Insect repellents – transmissive disease vectors prevention

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Introduction

In the course of evolution, a number of animal species has come into conflict with humans over food and habitat. This conflict is still ongoing, but not in its original form. Through evolution some species had to change their diet and habitat, leading to changes in the structure of the orifice and organs of movement. A number of arthropods got close to people and used all of their omissions for their own survival, without significant morphological and anatomical changes.

By conquering new areas, the man has, through his activities, eradicated a number of species, disturbing the ecological food chains of other species and diverting the flow circulation with infectious agents from the enzootic to the epizootic status leading to the appearance of numerous outbreaks. As a consequence, these shifts and changes lead to the appearance of new diseases in the form of pandemics. Faced with this problem, the man had to change his tactics and make use of all achievements in order to deal with harmful arthropods. However, the target species are becoming resistant, changing their behaviour, and occasionally migrating. In these situations, direct chemical treatments would not yield expected results. Thus, in the last decades there has been an emphasis on the development of various preventive measures, particularly emphasizing the individual protection of people by means of repellents.

The testing of substances’ repellent properties was initiated in the fifties of the twentieth century and is still ongoing. There were different approaches to defining repellents, but in our opinion the definition given by WHO (2006) is complete: repellents are products that are applied to the skin or clothing to prevent or deter arthropods from attacking humans and other animals. They are used in particular against outdoor biting insects and in situations where individual protection is a priority but treated mosquito nets, vaporizing mats and the chemical control methods are not appropriate. The property of repellents to, with their scent, discourage insects from plants, animals or humans was used in healthcare, veterinary and agriculture to protect humans, animals and plants from the attacks and bites of harmful species of arthropods, which, in the process of taking food, take over, maintain and transmit numerous pathogen transmissible infectious-diseases. Mosquitoes serve as vectors responsible for transmitting several forms of viral encephalitis, yellow fever, Dengue fever, Bancroftian filariasis and epidemic polyarthritis to humans; more than 700,000,000 people are infected yearly. Malaria, which is transmitted by the bite of a mosquito infected with the single-celled protozoa of the genus *Plasmodium*, is responsible for 3,000,000 deaths annually. In 1999, West Nile virus was detected for the first time in the Western hemisphere. Infected ticks can transmit Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, Q fever, babesiosis, tularemia, STARI (Southern tick-associated rash illness) and tick paralysis. Flies are the vectors responsible for transmitting African trypanosomiasis, leishmaniasis, onchocerciasis and loiasis to humans. Flea bites may transmit plague and, in South America, kissing bugs transmit Chagas disease.

In this region, apart from the Lyme disease, which was discovered in 1987 and transmitted primarily by ticks, we have seen recently the occurrence of tularemia and the increased number of patients with hemorrhagic fever, where ticks are also primary vectors, or one of the possible means of transmitting infectious agents.

The infectious potential of mosquitoes in our environment has not been sufficiently investigated. Although it is known that there are potential vectors for malaria pathogens in Serbia, so far there have been no conditions for the occurrence of indigenous cases. In our country there are also reg-
istered cases of patients with dirofilaria, which is caused by *Dirofilaria immitis* and *Dirofilaria repens*. Vectors of parasites (*D. repens* and *D. imitis*) are the types of mosquitoes that exist in our environment, belonging to the genera Anopheles, Aedes and Culex.

It is known from the literature that some species of mosquitoes in this region (*Aedes vexans*) carry Tahyna transmitted virus, while the two unknown etiological agents were isolated from anofelic mosquitoes. In recent years, there has been an increasing number of meningitis epidemics in our surroundings (Romania), and relevant vectors in our country, too.

These data indicate a need to combat harmful arthropods, to monitor them and research their infectious potential, habitat, abundance, movement and the diet-related behaviour.

Preventing people from being bitten by vectors and molesters, involves a series of activities that undermine conditions for their development and appearance of the habitat (draining fields, controlled reclamation, frequent changes of water in catchments), use of nets, impregnated clothing and use of repellents.

**Repellent properties and the mechanism of action**

Repellents are by their physical and chemical properties liquid substances, with a characteristic odour that evaporates at room temperature. The relation between chemical structure of substances and repellent efficacy is still unclear, because repellents belong to various groups of chemical compounds. Table 1 shows the structure of the most commonly represented repellents on the market.

