Insect Repellents

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Key Points

- Insect repellents are chemical substances that, when applied to the skin, are able to repel insects and block their attack on man.
- These compounds can block the insect's approach phase to the host by deviating the flight and hence taking the insect far from the target. Insect repellents exploit their action on many insects such as mosquitoes, flies, sandflies, horseflies, fleas, mites and ticks.
- There are three categories of insect repellents: physical repellents, synthetic repellents and natural-origin repellents.
- The insect repellents marketed in Europe possess a high level of safety due to especially low concentrations of the active ingredient. However, to increase the safety profile, dermatologists should suggest to their patients the following guidelines.
- The use of insect repellents is to be reserved to adults who, for professional or recreational activities, are at risk of contracting diseases transmitted by insect bites. Other forms of protection (e.g. the mosquito net) are recommended in common situations and for children.

General Principles and Classification

Insect repellents are chemical substances that, when applied on the skin, are able to repel insects and block their attack on man. These compounds can block the insect's approach phase to the host by deviating the flight and hence taking the insect far from the target. Insect repellents exploit their action on many insects such as mosquitoes, flies, sandflies, horseflies, fleas, mites and ticks. There are three categories of insect repellents:

- Physical repellents
- Synthetic repellents
- Natural-origin repellents

Physical repellents are instruments, usually employing ultrasound and claiming to modify insect flight and host identification. High-frequency sounds are used also in many smartphone applications. Their efficacy is questionable, so they will not be considered in this chapter.

Synthetic and natural repellents are particularly effective when directly applied onto the skin. Therefore there is an interaction between human skin and the repellent substance that may

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cause cutaneous and/or systemic toxicity by absorption. From the dermatotoxicological point of view, insect repellents have to be considered as 'leave on products', though they can be absorbed if applied frequently for a long period. These products, which are available over the counter, are indiscriminately used nowadays, so it is necessary to consider them with particular concern for the possible risks of their use, misuse or abuse.

The substance most used as an insect repellent since World War II is a synthetic molecule called N,N[1]-diethyl-m-toluamide (DEET), chemically belonging to the diethylamide family.

Natural-origin repellents are essential oils derived from different plants. These products, unlike the synthetic insect repellents, have been relatively poorly investigated.

In this chapter, insect repellent compounds and their mechanism of action and toxicity will be considered.

The Ideal Insect Repellent

The perfect topical repellent would repel multiple species of biting arthropods, remain effective for at least 8 h, cause no irritation to mucous membranes, possess no systemic toxicity, be resistant to washing off and be greaseless and odourless. No available insect repellent meets all of these criteria.

Mechanism of Action of Repellents

The relationship between chemical structure and repellent effectiveness has not been completely clarified, thus insect repellents cannot be classified on the basis of their mechanism of action. However, the most active repellents belong to the following chemical moieties: amides, imides, alcohols and phenols. There is also a kind of relationship between vapour-producing property and the level of repellency. The repellency activity is somehow related to the olfactory receptors of insects via:

- A block of neurons which sense attractive chemical stimuli
- Activation of receptors which promote inappropriate behaviour
- Activation of receptors for noxious odours
- Activation of too many receptors and loss of attractive messengers

Factors Affecting Effectiveness of Repellency

Multiple factors play a role in how effective a repellent is; these factors are product dependent, product independent and user dependent as listed in Table 144.1.

Repellents form a barrier between the skin and mosquito receptors, and this barrier extends to 4 cm from the skin when the repellent is freshly applied. Apart from some individual host characteristics, repellents are inactive due to excessive evaporation when the temperature exceeds 30 °C. In sweaty areas such as the forehead, the duration of protection is significantly decreased. Moreover, for unknown reasons some insect species are more sensitive to repellents than other related species, which remain unaffected. Among mosquito species, *Aedes taeniorhynchus* and *Culex pipiens* are more sensitive than *Aedes aegypti* and *Anopheles albimanus*.

