

***N,N*-Diethyl-*m*-toluamide (DEET)
[134-62-3]**

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

N,N-Diethyl-*m*-toluamide (DEET) was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high U.S. production volume and wide spread consumer use in commercial insect repellents.

It is a colorless to faintly yellow liquid with an aromatic odor that is used primarily by dermal application as an insect repellent against mosquitoes, ticks, fleas, leeches, and blackflies. It is commercially available at a concentration of 4% to 100% in formulations including lotions, creams, gels, aerosols, and pump sprays, usually with an ethyl or isopropyl alcohol base. Over 230 DEET-containing products are currently registered with the U.S. Environmental Protection Agency (EPA). Annual U.S. production plus imports is ~2.6-4.5 million pounds.

DEET can enter the environment via its release into waste streams during its production and use. In the atmosphere, it exists in the vapor phase and is degraded by reaction with photochemically produced hydroxy radicals; its atmospheric half-life is ~15 hours. DEET has moderate mobility and is not expected to volatilize in moist or dry soil or to biodegrade under either aerobic or anaerobic conditions.

A 1981-1983 survey by the National Institute for Occupational Safety and Health (NIOSH) estimated that ~9,275 workers were potentially exposed to DEET annually. Among the general population, ~6,943 cases of adverse reaction were reported between 1993 and 1994. The EPA estimates that ~200 million people are exposed annually to DEET worldwide.

DEET is an EPA-registered insecticide that recently underwent a comprehensive safety evaluation which resulted in better labeling requirements for DEET-containing products.

Exposure to DEET can occur via ingestion, inhalation, or dermal contact. In humans, reported symptoms of overexposure include seizures, coma, hypotension, bradycardia, confusion, acute psychosis, abdominal pain, nausea and vomiting, skin irritation, and urticaria or contact rash. The role of DEET in Gulf War Syndrome continues to be investigated. Veterans who used DEET-containing insect repellents showed signs of arthro-myo-neuropathy, a neurotoxic syndrome with symptoms including joint and muscle pain, fatigue after exertion, and tingling or numbing of the hands, arms, feet, and legs.

Human excretion is rapid, although it is less than that observed in animal models. In animals, DEET is absorbed rapidly from the skin and cleared rapidly from blood. It is metabolized in the liver and excreted rapidly in the urine; fecal elimination is minimal. Because excretion rates in animals are so high, bioaccumulation rarely occurs.

The oral LD₅₀ is 1,170 mg/kg (6.116 mmol/kg) in mice, 1,950 mg/kg (10.19 mmol/kg) in rats, and 1,584 mg/kg (8.280 mmol/kg) in rabbits. The dermal LD₅₀ is 3,170 mg/kg

(16.67 mmol/kg) in mice, 5,000 mg/kg (26.14 mmol/kg) in rats, and 3,180 (16.62 mmol/kg) in rabbits. Male Sprague-Dawley rats exposed to single oral doses of 2,000-5,010 mg/kg (10.45-26.19 mmol/kg) DEET showed signs of lethargy and respiratory distress. DEET toxicity decreased as the age of the rat increased and female rats were more sensitive to its effects than males. Guinea pigs given single dermal applications of 200 mL (occluded for 4 hours) showed no signs of irritation, while dermal application of 75-100% DEET to the abraded skin of rabbits caused mild irritation. Rabbits experienced edema of the nictitating membrane, lacrimation, conjunctivitis, purulent discharge, and occasional corneal cloudiness when exposed ocularly to 10-100 μ L of 100% DEET. Dogs and cats given either oral or dermal doses of 0.089-7.128 g/kg (0.46-37.26 μ mol/kg) of a flea and tick spray containing 9% DEET experienced ataxia, seizures, muscle tremors, hypersalivation, restlessness, depression, and incoordination.

In short-term and subchronic studies, CD rats given daily oral doses of 750 mg/kg (3.92 mmol/kg) for 21 days exhibited symptoms including hypoactivity, ataxia, decreased muscle tone, foot splay, urine stains, perinasal encrustation, and perioral wetness. Among female Sprague-Dawley rats exposed subcutaneously (s.c.) to 0.3-1.80 mL/kg (1.6-9.4 mmol/kg), none survived more than 10 days and liver and kidney weights were elevated. Male rats in the same study developed skin lesions at the injection site and showed gait disturbance; autopsy revealed grossly distended, urine-filled bladders. Rabbits exposed orally to 132-528 mg/kg (0.690-2.76 mmol/kg) DEET showed decreased body weight and increased kidney weight; serum calcium levels decreased while cholesterol and triglyceride levels increased. The skin of rabbits exposed dermally for 14 days had increased foldings and indentations on the skin surface, thinning of the epidermis, and cystic dilations of the dermis. Chickens exposed to 500 mg/kg (2.61 mmol/kg) s.c. 5 days/week for 8 weeks showed decreased activity and shortness of breath after a dose, but recovered within 24 hours after dosing.

In a chronic two generation reproduction study, the F₂ offspring of CD rats given 500-5000 ppm (2.91-39.12 g/m³; 20.4-204.5 mmol/m³) showed a slight increase in exploratory locomotor activity at the high dose level.

