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SAFETY OF THE INSECT REPELLENT *N, N*-DIETHYL-*M*-TOLUAMIDE (DEET) IN PREGNANCY

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Abstract. The safety of daily application of *N, N*-diethyl-*m*-toluamide (DEET) (1.7 g of DEET/day) in the second and third trimesters of pregnancy was assessed as part of a double-blind, randomized, therapeutic trial of insect repellents for the prevention of malaria in pregnancy (n = 897). No adverse neurologic, gastrointestinal, or dermatologic effects were observed for women who applied a median total dose of 214.2 g of DEET per pregnancy (range = 0−345.1 g). DEET crossed the placenta and was detected in 8% (95% confidence interval = 2.6−18.2) of cord blood samples from a randomly selected subgroup of DEET users (n = 50). No adverse effects on survival, growth, or development at birth, or at one year, were found. This is the first study to document the safety of DEET applied regularly in the second and third trimesters of pregnancy. The results suggest that the risk of DEET accumulating in the fetus is low and that DEET is safe to use in later pregnancy.

INTRODUCTION

Thirty percent of the population in the United States and 25% of the population in the United Kingdom apply an insect repellent containing *N, N*-diethyl-*m*-toluamide (DEET) at least once a year.[1] After 40 years of worldwide use and billions of applications, the safety profile of DEET is remarkable.[2] Some commercial preparations of DEET carry labels warning against prolonged use in pregnancy. However, there have been no reported attempts to evaluate systematically its safety in human pregnancy or in infants, although there is one isolated report of adverse effects following application of DEET in human pregnancy.[3]

Recent studies with radiolabeled DEET with human volunteers show that when normal doses of repellent were applied to the skin, less than 10% of the applied dose was absorbed.[4] All absorbed DEET was then metabolized prior to excretion in the urine within 4 hr of application. A substantial proportion of the safety database developed on DEET consists of toxicologic studies on rodents, with investigators showing the metabolism of DEET in humans to be similar to that in rats.[4] In early studies, when rats were given high doses of DEET by skin application, there was a reported increase in embryo mortality, decreased birthweight, delayed development, and a high postnatal death rate.[5] A high frequency of malformations was reported when DEET was applied in a mineral oil formulation to the chorioallantoic membrane of chick embryos.[6] However, other studies have not reported adverse effects with the use of DEET. No teratogenic effects were reported following exposure of rabbits to repeated topical applications of DEET at levels up to 1,000 mg/kg/day.[7] Similarly, no adverse effects on pregnant rats were observed after treatment with DEET administered intramuscularly at a dose of 30 ml/kg/day on gestational days (gd) 6−15,[8] or when undiluted DEET was administered by gastric lavage to rats (gd 6−15 at 0, 125, 250, and 750 mg/kg/day) or rabbits (gd 6−18 at 0, 30, 100, and 325 mg/kg/day).[9] In these last three studies, no evidence of embryotoxicity, impaired perinatal survival, or any treatment related increase in external, visceral, or skeletal malformations in the offspring was reported. Two other studies found no evidence of bioaccumulation of radioactively labeled DEET in animal fetuses, although limited placental transfer of DEET was noted.[10,11]

The effects of DEET on human pregnancy are of concern on the Thai-Burmese border where there are limited treatment options for malaria in pregnancy because of multidrug resistance in *Plasmodium falciparum*,[12] and the lack of effective preventative measures.[13] A mosquito repellent containing DEET was used in an effort to prevent malaria in pregnancy at this site.[14] This paper reports on the safety of DEET applied daily during the second and third trimesters of pregnancy.

MATERIALS AND METHODS

Study area and population. The study was carried out largely in Maela and Shoklo, camps for the displaced people of the Karen ethnic minority, 60 and 130 km north of the Thai town of Mae Sot. This is a hill-forested area where malarial transmission is low and seasonal. The effects of malaria in pregnancy[15] and the epidemiology of malaria[16] at this site have been described in detail previously. Women usually deliver at home aided by traditional birth attendants.

Ethical approval. The study received approval from the Ethical Review Committee of the Faculty of Tropical Medicine of Mahidol University, the Central Scientific Ethical Committee of Denmark, and the Karen Refugee Committee.

