REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 4, 625-630
www.aaem.pl

Repellents and acaricides as personal protection measures in the prevention of tick-borne diseases

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Cisak E, Wójcik-Fatla A, Zając V, Dutkiewicz J. Repellents and acaricides as personal protection measures in the prevention of tick-borne diseases. Ann Agric Environ Med. 2012; 19(4): 625-630.

Abstract

A number of preventive measures for the protection of humans against tick-borne diseases were evaluated. Measures involving the avoidance of tick bites with the use of protective clothing and insect repellents are the simplest and most effective. Repellents are applied directly to the skin or clothing and other fabrics, such as bednets, tents and anti-mosquito screens. Currently, DEET (N,N-diethyl-m-toluamide) is considered the most efficient arthropod repellent reference substance. The registered and recommended active repellent ingredients for skin and/or cloths application, among others, are: DEET, 1-methyl-propyl-2- (hydroxyethyl)-1-piperidinecarboxylate (picaridin), p-menthane-3,8-diol (PMD), ethyl butylactyloaminopropionate (IR3535), 1S,2S-2-methylpiperidinyl-3-cyclohexene-1-carboxamide (SS220), racemic 2-methylpiperidinyl-3-cyclohexene-1-carboxamide (AI3-37220) and synthethic pyrethroid – 3-phenoxybenzyl-cis-trans-3(2,2 dichlorovinyl)-2,2-dimethylcyclopropancarboxylate (permethrin) – an acaricide with repellent properties. To achieve the protection from tick bites by avoiding attachment and/or engorgement by the arthropod, acaricides with repellent properties, such as synthetic pyrethroid-permethrin are used. This pyrethroid is an acaricide of choice used for clothing impregnation, which is effective for personal protection against all three parasitic stages of western black-legged ticks. Products based on natural compounds, e.g. eugenol from *Ocimum basilicum,* 2-undecanone originally derived from wild tomato, geraniol – a natural product extracted from plants, and many others, represent an interesting alternative to common synthetic repellents and/or acaricides.

Key words

Tick transmitted diseases, personal protection measures, repellents, acaricides, occupational population

INTRODUCTION

Among the zoonotic agents causing occupational diseases those transmitted by ticks are very important, in particular the spirochete *Borrelia burgdorferi* and tick-borne encephalitis virus which are the common cause of occupational Lyme borreliosis and tick-borne encephalitis in forestry and agricultural workers [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13].

Lyme disease is the most common tick-borne zoonotic disease, caused by the bacteria *Borrelia burgdorferi*, which is transmitted to humans by infected ticks. The transmission of this pathogen depends on several factors, especially on the duration of the attachment of the tick to the host body [1, 5, 11, 12, 13, 14, 15, 16]. The lack of an effective vaccine implies that at present the best method of personal prevention are: avoiding areas with a high density of ticks, wearing protective clothes, application of tick repellents, checking the body and proper removal of ticks and in the case of tick bite, and regular examination of the bite site during following weeks in order to initiate an early curative treatment if erythema migrans is diagnosed [6, 17, 18, 19, 20, 21, 22].

Tick bites are best prevented by avoiding exposure to the vector, which is imperative, especially when vaccine and prophylactic treatments are not available. Personal protection measures (PPM) are essential and often the only means available when dealing with blood-sucking disease-transmitting arthropods. PPM include preventive personal behaviour, suitable clothing, application of insect repellents to the skin, the use of space repellents, impregnation of clothing, camping gear and bed nets with acaricide and, when necessary, ground spraying of insecticides/acaricides [17, 18, 19, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36].

Repellents. Repellents are an effective measure for reducing the risk of tick bites and can therefore minimize the transmission of tick-borne diseases. Bhate and Schwartz evaluated a number of preventive measures and concluded that those involving the avoidance of tick bites with the use of protective clothing and insect repellents are the simplest and most effective [17]. Similar conclusion was drawn by Vazquez et al., who stated that the use of protective clothing and tick repellents (on skin or clothing) are effective in preventing Lyme disease and that the strategies to prevent Lyme disease should be focused on personal protective measures [18].

According to a generally recognised definition, repellents are substances which induce a movement of the arthropod away from the host, this means that they jam an arthropod's sensors and confuse the arthropod (tick, mosquito). This prevents the anthropod from successfully biting the host successfully it approaches close to a host, attracted by skin odours and carbon dioxide from the breath of the host [27, 28].