Table 144.1 Factors affecting repellent effectiveness

Product-dependent factors	Product-independent factors	User-dependent factors
Evaporation rate from skin surface	Species of the biting insect	Activity level of the host
Absorption rate	Density of the biting insect	User attractiveness
Resistance to abrasion	Wind velocity	Frequency of application
Resistance to wash off	Air temperature	Uniformity of application
	Wet environment	Anatomical site

Factors Attracting Insects

Mosquitoes use visual, thermal and olfactory stimuli to locate a host. Visual stimuli are important for in-flight orientation, whereas olfactory stimuli are more important as a mosquito nears its host. Even host movement and wearing of dark-coloured clothing may promote orientation. Investigations about host-attracting factors have pointed out that some body odours may attract insects. These are eccrine sweat because of the presence of amino acids, urea and ammonia and apocrine sweat and sebum secretion due to the presence of cholesterol. Urine, carbon dioxide and sexual hormones are considered as attractants. In particular carbon dioxide is a long-range attractant, whereas at close range skin moisture and warmth are attractants. Body temperature is a discriminating factor: mosquitoes choose hosts with higher body temperatures. Body humidity is also a discriminating factor due to mosquitoes having hygrometric sensors (see Table 144.1).

Types of Insect Repellents

Synthetic Insect Repellents

Thousands of chemical compounds have been demonstrated to have repellence activity. However, only few of these are considered suitable for human use. These are:

- Dimethyl phthalate (DMP)
- Ethylhexanediol
- Diethyltoluamide (DEET)
- Ethyl butylacetylaminopropionate
- Picaridin

The discrepancy between the number of active substances and the registered ones is mainly due to skin absorption toxicity.

Dimethyl Phthalate (DMP)

This compound, registered in 1929, has been the reference repellent for many years. It is an oily, colourless, water-insoluble liquid with an aromatic odour. DMP has a mean protective duration of 80 min, and its effectiveness is variable among different insect species. It is used at 40 % preparation. The minimum amount of DMP necessary to inhibit mosquito biting has been determined to be 8–8.15 mg/square inch. The toxicological data available indicate that over a 40 % concentration, DMP exerts eye, mucous and skin irritation; by ingestion it is a central nervous system and respiratory depressant. Nowadays DMP is used exclusively in association with other repellents. Recently DMP was mentioned for its efficacy against ixodid ticks and advocated for the prevention of Lyme disease.

Ethylhexanediol

This compound was patented in 1935. It is an oily, colourless, water-insoluble, chemically stable liquid. It has a protective duration ranging from 1 to 8 h depending on the different insect species. Its repellency decreases as the temperature increases due to rapid evaporation. It is used from 30 to 50 % and at these concentrations is a mild skin irritant. The only data available on the toxicity of ethylhexanediol cites suspected teratogenicity via skin absorption.

Diethyltoluamide (DEET)

This compound was patented in 1943 and marketed since 1956. It is considered the reference repellent since it still remains the best one in thousands of comparative tests with other compounds. Today DEET is distributed worldwide, and it is estimated that 200 million people use DEET each year. The repellency of this compound covers a wide range of insect species: mosquitoes, biting fleas, gnats, chiggers, ticks and others. It is oily, colourless, odourless, water and glycerin insoluble, and soluble in alcohol, ether and polyethylene glycols. It has a protective duration of about 4 h. The protectiveness

decreases to 24 min at 40 °C. Of the marketed products, DEET concentration has a wide range (from 7 to 100 %). As opposed to the previously cited repellents, a great bulk of literature on DEET toxicology is available. DEET toxicology may be subdivided into: general, systemic and skin toxicology.

Pharmacology

Human studies show variable penetration of DEET ranging from 9 to 56 % of topically applied dose. Absorbed DEET is metabolized completely within 12 h with 99 % urinary elimination. Hepatic microsomal cytochrome P450 enzymes are involved in DEET metabolism. There is no evidence of stratum corneum or systemic accumulation.

General Toxicology

DEET applied to skin is absorbed in about 20 min. The systemic LD_{50} is 2 mL/kg in rats and 10 mT Ikg in rabbits. The poisoned animals manifested laboured respiration, ataxia and convulsions.

