

Insect repellents: Historical perspectives and new developments

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Arthropod bites remain a major cause of patient morbidity. These bites can cause local or systemic effects that may be infectious or inflammatory in nature. Arthropods, notably insects and arachnids, are vectors of potentially serious ailments including malaria, West Nile virus, dengue, and Lyme disease. Measures to curtail the impact of insect bites are important in the worldwide public health effort to safely protect patients and prevent the spread of disease. The history of insect repellent (IR) lends insight into some of the current scientific strategies behind newer products. Active ingredients of currently available IRs include N,N-diethyl-3-methylbenzamide (DEET), botanicals, citronella, and, the newest agent, picaridin. Currently, the Environmental Protection Agency's registered IR ingredients approved for application to the skin include DEET, picaridin, MGK-326, MGK-264, IR3535, oil of citronella, and oil of lemon eucalyptus. DEET has reigned as the most efficacious and broadly used IR for the last 6 decades, with a strong safety record and excellent protection against ticks, mosquitoes, and other arthropods. Newer agents, like picaridin and natural products such as oil of lemon eucalyptus are becoming increasingly popular because of their low toxicity, comparable efficacy, and customer approval. Various characteristics and individual product advantages may lead physicians to recommend one agent over another. (J Am Acad Dermatol 2008;58:865-71.)

Arthropods are the vector for infection with multiple organisms, including those that may cause West Nile virus, malaria, or dengue. Skin-based insect repellent (IR), along with protective clothing and limiting time outdoors, continues to be the mainstay in the prevention of bites. IRs intended for human skin and clothing are targeted to prevent the bites of mosquitoes, black flies, and ticks. When these insects bite or defecate on human beings, they produce local or systemic effects and may potentially transmit insect-borne diseases. In all areas of the world, but especially those where vector-borne diseases are endemic, the use of prophylactic IRs may not only prevent disease, but may also mitigate the severity of allergic reactions to many bites.^{1,2}

There are many formulations of IRs available today, including aerosols, pump sprays, lotions, creams, suntan oils, powders, grease sticks, and cloth-impregnating laundry emulsions.² Several

Abbreviations used:

CDC: Centers for Disease Control and Prevention
DEET: N,N-diethyl-3-methylbenzamide
EPA: Environmental Protection Agency
IR: insect repellent
OBP: olfactory binding protein

vehicle and formulation characteristics may contribute to an ideal IR (Table D).

To maximize the prevention of arthropod bites, the Canada Communicable Disease Report suggests using an integrated approach.³ In addition to the use of IRs, it is suggested that human beings avoid arthropods by staying indoors during the time of day the arthropods are more likely to bite (dawn and dusk). The Canada Communicable Disease Report also suggests the use of physical barriers such as clothing and bed nets. Buzz Off Insect Shield (Buzz Off Insect Shield, LLC, Greensboro, NC), which uses permethrin as its active ingredient, is the first and only IR apparel registered by the US Environmental Protection Agency (EPA). This line of apparel has shown to be effective for up to 25 washings, but loses its efficacy with dry cleaning, which removes the active ingredient.

Recent studies have focused on new ways to approach prevention of arthropod bites. Picaridin has been introduced into the US market as an IR, and the Centers for Disease Control and Prevention (CDC) has recommended it as an alternative to N,N-diethyl-3-methylbenzamide (DEET), the most

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Table I. Ideal insect repellent goals^{2,66-68}

1.	Prolonged efficacy against a wide variety of arthropods
2.	Nonirritating to the skin on application
3.	Odorless or has a pleasant odor
4.	No effect on clothing after application (ie, staining, bleaching, or weakening of fibers)
5.	Leaves no oily residue on the skin and resists removal by wiping, washing, or sweating
6.	Inert to commonly used plastics
7.	Chemically stable
8.	Economically viable for broad use
9.	Nontoxic
10.	Sufficient duration of effect

efficacious IR in the United States before the availability of picaridin.⁴ Of note is that the mosquito *Anopheles albimanus*, the chief malaria carrier in the United States, is becoming resistant to DEET.⁵ Other studies have confirmed the efficacy of 3 plant extracts with broad-spectrum repellent properties and the use of garlic as a mosquito repellent.^{6,7} Olfactory binding protein (OBP) has become a focus of IR research, and is now broadly viewed as a target for the next generation of IRs. Future repellents may actually be sprayed into the air, not on the body, potentially reducing toxicity.⁴

