

***N,N-Diethyl-3-methylbenzamide (DEET)***

**HIGHLIGHTS**

Few cases of toxicity when used properly

Skin, GI absorption

**SIGNS & SYMPTOMS**

Skin irritation, contact dermatitis, urticarial

Rarely: headache, restlessness, irritability, ataxia, unconsciousness, hypotension, seizures

**TREATMENT**

Decontaminate skin, eyes

Consider topical steroids, oral antihistamines for severe skin reactions

Consider GI decontamination following substantial ingestion

Control seizures with anticonvulsants

**CONTRAINDICATED**

Induced emesis

CHAPTER 14

**Insect Repellents**

Insect repellents are by nature different from all other pesticides because they are the one class of chemicals applied purposefully to humans. The exceptions to this rule are several insecticides (permethrin, lindane and malathion) that may be applied purposefully to human skin or hair to treat scabies and lice. Repellents are not insecticidal; rather they mask the human skin to detection by insects and arthropods (mosquitoes, gnats, ticks).

Hundreds of insect repellents are marketed in the United States. The primary synthetic insect repellents used in the U.S. are *N,N*-diethyl-3-methylbenzamide (also and formerly known as *N,N*-diethyl-*m*-toluamide, DEET) and KBR 3023 (picaridin). DEET was developed by the military around the time of World War II and has long been considered the gold standard of insect repellents. Picaridin was developed in the late 1990s and, prior to being marketed in the United States in the mid 2000s, was available in Europe and Australia. Several natural products have been used as insect repellents and are listed by the EPA as minimum risk pesticides, making them exempt from federal regulation. These include oil of citronella, cedar oil, lemongrass oil and others that are available in the retail market.<sup>1</sup> Oil of lemon eucalyptus, its synthetic analog PMD, picaridin, and IR3535 are recommended by the Centers for Disease Control and Prevention (CDC) as alternatives to DEET to control mosquitoes that carry West Nile virus.<sup>2</sup> Picaridin has a duration of action comparable to some formulations with 20%-30% DEET and other repellents.<sup>3</sup> It has not been approved for ticks.

***N,N*-DIETHYL-3-METHYLBENZAMIDE (DEET)**

This chemical is a widely used liquid insect repellent, suitable for application to skin or to fabrics. It comes in a wide range of concentrations from 5% (Off! Skintastic for Kids) to 100% (Muskol). Despite the widespread use of the product, there are relatively few cases of toxicity reported in the literature.<sup>4</sup> Improper use, ingestion and high-concentration usage on children are risk factors for the rarely observed severe toxicity.<sup>5</sup>

**Toxicology**

The toxicokinetics has been well studied in animal models and humans. Approximately 19%-48% of **DEET** penetrates the epidermis in about 6 hours in guinea pigs. DEET can be detected within the blood and other tissues in mice within 2 hours of application, and excretion in the form of inactive metabolites is the primary mode of elimination.<sup>6,7</sup> Similar absorption, distribution, metabolism and excretion are found in humans.<sup>8</sup> DEET is efficiently absorbed across the skin and by the gastrointestinal tract. Blood concentrations of about 3 mg/liter have been reported several hours after dermal application in the prescribed fashion.<sup>9</sup> DEET is rapidly absorbed, peaks at around 6 hours, and within 24 hours its metabolites are completely excreted.<sup>8</sup> Skin permeability for DEET is enhanced by an ethanol substrate, which is how most formulations are prepared.<sup>10</sup> Human skin permeability of DEET is decreased using a polyethylene glycol solvent.<sup>11,12</sup>

For many years, DEET has been effective and generally well tolerated as an insect repellent applied to human skin, although tingling, mild irritation and sometimes desquamation have followed repeated application. It should be pointed out that the label recommends “to avoid over application” and that the product should be washed off upon returning indoors. The chemical tends to leave an oily residue on the skin, and may dissolve plastic or other synthetic materials such as clothing, wrist watches and other objects.

## Signs and Symptoms of Poisoning

Most reports of adverse events following DEET exposure are skin-related findings. These include mild skin irritation, contact dermatitis, exacerbation of preexisting skin disease as well as generalized urticaria.<sup>13,14</sup> DEET is very irritating to the eyes but not corrosive.

Serious adverse cutaneous effects have occurred in tropical conditions, when applied to areas of skin that were occluded during sleep (mainly the antecubital and popliteal fossae). Under these conditions, the skin became red and tender and then exhibited blistering and erosion, leaving painful, weeping, denuded areas that were slow to heal. Severe scarring occasionally resulted from some of these severe reactions.<sup>15</sup>

Toxic encephalopathic reactions have been reported in rare instances following ingestion or dermal application. Manifestations of toxic encephalopathy have been headache, restlessness, irritability, ataxia, rapid loss of consciousness, hypotension and seizures. Some cases have shown flaccid paralysis and areflexia. Deaths have occurred following very large doses.<sup>4,5,16</sup> Plasma levels of DEET found in fatal systemic poisonings have ranged for 168 to 240 milligrams per liter.<sup>5</sup> One well-documented case of anaphylactic reaction to DEET has been reported.<sup>17</sup> One fatal case of encephalopathy in a child heterozygous for ornithine carbamoyl transferase deficiency resembled Reye’s syndrome, but the postmortem appearance of the liver was not characteristic of the syndrome.<sup>18</sup>