Human Systemic Toxicity

Some cases of encephalopathy in children after the application of DEET were reported in 1961. After this, several reports on systemic toxicity after DEET application were published. Among these, the most frequently described symptoms were encephalopathy ataxia, seizures, bradycardia and hypotension. Severe toxic reactions and death after the ingestion of repellents containing DEET were also reported. In 1988, an editorial in the *Lancet* suggested that products containing less than 50 % DEET were safe; however, in children even preparations containing 20 % DEET, applied to large areas repeatedly, caused slurred speech, agitations, tremors and convulsions.

A comprehensive review of side effects due to DEET was published in 1994 (Veltri et al. 1994).

Skin Toxicology

There are several reports on specific skin sensitivity to DEET, while some reports refer to skin irritation, contact urticaria, generalized urticaria and vesiculobullous reactions (Amichai et al. 1994; Von Mayenburg and Rakoski 1994; Wantke et al. 1996).

No photosensitivity has been reported. DEET is considered a substance with a high profile of safety.

Ethyl Butylacetylaminopropionate

Ethyl butylacetylaminopropionate was synthesized by Merck and was registered as IR3535 compound.

The structure of ethyl butylacetylaminopropionate is based on alanine and beta-alanine, and the *Environmental Protection Agency* (EPA) has classified it as a biochemical substance based on the fact that it is 'functionally identical' to beta-alanine: both repel insects and the end groups are not likely to contribute to toxicity.

Picaridin (1-Piperidinecarboxylic Acid 2-(2-Hydroxyethyl)-1-methylpropyl Ester)

Picaridin, synthesized by Bayer, is an insect and acarid repellent in the piperidine chemical family. The chemical name is 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropyl ester.

Mode of Action

Picaridin both repels and deters insects, so that insects move away from the chemical and do not feed if they encounter skin or clothing that has been treated. Insects appear to detect the chemical through olfactory sensing.

Toxicity

Picaridin is not considered a skin irritant and is not a sensitizer, but it can cause slight to moderate eye irritation and is considered to be slightly toxic for acute dermal and ocular exposure.

Insect Repellents of Natural Origin

All substances with repellent activity not produced by chemical synthesis are considered natural-origin insect repellents. Among these, some are of historical value such as smoke, plant

derivates, tars and animal urine. Plants whose essential oils have been identified as having repellent activity include cedar, citronella, clove, coconut, eucalyptus, geranium, lavender, menthe, onion, rosemary and thyme. Plant-derived insect repellents have been poorly studied, and when tested most of these tend to give short-lasting protection.

Oil of Citronella

Oil of citronella is the most studied and utilized essential oil as a repellent. Oil of citronella is extracted from *Cymbopogon nardus*, a Gramineae native to tropical Asia (Sri Lanka and Java). The active component is the aldehyde citronellal, present in the plant from 20 to 60 %, which gives the characteristic scent. The protective duration is variable from 40 to 90 min. Citronella at 10 % has been proved to repel flies but not mosquitoes.

Skin Toxicity

There are no scientifically trusted data on systemic toxicity due to absorption of essential oils. Citronella as with other essential oils is a mild irritant or rubefacient over 20 % concentration. Some reports indicate that essential oils are sensitizers and photosensitizers. Contact urticaria has also been reported.

Pyrethrum

Pyrethrum is derived from *Chrysanthemum cinerariaefolium* and the terms pyrethrum powder and extract are used to describe the crude products obtained from the crushed dried flowers. The pyrethrins are the active components. These substances are valid insecticides but weak insect repellents and thus no longer used in commercial repellents.

Permethrin

Permethrin, a pyrethroid synthesized in 1973, is mainly an insecticide four times as effective as natural pyrethrins. It also possesses some repellent activity, and for this reason it is included in many textbooks among insect repellents. Permethrin is considered a valid tick repellent. Systemic and skin toxicity of this compound is minimal. Permethrin should be applied directly to clothing or to tent and mosquito net fabrics. Permethrin is nonstaining, odourless and resistant to degradation by heat or sun and maintains its potency for at least 2 weeks.

The best barrier against biting insects is considered the combination of permethrin-treated clothing and skin application of DEET.

