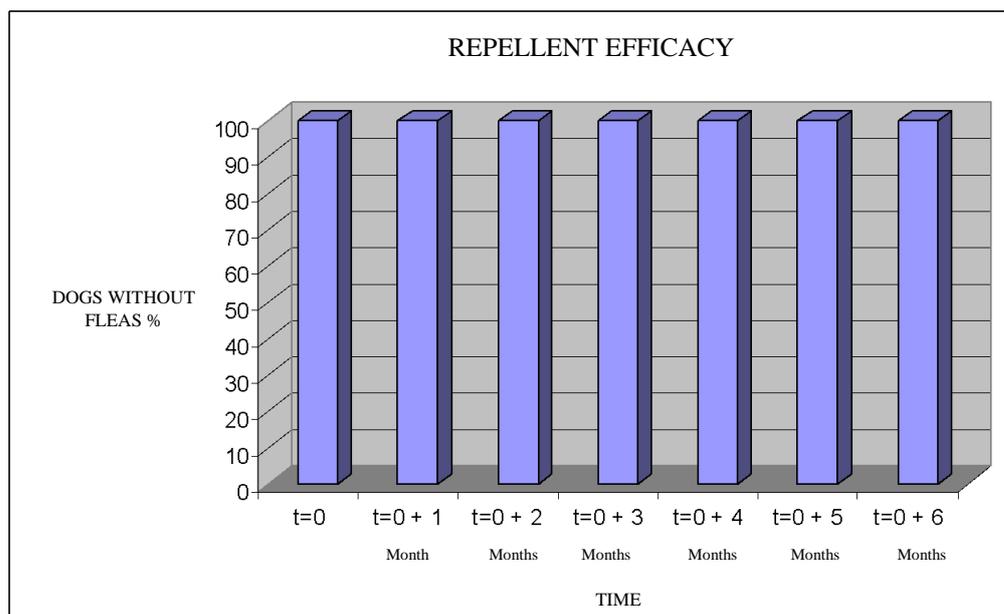
- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

At the end of the trial period (6 months) the blood test for Leishmania antibodies was repeated. (indirect immunofluorescence test).

5.3.2- Results.

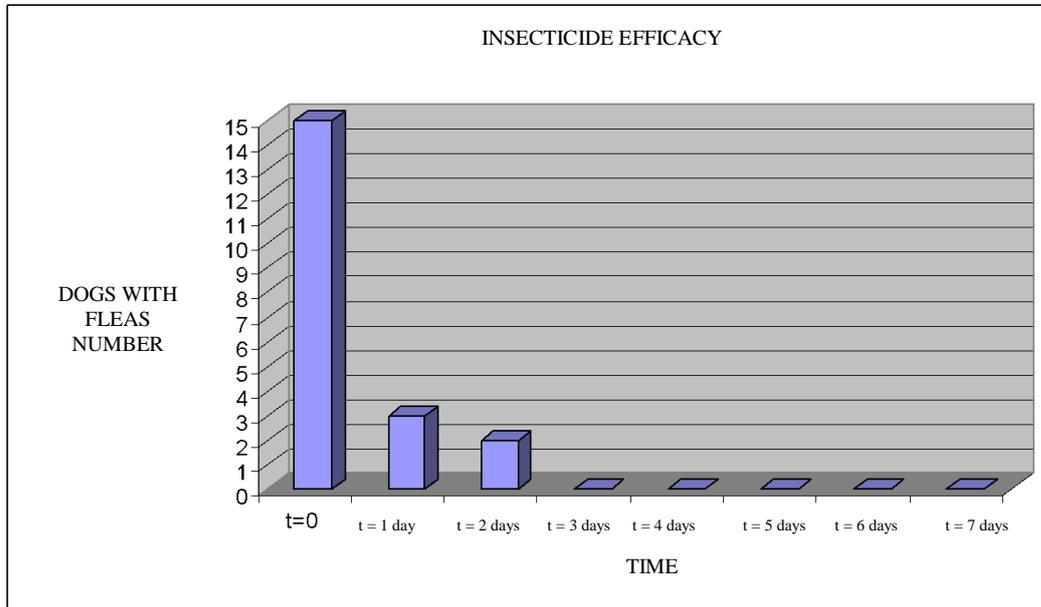
A) Anti parasitic effectiveness against fleas.

a1) Repellent effectiveness



Dogs in high-risk areas treated with a spot-on every 2 weeks remained protected against flea bites during the 6 month duration of the trials.

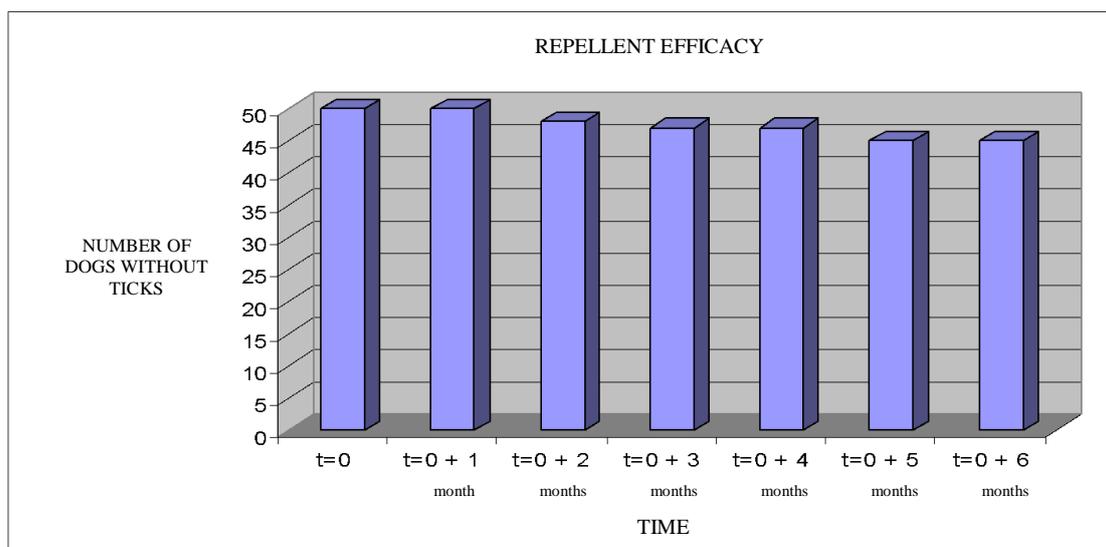
a2) Insecticidal effectiveness.

