Use of Repellents in Cosmetics

The Free Radical Transformation from Cosmetic Product to Skin

Interlaboratory Comparison on Preservation Challenge Testing (PCT) for Cosmetics

Detergents and Cleaning Products

8th International Fresenius Conference
In particular near slow-moving shallow water, blood-sucking parasites like midges can be a real menace. In Europe, they usually belong to the species of Culex and Anopheles, in some cases also Aedes. In the tropics, the latter two in particular can transmit life-threatening diseases including malaria (Anopheles) or yellow fewer (Aedes). In Europe, however, the main problem with midges is mainly just wheals. These result from histamines, injected with the midge’s saliva. A much greater threat to human health in Europe are the native tick species. The most common tick in Europe is the castor bean tick (Ixodes ricinus). This species can transmit the arbo-virus which causes tick-borne encephalitis (TBE). In severe cases this can be fatal for weak patients. There is no medical treatment after the outbreak of the illness. Borreliosis is another illness transmitted by the castor bean tick. This can lead to paralysis and impaired vision. However, this illness can be treated effectively with antibiotics when administered in time. In contrast to midges, protection from the castor bean tick is required only outdoors. Indoors, this tick quickly dries out due to low air humidity. Other species belonging to the family of hard ticks are the deer tick (Ixodes scapularis) and the lone star tick (Amblyomma americanum). Like the castor bean tick, the deer tick can transmit borreliosis and TBE. The lone star tick can transmit Rocky Mountain Spotted Fever (RMSF), which can be fatal if left untreated.

Both midges and ticks belong to the family of arthropods. As explained above, protection from parasitic arthropods does not just support well-being, but can also avoid serious infections.

### Mode of action of repellents and measurement of efficacy

Means of protection against blood-sucking parasites are manifold. Fly screens and mosquito nets can be very effective, in particular indoors. Another established method is the use of chemicals. For instance, clothing impregnated with Permethrin can provide reliable protection, even after being washed several times (1). Likewise, impregnating mosquito nets can enhance their effectiveness.

In cosmetics, mainly three synthetic chemicals are used: DEET, Saltidin® and IR3535®. Unlike insecticides, these repellents do not kill parasites. Instead they mask the smell of humans, so they cannot be identified as a potential host. All three repellents protect from several arthropods. However, effectiveness can vary significantly from species to species. Therefore it is advisable to do specific tests on the most critical parasites. Great care should be taken when assessing efficacy by using results obtained for another species.

There are two types of tests, field tests and laboratory tests. There are pros and cons for both of them. Field tests give results for protection under realistic use conditions. For this reason, results can be readily used for advising users in terms of use concentrations and expected protection times.

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**Abstract**

There is a rising interest in insect repellents. Whilst protection from midges in Europe contributes mainly to well-being, there are medical reasons for tick protection. Both borreliosis and TBE (tick-borne encephalitis) are serious diseases transmitted by ticks. There are a number of protection measures available which vary in terms of efficacy and impact on human health. This article offers an overview of several studies assessing the efficacy of repellent actives, with a particular focus on protection from ticks.
A serious issue with field tests is comparability. Even when testing repellents at the same time, results can be misleading. Even minor differences concerning locations of the probands can change the exposition scenario, e.g. in terms of wind speed and brightness. Since the proband is attacked not by laboratory raised parasites but by free living ones, there is the risk of infection during the test. For this reason the set-up of a field test always has to ensure that participants' health is not put at risk. In laboratory tests, however, infection can be avoided because special germ-free lines of parasites are used. These tests are also more standardized, offering better comparability. Nevertheless, there are still a number of parameters that can hardly be controlled. Among these are the aggressivity of the used parasite strains (this can vary even between representatives of the same species) and the different rate of attraction of the volunteers (2). For these reasons, the following comparisons of the three repellents are always based on the same study.

There are common problems of field tests and laboratory studies. For one, the number of volunteers is limited, due to the technical outlay. Another problem is the way in which the repellent is provided. Whilst DEET is effective in pure form due to the high vapor pressure, Saltidin® requires a carrier. On the other hand, excipients like vanillin can reduce the vapor pressure of a repellent and therefore prolong the duration of efficacy. Hence the efficacy of a formulation to protect from arthropods depends on the repellent as well as on the other ingredients that are being used. In order to overcome this issue to some extent, this survey lists both studies using simple solutions of repellents and studies on commercially available formulations. These formulations have been optimized for efficacy and account for the specific properties of the individual repellent.

