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REVIEW OF THE BIODISTRIBUTION AND TOXICITY OF THE INSECT REPELLENT *N,N*-DIETHYL-*m*-TOLUAMIDE (DEET)

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A review of the biodistribution and toxicity of the insect repellent N,N-diethyl-m-toluamide (DEET) is presented. Workers using repellent containing this compound may be exposed to greater than 442 g in 6 mo. In human studies, variable penetration into the skin of from 9 to 56% of a topically applied dose and absorption into the circulatory system of approximately 17% have been reported. Excretion of DEET by humans was initially rapid but not as complete as in animal models. Only about one-half of the absorbed DEET was excreted by humans over 5 d. Depot storage of DEET in the skin was also documented. Skin irritant effects, including scarring bullous dermatitis in humans, were reported. One animal study that reported embryotoxicity could not be confirmed by other investigators. The limited testing for mutagenicity and carcinogenicity provided negative results. Neurotoxic effects were observed in workers exposed to 4 g or more per week. Six young girls developed encephalopathies after exposure to unspecified amounts of DEET ranging from small to massive doses. Three of these girls later died. The cause of their death has not been resolved. Because of the lack of information, further research into the absorption, carcinogenicity, and neurotoxic effects is needed.

INTRODUCTION

N,N-Diethyl-*m*-toluamide, $C_6H_4CH_3CON(C_2H_5)_2$, is a clear liquid that is generally regarded as the most effective topical insect repellent in common worldwide use. It is known by the Entomological Society of America as DEET and by other researchers as *m*-DET. DEET is the most popular insect repellent in the United States. In the documentation supporting the 1980 EPA Pesticide Registration Standard, it was estimated that 38% of the American public uses insect repellents and that 22% of the general population is exposed to pressurized liquid products that contain 15–20% DEET as their active ingredient (U.S. Environmental Protection Agency, 1980). DEET was formulated for use as an insect repellent in 1953 (McCabe et al., 1954) and initially marketed in 1956 (Carlson, 1984). DEET is usually supplied in an ethyl alcohol or isopropyl alcohol base; the amount of DEET in commercial products

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ranges from about 11 to 95%. End-use products are formulated as solutions, lotions, gels, aerosol sprays, sticks, and impregnated towelettes (U.S. Environmental Protection Agency, 1980). There are at least five products on the market that claim to have a composition of 100% DEET. Because technical DEET, from which these products are formulated, must contain only greater than 95% *m*-DET, it is likely that none of those products contain 100% *m*-DET. The ortho (*o*-DET) and para (*p*-DET) isomers and moisture are the usual contaminants of technical-grade DEET.

DEET is a very effective commercial insect repellent, equalling and sometimes surpassing such products as Indalone, dimethyl phthalate, and ethylhexanediol in tests for efficacy and duration of action (Carlson, 1984; Buescher et al., 1982; Gilbert et al., 1955; Gilbert, 1966). DEET operates effectively against a range of insects, including the yellow-fever mosquito (*Aedes aegypti*), the malaria mosquito (*Anopheles quadrimaculatus*), the salt-marsh mosquito (*Aedes taeniorhynchus*), the tick, the sandfly, and the deerfly (Carlson, 1984; Gilbert et al., 1955; Gilbert, 1966). The para and ortho isomers of *N,N*-diethyltoluamide are generally similar to *m*-DET in effectiveness (McCabe et al., 1954), but *o*-DET is somewhat more toxic and *p*-DET slightly less toxic than *m*-DET (Ambrose and Yost, 1965).

DEET is partially absorbed through the skin of humans; it has been proposed as a pharmaceutical excipient to improve dermal and transdermal delivery of drugs (Windheuser et al., 1982). There have been a few cases of adverse systemic effects associated with the use of DEET, including encephalopathies, three deaths (Gryboski et al., 1961; Zadikoff, 1979; Pronczuk de Garbino and Laborde, 1983; Heick et al., 1980; Roland et al., 1985; McConnell et al., 1985; Miller, 1982), and some reports of adverse skin reaction (Lamberg and Mulrennan, 1969; Reuveni and Yagupsky, 1982; Rabinovich, 1966; Maibach and Johnson, 1975).

A bibliography of DEET, which contains mostly references on its effectiveness, was published by Rutledge et al. (1978). Its approximately 350 listings include references to the chemistry and toxicity of DEET that were published up to that date.

Despite its long history of use as a repellent, the toxicological characterization of DEET remains incomplete. In the 1980 EPA Pesticide Registration Standard documentation, it was concluded that there had never been an adequate animal study for oncogenicity or an adequate study on chronic toxicity from dermal exposure (U.S. Environmental Protection Agency, 1980). The absence of these toxicological assessments and the recent reports of encephalopathies in workers exposed to DEET (McConnell et al., 1985) necessitated the following critical review of the biodistribution and toxicity of DEET.

Efficacy

In concentrations of over 10%, DEET has remained effective for 3–14 h per dose against *Aedes aegypti* in controlled settings on human volunteers (U.S. Environmental Protection Agency, 1980). The minimum effective dosage reported by Maibach et al. (1974b) was 16 $\mu g/cm^2$. There is considerable individual variation in duration of effectiveness, which is thought to be related to total skin lipid content and the concentration of certain fatty acids in the skin lipids (Skinner et al., 1977). Efficacy can also be influenced by environmental conditions, which may be significantly different from those in a controlled laboratory setting. Under conditions of actual use, the rate of loss of an insect repellent by evaporation and removal from the skin surface is more important than the natural attractiveness of the host in determining the efficacy of the repellent (Smith et al., 1963; Smith, 1966). Evaporation from the skin of volunteers at an applied dose of 25 $\mu g/cm^2$ averaged 9.6% during the first hour after application (Spencer et al., 1979). Abrasion of the skin by contact with clothing or other objects is the principal mode of loss (Smith et al., 1963). In a controlled environment, airflow velocity of 192 m/min reduced the protection time by 66% compared to the time at normal air-exchange rates (Kahn et al., 1973; Maibach et al., 1974a). Increased volatility in a hot environment and sweating reduced the duration of efficacy (Maibach et al., 1974b). Penetration of the skin by the repellent also influences the rate of loss and, thus, the duration of repellency (Smith et al., 1963). DEET has a higher degree of persistence (resistance to loss) than other commercially available repellents (Gilbert, 1966; Smith et al., 1963). Thus, the applied dosage is depleted to the minimum effective dosage at a slower rate than other repellents (Smith et al., 1963).

