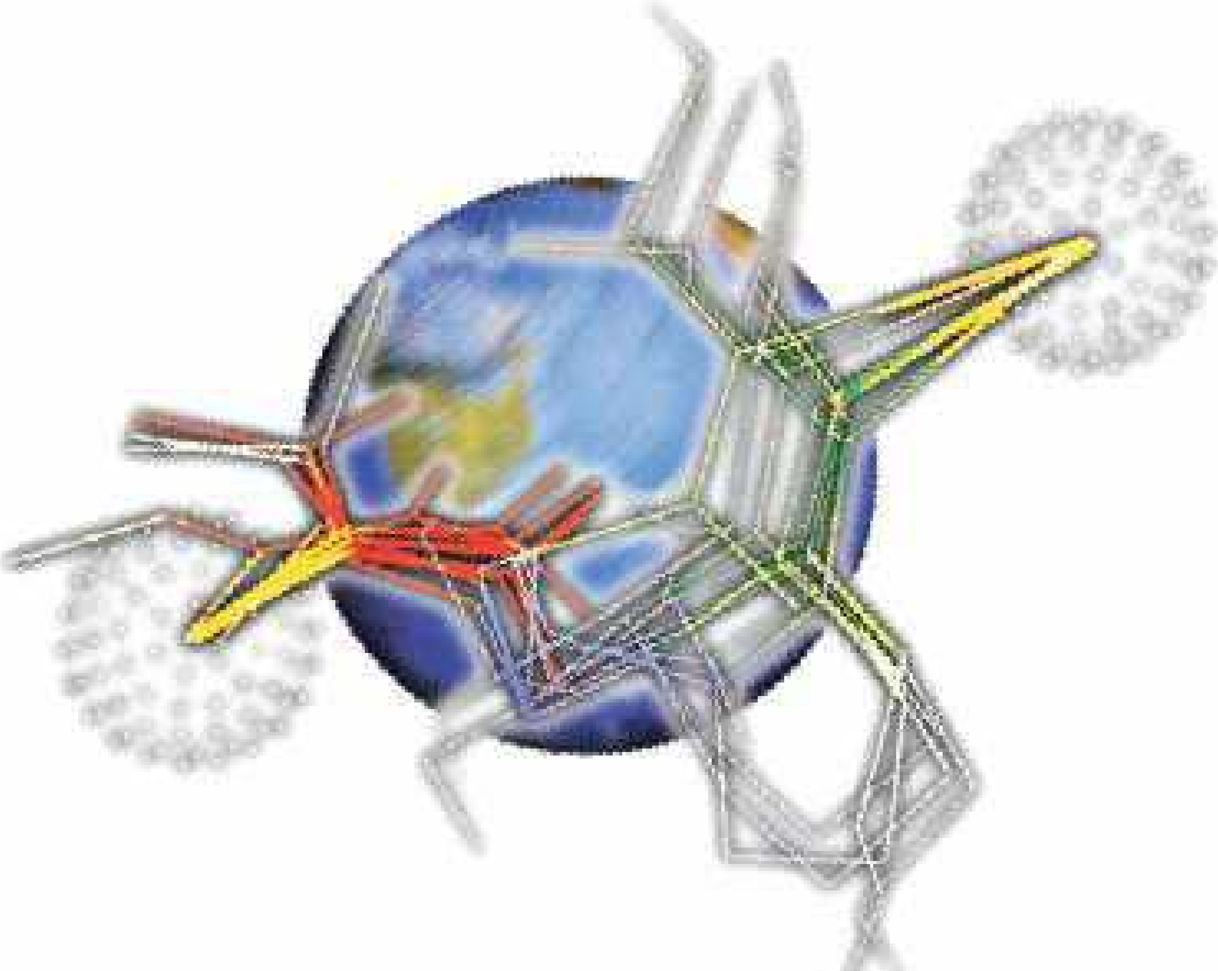
Bayrepel®

The new active ingredient in AUTAN®



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1. Introduction

1.1 The need for repellents

In many regions of the world, dangerous diseases, such as malaria, yellow fever, borreliosis (Lyme Disease) or tick-borne encephalitis are transmitted by mosquitos, flies, ticks and other insects. Statistics show that one person dies every 30 seconds from the complications of an arthropod insect bite. Malaria alone causes up to 3 million deaths per year .

In Europe and in the United States, mosquitos rarely transmit diseases, however in these regions malaria and yellow fever can develop, because tourists and business travellers contract infections during their trips to other parts of the world, in particular Asia and Africa. Approximate 1000 people per year are infected by malaria when travelling abroad. Additional, in Europe and North America, infections resulting from tick bites are becoming more and more prevalent.

The risk of being infected by a life threatening disease is not the only reason to protect ourselves against insects. Mosquitos or flies can turn every outdoor activity, such as a sports event, a fishing tour, a camping-trip or a barbecue into a real nightmare.

