

## PHARMACOKINETICS, FORMULATION, AND SAFETY OF INSECT REPELLENT *N,N*-DIETHYL-3-METHYLBENZAMIDE (DEET): A REVIEW

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**ABSTRACT.** This review is intended to provide the reader with an overview of the all-purpose topical insect repellent *N,N*-diethyl-3-methylbenzamide (deet), with emphasis on its pharmacokinetics, formulation, and safety aspects. *N,N*-diethyl-3-methylbenzamide is effective against a variety of mosquitoes, flies, fleas, and ticks, and its protection efficacy depends on factors such as type of formulation, application pattern, physical activity of the user, environment, and species and feeding behavior of the insects. It offers an inexpensive and practical means of preventing the attack of biting insects and, more importantly, the transmission of vector-borne diseases. In both humans and animals, deet skin penetration and biodistribution are rapid and extensive, and metabolism and elimination appear to be complete. As evidenced by over 4 decades of human experience and rigorous animal testing, deet is generally safe for topical use if applied as recommended, although it has occasionally been related to side effects such as toxic encephalopathy, seizure, acute manic psychosis, cardiovascular toxicity, and dermatitis, along with a few cases of death due to extensive skin absorption. *N,N*-diethyl-3-methylbenzamide may compete in metabolism with and alter the biodistribution properties of other compounds to which a subject is simultaneously exposed, resulting in an added risk of side effects. The appropriate use of formulation techniques and new formulation excipients not only offers a way to extend the duration of protection, but also reduces deet skin penetration. In addition to extended repellency, minimal skin penetration of deet should be an important consideration in the evaluation of a deet formulation during new product development.

**KEY WORDS** Insect repellent, deet, pharmacokinetics, formulations, safety

### INTRODUCTION

*N,N*-diethyl-3-methylbenzamide (deet) has been marketed for over 4 decades as an effective broad-spectrum topical insect repellent (Gupta and Rutledge 1994, Osimitz and Grothaus 1995, Mafong and Kaplan 1997). It can be directly applied to human skin, clothing, tents, bedrolls, screens, household pets, and livestock. In the United States, it is estimated that more than 30% of the population use deet-containing insect repellent products during the insect-biting seasons, and over 30 million packages of deet products are sold annually (Veltri et al. 1994). The molecular structure and physicochemical properties of deet are shown in Fig. 1 and Table 1, respectively.

The application of an effective insect repellent such as deet reduces vector-human contact and therefore minimizes the incidence of vector-borne disease transmission as well as the discomfort of insect bites (Gupta and Rutledge 1994, Mafong and Kaplan 1997). Since the early 1980s, Lyme disease, a multiple-organ-system, immune-mediated inflammatory disorder transmitted by the bite of ixodid ticks infected with *Borrelia burgdorferi*, has been a significant health problem in North America, and the use of deet-containing topical insect repellent formulations was recommended as the best personal approach to prevent the transmission of the disease (Pray 1991, Couch and Johnson 1992). The

use of deet products is strongly recommended as one of the personal protection measures for the prevention of malaria for persons traveling to malaria-endemic areas (Anonymous 1988). Indeed, deet benefits not only civilians participating in outdoor recreational activities and employees working in field environments infested with biting insects, but also military personnel involved in field combat and training (Hooper and Wirtz 1983, Fai and Lee 1996). In field operations, the use of an effective topical insect repellent such as deet appears to be the most practical means of interrupting the transmission of vector-borne diseases, which enables troops to perform in disease-endemic areas and maintain adequate fighting strength (Hooper and Wirtz 1983). Moreover, deet finds application in the protection of livestock. For instance, a 35% solution of deet in isopropanol has been marketed for the protection of horses from biting flies in Canada (Taylor et al. 1994).

The repellent efficacy of deet has been demonstrated for many genera of insects. In efficacy tests, deet was found to be highly effective against the yellow fever mosquito (*Aedes aegypti*), the common malaria mosquito (*Anopheles quadrimaculatus*), and the salt marsh mosquito (*Aedes taeniorhynchus*) and was also effective against flies such as the biting stable fly (*Stomoxys calcitrans*), the deer fly (*Chrysops atlanticus*), and the biting midge (*Culicoides canithorax*) (Gilbert et al. 1955, Gilbert 1966). *N,N*-diethyl-3-methylbenzamide was shown to be effective against the rat flea (*Xenopsylla cheopis*) (Rutledge et al. 1982), the squirrel flea (*Dipmanus montanus*) (Mehr et al. 1984), the deer tick (*Ixodes dammini*) (Schreck et al. 1986), the lone star tick (*Amblyomma americanum*) (Grothaus et al. 1976a, Mount and Snoddy 1983), and the Amer-

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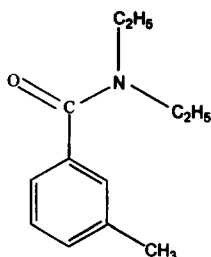


Fig 1. Molecular structure of insect repellent *N,N*-diethyl-3-methylbenzamide (deet).

ican dog tick (*Dermacentor variabilis*) (Mount and Snoddy 1983). In tests against biting midges, deet was highly effective in repelling *Culicoides furens*, *C. hollensis*, *C. mississippiensis*, and *C. floridensis* and was also effective against *C. barbosi* (Schreck et al. 1979, Harlan et al. 1983, Schreck and Kline 1983). *N,N*-diethyl-3-methylbenzamide was also efficacious in repelling the black flies *Prosimulium mixtum* and *P. fuscum* (Robert et al. 1992), the chigger *Eutrombicula alfreddugesi* (Clopton and Gold 1992), the phlebotomine sand flies (Schreck et al. 1982), and the mosquitoes *Culex vishnui*, *Cx. gelidus*, *Cx. tritaeniorhynchus*, *Anopheles albimanus* and *An. dirus* (Schreck 1985, Frances et al. 1996).

Smith et al. (1963) first reported that the minimum effective dose of deet against *Ae. aegypti* was 46–78  $\mu\text{g}/\text{cm}^2$ , and the application of an ethanol solution containing 10% deet to the forearms of human volunteers provided 5.6–6.2 h of protection. With the same amount of deet, Altman (1969) observed protection times of 2.0–2.2 h against *An. albimanus*. Gilbert et al. (1970) tested a 10% deet ethanol solution against *Culex quinquefasciatus* and obtained a protection time of 2.2 h. In a deet repellency test against *Ae. aegypti* with 16 volunteers, Gabel et al. (1976) found that the mean minimum effective dose of deet was 25  $\mu\text{g}/\text{cm}^2$ , and the mean protection time was 6.8 h at a dose of 0.32  $\text{mg}/\text{cm}^2$ . According to Maibach et al. (1974a), however, the

minimum effective dose of deet against *Ae. aegypti* was as low as 16  $\mu\text{g}/\text{cm}^2$ . In a repellency mechanism study, Wright (1975) observed that 0.01 mmol/liter (1.91 mg/ml) deet in the air repelled 90% of *Ae. aegypti* from landing on the target. The modes of action of deet on insects are complicated, and they are likely related to arthropod sensory mechanisms (Davis 1985, Sutcliffe 1994). It was demonstrated that deet repelled mosquitoes primarily by interfering with perception implemented via radiation, humidity, carbon dioxide, and other chemical sensors (Wright 1962, 1975; Skinner and Johnson 1980). The intrinsic repellencies of insect repellents are related to their physicochemical properties such as boiling point, vapor pressure, melting point, partition coefficient, lipophilicity, viscosity, surface tension, and thermodynamic factors (Garson and Winnike 1968, Skinner and Johnson 1980, Suryanarayana et al. 1991).