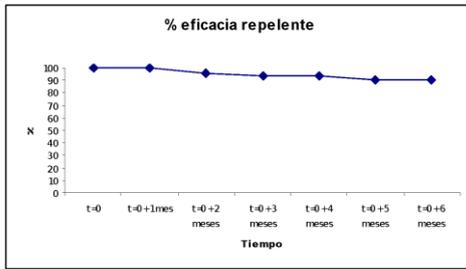


Besides being an excellent insect repellent, the product shows a significant insecticidal effect within a few days of starting treatment when tested on infested animals

b) Anti parasitic effectiveness against ticks.

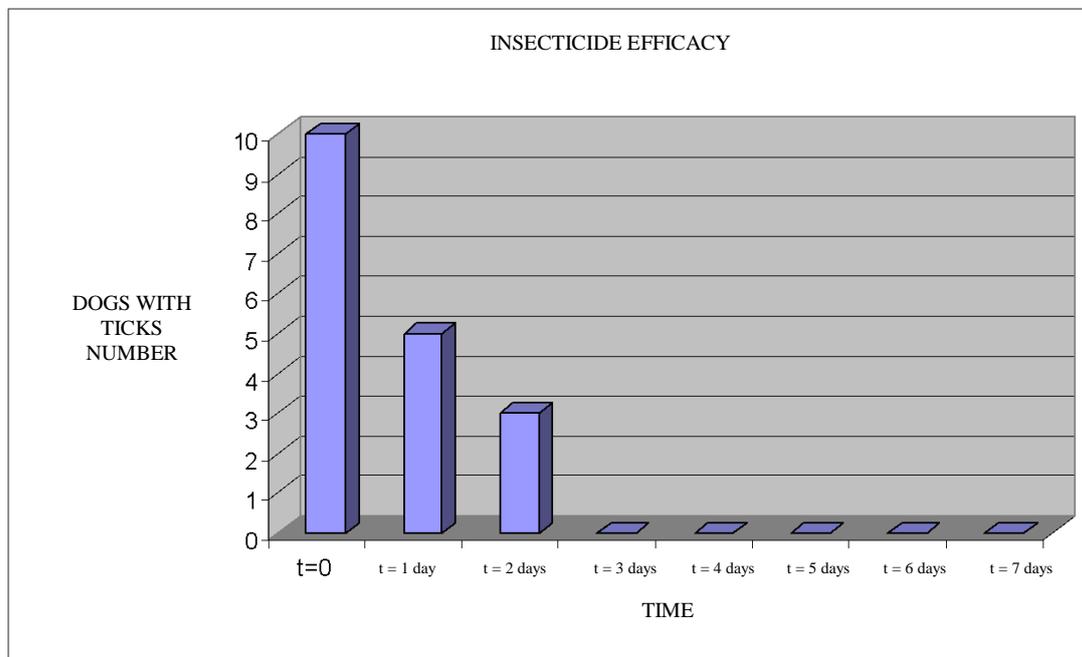
b1) Repellent effectiveness





The ANTI-INSECT REPELLENT SPOT-ON FOR DOGS product was effective against ticks in 90% of the dogs treated over 6 months. Ticks were observed to be attached to the inside leg (3) and the ears (2) of 5 dogs following treatment. All these cases were detected in animals whose habitats were considered to be of high-risk for infestation (dogs from rural areas).

b2) Insecticidal effectiveness



Besides being an excellent insect repellent, when the product was tested on infested animals it showed remarkable insecticidal effects within days of the treatment being started*.

* Applying the contents of the spot-on to the specific points where ticks were attached.

c) Anti parasitic effectiveness against mosquitoes (sand flies).

After the trial period for the product (six months), during which it was applied on a regular basis following the product instructions, (every 2 weeks) an analysis was performed on each of the dogs to detect Leishmania antibodies. The result was negative in all cases.

5.3.3- Conclusion

Taking into account the overall test results in the area of effectiveness, it may be concluded that the product ANTI-INSECT REPELLENT SPOT-ON FOR DOGS provides an excellent degree of anti parasitic effectiveness against fleas, ticks and mosquitoes when the recommended treatment guidelines are followed.

5.4-IN VIVO PRODUCT EFFECTIVENESS TESTING:

ANTI-INSECT REPELLENT SPOT-ON FOR CATS.

5.4.1- Description of testing method.

i) Anti parasitic effectiveness against fleas.

To test the effectiveness of the product, healthy cat volunteers (with no existing illnesses) were used and divided into two categories according to whether or not fleas were present on the animals. The prevalence of fleas in Spain, where higher temperatures and humid conditions prevail, was taken into account. The trials were undertaken between March and September 2015, on cats between 1 and 8 years old. They were selected from humid, warm areas, and had access to outside garden areas and could have frequent contact with other animals at risk of infestation (dogs).

Flea free cats.

17 cross breeds, 5 Siamese, 1 Exotic breed and 2 Persians: 25 cats were selected, with no fleas apparently visible on their bodies.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of fleas on the animals was checked on a monthly basis.

Cats with fleas (light or moderate visible infestation).

The test was performed on 12 cats with flea infestation of varying degrees: 6 Cross breeds, 3 Siamese, 1 Exotic breed and 1 Angora.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).

The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

ii) Anti parasitic effectiveness against ticks.

To test the effectiveness, healthy volunteered cats (with no existing illnesses) aged between 1 and 8 were used and divided into two categories, according to whether or

not ticks were present on the animals. The trials were conducted between March and September 2015 on cats selected from dry, continental areas.

Tick-free cats.

The test was performed on 35 cats of the following breeds: 22 Cross breeds, 5 Siamese, 3 Persians, 2 Exotic breeds, 2 Angoras and 1 Maine Coon.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of fleas on the animals was checked on a monthly basis.

Cats with ticks.

7 cats were used, with varying degrees of ticks in evidence: 5 Cross breeds and 2 Siamese.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).

The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

iii) Anti parasitic effectiveness against mosquitoes (sand flies).

To test the effectiveness of the product, healthy cat volunteers (with no existing illnesses) aged between 1 and 8 were used. It was checked beforehand that animals involved in the trials did not have symptoms of Leishmaniasis. A blood test was performed on each of them to determine this. The trials on cats took place between March and September 2015.

25 cats from warm and humid areas were selected: 17 cross breeds, 5 Siamese, 1 Exotic breed and 2 Persians.

