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Insect Repellents: An Updated Review for the Clinician

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CAPSULE SUMMARY

- The use of insect repellents to prevent systemic diseases constitutes a fundamental public health effort.
- This review summarizes currently available EPA-registered insect repellents: the origins, mechanisms of action, side effect profiles, and available formulations will be discussed.

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2

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4

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33

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35

36 **ABSTRACT**

37

38 Malaria, Zika virus, West Nile virus, Dengue fever, and Lyme disease are common causes of
39 morbidity and mortality around the world. While arthropod bites may cause local inflammation
40 and discomfort, a greater concern is the potential to develop deadly systemic infection. The use
41 of insect repellents (IR) to prevent systemic infections constitutes a fundamental public health
42 effort. Cost-effectiveness, availability, and high-efficacy against arthropod vectors are key
43 characteristics of an ideal IR. Currently, numerous IRs are available on the market, with DEET
44 (N,N-diethyl-3-methylbenzamide) being the most widely used. DEET has an excellent safety
45 profile and remarkable protection against mosquitoes and various other arthropods. Other EPA-
46 registered IR ingredients (permethrin, picaridin, IR3535, oil of lemon eucalyptus, oil of citronella,
47 catnip oil, and 2-undecanone) are alternative IRs of great interest due to some having efficacies
48 comparable to that of DEET. These alternative IRs possess low toxicity and favorable customer
49 experiences in utilization (e.g., cosmetically pleasant, naturally occurring). This review
50 summarizes currently available EPA-registered IRs: the origins, mechanisms of action, side
51 effect profiles, and available formulations will be discussed. This review will enable the clinician
52 to select the best IR option to meet patients' needs and provide the greatest protection from
53 arthropod bites and sequelae.

54 INTRODUCTION

55
56 In 2016, the World Health Organization reported nearly half the world's population being at risk
57 for malaria. Within this population, 216 million cases of malaria were reported in 91 countries.¹
58 Arthropods are the vector for infection of many diseases, including malaria, West Nile Virus, and
59 Zika Virus. Prophylactic use of insect repellents (IRs) are of great importance in areas where
60 arthropod-borne diseases occur, as these agents help prevent these disease and local
61 inflammation.^{2,3}

62
63 In order to optimize arthropod bite prevention, both physical and chemical vector control are
64 recommended. Examples of physical vector control include wearing long-sleeve, light-colored,
65 pyrethroid-sprayed clothing, removing large areas of debris that could be inhabited by
66 arthropods (tires, yard vegetation), utilizing nets, and staying indoors.⁴ Chemical vector control
67 includes widespread insecticide spray and applying topical IRs while outdoors. Biological
68 prophylaxis may also be utilized, such as supplying water reserves with fish species (*Gambusia*
69 *affinis*) and nonpathogenic bacteria (*Bacillus thuringiensis*) that consume mosquito larvae.⁵
70 Finally, genetic vector control methods may be used, such as genetically engineering male
71 mosquitoes to pass on fatal genes to their offsprings, or transferring a infertility-inducing
72 bacterium (*Wolbachia* species) to their female counterpart.^{6,7}

73
74 Many IR formulations are commercially available today, including cloth-impregnating laundry
75 emulsions, aerosols, lotions, creams, pump sprays, suntan oils, grease sticks, and powders.
76 This review summarizes currently available EPA-registered IRs: the origins, mechanisms of
77 action (MOA), side effect profiles, and available formulations will be discussed. This review will
78 enable the clinician to select the best IR option to meet patients' needs and provide the greatest
79 protection from arthropod bites and sequelae.

81 SYNTHETIC COMPOUNDS

83 DEET (N,N-diethyl-3-methylbenzamide)

84 DEET has been considered the most broad-spectrum, efficacious IR since the 1950s, and is
85 currently used by 50-100 million individuals in the U.S., annually. Originally created by the U.S.
86 Army, DEET was made commercially available in 1956. Currently, there are over 200 DEET
87 products available on the market, ranging from concentrations of 5-100%.⁸ In the majority of
88 circumstances, concentrations of 10-35% will enable adequate protection, with efficacy and
89 duration increasing with concentration and a plateau at 50%.^{2,9-11} At concentrations of 50-75%,
90 patients have been reported to rarely develop vesiculobullous skin necrosis, residual scarring,
91 and erythema.¹²