In field tests, formulations containing approximately 95% DEET have afforded protection times against mosquitoes for up to 20 h (U.S. Environmental Protection Agency, 1980). This extended protection time may have resulted from application of the higher-concentration product under identical application conditions (i.e., time of spraying, amount of spray contacting the skin, and area of skin covered).

Estimated Exposures

There is limited and insufficient information for estimating exposures from conventional consumer use practices. Also, there are only a few reported estimates of exposure to occupational groups. Estimates of exposure over 6 mo extrapolated from these limited data are compared in Table 1.

The suppliers that reported patterns of DEET usage to EPA based their predictions on limited mid-range data points (U.S. Environmental

TABLE 1. Estimated Exposure to DEET During a 6-Month Mosquito Season

Group	Concentration (%)	Estimated exposure to active ingredient reported	Exposure quantity[a] (g)	Reference
Upper 1% of	15	>1.65 g/d	>214	U.S. Environmental Protection Agency (1980)
general population[b]	75	>8.25 g/d	>1071	
Military personnel	75	43 g/season[c]	43	
Everglades biologist[d]	28.7	4.25 g/d	442	
Upper 5% of Everglades Park Service employees surveyed	15–75	>2 kg/7 mo	>1710	McConnell et al. (1985)

[a] Exposure quantity is estimated in this paper and is active ingredient applied to all exposed skin during May to October.
[b] Estimated from a survey of only 71 employees of one company.
[c] Annual exposure based on the U.S. Army's estimated usage of 1 ml of a 75% formulation, 60 times/yr.
[d] Exposure based on 4 d use per week.

Protection Agency, 1980). Thus, there may be considerable error associated with some of the estimates. In a NIOSH Health Hazard Evaluation, it was estimated that 5% of Everglades National Park Service employee users of DEET, surveyed in August 1984, were exposed to 2 kg or more of active ingredient in the 7-mo (April through October) mosquito season (McConnell et al., 1985). This estimate was derived by multiplying the reported usage of 6-oz aerosol cans by the percentage of DEET content and factor of 0.33, for the estimated fraction of the aerosol that reached the skin. This estimate is probably high since the usage data were gathered in August when the mosquito population and usage of repellents are the highest. The estimate of exposure for military personnel may be low due to the limited number of applications (only 60 per season) (U.S. Environmental Protection Agency, 1980).

A reported quantification of high-dose usage came from a research biologist working in the Everglades, who used 2 1-oz bottles of 28.7% DEET in a 4-d week (U.S. Environmental Protection Agency, 1980). From this information, EPA estimated that the exposure was 4.25 g DEET/d. Nevertheless, occupational exposures to DEET may well exceed that estimated for the Everglades biologist (442 g over 6 mo),if application of DEET occurs 5 d/wk rather than the 4 d/wk reported for that individual. The estimated exposure for the Everglades Park service employees (McConnell et al., 1985) and the upper 1% of the general population using a 75% formulation (U.S. Environmental Protection Agency, 1980) confirm this projection.

BIODISTRIBUTION

The literature on the biodistribution of DEET is confounded by the misuse of the term absorption. In many of the studies, penetration of a dermal dose was determined and the result was reported as absorption. Penetration occurs when a topically applied substance passes into the layers of the skin below the epidermis. Absorption is the passage of a substance through the skin or mucosa or other lipid barriers and entrance of the material into the bloodstream or lymphatic stream with subsequent participation in metabolism.

Penetration

Penetration of DEET was reported by several investigators. In the earliest study, Schmidt et al. (1959) reported variable penetration at 6 h (19–48% of the applied dose) in guinea pigs treated dermally with 0.99–1.14 mg DEET/cm^2. Smith et al. (1963) reported from 7 to 30% penetration of DEET in guinea pigs and 7–13% in 3 male and 2 female volunteers 2 h after topical application of approximately 1 mg/cm^2. In another experiment, Smith et al. (1963) obtained penetration ranging

from approximately 9% at a dose of 1.86 mg/cm^2 to 56% at a dose of 77 μg/cm^2 in two male volunteers. In the studies by both groups, the quantity penetrating the skin was calculated by subtracting the quantities collected in the evaporation and rinse traps from the quantity applied. The quantities were measured by ultraviolet spectrophotometric techniques. The results of Smith et al. (1963) at 77 μg/cm^2 are in agreement with the amount of DEET recovered as a skin residue in an in vitro experiment on human skin at 25 μg/cm^2, in which recovery of [^{14}C]DEET (50.8 ± 15.0%) was quantitated 1 h after application by measuring the ^{14}C evaporated, in the skin surface wash, and the residual in the skin (Spencer et al., 1979). However, in a recent in vitro study using human skin, approximately 30% penetration 1 h after application of [^{14}C]DEET at 27–32 μg/cm^2 and 36% at 12 h after application of 300 μg/cm^2 were measured (Reifenrath and Robinson, 1982).