Although the efficacy of deet is mainly determined by its intrinsic repellency, factors such as temperature and air motion of the environment, loss from abrasion, and wash-off after dermal application have impacts on the efficacy and protection time (Maibach et al. 1974a, 1974b; Gossel 1984). In an investigation on the effects of temperature on insect repellents with ambient temperatures ranging from 26°C to 50°C, the protection time of deet was found to decrease by one-half as the temperature increased 10°C, while other conditions remained the same (Khan et al. 1973). When applied to the skin surface at 0.16  $\text{mg}/\text{cm}^2$ , deet offered a protection time of 200 min at 26°C with static air currents. However, the protection time decreased to 73 min when the air flow was raised to 192 m/min (Khan et al. 1973).

Other factors, such as skin lipids and sweating conditions, alter the protection time that a deet formulation can offer (Maibach et al. 1966, Skinner et al. 1968). Skin lipids obtained from the foreheads or forearms of human volunteers were found to be repellents against *Ae. aegypti* (Skinner et al. 1965a). The primary repellency of these lipids was

Table 1. Physicochemical properties of the insect repellent deet.

Property	Description
Empirical formula	$\text{C}_{12}\text{H}_{17}\text{NO}$
Molecular weight	191.3
Physical state	Amberlike liquid
Odor	Aromatic
Density	0.990–1.000 $\text{g}/\text{cm}^3$ at 25°C
Solubility	9.9 mg/ml in water at 25°C, practically insoluble in glycerin; miscible with ethanol, ether, isopropanol, chloroform, benzene, and carbon disulfide
Boiling point	111°C at 1 atm
Flash point	155°C
Vapor pressure	$1.67 \times 10^{-3}$ mm Hg at 25°C
Viscosity	13.3 cp at 30°C
Octane/water partition coefficient	105

probably derived from the volatile fatty acids, and the hydrocarbon fraction exhibited a degree of repellency mainly due to the unsaturated components present (Skinner et al. 1967, 1977). Sweating is believed to influence the protection time of deet formulations by means other than acting on the radiation, humidity, and temperature sensors of the insects (Skinner and Johnson 1980, Gossel 1984). Skinner et al. (1965b) found that certain components of sweat were insect attractants. They demonstrated that *Ae. aegypti* was attracted to lyophilized human sweat that had been diluted with distilled water. Sweating could also result in quick dilution or removal of deet applied on the skin (Gossel 1984).

Extensive dermal absorption also contributes significantly to the efficacy and duration of protection, as it is another major route of loss of deet from the skin surface. In human volunteers, up to 16.7% of the dermally dosed deet was depleted from the skin surface over a period of 5 days by transdermal absorption (Feldmann and Maibach 1970). Within the first 14 h, the portion of deet that underwent transdermal absorption after the dermal application of an ethanol deet solution was as high as 72.9% in cattle (Taylor et al. 1994).

In general, the efficacy and duration of protection that a deet formulation can offer is influenced by many factors, such as temperature, humidity and wind condition of the environment, species, host preference and population density, physical loss of deet from the skin surface, type of formulation vehicle and concentration of deet in the repellent formulation, and attractiveness of an individual to the insects, all of which closely interact (Skinner and Johnson 1980, Gossel 1984). At concentrations of over 10%, deet remained effective against *Ae. aegypti* in human volunteers for 3–14 h per application in controlled settings, and formulations containing approximately 95% deet afforded protection for up to 20 h in field tests (Anonymous 1980).

## PHARMACOKINETICS

Despite the huge market for deet-containing insect repellent products and the cases of serious adverse effects associated with the use of deet, data on human skin absorption, distribution, metabolism, and elimination of deet are very limited. The main reason is probably that deet is potentially toxic, and conducting such human studies to obtain a complete deet pharmacokinetic profile is problematic. The toxicity rating of deet was reported 3 on a scale of 6 (Gosselin et al. 1984).

Extensive and rapid penetration of deet through human skin has been demonstrated both *in vitro* and *in vivo*, and the data appear to be quite variable. In 2 male human volunteers, Smith et al. (1963) obtained mean deet penetrations of 11%, 11%, 38%, and 54% 2 h after deet was applied in ethanol solutions to the forearms at doses of 1.86, 0.93,

0.16, and 0.08 mg/cm<sup>2</sup>, respectively. *N,N*-diethyl-3-methylbenzamide penetration was determined by subtracting the amount collected in the evaporation and rinse traps from the amount applied in the study. In an *in vitro* evaporation and skin penetration study, Spencer et al. (1979) found that an average of 50.8% of deet had penetrated into the skin 1 h after its application in an ethanol vehicle at 25 mg/cm<sup>2</sup>. The assessment was made with the use of <sup>14</sup>C-labeled deet and abdominal human cadaver skin with 6 replicates, and deet penetration was determined as the difference between the dermal dose and the amount recovered from evaporation and rinse traps. Using similar experimental techniques, Reifenrath and Robinson (1982) obtained deet skin penetration (absorption and oxidation) of approximately 30% at 1 h after application and of about 36% at 12 h after application at a dose of 300 µg/cm<sup>2</sup>.

Reports regarding the transdermal bioavailability of deet in humans are very limited. According to Feldmann and Maibach (1970), the mean percent transdermal absorption of deet in 4 human volunteers was 16.7%, as determined by measuring the radioactivity recovered in urine after dermal application of <sup>14</sup>C-labeled deet. In the study, urine was collected for 5 days following the dosing of deet in acetone to the ventral forearms of the subjects at 4 mg/cm<sup>2</sup>. With the aim of obtaining a complete profile of deet absorption, metabolism, and excretion following dermal application in humans, Selim et al. (1995) conducted a deet pharmacokinetic study in human volunteers. At doses of 0.625 and 0.5 mg/cm<sup>2</sup>, the mean deet transdermal bioavailabilities were found to be 5.6% and 8.4% for technical deet and a 15% deet solution in ethanol, respectively. Bioavailability values were determined in 6 volunteers as percent ratio of the total <sup>14</sup>C-radioactivity recovered in urine and feces to the dermal <sup>14</sup>C-radioactivity dose. The value appears to be lower than that reported by Feldmann and Maibach (1970). Recently, in an *in vitro* skin permeation study using human skin, Stinecipher and Shah (1997) demonstrated that the penetration of deet from several commercial deet-containing topical insect repellent products was significant.

*N,N*-diethyl-3-methylbenzamide skin penetration and transdermal absorption have been studied in a number of animal species, including rabbit, cow, monkey, rat, mice, pig, and dog (Reifenrath et al. 1980, 1984; Snodgrass et al. 1982; Moody et al. 1989; Taylor et al. 1994; Domb et al. 1995; Schoenig et al. 1996; Qiu et al. 1997b). Table 2 summarizes the results of these studies in comparison with the human data. Clearly, ranging from 7.2% in weaning pigs to 72% in cattle, the bioavailability values estimated in these animals are far apart. The differences can be attributed to factors such as skin structure, anatomical site, vehicle, dose, bioavailability determination method, sample collection regimen, and analytical method. So far, there has

Table 2. Transdermal absorption of deet in humans and animals.