Attempts to control or even eradicate insects worldwide have been largely unsuccessful and probably ecologically unsound in most cases. Other methods such as drug prophylaxis and vaccination can reduce the risk of getting insect transmitted diseases, but they are costly, specific to one insect species, and last but not least they protect only against the disease but not against the insect bites.

Repellents overcome these limitations. They provide effective, convenient and safe protection against insect bites during outdoor activities. Consequently, repellents have developed into an important segment of the consumer health care market in many parts of the world. Once applied to the skin, repellents form a protective layer which repels mosquitos, flies and ticks for hours.

1.2 Autan®, a worldwide brand for repellents

Bayer introduced its line of repellents under the Autan® brand in 1955. Today Autan® is the second largest brand worldwide in this product category and market leader in Europe, Latin America and Asia. The Autan® product line comprises a complete line of formulations including aerosols, lotions, creams, balms, sticks and sachets.

2. Biology of offending insects

2.1 Mosquitos: a worldwide nuisance and danger

Around 3000 species of mosquitos are found worldwide; their habitat stretches from the northern tip of Finland to the southern tip of Africa. In the marshlands of Alaska and Finland and in the former Soviet Union, swarms of mosquitos actually blot out the sun and make life unbearable for men and animals.

Predominantly in the subtropics and tropics mosquitos, also spread epidemics. Some important species and diseases are listed (see table 1). Malaria is the best known and most prevalent disease; it is transmitted by the Anopheles mosquito.

Table:

Species	Insect	transmitted disease	regions	importance
Anopheles sp.	mosquito	malaria	tropics, subtropics	3 mio death cases/year
Aedes aegypti	mosquito	yellow fever	tropics	30000 death cases/year
Culex sp.	mosquito	filariasis	tropics	
Phlebotomus sp.	sandflies	leishmaniasis	tropics, subtropics, mediterranean countries	

Why do mosquitos bite?

Male mosquitos are harmless vegetarians, content to feed on nectar. They do not bite. However, females require a blood meal as a source of protein, which is indispensable for egg production: no blood, no reproduction.
In order to find their host and "blood donor" mosquitos are equipped with a complex sensory system allowing them visual orientation and piloting by other stimulants. The most important are: heat, humidity, carbon dioxide and chemical attractants.

Mosquito attracting chemicals include various amino acids, ammonia, lactic acid, butyric acid and other substances excreted by human skin.

To put it simply, mosquitos "like" the smell of their host and can trace him or her by following the concentration gradient in the air. They fly in whichever direction the smell is strongest. As soon as the insect has found an attractive spot on the skin, it will start to feed. To do so it pierces the skin with its proboscis, a combined salivary and sucking tube equipped with small teeth. The piercing normally goes unnoticed, since the proboscis does not usually come into contact with any nerve endings. A secretion is then injected into the wound and dilates the blood vessels to increase the flow of blood. At the same time, the substances secreted prevent the blood from clotting and blocking the proboscis. Although the bite is perceived at this stage, the victim will do better to leave the mosquito alone whilst sucking, so no parts of the proboscis is left in the skin.

After the insect has sucked sufficient blood it leaves the host and will not attack another victim. It will drop the eggs and another life cycle of the insect begins.

2.2 Flies

Flies belong to the same order (Diptera) as mosquitos. Some species are dangerous because they contaminate food, others bite or suck human blood, causing painful wounds and transmitting diseases.

House flies (Muscidae),

The Muscidae are a large family of flies typified by three species: The Common House-fly Musca domestica whose larva live in rotting matter and dung; the lesser house fly Fannia canicularis which tends to fly indoors. Both species do not bite and are more a problem of hygiene and a nuisance. This distinguishes them from the third species known as the common stable fly (Stomoxys calcitrans) or biting house fly.

Stable flies are not tied to livestock; they will also bite people. They remain on their hosts only while trying to feed, and travel widely in search of hosts or breeding sites.

In contrast to other species, the mouthparts of both males and females of members of this family are essentially identical, and both sexes bite. Also, their mouthparts are constructed on an entirely different principle: They force the entire proboscis into the skin like a needle. Small recurved spines at the tip of the proboscis are moved sideways away from each other to rasp a hole and pull the proboscis deeper and deeper with painful effects on the victim.

Larvae of the stable fly develop in cattle dung or any other decomposing vegetable refuse, such as lawn clippings, refuse from packing plants, or waterweed cast ups. Stable flies develop rapidly and may complete several generations each summer. Unlike members of the preceding families, stable flies hibernate in the pupal stage. Stable flies can transmit bacteria with their mouthparts causing f.e. tularaemia and anthrax. Like tabanids, they are wary feeders, and may bite several animals many times before feeding to completion.

Black Flies (Simuliidae)

No other biting flies cause such apprehension, as do black flies. If you visit a Canadian forest in June and July, you will see that this fear is justified. Black Flies of the Simulium venustum species complex can be so numerous and their attacks can be so unrelenting, that any outdoor activity during the day becomes almost impossible without protection.