### Studies on midges

#### Methods

The standard laboratory method to measure the efficacy of repellents is the arm-in-cage-test. A defined area on the arm of the volunteer is treated with the repellent, while the remaining surface is covered by a rubber glove. The volunteer then puts his arm into a laboratory cage filled with midges. In order to ensure a sufficient level of aggressivity, the midges are not fed for a defined time before the test. Repellent efficacy can be measured in protection time or percentage of protection benchmarked against a control. There are different criteria to define the end point of protection. This might be the moment a midge lands on the treated surface, or the first bite. Since the first bite depends on one singular specimen only, there can be considerable statistical fluctuations. For this reason,
the study can continue until the second or third bite.
For measuring the percentage of protection, the number of bites on the treated area is compared to a control. The result is denoted in effective dose levels (ED). Thus an effective dose of 95 % (ED$_{95}$) means a reduction of bites by 95 %.
In field tests, attacks on probands in heavily infested locations are measured. Typically a defined area of the upper arm or the lower leg is exposed. Landing, ready to bite midges are caught and identified. This is important in particular to assess the efficacy against different species which can vary depending on the repellent. At the same time, the percentage of carriers can be obtained for every species. Protection time is usually given in relation to percentage of protection (e.g. the ED$_{95}$ might be 6 h).

**Studies**

One of the most comprehensive field studies to compare the protection of DEET, Saltidin® and IR3535® against biting midges was performed by Constantini et al. (3). In this study the repellents were dissolved in ethanol and tested in four different application concentrations (0.1 g/cm$^2$, 0.3 g/cm$^2$, 0.6 g/cm$^2$ und 0.8 g/cm$^2$). The efficacy against an Anopheles-species was monitored over a time period of 10 h. The best protection was achieved with DEET and particularly with Saltidin®. Even after 10 h, the efficacy of the Saltidin®-solution was still at a level of 99 %. During this time frame, no loss of efficacy was observed for Saltidin®, in contrast especially to IR3535® (Fig. 1).

A superior performance of Saltidin® was also found when comparing the average repellency over all concentrations, which was 10 percentage points above that of DEET and nearly 20 percentage points above that of IR3535® (Fig. 2).

A similar ranking was found in a laboratory test performed by Barnard et al. (4). In contrast to the study mentioned above, this study used commercially available formulations of DEET, Saltidin® und IR3535®. IR3535® showed weaknesses in particular against Aedes, the protection time was less than half the time observed for DEET and Saltidin® (Fig. 3).
It has to be considered that the concentration of the IR3535® formulation was 7.5 %, while the Saltidin® concentration in the respective formulation was 10 %. However, this difference cannot sufficiently explain the reduced protection time of this magnitude.

Less significant differences were found in the case of the Culex-species. For this test, the slightly shorter protection time of the IR3535® formulation might in fact result from the lower concentration of the repellent. The longest protection time was found for Saltidin®. It was 1 h longer than the most efficient DEET formulation, though the latter one had a significantly higher repellent concentration of 15 %.

The tendency of a lower efficacy of IR3535® versus Aedes- and Culex-species in comparison to Saltidin® was confirmed in another laboratory study (5). In this case, aqueous-alcoholic solutions of the repellents were used, both had a concentration of 20 %. This study showed a protection time for the Saltidin® formulation that was 4–5 times longer than the protection time of the IR3535® solution (Fig. 4).

An evaluation of the three studies mentioned above leads to the following conclusion: both in plain solutions and in commercially available formulations IR3535® proved to be less effective than DEET and Saltidin®. Less significant differences were found comparing DEET and Saltidin®. However, in particular the study performed by Constantini suggests the fact that Saltidin® achieves the same protection at a lower concentration than DEET.

Studies on ticks

Methods

Even in the European region, field tests are very critical due the possible infection with dangerous pathogens. Moreover, field tests on ticks hardly ever deliver statistically valid results, since the biting rate of ticks in the field is significantly lower than for...
midges. Therefore, only laboratory tests are discussed in the following.