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Received: 20 August 2012; accepted: 5 November 2012

Repellents are used primarily on the skin, but also on materials. At present, repellents are applied directly to the skin or to clothing and other fabrics, such as like bednets, tents and anti-mosquito screens [24, 26, 29, 30, 31, 32, 33].

The duration of protection by a repellent applied to the skin depends on its concentration and may range from 15 minutes to 10-12 hours [29, 30]. The effectiveness and duration of protection depend on the type of repellent (active substance and formula), the way of application, local environmental conditions (temperature, humidity) and tick species [29, 30, 37, 38, 39, 40].

The first components used for this purpose were of plant origin and some of them are still in use [29, 35, 41, 42, 43, 44, 45, 46, 47, 48]. For the production of synthetic repellents with improved properties (which began in the 1930s) over 7,000 compounds were tested. The most effective compound resulting from these efforts proved to be DEET (N,N-diethyl-m-toluamide) [29, 37, 38, 49, 50, 51, 52].

Currently, DEET is considered as the most efficient arthropod repellent, which has been widely used for the last 60 years decades as a repellent reference substance. Insect/acarid repellents containing DEET have been used by millions of people worldwide to repel mosquitoes, ticks, fleas, biting flies and chiggers. These products are available in many forms, including lotions, creams, gels, aerosols, pump sprays, and towelettes. Insect/acarid repellents can considerably reduce the risk of mosquito and tick bites [19, 23, 29, 31, 32, 38, 49, 48, 51].

The registered and recommended active repellent ingredients for application to the skin and/or clothes are: DEET, 1-methyl-propyl-2-(hydroxyethyl)-1-piperidinecarboxylate (picaridin), p-menthane-3,8-diol (PMD), ethyl butylactyloaminopropionate (IR3535), 1S,2S-2-methylpiperidinyl-3-cyclohexene-1-carboxamide (SS220), racemic 2-methylpiperidinyl-3-cyclohexene-1-carboxamide (AI3-37220) and synthethic pyrethroid – 3-phenoxybenzyl-cis-trans-3(2,2 dichlorovinyl)-2,2-dimethylcyclopropancarboxylate (permethrin) – an acaricide with repellent properties [24, 29, 31, 32, 33, 34, 37, 38], among others.

The effective properties of the above-mentioned repellents have been indicated by many authors in the last 10 years [17, 37, 38, 40].

In the 2008 report by Carroll [39], the first findings were shown of the consistently high, long-duration efficacy of the IR3535 formula in the United States. Complete protection times of this repellent ranged from 9.1-12.2 hours for black-legged ticks.

Further investigation by Carroll et al., conducted in 2010 [31], indicated that the formulation of DEET, picaridin and IR3535, containing over 20% of active ingredient, when applied to skin were highly effective for nymphal *Amblyoma americanum* during 12 hours, compared to those containing less than 10% of active substance, and that at least 40% of ticks exposed to any formula for any challenge fell or crawled off the volunteers.

It was found by Semmler et al. [37] that high concentrations of DEET were needed to repel the ticks *Ixodes ricinus* and *Dermacentor reticulatus*, while essential oils are mostly inefficient. On the other hand, saltidin=picaridin, p-menthan-diol and IR 3535 showed long-lasting effects, which in the case of combinations of saltidin and Vitex extracts were even increased.

A long-lasting repellent-treated net (LLRTN) has been designed by Faulde et al. [32] by binding the skin repellents N,N-diethyl-m-toluamide (DEET), or IR3535, onto the fibres of bed net fabric using a new polymer-coating technique. The repellent toxicological effectiveness and residual activity of a factory-based repellent-impregnated fabric has been evaluated by laboratory testing against nymphal *Ixodes ricinus* ticks. Both DEET- and IR3535-impregnated fabrics revealed a dose-dependent insecticidal as well as acaricidal activity. The extent to which DEET skin absorption can be reduced and evaporation sustained through encapsulation was investigated by Karr et al., [52] who found that two microcapsule DEET formulations exhibited 36-40% higher cumulative evaporation from the skin than a non-encapsulated DEET ethanol standard solution [52].

Bissinger et al. [53] described the BioUD (containing 7.75% 2-undecanone) which is an arthropod repellent containing the active ingredient 2-undecanone, originally derived from wild tomato plants. Repellency of BioUD was compared with 5 commercially available arthropod repellents against the ticks *Amblyomma americanum* and *Dermacentor variabilis*. BioUD provided significantly greater overall mean percentage repellency than IR3535 for *A. americanum* and *D. variabilis*. BioUD was significantly more repellent than oil of lemon eucalyptus for *A. americanum*, but did not differ significantly in repellency against *Dermacentor variabilis*. No statistically significant difference in overall mean percentage repellency was found between BioUD and DEET for *A. americanum* or *D. variabilis*.