Indications for Safe Use of Insect Repellents

The insect repellents marketed in Europe possess a high level of safety due to especially low concentrations of the active ingredient. However, to increase the safety profile, dermatologists should suggest to their patients the following guidelines:

- Verify that the product has been registered.
- Read the label information.
- Use the repellent only as suggested by the manufacturer.
- Use the repellent only for the insects it claims to be effective against.
- Keep repellents out of the reach of children.
- Apply repellents only to body parts suggested by the manufacturer.
- Avoid use of repellents on or near wounds or on inflamed skin.
- Avoid use around the eyes and mouth.
- Wash repellent off skin with soapy water when protection is no longer needed.
- Contact the local poison control centre if repellent-induced toxicity is suspected.

Insect repellents are useful compounds to avoid the annoyance of many insects or to prevent the transmission of some infectious diseases. In Table 144.2 insect repellent sensitivity and infectious diseases transmitted by principal arthropods are summarized. However, the insect repellents are far from being the ideal product from a pharmacological point of view. The correct use of these products is fundamental to their safety (see Table 144.2).

Table 144.2 Insect repellent sensitivity and infectious diseases of principal arthropods

Class	Common names	Species	Blood sucking	Repellent sensitivity	Vectors for
Acars	Ticks	*Ixodes*	+	+	Borrelia, rickettsiae, arbovirus
	Trombidium larvae	*Trombidium*	+	+	Rickettsiae
Insects	Lice	*Pediculus*	+	+	Rickettsiae, borrelia
	Human fleas	*Pulex*	+	+	Yersinia, rickettsiae
	Bedbugs	*Cimex*	+	–	Nothing
	Deerflies	*Chrysops*	+	+	Filaria
	Tsetse flies	*Gliossina*	+	+	*Trypanosoma*
	Houseflies	*Musca*	–	+	
	Black or buffalo flies	*Simulium*	+	+	*Onchocerca*
	Biting midges or sandflies	*Phlebotomus*	+	+	Leishmania
	Mosquitoes	*Anopheles*	+	+	*Plasmodia*
		Aedes	+	+	Arbovirus, yellow fever virus
		Culex	+	+	Arbovirus
		Mansonia	+	+	Filaria
	Ants	*Formica*	–	+	Nothing
	Bees	*Apis*	–	–	Nothing
	Wasps and hornets	*Vespula*	–	–	Nothing
		Vespa	–	–	Nothing

Relief from Arthropod Bites

Skin responses to arthropod bites range from wheal-and-flare reactions to delayed papules to rare systemic Arthus reactions and anaphylaxis. Several strategies may be considered for the relief of the itch of insect bites. Topical corticosteroids may reduce erythema, induration and itching, but the time of effectiveness after skin application is considered too long (about 20 min) for relief of wheal-and-flare reaction that usually lasts 20 min.

Diphenhydramine and benzocaine should be avoided due to allergic contact sensitivity. Oral antihistamines are effective in reducing the symptoms of insect bites, but they are poorly employed due to the delay in reducing symptoms.

Ammonium solution 3.6 % is used after bite treatment to relieve symptoms, but caution should be adopted due to causticity of the product.

Aluminium chloride hexahydrate hydroalcoholic gel 5 % (see Chap. 152) is effective in suppressing itching and burning and possesses a good safety profile.

Aluminium chloride 5 % gel is at the same time astringent and antiseptic.

Controversies in Insect Repellents

Risk Assessment

One of the main problems in the use of insect repellent is the risk of toxicity via transcutaneous absorption. Regarding this topic, toxicological studies have been performed only for the DEET molecule, while for the other insect repellents, present studies about absorption must be considered insufficient. For this reason we can say prudentially that insect repellents are not suitable for their use in children, although they are the main victims of insect bites.

Application on Clothes

Efficacy studies of insect repellents are performed on forearm bare skin placed in cages containing insects; on the other hand there are no conclusive studies on the application of the same insect repellent on clothes in the same conditions and the relationship between application on clothes and its effectiveness.

Long-Lasting Protection

Some studies have related the long-lasting protection with the repellent concentration as Fradin and Mittal. This relationship, however, is not supported by conclusive studies. Moreover no studies can confirm a night-lasting protection.

For the above considerations, we believe that the use of insect repellents is to be reserved to adults who, for professional or recreational activities, are at risk of contracting diseases transmitted by insect bites. Other forms of protection (e.g. the mosquito net) are recommended in common situations and for children.

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