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Unique repellents as ethyl butylacetylaminopropionate: easy and safe protection against head lice

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ABSTRACT: Repellents are worldwide used in personal protection against biting insects which are potential vectors of diseases. Head lice are not vectors of diseases, but control measures against head lice are necessary to prevent spread of infestations. Repellents are only used in some countries currently for personal louse protection. However, repellent products containing unique actives like Ethyl butylacetylaminopropionate (IR3535®) could complete control measures against head lice worldwide.

INTRODUCTION

While repellents are globally used for protection against biting insects, the use for head lice protection is established in some countries only. The principles of control measures against invasive insects, like the tiger mosquito and potential head lice epidemics are the same: scientific researches on characteristics and behaviour of the species, monitoring of the species, information campaigns and recommendations to population as well as use of insecticides or other treatments against the species (1, 2). Control measures established for biting insects serves as control of vectors of diseases. Control of head lice is the control of a nuisance, as they are not vectors of disease and only secondary infections could be deemed as a risk (2). However, if the control measures fail, the use of repellents for personal protection has only taken for granted in protection against other biting insects. Insecticides are an important tool in head lice control, but some of them were withdrawn due to mammalian toxicology or are no longer used due to the development of widespread insecticide resistance in louse populations. Besides the difficulties in identification of lice infestations, non-compliance with treatment instructions and ineffective pediculicides, resistance against insecticides is a reason for increasing incidence of lice infestations (3). Furthermore, introducing a sense of shame among infested families is counterproductive for the identification of cases. Repellents like Ethyl butylacetylaminopropionate (IR3535®) can provide protection in a high risk environment for lice infestation and help to protect children against treatment with insecticides. Proper product ranges consisting of treatment, combs and a repellent can provide attractive support to families to counteract the lice infestation. Last but not least, excellent product information can help

to improve enlightenment and image. This article will provide background information about lice and lice infestations and is an experience report about required marketing information to support the development of head lice repellents especially for the use of Ethyl butylacetylaminopropionate as active substance.

DESCRIPTION OF THE MARKET AND TARGET GROUP

There is a global market potential for lice repellent products. The WHO report "Human lice, their prevalence and resistance to insecticides, a review, 1985-1997" showed, that there is worldwide no country without a noteworthy number of lice infestations. Head lice infestations are well known in developed and developing countries (4) and found in all level of society (2).

The main target group for head lice repellents is children between 3 and 13 years of age with a peak age between 6-8 years. Girls are more often infested than boys (2, 5).

SCIENTIFIC BACKGROUND INFORMATION FOR LICE PROTECTION PRODUCTS

Life cycle of a head louse

Pediculus humanus var. capitis, the head louse, is an insect of the order Anoplura and is an ectoparasite whose only host is humans. The louse feeds on blood several times daily, and resides close to the scalp to maintain its body temperature. The life cycle of the head louse has three stages: Eggs, nymph, and adult. 6-8 eggs are laid by adult female per day and are cemented at the base of the hair shaft near the scalp. The egg hatches to release a nymph after 5-10 days (Figure 1).

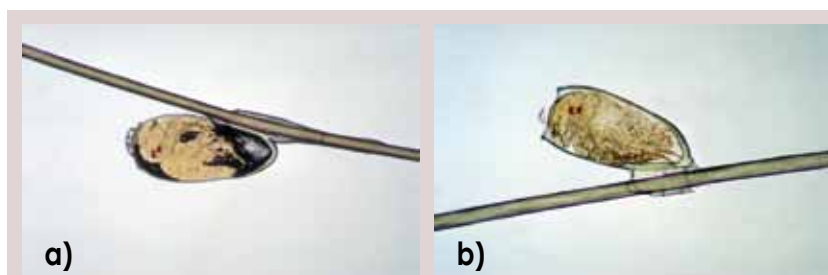


Figure 1. a) Unhatched nit of a head louse, *Pediculus humanus var capitis* parasite (source: CDC Public Health Image Library, ID# 378); b) after 5-10 days nymph of head louse emerge from egg (source: CDC Public Health Image Library, ID# 379).



Figure 2. This is an enlarged view of a female head louse, *Pediculus humanus var. capitis* (source: CDC Public Health Image Library, ID# 5269).

The nymphal stages is about 7-10 days. The nymph looks like an adult head louse, but is about size of a pinhead. The adult louse is about size of a sesame seed (3-4 mm) and has 3 pairs of legs, each with claws (Figure 2). The life time of a louse is about 2-4 weeks. Most individuals being infested have only 10-20 head lice, but under very severe infestations the hair may become matted with a mixture of eggs, nymphs, adults and pustules resulting from bites of the lice (6, 7). The complete life cycle of louse is shown in Figure 3.