The repellent properties of 2-tridecanone, another compound found naturally in the trichomes of wild tomato plants, were indicated by Kimps et al., [54], but according to these authors the effectiveness of 2-tridecanone as a tick repellent against *Amblyomma americanum* and *Dermacentor variabilis* is uncertain.

Schwantes et al. [10] developed and tested 7 different dodecanoic acid (DDA)-formulae by laboratory screening for their efficacy in repelling host-seeking nymphs of *Ixodes ricinus*. Repellency investigations in humans showed that the most effective 10% DDA-based formula applied to the skin (~1.67 mg/cm^2) strongly prevented the attachment of *I. ricinus* nymphs and adults for at least 6 hours. The test repellent always provided protection (63-83%) against *I. ricinus* nymphs equivalent to the natural coconut oil based reference product, and a better protection (75-88%) against adult ticks than the synthetic Icaridin-containing reference repellent.

According to Katz et al. [50], newer agents, like picaridin and natural products such as oil of lemon eucalyptus are becoming increasingly popular tick repellents because of their low toxicity, comparable efficacy, and customer approval. The registered by the Environmental Protection Agency in Texas (USA) insect repellents ingredients approved for application to the skin include DEET, picaridin, N-octylbicycloheptene dicarboximide (MGK-326), MGK-264, IR3535, oil of citronella, and oil of lemon eucalyptus [50].

Tick repellents of plant origin such as methyl jasmonate (MJ) can be used as alternatives to commercial arthropod repellents. Garboui et al. [47] showed that the numbers of *Ixodes ricinus* nymphs on clothes treated with methyl jasmonate were significantly lower than those on the untreated clothes. Thus, MJ – at the concentrations tested – has significant repellent activity against *I. ricinus* nymphs.

Products based on natural compounds represent an interesting alternative to common synthetic repellents. In the study of Del Fabbro and Nazzi [44], the repellency of sweet basil (*Ocimum basilicum*) was tested against the tick *Ixodes ricinus*, by using a laboratory bioassay. According to this study, eugenol from *Ocimum basilicum* appeared to be as repellent as DEET at 2 tested doses. Jaenson et al. [45] reported the repellent features of a commercially available product containing oils of lemon, eucalyptus, geranium, and lavender, which exhibited 100% repellency against host-seeking nymphs of *Ixodes ricinus* from central Sweden.

Chemical analyses of the oils obtained from *Tanacetum vulgare* carried out by Pålsson et al. [48] showed that the population of *Tanacetum vulgare* from Uppsala and Stockholm may represent different chemotypes, but exhibited similar tick repellency against host-seeking nymphs of *I. ricinus*.

Another 14 natural products isolated from essential oil components extracted from the heartwood of Alaska yellow cedar, *Chamaecyparis nootkatensis*, were evaluated by Dietrich et al. [46] against nymphal *Ixodes scapularis*, and compared with technical grade N,N-diethyl-3-methylbenzamide. Although they were not significantly more active than DEET, the ability of these natural products to repel ticks at relatively low concentrations may represent a potential alternative to synthetic commercial repellents.

According to recent studies in 2012 conducted by Oh et al. [55] in the USA, repellents are critical means of personal protection against biting arthropods and disease transmission.The cited authors also stated that the essential oil obtained from *Lindera melissifolia* showed a significant dose-dependent repellency for ticks, and a moderate mosquito repellent effect.

The major problem associated with arthropod repellents are: lack of effectiveness against certain species or strains, potential toxicity and irritancy due to repeated skin application, short duration of action, plasticizing effects, disagreeable cosmetic effects and odours, undesirable wash-off and rub-off characteristics, and necessity for covering all available exposed areas due to weak effectiveness.

The most important requirements of a tick repellent are: effective protection of the skin from tick bite, long-lasting repellent action, maximum skin tolerance without toxic and allergic properties, no skin penetration, high chemical stability under conditions of use, good aesthetic reactions, and acceptable cost per use of the final product [29, 36].

A chance to improve the repellents'properties (decrease in skin absorption, longer duration efficacy) is the development of new formulae [23, 52]. In 2003, Netwig [23] stated that applications other than dermal are the use of repellents with slow release formulae to achieve a long range effect, and the development of systemic compounds which could be taken orally.