Study procedures. *Treatment groups, antenatal clinics, and infant follow-up.* A total of 897 women who attended the weekly antenatal clinics (ANCs) and were 3−7 months pregnant gave fully informed consent to participate in the study. Subjects were randomly allocated to receive a daily target dose of either DEET and thanaka (1.7 g of DEET/day and 3.2 g of thanaka/day) or thanaka alone (3.2 g of thanaka/day) until delivery. Thanaka, a paste derived from the crushed branches of a tree (*Limonia acidissima*), is a popular local cosmetic, and was used as a carrier for the repellent. Women were instructed to apply the treatment daily after the

evening shower to the exposed areas of the arms and legs. Participants were given a new bottle each week, identifiable only by a study code number. Women were followed for the duration of their pregnancy at the weekly ANC visit where medical and obstetric care were provided. Each week the dermatologic, gastrointestinal, and neurologic effects of repellent were assessed by asking the women if they had experienced skin warming, skin rashes, headache, dizziness, nausea, or vomiting or had any other complaints from the previous week. Daily compliance was self-reported weekly. Women who received repellent formulation for more than 15 weeks and who reported using repellent more than 85% of the time were defined as 'prolonged users'.

Mothers were encouraged to deliver in the unit healthcare facilities and attendance was entirely voluntary. The newborn and placenta were weighed with a Salter® (Salter Weighing Product, Minneapolis, MN) scale (Model 810, accurate to ± 50 g), and the child's head circumference, length, and arm circumference measured using a standard tape measure (accurate to ± 1 mm). Babies born at home were weighed within the first five days of life. All newborns were assessed for gestational age within five days of birth with the Dubowitz examination.[17] Newborns were examined using a modified neurologic test,[18] which primarily assesses tone, movement, behavior, and visual and auditory alertness. Optimality score refers to the scores that 90% of the infants achieved.[19] Infants were followed up monthly until six months old, and every three months until 12 months old for growth (weight, height, arm circumference, head circumference) and basic developmental milestones (age of first sitting, crawling, walking).

Detection of DEET in urine and cord blood. A cohort of prolonged users (30 DEET users and 10 controls) provided a urine sample at 7−8-months gestation. Mid-stream urine specimens were collected at the morning ANC visit and stored at −30°C within 20 min of sampling.

All women who delivered in the unit were asked for a sample of cord blood and 5 ml was collected in a tube containing lithium-heparin from each woman. Blood samples were centrifuged at 2,000 rpm for 5 min and the plasma stored at −30°C within 20 min of sampling. Analysis of cord samples was limited to 50 women in the DEET group.

Chemical analysis. DEET was quantified using high-performance liquid chromatography (HPLC) based on the method described by Qui and Jun.[20] Urine samples were clarified by centrifugation at 10,000 rpm for 10 min. Stored plasma was centrifuged at 14,000 rpm for 5 min and 1 ml of supernatant was added to 4.5 ml of phosphate-buffered saline (PBS). Stock solutions of 1.0 mg/ml of DEET (Sigma Chemical Co., St. Louis, MO) and the reference standard *N, N*-diethyl-*m*-toluidine were prepared in acetonitrile at a concentration of 1 mg/ml and stored at 4°C. To monitor recoveries, all urine and blood plasma samples were spiked with *N, N*-diethyl-*m*-toluidine to give a final concentration of 10 μg/ml prior to processing. The *N, N*-diethyl-*m*-toluidine was then used to monitor recovery of DEET during the analysis.[20]

For sample preparation, solutions were passed through C_{18} Bond-Elut® extraction cartridges using a Vac-Elut™ manifold (Varian; Phenomenex, Anachem, Luton, Bedfordshire, UK.) connected to a water pump. Each extraction cartridge was preconditioned with 3 ml of acetonitrile, followed by 12 ml of double-distilled, deionized, filtered water. A 5 ml sample of urine or blood was then passed through the cartridge, which was then washed with 12 ml of water. In the case of the urine samples, DEET and *N, N*-diethyl-*m*-toluidine were recovered by washing the cartridge with 5 ml of 0.03 M ammonium acetate (pH 4.5):acetonitrile (6:4 v/v). For the plasma samples, 3 ml of 100% methanol was used to recover DEET from the extraction cartridge.

Samples were transferred to autosampler vials, loaded onto a Gilson® (Gilson Medical Electronics, Viliers-le-Bel, France) model 231 autosampler connected to a Gilson HPLC system, and 50 μl was injected onto a C8 reversed-phase column (250 mm × 4.6mm internal diameter, HPLC Technology, Maclesfield, Cheshire, UK). The column was eluted with acetonitrile-ammonium acetate (pH 4.5: 0.03 M; 36:64 v/v) delivered at a flow rate of 1.0 ml/min and the eluent was monitored for UV absorbance at 230 nm. DEET and *N, N*-diethyl-*m*-toluidine were identified by co-chromatography with authentic standards and quantified by calibrating the HPLC using reference standards in the concentration range 0.1 μg/ml to 1 mg/ml of both DEET and *N, N*-diethyl-*m*-toluidine.