HISTORY

IRs date back to ancient times, with the use of tars, smokes, plant oils, and other modalities.⁸ In 1946 the US Department of Agriculture developed DEET for use by the military. Since its marketing began in 1956, DEET has remained the most widely used and, to many, the most efficacious IR. Before the introduction of DEET the 4 main IRs included oil of citronella, Dialkyl Phthalates, indalone, and Rutgers 612.²

Citronella oil, discovered in 1901, was the most widely used repellent before the 1940s, and is still used today in many formulations despite inferior efficacy to that of newer products.² At one point it was used as a hair dressing for control of fleas and lice.⁸ Natrapel (Tender Corporation, Littleton, NH), Herbal Armor (All Terrain, Sunapee, NH), and Green Ban (Green Home, San Francisco, Calif) are 3 products available today that contain citronella, however, these products only last up to 20 to 30 minutes.

COMPOUNDS

DEET (N, N-diethyl-3-methylbenzamide; previously N, N-diethyl-m-toluamide)

DEET has been considered the most broad-spectrum, efficacious IR since the 1950s, and is currently

used by approximately 30% of the US population. DEET serves as an effective repellent of mosquitoes, ticks, and other arthropods when used on the skin or clothing.¹ DEET is available in the United States in concentrations ranging from 5% to 100%, although most products contain less than 40%; as the concentration increases, the duration of activity increases, with a plateau at 50% (Table II).^{1,3,9} 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.¹⁰ Of note is that 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 (ie, eyeglass frames) and vinyl (ie, certain car seats).²

The mechanism of action of DEET, along with certain other IRs, is to provide a vapor barrier that deters the insect from coming into contact with the skin. This vapor presents the insect with an offensive odor and a bad taste.² The vapor's efficacy to repel is related to the boiling point of the chemical. Compounds with low boiling points may vaporize too rapidly, leading to rapid degradation of the product. On the contrary, those with high boiling points do not vaporize sufficiently to create the desired repellent environment. A boiling point between 230°F and 260°F is the most desirable range for an effective repellent.²

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. Reported central nervous system symptoms include lethargy, confusion, acute manic psychosis, headaches, ataxia, disorientation, acute encephalopathy, convulsions, tremors, and seizures.¹¹⁻²⁸ Cardiovascular symptoms described include bradycardia and hypotension.^{29,30} Cutaneous and allergic symptoms reported include anaphylaxis, urticaria, hemorrhagic bullae, and erosions.³¹⁻³⁸ Of 6 reported deaths involving DEET, 3 were caused by intentional ingestion of DEET, one involved a child with ornithine carbamoyl transferase deficiency, and two were in children who had central nervous system symptoms after overuse of DEET.^{13,14,16,17,27,28,39} Most reported cases of adverse or lethal events involved overuse or incorrect use of the product.¹⁰

Of interest, increased systemic absorption of DEET has been described with concurrent use of sunscreen and DEET-containing repellents. A mouse model has demonstrated transdermal penetration of DEET detectable 6 times faster when combined with topical sunscreen compared with DEET alone,

Table II. Insect repellents and length of duration^{1,3}

Main ingredient	Brand name*	Duration	Formulation
DEET < 10%	Cutter, Skedaddle, Skintastic (Off)	1-3 h	Pump spray, aerosol, gel, lotion
DEET 10%-30%	Cutter, Cutter Backwoods, Cutter Backyard, Deep Woods Off!, Muskol, Off!, Outdoorsman	4-6 h	Pump spray, aerosol, lotion, stick
DEET 20%-33%, extended duration	Sawyer, Ultrathon	6-12 h	Lotion, aerosol
Citronella oil 5%-15%	Buzz Away, ⁵ Green Ban, Herbal Armor, Natrapel,	20-30 min	Pump spray, lotion, oil, towelette
Lemon eucalyptus oil 10%-30% [†]	Repel, Off Skintastic	2-5 h	Lotion
Picaridin 7%	Cutter Advanced	3-4 h	Pump spray
Picaridin 15%	Cutter Advanced Sport	6-8 h	Aerosol
Permethrin 0.5% [‡]	Duranon Tick Repellent Repel Permanone, Cutter Outdoorsmen Gear Guard, Sawyer Clothing Tick Repellent, 3M Clothing and Gear Insect Repellent, No Stinkin' Ticks	Several washings	Aerosol, pump spray

DEET, N,N-diethyl-3-methylbenzamide.