Mental retardation, muscular hypotonia, hearing loss, and coarctation of the aorta have been reported among infants whose mothers were exposed to DEET during pregnancy; however, a direct relationship between the use of DEET and birth defects has not been demonstrated. In female rats given 125-750 mg/kg/day (0.653-3.92 mmol/kg/day) orally on gestational days 6-15, no external, visceral, or skeletal malformations were observed in fetuses; however, reduced fetal weight gain was noted at 750 mg/kg. No significant reproductive or developmental effects were observed in the fetuses of female and male rats or rabbits given DEET. In chick embryos, however, gross malformations, including ventricular septal defects, anomalous aortic arch patterns, absence of a rump, absence of or malrotated limbs, and central nervous system

(CNS) malformations were seen in those exposed to 1.27 μ mol (243 μ g) DEET by topical application to the chorioallantoic membrane on the second day of incubation.

Mice and rabbits exposed dermally to 0.02 mL (0.02 g; 0.1 mmol) of 10, 50, and 100% concentrations of DEET twice a week for 160 weeks had no significant differences in the number of tumors compared to controls.

DEET was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98 with or without activation when tested in a preincubation assay. Exposure of *Tradescantia paludosa* pollen mother cells in early prophase I to 1-3 spray of a commercial insect repellent containing DEET did not induce micronuclei in later stages of pollen maturation.

DEET can cause a hypersensitive response characterized by the development of contact urticaria, anaphylactic hypersensitivity, and toxic encephalopathy.

DEET-inhibited synthesis of urea from ammonia resulting in elevated blood ammonia levels has been suggested as a mechanism of DEET neurotoxicity.

When administered orally to rats (0.4 g/kg; 2 mmol/kg), it increased the hypnotic effect of pentobarbital when given prior to pentobarbital administration and decreased the effect when given after pentobarbital.

When applied in combination, DEET decreased the absorption of 2,4-D-amine and di-*n*-propylisocinchomeronate in human skin. In animals, DEET increased the absorption of fenitrothion in both rats and monkeys, and methotrexate in rabbits.

No data on structure-activity relationships were located.

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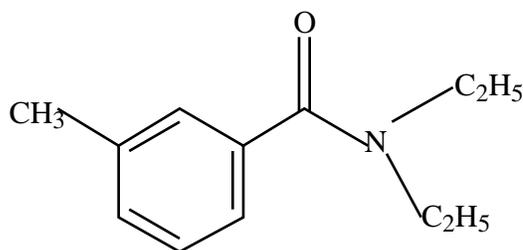
1.0 BASIS FOR NOMINATION

N,N-Diethyl-*m*-toluamide (DEET) was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high U.S. production volume and widespread use in commercial insect repellents.

2.0 INTRODUCTION

N,N-Diethyl-*m*-toluamide

[134-62-3]



2.1 Chemical Identification

N,N-Diethyl-*m*-toluamide (C₁₂H₁₇NO; mol. wt. = 191.3) is also called:

Autan
Benzamide, *N,N*-diethyl-3-methyl
Chemform
Delphene
DET
DETA
DETA-20
Detamide
Dieltamid
Diethyltoluamide
m-Delphene
m-DET
m-DETA
m-Diethyltoluamide
MGK
m-Toluic acid diethylamide
N,N-Diethyl-3-methylbenzamide
Naugatuck det

Tradenames include Off! , Deep Woods , Muskol , Baker's Antifol, Chigger-wash, Flypel, Repudin, Everglades , Repel Deerhunters , Skedaddle , and Skintastic .

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	colorless to faintly yellow liquid	ChemFinder (1998); Radian (1991)
Odor	aromatic	Pronczuk de Garbino and Laborde (1983)
Taste	bitter	Dorman (1990)
Boiling Point (°C @ 19 mm Hg)	160	Lewis (1996); Budavari (1996)
Melting Point (°C)	-45	Radian (1991)
Density (20°C/4°C)	0.996	Lewis (1996); Budavari (1996)
Solubility in water (@ 20°C):	<0.1 g/100 mL	ChemFinder (1998); Radian (1991)
Other solubilities:	<ul style="list-style-type: none"> • Soluble in ethanol, benzene, and ether • Sparingly soluble in petroleum ether • Miscible with 2-propanol, cottonseed oil, and propylene glycol 	HSDB (1998); Budavari (1996)
Vapor Density	6.7	Radian (1991)
Vapor Pressure (mm Hg @ 111°C)	1	Radian (1991)
Flash Point (°C)	155	ChemFinder (1998); Radian (1991)
Evaporation Rate (butyl acetate = 1)	<1	Radian (1991)
Refractive Index (@ 20°C)	1.5212	Radian (1991)

2.3 Commercial Availability

In the United States, DEET is manufactured by Hoechst Celanese Corporation (Mount Holly, NC) and Morflex Chemical Company, Inc. (Greensboro, NC) (HSDB, 1998). It is available with a technical purity of 85-95% *meta* isomer, which is more active than the *ortho* and *para* isomers. Commercially, it is available in 4% to 100% concentrations in insect repellent formulations, including solutions, lotions, creams, gels, aerosols, pump sprays, and impregnated towelettes, usually with an ethyl or isopropyl alcohol base (Fradin, 1998; Pronczuk de Garbino and Laborde, 1983). Approximately 230 DEET-containing products are currently registered with the U.S. Environmental Protection Agency (EPA) by about 70 different companies (OPP, 1998).

3.0 PRODUCTION PROCESSES AND ANALYSES

DEET is prepared from *m*-toluoyl chloride and diethylamine in benzene or ether (Budavari, 1996).