Species	deet formulation	Dose	Dose site	Quantitation	Absorption <sup>2</sup> %	Reference
Human (n = 4)	Acetone solution ( <sup>14</sup> C-labeled)	4 µg/cm <sup>2</sup>	Ventral forearm	Radioactivity	16.7 <sup>3</sup>	Feldmann and Maibach (1970)
Human (n = 6)	Technical deet (98.5%, <sup>14</sup> C-labeled)	0.625 mg/cm <sup>2</sup>	Volar forearm	Radioactivity	5.6 <sup>4</sup>	Selim et al. (1995)
	Ethanol solution (15%, <sup>14</sup> C-labeled)	0.5 mg/cm <sup>2</sup>	Volar forearm	Radioactivity	8.4 <sup>4</sup>	
Beagle dog (n = 4)	Commercial cream (7.125%)	15 mg/kg	Anterior dorsal	HPLC <sup>1</sup>	17.5 <sup>5</sup>	Qiu et al. (1997b)
	Gel emulsion (7.5%)	15 mg/kg	Anterior dorsal	HPLC	13.4 <sup>5</sup>	
Rabbit (n = 8)	Liposphere (10%, <sup>14</sup> C-labeled)	100 mg/kg	Unspecified	Radioactivity	16 <sup>6</sup>	Domb et al. (1995)
	Ethanol solution (10%, <sup>14</sup> C-labeled)	100 mg/kg	Unspecified	Radioactivity	45 <sup>6</sup>	
Cow (n = 4)	Ethanol solution (38.6–60 mg/ml)	1.0 mg/cm <sup>2</sup>	Backline area	GC <sup>1</sup>	72.9 <sup>7</sup>	Taylor et al. (1994)
Monkey (n = 8)	Acetone solution (0.44 mg/ml, <sup>14</sup> C-labeled)	10.5 µg/cm <sup>2</sup>	Forehead Forearm Ventral forepaw Dorsal forepaw	Radioactivity Radioactivity Radioactivity Radioactivity	33 <sup>8</sup> 14 <sup>8</sup> 68 <sup>8</sup> 27 <sup>8</sup>	Moody et al. (1989)
Rat (n = 8)	Acetone solution (0.44 mg/ml, <sup>14</sup> C-labeled)	10.5 µg/cm <sup>2</sup>	Middorsal	Radioactivity	36 <sup>8</sup>	Moody et al. (1989)
Nude mouse	Ethanol solution (0.51 mg/ml, <sup>14</sup> C-labeled)	4 µg/cm <sup>2</sup>	Rear ventral	Radioactivity	53.5 <sup>9</sup>	Reifenrath et al. (1984)
Human-skin-grafted nude mouse		4 µg/cm <sup>2</sup>	Rear ventral	Radioactivity	25.8 <sup>9</sup>	
Pig-skin-grafted nude mouse		4 µg/cm <sup>2</sup>	Rear ventral	Radioactivity	27.5 <sup>9</sup>	
Weaning pig (n = 3)		4 µg/cm <sup>2</sup>	Front dorsal	Radioactivity	7.2 <sup>9</sup>	
Rabbit	Ethanol solution (75%, <sup>14</sup> C-labeled)	4 µg/cm <sup>2</sup>	Midlumbar	Radioactivity	38.3 <sup>10</sup>	Snodgrass et al. (1982)
Beagle dog		4 µg/cm <sup>2</sup>	Midlumbar	Radioactivity	31.2 <sup>10</sup>	
Rat (male)		4 µg/cm <sup>2</sup>	Midlumbar	Radioactivity	43.6 <sup>10</sup>	
Rat (female) (n = 6)		4 µg/cm <sup>2</sup>	Midlumbar	Radioactivity	32.8 <sup>10</sup>	
Hairless dog (n = 3)	Ethanol solution (40 mg/ml, <sup>14</sup> C-labeled)	4 µg/cm <sup>2</sup> 320 µg/cm <sup>2</sup>	Dorsal Dorsal	Radioactivity Radioactivity	11.6 <sup>10</sup> 8.5 <sup>10</sup>	Reifenrath et al. (1980)

<sup>1</sup> HPLC, high pressure liquid chromatography; GC, gas chromatography.<sup>2</sup> Mean value.<sup>3</sup> Assessed as percent ratio of the <sup>14</sup>C radioactivity recovered in urine to total <sup>14</sup>C radioactivity dermally applied; urine collected for 5 days after dermal dosing.<sup>4</sup> Assessed as percent ratio of the <sup>14</sup>C radioactivity recovered in urine and feces to total <sup>14</sup>C radioactivity dermally applied; urine and feces collected for 128 h after dermal dosing.<sup>5</sup> Assessed by the noncompartmental method; blood samples collected for 18 and 16 h, respectively, after intravenous and dermal dosing.<sup>6</sup> Assessed by the noncompartmental method; blood samples collected for 10 and 24 h, respectively, after intravenous and dermal dosing.<sup>7</sup> Assessed by noncompartmental method; blood samples collected for 24 h after both intravenous and dermal dosing.<sup>8</sup> Assessed as percent ratio of the <sup>14</sup>C radioactivity recovered in urine to total <sup>14</sup>C radioactivity dermally applied; urine collected for 7 days after dermal dosing.<sup>9</sup> Assessed as percent ratio of the <sup>14</sup>C radioactivity recovered in urine and feces to total <sup>14</sup>C radioactivity dermally applied; urine and feces collected for 5 days after dermal dosing.<sup>10</sup> Assessed as percent ratio of the <sup>14</sup>C radioactivity recovered in urine to total <sup>14</sup>C radioactivity dermally applied; urine collected for 7 days after dermal dosing.

been no definitive study on the simultaneous evaluation of deet transdermal absorption from identical vehicles in human and animal species. Conclusive data as to which animal species would have similar deet transdermal absorption properties to those of humans and thus could be validated as a suitable model for optimizing deet formulations are not available.

*N,N*-diethyl-3-methylbenzamide is rapidly absorbed into the systemic circulation of human subjects following dermal application. As assessed by the  $^{14}\text{C}$ -radioisotopic technique, the mean hourly absorption of deet for the 1st 12 h was 0.773% of the dermal dose after deet was applied to the ventral surface of the forearm at  $4\ \mu\text{g}/\text{cm}^2$  (Feldmann and Maibach 1970). The radioactivity in plasma peaked approximately 6 h after the dermal application, and 73–75% of the dermal absorption was completed within the 1st 12 h (Selim et al. 1995). In a brief deet transdermal absorption test, the mean absorption times of deet observed for 2 human volunteers who exposed 75% of their body surface to deet at 148 mg/kg were 4.1 h and 5.5 h, respectively (Davies et al. 1988). Monitoring the deet blood levels of several National Park employees using a deet-specific liquid chromatographic method, deet serum concentrations of up to  $1.17\ \mu\text{g}/\text{g}$  were observed to peak 1–2 h after dermal application of a lotion containing 71% deet (Smallwood et al. 1992). This was consistent with the observation of Dremova et al. (1971), who investigated the skin absorption of various insect repellents in human volunteers. After 1 g of a deet cream was applied to the hands, feet, and backs of the volunteers over an area of  $1,250\ \text{cm}^2$ , maximum blood deet concentration of about  $20\ \mu\text{g}/\text{ml}$  was detected 2 h after dermal application using a thin-layer chromatography technique.

