

Therapeutic Insights

DEET-based insect repellents: safety implications for children and pregnant and lactating women

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Abstract

REDUCING THE RISK OF MOSQUITO BITES is currently the only way to reduce the risk of West Nile virus infection. Methods for avoiding mosquito bites include limiting the time spent outdoors at dawn and dusk, wearing protective clothing and using an insect repellent. Repellents containing DEET (*N,N*-diethyl-*m*-toluamide, also known as *N,N*-diethyl-3-methylbenzamide) are the most effective and most widely used. However, concerns have been raised over the risk of adverse toxic effects, especially in young children and pregnant and lactating women. In this article, we review the available evidence on the effectiveness and safety of DEET-based products. The evidence does not support increased risk in young children.

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The emergence of West Nile virus (WNV) infection in Canada has led to high levels of anxiety and vigilance. As there is no vaccine currently available, illness is prevented by avoiding bites of infected mosquitoes.

DEET (*N,N*-diethyl-*m*-toluamide, also known as *N,N*-diethyl-3-methylbenzamide) is the most effective and most widely used insect repellent. It was first used by the US military in 1946 and has been sold commercially for almost half a century. Products are available with concentrations of 5% to 100% of DEET and come in a variety of forms: aerosols, pump sprays, lotions, creams, liquids, sticks, roll-ons, towelettes and wristbands. The US Centers for Disease Control and Prevention (CDC) has estimated that 30% of Americans are using DEET-based insect repellents to avoid mosquito bites, as well as bites of other insects, such as the ticks responsible for transmitting Lyme disease.¹ An estimated 23%–29% of American children are exposed to DEET.²

Although DEET is very effective, its use in young

children has been limited because of case reports associating it with seizures.^{1,3–8} Yet, young children may be outdoors for extended periods, and suboptimal use of mosquito repellents may increase their risk of WNV infection. There is also apprehension about DEET's potential effects on the developing fetus and child when used by pregnant and lactating women. In this review we attempt to address this complex issue by critically analyzing existing evidence.

Pharmacology

Although the mechanism of action of DEET is unknown, the main theory is that the chemical disturbs the function of receptors in the mosquito's antennae that allow it to locate humans. The effectiveness of DEET in repelling mosquitoes is directly related to the concentration of the chemical applied (Table 1).⁹ However, the duration of action reaches a plateau at a concentration of 50%.¹⁰ This is in part why Health Canada is phasing out insect repellents containing DEET at concentrations higher than 30% by December 2004.¹⁰

Although DEET's effectiveness is related to its topical use, its systemic adverse effects are related to the amount that is absorbed into the blood. After 6 hours, 9%–56% of the dose appears in the circulation (systemic bioavailability). However, if DEET is ingested, intentionally or un-

Table 1: Examples of protection times of insect repellents containing various concentrations of DEET³

Concentration of DEET, %	Approximate protection time, h
30	6
15	5
10	3
5	2

Note: DEET = *N,N*-diethyl-*m*-toluamide, also known as *N,N*-diethyl-3-methylbenzamide.

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intentionally, peak plasma levels are much higher and are achieved within 1 hour.¹¹ For example, 10–12 g of a 75% DEET solution applied to the skin can lead to a blood concentration of about 0.0005 mmol/L; ingestion of a similar amount of DEET can result in a blood concentration that is hundreds of times higher (1 mmol/L). The latter concentration has been associated with seizures and death.¹¹ The elimination half-life of DEET is 2.5 hours, and most of the body load is metabolized by hepatic P450 enzymes, with only 10%–14% recovered unchanged in the urine.