Statistical analysis. Normally distributed data (e.g., birthweight) were described by the mean and standard deviation and groups were compared by the Student's *t*-test. Data not conforming to a normal distribution (e.g., gravidity) were described by the median and range and compared between groups by the Mann-Whitney U test. Dichotomous data (e.g., primipara/multipara) were compared using the chi-square test with Yates' correction. One-year survival rates of the infants were examined visually by plotting the Kaplan-Meier survival curves for both groups (i.e. DEET and thanaka versus thanaka alone) and compared using the Mantel-Haenszel log-rank test. All statistical computations were performed by the program SPSS for Windows (SPSS for Windows 8; SPSS, Inc., Chicago, IL).

RESULTS

Study groups. Between April 1995 and September 1996, 897 pregnant women were enrolled in the study, 449 into the DEET and thanaka group and 448 into the thanaka alone group. The characteristics of both groups were similar at enrolment, for delivery outcomes, duration of repellent use, and compliance (Table 1). Although there was no statistical difference in the proportion or type of congenital abnormalities following use of DEET in pregnancy, the abnormalities have been detailed for completeness of toxicologic reporting (Table 2). The median (range) amount of DEET applied per woman during pregnancy was 214.2 (0−345.1) grams in total.

Outcomes for newborns. Of the 897 women recruited to the study, there were 741 (82.6%) singleton live births for whom data were available on birthweight for 703 (94.9%), and data were available on length, head circumference, and arm circumference for 473 (64%). The newborn growth parameters were similar for the DEET and thanaka group versus the thanaka only group. The prolonged DEET users' group and the prolonged thanaka users group

TABLE 1
Baseline data of women on enrollment and birth outcomes by group

	DEET* and thanaka (n = 449)	Thanaka alone (n = 448)
Maternal characteristics		
Age on entry, years	24 [15–44]	24 [15–43]
Entry gestational age, weeks	16 [8–32]	17 [8–32]
Gravidity on entry	3 [1–12]	3 [1–14]
Number of primipara on entry	157 {35}	148 {33}
Birth outcomes		
Livebirths†	368 {82.7}	373 {84.0}
Abortions†	9 {2.0}	6 {1.4}
Stillbirths†	6 {1.3}	6 {1.4}
No outcome available	62 {13.9}	59 {13.3}
Male†	176 {48.6}	216 {59.5}
Birthweight, grams†	2,868 (492.1)	2,853 (487.6)
Estimated gestational age, weeks†	38.8 (1.3)	38.9 (1.3)
Proportion of low birthweight (<2,500 grams)†	52/351 {14.8}	71/352 {20.2}
Proportion premature (<37 weeks)†	25/351 {7.1}	25/352 {7.1}
Repellent usage and compliance		
Duration of repellent use, weeks	18 [0–29]	18 [0–32]
Self-reported compliance >85%	335 {74.6}	325 {72.5}
Self-reported compliance <85%	114 {25.4}	123 {27.5}

* DEET = *N, N*-diethyl-*m*-toluamide. Data given are for median values [range], total number {%}, or mean (SD).
† Twins were excluded from analysis (DEET and thanaka, n = 444; Thanaka alone, n = 445).

also had similar distributions for newborn growth parameters (Table 3).

Of the 741 singleton live births, 640 (86%) had gestational age assessments performed and 371 (58%) of these infants had complete data for all items of the Dubowitz newborn neurologic examination. Neurologic performance was compared for infants whose mothers were in either the DEET and thanaka group (n = 181) or the thanaka alone group (n = 190). The median total optimality score (possible range = 0−25) of the 25 neurologic items assessed were compared for the groups and no significant difference was found: DEET and thanaka 18.5 (range = 8−23) and thanaka alone 19 (range = 5−22.5); $P = 0.164$.

Outcomes for infants. Of the liveborn singletons, 81% (597 of 741) were followed in the first year of life. Comparison of outcomes for children whose mothers used DEET and thanaka or thanaka alone were not significantly different for developmental delay (2.3% [5 of 218] versus 1% [3 of 298]; $P = 0.72$), death (4.7% [14 of 299] versus 5.7% [17 of 298]; $P = 0.71$), or lost to follow-up (12.0% [36 of 299] versus 13.1% [39 of 298]; $P = 0.89$), respectively. The cumulative one-year survival rates for the groups DEET and thanaka (95.2%, 95% confidence interval [CI] = 92.7−97.7%) and thanaka alone (94.0%, 95% CI = 91.3−96.7%), were similar ($P = 0.57$).