Very limited information on deet tissue distribution in humans is available. According to Tenenbein (1987), a 33-year-old woman who died after ingesting 50 ml of insect repellent containing 95% deet had the following deet tissue levels: gastric lavage returns, 10.4 mg/dl; blood, 16.8 mg/dl; post-mortem blood, 11.2 mg/dl; and liver, 17.7 mg/dl. In a 26-year-old man who committed suicide by ingesting 50 ml of 95% deet, the following tissue deet concentrations were obtained: blood, 24 mg/dl; vitreous, 15 mg/dl; and urine, 10 mg/dl. These data, in addition to the rapid onset of toxic symptoms, suggest that deet is quickly and extensively absorbed in the gastrointestinal tracts.

Extensive extravascular deet distribution is evident in various animal species. Qiu et al. (1997a) recently studied the pharmacokinetics of deet in beagle dogs by employing a newly established liquid chromatographic procedure (Qiu and Jun 1996). The volume of distribution at steady state ( $V_{ss}$ ) was found to be as high as 6.21 liters/kg. According to Taylor et al. (1994), who used a deet-specific gas chromatographic method to delineate deet phar-

macokinetics in cattle, the mean value for  $V_{ss}$  was determined to be 2.7 liters/kg. The extensive distribution property of deet was also demonstrated in rabbits, rats, and mice with the use of radioisotopic techniques. Snodgrass et al. (1982) reported that  $^{14}\text{C}$  radioactivity was amply present in the lung, liver, spleen, kidney, blood, fetuses and brain of rabbits after low-dose intravenous injection of  $^{14}\text{C}$ -labeled deet at 18–20 mg/kg. A recent deet pharmacokinetic study conducted by Schoenig et al. (1996) showed that, in rats sacrificed at peak blood radioactivity levels after oral or dermal routes of administration of  $^{14}\text{C}$ -labeled deet,  $^{14}\text{C}$  radioactivity existed at various levels in the following tissues: brain, heart, lungs, kidneys, muscle, stomach, small and large intestines, cecum, fat, bone, spleen, spinal cord, sciatic nerve, blood, plasma, and carcass. According to Blomquist and Thorsell (1977), who used a whole-body autoradiography technique to study the distribution of  $^{14}\text{C}$ -labeled deet in mice,  $^{14}\text{C}$  radioactivity was widely found in tissues such as lacrimal gland, liver, kidney, and nasal mucosa in addition to skin 2 h after dermal application of deet at 15 mg/kg. High levels of radioactivity were found in bile, intestinal contents, and urine. A similar radioactivity distribution profile was observed in mice after intravenous administration of deet (Blomquist et al. 1975).

In humans, deet undergoes extensive metabolism before being excreted in urine. Selim et al. (1995) reported that at least 6 metabolites were present in the urine of human volunteers who were dermally treated with 12 or 15 mg of deet on the forearms. No unchanged deet was detected in the urine by a liquid chromatographic method. Two of the identified metabolites were *N,N*-diethyl-3-carboxylbenzamide and *N*-ethyl-3-carboxylbenzamide. These 2 metabolites were further confirmed as metabolites of deet in rats in a later study (Schoenig et al. 1996). Schoenig et al. (1996) found that in rats treated with  $^{14}\text{C}$ -labeled deet orally or dermally, no parent compound was present in the urine, and *N,N*-diethyl-3-carboxylbenzamide and *N*-ethyl-3-carboxylbenzamide were identified as the major metabolites. In contrast, according to Wu et al. (1979), deet metabolism in humans was incomplete. In the urine of a 30-year-old male human volunteer who exposed 75% of his skin surface to 10.4 g of deet in the form of a commercial lotion, the amount of unchanged deet recovered accounted for 10–14% of the topical dose, and oxidation of the benzylic moiety and hydroxylation of the side chain of deet molecules were found to be the predominant routes of metabolism. The discrepancy between the results of Selim et al. (1995) and Wu et al. (1979) is likely due to overloading of the metabolic capabilities of the human subjects in the latter study. In fact, the amount of deet applied to the volunteers participating in the experiment of Wu et al. (1979) was about 700 times higher than that applied to the volunteers of Selim et al. (1995). Extensive deet me-

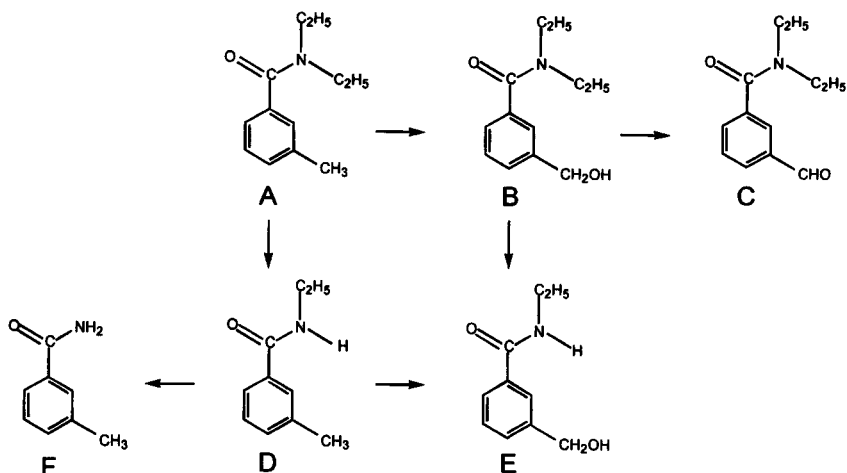


Fig 2. Proposed metabolic pathway for deet in rat liver microsomes. A. *N,N*-diethyl-3-methylbenzamide B. *N,N*-diethyl-3-hydroxymethylbenzamide C. *N,N*-diethyl-3-formylbenzamide D. *N*-ethyl-3-methylbenzamide E. *N*-ethyl-3-hydroxymethylbenzamide F. 3-methylbenzamide.

tabolism also occurs in Wistar rats. Using the gas chromatography-mass spectroscopy (GC-MS) technique, Taylor (1986) identified *N,N*-diethyl-3-hydroxymethylbenzamide and *N*-ethyl-3-methylbenzamide as the major metabolites and *N*-ethyl-3-hydroxymethylbenzamide, 3-methylbenzamide, and *N,N*-diethyl-3-formylbenzamide as the minor metabolites of deet in phenobarbital-induced rat liver microsomes. A similar *in vitro* metabolic profile was obtained by using a high pressure liquid chromatography (HPLC) method with UV detection, and the degradation of deet by the microsomal preparations from males was faster than that by those from females (Yeung and Taylor 1988). Figure 2 shows the *in vitro* metabolic pathway of deet (Taylor 1986, Yeung and Taylor 1988). These *in vitro* results were consistent with the *in vivo* observations for rats. It is very likely that, under *in vivo* conditions, *N,N*-diethyl-3-formylbenzamide and *N*-ethyl-3-hydroxymethylbenzamide are intermediates that are transformed to final metabolites *N,N*-diethyl-3-carboxylbenzamide and *N*-ethyl-3-carboxylbenzamide, respectively, after further oxidation of the hydroxymethyl and the formyl group.