Toxic effects

Adults

Most of the data on DEET's toxic effects in humans stem from case reports of ingestion of the chemical. Such ingestion may lead to hypotension, seizures and coma within as little as 1 hour.¹² Deaths have been associated with serum concentrations of 1 mmol/L.¹¹

The mechanism leading to seizures is unknown. They may occur as soon as 1 hour and as long as 48 hours after ingestion.¹¹ Although seizures may theoretically occur more often in people using DEET who are concurrently using drugs that lower the seizure threshold (e.g., bupropion, antipsychotic agents, systemic steroids and antimalarial agents), no interactions have been confirmed.

Psychosis was described in an adult who had applied a product containing 70% DEET to the skin.¹¹

Immediate contact dermatitis following dermal application has been described, as have generalized pruritus and generalized angioedema.¹¹ Conjunctival damage may result from application to the eye.

Children

Extrapolating from data on toxic effects in adults, one might expect seizures to be a major adverse effect in children. However, we found only 10 reports describing seizures in children following dermal application of DEET that were published in the almost 50 years since DEET has been available;^{1,3–8} none was published after 1992. Nevertheless, these case reports have been widely quoted and have led regulatory agencies and pediatric societies to limit the use of DEET in young children.

However, because seizure disorders occur in 3%–5% of children¹³ and an estimated 23%–29% of children in this continent are exposed to DEET,² it would not be surprising to see an association just by chance in some cases. Epidemiologically, when 2 events (i.e., DEET application and seizures) are both prevalent, case reports are not useful in determining causation.

In addition, other features of these case reports are not very helpful because they do not appear to be pathognomonic. For example, viral encephalitis was not ruled out in

any of the cases. The differential diagnosis of encephalitis was entertained in 3 cases, and there was “nonspecific rash” reported in 1 case. In another case, the clinical picture resembled Reye's syndrome, which on its own could predispose a child to seizures.¹⁴ In 1989, the CDC, after discussing 5 pediatric cases of seizures associated with dermal application of DEET, cautioned against the use of these cases as proof of causation.¹ Specifically, the CDC wrote that “DEET should not be accepted as the cause of a seizure until appropriate evaluation has reliably excluded other possible etiologies.” Yet, appropriate evaluation has not been conducted in any case before or after 1989, whereas the causation has been implied by authorities numerous times.

A large-scale population-based study on the safety of DEET was published in 2002 based on data collected by the American Association of Poison Control Centers between 1993 and 1997.¹⁵ This study refutes the long-held, unproven perception that young children are more sensitive than adults to the adverse effects of DEET. After collecting data on 20 764 pediatric and adult cases of accidental DEET exposure, the authors analyzed the cases by severity of adverse events (from none to fatal) and by age. A total of 1151 infants and children and an additional 101 adolescents were accidentally exposed to DEET dermally. Analysis of the severity of adverse events revealed that the infants and children had lower rates of each of moderate, severe and fatal events than did the adults. The authors summarized that, “overall, children experienced more of the less severe outcomes and adults experienced more of the worst outcomes associated with an exposure.”

Pregnant and lactating women

Women are often concerned about using DEET during pregnancy, but the available data on toxic effects in humans and animals are reassuring. An animal study published in 1994 reported no adverse effects in the offspring of rats and rabbits force fed different concentrations of DEET at different times of gestation, with one exception.¹⁶ The highest DEET dose (325 mg/kg daily), by orders of magnitude higher than the normal human dose, resulted in maternal toxic effects and low birth weights of offspring. There was no evidence of fetal toxic effects or malformations in the offspring of exposed animals, regardless of the dose used. No observations on behaviour or neurologic development were reported.¹⁶

The first study of the safety of DEET when used regularly during the second and third trimesters was a randomized, double-blind trial involving 897 pregnant women in Thailand who continuously applied therapeutic doses of DEET topically (1.7 g/d) — a dose similar to that recommended to prevent malaria¹⁷ — or placebo to prevent malaria.¹⁷ The DEET group received a median cumulative dose of 214.2 g. DEET levels were measured in cord

blood samples in a subgroup of 50 women; it was detected in 4 (8%), which provides evidence that the chemical crosses the placenta. In the group as a whole, no adverse neurological, gastrointestinal or dermatological effects were observed in the women exposed to DEET, and no adverse effects on survival or growth and development at birth and at 1 year of age were detected in the babies whose mothers used DEET.