While most severe toxicity reports relate to multiple dermal applications of various concentrations including as low as 10%,<sup>16,19,20,21</sup> seizures following less frequent dermal exposure has also been reported.<sup>22,23</sup> A summary of the 22 cases reported in the medical literature was reviewed in *Pediatric Annals*.<sup>24</sup> The difficulty of such case reports is that exposure details cannot always be ascertained. The more severe cases of systemic toxicity have often occurred following ingestion.<sup>4</sup> No dose-response patterns appear to exist among the small number of human toxicity reports.

The National Poison Data System, formerly known as the Toxic Exposure Surveillance System, is used by the American Association of Poison Control Centers (AAPCC) and allows a retrospective review of reports to poison control centers. Every year in the annual report of poison control centers (PCCs), reports of adverse events following insect repellents number in the hundreds, but most are listed as mild-to-moderate effects, and no details are given as to the nature of the symptoms. Generally, data are based on reports to PCCs, sometimes with or without follow-up information, so the data are limited by what is reported and collected. Greater detail can be found in a review published in 2002, based on 1993-1997 reports to poison control. Of 20,764 exposures reported to PCCs, information on outcomes was reported for 11,600. Of these, 11,159 (96.2%) were considered minor, and 437 (3.8%) were classified as moderate (409), major (26) or fatal (2). The two deaths occurred in adults, both following exposure to a concentration greater than 50% DEET. Of the 26 cases with major effects, half were adults and half were 0-19 years of age. Two patients were exposed to less than 11% DEET, one of whom had neurological effects and the other was admitted to critical care although symptoms were not reported. Thirteen of the 26 cases did not have DEET concentrations available,

### *N,N*-Diethyl-3-methylbenzamide (DEET) COMMERCIAL PRODUCTS

Auton  
Cutter  
Detamide  
Metadelphene  
MGK  
Muskol  
OFF!  
Sawyer  
Skeeter Beater  
Skeeter Cheater

and 7 did not have symptom data available. Of those with symptom data available (17), 11 reported neurological symptoms.<sup>25</sup>

Discretion should be exercised in recommending DEET for persons who have acne, psoriasis, an atopic predisposition or other chronic skin condition. According to the label, it should not be applied over cuts, wounds or irritated skin. In addition, it should not be applied to any skin area that is likely to be opposed to another skin surface for a significant period of time (antecubital and popliteal fossae, inguinal areas).<sup>15</sup>

Great caution should be exercised in using DEET on children. A wide variation in applied concentrations has been associated with the reported cases of pediatric seizures or major effects. Care should be taken to balance the risks of prevention of arthropod-borne diseases, possible adverse effects and the duration of time the child may be exposed. The adverse event reports suggest that multiple applications can play a role in toxicity and reinforce the need to follow the product label on reapplication. Specifically, the label says “Avoid over application. Frequent reapplication and saturation are unnecessary.” The product should also be washed off after returning indoors. To avoid multiple applications, use the concentration that best fits the duration of possible exposure. If the child is going to be outside for 1-2 hours, a product containing 10% DEET is likely to be effective. If the exposure time is longer, a product with 5-7 hours of protection time (such as 25%-30% DEET) may be more appropriate.<sup>3</sup> The application should be limited to exposed areas of skin, using as little repellent as possible. If headache or any emotional or behavioral change occurs, use of DEET should be discontinued immediately. The American Academy of Pediatrics does not recommend using products that contain DEET on infants less than 2 months of age.

### Confirmation of Poisoning

Methods exist for measurement of DEET in plasma and tissues and of DEET metabolites in urine, but these are not widely available. The Centers for Disease Control and Prevention (CDC) has developed a method for measuring DEET (not the metabolite) in the urine. In the nationally representative sample of U.S. residents conducted by CDC for the years 2001 and 2002, DEET was detected in approximately 10% of the U.S. population, with a 90<sup>th</sup> percentile geometric mean of 0.100 µg/l, and a 95<sup>th</sup> percentile geometric mean of 0.170 µg/l.<sup>26</sup> Because the parent compound is excreted within 24 hours of exposure, this likely reflects individuals with recent exposure.