*Brand name formulations are subject to change; labels should always be read to ensure exact ingredients.

[†]Not proven to be effective against ticks.

[‡]Permethrin is not formulated for direct application to the skin.

⁵Manufactured by Dirt Works, New Haven, Vt.

adding concern for potential toxicity with this common combination.³⁹ In addition, one study found a decrease in sun-protection factor with concurrent use of an IR, intimating that DEET may have a deleterious effect on the overall efficacy of certain sunscreen products.⁴⁰ Certain topical retinoid products, including topical bexarotene and alitretinoin, have also been reported to increase potential DEET toxicity, requiring caution with combined application.¹⁰

DEET is currently available in commercial products such as Off (SC Johnson, Racine, Wis), Cutter (Spectrum Brands, Atlanta, Ga), Outdoorsman (Spectrum Brands), Skedaddle (Minnetonka Brand Inc, Chaska, Minn), Sawyer (Sawyer Products, Safety Harbor, Fla), and Ultrathon (3M, St. Paul, Minn). A long-acting formula has been developed for the armed forces with either 23.75% (aerosol) or 31.5% (lotion) DEET that is available commercially as Ultrathon (3M). Extended-release products, based on a microencapsulated sustained-release formulation, include Ultrathon (3M) and Sawyer's Controlled Release, which is available as a 20% lotion. Although DEET has been the

primary IR for the last 60 years, it is possible that newer ingredients with more ideal characteristics, including improved odor and residue, may overtake the popularity of this agent.

Permethrin

First marketed in 1973, permethrin, 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. Strong excitation of the insect's nervous system and blockade of sodium movement into nerve cells via inhibition of adenosine triphosphatase, acetylcholinesterase, and the γ -aminobutyric acid_A receptor, leads to paralysis.^{41,42} Permethrin has been used in agriculture, home pest control, forestry, and public health programs, including head lice control.⁴³ Permethrin may be used on clothing, shoes, bed nets, and camping gear, and requires reapplication after every 5 washings.¹ Toxicities have been

reported at high doses and include neurotoxic effects such as tremors, loss of coordination, hyperactivity, paralysis, and an increase in body temperature. Other side effects include eye and skin irritation, reproductive effects, mutagenicity, and alterations in the immune system.⁴³ Permethrin-treated mosquito nets offer affordable protection and have been widely tested in the control of malaria. These nets have shown a benefit in decreasing morbidity and mortality associated with malaria.^{44,45} Permethrin is very effective against ticks, and has been found to be more so than DEET.^{46,47} Brands of permethrin 0.5% products include Duranon Tick Repellent Repel (Sawyer Products) Permanone (Bayer, Pittsburgh, Pa), Cutter Outdoorsmen Gear Guard (Spectrum Brands), Sawyer Clothing Tick Repellent (Sawyer Products), 3M Clothing and Gear IR (3M), and No Stinkin' Ticks (Robinson Outdoors, Cannon Falls, Minn).

Picaridin (KBR 3023)

Picaridin [2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester], a recently approved IR in the United States, contains one of the most commonly used active ingredients in European and Australian products. Picaridin has been used as an IR in Australian products since 1998. Picaridin has many characteristics of the ideal IR as it is odorless, does not feel sticky or greasy on application, is less likely to irritate the skin, and will not damage plastics or fabrics. In Europe, solutions with concentrations up to 20% have been demonstrated as protective for up to 8 to 10 hours. No serious adverse events have been reported in European or Australian trials.

Like DEET, picaridin's mechanism of action is unknown, but is thought to provide a vapor barrier that works to deter the insect from biting. Picaridin is effective against mosquitoes, biting flies, and ticks.