Black flies often land and take off repeatedly without biting. Their number and their readiness to bite, increases as sunset approaches. However, even when they are not biting, their buzzing presence and constant crawling is as irritating as the bloodsucking itself. Relief comes after dark, for unlike mosquitos and biting midges (Culicoides sp), black flies do not attack at night.

Although they cannot bite through clothing, black flies have a predilection for crawling into hair or under clothing, biting in accessible places such as the ankles and belt line. Black flies are strongly influenced by color - they find dark hues more attractive than pale ones, and blue, purple, brown, and black more attractive than white or yellow. A light-colored shirt, therefore, is a much better choice of clothing than a dark blue one.

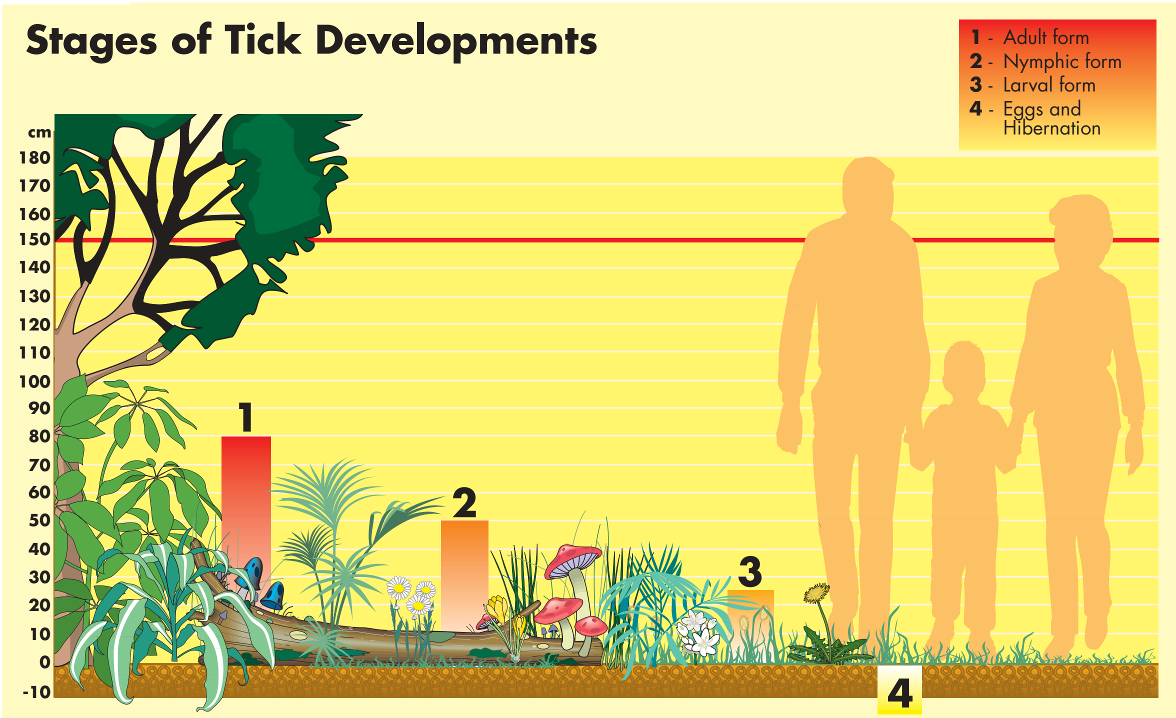
Black flies are more selective in their choice of host than are mosquitos, and comparatively few species take human blood. Most species seem to feed only on the blood of birds and a substantial percentage apparently do not take blood at all, because their mouthparts have degenerated and appear useless for bloodsucking. Bird biters, however, may be attracted to people, and when numerous they can be annoying, even though they do not bite.

2.3. Ticks

Ticks (Arachnida, Acari) are a group of around 800 species worldwide. Sheep and deer ticks are the most important vectors of diseases, transmitting Lyme disease and tick-borne encephalitis as the most detrimental infections.

In North America and Europe the tick season lasts from May to November. In years with dry, hot weather the risk of infection is particularly high in May, June and September and less so in July and August.

Like mosquitos, ticks transmit diseases while sucking blood, which is necessary for their development. Unlike mosquitos, the tick usually needs several blood meals. To find a donor, it waits - frequently for several weeks - on blades of grass, ferns, bushes or on the undersides of leaves.



Source: AUTAN®

When a tick locates a potential host, it attaches itself to the host and looks for a suitable site to suck blood. In humans, it prefers to attach itself to warm, moist parts of the body such as the scalp, the armpits or the pubic region. The tick pierces the skin and starts to suck the blood. If undisturbed, it may continue to do so for up to nine days. When the tick has finished feeding, it drops to the ground and soon it will start to develop eggs. At that time it may be several times its original size.

Tick bites are sometimes hard to detect because the victim barely feels the bite. The reason for this is, that anaesthetic substances are secreted by the tick during the sucking process. At the end, a slight reddening of the skin around the wound often may be the only clue of a tick bite.