Guidelines for standardized monthly preventive treatment were provided:

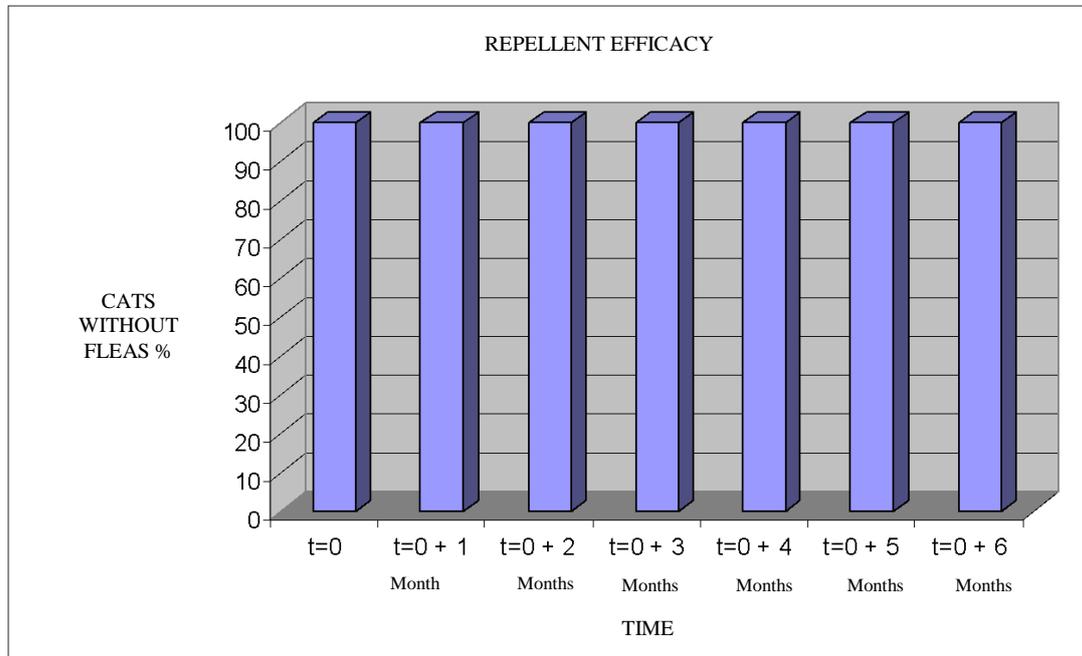
- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

At the end of the trial period (6 months) the blood test for Leishmania antibodies was repeated. (indirect immunofluorescence test).

5.4.2- Results.

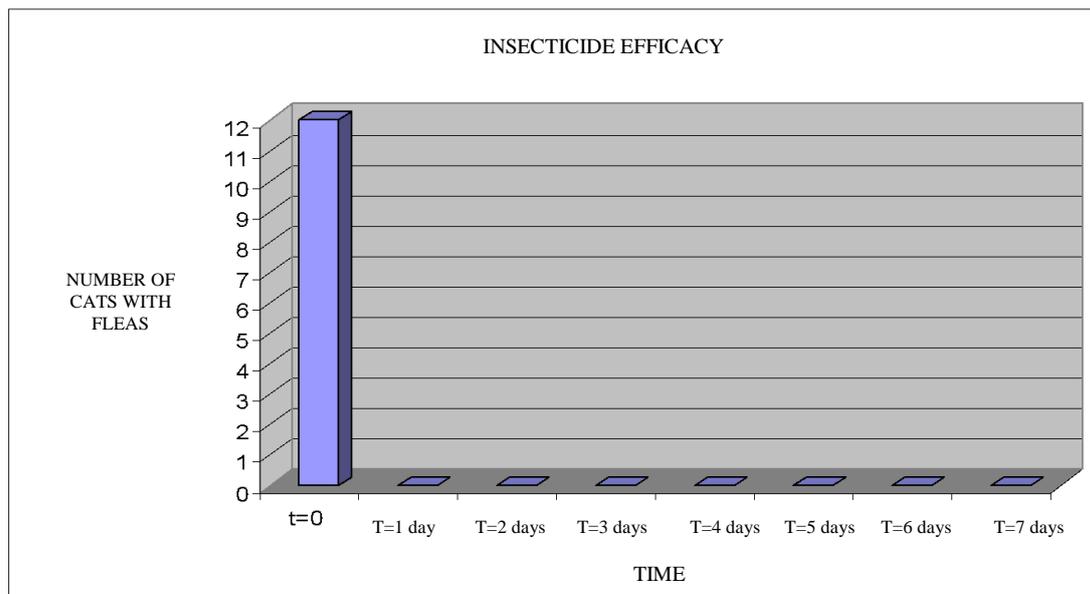
a) Anti parasitic effectiveness against fleas.

a1) Repellent effectiveness



Cats in high-risk areas treated with a spot-on every 2 weeks remained protected from flea bites during the 6-month duration of the trials.

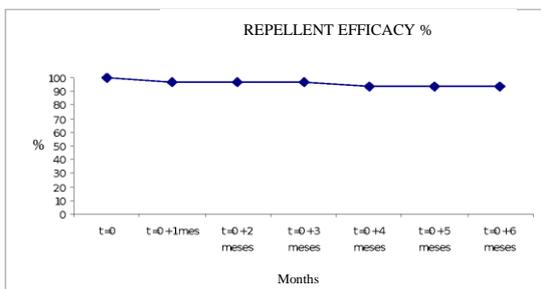
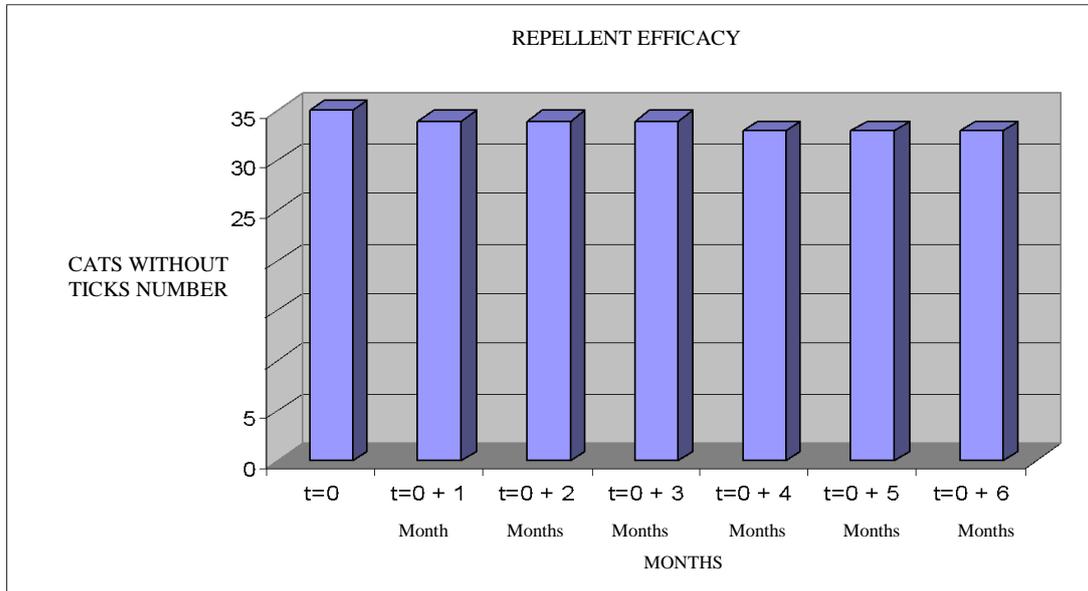
a2) Insecticide effectiveness.