Accumulation of DEET in the skin with persistence for long periods was seen in animals and humans. After topical application of [^{14}C]DEET to mice and washing the skin 2 h later, an average of 21% ^{14}C was found on the skin at 36 d after application (Blomquist and Thorsell, 1977). Spencer et al. (1979), in in vivo experiments on human volunteers, determined the total recovery of DEET by evaporation, wiping, and stripping the skin to be 48.3 ± 6.3% of the applied dose. The ^{14}C remaining penetrated the skin to layers below the strippable stratum corneum and was partially absorbed. Persistent deposition of DEET in human skin was also demonstrated by Blomquist and Thorsell (1977). They recorded peak urinary radioactivity 8 h after washing the application site with ethanol, and only about 5% of the ^{14}C in the urine during 48 h in their study of the single human volunteer.

Absorption

Table 2 contains a summary of urinary recovery of ^{14}C and absorption of [^{14}C]DEET obtained from the literature. The investigators who quantitated ^{14}C in excreta after topical application of [^{14}C]DEET attempted to determine absorption, but recovery fractions must be corrected for the portion of DEET that is not excreted during the collection period if such data are going to be used to estimate absorption. The correction factor is determined by the intravenous (iv) administration of the test material and measuring urinary ^{14}C recovery. In the world literature, there are three studies that attempted to determine dermal absorption of DEET in human subjects by excretion measurements. These are included in Table 2. The dependence of absorption on dose was studied by Reifenrath et al. (1981). A slight, but insignificant (95% confidence level using the two-tailed *t*-test), increase in the average absorption with the lower dose was observed (12.8 ± 4.6% at 4 μg/cm^2 and 9.4 ± 3.6% at 320 μg/cm^2). Additionally, varying dose levels did not

TABLE 2. Urinary Recovery and Absorption of Topically Applied [^{14}C]DEET

Species (n)[a]	Dose ($\mu g/cm^2$)	Collection period	Urinary recovery of ^{14}C (% of applied)	Recovery of ^{14}C in urine after iv administration (% of administered)	Absorption (% of applied)	Reference
Rat, male (6)	4[b]	7 d	43.2	90	48[c]	Snodgrass et al. (1982)
Rat, female (6)	4[b]	7 d	32.4	92	35[c]	Snodgrass et al. (1982)
Rabbit, female (6)	4[b]	7 d	36.1	93	39[c]	Snodgrass et al. (1982)
Dog, beagle, male (3)	4[b]	7 d	30.8	52	59[c]	Snodgrass et al. (1982)
Dog, hairless (3)	320[d]	5 d	N.R.[e]	90.6 ± 2.7[f]	7.9 ± 2.5[f]	Reifenrath et al. (1980)
Dog, hairless (3)	4[d]	5 d	11.6 ± 4.2[f]	N.R.[e]	12.8 ± 4.6[f]	Reifenrath et al. (1981)
Dog, hairless (3)[g]	320[d]	5 d	8.5 ± 3.3[f]	N.R.[e]	9.4 ± 3.6[f]	Reifenrath et al. (1981)
Human (40)	Various[h]	N.R.[e]	"Traces"[i]	N.R.[e]	N.R.[e]	Markina and Yatsenko (1971)
Human, female (3)	830[j]	48 h	3.8, 5.5[k]	N.R.[e]	N.R.[e]	Blomquist and Thorsell (1977)
Human (4)	4[l]	5 d	N.R.[e]	52.3	16.7 ± 5.1[f]	Feldman and Maibach (1970)

[a] n, Number studied.
[b] Covered with nonocclusive patches up to 7 d.
[c] Calculated in this paper by dividing urinary recovery by the fraction recovered after iv administration.
[d] Covered with nonocclusive patches up to 48 h, then washed with alcohol swab.
[e] N.R., not reported.
[f] Error term is ±1 SD.
[g] Data for two dogs from Reifenrath et al. (1980).
[h] Various: lotions and creams containing 20–40% active ingredients.
[i] "Traces" of DEET were determined in urine using a chromatographic technique.
[j] Site of application not protected, washed at 8 h.
[k] Two experiments with one volunteer.
[l] Site of application not protected, washed at 24 h.

affect the recovery of ^{14}C in pregnant rabbits receiving repeated topical applications of [^{14}C]DEET (Snodgrass et al., 1982).

Greater absorption of ^{14}C in animal models compared to humans may be explained by differences in the skin. The kinetics of human skin absorption for low-molecular-weight lipid-soluble substances, like DEET, combine an initial dominant transient phase of diffusion through the follicles and ducts, lasting 2–3 h, followed by a steady-state diffusion through the stratum corneum (Scheuplein, 1967). Therefore, based on this model, topical application to animal epidermis, with its greater number of hair follicles and complex duct networks, may favor greater absorption by the appendageal route during the initial transient phase. After that, during the steady-state absorption phase, the thickness of the stratum corneum will be the diffusion-limiting factor (Snodgrass et al., 1982). Absorption in the hairless dog (Reifenrath et al., 1980, 1981) compared favorably with human absorption. Apparently, the permeability of the hairless dog's skin may be similar to that of human skin. The hairless dog is considered a suitable animal model for the penetration of DEET (Reifenrath et al., 1980). Recovery of radioactivity in the urine (90.6%) after iv administration was considerably higher than that reported for humans (52.3%) (Feldmann and Maibach, 1970) and for the beagle dog (52%) (Snodgrass et al., 1982). Thus, the metabolic treatment and bioelimination of the compound once it reaches the systemic circulation is quite different in the hairless dog compared to humans and the beagle dog. In the study of absorption, wherein correction is made for the portion of DEET not excreted during the collection period, it may be better to use an animal model that can absorb a greater percentage of the compound and that has a more similar metabolic treatment and bioelimination of it.