It is believed that the demonstration of biological efficacy requires the presence of amides, imides, alcoholic or phenol groups in the molecule. Another important parameter for assessing the effectiveness of a repellent is the boiling point, on which evaporation and the effect substances have on insect olfactory cells (some substances acting mechanically, through contact or on insect’s sense of taste).

Volatile repellent molecules behave according to the Fick’s diffusion model and evaporate into the atmosphere and penetrate into the skin. Due to this process, there is a decline in its concentration, “sink conditions” on the skin surface and the weakening of the biological response.

Understanding the mechanism of repellent’s loss from the skin surface is important both from the entomological and the toxicological point of view. If a repellent evaporates faster from the application site than it is absorbed, it will be more effective, and the duration of its response depends on many external and internal factors. Absorbed through the skin, the repellent reaches the systemic circulation and further on all organs and tissues, which can lead to adverse effects to user’s body.

Studies on insects’ neurophysiology show different classes of chemoreceptors on their bodies, which are differently sensitive to certain chemical groups in molecules of repellent substances. According to their irritating effect, chemical dosage groups are classified in the following order: amides > imides > alcohols > phenols.

**Biological efficacy of repellents**

Two parameters are vital for assessing the biological efficacy of repellents in terms of a minimum effective dose and the time of protection. The minimum effective dose (MED) is the smallest amount of repellent that is sufficient to prevent insect bites. Its values are different for different repellents. Also, the same repellent can have different values depending on the type of insect. Maibach et al. define MED as the minimum effective dose of repellent that protects 99% of the body from the bites of hematofage arthropods for 30 min. It is expressed in mg/cm².

Figure 1 shows relationship of the time of protection and concentrations of repellents on the skin surface. Immediately after the application of a repellent at the initial time (t₀)

![Fig. 1 – The time of protection (t) is the change in concentration of repellent of the skin surface over time](image)

\[
(t) = \frac{C_{med} - C_0}{t_{med} - t_0}
\]

**t₀** – the initial time (immediately after the application of a repellent on the skin surface); **C₀** – the initial concentration of a repellent (immediately after the application on the skin surface); **t_{med}** – the time during which the concentration of repellent decreases to the minimum effective dose (MED).
its concentration \( (C_o) \) is highest. Over time, its concentration decreases reaching in time \( (t_{MED}) \) a concentration \( (Ct_{med}) \) equal to the minimum effective dose. The period in which the concentration of \( C_o \) is reduced to \( Ct_{med} \) is called the time of repellent’s protection \(^{37}\). In addition to determining the minimum effective dose and the time of protection afforded by concentrated substance when applied to the skin, it is more realistic to assess these parameters for the preparations of those substances, which, apart from the repellent substance, contain excipients that significantly influence the behaviour of agents in course of application.

To assess the biological efficacy of repellents, many factors should be taken into account: environmental factors (temperature, time of day, wind speed, light intensity, humidity); factors related to characteristics of the host (individual susceptibility, diet, movement, absorption through the skin, sweating); product characteristics (skin retention time, the ability to form coating, smell, the type of formulation, the concentration of repellent); factors related to the zones or areas for protection (skin characteristics: thickness, age, attrition, the degree of vascularization, injuries).

### Categories of insect repellents

Commercially available insect repellents can be divided into two categories: synthetic chemical repellents and plant-derived essential oils (Table 1).

#### Table 1

<table>
<thead>
<tr>
<th>Substances (INCI name)</th>
<th>Structural formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl toluamide (DEET)</td>
<td><img src="image1" alt="Structure of DEET" /></td>
</tr>
<tr>
<td>Dimethyl phtalate</td>
<td><img src="image2" alt="Structure of Dimethyl phtalate" /></td>
</tr>
<tr>
<td>Ethyl hexanediol</td>
<td><img src="image3" alt="Structure of Ethyl hexanediol" /></td>
</tr>
<tr>
<td>Ethyl butylacetylaminopropionate (IR 3535)</td>
<td><img src="image4" alt="Structure of Ethyl butylacetylaminopropionate" /></td>
</tr>
<tr>
<td>Permethrin</td>
<td><img src="image5" alt="Structure of Permethrin" /></td>
</tr>
<tr>
<td>Hydroxyethyl isobutyl piperidine carboxylate (Piperidin)</td>
<td><img src="image6" alt="Structure of Hydroxyethyl isobutyl piperidine carboxylate" /></td>
</tr>
</tbody>
</table>