Elimination of deet in humans appears to be fast, and bioaccumulation is thus unlikely. In the pharmacokinetic study of Selim et al. (1995), it was demonstrated that over 99% of the radioactivity absorbed was eliminated in the urine after technical deet or a 15% deet solution in ethanol was dermally applied to human volunteers. Meanwhile, the elimination of deet in the feces was found to be minimal, accounting for less than 0.1% of the dermal dose. The amounts of deet recovered from the tape strippings that were collected after the removal of the remaining portion of the dermal application at 8 h postdose were only 0.07% and 0.08% of the technical deet dose and the ethanol solution dose,

respectively, indicating that deet does not significantly persist in the stratum corneum. In rats, Schoenig et al. (1996) detected only trace levels of radioactivity 7 days after oral or dermal administration of  $^{14}\text{C}$ -labeled deet in the following tissues: brain, heart, lungs, kidneys, muscle, stomach, small and large intestines, cecum, fat, bone, spleen, spinal cord, sciatic nerve, blood, plasma, and carcass. Rapid elimination of deet also occurs in dogs and cattle, as indicated by the pharmacokinetic parameter values. According to Qiu et al. (1997a), the mean values for systemic clearance, mean residence time, and terminal elimination half-life in beagle dogs evaluated after intravenous administration of deet were 2.66 liters/h/kg, 2.34 h, and 2.56 h, respectively. In cattle, the mean values for these pharmacokinetic parameters were 1.89 liters/h/kg, 2.53 h, and 1.44 h, respectively (Taylor et al. 1994).

Due to its unique physicochemical properties, deet has been shown to be an effective skin penetration enhancer for some drug compounds. Windheuser et al. (1982) examined the influence of deet on the skin absorption of hydrocortisone by incorporating 5% deet in hydrocortisone ointments and creams. They observed 167% and 200% increases in hydrocortisone penetration through hairless mouse skin within 24 h for an ointment formulation and a cream formulation, respectively. Higher skin blanching responses were also observed in human volunteers for the deet-containing ointment and cream formulations. In an *in vivo* study using rats, Kondo et al. (1988) achieved increased nifedipine transdermal absorption by formulating the drug in a propylene glycol-deet system. The enhancement effect of the propylene glycol-deet system was found to be comparable to that of Azone, a powerful skin permeation enhancer, although the modes of action were believed to be different. Recently,

Lu et al. (1997) investigated the possibility of using transdermal drug delivery techniques to target methotrexate to joints for rheumatoid arthritis treatment. Employing rabbit and rat models, they found that deet, formulated at 4% in a methotrexate gel system, significantly increased disposition of methotrexate in the stratum corneum and enhanced the permeation of methotrexate in the muscle by 2-fold over a 4-h period after dermal application of the gel. The skin penetration enhancement mechanisms of deet are not completely understood. It was suggested that deet enhanced the skin permeation of nifedipine partly due to its solubilizing effects (Kondo et al. 1988).

### FORMULATION

For effective use, deet has been employed in various formulations, such as pump spray, aerosol spray, lotion, stick, gel, soap, and impregnated towelette for consumer use (Anonymous 1980). Insect repellent jackets, hoods, and netting of deet have also been developed and tested in fields against mosquitoes, biting midges, ticks and other insects (Grothaus et al. 1976a, 1976b; Lindsay and Mcandless 1978; Zaugg 1978; Schreck et al. 1979, 1986; Harlan et al. 1983; Mount and Snoddy 1983; Schreck and Kline 1983; Ralph et al. 1990).

Topical deet formulations are classified as over-the-counter (OTC) products and were sold on the market under at least 56 trade names in the United States between 1985 and 1989 (Veltri et al. 1994). Similar to many of the dermatological products, the design of deet formulations has been focused primarily on aesthetic qualities such as feel, physical properties, and convenience of application. To achieve extended repellency, deet is usually formulated at high concentrations, even up to 100% in some commercial products (Sadik 1990). In the United States, two of the insect repellent formulations registered for military use contain 75% deet in ethanol and 33.3% deet in a lotion base, respectively (Gupta and Rutledge 1991). A deet lotion used by National Park employees (Insect Repellent, Type IIA, Federal Specification O-1-503D) contains 71% deet (Smallwood et al. 1992). Currently, the Singapore Armed Forces uses a 75% deet insect repellent formulation for personal protection during field operations (Fai and Lee 1996).

Studies have been conducted to evaluate the relationships between dose and persistence and between effectiveness and persistence for deet (Buescher et al. 1983, Rutledge et al. 1985). In general, formulations containing higher concentrations of the active repellent provide more effective and longer-lasting protection, but the aesthetic qualities of the formulation tend to determine the amount and frequency of use of various products (Gupta and Rutledge 1994). There has been debate as to whether formulating insect repellent products with high deet concentrations would be safe and offer

added benefits in terms of protection time. According to the Department of Environmental Conservation of the State of New York, there was no clear incremental benefit with deet concentrations over 30% (Anonymous 1994).

In spite of the fact that deet is the best broad-spectrum insect repellent currently available, its short protection time has been recognized for many years as a deficiency (Gupta and Rutledge 1989). Recently, deet has been encapsulated in hydrogel emulsions, lipospheres, microcapsules, and microparticles for continuous long-term protection by using sustained-release technology and new polymers (Gupta and Rutledge 1989, Domb et al. 1995, Rutledge et al. 1996, Qiu et al. 1997b). Qiu et al. (1997b) developed a hydrogel emulsion system based on polyethylene glycol 400 and polyacrylic acid polymers Carbopol 940 and Pemulen TR-2. The system exhibited 23% reduction in deet transdermal bioavailability in beagle dogs in comparison with a major brand commercial deet cream of the same deet content; it also demonstrated better protection against fasted *Ae. aegypti* mosquitoes in laboratory testing for a period of 6 h. The formulation approach adopted was to decrease the deet skin/formulation partition and regulate the release of deet molecules into the hydrogel from deet droplets. In a laboratory repellency test using rabbits and *Ae. aegypti* and *An. albimanus* mosquitoes, a polymer formulation containing a high-molecular-weight fatty acid and several microcapsule formulations containing lanolin, gum arabic, gelatin, tannic acid, stearic acid, and propylene glycol offered more effective protection than unformulated deet at same strength (Rutledge et al. 1996). Domb et al. (1995) reported the encapsulation of deet in a liposphere system to reduce deet transdermal absorption and increase the protection time. A liposphere formulation consisting of solid hydrophobic triglycerides and 20% deet was shown to provide 6-h protection against aggressive *Ae. aegypti* and *Anopheles stephensi* mosquitoes. One of such liposphere formulations containing 10% deet was reported to reduce the deet transdermal bioavailability by 29% in rabbits compared to an ethanol solution of 10% deet. The liposphere system was also successfully used in the formulation of antibiotics and anti-inflammatory agents for sustained delivery (Domb 1993a, 1993b). The use of a commercial polymer that contains copolymers of hydro-vinyl chloride-acetate and sebacic acid, modified maleic resin ester, and glycolate plasticizers in a deet-containing formulation was reported to enhance resistance to abrasion and wash-off but decrease cosmetic acceptability (Khan et al. 1977).