We found no human studies of exposure to DEET in the first trimester. However, the very high dose administered orally in the animal study¹⁶ suggests that DEET is safe when used as recommended. The CDC has advised that pregnant women take precautions to reduce their risk of WNV infection and other arboviral infections by avoiding mosquito bites and using protective clothing and DEET-based repellents.¹⁸ There is no evidence that the use of DEET by pregnant or lactating women poses a health hazard to unborn babies or children who are breast-feeding.¹⁹

Alternatives to DEET

Insect repellents other than DEET-based ones are available in Canada, although data on their safety are sparse. Products containing citronella oil for topical use are available at concentrations of 5%–15%. Citronella-based candles and incense are also available. Protection time with the dermally applied products is considered to be between 30 minutes and 2 hours, although in a recent study the mean protection time was less than 20 minutes with a product that contained a concentration of 10%.²⁰ Lavender oil at a concentration of 6% applied topically protects for less than 30 minutes.⁹ Citronella oil and lavender oil are generally considered safe but are not recommended for topical use on children under 2 years of age because of the lack of evidence. Aspiration pneumonia could be a concern if either oil is ingested.

A product containing 2% soybean oil was found to protect for about 90 minutes, a period similar to that of a product containing 4.75% DEET.²⁰ However, DEET at a concentration of 6.65% and 20% protected for a mean of 110 and 230 minutes respectively.⁹ Although repellents containing soybean oil are registered in Canada, none is currently available on the market. Aspiration pneumonia could be a concern if soybean oil is ingested by a young child.

A new product, containing *p*-menthane-3,8-diol at a concentration of 10% (OFF! Botanicals Lotion Insect repellent 1), was found to be effective for at least 90 minutes in one field trial.²¹ It can be applied up to twice a day on children over 3 years old, the age limit merely reflecting lack of data.^{21,22} Although the manufacturer states that no adverse effects are expected to occur with appropriate use, there are no epidemiological studies of the product's safety after dermal exposure or oral ingestion.

In a controlled study that compared DEET-based repel-

lents with non-DEET-based repellents, the latter failed to show appropriate protection against mosquito bites.²⁰

Areas of potential confusion

Both Health Canada and the Canadian Paediatric Society advise against the use of DEET on children under 6 months of age. Children aged 6 months to 2 years should be limited to one application per day, and children aged 2 to 12 years should be limited to 3 applications per day. The maximum concentration used should be 10% or less for children up to 12 years of age.^{9,21,22} However, these low concentrations are effective in repelling mosquitoes for only 2–3 hours (Table 1); therefore, young children would theoretically not be protected when outside for extended periods. Moreover, if the child goes swimming, the DEET will be washed away. Given the lack of evidence of increased toxicity of low-concentration DEET in young children, a second application of DEET may be warranted if the child is outdoors for more than 4 hours and WNV infection is a serious concern. Similarly, it may be prudent to reapply DEET after a session of swimming. In areas of high risk where WNV is present and mosquitoes are abundant, the risk of infection must be balanced against potential toxic effects.

Summary

DEET-based insect repellents are relatively safe when used as recommended. The suggestion that young children are more prone than adults to the neurotoxic effects of DEET is not supported by critical evaluation of existing evidence. Non-DEET-based insect repellents are available, but based on a one-time application comparison, a product containing 10% DEET will provide a longer period of protection (3 hours) than any other repellent currently available in Canada.

This article has been peer reviewed.