One of the earliest techniques used to identify the metabolites of DEET in humans was high resolution gas chromatography/mass spectrometry (GC/MS) (Wu et al., 1979). Gas chromatography with a nitrogen-phosphorus detector has been used to detect it in postmortem human tissues (Crowley et al., 1986). Additionally, DEET has been detected in human urine and serum by high performance liquid chromatography (HPLC) with a UV detector (Smallwood et al., 1992). The compound is removed from urine by partitioning into diethyl ether and from serum by solid-phase extraction. The limit of detection for this method is 0.09 μ g/mL (0.5 μ M) for urine and 0.09 μ g/g (0.5 nmol/g) for serum.

4.0 PRODUCTION AND IMPORT VOLUMES

DEET is included on the EPA's High Production Volume Chemical List compiled by the Office of Pollution Prevention and Toxics (OPPT). The EPA estimates that U. S. production plus imports is 2.6-4.5 million pounds per year (USEPA, 1998).

5.0 USES

DEET was developed by scientists at the U. S. Department of Agriculture and patented by the U. S. Army in 1946. It was registered for use by the general public in 1957 (Fradin, 1998). Since then, DEET has been popularly employed using dermal application as an insect repellent against mosquitoes, ticks, fleas, leeches, and blackflies (Leikin and Paloucek, 1998). It also has veterinary uses, such as in flea and tick sprays. It is, however, not approved for use on foods (OPP, 1998). Until 1989, the standard-issue insect repellent used by the U. S. military contained 75% DEET, but concerns about its toxicity led to a search for new formulations. The 3M Company therefore developed a slow-release product containing only 35% DEET, which is the repellent currently used by military personnel (Fradin, 1998).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

DEET can enter the environment via its release into waste streams during its production and use (HSDB, 1998). In the atmosphere, it exists in the vapor phase, where it is degraded by

reaction with photochemically produced hydroxy radicals. Its atmospheric half-life is approximately 15 hours. It is not expected to volatilize in moist or dry soil, where it has moderate mobility, or biodegrade under either aerobic or anaerobic conditions (HSDB, 1998).

DEET was found at concentrations of 5-201 ng/L (0.03-1.05 nmol/L) in samples taken from the Mississippi River and its tributaries during July-August 1991 (Pereira and Hostettler, 1993). It is not predicted to bioconcentrate in aquatic organisms (HSDB, 1998).

7.0 HUMAN EXPOSURE

Exposure to DEET can occur in the workplace during its production or use. A 1981-1983 National Occupational Exposure Survey (NOES) estimated that approximately 9,275 workers were potentially exposed to DEET annually (NIOSH, 1990). An earlier National Occupational Hazard Survey (NOHS) reported 3,364 workers potentially exposed annually (NIOSH, 1977).

Members of the general population are exposed primarily through the use of insect repellents in the form of sprays, lotions, or sticks containing 1% to 100% DEET (Veltri et al., 1994; Abrams et al., 1991). From 1985 to 1989, 9,086 cases of adverse reaction to DEET were reported, with 82 percent occurring between May and September (Veltri et al., 1994). During 1993 and 1994, 6,943 cases of adverse reaction were reported to the American Association of Poison Control Centers (AAPCC) (Page et al., 1996). A 1980 EPA report estimated that approximately 38% of Americans are exposed to DEET each year and that 200 million people are exposed annually worldwide (Chrislip et al., 1985; Fradin, 1998).

8.0 REGULATORY STATUS

U. S. government regulations pertaining to DEET are summarized in **Table 1**.

DEET is an EPA-registered insecticide. In 1991, notice was sent to manufacturers, formulators, producers, and registrants of DEET-containing products regarding new label requirements implemented under the Label Improvement Program (LIP) established in 1980 (USEPA, 1991). The new label requirements were a result of EPA concern for individuals who may be hypersensitive to DEET, based on reports of adverse reactions from topical applications

of the chemical and from accidental exposures, such as swallowing or spraying in the eye. The EPA mandated that labels should include the following statements:

- “Read all directions before using this product.”
- Do not spray in enclosed areas. (For sprays and aerosols only)
- Do not apply over cuts, wounds, or irritated skin.
- Do not apply to eyes and mouth and do not apply to the hands of young children. Do not spray directly on face.
- Use just enough repellent to cover exposed skin and/or clothing. Do not use under clothing. Avoid overexposure. Frequent reapplication and saturation is unnecessary for effectiveness.
- After returning indoors, wash treated skin with soap and water. Wash treated clothing.
- Use of this product may cause skin reactions in rare cases. If you suspect that you or your child is reacting to this product, wash treated skin and call your local poison control center. If you go to a doctor, take this repellent with you.

Changes made to FIFRA in 1988 called for the EPA to re-evaluate all registered pesticides initially evaluated before November 1, 1984, to meet more stringent health and safety requirements. The re-evaluations are based on any new information of risks of a compound to human health or the environment. In 1996, the EPA announced its Reregistration Eligibility Decision (RED) Development Schedule (OPP, 1998), and DEET, along with 40 other pesticides, underwent a comprehensive safety re-evaluation. This resulted in the requirement that manufacturers of DEET-containing products display prominently on the label the product’s use as an insect repellent before any cosmetic claims. Also, EPA no longer allows child safety claims on the labels of products that contain 15% or less DEET, since scientific data have yet to support such claims based on the percentage of active ingredient.

In the early 1990s, when reports of adverse health effects, particularly from those containing high DEET concentrations, were published, the New York Department of Environmental Conservation (NYDEC) proposed a ban of insect repellents containing more than 30% DEET (Anonymous, 1993). The ban was to go into effect on May 8, 1992; however, it was not implemented pending further investigation into the safety of DEET. The New York

Supreme Court later overturned the ban because proper procedures were not followed for the cancellation of product registration.