**Diethyl toluamide**

DEET serves as an effective repellent against mosquitoes, ticks and other arthropods when used on the skin and clothing \(^{38}, \ 39\). DEET is available in repellent preparation concentrations ranging from 5% to 100% although most products contain less than 40%, as the concentration increases with a plateau at 50% \(^{40}, \ 41\) (Table 2). In most situations a concentration of 10% to 35% DEET will provide adequate protection. Higher concentrations may be indicated if a high-risk exposure is anticipated. DEET is safe for use on cotton, wool and nylon, although it has been found to damage spandex, rayon, acetate and pigmented leather. DEET may dissolve plastic and vinyl. With proper application the safety record of DEET remains excellent. There have been 43 case reports on DEET toxicity during the past 5 decades including 25 cases with central nervous system symptoms, one case with cardiovascular involvement, and 17 with cutaneous/allergic reactions \(^{42}\). Reported central nervous system symptoms include lethargy, confusion, acute manic psychosis, headaches, ataxia, disorientation, acute encephalopathy, convulsions, tremors and seizures \(^{43}, \ 44\). Cardiovascular symptoms include bradycardia and hypotension. Cutaneous and allergic symptoms include anaphylaxis, urticaria, hemorrhagic bullae and erosions \(^{45}\). The safety of DEET for children has often been questioned. Of 6 reported deaths involving DEET, 3 were caused by intentional ingestion of...
DEET, one involved a child with ornithine carbamoyltransferase deficiency, and 2 were in children who had central nervous system symptoms after overuse of DEET. Most reported cases of adverse or lethal events involve overuse or incorrect use of the product. Interestingly, increased systemic absorption of DEET has been described with a concurrent use of sunscreen of DEET-containing repellents. A mouse was reported at high dose and included neurotoxic effects such as tremors, loss of coordination, hyperactivity, paralysis, and an increase in body temperature. Other side effects included eye and skin irritation, reproductive effects, mutagenicity, and alterations in the immune system.

Permethrin

Permethrin is a synthetic pyrethroid, acts as a repellent and an insecticide that is highly effective against ticks, mosquitoes, and other arthropods. Permethrin's mechanism of action requires direct contact with the insect, making this compound poorly suited for skin application. Permethrin acts on the nervous system of insects. It interferes with sodium channels to disrupt the function on neurons, and causes muscles to spasm, culminating in paralysis and death. Permethrin has low mammalian toxicity, is poorly absorbed by the skin, and rapidly by skin and blood esterases. Permethrin may be used on clothing, shoes, bed nets, and camping gear and requires reapplication after every 5 washings. Permethrin insecticide increases the effect of DEET, and this combination is currently mostly used for impregnating clothing and other materials. The application of impregnated materials is common in malaria endemic areas and other areas, to protect military operational units.

Ethyl butyrateaminopropionate (IR3535)

IR3535 is a new alternative to DEET. It has been available in Europe for 20 years and has been sold in the United States since 1999. In our country IR3535 appeared in 2001 in Pest off (stick and spray) preparation at a concentration of 18%. IR 3535 is labelled for use against mosquitoes, ticks, and biting flies. IR 3535 fulfils all the following requirements for the outstanding properties of a repellent: effective protection of the skin from insects, long-lasting repellent action for several hours, also under difficult climatic conditions, maximum skin and mucous membrane tolerance without toxic allergic or sensitising properties, high chemical stability under use conditions, cosmetic properties, good formulability with common cosmetic and pharmaceutical basic formulations, acceptable costs per use/application of the