To better prevent military personnel from contracting vector-borne diseases in combat fields and maintain effective fighting strength, a number of special deet formulations have been developed. In a repellency study, a polymer cream formulation (Controlled-Release Personal Use Arthropod Re-

pellent Formulation, 33% deet) developed by the Consumer Specialties Division of 3M Company (St. Paul, MN) and a microparticulate formulation (Sustained Action Arthropod Repellent, 41.8% deet) developed by Biotek Corporation (Woburn, MA) were tested against various species of mosquitos under 3 climatic regimens in comparison with a standard military repellent containing 75% deet (Gupta and Rutledge 1991). The results indicated that the polymer cream formulation developed by 3M Corporation provided superior overall protection against the species, although it had the lowest deet content (Gupta and Rutledge 1991). *N,N*-diethyl-3-methylbenzamide was formulated with permethrin in soap formulation to provide added efficacy for effective malaria control. In a field test carried out on the Pacific coasts of Ecuador and Peru, where malaria was endemic and the transmission was seasonal, subjects protected with a repellent soap containing 20% deet and 0.5% permethrin were bitten 94.2% less than unprotected control subjects by *An. albimanus*, *An. punctimacula* or *An. pseudopunctipennis* 2 h after application of the soap; the protective efficacy was reduced to 81% after 6 h. The efficacy of the soap was shown to be greatly reduced by physical activity and sweating of the subjects (Kroeger et al. 1997). Other studies on the formulation of deet and efficacy evaluations of deet formulations have been reported (Mehr et al. 1985; Schreck et al. 1986; Frances 1987; Rutledge et al. 1989; Schreck and Kline 1989; Annis 1990, 1991; Harbach et al. 1990; Ralph et al. 1990; Mani et al. 1991; Robert et al. 1992; Solberg et al. 1995; Alexander et al. 1996).

The addition of fixatives to perfume formulations prolongs the duration of the fragrance. Efforts have been made to prepare long-lasting deet repellent formulations by using this technique. Khan et al. (1975a) showed that, at a dermal dose of 0.16 mg deet/cm<sup>2</sup>, the coapplication of the synthetic fixative Tibetene® (2,6-dinitro-3,4,5-triethyl-t-butyl-benzene) with deet at a dose ratio of 1:1 increased the protection time against *Ae. aegypti* by 29%, and the increases in protection time rose to 47% and 88% when the dose ratio was raised to 2:1 and 3:1, respectively. Similar trends were observed when the dermal dose of deet was doubled. Other synthetic fixatives such as musk ambrette (2,4-dinitro-3-methyl-6-t-butyl anisole), givambrol (2,4-di-butyl-4-methoxybenzaldehyde), and musk xylol (5-t-butyl-2,4,6-trinitro-m-xylene) also exhibited certain synergistic effects on deet protection time (Khan et al. 1975a). According to Khan et al. (1975b), the addition of vanillin to dermally applied deet (0.16 mg/cm<sup>2</sup>) at dose ratios of 1:1, 2:1, and 3:1 increased the protection time by 95%, 142%, and 179%, respectively, using *Ae. aegypti* as the test insect. The modes of action of these additives were not completely understood. It was suggested that the incorporation of the additives could have lowered the vapor pressure of deet and, thus, the evaporation

rate (Khan et al. 1975a, 1975b). Influences of additives on deet evaporation have been observed in *in vitro* deet evaporation and skin penetration studies using pig skin. At dose of 0.32 mg/cm<sup>2</sup>, the addition of insect repellent dimethyl phthalate to a deet formulation at dose ratio of 1:1 was reported to significantly slow down the evaporation and skin penetration of deet, at least during the first 15 h of deet formulation-skin contact (Reifenrath et al. 1989).

In actual use conditions, there are two elimination pathways for deet in a dermally applied repellent formulation—evaporation into the air from the application site and penetration through the skin. Due to its high skin permeability, deet is readily absorbed into the human body upon dermal application (Feldmann and Maibach 1970, Dremova et al. 1971, Smallwood et al. 1992). The dermal absorption constitutes a major route of loss of deet from the skin, which not only undermines the protection time a deet product can provide, but also imposes potential risks of deet-related systemic and local side effects on the users. As previously discussed, more sophisticated deet formulations that are safer and more pleasant to use while being capable of providing extended protection can be developed through the following approaches: 1) regulating deet evaporation by controlling the release of deet and/or lowering the vapor pressure of deet in the formulation; 2) preventing or reducing deet transdermal absorption *via* minimizing the deet skin/formulation partition; and 3) enabling the formulations to be more resistant to loss due to wiping off and sweating.

## SAFETY

*N,N*-diethyl-3-methylbenzamide has been generally regarded as safe for dermal use, as evidenced by over 4 decades of human experience. However, incidences of serious adverse effects associated with the use of deet products have become higher in the past few years, especially in infants and young children (Osimitz and Grothaus 1995). According to an analysis on the calls to the Poison Control Centers relating to exposure to deet during 1985–89, the number of calls per million packages of deet products sold annually increased by 103% from 35.8 in 1985 to 72.8 in 1989 (Veltri et al. 1994). Recently, the safety concerns over deet have escalated, because deet was suspected to have contributed to the so-called “Gulf War Syndrome,” a condition characterized by multiple symptoms, including chronic fatigue, rashes, headaches, weight loss, and joint pain, experienced by some Gulf War veterans who used the insect repellent deet and the anti-nerve-gas agent pyridostigmine bromide simultaneously while wearing uniforms impregnated with the insecticide permethrin (Anonymous 1995).

As shown in Table 3, severe systemic adverse effects associated with skin exposure to deet re-



Table 3. Cases of severe systemic adverse effects associated with skin exposure to deet.

Effect	No. of Patients	Age (sex)	deet level (%)	Use pattern	Symptoms	Reference
Death	1	17 months (female)	20	Frequent for 3 wk	Acute encephalopathy	Pronczuk et al. (1983)
Death	1	6 years (female)	15	Heavy	Abdominal pain, vomiting, headache, lethargy, ataxia and general convulsions	Heick et al. (1983)
Death	1	6 years (female)	10	Heavy	Headaches, agitation, athetosis, disorientation, involuntary movements, and convulsions	Zadikoff (1979)
Encephalopathy	1	5 years (female)	95	2 applications, all over	Convulsion	Lipscomb et al. (1992)
Encephalopathy	1	8 years (male)	Unspecified	Sprayed on carpet	Convulsion	Osimitz and Grothaus (1995)
Encephalopathy	5	3-7 and 29 years (male)	Unspecified	Unspecified	Seizures, one developed urticaria	Oransky et al. (1989)
Encephalopathy	1	18.5 months (female)	20	Frequent	Tremors, progressive ataxia and weakness, bizarre movements	Edwards and Johnson (1987)
Encephalopathy	1	8 years (female)	100	Heavy	Seizures, convulsions, erythematous and pruritic rash, unusual restlessness	Roland et al. (1987)
Encephalopathy	1	3.5 years (female)	15	Heavy	Convulsions, incoherent speech, stiff arms and legs	Gryboski et al. (1961)
Acute manic psychosis	1	30 years (male)	Unspecified	Daily for 2 wk, heated under light-bulb for 1 to 1.5 h	Psychomotor hyperactivity, rapid and pressured speech, tangentiality, flight of ideas, and grandiose delusions	Snyder et al. (1986)
Cardiovascular toxicity	1	61 years (female)	Unspecified	Used sun-screen and then deet spray	Lightheadedness, nausea, vomiting, explosive diarrhea, hypotension	Clem et al. (1993)
Anaphylaxis	1	42 years (female)	52	Touched a man who had just been sprayed with deet	Generalized angioedema, nausea, loss of consciousness, and hypotension	Miller (1982)
Reproductive toxicity	1	4 years (male)	Unspecified	Mother used deet with chloroquine daily during pregnancy	Mental retardation, impaired sensorimotor coordination, craniofacial dysmorphism	Schaefer and Peters (1992)