Acaricides. Currently, prevention of arthropod bites is mainly achieved by prevention of attachment and engorgement. To achieve this, acaricides with repellent properties, such as synthetic pyrethroid-permethrin, are used [56]. Permethrin, a compound with neurotoxic action, is an ideal compound to reach this goal [54]. It was synthetized for wide use. Permethrin (3-phenoxybenzyl-cis-trans-3-(2,2dichlorovinyl)2-2-dimethylcyclopropanecarboxylate) occurs as a natural ingredient in chrysanthemum plants. It is photostable, with a low mammalian toxicity (LD_{50} above 3,000 mg/kg). Permethrin is a repellent of choice used for clothing impregnation [24, 26, 34, 57, 58, 59, 60].

The effective prevention of arthropods bites by application of a syntethic pyrethroid – permethrin has been indicated in many scientific institutions. Permethrin, when applied to clothing with a pressurized spray (application rate (4 $\mu g/cm^2$), was first reported by Lane [26] in 1989. This acaricide was 100% effective for personal protection against all 3 parasitic stages of the western black-legged ticks.

Roma et al. [59] confirmed that currently the most effective and widely-used tick control is still achieved by the treatment clothing with acaricides, especially permethrin.

The effectiveness and residual activities of permethrin-impregnated military battle dress uniforms were evaluated by Faulde et al. [57] who compared a new company-manufactured ready-to-use polymer-coating method with 2 'dipping methods' used to treat uniforms in Germany, indicated that the polymer-coating method is more effective and efficient , compared with the dipping methods. After 100 launderings, a 100% knockdown of *Ixodes ricinus* nymphs was reached at 15.2 ± 1.04 min. using the polymer-coating method.

Based on the results reported by Appel et al. [24], it can be assumed that the normal use of permethrin-treated soldiers uniforms by the Federal German Armed Forces (1.25 $\mu g/cm^2$) does not affect human health to a clinically relevant extent. The cited authors recommend that the release rate of permethrin from the textile material should be strictly monitored by means of a quality assurance method.

The studies by Vaughn and Meshnick [60] determined the effectiveness of the permethrin-based Insect Shield-treated clothing for the prevention of tick bites among 16 outdoor workers from the North Carolina Division of Water Quality under actual field conditions. These indicated that subjects wearing Insect Shield-treated clothing had a 93% reduction ($p<0.0001$) in the total incidence of tick bites, compared to subjects using standard tick bite prevention measures. This study provided preliminary evidence that long-lasting use of permethrin-impregnated clothing may be highly effective against tick bites.

Millner et al. [34] demonstrated that permethrin-treated summer clothing significantly reduced tick bites and tick-borne pathogens, and concluded that subjects wearing permethrin-treated sneakers and socks were 73.6 times less likely to have a tick bite than subjects wearing untreated footware. Subjects wearing permethrin-treated shorts and T-shirts were 4.74 and 2.17 times, respectively, less likely to receive a tick bite in areas related to those specific garments than subjects wearing untreated shorts and T-shirts.

The effect of permethrin, a sodium channel blocker, was tested by McMahon et al. [61] in a deterrent assay measuring the arrestment of *Ixodes ricinus* adults on its own faeces and faecal constituents. Permethrin deterred arrestment at doses of 670 fg/cm^2 – 67 ng/cm^2, i.e. at levels 5 times lower than the dose of chemostimuli present in the arrestment stimulus. This sensitivity to permethrin suggests that it acts via the contact chemoreception channel.

In 2004, Foil et al. [62] reported that farmers from Queensland, Australia, for the protection of cattle continued to use amitraz (*N,N'*-[(methylimino) dimethylidyne] di-2,4-xylidine) as the major acaricide for tick control, even after the diagnosis of its resistance.

In the same year, Li et al. [63] also indicated a resistance to amitraz in cattle tick *Boophilus microplus.*

Pohl et al. [64] documented in 2012 the presence of a *Rhipicephalus microplus* tick population resistant to 4 acaricide classes: organophosphates, synthetic pyrethroids, amitraz and macrocyclic lactones, and suggested that ABC transporter proteins can protect the cattle ticks against a wide range of acaricides, and have an important implication in drug resistance development as a multidrug detoxification mechanism based on the ABC transport protein.

According to Kiss et al. [65], chemical acaricides represent the main line of anti-tick defence in both humans and domestic animals, but increasing concerns regarding development of acaricide resistance, especially in the cattle tick *Rhipicephalus microplus*, and environmental safety issues, indicate the need for other, less aggressive but equally efficient methods.