### Table 2

<table>
<thead>
<tr>
<th>Active ingredient concentration</th>
<th>Protection time (h)</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl toluamide (DEET) &lt; 10%</td>
<td>1–3</td>
<td>Pump spray, aerosol gel, lotion, stick</td>
</tr>
<tr>
<td>Diethyl toluamide (DEET) &lt; 10–33%</td>
<td>4–6</td>
<td>Pump spray, aerosol gel, lotion, stick, emulsion</td>
</tr>
<tr>
<td>Diethyl toluamide (DEET) 15%</td>
<td>6–7</td>
<td>Lotion, stick</td>
</tr>
<tr>
<td>Permethrin 0.2%</td>
<td>5-6</td>
<td>Pump spray, stick</td>
</tr>
<tr>
<td>Ethyl butyrateaminopropionate</td>
<td>3–4</td>
<td>Pump spray</td>
</tr>
<tr>
<td>(IR 3535) 18%</td>
<td>6–8</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Hydroxyethyl isobutyl piperidine carboxylate (Piperidin) 7%</td>
<td>20–30 min</td>
<td>Pump spray, lotion, oil, towelette</td>
</tr>
<tr>
<td>Hydroxyethyl isobutyl piperidine carboxylate (Piperidin) 15–20%</td>
<td>2–5</td>
<td>Lotion</td>
</tr>
<tr>
<td>Citronella oil 5–15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemon eucalyptus oil 10–30%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
final product. On the basis of toxicological studies the US Environmental Protection Agency (EPA) has concluded that the IR3535 is practically non-toxic to mammals, including infants and children.

**Plant-based repellents**

Thousands of plants have been tested as sources of insect repellents. Although none of the plant-derived chemicals tested to date demonstrates the broad effectiveness and duration of the protection of DEET, a few do show repellent activity. Plants whose essential oils reportedly have repellent activity include citronella, neem, tansy, cedar, verbena, pennyroyal, geranium, lavender, pine, cajuput, catnip, cinnamon, rosemary, basil, thyme, allspice, garlic and peppermint. Unlike synthetic insect repellents, plant-derived ones have been relatively poorly studied. When tested, most of the essential oils yielded short-lasting protection, lasting from a few minutes to as long as 2 hours.

**Relief from insect bites**

Cutaneous responses to arthropod bites are polymorphic and range from the common localized wheal-and-flare reactions (type I hypersensitivity) to the delayed bite lesions (type IV hypersensitivity). Rarely, systemic arthritic reactions and even anaphylaxis may occur.

Bite reactions are the result of sensitization to salivary antigens, which leads to the formation of both specific immunoglobulin E (IgE) and immunoglobulin G (IgG) antibodies. Immediate-type reactions are mediated by IgE, IgG and histamine, while cell-mediated immunity is responsible for the delayed reactions. Several modalities exist to alleviate the itch of insect bites.

Topical corticosteroids are useful to reduce the associated erythema, itching, and induration of insect bites. In cases of extensive and intensely itching bites, a short and rapidly tapered course of oral prednisone (or its equivalent) is effective in reducing the uncomfortable symptoms of extensive bite reactions. Application of diphenhydramine or benzoic acid (an ester-type topical anesthetic) should be avoided because of the risk of these compounds inducing allergic contact sensitivity. Pramoxine-containing lotions can also help reduce itching.

Oral antihistamines, such as cetirizine and levocetirizine, are effective in reducing itching and swelling associated with insect bites. In individuals who are highly sensitive, nonsedating antihistamines may be successfully taken prophylactically to reduce the subsequent cutaneous reactions to arthropod bites. After Bite (an over-the-counter solution containing ammonium) has been found to relieve the type I hypersensitivity symptoms associated with mosquito bites.

Recommendations for the use of insect repellent products are: the product should be applied in a thin layer on the skin; the product is applied only on the skin surface, clothing, or both; it should not be applied under clothing; for the use on face, the product should be first applied on the hand and then carefully spread on the face; contact with the eyes and mouth should be avoided; the person who is applying the product to a child, should carefully apply it on a child’s skin, except around the eyes and mouth; children younger than ten years, should not be allowed to independently apply a repellent product; insect repellents should be kept away from children; repellent preparations should not be used for children under two years; a mosquito net should be used for their protection; products that contain DEET in concentrations of less than 10% should be used for the protection of children; after applying repellent products, hands should be wiped (cleaned) to avoid contact with eyes and lips; repellent product should never be applied to cuts, wounds or irritated skin; manufacturer’s instructions should be read before the use of a repellent product.

**Conclusion**

Vector repellent is one element in the prevention of vector-borne diseases. Use of skin repellents can reduce the risk of insect bites and thus infection.

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**REFERENCES**


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