Tick-borne pathogens which may be viruses or bacteria usually are transmitted with the saliva, or sometimes with the tick`s excrement. Signs and symptoms of tick transmitted diseases in humans may take weeks or months to develop and are rather unspecific. This explains why it took until 1970 before a connection was established between Lyme Disease and the bites of deer ticks (Ixodes scapularis) and between summer encephalitis (FSME) and the bites of sheep ticks (Ixodes ricinus).

3. Repellent products and active ingredients

3.1 History of repellent development

In early history, man discovered that insects could be repelled by burning aromatic or strong smelling plants or wood. In ancient Egypt, strong smelling substances were applied to the skin to serve as mosquito repellent. The Romans used camphor, cypress, galbanum, pomegranate skin, lupin and cinnamon. In the 16th century hemp was found to be effective against insects, and later discoveries included numerous plant extracts, such as garlic, olive oil, pennyroyal oil and raw tomato juice. At the turn of the century the following oils were known as naturally effective insect repellents:

Natural substances with a repellent effect

aniseed oil	lavender oil
bergamot oil	lemon oil
camphor	nutmeg oil
cinnamon oil	orange-flower oil
clove oil	pennyroyal oil
coconut oil	pine oil
eucalyptus oil	pyrethrum
geranium oil	thyme oil

Today these substances are rarely used for two reasons: a) they are not sufficiently effective b) high concentrations are required and their odor is not well tolerated by the users. Hence synthetic repellents replacing these natural oils were sought and developed during World War II to better protect soldiers in the tropics and subtropics from dangerous diseases.

3.2 Mode of action

Today`s repellents contain an active ingredient, solvents and in most cases a fragrance. After application, the solvents in the formulation evaporate, leaving the active ingredient on the skin. The repellent is effective as long as the active slowly evaporates forming a layer of "scent" over the skin. This "scent" interferes with the mechanism that attracts mosquitos, flies or ticks to human skin. The resulting neural pattern seems to be the reason that insects avoid repellent treated surfaces.

Chemically, most repellents are amides, alcohols, esters or ethers. They are liquids or (readily) low-melting solids with boiling points over 150 °C. They evaporate slowly at room temperature.

3.3 N,N-diethyl-m-toluamide (DEET)

Since the mid-fifties, DEET has been regarded worldwide as the most effective active in all-round repellents. DEET protects humans and animals for 2-8 hours against all relevant mosquitos, flies and ticks.

On the other hand, DEET has some disadvantages.

- The solvent and plasticiser effects on many plastic items and laquered surfaces can cause substantial damage so that complex warning and precautions have to be on the label. Nevertheless consumer complaints about damage to glasses, plastic watches etc. have been quite numerous and the existence of the warnings cause consumers to believe that DEET is a very agressive product to the skin as well.
- The high potential to irritate eyes and mucous membranes makes application to the face difficult.
- The sticky, greasy skinfeel and the strong, longlasting odor lead to the instinctive rejection of these products.

3.4 Non-DEET repellents

Besides DEET some plant extracts, mostly citronella oil and limonen, are being used as active ingredients for repellents. Since they occur naturally, some consumers tend to think them as ″safer″ than ″chemical″ substances.

Formulations containing these active ingredients have been tested under laboratory and field conditions. The efficacy results show clearly that these products:

- will work only for a rather short period
- will protect only against some insect species
- will not provide reliable protection against very aggressive insects, in particular mosquitos.

4. Bayrepel®

4.1 What have we been looking for: the ideal repellent

Bayer, who outside North America is the market leader in insect control (household insecticides and repellents) with Baygon® and Autan® began research for a new repellent agent in the eighties.