Distribution

Clearance from blood of animals was studied after dermal and intravenous administration. Lure et al. (1978) applied 100 mg [^{14}C]DEET/kg dermally to mice and found peak activities in 1 h and complete elimination from the blood in 2–3 d. Snodgrass et al. (1982) administered [^{14}C]DEET intravenously to dogs and rabbits and found peak activities at 15 min and biological half-lives of 35 min for dogs and 30 min for rabbits. Reifenrath et al. (1980) likewise found peak activities early (1–5 min) in the blood of the hairless dog after intravenous administration of ^{14}C-DEET, with radioactivity levels near background in 4–8 h.

Distribution of ^{14}C-labeled DEET was studied by autoradiography after dermal and iv administration of DEET to mice (Blomquist and Thorsell, 1977; Blomquist et al., 1975). Two hours after dermal application of 15 mg/kg, in addition to high skin concentrations, tissue concentrations of radioactivity were found in the lacrimal gland, liver, kidney, and nasal mucosa. Very high levels of activity were observed in

the bile and intestinal contents and in the urine (Blomquist and Thorsell, 1977). Enterohepatic elimination of DEET, on the other hand, appears to be very small. Only fractional quantities of the radioactive doses were detected in feces (Snodgrass et al., 1982). At 6 and 36 d after application, a high concentration was seen only in the smeared skin (Blomquist and Thorsell, 1977). Intravenous studies confirmed the tissue distribution after dermal application with uptake by the various tissues occurring earlier in the iv studies (Blomquist and Thorsell, 1977). In another study, distribution in mice, using doses of 2000 mg/kg or more and a chemical method for the determination of DEET, provided different results (Gleiberman and Voronkina, 1972). These investigators found high concentrations in the brain, lungs, and adrenals. However, they did not specify the DEET isomer, and methodological differences may explain their divergent findings; for example, the chemical method determines only unmetabolized DEET, whereas the autoradiographic method determines [^{14}C]DEET and the ^{14}C-labeled metabolites. Residual amounts of [^{14}C]DEET were detected in skin, fatty tissue, and muscle of mice for 1–3 mo after dermal application of 100 mg/kg (Lure et al., 1978). In another study, monitoring evaporation and penetration of DEET from human skin in vivo, it was suggested that retention of the repellent in the epidermis may occur (Spencer et al., 1979). A reservoir or depot effect and subsequent slow release to the circulation was postulated (Snodgrass et al., 1982; Blomquist and Thorsell, 1977).

Several investigators have reported evaluations of placental transfer of DEET. Gleiberman et al. (1975) observed residual diethyltoluamide (isomer not specified) in the body tissues of rats for 3 mo after birth from females treated repeatedly with 1000 mg/kg. While other studies suggest placental transfer of DEET, bioaccumulation was not demonstrated in mice (Blomquist et al., 1975) or rabbits (Snodgrass et al., 1982). This is an indication of rapid fetal excretion.

Metabolism

Conversion of absorbed DEET to metabolites is indicated by some investigators. In the study of Schmidt et al. (1959), the recovery of ^{14}C in urine of guinea pigs in 7 d was equivalent to 95% of the dose that penetrated, but there was no unmetabolized DEET detected by ultraviolet absorption spectroscopy in their urine samples. Smith et al. (1963), using ultraviolet spectroscopy, found no DEET in its original form in the urine of volunteers collected for 2 d following dermal application. Christensen et al. (1969) reported detection of metabolites of DEET in urine of rats and rabbits exposed to aerosol mists of DEET. They found *m*-toluric and hippuric acids using thin-layer chromatography, and benzoic acid and toluric acid using gas chromatography, but they did not determine quantities of these metabolites, nor did they identify

DEET in the urine (Christensen et al., 1969). On the other hand, Wu et al. (1979), using gas chromatography/mass spectrophotometry (GC/MS) to identify DEET and its metabolites in the urine of an exposed human volunteer, estimated that 10–14% of the topical dose of DEET was excreted in urine in the first hour as unmetabolized DEET. DEET was applied to 75% of the skin surface with a gauze wrap covering the limbs and trunk. Detection of DEET in the urine of this volunteer may have resulted from (1) the improved detection capabilities of GC/MS; (2) overloading of the volunteer's metabolic capabilities for DEET, because it was applied to a major portion of the skin; or (3) more penetration and absorption than evaporation of the dose occurring, because of the gauze wrap. Oxidation of the benzylic moiety of DEET to produce *m*-carboxyl-*N,N*-diethylbenzoylamide and hydroxylation of the sidechain to produce the glucuronide of *N*-hydroxyethyl-*N*-ethyl-*m*-toluamide were also demonstrated (Wu et al., 1979). Rats given anesthetic doses of pentobarbital exhibited both a prolonged and shortened sleep time when pretreated orally with 400 mg DEET/kg (Liu et al., 1984). This is an indication of active oxidation of DEET occurring in the liver microsome P-450 system.

Excretion

Urinary excretion of DEET, which accounted for most of the absorbed repellent, occurred primarily in the first 24 h in animal models. Table 3 is a comparison of data for excretion of ^{14}C after dermal application of [^{14}C]DEET. Schmidt et al. (1959) reported their results as the percentage of the dose that penetrated. They also noted that urinary radioactivity peaked within 12 h of administration. Since there appears

TABLE 3. Excretion of Topically Administered [^{14}C]DEET

		Cumulative urinary excretion		Cumulative fecal excretion		
Species (*n*)[a]	Dose ($\mu g/cm^2$)	Percent of applied	Time	Percent of applied	Time	Reference
Guinea pig (2)	1000	82[b]	24 h			Schmidt et al. (1959)
		89[b]	48 h			
		92[b]	8 d	1[b]	8 d	
Mouse (6)	33	13	2.5 h			Blomquist and Thorsell (1977)
		34	2 d	<3	2 d	
Rat (6)	330–400	42	6 h			Lure et al. (1978)
		68	24 h	N.R.[c]		

[a] *n*, Number studied.