92
93 CDC recommends DEET to be used to prevent West Nile virus and Lyme disease, as this agent
94 also repels ticks safely, even in pregnant women.^{13,14} One case study reports DEET boasting
95 the longest protection against mosquito bites, outperforming other IRs.¹⁵ DEET at 23.8%
96 concentration was reported with a mean complete-protection time of 301.5 minutes.¹⁵ In the
97 Zika virus guidelines, DEET was named the repellent of choice.¹⁶

98

99 Though still ultimately unknown, a proposed MOA is disturbing mosquito antenna receptors,
100 impairing the mosquitoes' ability to locate humans.¹⁷ Other proposed mechanisms include
101 masking the host's smell by impairing arthropod olfactory receptors and serving as a vapor
102 barrier, possessing poor taste and noxious odor, that averts arthropods from the host's skin.
103 DEET does not kill the arthropod.³

104

105 DEET's safety and toxicity was reviewed by the EPA in 1998, and reaffirmed in 2014. With
106 proper application, DEET's safety record remains excellent with little adverse effects, such as
107 rare local skin reactions. In between 1956 to 2008, 43 case reports on DEET toxicity have been
108 reported.¹⁸⁻³¹ Twenty-five cases presented with neurologic symptoms (lethargy, confusion,
109 acute encephalopathy, seizures),^{18-20,22-32} 17 with allergic and/or cutaneous reactions
110 (anaphylaxis, urticaria, hemorrhagic bullae, and erosions),^{12,33-39} and 1 with cardiovascular
111 involvement (hypotension, bradycardia).^{40,41} Of 6 reported deaths involving DEET, 3 were
112 caused by intentional DEET ingestion, 1 involved a child with ornithine carbamoyl transferase
113 deficiency, and 2 in children after significant overuse of DEET.^{20,22,23,42-45} A significant portion of
114 lethal reported events are associated with incorrect, or overuse of the product.⁴⁶

115

116 The EPA has concluded, based on comprehensive available data, that DEET is safe for
117 pregnancy, and should not cause birth defects as the small number of reports are insufficient to
118 generate a significant correlation between DEET and teratogenicity.⁴⁷⁻⁴⁹ DEET is deemed safe
119 for use in pregnant women in the second and third trimester by the FDA.⁵¹ Few safety studies
120 have been performed for DEET use in the first trimester. Although placental transfer of DEET
121 occurs,⁵⁰ all children exhibited normal neurologic and physical examinations at birth and through
122 one year of age.⁵¹

123

124 According to the American Academy of Pediatrics, all children over the age of 2 years should
125 use a maximum DEET concentration of 33%.⁵² The FDA recommends children under 2 years of
126 age to not utilize DEET at all.

127

128 DEET is metabolized by the kidney, and undergoes rapid excretion within 24 hours.⁸ Acute
129 toxicity is rare, even with accidental ingestion by contaminated hands, or unintended inhalation
130 with aerosols. Higher concentrations may be indicated if a high-risk exposure is anticipated.¹⁵
131 DEET may degrade vinyl, such as certain car seats, and plastics, such as eyeglass frames, and
132 are found to additionally damage acetate, rayon, pigmented leather, and spandex. However,
133 DEET is deemed safe to use on fabrics.³

134

135 Increased systemic absorption was discovered when DEET was applied underneath sunscreen
136 on a mouse model.⁴⁵ DEET's transdermal penetration was 6 times faster when paired with
137 topical sunscreen compared to DEET alone. The results from this study poses several concerns
138 for possible toxicity, as IRs are commonly paired with sunscreen during outdoor activities.⁴⁵
139 Additionally, one study demonstrated that DEET may reduce the efficacy of certain sunscreen
140 products' sun-protection factor.⁵³ When paired with certain topical retinoids, DEET increases the
141 retinoids' potency. Caution is advised when combining DEET with additional topicals.¹⁵

142

143 Picaridin

144 Picaridin, a recently approved IR in the U.S., is one of the most commonly used active
145 ingredients in European and Australian IR products. The popularity of picaridin stems from the
146 IR being more cosmetically pleasant to use. Picaridin does not feel sticky or greasy on
147 application, is less likely to irritate the skin, and will not damage plastics or fabrics. Furthermore,
148 picaridin is odorless. Picaridin formulations are most commonly found in concentrations of less
149 than 30%. In Europe, solutions with concentrations up to 20% have been demonstrated to last
150 up to 8-10 hours of protection.⁵⁴ No serious adverse events have been reported in European
151 trials.⁵⁴

152

153 Picaridin is most effective against Culicine (arbovirus) mosquitoes, flies, and biting midges. This
154 IR is also effective against Anophele (malaria) mosquitoes and ticks.⁶¹ The EPA states that
155 picaridin exhibits no toxicologically significant effects in animal studies. In animal experiments,
156 no picaridin toxicity is found in fetuses.⁵⁸ Side effects include potential skin irritation, and no
157 harm to clothing or plastics.