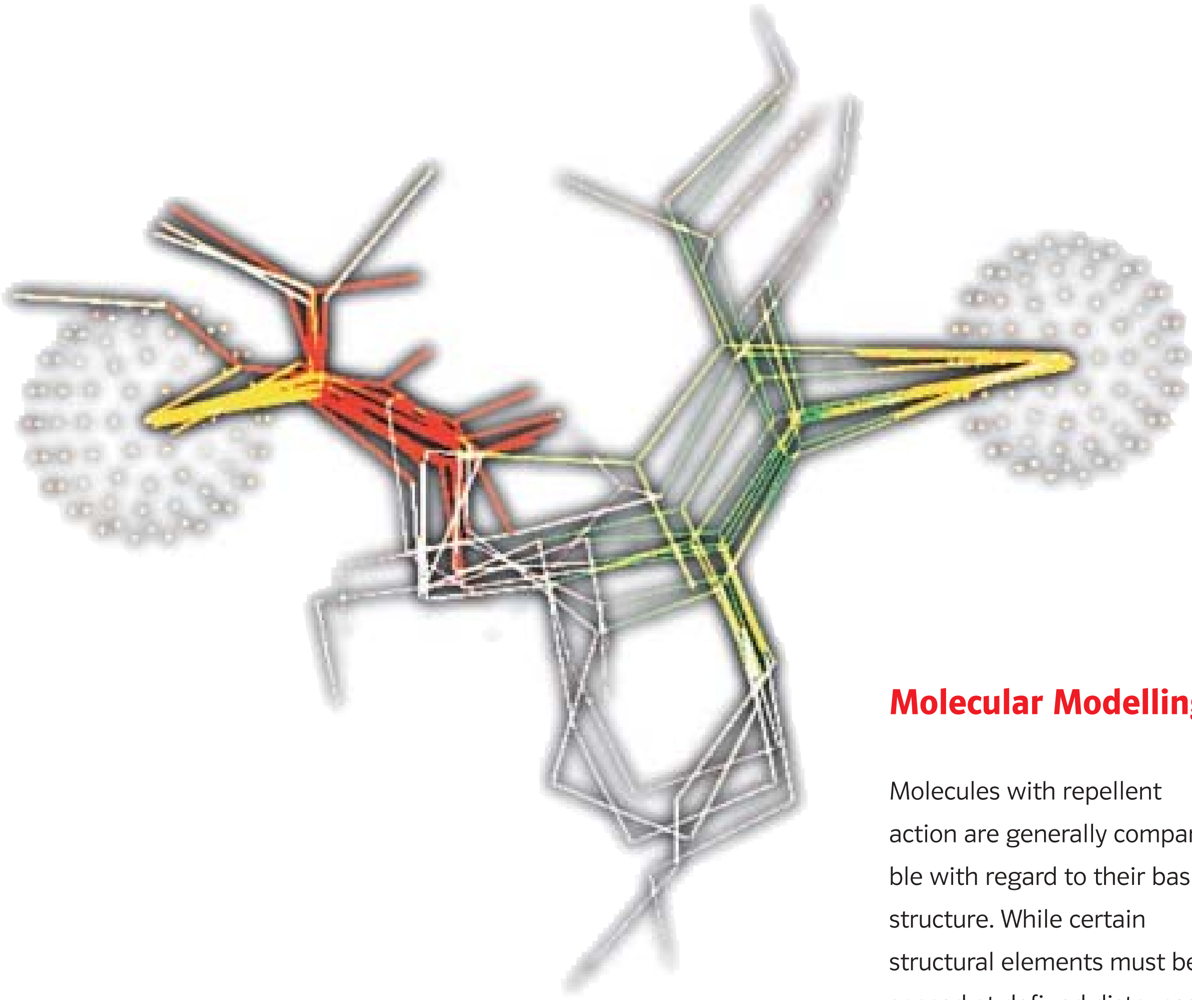
Our long history of investigating, developing and producing repellents has given us indepth knowledge of the strengths and weaknesses of all repellent active ingredients available. Based on this expertise we defined the perfect profile of a new repellent substance before we initiated the research program.

Profile of the ideal repellent:

effective - long lasting - broad spectrum of insects	**compatible with other materials** - not a solvent to plastics, coatings, sealants
safe - non toxic - non irritating - low absorption	**easy to formulate** - good solubility - highly stable - not corrosive
good cosmetic properties - colorless - odorless - pleasant skinfeel.	**patentable**

4.2 Bayrepel®: a tailor-made molecule

Our search for new actives was based on the hypothesis that the repellent effect is triggered by the action of a given substance on specific olfactoric receptors of the insects.
Investigations were supported by molecular modelling. This technique allows the three-dimensional construction and mapping of different molecules. Substances already well-known as repellents formed the basis for this molecular modelling. Their molecules were altered at specific sites where an interaction with an insect's receptor model was anticipated.



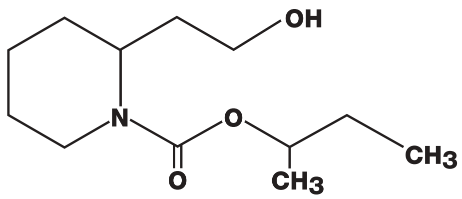
Molecular Modelling:

Molecules with repellent action are generally comparable with regard to their basic structure. While certain structural elements must be spaced at defined distances variations are acceptable in the lipophilic areas of the molecule (middle of the picture)

For ease of understanding let´s look at the proposed receptors: In simplified terms they work like a lock which can be opened with the proper key, in other words by a specifically tailored molecule. The repellent effect is triggered only if the key fits smoothly into the lock. Logically our objective was to perfect a molecule that would fit like a key.
Guided by our operational model, especially within the lead structure search, we found several new repellent classes with interesting properties. Bayrepel®, a piperidine derivate, was selected because its overall profile proved the most promising.