### Treatment of DEET Toxicosis

1. Decontaminate the skin with soap and water as outlined in **Chapter 3, General Principles**. Eye contamination should be removed by prolonged flushing of the eye with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained. Topical steroids and oral antihistamines have been used for severe skin reactions that occasionally follow application of DEET.<sup>15</sup>
2. If a substantial amount of DEET has been ingested within an hour of treatment, consider gastrointestinal decontamination as outlined in **Chapter 3**. Induced emesis is usually considered contraindicated in these poisonings because of the rapid onset of seizures.
3. Provide supportive treatment, controlling seizures with anticonvulsants as outlined in **Chapter 3**. Persons surviving poisoning by ingestion of DEET have usually recovered within 36 hours or less.<sup>4,5</sup>

## PICARIDIN

Picaridin, also known as KBR 3023, is a relatively new synthetic insect repellent. Marketed in Europe in the 1990s, it was introduced to the U.S. market in 2005. It has been shown to have relatively similar protection time as DEET when tested in similar concentrations. It tends to be less oily, better tolerated and less pungent than DEET and, unlike DEET, does not damage plastics and synthetic fabrics.<sup>27</sup>

### Toxicology

The mechanism of action of **picaridin** is unknown.<sup>28</sup> Animal studies have not demonstrated dermal, organ-specific or reproductive toxicity.<sup>29</sup> Duration of protection from mosquito bites depends on its concentration. Animal studies did not reveal acute toxicity in doses as high as 200 mg/kg body weight.<sup>30</sup> Likewise, animal studies did not demonstrate any teratologic, developmental or neoplastic abnormalities.<sup>30,31</sup> Most commercially available products contain 7.5%, 10% and 15% picaridin, with the lower-concentration product lasting approximately 2 hours and the 15% picaridin lasting approximately 4-6 hours. Protection appears comparable to DEET, and this agent seems better tolerated.<sup>27,32,33,34,35</sup>

### Signs and Symptoms of Poisoning

Allergic contact dermatitis has been reported in a human following routine application and produced erythema and pruritis. It is not clear whether the solvent methyl glucose-dioleate had a causative or additive effect.<sup>36</sup> Other than the skin irritation, there are no additional reports of toxic effects in humans.

### Treatment of Picaridin Toxicosis

1. Treat skin irritation with oral antihistamines and topical steroids.
2. For eye exposure, irrigate eyes with copious amounts of water or normal saline. If contact lenses are present, they should be removed.
3. Otherwise, provide supportive treatment.

## ESSENTIAL OILS

Numerous natural or essential-oil-based products are in use as insect repellents. The repellency activity is thought to derive from camphor in some of the products, but other activity is unknown. There is marked variability of the ingredients of oils in various repellents and their efficacy, with some results supporting an essential oil as effective or almost as effective as DEET,<sup>37,38,39</sup> while other results do not support these efficacy findings.<sup>3,40</sup> Of the oils, oil of lemon eucalyptus is the only one that has been recommended by the CDC as being an effective alternative to DEET.<sup>41</sup> Several essential oils are considered by the EPA to be minimum risk pesticides and are not subject to federal registration requirements.

### Toxicology

**Oil of lemon eucalyptus** is colorless to pale yellow in color and has an aromatic odor and pungent taste. It primarily contains 1,8 cinole, along with a small amount of

### *Picaridin* HIGHLIGHTS

Similar protection time as DEET with fewer undesirable impacts

Unknown mechanism of action

### SIGNS & SYMPTOMS

Skin irritation

### TREATMENT

Oral antihistamine, topical steroid

Irrigate eyes if exposed

Essential Oils  
COMMERCIAL  
PRODUCTS

cedar oil  
lemongrass oil  
oil of citronella  
oil of lemon eucalyptus

HIGHLIGHTS

Variability of ingredients and efficacy  
CNS impacts from ingestion

SIGNS & SYMPTOMS

Most toxicities from ingestion  
Vomiting, lethargy, coma, seizures  
Dermal irritation possible

TREATMENT

Supportive  
Consider GI decontamination

other compounds, including hydrocyanic acid, which is thought to be the source of its toxicity. Ingestion of eucalyptus oil is known to cause significant neurological toxicity, and an adult fatality has been reported following ingestion of as little as 3.5 mL.<sup>42,43,44,45</sup>

Signs and Symptoms of Poisoning

Most reports of toxicity from eucalyptus oil have arisen from ingestion.<sup>43,44,45,46</sup> Most preparations include a combination of camphor, eucalyptus oil and menthol, such as those used in a vaporizer solution or other medicinal purposes.<sup>47,48</sup> The main symptoms reported include vomiting, lethargy, coma and seizures.<sup>43,44</sup>

One published case report of systemic toxicity from essential oils related to dermal application.<sup>42</sup> In this case, a 6-year-old girl had numerous applications of occlusive bandages soaked in a homemade solution including eucalyptus oil. Approximately 24 hours after the applications were initiated, she appeared intoxicated and progressed to complete loss of consciousness. Removal of the exposure and rinsing her skin with water resulted in a full recovery within 24 hours.<sup>42</sup> Several cases of irritant dermatitis have also been reported, with signs and symptoms including erythema, pruritis and a burning sensation.<sup>45,49</sup>

Treatment of Essential Oil Toxicosis

1. Provide supportive care, as there is no antidote.
2. If the patient is symptomatic or has ingested a large amount of essential oils, consider GI decontamination.<sup>45</sup> For specific information on GI decontamination, please see **Chapter 3, General Principles**.

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