The results obtained by Cetin et al. [66] showed that an insecticide spinosad, based on a compound found in a recently-discovered bacterial species *Saccharopolyspora spinosa,* would be a useful addition in a tick control programme as an alternative for pyrethroids and organic phosphorus acaricides against *Rhipicephalus turanicus* and *Argas persicus* ticks.

Khallaayoune et al. [43] clearly revealed that 1% geraniol has a preventive effect against *Hyalomma* ticks and the data provides evidence that geraniol, a natural product extracted from plants, could be an alternative to limit the use of chemical acaricides, the efficacy of which is compromised by resistance development.

Because arthropod-borne diseases continue to pose a significant threat for United States military forces, Kitchen et al.[49] reported that these forces played a vital role in vector identification tools and the development and testing of many of the most effective PPM and vector control products available today, including the topical repellent DEET and the repellent/acaricide permethrin, which is applied to clothing and bed nets.

Use of repellents by endangered occupational population. Current own studies conducted among forestry workers in the Lublin region of eastern Poland, indicate that the majority (51.8%) of 110 intervieved forestry used repellents when working in the forest, but a large proportion of them (41.8%) did so only sporadically. Also, workers of the lowest group of employment (physical workers) used repellents statistically more frequently than the other workers. This study also showed that the use of repellents by the forestry workers was positively related to finding ticks on the body ($p<0.001$), checking the body after returning from the forest ($p<0.01$), frequent removal of the ticks from body ($p<0.01$), self-reporting of great exposure to ticks ($p<0.05$), reporting of a large number of ticks on the body ($p<0.05$), and knowledge of the pathogens transmitted by ticks ($p<0.05$).

A negative correlation was found between the use of repellents and job duration ($p<0.05$) [12]. Earlier own studies from 2011 showed that among 157 forest exploitation workers from eastern Poland, 118 (76%) applied repellents to the skin at work. Considering own or employer's initiative, or both, for use of repellents, the percentage of positive answers were similar: 36%, 33% and 31%. A considerably smaller number of examined forestry workers (59%) applied repellents on clothes [11].

The research of Bartosik et al. [67] on the prevention of tick bites and protection of tick-borne diseases, which covered 300 inhabitants of south-eastern Poland, indicated that according to the questionnaire survey the most frequently applied method of prevention was the application of a repellent (38% of respondents).

In 2007, Patey [16] reported that in France, the most effective prophylactic methods protecting against infection with *Borrelia burgdorferi* were as follows: protective clothes, application of repellents, checking body surface and removal of ticks after return from endemic areas and, if tick bites had occurred, observation of the site of the bite for the next few weeks in order to begin therapy in the case of occurrence of erythema migrans.

The study conducted by Gould et al. [25] showed that 99% of respondents – residents of 3 Connecticut health districts in the USA – used personal protective behaviours to prevent Lyme disease, and that the percentage of respondents using repellents increased by 5% in 2004 when compared to 2002.

According to Philips et al.[68], 86% of the residents of Nantucket Island in Massachusetts, USA, practiced at least one behaviour to prevent Lyme disease. The most frequently reported preventive behaviour was checking oneself for ticks (80%), followed by wearing protective clothing (53%), avoiding tick areas (34%), and using tick repellent (11%).

Vazguez et al. [18], on the basis of an interview study on participants from the State of Connecticut State in the USA, showed that use of protective clothing was in 40% effective in preventing Lyme disease, with routine use of tick repellents on skin or clothing effective in 20%, but checking one's body for ticks and spraying property with acaricides were not effective.

SUMMARY

The best approach for those who may be exposed to infected ticks is to apply a repellent to the skin and an acaricide or a repellent on clothing. The currently most efficient arthropod repellent which repels mosquitoes, ticks, fleas, biting flies and chiggers is DEET (N,N-diethyl-m-toluamide). Products containing DEET are available in many formulations, including lotions, creams, gels, aerosols, pump sprays, and towelettes.

To achieve protection from tick bites by avoidance of attachment and/or engorgement by an arthropod, acaricides with repellent properties, such as synthetic pyrethroid-permethrin, are used. This pyrethroid is an acaricide of choice, used for the impregnation of clothing, which is effective for personal protection against all 3 parasitic stages of the western black-legged ticks.

Products based on natural compounds, e.g. eugenol from *Ocimum basilicum,* 2-undecanone originally derived from wild tomato, geraniol – a natural product extracted from plants, and many others, represent interesting alternatives to common synthetic repellents and/or acaricides.

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