For these tests, ticks are manually put on or near to the treated skin area, for example the forearm or the lower leg. In case of strong repellency, ticks will fall off, either directly on or close to the treated area. A loss of repellency is noted when ticks stay on the treated area or if they move a defined distance on the treated skin.

**Results**

«Stiftung Warentest» (a German institution which tests a huge variety of consumer products) made a comparison of commercially available products concerning their protection efficacy against nymphs of the castor bean tick (*Ixodes ricinus*) (6). A protection time from 1 h to 3 h was found. One result of this test is the significance of the total formulation. The shortest protection time was found for a product containing Saltidin®, however this repellent was also used in one of the products showing the longest protection time. When the protection time against adult ticks was tested, this Saltidin®-formulation showed even the longest protection time compared to DEET and IR3535® (Fig. 5).

Another laboratory study determined the efficacy of repellents against the lone star tick (*Amblyomma americanum*) (7). For this test a DEET-formulation, developed for the American military, was tested against Saltidin®- and IR3535®-formulations provided by the respective manufacturers of the repellents. After 10 h, a formulation containing 10 % IR3535® showed the lowest efficacy. Also at 20 % IR3535® showed significantly poorer performance than formulations with the same concentration of Saltidin®. Whilst the IR3535® product provided 94 % protection (corresponding to 6 % of ticks not repelled), a value of 98 % and 99 % percent was found for the Saltidin®-formulations (which means only 2 % and 1 %, respectively of ticks were not repelled). Hence the most effective formulation containing Saltidin® showed the same efficacy as the DEET-formulation, however at a concentration 13 percentage points lower (Fig. 6).

In view of this finding, another study is of particular interest in which Saltidin® and DEET were compared at an identical concentration of 20 % (8). These were tested in their efficacy against the deer tick (*Ixodes scapularis*). The persistence time of Saltidin® was found to be 2.5 h, which was more than five times greater than the persistence time of DEET, which was less than 30 min (Fig. 7).

The tick studies discussed above show that good protection from ticks can be achieved using the appropriate repellent. In particular formulations containing Saltidin® showed very good results with regard to all three species studied.

**Fig. 5 Protection time of commercial formulations against the tick species *Ixodes ricinus* (6).**

**Fig. 6 Protection of repellent formulations against the lone star tick (7).**
Health and compatibility aspects

As can be seen from the afore-mentioned studies, DEET and in particular Saltidin® offer very good protection from both midges and ticks. In addition to high efficacy, there are also other relevant criteria for the use of repellents in cosmetic applications. A very important factor is the health aspect. In principal, the dermal uptake of the topically applied repellent should be as low as possible. This is a strong argument for Saltidin®; absorption is six times lower compared to DEET, according to research done by Nentwig (9).

Furthermore, there is reason to assume that DEET can have neurotoxic effects for humans (10). Considering the higher efficacy at the same dosage achieved by Saltidin® compared to DEET (e.g. found by Constantini (3)), choosing Saltidin® means using the less critical repellent at a lower dosage, with a significantly lower absorption.

There are a number of additional advantages in favor of Saltidin®. In contrast to DEET it is virtually odorless. Saltidin® also shows good compatibility with other materials. DEET, in contrast, is a solvent that can damage material like plastic watches or rubber parts of fishing equipment. Last but not least, Saltidin® can easily be incorporated into cosmetic formulations.

Summary

DEET, Saltidin® and IR3535® are valuable ingredients for formulators designing repellents against parasitic arthropods. Considering the difficulties of comparing results obtained in different studies – in regard to the number of parameters affecting repellent efficacy – DEET and in particular Saltidin® seem to offer especially effective protection. Due to the number of additional benefits of Saltidin® in terms of health aspects and material compatibility, this is a highly recommendable repellent. Its beneficial toxicological profile makes Saltidin® an ideal active for repellent formulations that can also be used by children aged two and older.

References


(5) Mehlhorn H, Report on the activity of two formulations (XT00 00031, XT00 00032) to repel two species of mosquitoes (Culex quinquefasciatus, Aedes aeegypti), Unpublished Alpha-Biocare GmbH Report (2010)

(6) Anti-Zecken-Mittel, Stiftung Warentest (5) 82-86 (2008)


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