[b] Percent of dose that penetrated; the repellent that penetrated was calculated by subtracting that in the rinse and traps from the applied dose.

[c] N.R., not reported.

to be little difference in the distribution and elimination of DEET following either iv or topical administration (Snodgrass et al., 1982), recoveries of ^{14}C from intravenously administered doses can be used to assess excretion of absorbed repellent. Table 4 is a comparison of data on the excretion of ^{14}C after iv administration of [^{14}C]DEET. In addition to the 52% recovery of ^{14}C in urine over 5 d, Feldmann and Maibach (1970) also reported in their study of human volunteers that urinary recovery of ^{14}C had a half-life of 4 h. This indicates that urinary radioactivity peaked within the first day. Excretion after repeated topical exposure was reported by one group. Pregnant rabbits were given repeated dermal applications of [^{14}C]DEET for 29 d. Excretion (^{14}C recovery) reached a steady state of 45% of each day's dose during the first 24 h and throughout the study (Snodgrass et al., 1982).

Summary

From the collective animal literature, DEET appears to penetrate the skin partially and to be absorbed rapidly. Persistent deposition of DEET in the skin was observed. Absorption ranges from around 10 to 60% depending on the animal model. DEET is cleared rapidly from the blood. In animals, metabolism of DEET in the liver occurs with rapid excretion of metabolites in the urine. Fecal excretion is minimal. The liver, kidney, bladder, and lacrimal glands are the preferred organs for uptake in mice, but excretion rates are so high (97% of the absorbed dose in 40 hours) that there is no evidence of bioaccumulation in that species. Accumulation by fetal organs, observed by one group, was not substantiated by two other groups.

Human absorption of DEET is similar to that in the hairless dog (16.7% versus 12.8%). Persistent skin deposition was also observed. The distribution of DEET in humans must be inferred from the animal studies. Excretion of DEET by humans is likewise rapid, but apparently not as complete as in most animal models. Comparison of animal and human absorption studies is difficult because of differences in methodologies, e.g., lack of protection devices in human studies and differences in anatomic site. Most of the studies (animal and human) have not assessed the results of probable human exposure conditions, in which the repeated doses are not washed off and an effort is made throughout the day to maintain DEET on the skin. In one study of repeated application to rabbits, a steady state of absorption and elimination of DEET occurred after the initial dose.

TOXICITY

Based on the effects of DEET on animals and the low incidence of reports of untoward human effects, DEET has generally been thought to be of low toxicity. Although the dermal absorption of DEET has been

TABLE 4. Excretion of Intravenously Administered [^{14}C]DEET

Species (*n*)[a]	Dose (mg)	Cumulative urinary excretion		Cumulative fecal excretion		Reference
		Percent of administered	Time	Percent of administered	Time	
Mouse (8)	30	95.6	8 h			Blomquist et al. (1975)
		97.3	40 h	0.6	48 h	
Dog, hairless (8)	348	80	8 h			Reifenrath et al. (1980)
		88	24 h			
		91	7 d	<l.d.[b]	7 d	
Rat, male (N.R.[c])	28	87	24 h			Snodgrass et al. (1982)
		90	7 d	<3	7 d	
Rat, female (N.R.[c])	28	90	24 h			Snodgrass et al. (1982)
		92	7 d	<3	7 d	
Rabbit, female (N.R.[c])	70	75	24 h			Snodgrass et al. (1982)
		93	7 d	<3	7 d	
Dog, beagle, male (N.R.[c])	141	45	24 h			Snodgrass et al. (1982)
		52	7 d	<3	7 d	
Human (4)	N.R.[c]	52	5 d	N.R.[c]		Feldman and Maibach (1970)

[a] *n*, Number studied.
[b] l.d., Limit of detection.
[c] N.R., not reported.

known since its introduction, its use has continued because it is believed not to present a dermatologic or toxic hazard to humans. A summary of the recognized toxic effects of DEET follows.

Animal Toxicity—Acute and Subchronic Doses

The rat oral LD50s were 2 g/kg for females and 3 g/kg for males (Haight et al., 1979; Carpenter et al., 1974; Ambrose et al., 1959). The LC50 for rats exposed to airborne concentrations of DEET for 4 h was about 6 g/m^3 (Macko and Bergman, 1979). In the rabbit, the LD50 for dermal application was 3 g/kg (Carpenter et al., 1974). In addition, increased kidney weights and marked histopathological changes were observed in rabbits after a 90-d dermal exposure to 1.3 g/kg · d (U.S. Environmental Protection Agency, 1980). Because the study lacked growth curves, blood chemistries, and individual animal data, it was not used in the EPA Pesticide Registration Standard (U.S. Environmental Protection Agency, 1980).

In subchronic inhalation studies performed by the U.S. Army Environmental Hygiene Agency, periodic nausea and vomiting were observed in dogs at 750–1500 mg/m^3 and an exudate from the nose and eyes was observed in rats exposed to 1500 mg/m^3 for 13 wk (Macko and Bergman, 1979). Ambrose et al. (1959) observed a slight nose bleed in an unspecified number of five rats during daily exposure to a saturated vapor of DEET. The saturated vapor was estimated to contain approximately 1 ml of 85–95% DEET/14,000 l in 40 h and exposure lasted for 8 h/d, 5 d/wk, for 7 wk. No systemic toxic signs and effects were observed. *Tracheitis and pulmonary edema were observed in rats* following exposure to an aerosol mist of DEET for two 1-h periods for 30 d, but the high rate of murine pneumonia in controls and exposed animals confounded these results (Christensen et al., 1969).