158

159 Like DEET, picaridin's MOA is largely unknown, but the mechanism is thought to provide a
160 vapor barrier deterring insect bites or affect insect olfactory sensory neurons.⁶⁰ The efficacy of
161 picaridin is similar to DEET, although little comparative data is available.⁶² Picaridin has been
162 shown to be superior when DEET concentrations are less than 30%.^{55,56} Picaridin has odorless
163 properties and has not been documented to demonstrate any severe neurological adverse
164 effects as found in DEET, which increases user compliance.^{57,58} Hallucinations that may occur
165 with picaridin toxicity is rare and easily reversible with supportive treatment.⁵⁶ In a comparative
166 study, participants reported feeling more comfortable utilizing picaridin over DEET due to
167 picaridin's lack of odor.⁵⁹ If higher concentrations (greater than 50%) are needed, then DEET
168 should be used, as picaridin concentrations are not available in that concentration.⁵⁵
169 Formulations include aerosols with concentrations of 7-15% and wipes with concentrations of 7-
170 20%.

171

172 IR3535

173 IR3535 is a synthetic compound based on the amino acid alanine that was FDA-approved in
174 1999. IR3535 was introduced to the market in the U.S. as a skin emollient and moisturizer with
175 improved repellent effects against biting midges compared to that of DEET. This repellent was
176 designed to target mosquitoes, deer ticks, body lice, and biting flies.⁶³ The MOA of IR3535
177 remains poorly understood, but has been proposed to be involve odorant-dependent inhibitory
178 and odorant-independent excitatory activities on olfactory neurons.⁶⁰

179

180 IR3535 is colorless, almost odorless, and biodegradable. Formulations of IR3535 include
181 aerosols, lotions, pump sprays, and wipes, with concentrations of 7.5-19.7%. IR3535 is most
182 effective against Culicinae mosquitoes (arbovirus carriers) and ticks, lasting up to approximately
183 2 hours. Side effects of IR3535 include eye irritation. IR3535 may also cause damage to
184 clothing and plastic.⁶⁴

185

186

187 NATURAL COMPOUNDS

188 The natural compounds is a category of IRs approved by the FDA that encompasses variety of
189 essential plant oils, or their active compounds, that act as the main active ingredient. These
190 natural products are generally safer for human use compared to synthetic non-biodegradable
191 products such as DEET.⁶⁵⁻⁶⁷ The list of plant-derived IRs are numerous. In this section, we
192 focus on the EPA-registered natural compound IRs.

193

194 Oil of Lemon Eucalyptus

195 Oil of lemon eucalyptus, or active compound p-menthane-3,8-diol (PMD), is an extract from
196 lemon eucalyptus, *Corymbia citriodora*. PMD can also be industrially synthesized.⁶⁸ The first
197 documented use of oil of lemon eucalyptus was during the 1960s, during which mass
198 screenings of plants used in Chinese traditional medicine were performed.⁶⁹ Oil of lemon
199 eucalyptus, also known as Quwenling in China, became investigated in the U.S. in the early
200 1990s with subsequent identification of PMD. In 2000, the EPA recognized the oil of lemon
201 eucalyptus and PMD as an IR.

202

203 Although the MOA of oil of lemon eucalyptus and PMD are unclear, the IR effectiveness for both
204 has been consistently demonstrated. The efficacy of lemon eucalyptus is comparable to low
205 concentrations of DEET, lasting up to 6 hours for aggressive mosquitoes and 12 hours for less
206 aggressive mosquitoes.⁵⁴ PMD formulations can be found in pump sprays ranging in
207 concentrations of 10-40%. Ten EPA-registered products of lemon eucalyptus or PMD are
208 available.⁷⁰ Carrol et al. has demonstrated that PMD has mosquito repellent efficacy and
209 duration equal to that of DEET.⁶⁸ PMD along with picaridin may have better efficacy against
210 ticks compared to that of DEET.⁶⁸ PMD has been shown to be effective against biting midges
211 and tick vectors of Lyme disease and Rocky Mountain spotted fever.⁷¹ Concentrated form of its
212 synthetic counterpart, PMD, is suggested to not be used on children less than 3 years of age.⁷²