There were no differences in the overall growth parameters of the children at one year of age between DEET and thanaka and thanaka only users: mean (SD) weight = 7,983 (775) versus 7,984 (919) grams; $P = 0.99$; mean (SD) height = 69.9 (2.6) versus 70.1 (2.9) cm; $P = 0.40$; mean (SD) head circumference = 43.9 (1.4) versus 43.9 (1.4) cm; $P = 0.97$; and mean (SD) arm circumference = 13.6 (1.0) versus 13.5 (1.1) cm; $P = 0.42$, respectively.

DEET in urine. Of the 30 urine samples provided by the mothers, none were found to have DEET levels above the limit of detection (0.1 μg/ml). Although most of percutaneously applied DEET is known to be rapidly metabolized and the polar derivatives excreted in the urine, traces of unmetabolized DEET can be detected in the urine up to 22 hr post-exposure at levels well above our limit of detection.[21]

TABLE 2
Details of congenital abnormalities, maternal age (years), gravidity, and weeks of exposure for each group

	DEET* and thanaka (n = 6)	Thanaka alone (n = 6)
1	Hydrocephalic, IUFD*	Anencephalic
	21 years, G3*, 2 weeks	20 years, G3, 18 weeks
2	Microcephalic, grossly asymmetric eyes, microphthalmia, IUFD*	Microcephalic, abnormal face
	40 years, G14, 14 weeks	42 years, G12, 16 weeks
3	Cleft palate	Anencephalic
	22 years, G2, 8 weeks	20 years, G1, 19 weeks
4	Multiple joint torsions	Bilateral club foot with tibial involvement
	25 years, G3, 14 weeks	29 years, G7, 20 weeks
5	Talipes right foot—mild	Imperforate anus
	21 years, G1, 10 weeks	39 years, G4, 20 weeks
6	Down's syndrome	Microcephalic, hirsute, micrognathia
	30 years, G3, 21 weeks	28 years, G3, 16 weeks

* DEET = *N, N*-diethyl-*m*-toluamide; IUFD = intrauterine fetal death; G = gravidity.

TABLE 3
Newborn growth parameters for singleton live births

Growth parameters	Prolonged† DEET* users	Prolonged† Thanaka users	All DEET* users	thanaka alone
Birthweight, grams	2,946 (459)	2,935 (462)	2,868 (492.1)	2,853 (487.6)
Height, cm	48.8 (2.2)	48.7 (2.2)	48.0 (3.2)	48.5 (2.4)
Head circumference, cm	32.9 (1.4)	32.7 (2.7)	32.7 (2.8)	32.8 (1.5)
Arm circumference, cm	10.1 (0.8)	10.3 (0.9)	10.1 (1.1)	10.0 (0.9)

* DEET = *N, N*-diethyl-*m*-toluamide. Values are the mean (sd).
† Prolonged repellent user defined as more than 85% compliant and applied repellent daily for more than 15 weeks.

We can therefore conclude that the levels of DEET administered were well within the capacity of the subjects to metabolize and clear the repellent from their bodies.

DEET in cord blood. A total of 391 cord samples were collected during the study and 192 were from women in the DEET group. The efficiency of the analytical method was confirmed by monitoring recoveries of the internal standard, with mean recoveries of 93% being determined for serum samples. No DEET was detected in 46 of the 50 samples of subjects exposed to DEET. In four subjects UV absorbing metabolites co-chromatographing with DEET were observed. One sample contained 2.44 μg/ml of DEET, with three samples containing 1.0 μg/ml.

The mothers with detectable cord blood results applied a total DEET dose of 190.4, 204.0, 246.5, and 249.9 grams of DEET during the 16.0, 17.1, 20.7, and 21 weeks, respectively, that they were in the study. Their infants were all born at term and had normal physical and neurologic outcomes. These four births took place after 4:00 AM, more than 10 hr after the last application of DEET. One of the mothers who had trace amounts (1 μg/ml) in cord blood received topical treatment during the pregnancy for a fungal (tinea corporis) infection involving her arms and legs. The infection improved, but was still present at the time of delivery.