Other effects on animals in high-dose application include progressive weight loss in rabbits given 528 mg/kg (one-third the LD50) orally for 15 d (Haight et al., 1979); and irritation of the conjunctival epithelium and corneal opacification after 4 d of treatment with 71% DEET aerosol directly to the face for 5 s 4 times/d and direct application of 1 drop of 100% DEET to rabbits' eyes each day (Christensen et al., 1969). Subchronic feeding studies (15 d duration) on rabbits at 528 mg/kg (one-third the LD50), have produced significant decreases in serum calcium and increases in serum triglyceride and cholesterol (Haight et al., 1979). These changes in clinical chemistry parameters were not targeted to specific organ functions and were considered reflections of decreases in body weight of rabbits that occurred at the 528-mg/kg level (Haight et al., 1979).

Animal Toxicity—Dermatologic

Irritant skin effects, but not sensitization, have been reported in animals (U.S. Environmental Protection Agency, 1980; Ambrose et al.,

1959; Phillips et al., 1972; Wong and Yew, 1978; Blume et al., 1971; Palmer, 1969). Mild erythema, desquammation, and dryness of the skin have been observed in rabbits treated with 2 ml/kg of 50% DEET (1 g/kg) for 3 d (Ambrose et al., 1959; Wong and Yew, 1978). Horses sprayed with 50 and 75% DEET aerosol (36 g/d) for 60 d had severe dermatosis (Palmer, 1969).

Animal Toxicity—Reproductive and Teratologic

Spermhead abnormalities and altered sperm motility in rats after daily dermal doses of 100 and 1000 mg/kg for 1.5 and 6 mo were reported by Gleiberman et al. (1976). The significance of their findings could not be evaluated due to insufficient details in their report. In another study, a small increase in frequency of abnormally shaped sperm has been observed in rats following inhalation exposure of 1500 mg/m^3 for 6 h/d, 5 d/wk for 13 wk (Macko and Bergman, 1979). Since the increases in abnormally shaped sperm were quite small, these investigators found their data difficult to interpret. Their findings did not confirm the findings of the Russian investigators (Gleiberman et al., 1976), who found a two- to fivefold difference in the number of abnormal sperm. Additionally, a recent dermal study in the rat showed a statistically significant absence of morphological abnormalities following 9 wk at doses of 100, 300, and 1000 mg/kg · d (Lebowitz et al., 1983).

In male rats, significant testicular hypertrophy was observed after 200 d on a diet containing from 48 to 531 mg DEET/kg · d (Ambrose et al., 1959). In a study reported by Angerhofer and Weeks (1980), female rabbits were treated daily on gestation d 0–29 with dermal doses of 50–1000 mg DEET/kg (from one-hundredth to one-fifth the rabbit LD50). No effects on fertility index, number of implantations per animal, number of fetuses per animal, fetal weight, fetal length, or placental weights were detected. Also, there were no increases in the incidence of skeletal or soft-tissue anomalies in the treated groups compared to untreated controls (Angerhofer and Weeks, 1980). In an unpublished study cited in the EPA Pesticide Registration Document (U.S. Environmental Protection Agency, 1980), pregnant rats were orally dosed with 8–80 mg/kg · d from d 5 through 15 of gestation. There were no significant differences in fertility, fetuses per liter, fetal weight, or fetal survival between control and treated mothers. However, the significance of a suggested embryotoxicity at the 80-mg/kg dose level could not be determined because low body weights of some of the dams in this group suggested impaired maternal health prior to administration of DEET (U.S. Environmental Protection Agency, 1980). In the Soviet literature, there is a report of a significant decrease in the number of implantations and an increase in the number of postimplantation resorptions in rats after dermal doses of 1000 mg/kg · d administered from d 1 to 19 of pregnancy (Gleiberman et al., 1975). However,

the chemical administered was not characterized and there was insufficient information to assess the study protocol. In a preliminary report of a study of the reproductive toxicity and teratogenic effects of DEET, pregnant rats were treated subcutaneously with 0.3 ml/kg · d (LD10) of 97–98% DEET on gestation d 6–15 (Brian D. Hardin, personal communication, 1984). Mortality, fetal malformations, postnatal growth, and survival of pups were observed. There were no treatment-related adverse effects on the indices of reproduction and no significant teratologic findings (Brian D. Hardin, personal communication, 1984). In the same study, male rats were subcutaneously dosed with 0.3 (LD10) and 0.7 (LD50) ml/kg · d for 5 d/wk for 9 wk and then bred with female rats. No apparent treatment-related effects on growth or survival of pups from the treated males or on male fertility were observed (Brian D. Hardin, personal communication, 1984).

In another study, 0.242 mg pure DEET in mineral oil was injected directly into fertilized chicken eggs as a single dose between h 33 and 52 of incubation (Kuhlman et al., 1981). This dose was estimated to be equivalent to a human exposure to 10 ml of 80% DEET per day for 9 d. Profound teratogenic consequences, particularly for heart development, were routinely observed. However, the mineral oil alone produced a marked increase in mortality rate compared with untreated embryo, and a synergistic effect of the mineral-oil vehicle was not ruled out in this study (Kuhlman et al., 1981). The correlation between negative results in this type of chicken embryo test and the lack of mammalian teratogenic sequelae has been high; however, the correlation between positive results and sequelae has been low. The results of this study must be considered in light of all of these facts.

Fetal accumulation was studied by applying [^{14}C]DEET to the skin of pregnant rabbits daily on d 1–29 of gestation (Snodgrass et al., 1982). Analysis of fetuses at full term showed no evidence of radioactivity above background. Additionally, in a follow-up experiment, [^{14}C]DEET was administered to rabbits intravenously, to maximize placental transfer, on d 15 (mid-term) of their pregnancy. Fetuses registered the lowest radioactivity of the specimens, which included blood, kidney, spleen, liver, lungs, and fetuses, at all times monitored through 24 h, and had one-sixth the DEET concentrations of maternal blood samples (Snodgrass et al., 1982). When female mice in "advanced pregnancy" were given radioactive DEET intravenously, very little radioactivity was found in the fetuses, but the concentration of DEET in the uterine cavity close to the yolk-sac villi was greater than that found in maternal blood (Blomquist et al., 1975).