5. Bayrepel® / Chemical and Physical properties

1. Formula



2.	Empirical formula:	$C_{12}H_{23}NO_3$
3.	CAS name:	1- Piperidinecarboxylic acid, 2-(2-hydroxyethyl)-, 1-methylpropylester
4.	Trade name:	Bayrepel⌋
5.	INN name (proposed)	Picaridin/Hepidanin
6.	Eilincs number	423- 210- 8
7.	CAS No.:	119515- 38- 7
8.	Molecular weight:	229.3 g/Mol
9.	Physical state:	liquid
10.	Solidifying point:	31 °C
11.	Viscosity:	30,7 sec. flow time accord. to DIN 53211
12.	Initial boiling point:	approx. 280 °C at 1013 hPa
13.	Vapour pressure:	3 hPa at 20 °C 17 hPa at 50 °C 23 hPa at 55 °C
14.	Color:	colorless liquid
15.	Odor:	nearly odorless
16.	Purity of technical grade:	97.0 – 100 %
17.	Flashpoint:	400 °C
18.	Density:	1,040 g at 20 °C
19.	Solubility:	
	in water:	insoluble
	in 2-propanol:	miscible
	in ethanol:	miscible
20.	Storage conditions:	store at room temperature

6. Efficacy Data on Bayrepel®

6.1 Overview

Bayrepel® was tested against the relevant insect species including mosquitos, flies and ticks. The following overview lists the species which were effectively repelled by Bayrepel® in laboratory and field tests.

Mosquitos	Flies	Ticks	other
Aedes aegypti	Musca domestica	Ixodes ricinus	Biting midges/No-seeums
Aedes taeniorhynchus	Stomoxys calcitrans	Ixodes scapularis (damini)	Culicoides spp.
Aedes albopictus	Simulium venustum	Ripicephalus sanguineus	
Culex quinquefasciatus	Tabanidae		
Culex pipiens fatigans			
Anopheles stephensi			
Anopheles sinensis			
Anopheles dirus			

6.2 Methodology

The following test designs have been used for testing on mosquitos and flies:

- **Cage testing on guinea pigs:** This test model was specifically developed to screen 800 newly synthesized potential actives for their repellency. The test is rather simple and delivered fast and reliable biological efficacy data, comparable to those obtained in man.
- **Cage tests on humans / arm in cage:** This testing method provides highly reliable, comparative data on the active ingredient and its various formulations under standardized laboratory conditions.
- **Field tests on humans** to investigate the efficacy of the active and various formulations under in-use conditions

In all these tests DEET or DEET-based formulations were used as a reference.

6.3 Efficacy testing against mosquitos and flies in guinea pigs

Test method description:

Guinea pigs had a patch of 50 cm^2 shaven on their backs; the area was subsequently treated with depilatory cream. The animals were then fixed in narrow cages in such a way, that only the shaved patch is accessable to the insects.The test substance is diluted to a 3% concentration in ethanol; 0,4 ml of this solution were evenly applied to the shaved skin of the guinea pig.
On evaporation of the solvent the guinea pigs were exposed to around 1000 biting active mosquitos or flies for 3 minutes. The mosquito bites incurred within this period were recorded. The 3-minute-test was repeated at hourly intervals and was discontinued when a guinea pig had incurred 3 or more bites within the test period. Each test comprises at least 4 replicates.

Table: Efficacy testing in guinea pigs

Species	hrs of protection	
	Bayrepel®	DEET
Aedes aegypti	3.0	3.0
Culex quinquefasciatus	>9.0	6.0
Anopheles stephensi	6.0	4.0
Stomoxys calcitrans	9.3	2.4

6.4 Cage tests in human volunteers

The biological data generated by tests on guinea pigs were verified by cage tests with human volunteers. The experiments described in the following table were designed to compare DEET vs Bayrepel®.

Description of test method:

Test subjects had a predefined amount of repellent active (effective doses: 0,01- 0,02 mg of active ingredient per cm^2) applied to a rectangular area of 90 cm^2 on each forearm, one forearm being treated with DEET, and the other with Bayrepel®. Ten minutes later a sleeve with an opening of 3.1 x 8 cm (25 cm^2) was fastened around the arm. The hands were protected by latex gloves. The pretreated areas of both forearms were exposed to the insects for 3 minutes: exposure consisted of roughly 1000 biting active mosquitos in a 60 x 60 x 60 cm cage . The test was repeated every hour. When 3 bites within the 3 minute period were observed the product was considered to be no longer effective and the test was discontinued. In the table below the results obtained are shown as the mean of all replicates (4 to 10 subjects per test).

Table: Cage tests in human volunteers

Species	Location	Bayrepel®		DEET	
		quantity mg/m^2	hrs Efficacy	quantity mg/m^2	hrs Efficacy
Aedes aegypti	Malaysia	2400	4.0	3400	4.0
Aedes aegypti	Germany	2800	4.0	2800	4.0
Aedes aegypti	Germany	1700	2.0	1700	1.0
Aedes aegypti	Switzerland	16000	11.3	16000	9.0
Aedes albopictus	Malaysia		8.0		4.0
Aedes albopictus	Malaysia		6.0		3.0
Culex quinquef.	Germany	2800	>8.0	2800	>8.0
Anopheles st.	Germany	2800	>8.0	2800	7.0
Anopheles st.	Switzerland	16000	11.3	16000	9.7
Anopheles dirus	Malaysia	2400	>8.0	2400	>8.0
Stomoxys c.	Germany	4000	>8.0	4000	5.5
Stomoxys c.	Germany	2000	6.0	2800	3.0
Stomoxys c.	USA	4700	7.7	4700	4.5

Result:
At identical concentrations Bayrepel® provides equal or longer protection than DEET against several Aedes and Anopheles species, Culex quinquefasciatus and especially against Stomoxys calcitrans.