ported in the literature include death, neurotoxicity, cardiovascular toxicity, acute manic psychosis, and immunologic response such as anaphylaxis. Three deaths associated with the dermal use of deet in

young children have been reported. Pronczuk et al. (1983) reported on a 17-month-old girl who died of acute encephalopathy after receiving frequent skin application of a deet-containing lotion for 3

wk. Heick et al. (1983) reported that a 6-year-old girl used a spray containing 15% deet on at least 10 occasions on extensive area of skin and died 8 days after she was admitted to a hospital. She experienced abdominal pain, vomiting, headache, lethargy, ataxia, and general convulsions during hospitalization. Zadikoff (1979) reported that a 5-year-old girl died 24 days after dermal application of a 10% deet spray daily for 3 months. Her major symptoms were irritability, headaches, agitation, disorientation, athetosis, involuntary movements, and convulsions. At autopsy, the brain showed generalized edema with intensive congestion of the meninges. In addition to the 3 cases of death, there were 6 reports of toxic encephalopathy involving 10 individuals (Gryboski et al. 1961, Roland et al. 1985, Edwards and Johnson 1987, Oransky et al. 1989, Oransky 1991, Lipscomb et al. 1992). Nine out of the 10 patients were children 8 years of age or younger. Four of them used a repellent formulation with a deet concentration of 15% or higher. *N,N*-diethyl-3-methylbenzamide concentrations of the formulations used by the others were not documented, and the dose received by each patient was unclear. Convulsions and seizures were the most common symptoms among these patients.

In the literature, the use of topical deet products has been linked to other cases of systemic adverse effects, such as acute manic psychosis, cardiovascular toxicity, anaphylaxis, and reproductive toxicity, in addition to death and toxic encephalopathy. For the purpose of self-medication, a healthy 30-year-old man applied on himself daily a deet-containing insect repellent formulation followed by a stay of 1 to 2 h in a homemade sauna heated by light bulbs. Two weeks later, he was hospitalized because of his aggressiveness and mental disorientation. He displayed psychomotor hyperactivity, rapid and pressured speech, tangentiality, flight of ideas, and grandiose delusions. However, clinical improvement was complete within 6 days with haloperidol treatment (Snyder et al. 1986). A healthy 61-year-old white woman was reported to work in the yard after she used a sunscreen and a deet-containing spray. She shortly developed hypotension, with her systolic blood pressure dropping to 80 mm Hg, and also experienced nausea, vomiting, and diarrhea. The patient became completely asymptomatic and had a stable blood pressure several hours after she was admitted to a hospital (Clem et al. 1993). According to Miller (1982), a healthy 42-year-old woman with no prior atopic history developed generalized pruritus, which rapidly progressed to generalized angioedema after touching a companion who had just sprayed himself with an insect repellent containing 52% deet. The patient also experienced hypotension, with a systolic blood pressure of 40 mm Hg. She responded to treatment with epinephrine, diphenhydramine, and corticosteroids. In a test to investigate the role of deet in the reactions that she

experienced, pruritus occurred in her forearm 15 min after she was challenged with a small amount of deet. The pruritus progressed to localized urticaria despite immediate washing of her arm. The patient was then required to have subcutaneous epinephrine and intravenous diphenhydramine treatment. The localized urticaria persisted for over an hour without further systemic symptoms. One case of reproductive toxicity has been associated with the chronic use of deet by a pregnant woman. According to Schaefer and Peters (1992), a 4-year-old boy whose mother applied deet daily throughout her pregnancy, in addition to the prophylactic use of chloroquine, suffered from mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphism.

Dermatitis is the major local adverse effect associated with the dermal use of deet-containing insect repellent formulations. Reuveni and Yagupski (1982) reported that 10 male soldiers ranging in age from 18 to 20 years developed acute dermatitis in the antecubital fossae a few hours after using an insect repellent formulation containing 50% deet. The symptoms and clinical findings for these soldiers were those of a burning sensation, erythema, and blisters at the onset, followed by ulceration and scarring in some individuals. Repeat examinations showed that the erythema progressed to hemorrhagic blisters, which spontaneously drained after a couple of days. The authors thus suggested that precautions in the use of this commonly used repellent should be advised. According to Maibach and Johnson (1975), a 35-year-old woman frequently noted red raised lesions after she prophylactically applied a commercial deet product while camping in insect-infested areas. The lesions were cleared after the insect repellent was removed by washing. A study following this case indicated that deet caused immediate-type hypersensitivity. A paper by Lamberg and Mulrennan (1969) reported that a baffling bullous eruption appeared sporadically in the antecubital fossae of several military personnel who used a deet formulation before sleep. The blistering eruptions healed slowly with scarring. In a test to determine the mechanism of the bullous eruptions, 48% of the 77 volunteers who were exposed to deet developed blisters or eruptions in the antecubital fossae but not in the upper forearm. The explanation for this phenomenon was that the antecubital fossa area was more likely to be occluded and became macerated (Lamberg and Mulrennan 1969). According to Ambrose et al. (1959), no irritation was observed on the arms of 5 human volunteers participating in a deet cutaneous toxicity test during which they were challenged with an isopropanol solution of 50% deet on the arms and face for 5 consecutive days. However, all of the volunteers experienced a slight tingling sensation and a feeling of dryness and astringency. They all felt dry and astringent on the face, and were observed to have desquamation around the nose. Recently, a case re-

port revealed that a 4-year-old boy developed generalized urticaria shortly after a deet-containing insect repellent was applied topically on his legs and forearms to prevent mosquito bites (Wantke et al. 1996).

Ocular exposure to or ingestion or inhalation of deet can cause certain adverse effects. Veltri et al. (1994) summarized 9,086 human exposures to deet-containing repellent products that were reported to the Poison Control Centers from 1985 to 1989; 32% of them were related to ocular symptoms such as corneal abrasion due to accidental spraying of deet products into the eyes. Of these patients, 74.8% were followed up long enough to determine a definitive outcome. In these cases, 98% experienced either no effect or had symptoms that were transient, resolved rapidly, and usually involved the skin or mucous membranes. Generally, persons who had a deet product in their eyes or who had inhaled a deet product were most likely to have a minor effect, while patients who ingested the products were least likely to have any effect. Nevertheless, severe toxic effects can occur when a significant amount of deet is ingested. A 33-year-old man, who was reported to purposely drink 8 ounces of an insect repellent with unknown deet concentration, developed cerebral edema and died in a hospital 9 days after the ingestion (Veltri et al. 1994). In addition, 5 cases of oral ingestion of deet were reported by Tenenbein (1987). All of the patients were believed to have ingested large amounts of concentrate deet products (47.5–95%). Their common symptoms and signs were coma, seizures, and hypotension occurring within 1 h of ingestion. Two of them died, and the 3 survivors experienced no sequelae.