Skin, gastrointestinal, and neurologic side effects in pregnant women. Skin warming was reported more often for DEET and thanaka users (80%, 359 of 449), than for thanaka only users (57.6%, 258 of 448; $P < 0.001$). The frequency of weekly reporting of headache, dizziness, nausea, and vomiting did not differ between groups (Table 4). Regular usage of DEET and thanaka was associated with a reduced risk of scabies compared with the thanaka alone group (11.6% [52 of 449] compared with 16.7% [75 of 448], relative risk = 0.70, 95% CI = 0.5−0.97; $P = 0.034$), but not of fungal skin infections.

DISCUSSION

The use of 20% DEET solution in the second and third trimesters of human pregnancy appears safe. Apart from the sensation of skin warming with application of DEET, no significant adverse effects for the mother or the fetus following daily use of DEET could be detected. Survival, growth, and neurologic development in infants followed from birth up to one year of age did not differ from infants whose mother received thanaka alone.

Confirming results of earlier studies in animals[10,11] DEET was capable of crossing the placenta. One woman, representing 2% (95% CI = 0.1−9.5) of the DEET users, had a measurable level of DEET (2.44 μg/ml) in the cord blood. When the other three cases of cord blood containing the lower levels of DEET are included, the presence of the repellent in blood samples remains low (8%, 95% CI = 2.6−18.2). Since one of the four women who had a positive cord blood DEET result had a disrupted skin integument due to a fungal infection, caution may be required with the use of DEET in such cases.

Supporting the low incidence of systemic transfer of DEET to the fetus, the absence of unchanged DEET in the urine of treated subjects demonstrated that repeated applications of repellent did not lead to a damaging accumulation of DEET in the bodies of treated subjects during pregnancy. Earlier studies with human volunteers demonstrated that dermally applied DEET (between 0.14 g and 1.86 g per subject) resulted in excretion of unchanged DEET in the urine up to 22 hr after exposure, with the dose exceeding the body's ability to completely metabolize the compound.[21] In part, the absence of detectable DEET in the urine may result from reduced absorption of the repellent due to venous distension which increases approximately 150% during gestation, causing reduced blood flow.[22] In addition, metabolism in the liver

TABLE 4
Dermatologic, gastrointestinal, and neurologic effects in women

Signs and symptoms	DEET* and thanaka: No. of women (% affected)	Thanaka alone: No. of women (% affected)	Crude relative risk (95% CI)	*P*
Skin warmth	359 (80.0)	258 (57.6)	1.39 (1.27–1.52)	**<0.001**
Fungal infection	30 (6.7)	40 (8.9)	0.75 (0.47–1.18)	0.258
Insect bites	5 (1.1)	14 (3.1)	0.36 (0.47–1.01)	0.063
Scabies	52 (11.6)	75 (16.7)	0.69 (0.50–0.96)	**0.034**
Headache	338 (75.3)	347 (77.5)	0.97 (0.90–1.05)	0.491
Dizziness	329 (73.3)	312 (69.6)	1.05 (0.97–1.14)	0.258
Nausea	190 (42.3)	214 (47.8)	0.89 (0.77–1.02)	0.116
Vomiting	91 (20.3)	113 (25.2)	0.80 (0.63–1.02)	0.091
Sleep disturbance	226 (50.3)	200 (44.6)	1.13 (0.98–1.29)	0.101

* DEET = *N, N*-diethyl-*m*-toluamide. *P* values in bold are significant at the 5% level.

and blood flow to the kidney increase in pregnancy, so the potential for DEET accumulation in the fetus should be reduced if the woman has normal skin integument and liver and kidney function.

Interestingly thanaka (*L. acidissima*) is reported to have antiseptic, antifungal, and antiarthropodal activity.[23–25] However, thanaka reduced scabies infections significantly only in the presence of DEET compared with thanaka alone. We were unable to find any other reports on the acaricidal effect of DEET in the literature.

This study suggests that DEET is safe in the second and third trimesters of pregnancy. With no evident adverse effects in 449 DEET-exposed pregnancies, the upper 95% CI for the incidence of adverse effect is one in 150. The potential for adverse effects on the fetus, particularly in women with disrupted skin integument and potentially in those with abnormal liver and kidney function, therefore remains a minor possibility. With the current large-scale, worldwide distribution of DEET, it is now important to define its safety in pregnancy. In this study, we did not attempt to look at the effects of DEET during the first trimester of pregnancy, a period when the development of the fetus is vulnerable and when many women do not realize they are pregnant.[26] Thus, more work is needed to define the safety of DEET in early pregnancy.

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