In order to confirm the prolonged efficacy of Bayrepel® vs DEET a commercially available repellent aerosol containing 14,25% DEET was compared directly to a 10% Bayrepel®-based aerosol.

Results

Species	hrs of Efficacy	
	Bayrepel® (10 %)	DEET (14,25 %)
Culex quinquefasciatus	>8	>8
Anopheles stephensi	>8	6
Anopheles dirus	>8	4
Aedes aegypti	4	4
Stomoxys calcitrans	5	3

6.5 Field tests against mosquitos and flies

Field tests following different test protocols have been performed by Bayer R&D, universities and other research institutions in the USA, in South-East Asia and in Europe.

Table: field tests

Species	Location	Bayrepel®	DEET		
		quantity	Efficacy (hrs)	quantity	Efficacy (hrs)
Simulium spp.	USA	3900 mg /m²	9.7	3900 mg / m²	8.5
Aedes spp.	USA	2300 mg /m²	5.2	2300 mg / m²	4.5
Aedes spp.	Malaysia	300 mg /arm and leg	6.0	300 mg / arm and leg	4.0
Aedes albopictus	Malaysia	113 mg /arm and leg	>8.0	160 mg / arm and leg	6.0
Aedes taeniorh.	USA	2300 mg /m²	4.2	2300 mg / m²	3.3
Culex quinquef.	Malaysia	113 mg /arm and leg	>8.0	160 mg / arm and leg	6.0
Anopheles spp.	Malaysia	113 mg /arm and leg	>8.0	160 mg /arm and leg	6.0
Tabanidae	Austria	1500 mg /m²	5.0	2000 mg / m²	6.0
Culicidae	Austria	3000 mg /m²	4.0	4000 mg / m²	6.4

* Both active ingredients screened for effectiveness for indicated duration

Results summary: Field tests proved the efficacy of Bayrepel® at least equal to and in most cases superior to that of DEET.

Summary: Efficacy against mosquitos and flies

The assessment of all results show that Bayrepel® protects equal to or longer than DEET against mosquitos and the biting fly Stomoxys calcitrans in all tests.

6.6 Efficacy on ticks

Efficacy on ticks has been demonstrated in laboratory tests against Ixodes ricinus, the European vector of FSME and against Ixodes scapularis, the vector of North American Lyme disease. Efficacy against Ixodes ricinus was confirmed by a field test in Austria.

Since Ixodes ricinus is biologically extremely close to Ixodes scapularis, the American registration authority - the Environmental Protection Agency (EPA) - has accepted the field efficacy data on Ixodes ricinus to substantiate the "tick-claim" in the US.

In addition we have demonstrated the efficacy of Bayrepel® in laboratory tests against Ripicephalus sanguineus (dog tick).

7. Cosmetic properties

Bayrepel® has been tested intensively in typical repellent formulations to evaluate its cosmetic properties. Tests were performed in Bayer´s laboratories, in a special test institute for cosmetic products and with consumers in various countries including Spain, Mexico and France. Laboratory investigations focused specifically on the smell and the skinfeel of Bayrepel®-containing finished products in the form aerosols, lotions, balms and creams. All testing was carried out in direct comparison with the corresponding DEET-products.

Results summary: Bayrepel® is significantly more suitable for cosmetically attractive formulas.

8. Compatibility with other materials

Bayrepel® was tested against a broad variety of common household materials including plastics, coatings, foils and varnishes. The following results show, that Bayrepel® alone and in typical formulations will not significantly attack the materials listed below:

Material	Bayrepel® 1h	3h	6h	24h	DEET 1h	3h	6h	24h
Polystyrene	0	1	2	2	4	4	4	4
PVC	0	0	0	0	0	1	1	2
Laguered wood	0	1	1	2	2	4	4	4
Plastic foil. soft	0	0	0	1	4	4	4	4
Plastic foil. hard	0	0	0	1	0	1	2	4

0 = no effect, 1 = weak effect, 2 = medium, 3 = strong, 4 = very strong

Improved material compatibility is a significant advantage because:

- consumer complaints concerning property damage are virtually eliminated
- negative associations of consumers concerning the aggressiveness of the products will disappear; a higher degree of safety is communicated
- warning statements and handling instructions on the label will become significantly shorter and less alarming
- restrictions concerning packaging materials, label materials, printing inks and sealants will be significantly reduced offering potential for more economic materials

9. Consumer and Environmental safety

9.1 Consumer safety / Toxicological data

To guarantee consumer safety and to comply with worldwide registration requirements, a comprehensive toxicology program has been performed. The program and the tests were designed in close cooperation with the EPA of the United States. To get the most meaningful results, all studies in the second block have been performed by the consumer relevant dermal route of exposure.
None of the tests resulted in adverse findings. Final reports of all studies as well as an executive summary have been prepared and have been submitted with the complete data package to the registration authorities worldwide.