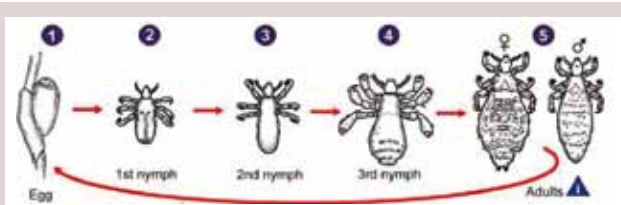


Figure 3. Illustration of the life cycle of *Pediculus humanus capitis*:

1. Egg is laid on hair shaft (day 0)
 2. Louse emerges after 6-7 days and first moult occurs about 2 days after hatching
 3. Second moult 5 days after hatching
 4. Third moult 10 days after hatching
 5. Emerging from their third moult as adult lice, the female and slightly smaller male begin to reproduce. The infective stage is reached (i).
- (Source: CDC Public Health Image Library, ID# 3401)

Lice transfer

Lice do not fly or jump. Mostly head lice are transmitted when an infested person comes into close contact with another. Such contact is common among children during play at school, home, sports or play activities. The transfer is optimal to hairs that are parallel and slow-moving relative to the infested hair. Adult lice are more often transferred than the other two development stages (8). Head lice are difficult to maintain in culture and have short lives after being removed from the host (9). Whether people can become infected by inanimate objects like coats, bedding, towels, and upholstered furniture is a topic of controversy (10). Dogs, cats, and other pets do not play a role in the transmission of human lice. Infestation is more common during warm month (11). Survival of head lice depends on temperature and humidity. The highest percentage of survival of head lice was recorded at 18°C and 97 percent RH under laboratory conditions (12).

IMPORTANT REQUIREMENTS FOR ACTIVES AND PRODUCTS

Control and treatment

To avoid lice infestations the attention of parents, school personnel, and health care professionals is needed during every season of the year. Early identification of lice infestation cases can prevent fast spread of lice infestations. If cases are detected at a pre-school or school, products with a repellent

active like Ethyl butylacetylaminopropionate can be used to protect children without infestations and children after anti-lice treatment against re-infestation. In addition, examination, anti-lice treatment and protection of sisters and brothers should be included in respective precautions. Repellent formulations should be applied on hair close to the scalp, behind ears, on the neck and on total hair. Only leave-on products are suitable. As described above, the main target group for lice repellent products is children between 3 and 13 years of age. The effective and safe use of the products by parents is essential. Therefore, comprehensive use instructions and labelling will help parents to understand and to adopt the product properly. If lice repellents are not part of a product kit with anti-lice treatment product and lice comb, there should be a clear advice like "treat infested children first with anti-lice product before you will continue with use of this lice repellent". Lice Repellent products are mainly launched in the beginning of a year, during spring or after summer holidays. An appropriate product presentation for children – light colour schemes, illustrations and pleasant pictures – will help parents and children to get a positive impression of situation and respective products.

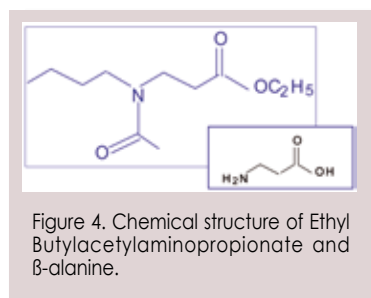
Efficacy and mode of action

To generate a protection time claim efficacy studies are necessary. Bio-Clinical studies with Ethyl butylacetylaminopropionate showed that protection is possible for at least two days, if the product is not rinsed with water in between. This is an excellent protection time period in comparison to some natural actives used as lice repellents. The efficacy of Ethyl butylacetylaminopropionate was investigated by *in-vitro* testing and *in-vivo* testing. The head louse is very sensitive to environmental conditions in laboratory testing (12). Therefore, the body louse was used for *in-vitro* testing instead of head louse. The distance from treated fabric travelled by lice compared with a distance from fabric without repellent as a function of time was the objective of observation. Ethyl butylacetylaminopropionate showed a strong repellent effect on body louse (13). Because of this positive *in-vitro* test result two *in-vivo* tests (Bio-Clinical studies) with head lice were performed. The ability of Ethyl butylacetylaminopropionate to prevent re-infestation was examined in both studies. A 20 percent solution in ethanol of the active substance was used for the first Bio-Clinical study. Two groups of 30 heavily infested volunteers (males and females aged between 4 and 30) were compared. The preventive treatment with Ethyl butylacetylaminopropionate was provided on study day 1 (after anti-lice treatment) and study day 4 in the treatment group. Volunteers of the control group received no preventive treatment after anti-lice treatment. After 8 days, only 3 adult lice were collected in the group protected by Ethyl butylacetylaminopropionate in comparison to 116 adult lice in the control group. In this study Ethyl butylacetylaminopropionate showed a strong protective effect against lice for 4 days (13). Recently a second Bio-Clinical study was performed for registration purposes in the EU which based on the protocol of the first Bio-Clinical study. Two groups of 40 heavily infested children aged between 6 and 12 years were enrolled into the study. One group received a 20 percent formulation with Ethyl butylacetylaminopropionate and the other group received a placebo after anti-lice treatment and then on every second day. A significant difference between the Ethyl butylacetylaminopropionate protected group and the placebo group was observed after 8 days. This study is currently not published. However, this study supports together with the first Bio-Clinical study the claim, that Ethyl butylacetylaminopropionate protects at least for two days without re-application against head lice.