Table 1. Regulations Relevant to DEET

	Regulation	Summary of Regulation
E P A	40 CFR Part 455	<p>DEET is regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as an organic pesticide active ingredient (PAI). The following requirements are included in this section:</p> <ul style="list-style-type: none"> • EPA Census Code – 171 • Pesticide/Shaugnessy Code – 80301 • Pollution Control Devices – Activated Carbon Filtration <p>DEET also appears in Table 10 to Part 455, “List of Appropriate Pollution Control Technologies,” which lists pollution control devices or substrates for compliance with the Zero/P2 discharge standards adopted by EPA.</p>
F E M A	44 CFR Part 323	<p><u>Guidance on Priority Use of Resources in Immediate Post Attack Period (DMO-4):</u> DEET (75% in denatured alcohol) is listed in Appendix 1 to Part 323 and is considered an item “essential to sustain life at a productive level to assure national survival in an emergency.”</p>

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

Exposure to DEET can occur via ingestion, inhalation, or dermal contact. In humans, the signs and symptoms of DEET toxicity can include comas and seizures occurring 30-60 minutes after ingestion, hypotension, bradycardia, confusion, urticaria, abdominal pain, nausea, vomiting, skin irritation, contact rash, acute psychosis, and a burning sensation of the eyes, lips, tongue, and mouth (Leikin and Paloucek, 1998).

Osimitz and Murphy (1997) conducted a comprehensive review of animal toxicology studies, clinical reports of neurological adversities in children and adults, and available Poison Control Center records and concluded that the risk of adverse effects from label-directed use was low. However, a recent criticism of this review calls for continued caution for the use of DEET in children, pointing out that Osimitz and Murphy reviewed single dose data and did not address the possible effects of accumulation (Garrettson, 1997).

9.1.1.1 DEET and the Gulf War Syndrome

In veterans of the Persian Gulf War, impaired cognition was found in those having worn pet flea-and-tick collars containing cholinesterase-inhibiting chemicals during the war (Haley and Kurt, 1997; Haley et al., 1997). Common symptoms included distractibility, difficulty remembering, depression, insomnia, fatigue, slurring of speech, confused thought process, and migraine-like headaches (Haley and Kurt, 1997). Some veterans were also exposed to organophosphates and other cholinesterase-inhibiting chemicals such as pesticides and pyridostigmine bromide, an anti-nerve gas tablet used prophylactically (Haley and Kurt, 1997). Those applying insect repellent formulations containing 33% to 75% DEET to their skin showed signs of arthro-myo-neuropathy. The prevalence of this neurotoxic syndrome increased with the amount of DEET used (Haley and Kurt, 1997). Common symptoms included joint and muscle pain, difficulty in lifting heavy objects, muscle fatigue after exertion, and tingling or numbing of the hands, arms, feet, and legs.

Prolonged exposure of hens to the combination of DEET, pyridostigmine bromide (PB), and the insecticide permethrin (doses and duration n.p.) resulted in enhanced neurotoxicity, which was linked to inhibition of cholinesterase activity (CA) (Weitz et al., 1997). Inhibition of CA was believed to be a contributing factor in Gulf War Syndrome. In a similar study, hens exposed 5 days/week for 2 months simultaneously to 500 mg (2.61 mmol) DEET/kg/day (s.c.), 5 mg PB/kg/day in water (gavage), and 10 mg chlorpyrifos (an organophosphate insecticide)/kg/day (s.c.) showed significantly greater (and dose-dependent) neurotoxicity than observed from any binary treatment combination, or from treatments with the agents alone (Abou-Donia et al., 1996a). However, Weitz et al. (1997) observed no synergistic inhibition of CA or binding to receptors *in vitro*. In a recent study, DEET (200 mg/kg; 1.05 mmol/kg) significantly decreased CA in rat whole brain to 60% of control when administered in conjunction with PB (Chaney et al., 1998).

9.1.1.2 Case Studies

The studies discussed in this section are presented in **Table 2**.

Most case reports of DEET toxicity involved ingestion or dermal contact resulting in symptoms including encephalopathy (Gryboski et al., 1961), convulsions and seizures (Lipscomb et al., 1992; Oransky et al., 1989; Tenenbein, 1987), cardiovascular effects (Fraser et al., 1995; Clem et al., 1993), manic psychosis (Snyder et al., 1986), and dermatitis or contact urticaria (Amichai et al., 1994; von Mayenburg and Rakoski, 1983; Reuveni and Yagupsky, 1982; Miller, 1982; Lamberg and Mulrennan, 1969). There are also reports of deaths following exposure to DEET (Tenenbein, 1987; Heick et al., 1980).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In this section some authors distinguish between the terms “penetration” and “absorption,” while others use them interchangeably. Those who make the distinction suggest that penetration occurs when a topically applied substance passes into the layers of skin below the epidermis, whereas absorption occurs when a substance passes through the skin or mucosa or other lipid barriers and enters the bloodstream or lymphatic system of an organism with distribution to other tissues and subsequent metabolism (biotransformation) or elimination (clearance) (Robbins and Cherniack, 1986).

Review by Robbins and Cherniack (1986)

The biodistribution of DEET has been studied extensively in animal models as well as in humans. Robbins and Cherniack (1986) conducted a comprehensive review of studies published prior to 1986.