Animal Toxicity—Carcinogenicity, Mutagenicity, and Genetics

In the only animal study evaluating DEET as a potential carcinogen, Stenbaeck (1976, 1977) showed an absence of tumor induction in mice

and rabbits that were treated cutaneously with approximately 20, 10, and 1 mg DEET (50 mice and 5 rabbits per group) in acetone twice a week for the life of the test animal (40–120 wk for mice and 20–80 wk for rabbits). There was no statistical difference in the number of tumors observed in the test animals versus those observed in an untreated control group. A positive control group was given the known carcinogen 9,10-dimethylbenz[a]anthracene (DMBA). The EPA, in its Pesticide Registration Standard documentation (U.S. Environmental Protection Agency, 1980), reviewed this work and judged it to be inadequate for various reasons, including the fact that no clinical data were reported and pathological examination of the rabbit tumor types was not done. The EPA reviewers were concerned that the early and abrupt deaths of rabbits were an indication that the study was not conducted properly.

Mutagenicity studies performed by Litton Bionetics for the U.S. Army showed that DEET did not induce reverse mutations in five strains of *Salmonella typhimurium* with or without S9 activation and did not induce gene conversions in *Saccharomyces cerevisiae* D4 without activation (U.S. Environmental Protection Agency, 1980). However, uncertainties in the preincubation suspension technique caused EPA scientists to draw no conclusion regarding the S9 activation system and *Saccharomyces cerevisiae* D4 in the same study (U.S. Environmental Protection Agency, 1980). In a survey of pesticides for mutagenicity in the bacterial plate assay method, 50% DEET gave a negative mutagenic response (Ficsor and Nii Lo Piccolo, 1972).

A dominant lethal effect study was conducted in mice by the U.S. Army Environmental Hygiene Agency. Three groups of 10 male mice were given single oral doses of corn oil at 5 mg/kg (control), triethylenemelamine (TEM) at 10 mg/kg (positive control), and DEET at 600 mg/kg (one-fifth the mouse oral LD50), respectively. The study resulted in no dominant lethal effects; however, a slight, but statistically significant, reduction in the number of implants was noted in pregnant females. The reduction was attributed to aspermia or reduced motility of the spermatozoa (U.S. Environmental Protection Agency, 1980; Swentzel, 1977). Reduced motility of spermatozoa was observed in male rats treated with repeated dermal applications of DEET (Gleiberman et al., 1976). Preliminary results from a recent study at the National Institute for Occupational Safety and Health (Brian D. Hardin, personal communication, 1984) indicated that there were no treatment-related dominant lethal mutations in male rats given subcutaneous injections of 0.30 and 0.73 ml DEET/kg · d for 5 d each week for 9 wk, no effect on fertility, and no reduction in implants.

Animal Toxicity—Neurological and Behavioral

Central nervous system symptoms have been reported in rats and rabbits given doses approaching the oral LD50 (approximately 1.8 g/kg)

(Ambrose et al., 1959). Gleiberman and Voronkina (1972) observed central nervous system disorders (excitation, stiffness of movement, and lack of coordination) in mice 15 min to 2 h after dermal application of 2000, 3500 (dermal LD50), and 5000 (dermal LD100) mg/kg diethyltoluamide. Dogs given oral doses of 0.1 and 0.3 ml/kg · d of 85% DEET with 10% other isomers for 13 wk showed mild central nervous system stimulation (tremors and hyperactivity) after each daily dose (U.S. Environmental Protection Agency, 1980; Keplinger et al., 1961). Michael and Grant (1974) observed a tranquilizing effect on mosquito fish swimming in tanks containing 125, 200, 315, and 500 ppm DEET (LC50 was approximately 235 ppm).

In 1979 the U.S. Army conducted acute and subchronic behavioral tests on rats exposed to aerosols of DEET (Sherman, 1979a,b). In the acute study a battery of tests, which included balance-beam performance, passive and quick avoidance, and endurance performance, was given to male and female rats after 4 h of exposure to 4100 (high), 2900 (medium), 2300 (low), and 0 (control) mg/m^3. Distinctions were made between performances at the high, medium, and low levels and controls for both males and females. No toxic signs were noted in the control, low-exposure, or medium-exposure groups, while shaking, prostration, and loss of balance were noted in high-exposure females and shaking was noted in high-exposure males. The investigators noted that, while the combination of behavioral measures reliably demonstrated performance decrements occurring in a concentration-related pattern ($p = 0.01$), more work at lower concentrations is needed to assess biological significance. The lowest concentration assessed (2300 mg/m^3) was calculated to be 3.3 times a typical exposure concentration from human use of the repellent and a factor of 400 times as long in duration as the exposure from a 71% DEET aerosol can, releasing 1 g/s for 10 s, in a 10-cm^3 room, 4 times/d (Sherman, 1979a).

The subchronic exposure study was performed at three exposure levels (1500, 750, and 250 mg/m^3), 6 h/d, 5 d/wk for 13 wk. The battery of tests included tactile sensitivity, passive and quick avoidance tests, endurance performance, and balance-beam performance. Only by combining all the test results could all of the concentrations be distinguished from one another ($p = 0.01$) (Sherman, 1979b). In this study, it was noted that the only concentration low enough to be within the range of normal use (250 mg/m^3) was not significantly different from the controls for most tests until 6 wk of exposure had been completed ($p = 0.01$).