Besides being an excellent insect repellent, when tested on infested animals the product showed a considerable immediate insecticidal effect.

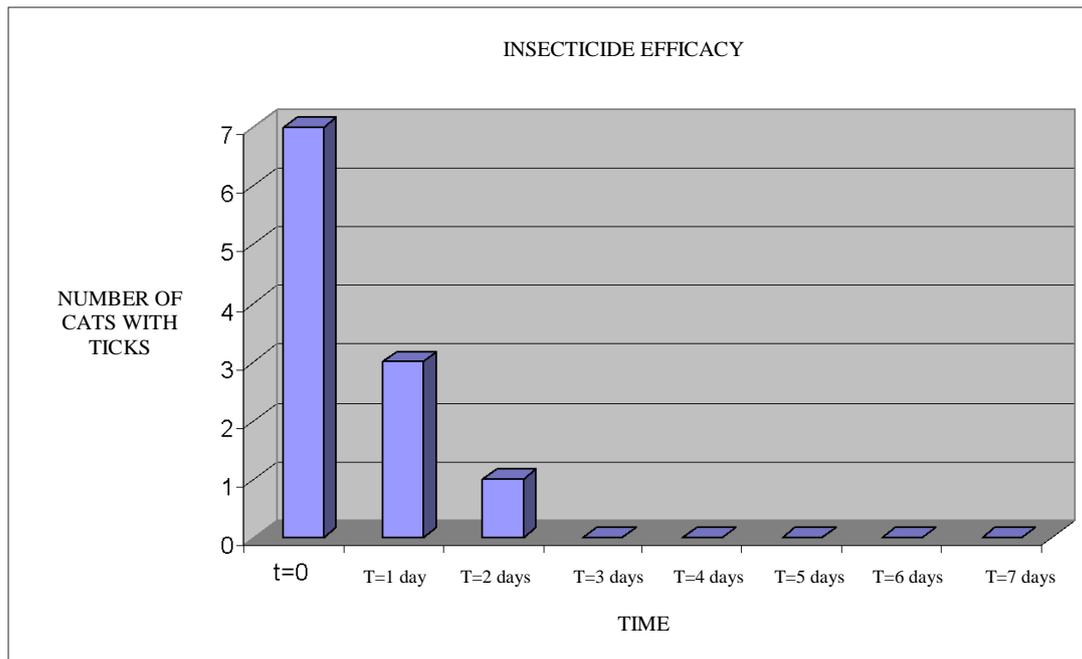
b) Anti parasitic effectiveness against ticks.

b1) Repellent effectiveness.



The ANTI-INSECT REPELLENT SPOT-ON FOR CATS product proved effective against ticks in 94% of cats treated over a 6 month period. In the two cases where ticks were present the dosage guidelines had not been followed and the cats were from highly endemic areas (with the presence of tick infested cats in the vicinity.)

B2) Insecticidal effectiveness.



The insecticidal effect is excellent within days of starting treatment *.

* Applying the contents of the spot-on to the specific points where ticks were attached.

c) Anti parasitic effectiveness against mosquitoes (sand flies).

After the product's trial period (six months), when it had been applied on a regular basis, according to the product guidelines (every 2 weeks), an analysis was performed on each of the cats to detect Leishmania antibodies. The result was negative in all cases.

5.3.3- Conclusion

Taking into account the overall test results in the area of effectiveness, it may be concluded that the ANTI-INSECT REPELLENT SPOT-ON FOR CATS product offers an excellent degree of anti parasitic effectiveness against fleas, ticks and mosquitoes, when following the guidelines recommended for treatment.

4- Comparative clinical trial with current treatment.

This trial aims to compare the anti parasitic, repellent and insecticide effectiveness against fleas and ticks, of the current spot-on compared to the new, more reinforced alternative.

6.1- IN VIVO PRODUCT EFFECTIVENESS TESTING:

MENFORSAN REPELLENT SPOT-ON FOR DOGS. Geraniol

6.1.1- Description of testing method.

i) Identification of the active substance

The product is a spot-on of 1.5 ml.

Active ingredients: Geraniol (CAS: 106-24-1) 1%

ii) Anti parasitic effectiveness against fleas.

To test for effectiveness, healthy volunteered dogs (with no existing illnesses) were used and divided into two categories according to whether or not fleas were present on the animals. The prevalence of fleas in Spain, where conditions of higher temperature and humidity prevail, was taken into account. These trials took place between March and September 2015 on dogs between 3 months and 10 years selected from humid, warm areas.

Flea free dogs.

10 dogs were selected: 4 Cross breeds, 2 Fox Terriers, 3 Poodles, 1 German Shepherd, with no fleas apparently visible on their bodies.

Guidelines for standardized monthly preventive treatment were provided:

-An initial spot-on of 1.5 ml. (t=0).

-A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of fleas on the animal was checked on a monthly basis.

Dogs with fleas.

The test was performed on 15 dogs with flea infestation of a greater or lesser degree: 7 Cross breeds, 3 Yorkshire Terriers, 2 Pit Bulls and 3 Greyhounds.

Guidelines for standardized monthly preventive treatment were provided:

-An initial spot-on of 1.5 ml. (t=0).

The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

iii) Anti parasitic effectiveness against ticks.

To test for effectiveness, healthy volunteered dogs (with no existing illnesses) were used and divided into two categories according to whether or not fleas were present on the animals. The trials took place between March and September 2015 on dogs selected from dry, continental areas.

Tick-free dogs.

The test was performed on 10 dogs of the following breeds: 4 German Shepherds, 4 Cross breeds and 2 Belgian Shepherds.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of ticks on the animal was checked on a monthly basis.

Dogs with ticks.