Years of experience and several *in-vivo* and *in-vitro* efficacy tests performed with mosquitoes, flies, ticks, bees, wasps, ants

and cockroaches and Ethyl butylacetylaminopropionate showed that Ethyl butylacetylaminopropionate acts via the vapour phase and direct contact. The mode of action of Ethyl butylacetylaminopropionate is not a passive masking of an attracting odour of a victim, but an active repellent effect as insects avoid entering regions with Ethyl butylacetylaminopropionate vapours. The exact biochemical mode of action of insect repellents is not yet known. However, an olfactory-based repellent effect seems to be evident for some insect repellents. The mode of action of repellents like Ethyl butylacetylaminopropionate based on similar mechanism as the chemical communication of insects (airborne chemical signals). Chemical communication is used among insects like mosquitoes to find and determine the suitability of hosts for blood feeding or sites of oviposition (14). In comparison to mosquitoes, flies and ticks, lice are less flexible concerning the natural habitat. Therefore, lice will avoid entering regions with Ethyl butylacetylaminopropionate, but Ethyl butylacetylaminopropionate will not remove lice from already infested hair.

Safety



solubility profile, Ethyl butylacetylaminopropionate dissolves mainly in oils but also mixes well in aqueous phases in the presence of an alcoholic solvent. A 5 percent solution of Ethyl butylacetylaminopropionate in water shows a pH between 4.0 and 6.0. For optimal stability of final formulations the pH value should be adjusted between 6.0 – 7.5 in the end product. To obtain an adequate repellency, the concentration of Ethyl butylacetylaminopropionate should be between 10 and 20 percent in the lice repellent product. The previous mentioned efficacy tests were performed with formulations containing 20 percent Ethyl butylacetylaminopropionate. All these characteristics of Ethyl butylacetylaminopropionate allow the development of convenient, effective and safe products to protect children against head lice infestations.

Regulations

Repellent actives are currently under review in accordance to Biocidal Product Directive in Europe. There will be a harmonized approach for the market approval on repellent products in future. In USA and Australia for example, repellent actives are classified as pesticides. In each case, the classification of repellent product depending on the claim and an early contact with authorities during registration process may help to avoid uncertainties.

Besides adequate efficacy the active should be approved as safe for children use. WHO reviewed different repellents, as they are important for the protection against biting insects which can potentially transmit diseases. Ethyl butylacetylaminopropionate was reviewed by WHO and therefore a WHO-Specification is available for this active substance (15). In 1997, EPA-OPP's Biochemical Classification Committee classified Ethyl butylacetylaminopropionate as a biochemical, based on the fact that it is functionally identical to naturally occurring beta alanine. The basic molecular structure is identical (Figure 4). US-EPA states that the end groups are not likely to contribute to toxicity and Ethyl butylacetylaminopropionate acts to control the target pest via a non-toxic mode of action. Finally, US-EPA summarized that there are reliable data to support the conclusion that IR3535® is practically non-toxic to mammals, including infants and children (16). The excellent toxicological profile of Ethyl butylacetylaminopropionate led to worldwide preferred use in specific children products intended for protection against mosquitoes, flies and ticks.

Formulation development

Currently mainly pump sprays are marketed for head lice. Recently, a mousse formulation with Ethyl butylacetylaminopropionate was launched. Formulations like mousse and gel may simplify product application and may avoid getting solution into the child's eyes. Appropriate use instructions for pump sprays can have a similar preventive effect. Furthermore, a pleasant product flavour and a good hair feeling may improve product acceptance by children and parents. Ethyl butylacetylaminopropionate is a clear, colourless and practical odourless fluid. Due to its

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