213

214 Citronella Oil

215 Oil of citronella is extracted from *Cymbopogon nardus*, a type of grass, and originally used for
216 perfumery in France around 1858. The name citronella is derived from the French citronelle.⁶⁹
217 The oil is a mixture of components, including citronellal, citronellol, and geraniol. Citronella oil's
218 insecticidal properties were discovered in 1901;⁷³ eventually, citronella oil was registered in the
219 U.S. in 1948.⁷⁴ Formulations of oil of citronella can be found in bath oils, candles, and lotions
220 (ranging in concentrations 0.5-20%).^{61,75} EPA has registered 3 products containing citronella
221 oil.⁷⁰ This IR's primary weakness is poor stability in the presence of air and high temperature,
222 limiting citronella oil's practical applications. Further, citronella oil has a short duration of 2
223 hours.^{76,77} Citronella oil has benign side effects, which include eye irritation and potentially
224 allergic contact dermatitis. This agent is most effective against Anopheline mosquitoes (malaria)
225 and Culicine (arbovirus) mosquitos. Citronella oil is not effective against ticks, fleas, flies and
226 biting midges.⁷⁸ Several areas of research are focusing on prolonging the duration of action,
227 such as encapsulated nanonemulsion⁷⁹ and microencapsulation using gelatin-arabi gum
228 microcapsules.⁸⁰ However, for the time being, citronella oil is not recommended for traveler use
229 in disease endemic areas.⁷⁷

230

231 Catnip oil

232 Catnip oil is extracted from *Nepeta cataria*, or colloquially, catnip, native to temperate and
233 tropical zones in Asia and Europe.⁸¹ The oil is a mixture of components, with Nepetalactone
234 being catnip oil's active IR component.⁸²⁻⁸⁴ Moreover, *N. cataria* exhibits a more favorable
235 safety profile than DEET.⁸⁵ Catnip oil was registered by the EPA in 2008.⁸⁶ There are currently 4
236 EPA-registered products for catnip oil in the U.S., and they are designed to target mosquitoes
237 and black flies.⁷⁵ All 4 products are stated to have 7 hours of protection tie against mosquitoes.
238 Currently, there are no satisfactory research studies done for catnip oil and nepetalactone. The
239 MOA of nepetalactone is unknown. Formulations of catnip oil include spray and lotion (ranging
240 in concentrations of 7-15%).⁷⁵

241

242 2-undecanone (methyl nonyl ketone)

243 2-undecanone was originally EPA-registered as a repellent against dogs and cats in indoor and
244 outdoor settings in 1966.⁸⁷ Further research later demonstrated 2-undecanone's equivalent
245 mosquito repellent efficacy to that of DEET,^{88,89} this compound was eventually re-registered as
246 a biochemical pesticide repellent in 2012.⁸⁷ 2-undecanone can be extracted from the wild
247 tomato (*Lycopersicon hirsutum* Dunal f. *glabratum* C. H. Müll) plants, or synthesized
248 industrially.⁸⁸ Similar to that of most plant-based IRs, the MOA of 2-undecanone is not well
249 understood and is suggested to be related to insect olfactory sensory neurons.⁶⁰ BIO-UD-8
250 Spray (Homs, LLC, Pittsboro, NC) is the only 1 EPA-registered formulation of 2-undecanone.⁷⁵
251 Due to 2-undecanone's recent introduction as an IR, a paucity of research and clinical
252 recommendations currently exist.

253

254 ONLY CLOTHING-APPLIED IR

255

256 Permethrin

257 Pyrethrins, the class permethrin is part of, are an extract of the chrysanthemum flower.
258 Permethrin should not be applied directly to the skin.⁹⁰ This product is intended to be used only
259 to treat clothing, and represents the only repellent currently registered to treat fabric in the
260 U.S.⁹¹ First marketed in 1973, permethrin acts as an IR and insecticide that is highly effective
261 against mosquitoes, ticks, and flies equally,⁶¹ even shown to repel ticks more effectively than
262 DEET.⁹² Permethrin-treated mosquito nets offer cost-effective protection and have been
263 extensively utilized in malaria prevention.^{93,94}

264

265 The MOA is attributed to the blockade of sodium movement into neurons by inhibiting
266 acetylcholinesterase and geaminobutyric acid A receptor, leading to paralysis of the
267 arthropod.^{95,96} Permethrin is toxic to cold-blooded organisms, such as insects, and fish.⁹⁷
268 Permethrin is quickly metabolized by the liver, and is poorly absorbed by the GI tract.¹⁶
269 Elimination of metabolites is near completed by 1 week.^{98,99}

270

271 Toxicities have been reported at high doses and include neurologic symptoms such as
272 paresthesias, tremors, ataxia, paralysis, and seizures.⁵⁴ Other side effects include eye and skin
273 irritation, reproductive effects, and alterations in the immune system.¹⁰⁰ Prenatally, permethrin

274 may adversely affect learning and behavior in fetuses.^{16,101} However, the studies done involve
275 significantly higher exposure than typical.