The test was performed on 10 dogs with tick infestation of varying degrees: 8 Cross breeds, one German Shepherds and 1 Greyhound.

Guidelines for standardized monthly preventive treatment were provided:

- A initial spot-on of 1.5 ml was applied to the specific points where ticks were adhered to the skin of the animal (t=0)
- The behaviour of these ticks in treated animals was checked every 24 hours for 7 days.

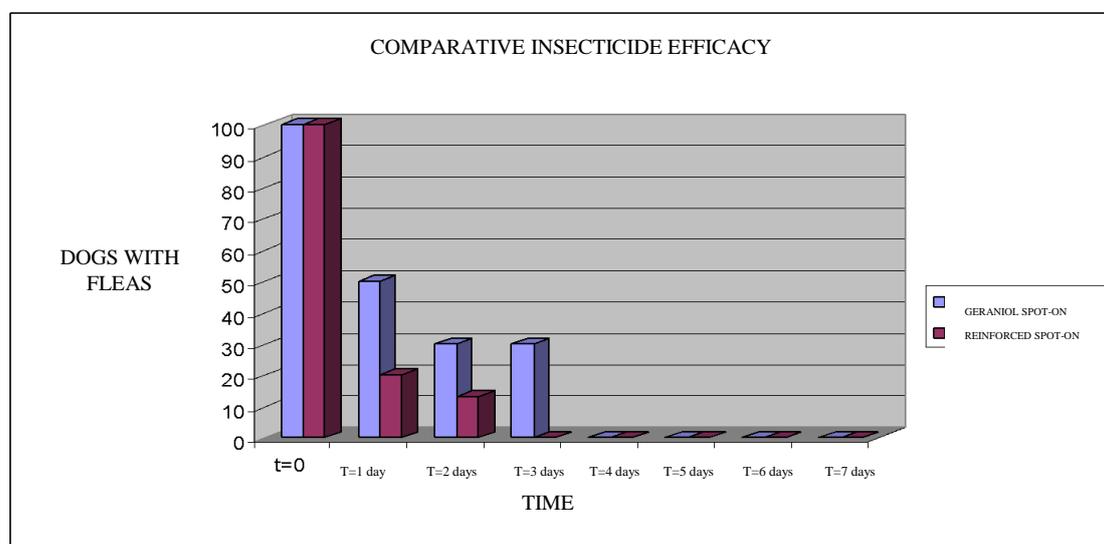
6.1.2- Results

a) Comparison of anti parasitic effectiveness against fleas.

a1) Repellent effectiveness

The repellent effectiveness against fleas was very similar with the two spot-on treatments, being slightly higher with the reinforced spot-on.

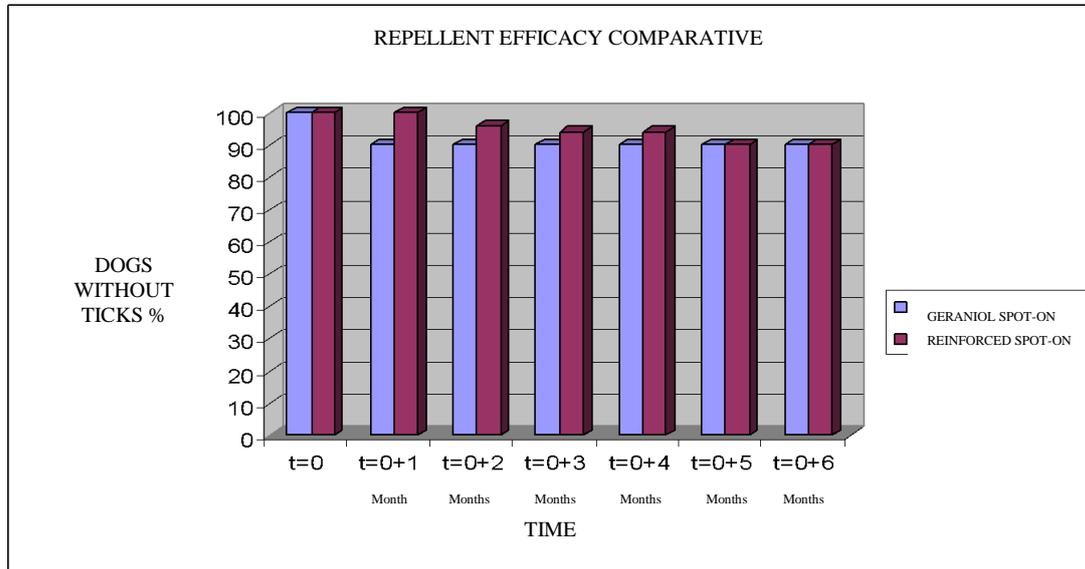
a2) Insecticidal effectiveness.



The new reinforced spot-on has greater insecticide effectiveness against fleas than the current one which contains geraniol exclusively.

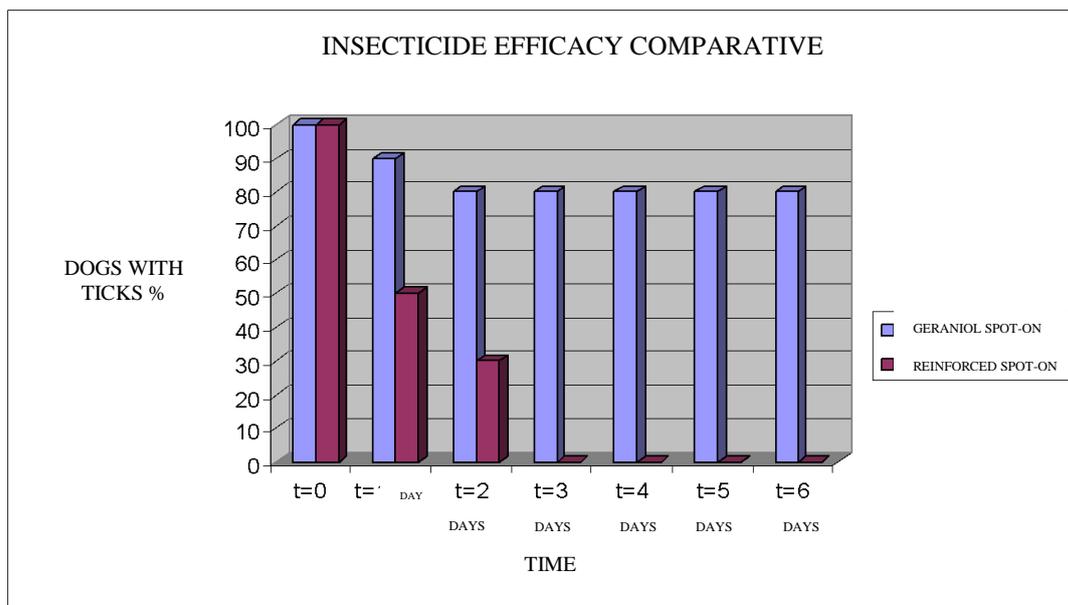
b) Comparison of anti parasitic effectiveness against ticks.

b1) Repellent effectiveness



(*) The % of repellent protection against ticks, whilst being very similar, was slightly higher when the reinforced spot-on was used, especially during the first 4 weeks

b2) Insecticide effectiveness



The reinforced spot-on has a greater insecticidal capacity than the current one.