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References

1. Epidemiologic notes and reported seizures temporally associated with use of DEET insect repellants — New York and Connecticut. *MMWR Morb Mortal*

- Wkly Rep* 1989;38:678-80.
- Osimitz TG, Murphy JV. Neurological effects associated with use of the insect repellent N,N-diethyl-m-toluamide (DEET). *J Tox Clin Toxicol* 1997;35:435-41.
 - Gryboski J, Weinstein D, Ordway NK. Toxic encephalopathy apparently related to the use of an insect repellent. *N Engl J Med* 1961;264:289-91.
 - Roland EH, Jan JE, Rigg JM. Toxic encephalopathy in a child after brief exposure to insect repellents. *CMAJ* 1985;132(2):155-6.
 - Edwards DL, Johnson CE. Insect-repellent-induced toxic encephalopathy in a child. *Clin Pharm* 1987;6:496-8.
 - Heick HMC, Shipman RT, Norman MG, James W. Reye-like syndrome associated with use of insect repellent in a presumed heterozygote for ornithine carbamoyl transferase deficiency. *J Pediatr* 1980;97:471-3.
 - Lipscomb JW, Kramer JE, Leikny JB. Seizure following brief exposure to the insect repellent N,N-diethyl-m-toluamide. *Ann Emerg Med* 1992;21:315-7.
 - Letter from S.L. Oransky to the Department of Environment, Albany, NY; 1991 July 16. On file with the Department of Environment, Bureau of Pesticides Management, Hudson Valley Regional Poison Center, Albany, NY.
 - Safety tips on using personal insect repellent. Ottawa: Pest Management Regulatory Agency, Health Canada; 2003. Available: www.hc-sc.gc.ca/english/westnile/insect_repellents.html (accessed 2003 July 7).
 - Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds) [Re-evaluation Decision Document RRD2002-01]. Ottawa: Pest Management Regulatory Agency, Health Canada; 2002 Apr 15. Available: www.hc-sc.gc.ca/pmra-arla/english/pdf/rrd/rrd2002-01-e.pdf (accessed 2003 July 7).
 - Ellenhorn M. *Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning*. 2nd ed. Baltimore: Williams & Wilkins; 1997.
 - Teinenbein M. Toxicity of diethyltoluamide-containing insect repellents [letter]. *JAMA* 1988;259:2239-40.
 - Behrman RE, Kliegman R, Jenson HB, editors. *Nelson's textbook of pediatrics*. 16th ed. Philadelphia: Saunders; 2001.
 - Briassoulis G, Narioglou M, Hatzis T. Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children. *Hum Exp Toxicol* 2001;29:8-14.
 - Bell JW, Veltri JC, Page BC. Human exposures to N,N-diethyl-m-toluamide insect repellents reported to the American Association of Poison Control Centers 1993-1997. *Int J Toxicol* 2002;21:341-52.
 - Schoenig GP, Neeper-Bradley TL, Fisher LC, Hartnagel RE Jr. Teratological evaluations of DEET in rats and rabbits. *Fund Appl Toxicol* 1994;23:63-9.
 - McGready R, Hamilton KA, Simpson JA, Cho T, Luxemburger C, Edwards R, et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. *Am J Trop Med Hyg* 2001;65:285-9.
 - Intrauterine West Nile virus infection — New York, 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:1135-6.
 - West Nile virus: pregnancy and breastfeeding [fact sheet]. Ottawa: Health Canada; 2003. Available: www.hc-sc.gc.ca/english/westnile/pregnancy.html (accessed 2003 July 7).
 - Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med* 2002;347:13-8.
 - p-Menthane-3,8-diol [Proposed Regulatory Decision Document PRDD2002-02]. Ottawa: Pest Management Regulatory Agency, Health Canada; 2002. Available: www.hc-sc.gc.ca/pmra-arla/english/pdf/prdd/prdd2002-02-e.pdf (accessed 2003 July 7).
 - Insect repellents for children. Ottawa: Canadian Paediatric Society; 2002. Available: www.caringforkids.cps.ca/keepingkidssafe/repellents.htm (accessed 2003 July 8).

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