Human absorption of DEET is similar to that seen in the hairless dog. Because there are no studies of DEET distribution in human tissue, data must be extrapolated from animal data. Human excretion of DEET is rapid, although to a lesser extent than that observed in most animal models. Comparison of human and animal absorption data is confounded by differences in methodologies, and a lack of standardization in the testing of human skin both *in vitro* and *in*

vivo. Most studies that have been performed did not take into consideration probable human exposure, in which the applied DEET is not washed off.

In animals, DEET appears to be partially and rapidly absorbed from the skin after dermal administration (~10-60%, depending upon species), and rapidly cleared from the blood, with persistence in the skin. DEET is metabolized in the liver with rapid excretion in the urine, and minimal fecal elimination.

Table 2. Case Reports of Human Toxicity

Sex and Age of Individuals	Chemical Form and Concentration	Route/Dose	Exposure	Results/Comments	Reference
F, 3.5 yr old	DEET, 15%	Dermal: 180 mL	Spraying child, bedding, and nightclothes with OFF! for 2 wk	Encephalopathy, which included symptoms of tremors, crying spells, confusion, slurred speech, stiffening of extremities, and staggering gait.	Gryboski et al. (1961)
M, 5 yr old	DEET, 95% in Muskol , % in OFF! n.p.	Dermal: dose n.p.	Single application of Muskol then application of OFF! later in the day	Seizures. A urine sample collected 9-30 h after exposure revealed a DEET concentration of 0.003 µ g/mL (method of analysis n.p.).	Lipscomb et al. (1992)
5 M, 3-7 yr old, 29 yr old	DEET, concn. n.p.	Dermal: dose n.p.	< 3 topical applications	Seizures 8 to 48 h after application. Physical exams and laboratory tests were normal. One patient developed urticaria before his seizure.	Oransky et al. (1989)
F, 1 yr old	DEET, 47.5%	Oral: ~25 mL	Single exposure, ingestion of half of 50-mL bottle of insect repellent	Unresponsiveness, seizure, and hypertonia. Patient showed a positive response to treatment with activated charcoal and a saline cathartic and was normal 20 h later.	Tenenbein (1987)
F, 14 yr old	DEET, 95%	Oral: 50 mL	Single exposure	Unconsciousness, hypertonia, dilated pupils, and tremors.	Tenenbein (1987)
F, 16 yr old				Comatose state: no corneal, blink, gag, or deep-tendon reflexes. Patient showed a positive response to treatment and was normal 30 h later.	
F, 33 yr old				Unconsciousness, irregular breathing, comatose, pulseless, seizure during first 24 h after exposure, bowel infarction, and death on second day.	
M, 26 yr old				Death. Urine level was 0.52 mmol/L. Drug screening was positive for cannabinoids.	
F, 19 yr old	DEET, 95%	Oral: 15-25 mL	Ingestion of Muskol	Cardiac abnormalities, including right and left atrial enlargement 2 h post-ingestion. Patient returned to normal 24 h later.	Fraser et al. (1995)

Table 2. Case Reports of Human Toxicity (Continued)

Sex and Age of Individuals	Chemical Form and Concentration	Route/Dose	Exposure	Results/Comments	Reference
F, 16 yr old	DEET, concn. n.p.	Dermal: dose n.p.	Spraying on insect repellent	Lightheadedness, nausea, vomiting, diarrhea, tremors, chills, and hypotension. Patient returned to normal 24 h later.	Clem et al. (1993)
M, 30 yr old	DEET, concn. n.p.	Dermal: dose n.p.	Daily topical application of insect repellent for 3 wk	Pigmented skin, macular lesions, manic psychosis, including aggressiveness, hyperactivity, rapid speech, and grandiose delusions.	Snyder et al. (1986)
M, 20 yr old	DEET, 33%	Dermal: dose n.p.	Topical application of repellent	Burning sensation and skin eruption 8 h post-application. Diagnosis of irritant contact dermatitis.	Amichai et al. (1994)
M, 4 yr old	DEET, concn. n.p.	Dermal: dose n.p.	Topical application of Autan to entire body in 2 separate incidents	Generalized erythema with severe pruritus 10 min after exposure. 1 h after being in the water, skin was normal in both incidents.	von Mayenburg and Rakoski (1983)
10 M, 18-20 yr old	DEET, 50%	Dermal: dose n.p.	Nightly topical application of repellent to face, neck, upper trunk, and legs	Dermatitis consisting of erythema, hemorrhagic blisters, and deep ulcerations.	Reuveni and Yagupsky (1982)
F, 42 yr old	DEET, 52%	Dermal: dose n.p.	Touching someone who had been sprayed with DEET	Generalized pruritus and angioedema, nausea, and unconsciousness. Periorbital edema developed 1 wk after exposure.	Miller (1982)
63 M, ages n.p.	DEET, 75%	Dermal: dose n.p.	Exposure to liquid or aerosol, 10 drops on one-inch gauze squares	Bullae or erosions resembling an abrasion or burn, blisters, and local necrosis.	Lamberg and Mulrennan (1969)
F, 6 yr old	DEET, 15%	Dermal: dose n.p.	Spraying on at least 10 locations on body	Reye-like syndrome that included lethargy, mood changes, nightmares, vomiting, colicky abdominal pain, headaches, ataxia, disorientation, convulsions, coma, and death 8 d after exposure.	Heick et al. (1980)

Abbreviations: concn. = concentration; d = day(s); F = female; h = hour(s); M = male; min = minute(s); n.p. = not provided; wk = week(s); yr = year(s).