* Applying the contents of the spot-on to the specific points where ticks were attached.

6.1.3- Conclusion

Taking into account the overall test results in the area of effectiveness of both spot-on treatments it may be concluded that the reinforced ANTI-INSECT REPELLENT SPOT-ON FOR DOGS product is more effective in killing fleas and ticks than the current repellent spot-on treatments with geraniol.

6.2- IN VIVO PRODUCT EFFECTIVENESS TESTING:

MENFORSAN REPELLENT SPOT-ON FOR CATS. Geraniol

6.2.1 Description of testing method.

i) Identification of the active substance

The product is a spot-on of 1.5 ml.

Active ingredients: 1% Geraniol (CAS: 106-24-1)

ii) Anti parasitic effectiveness against fleas.

To test the effectiveness of the product, healthy volunteered cats (with no existing illnesses) were used and divided into two categories according to whether fleas were present or not on the animals. The prevalence of fleas in Spain, where higher temperature and humidity conditions prevail, was taken into account. These trials were undertaken between March and September 2015 on cats (aged between 1 and 8) selected from humid, warm areas with access to outside garden areas and which could have frequent contact with other animals susceptible to infestation (dogs).

Flea-free cats.

10 cats with no fleas apparently visible on their bodies were selected: 6 Cross breeds, 3 Siamese and 1 Persian.

Guidelines for standardized monthly preventive treatment were provided:

-An initial spot-on of 1.5 ml. (t=0).

-A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of fleas on the animal was checked on a monthly basis.

Cats with fleas (light or moderate visible infestation).

The test was performed on 10 cats with flea infestation of a greater or lesser degree: 5 Cross breeds, 3 Siamese and 2 Angoras.

Guidelines for standardized monthly preventive treatment were provided:

-An initial spot-on of 1.5 ml. (t=0).

The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

Anti parasitic effectiveness against ticks.

To test the effectiveness of the product, healthy volunteered cats (with no existing illnesses) between 1 and 8 years old were used, and divided into two categories according to whether ticks were present or not on the animals. The study was conducted between March and September 2015 on cats selected from dry, continental areas.

Tick-free cats.

The test was performed on 10 cats of the following breeds: 8 Cross breeds and 2 Persians.

Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- A top up spot-on every 2 weeks over the 6-month trial period.

The presence or absence of ticks on the animal was checked on a monthly basis.

Cats with ticks.

7 cats with varying degrees of tick infestation were used: 6 Cross breeds and 1 Siamese.

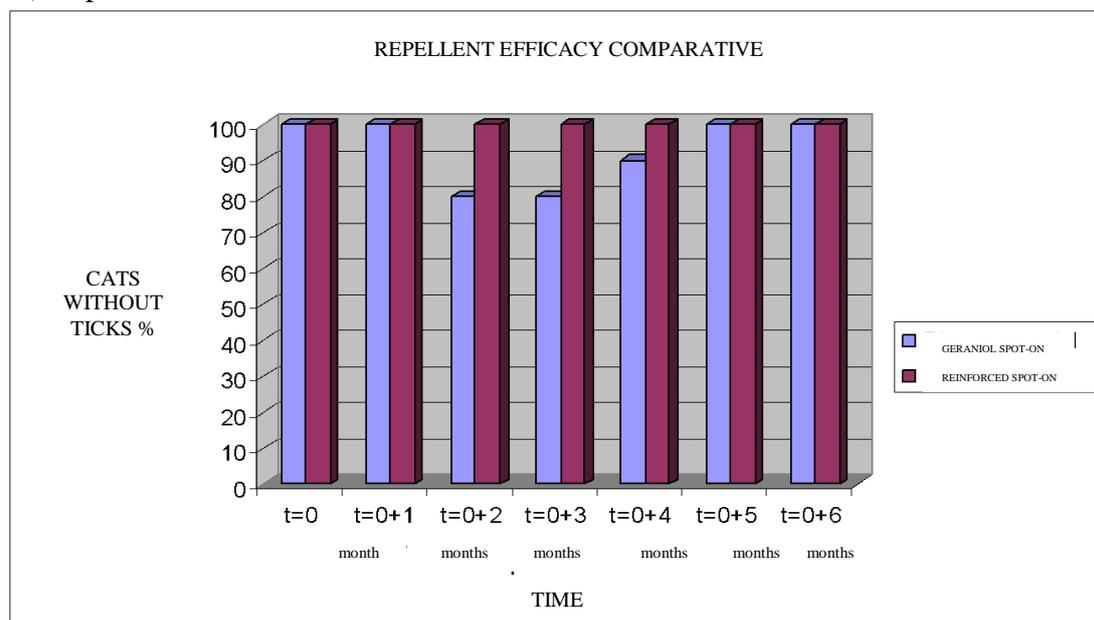
Guidelines for standardized monthly preventive treatment were provided:

- An initial spot-on of 1.5 ml. (t=0).
- The presence or absence of fleas on the treated animals was checked every 24 hours for 7 days.