In studies of reproductive toxicity and teratology performed by Brian D. Hardin (personal communication, 1984), both female and male rats developed a gait disturbance involving the rear limbs. Therefore, a preliminary study of behavioral effects on rats dosed subcutaneously with 0, 0.30, 0.73, and 1.8 ml DEET/kg · d was begun by another scientist

at the National Institute for Occupational Safety and Health. In a rotorod test administered before and 4 wk after the dosing, he found a dose-related decline in performance after dosing (David W. Chrislip, personal communication, 1984). Because these results could be confounded by irritation at the injection site, a follow-up study using a dermal route was planned. However, there is an indication that there may be behavioral effects in rats even at the lowest dose.

Human Toxicity

There have been only a few reports of adverse effects from DEET in the medical literature, but these support the potential for neurotoxicity, allergic responses, and dermatitis. Although similarly rare, clinical studies contained sporadic allergic reactions and dermatitis.

There are 5 accounts containing a total of 6 cases of girls, ages 1–8 yr, developing encephalopathies, with convulsions and ataxia, following personal spraying with DEET (Gryboski et al., 1961; Zadikoff, 1979; Pronczuk de Garbino and Laborde, 1983; Heick et al., 1980; Roland et al., 1985); there were 3 deaths (Zadikoff, 1979; Pronczuk de Garbino and Laborde, 1983; Heick et al., 1980). The etiology is purely presumptive. In one of the fatalities, it was thought that the illness may have been precipitated by use of copious quantities of DEET and that the mechanism of the toxic action may have been either hypersensitivity to the product and/or toxic effects of its metabolites, which are enhanced by enzyme deficiencies [like ornithine carbamoyltransferase (OCT) deficiency] (Heick et al., 1980). The blood ammonia values (an indicator of OCT deficiency) were not measured in the other children who died. Their physicians felt the fatalities were due to a hypersensitivity to DEET (Zadikoff, 1979; Pronczuk de Garbino and Laborde, 1983).

National Park Service workers in the Florida Everglades, who rely heavily on DEET in summer months, have anecdotally reported episodes of confusion and an abnormal sensation of decreased sweating while using DEET (McConnell et al., 1985). Response to a neurobehavioral questionnaire by 143 of these workers indicated that there was a significant increase in the prevalence of certain neurological signs and symptoms, specifically muscle cramping, insomnia, and affective symptoms (irritability and depression), among the workers who had an estimated dermal exposure to 4.25 g or more of DEET in an average week. Also, skin rash or blisters and difficulty in starting or stopping the urinary stream were significantly higher in this group of workers.

A woman was documented to have had anaphylaxis resulting from DEET (Miller, 1982). She showed signs of angioedema, hypotension, and asthma (a type I immunological pattern) upon exposure. Patch testing in a controlled setting produced contact urticaria progressing to

systemic symptoms. Since isopropyl alcohol was the only other ingredient in the product, DEET is the probable etiologic agent.

Skin symptoms have been considered a rare consequence of DEET exposure; however, scarring bullous dermatitis, occurring in the antecubital fossae, was reported as a sporadic problem among combat personnel in Vietnam (Lamberg and Mulrennan, 1969). Patch testing with 75% DEET on 63 unaffected servicemen at Da Nang showed 29 positive reactions when patches were applied to the antecubital fossae with the arm in the extended position. However, no positives occurred when patches were simultaneously applied to the upper part of the arm. The same response was observed in 6 of 10 servicemen in Oakland, California, using 75% DEET from another supplier. There was no response when DEET was used in a 5% solution for both the Vietnam and Oakland soldiers. Rabinovich (1966) reported skin lesions in 3 of 85 men using DEET; in one, contact dermatitis was proven. In another report, 10 soldiers developed bullous eruptions in the antecubital fossae after use of 50% DEET repellent (Reuveni and Yagupsky, 1982). Five volunteers, on whom 1 ml and 2 ml of a 50% DEET in isopropanol solution were applied to the face and each arm, respectively, demonstrated no irritation on the arms after 5 consecutive days of this treatment, but some desquamation of the skin around the nose after 3 d (Ambrose et al., 1959). Finally, a woman complaining of severe pruritis caused by DEET, but on whom 48- and 96-h patch tests for delayed hypersensitivity were negative, demonstrated a highly positive open patch test within 1 h, which resolved totally over 2 d (Maibach and Johnson, 1975). Passive immunologic transfer was positively demonstrated in two controls, suggesting an immunologic mechanism in the hypersensitivity to DEET. An immunological mechanism was also demonstrated in the case of a 4-yr-old boy who developed contact urticaria after application of DEET (vonMayenburg and Rakoski, 1983).

CONCLUSION

As a repellent, DEET is a highly effective agent. Outdoor workers, such as those employed in the National Park Service, may have an elevated level of DEET exposure. They may be exposed to yearly levels that exceed general consumer use patterns. Although DEET appears to be absorbed to some extent by animals and humans, there are information gaps in regard to its absorption and toxicity. Absorption and distribution of DEET and its metabolites after repeated application to humans has not been studied. Also, the risks from the use of DEET would have to be evaluated in light of relief from considerable morbidity associated with insect infestation.

The review of the toxicology of DEET identifies several areas of con-

cern. The existing occupational usage reports and occurrence of dermatitis suggest the need for some restrictions in patterns of application. Reports of adverse human skin effects are not abundant in the literature. This may infer that they are of limited severity. Even though there is one report of embryotoxic effects in mice, other investigators have not been able to confirm the observation. The reports of encephalopathies in children are an indication of a possible age-related absorption that should be investigated. The reports of neurological signs and symptoms occurring in the National Park Service personnel and central nervous system symptoms in animals are a substantive indication of the need for more in-depth epidemiological studies. Carefully conducted chronic studies of dermally applied DEET for carcinogenic effects are also needed.

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