276
277 Permethrin has many applications, and has been used in public health programs, agriculture,
278 home pest control, forestry, and even head lice control.¹⁰⁰ Permethrin may be used on clothing,
279 shoes, bed nets, and camping gear, and requires reapplication after every 5 washings.²
280 Formulations include sprays for physical IR barriers, including insect nets, sleeping bags, boots,
281 and clothes at a concentration of 0.5%.

282
283 **CONCLUSION**

284 Prevention of arthropod bites to reduce the burden of several systemic diseases as well as
285 insect bites' local inflammation are of great interest to public health efforts. As of 2018, EPA-
286 registered skin applied IR ingredients currently include DEET, permethrin, picaridin, IR3535, oil
287 of lemon eucalyptus, oil of citronella, catnip oil, and 2-undecanone.⁷⁰ DEET remains the most
288 efficacious and commonly used IR for the last seven decades. Further research advances are
289 being made for IRs alternative to DEET.

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594 **Table legend**

595 Table 1. "Summary table of insect repellents"

Insect Repellent Compound	Available Concentrations	Average Duration	Efficacy Against Mosquitoes and Ticks	Popular Brands	Possible Side Effects	Special Considerations
Synthetic						
DEET	5% - 100%	5 hr (at 24%)	Mosquitoes & Ticks	-OFF!® (S.C. Johnson & Son, Racine, WI) -Cutter® (Spectrum Brands, Atlanta, GA) -Outdoorsman® (Spectrum Brands, Middleton, WI) -Sawyer® (Sawyer Products, Safety Harbor, FL) -Ultrathon® (3M Company, St. Paul, MN)	Urticaria, vesiculobullous skin necrosis at 50-75% concentration, anaphylaxis, cardiovascular (hypotension, bradycardia), neurologic (lethargy, confusion, headaches, ataxia, disorientation, seizures, tremors),	Sunscreen and topical retinoids increase risk of toxicity. May cause fabric and plastic degradation.
Picaridin	7-20%	8-10 hr (at 20%)	Mosquitoes & Ticks	- Cutter® (Spectrum Brands, Atlanta, GA) -Avon Skin-So-Soft Bug Guard® (Avon Products, London, United Kingdom) -Natrapel® (Tender Corporation, Littleton, New Hampshire) -Sawyer Premium® (Sawyer Products, Safety Harbor, FL) -OFF!® (S.C. Johnson & Son, Racine, WI)	Minor skin irritation	Odorless, non-sticky, no harm to clothing or plastics

IR3535	7.5-19.7%	2-3 hr	Mosquitoes & Ticks	-Avon Skin-So-Soft Bug Guard Plus® (Avon Products, London, United Kingdom) -Coleman Skin Smart® (Wisconsin Pharmacal Company LLC, Jackson, Wisconsin)	Eye irritation	Odorless, biodegradable
Natural						
Oil of lemon eucalyptus	10-40%	6 hr	Mosquitoes only	-OFF! Botanicals® (S.C. Johnson & Son, Racine, WI)	Minor skin irritation	---
Oil of citronella	0.5-20%	2 hr	Mosquitoes only	-Buzz Away Insect Repellent® (Quantum Health, Columbus, OH)	Eye and minor skin irritation	---
Catnip oil	7-15%	7 hr	Mosquitoes only	-Refined Oil Of Nepata Cataria® (DowDuPont, Wilmington, DE)	---	---
2-undecanone	1-2%	5 hr	Mosquitoes & Ticks	-BIO-UD-8 Spray® (Homs, LLC, Pittsboro, NC)	---	---
Only Clothing Applied						
Permethrin	0.5%	6 weeks or reapply after 6 washings	Mosquitoes & Ticks	-Sawyer Premium® (Sawyer Products, Safety Harbor, FL) -Repel® (Spectrum Brands, Atlanta, GA)	Eye and skin irritation, neurologic (numbness, tingling, tremors, and at high exposures, paralysis and seizures)	Clothing applied only. Uniquely both an insect repellent and an insecticide (repels and kills).

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