Study	Species	Results
Acute:		
Oral	Rat	LD_{50}: 4743 mg/Kg b.w.
Dermal	Rat	LD_{50}: >5000 mg/Kg b.w.
Inhalation	Rat	LD_{50}: >4364 mg/Kg b.w.
Irritation:		
Skin	Rabbit	no irritation
Eye	Rabbit	slight irritation
Sensitization:		
Dermal	Guinea pig	no sensitization
Phototoxicity	Human	no phototoxicity or photosensitization
Genotoxicity:		
Gene mutation	in vitro	no genotoxic potential identified in
DNA-damage	in vitro	all studies
Structural ChromosomeAberration	in vitro	
Resorption	Human	5 %
Metabolism:*	Rat	no bioaccumulation, fast renal excretion,
Teratogenicity:*	Rat	NOEL: 200 mg/Kg b.w.
	Rabbit	NOEL: 200 mg/Kg b.w.
Reproduction:*	Rat	no reproduction toxicity (200 mg/Kg b.w.)
Neurotoxicity:	Rat	no neurotoxic potential
Subchronic:*	Rat	NOEL: 200 mg/Kg b.w.
	Dog	Extended to chronic study
Chronic:*	Rat	
	Dog	NOEL: 200 mg/Kg b.w.
	Mouse	

*All studies performed by the dermal route of exposure

9.2 Environmental Safety

Daphniae test:	EC 50 > 100 mg/l
Fish toxicity:	LC 50 > 100 mg/l
Algae toxicity:	EC 50 = 87 mg/ l
Avian toxicity:	LC 50 > 5000 ppm

10. End User Product Line

Bayrepel® can be easily formulated as aerosol, pump spray, liquid, cream, balm or stick. While all of these have superior cosmetic properties, formulas containing 10 % active provide 3 to 5 hrs protection; formulas with 20 % active ingredient protect the user for up to 10 hrs. Dosing of the active may also be reduced to below 10% supplying a formula for short term protection.

Representative Composition of a 10 % Bayrepel® Liquid/Pumpspray

Bayrepel®	10 %
Water	44 %
Ethanol	45 %
Perfume	1 %

Representative Composition of a 20% Bayrepel® based Aerosol

Premix	
Bayrepel®	20 %
Water	39 %
Ethanol	40 %
Perfume	1 %

fill 80 g of premix in 100 g can,
fill up with 20 g Propane/Butane 20:80
Final formula

Bayrepel®	16.0 %
Water	31.2 %
Ethanol	32.0 %
Perfume	0.8 %
Propellant	20.0 %

All formulations have been thouroughly tested concerning chemical stability and compatibility with packaging material. Results show that:

Bayrepel® is easy to formulate in all typical repellent products because it is:
- not corrosive or incompatible with plastics, sealants, coatings or other packaging materials
- highly stable as an active ingredient and in all formulations under normal conditions

These properties reduce the manufacturer`s risk of product quality/package problems as compared with DEET containing formulations.

11. Registrations

Regulations governing the marketing of repellents vary from country to country. In the majority of countries, repellents are grouped with household insecticides for regulation. Those countries include Italy, Brazil and the United States.

11.1 Registration as Insecticidal Active

We chose the US Environmental Protection Agency (EPA) as the guiding authority in the development of the compound for the following reasons:

- Like Bayer the US EPA applies high and strict standards of safety, efficacy and product quality
- The catalogue of requirements to be met for EPA approval is predefined
- EPA has a high level of knowledge and experience in the assessment of repellent active ingredients

In 1990 Bayer and EPA began discussions defining criteria to be met and protocols to be followed when building a safety database in support of Bayrepel® approval. With regard to the intended use of product as an insect repellent for application to human skin, a novel approach was used for toxicity testing: the chemical was dosed dermally instead of administering it in the animals` diet as would be the classical procedure.
This permitted a more accurate evaluation of effects the chemical produced upon repeated application to the skin throughout the lifetime of the test animals, including reproduction.
The entire registration dossier including product chemistry, efficacy and safety data was submitted for registration into many countries. Meanwhile registrations from more than 20 countries are on hand (Status Jan. 2000).

11.2 Approval as a cosmetic product

In many countries repellents are regulated as cosmetic products. In many countries in Europe a new active ingredient has to comply with the requirements of the European Community (EC) Cosmetic Directive. Since these requirements are covered by the EPA data package, Bayrepel® also fulfills the requirements of the EU Cosmetic Directive and may thus be marketed in those countries as cosmetic product.

12. Trademark of the active ingredient Bayrepel®

Bayer will use the trademark Bayrepel® on all Autan®-products containing this ingredient.

The INN names Picaridin and Hepidanin are applied for.