6.2.2- Results

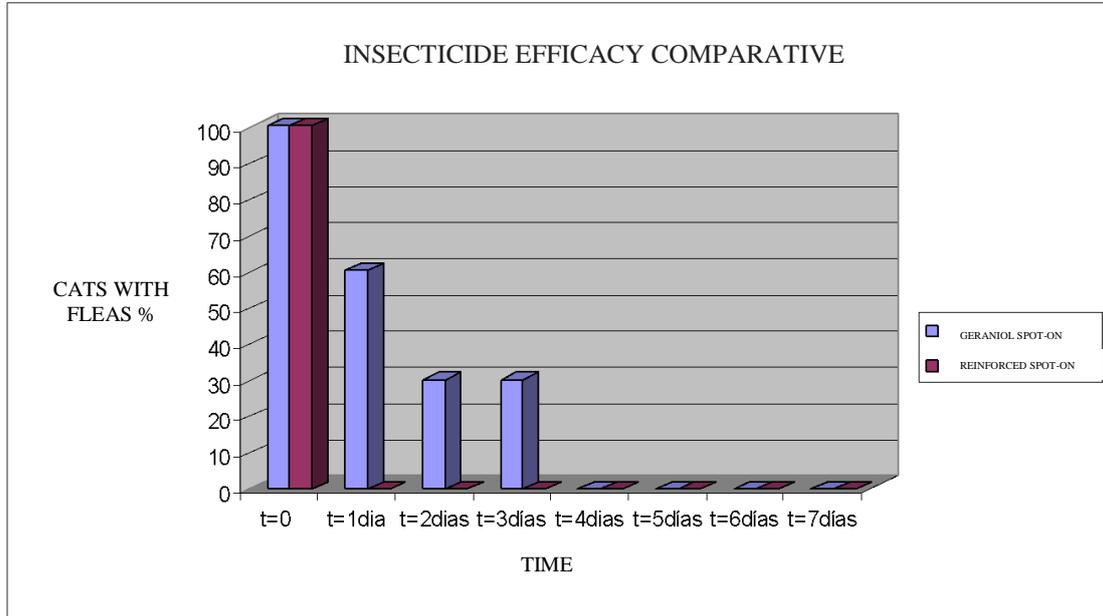
a) Comparison of anti parasitic effectiveness against fleas.

a1) Repellent effectiveness



The reinforced spot-on offers greater protection than the current geraniol spot-on.

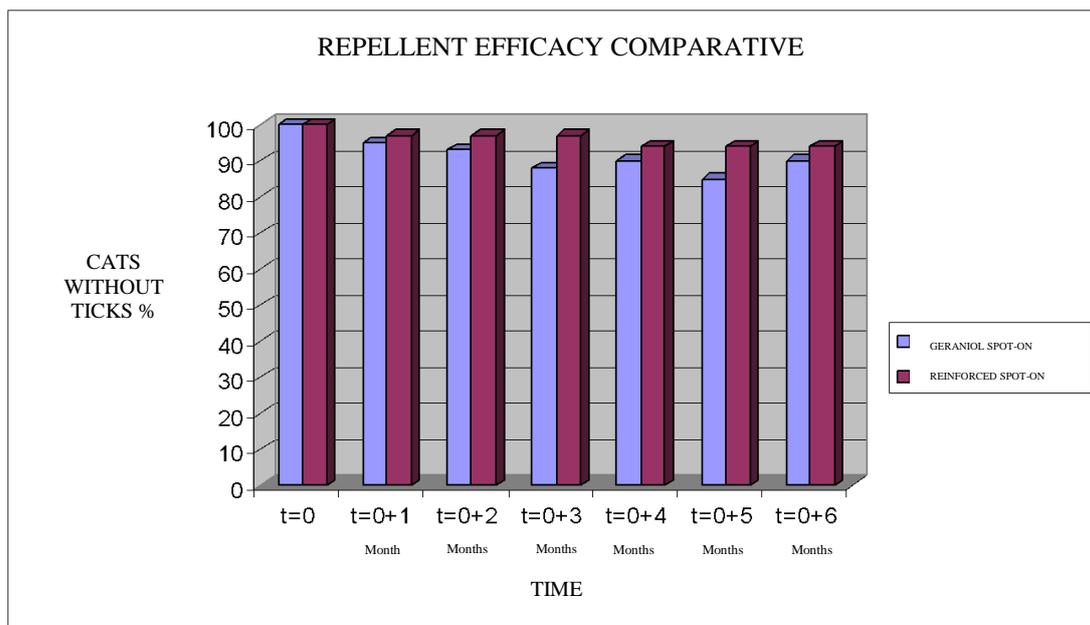
a2) Insecticide effectiveness.



The reinforced spot-on has a greater insecticide effect than the geraniol spot-on.

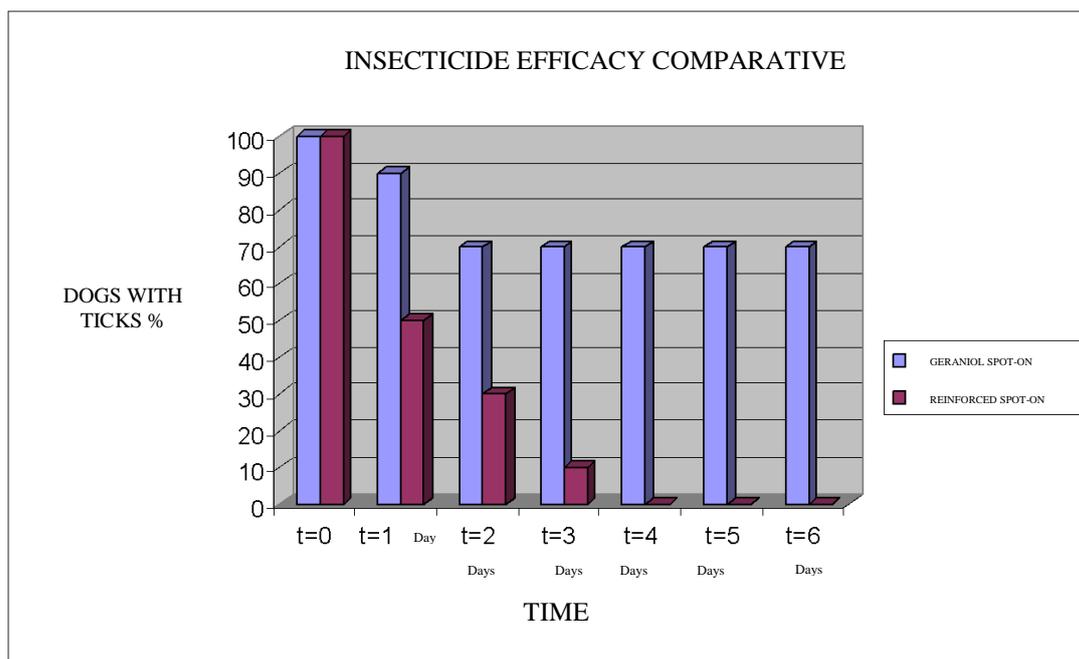
b) Comparison of anti parasitic effectiveness against ticks.

b1) Repellent effectiveness.



The new reinforced spot-on is more effective than the current one.

b2) Insecticidal effectiveness.



The insecticide effect is more evident in the new reinforced spot-on.

* Applying the contents of the spot-on to the specific points where ticks were attached.