Picaridin, marketed under the name Cutter Advanced, is now available in the United States as a 7% solution pump spray bottle. Cutter Advanced Sport, available since 2006 as an aerosol spray, has a picaridin concentration of 15% and lasts twice as long. The manufacturers do not recommend the use of these products in children younger than 2 years of age.⁴⁸ Picaridin appears to have similar efficacy to DEET, but there is little comparative data available.⁵ In 2000, the World Health Organization proclaimed that, because of its safety, effectiveness, and cosmetic properties, picaridin was the recommended product for repelling the mosquitoes that carry malaria noting that, under some circumstances, it was more effective than DEET.⁴⁹ In addition, the EPA states that no toxicologically significant effects have been demonstrated in animal studies.

Botanicals

Botanicals contain one of several essential plant oils including oil of lemon eucalyptus (p-menthane 3,8-diol), soybean oil, or geraniol as the sole active ingredient.⁵⁰ Natural products may be safer for human use and may offer an ecologic advantage when compared with synthetic, nonbiodegradable compounds such as DEET.^{7,51,52} Three different plant essential oils have been studied as a mosquito repellent including *Zanthoxylum limonella* (fruits), *Citrus aurantifolia* (leaf), and petroleum ether extract of *Z limonella* (fruits), in both a mustard and coconut oil base. The extracts were reported to possess effective repellent properties against mosquitoes with superior protection in the mustard oil rather than the coconut oil base. Maximum protection (294-304 minutes) was noted with a 30% concentration in mustard oil whereas the extract of *Z limonella* showed the greatest protection time against mosquito bites at any concentration in either base.⁷

According to one study, benzene and methanol extracts of *Artemisia vulgaris* have repellent activity against the *Aedes aegypti* mosquito.⁵³ Other botanicals used for mosquito protection include *Lantana camara* flowers, quelling derived from extract of lemon grass and eucalyptus plants, and *Vitex negundo*.^{54,55}

Oil of lemon eucalyptus is the active ingredient available under the Repel brand (Spectrum Brands), available in a 40% pump, and has been found to be equally efficacious as lower concentrations of DEET (7%-15%).⁵⁶ *Consumer Reports* tested Repel lemon eucalyptus spray against a 10% DEET repellent. Repel was shown to prevent bites for 4 to 7 hours after application for aggressive species of mosquito and for greater than 12 hours for less aggressive mosquitoes, a period of prevention greater than both the studied DEET repellent or picaridin.⁴⁸ Repel is registered with the EPA, who warn that this product is effective only for mosquitoes, biting flies, and gnats. This product has not been demonstrated as efficacious against ticks. The EPA also states that this product should not be used in children younger than 3 years of age.⁴⁸

Garlic

A systemic agent with the ideal characteristics of low toxicity and minimal environmental hazard would present a breakthrough in repellent technology. Prompted by the lay community's conviction of the effectiveness of garlic to repel insects, research has been conducted to confirm this possibility. A randomized, double-blinded, placebo-controlled study examining the effect of garlic ingestion as an IR was designed to evaluate such an agent. Participants initially consumed either garlic or placebo the

evening before their first visit with subsequent exposure to laboratory reared *Aedes aegypti*. At a second visit 28 days later, in crossover fashion participants received the alternative treatment. Data analysis investigated the number of mosquitoes that did not feed on the participants, the number of mosquito bites, the weights of the mosquitoes after feeding, and the amounts of blood ingested.⁶ Data from this limited study failed to provide evidence of significant systemic mosquito repellence. Future studies may further investigate whether timing and length of garlic exposure may be altered to allow systemic protection.

A second investigation of garlic involving the Swedish Army found a significant reduction in tick bites by groups consuming garlic compared with placebo; however, this study's methods have been criticized.⁶ Further studies may elucidate the role this product may play in systemic arthropod bite prevention.

Olfactory binding proteins

A new concept under investigation by scientists with the International *Anopheles* Genome Project, who have uncovered the genome of Africa's chief malaria vector *Anopheles gambiae*, focuses on the olfactory biology of the insect. Female mosquitoes rely on smell to find food, including blood. Human skin, along with commensurate bacteria, release a molecular cloud of human-specific odorants that are detected by the OBPs of mosquitoes.⁴ Once these molecules bind to the OBPs, they are transported to the mosquito's olfactory neurons, which alert the mosquito to the presence of a potential meal. Preliminary theories suppose that destruction of the olfactory binding receptors may interfere with the olfactory pathway of the insect, effectively decreasing bites.