In mice, DEET is distributed to the liver, kidney, bladder, and lacrimal glands. Because excretion rates are high (97% of absorbed dose within 40 hours), bioaccumulation rarely occurs.

Accumulation in fetal organs, while reported (Gleiberman et al., 1975; cited by Robbins and Cherniack, 1986), has been disputed (Blomquist et al., 1975; cited by Robbins and Cherniack, 1986).

Studies Not Previously Reviewed

Details of these studies are presented in **Table 3**.

9.1.2.1 Human Studies

In vitro permeation studies comparing pure DEET (100%) to commercial mosquito repellents containing 6.2-95% DEET and solutions containing 10% DEET in 30-90% ethanol were conducted using excised human skin (Stinecipher and Shah, 1997). The cumulative amount of DEET which penetrated human skin from commercial products corresponded to the amount of DEET in the formulation, with 100% DEET having penetrated to the greatest extent. Ethanol was found to enhance the penetration of DEET, since the amount of DEET that penetrated from ethanolic solutions was greater than that from pure DEET, with optimal performance from preparations containing 30-45% ethanol.

The *ortho* and *para* isomers of DEET are by-products in the synthesis of *meta*-DEET, the main form used in many commercial products. Based on reported oral LD₅₀ values (species n.p.), the *ortho* isomer is twice as toxic as the *meta* and *para* isomers, (Ambrose et al., 1959; Ambrose and Yost, 1965; both cited by Stinecipher and Shah, 1998). Reports of adverse effects following topical use of DEET-containing formulations prompted an investigation to determine the extent of dermal penetration of each isomer, the effect of vehicle on the penetration of each, and which isomer, if any was responsible for the toxic effects observed (Stinecipher and Shah, 1998). The steady-state penetration rates of *ortho*, *para*, and *meta* isomers of DEET, applied neat in aqueous solution, or in solutions containing 45 or 90% ethanol to excised human skin, were determined. Steady-state fluxes were not affected by the composition of the vehicle, except for the *ortho* and *para* isomers in 45% ethanolic solutions, which had significantly higher

penetration rates than with other vehicles. Despite the higher flux rates observed in some instances, the authors concluded that the toxic effects observed after topical use of DEET could not be directly attributed to the small amounts of the *ortho* or *para* isomers present in the formulations.

9.1.2.2 Animal Studies

When administered intraperitoneally (i.p.) at 0.5 g/kg (2.6 μ mol/kg) in corn oil to CD-1 mice DEET increased plasma ammonia levels (Heick et al., 1988). The DEET-dosed animals became drowsy, then comatose, with complete recovery within 1-2 hours. The level of consciousness of the animal could not be correlated to the level of plasma ammonia.

DEET (200 μ M; 38.3 μ g/mL) was rapidly metabolized in liver microsome incubations prepared from male Wistar rats having unlimited access to 0.1% phenobarbital in drinking water for 7 days prior to sacrifice (Taylor, 1986). Benzylic hydroxylation, *N*-deethylation, and combinations of these reactions were confirmed by detection of the presence of the metabolites *N,N*-diethyl-*m*-hydroxymethylbenzamide, *N*-ethyl-*m*-toluamide, *N*-ethyl-*m*-hydroxymethylbenzamide, and *m*-toluamide, as well as *N,N*-dimethyl-*m*-formylbenzamide, in methyl *tert*-butyl ether extracts using capillary GC and verified by comparison with authentic standards. In another study, DEET (200 μ M; 38.3 μ g/mL) degraded more rapidly in liver microsome incubations prepared from male Wistar rats than from those of female rats, with half-lives of 10 and 15 minutes, respectively. The results suggest a sex difference in the metabolism of DEET. The benzylic methyl hydroxylated metabolite and the *N*-demethylated metabolite were identified in males and female rats (Yeung and Taylor, 1988).

The absorption, distribution, metabolism, and elimination of DEET (single or repeated doses of 100 or 500 mg/kg (0.523 or 2.61 mmol/kg) orally or 100 mg/kg (0.523 mmol/kg) dermally) were studied in male and female CD rats (Schoenig et al., 1996). After oral administration, 85-91% of the dose was recovered in urine and 3-5% in feces. The overall pattern of distribution was similar for males and females. The fastest excretion rate was found in the repeated low-dose oral group, followed by the single low-dose oral and single high-dose oral

groups. In the dermal group, 74-78% of the dose was recovered in the urine, 4-7% in feces, and 6.5% on the surface of the skin at the application site. Amounts recovered from tissues of all dose groups after 7 days ranged from 0.15-0.67%. Peak blood concentrations were significantly higher in orally versus dermally dosed animal groups; the liver, kidney and fat retained higher levels of radioactivity than blood for either route. DEET was completely metabolized before being excreted in the urine, with little or no unchanged parent compound remaining.

A study was performed to determine the effect of the vehicle on DEET penetration using excised abdominal cotton rat skin in Franz-type diffusion cells, with the goal of formulating products for human use effective in reducing DEET penetration (Qiu et al., 1998). Incorporation of up to 50% ethanol into gel formulations significantly increased DEET steady-state penetration rates, while greater amounts of ethanol had the opposite effect, possibly due to its dehydrating effect on skin. Incorporation of moisturizing agents had no significant effect, but the addition of various polymers and 75% ethanol into gel emulsion DEET formulations decreased steady-state penetration rates up to 22.7%. A topical formulation incorporating PEG 400, Carbopol 940F, and Pemulen TR-2 was also effective in inhibiting DEET skin penetration.