6.2.3. Conclusion

Taking into account the overall test results in the area of effectiveness of both spot-on treatments, it may be concluded that the reinforced ANTI-INSECT REPELLENT SPOT-ON FOR CATS product is more effective in killing fleas and ticks than the current repellent spot-on with geraniol.

7- COMPARISON WITH INSECTICIDE SPOT-ON

7.1- DOGS

7.1.1 Description of testing method.

A market survey of an internal nature was carried out, to test and compare ANTI-INSECT REPELLENT SPOT-ON FOR DOGS by LABORATORIOS BILPER GROUP with FIPRONIL INSECTICIDAL SPOT-ON, which is currently available on the market. 10 anonymous samples of each were prepared and delivered randomly to 20 consumers: 10 with flea infested dogs and 10 with tick infested dogs.

In all the cases the volunteers reported results within 24 hours of applying the spot-on. Their effectiveness in killing fleas and ticks was assessed respectively.

7.1.2- Results.

	DOGS TREATED WITH ANTI- INSECT REPELLENT SPOT-ON FOR DOGS	DOGS TREATED WITH FIPRONIL INSECTICIDE SPOT-ON
PRESENCE OF FLEAS. T=0 (Before treatment)	5	5
PRESENCE OF FLEAS. T=24 H (After treatment)	2	1
Ticks. T=0 (Before treatment)	5	5
Ticks. T=24 H (After treatment)	2	1

The presence of fleas and ticks in dogs treated with Fipronil Spot-on was reduced by 80%, while in those using the ANTI-INSECT REPELLENT SPOT-ON FOR DOGS it was reduced by 60%.

7.2- CATS

7.2.1- Description of testing method.

The ANTI-INSECT SPOT-ON REPELLENT FOR CATS BY LABORATORIES BILPER GROUP was tested and compared with FIPRONIL INSECTICIDE SPOT-ON, which is also available on the market. 10 anonymous samples of each were prepared and delivered at random to 20 consumers, 10 with flea infested cats and 10 with tick infested cats.

In all the cases the volunteers reported results within 24 hours of applying the spot-on. Their effectiveness in killing fleas and ticks was assessed respectively.

7.2.2- Results.

	CATS TREATED WITH ANTI INSECT REPELLANT SPOT-ON	CATS TREATED WITH FIPRONIL INSECITICIDE SPOT-ON
PRESENCE OF FLEAS. T=0 (Before treatment)	5	5
PRESENCE OF FLEAS. T=24 H (After treatment)	2	1
Ticks. T=0 (Before treatment)	5	5
Ticks. T=24 H (After treatment)	2	1

The presence of fleas and ticks in cats treated with Fipronil Spot-on was reduced by 80%, while in those using the ANTI-INSECT REPELLENT SPOT-ON FOR CATS it was reduced by 60%.

Clinical Safety

8.1-ANTI-INSECT REPELLENT SPOT-ON FOR DOGS: PRE CLINICAL TRIAL

8.1.1- Description of testing method

Before testing the anti parasitic effectiveness of the product, a primary irritation test of an internal nature was carried out with the ultimate aim of protecting animal health and ensuring proper care in areas where the effectiveness of the spot-on would be tested.

3 dogs of over 3 months old were selected, provided by volunteers from the company. All the subjects had good skin and hair condition. Following the guidelines for use, the spot-on was applied to the nape of the neck of each dog.

8.1.2- Interpretation and assessment of the observations

The area where the product was applied was kept under observation for 24 hours, pending the appearance of possible adverse skin reactions (erythema and edema).

Erythema values

- Absent 0
- Very slight erythema 1
- Slight erythema 2
- Moderate erythema 3
- Severe erythema 4

Edema values

- Absent 0
- Very slight edema 1
- Mild edema 2
- Moderate edema 3
- Severe erythema 4

8.1.3- Criteria for evaluating the results.

Results:

DOGS	Erythema		Edema	
	PRESENT	VALUE	PRESENT	VALUE
NUMBER 1	NO	0	NO	0
NUMBER 2	NO	0	NO	0
NUMBER 3	NO	0	NO	0

Conclusions:

In accordance with the experimental conditions of the trials, we believe that the ANTI-INSECT REPELLENT SPOT-ON FOR DOGS product may be considered to be non-irritant, because after its application is no adverse skin reactions were observed.

8.2- ANTI-INSECT REPELLENT SPOT-ON FOR CATS: PRE CLINICAL TRIAL

8.2.1- Description of testing method

Before evaluating the anti parasitic effectiveness of the product, a primary irritation test of an internal nature was carried out with the ultimate aim of protecting animal health and ensuring proper care in the area where the effectiveness of the spot-on would be tested.

3 cats, each weighing more than 3 kg were selected, provided by company staff volunteers. All of the subjects had good skin and hair condition.

Following the guidelines for use, the spot-on was applied to the nape of the neck of each cat.

8.2.2- Interpretation and assessment of the observations

The area where the product was applied was kept under observation for 24 hours pending the appearance of possible adverse skin reactions (erythema and edema).

Erythema Value

Absent 0

Very slight erythema 1

Slight erythema 2

Moderate erythema 3

Severe erythema 4

Edema values

Absent 0

Very slight edema 1

Mild edema 2

Moderate edema 3

Severe edema 4

8.2.3- Criteria for evaluation of results.

Results:

CATS	Erythema		Edema	
	PRESENCE	VALUE	PRESENCE	VALUE
NUMBER 1	NO	0	NO	0
NUMBER 2	NO	0	NO	0
NUMBER 3	NO	0	NO	0

Conclusions:

In accordance with the experimental conditions of the trials, we believe that the ANTI-INSECT REPELLENT SPOT-ON FOR CATS product may be considered to be non-irritant, because after its application ~~is~~ no adverse skin reactions were observed.

8.3- ANTI-INSECT REPELLENT SPOT-ON FOR DOGS: EXTERNAL IRRITATION TESTING.

(Attachment)

8.4- ANTI-INSECT REPELLENT SPOT-ON FOR CATS: EXTERNAL IRRITATION TESTING.

(Attachment)

STABILITY

It must be taken into account that in such high concentrations, and due to interaction with the other components of the formula, NEEM may be sensitive to ultraviolet rays, which may affect the effectiveness of the product. Therefore, it may be necessary to use opaque packaging to protect the product from the effects of light.

8- PACKAGING

[See attachment]





Guillermo Picabea
 Product Manager
 Degree in Veterinary Pharmacy

Laboratorios Bilper Group



Jose Ignacio Luis Hernandez
 Technical Director