Jones et al have identified the protein GPRor7 as a potential target for IRs. Knockout of this protein, which facilitates the binding of the OBP-odorant complex to the receptor, may result in eliminating the insect's sense of smell.^{4,57} Hallem has focused on human-specific odorants including the protein Or1, an olfactory receptor in *Anopheles gambiae*, which binds the 4-methylphenol found in human sweat.^{4,58}

Benefits of targeting OBPs include potential repellents that may be released directly into the air, eliminating the need to apply the IR directly to the skin. This formulation may also be used to more easily protect a larger geographic region.

PEDIATRICS

Of constant concern in the wake of West Nile virus and other arthropod-borne diseases is the safety of

IRs among the pediatric population, as children are generally at increased risk of toxic effects. Several case reports have associated DEET with seizures in children, and parents often express fear of DEET toxicity because of adverse media reports.^{14,19-24,56} Understanding the true risks of DEET use is necessary to properly educate parents and to help influence good clinical practice, as an estimated 23% to 30% of US children are exposed to DEET at some point.²⁶

The safety of DEET for children has often been questioned. One review looked at two large case series and concluded that the risk of DEET toxicity is low, with toxicities reported in 0.05% to 0.1% of users.⁵⁹ Reported reactions include hypotension, seizures, respiratory distress, hypotonic reaction, syncope, and death, one of which was suicide caused by ingestion. Conclusions show low overall risk of toxicity and a lack of a dose-dependent relationship between exposure and the severity of neurologic manifestations.⁶⁰ Although extremely rare, most serious outcomes occurred in adults. A recent narrative review found that DEET posed essentially no risk to the pediatric population whereas a second review, sponsored by SC Johnson and Company, also attests to the safety of DEET in children.^{26,61} Other case reports describing children with seizures from DEET suggest a lack of causality, failing to rule out other causes of the seizures, a publication oversight also highlighted by the CDC.⁶¹

One cross-sectional survey evaluating parental use of IRs indicated that an educational outreach to improve parents' use of IRs may prove beneficial. The authors found that education plays a key role, as parents often do not read labels and many left repellents on their children's skin overnight, theoretically increasing potential chemical exposure.⁶² In addition, some parents treated the child's face directly, a method discouraged in this population because of warnings from poison control centers that eye contact may be associated with a high rate of adverse symptoms.

Effects of DEET on pregnant and lactating women have also been examined.⁶¹ In a study investigating effects of DEET on fetuses of pregnant women, no adverse effects on survival of growth and development at birth and at 1 year of age were detected after maternal exposure during the second or third trimester.^{61,63} In lactating women, no evidence exists that using DEET while breast-feeding causes toxicity to infants.^{61,64}

The American Academy of Pediatrics Committee on Environmental Health recommends that only children older than 2 months be exposed to DEET products. The recommended concentration ranges

are between 10% and 30%.⁶⁵ Using DEET and sunscreen products at the same time is an acceptable practice. However, the use of combination products is not recommended because the sunscreen needs to be reapplied after swimming, whereas the mosquito repellent generally does not need to be reapplied.⁶⁵ Also, as previously discussed, questions regarding cutaneous DEET penetration and sunscreen efficacy remain when considering combined products.

Conclusion

Currently, the EPA's registered IR ingredients approved for application to the skin include DEET, picaridin, MGK-326, MGK-264, IR3535, oil of citronella, and oil of lemon eucalyptus.¹ DEET has reigned as the most efficacious and broadly used IR for the last 6 decades, offering excellent protection against ticks, mosquitoes, and other arthropods with an excellent record of safety. Newer agents such as picaridin are becoming increasingly popular because of their low toxicity and comparable or greater efficacy, and customer appeal. Many advances have been made in existing IRs on the market with several new concepts focusing on OBPs. IRs are safe, when correctly applied, for use in both the pediatric and adult population. Parents need to be educated to read the labels on products before use and use only as directed by the manufacturer. Because of the industry's changing of brand names and formulations, it should not be assumed that the ingredients of a particular brand name are stable, indicating further need for close evaluation of labels and ingredients of IRs.

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