Using rabbit liver homogenate (study details n.p., therefore not included in Table 3), DEET was shown to be metabolized *in vitro* predominantly by an oxidation of the aromatic methyl group and, to a lesser extent, by an oxidative *N*-dealkylation (Stinn et al., 1986, abstract). The main metabolites, accounting for more than 90% of those detected, were *N,N*-diethyl-*m*-hydroxy-methylbenzamide and *N*-ethyl-*m*-toluamide.

In rabbits, peak blood levels of the parent compound were reached 2-4 hours after topical application of a formulation containing 10.34% DEET (study details n.p., therefore not included in Table 4) (Maniar et al., 1991, abstract). A study conducted in male New Zealand white rabbits to determine the acute dermal absorption of 1 g/kg (5.23 μ mol/kg) of a formulation containing 10% DEET in liposphere or ethanol vehicle found the bioavailability of DEET from the ethanol solution to be 45% versus 16% from the lipospheric solution (Domb et al., 1995). Following i.v. administration of DEET (0.1 mL/kg of a formulation containing 10% DEET in ethanol), 74% was recovered in urine versus 39% and 19%, respectively, from dermal dosing of

10% DEET in the ethanolic and lipospheric solutions. About 12% of the dermally administered dose was recovered from skin at the application site.

Following an i.v. dose of 2.5-6.0 mg/kg (0.013-0.031 mmol/kg) DEET in 4 adult male beagles, linear pharmacokinetics, in which DEET underwent distribution and rapid elimination, were demonstrated (Qiu et al., 1997). When two commercial gel emulsion preparations containing DEET (one with 7.125% and another with 7.5%) were applied dermally (15 mg/kg; 0.078 mmol/kg), the repellent was absorbed faster from the formulation containing the 7.125% concentration.

In Yorkshire pigs, DEET ($4 \mu\text{g}/\text{cm}^2$; $0.021 \mu\text{mol}/\text{cm}^2$) was used to determine the effect of air flow velocity over the skin surface during skin penetration (Reifenrath et al., 1991). Increasing the rate of air flow over the skin from 60 mL/min to 600 mL/min significantly increased evaporation from the skin surface, decreased the residues in the upper skin layer, and decreased the penetration of DEET in the epidermis.

In a study of dermal versus i.v. administration of DEET conducted using 4 Hereford heifers, elimination rate constants were not significantly different at concentrations of 10 mg/kg (0.052 mmol/kg) or 2.5 mg/kg (0.013 mmol/kg) (Taylor et al., 1994).

9.1.2.3 Species Comparisons

The dermal absorption of radiolabeled DEET was determined *in vivo* in male Sprague-Dawley rats and Rhesus monkeys following application of single ($44 \mu\text{g DEET}/100 \mu\text{L acetone}$; $0.23 \mu\text{mol}/100 \mu\text{L acetone}$) or repeated doses of DEET (three $33\text{-}\mu\text{L}$ doses, at 2-hour intervals in the rat or 0.5-hour intervals in the monkey) (Moody et al., 1989). Skin penetration in rats dosed mid-dorsally was comparable to that obtained in monkeys dosed on the forehead and dorsal side of the paw. The extent and rate of absorption in the monkey were highly dependent upon the anatomic site, with the greatest penetration observed for the ventral side of the forepaw, followed by the forehead, dorsal side of the forepaw, and forearm. No significant differences in the dermal absorption of DEET were noted after single or repeated dosing in either species.

A study was conducted to evaluate the *in vitro* skin penetration of five DEET-containing

formulations applied at a concentration of 320-360 $\mu\text{g}/\text{cm}^2$ 1.6 (7-1.88 $\mu\text{mol}/\text{cm}^2$) using human and pig skin (Reifenrath et al., 1989). No significant differences in the penetration and evaporation of formulations containing silicone polymer, acrylate polymer, and fatty acid versus control (10 $\mu\text{g}/\text{cm}^2$; 0.052 $\mu\text{mol}/\text{cm}^2$) were seen. However, a formulation consisting of a proprietary polymer reduced the evaporation and penetration rates compared to controls. Tests using fresh and frozen pig skin showed no significant differences, indicating that DEET was not significantly metabolized by pig skin at the dose studied. A minimum evaporation rate of 5 $\mu\text{g}/\text{cm}^2/\text{h}$ (0.03 $\mu\text{mol}/\text{cm}^2/\text{h}$) for DEET over 5-15 minutes was determined for human and pig skin. Combining two repellents, DEET and dimethyl phthalate, had no effect on the total penetration and evaporation of the other, although the maximum penetration and evaporation rates were lower and extended over a longer time period, indicating that the two chemicals share common routes of loss.

In vitro, penetration of DEET in the mouse (33.3 $\mu\text{g}/\text{cm}^2$; 0.174 $\mu\text{mol}/\text{cm}^2$), rat (38.7 $\mu\text{g}/\text{cm}^2$; 0.202 $\mu\text{mol}/\text{cm}^2$), hairless guinea pig (12.5 $\mu\text{g}/\text{cm}^2$; 0.0653 $\mu\text{mol}/\text{cm}^2$), pig (19.4 $\mu\text{g}/\text{cm}^2$; 0.101 $\mu\text{mol}/\text{cm}^2$), human (44.7 $\mu\text{g}/\text{cm}^2$; 0.234 $\mu\text{mol}/\text{cm}^2$), as well as cultured human skin (27.9 $\mu\text{g}/\text{cm}^2$; 0.146 $\mu\text{mol}/\text{cm}^2$) was assessed using an automated, flow-through skin penetration apparatus (AIDA) (Moody and Nadeau, 1993). In addition, *in vivo* dermal penetration was also measured in the rat and hairless guinea pig. *In vitro*, the percentage penetrated dose ranged from 11-38%, in the following order: guinea pig < cultured human skin < pig < rat < human < mouse. In general, *in vitro* data tended to underestimate *in vivo* dermal penetration of DEET.