The toxicity of deet, as well as its insect repellency and other properties, has been vigorously assessed in animal subjects. The critical review on deet toxicity and biodistribution by Robbins and Cherniack (1986) and the extensive bibliography of deet by Rutledge et al. (1978) analyzed the literature on the topic up to the dates of their respective publications. In recent years, additional studies have been conducted to evaluate the teratologic and developmental toxicity, neurotoxicity, and cardiovascular toxicity to address increased concerns over the safety of the insect repellent. According to Schoenig et al. (1994), in female rats (in groups of 25) that were treated with 125, 250, and 750 mg/kg/day undiluted deet by gavage on gestational days between 6–15, maternal toxicity occurred only at the 750 mg/kg/day dose; clinical signs included two deaths, depressed body weight and food consumption, and reduced fetal body weight. In female rabbits in groups of 16 that were orally treated with undiluted deet at 30, 100, and 325 mg/kg/day on gestational days 6–18, maternal toxicity in terms of depressed body weight and food consumption was observed, but only at the high dose level of 325 mg/kg/day. These observations were consistent

with the findings of Angerhofer and Weeks (1981) and Wright et al. (1992) which showed deet to be nonteratogenic in rabbits and rats following dermal or subcutaneous administration, respectively, but contradicted results of an earlier study in which the rats were dermally treated with a dose of 1,000 mg/kg/day (Gleiberman et al. 1975). Since the toxic effects were not observed by Angerhofer and Weeks (1981), who treated the rats with deet at a dermal dose as high as 5,000 mg/kg/day, it was concluded that deet was not a developmental toxicant in rats and rabbits (Schoenig et al. 1994).

No severe neurotoxicity was observed in rats treated with acute or chronic dose regimens of deet (Schoenig et al. 1993). In rats that were evaluated for deet neurotoxicity following acute oral administration of undiluted deet at 50, 200, and 500 mg/kg, the treatment-related effects were increased in thermal response time, but the decreased rearing activity was noted for the highest dose only. In a multigeneration plus chronic dietary administration study, rats were administered deet at 500, 2,000, and 5,000 ppm continuously over 2 generations and chronically for 9 months, and the only possible treatment-related effect was a slight increase in exploratory locomotor activity at the 5,000-ppm dose. However, deet caused neurotoxicity when it was coadministered with other compounds in hens (Abou-Donia and Wilmarth 1996). In a study attempting to explore the cause of the so-called "Gulf War Syndrome," Abou-Donia and Wilmarth (1996) treated hens with deet (500 mg/kg/day), the anti-nerve-gas agent pyridostigmine bromide (5 mg/kg/day), and the insecticide permethrin (500 mg/kg/day) individually and in combination 5 days/wk for 2 months. It was found that deet alone caused only minimal neurotoxicity in the animals, while coadministration of deet with one of the other compounds produced greater neurotoxicity, and concurrent dosing of deet with the other 2 agents further enhanced the neurotoxicity. It was hypothesized that competition for liver and plasma esterases by the 3 compounds led to their decreased breakdown and increased transport of the parent compounds to the nervous system. A similar neurotoxicity study conducted by Abou-Donia et al. (1996b) with deet, pyridostigmine bromide, and the insecticide chlorpyrifos demonstrated that coadministration of deet with the other compounds in binary or tertiary fashion significantly enhanced the neurotoxicity, as indicated by increased inhibition of brain acetylcholinesterase (AChE) and inhibition of brain neurotoxicity target esterase (NTE). The investigators proposed that the compounds might compete for xenobiotic metabolizing enzymes in the liver and blood and might also compromise the blood-brain barrier, leading to an increase in their "effective concentrations" in the nervous system to levels equivalent to the toxic doses of individual compounds. In a toxicity study in rats (Verschoyle et al. 1992), oral deet at 1–3 g/kg caused ataxia that

was associated with a spongiform myelinopathy, which was largely confined to the cerebellar roof nuclei. These doses also produced a severe and often fatal prostration and clear electrophysiological signs of prolonged suppressed seizure activity. As indicated by LD<sub>50</sub>, deet showed decreasing toxicity with increasing age and was more toxic to female rats than to male rats that were 11–56 days old (Verschoyle et al. 1992). This gender-dependent toxicity is in good agreement with the conclusion of the case analysis that deet seems to be more toxic in female humans, which is likely due to slower metabolism of deet in females (Yeung and Taylor 1988).

*N,N*-diethyl-3-methylbenzamide causes hypotension in rats and dogs (Leach et al. 1988). In anesthetized rats that received 56, 113, and 224 mg/kg deet in 25% ethanol vehicle intraperitoneally, decreases in mean blood pressure and heart rate in a dose-related fashion were observed. Dogs treated with intraperitoneal deet of 224 mg/kg also exhibited similar marked hypotension. It was concluded that the hypotension was due to a reduced cardiac output, because there was no change in peripheral resistance or stroke volume. The finding offers an explanation as to what might have caused the hypotension that developed in 2 patients after they had used or had contact with deet (Miller 1982, Clem et al. 1993).

*N,N*-diethyl-3-methylbenzamide can perturb ammonia metabolism. In an animal study, Heick et al. (1988) observed that blood ammonium levels were significantly higher in rats treated intraperitoneally with deet than in control subjects 3 and 5 h after dosing, which indicates that individuals with genetic or acquired defects in ammonium metabolism such as the female carriers of ornithine carbamoyl transferase deficiency can be at increased risk if they are exposed to deet. This observation confirms the clinical finding of Heick et al. (1983) in a 6-year-old girl who was a heterozygote for ornithine carbamoyl transferase deficiency. The girl was reported to have developed a Reye-like syndrome accompanied by high blood ammonium levels and died of toxic encephalopathy following heavy exposure to deet.

## DISCUSSION

In spite of its occasional adverse effects and relatively short protection time, deet has been the most common all-purpose insect repellent of health, military, and economic significance for the past 4 decades. It is safe if appropriately used, since the incidence of adverse effects is low considering its wide application. However, caution should be exercised to prevent excessive amounts of deet from being absorbed into the body. In actual use conditions, deet products are usually applied all over the skin surface that is prone to insect attacks, which is usually a large area, to achieve the desired pro-

tection. Theoretically, the quantity of deet transdermally absorbed is proportional to the applied skin area.

Human safety data on extensive, repetitive, and long-term use of deet are incomplete. Further studies on the toxicology, biodistribution, and metabolism of deet and its metabolites need to be conducted to obtain a complete deet safety profile. The interaction of deet with common medications and household chemicals and its possible adverse effects need to be further explored. The absorption of deet at different anatomical sites in humans remains to be investigated, as up to a 4-fold difference in deet transdermal bioavailability was observed in monkeys among different sites of the body surface (Moody et al. 1989).

In particular, deet products should be used cautiously for infants, young children, people with hypotension condition, metabolic deficiency, and skin hypersensitivity. For safety reasons, the benefits of formulating high concentrations of deet in topical insect repellent products need to be reevaluated. While searching for new insect repellents with better repellency and safety characteristics, it is worthwhile to invest efforts in developing new deet formulations by using new formulation excipients and techniques to achieve safer and extended personal protection with deet.

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### MID-ATLANTIC MOSQUITO CONTROL ASSOCIATION

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