A species comparative *in vitro* skin study of the penetration of commercial preparations (OFF! , Deep Woods , and Muskol , containing 14, 24 , and 95% DEET, respectively) used the skin of male Sprague-Dawley rats, female guinea pigs, and female humans (Moody et al., 1995). Washing the skin with soap and water at 24 hours post-application increased the percentage of DEET recovered in the wash with the more concentrated formulations. Moody et al. (1995) proposed that this “wash-in” effect may have toxicologic consequences by increasing the systemic absorption of DEET. Rather than decreasing systemic concentration, washing has the

opposite effect than simply rubbing off the dose, presumably by enhancing the penetration of DEET which otherwise would have remained within the skin layers. While the skin of rats and guinea pigs had similar dermal penetration, pharmacokinetic profiles were markedly different between the two species.

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
9.1.2.1 Human Studies						
Excised human skin samples obtained from elective plastic surgery	n.p.	DEET, 97% Commercial preparations: Everglades (95% DEET), Repel Deerhunters (52.25% DEET), OFF! Skintastic (6.65% DEET), Skeddadle (6.2% DEET)	300 μ L samples applied to donor skin: Everglades (444.2 mg/cm ² ; 2.322 mmol/cm ²), Repel Deerhunters (206.34 mg/cm ² ; 1.0786 mmol/cm ²), OFF! Skin-tastic (45.56 mg/cm ² ; 0.2382 mmol/cm ²), Skeddadle (18.09 mg/cm ² ; 0.09456 mmol/cm ²)	Sampling and HPLC analysis occurred at various intervals up to 36 h	For the commercial preparations, the order of cumulative DEET penetration was DEET (control) Everglades >Repel Deerhunters >Skeddadle OFF! Skintastic .	Stinecipher and Shah (1997)
			300 μ L (46.88 mg/cm ² ; 0.2451 mmol/cm ²) homogeneous solutions of 10% DEET in 30, 45, 60, 75, and 90% ethanol		Ethanol enhanced the penetration of DEET. The cumulative amount that penetrated was about 2 times greater for 10% DEET in 30 or 45% ethanolic solutions than for pure DEET.	
Excised human skin samples obtained from elective plastic surgery	n.p.	<i>m</i> -DEET, 97%; <i>p</i> -DEET and <i>o</i> -DEET, concn. n.p.	300 μ L samples applied to donor skin: neat isomer (78.13 mg/cm ² ; 0.4084 mmol/cm ²), 5 mg/mL solution (7.81 mg/cm ² ; 0.0408 mmol/cm ²), 10% isomer in 90% ethanol (46.88 mg/cm ² ; 0.2451 mmol/cm ²), 10% isomer in 45% ethanol (46.88 mg/cm ² ; 0.2451 mmol/cm ²)	Sampling and HPLC analysis occurred at various intervals up to 36 h	There was no statistically significant difference in the permeation of the three isomers. Significantly higher amounts of DEET and its isomers penetrated the skin from solutions containing 45% ethanol versus neat, water, and 90% ethanol solutions. The permeation of the <i>para</i> isomer was enhanced to a greater extent than that of the <i>meta</i> and <i>ortho</i> isomers.	Stinecipher and Shah (1998)

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
9.1.2.2 Animal Studies						
Mouse						
CD-1, age n.p.	5 M	DEET, concn. n.p.	i.p.: 0.5 g/kg (2.6 μ mol/kg)	Plasma sampling and HPLC analysis at 0.5, 1.0, 1.5, 2.0, 3.0, and 5 h	Significant increase in ammonia levels in treated mice versus controls at 3 and 5 h. DEET-dosed animals became drowsy, then comatose, with complete recovery within 1-2 h. The level of consciousness of the animal could not be correlated to the level of plasma ammonia.	Heick et al. (1988)
Rat						
phenobarbital-induced liver microsomes from Wistar rats (age n.p.)	M	DEET, concn. n.p.	<i>In vitro</i> : 200 μ M (38.3 μ g/mL)	Incubated at 37° C for 45 min	Metabolism corresponding to benzylic hydroxylation and <i>N</i> -deethylation, and combinations of these reactions, were detected in methyl <i>t</i> -butyl ether extracts via capillary GC. The two major metabolites had a mean yield of 69%.	Taylor (1986)
phenobarbital-induced liver microsomes from 12 wk old Wistar rats	M and F,	DEET, concn. n.p.	<i>In vitro</i> : 200 μ M (38.3 μ g/mL)	Incubated at 37° C for 2 h	DEET degraded more rapidly from incubations prepared from male rats than those from female rats, with half-lives of 10 and 15 min, respectively. The results suggest the presence of a sex difference in the metabolism of DEET.	Yeung and Taylor (1988)

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
CD	M and F Group I: 4/sex Group II: 6 dose groups of 5/sex Group III: 5/sex	¹⁴ C-labelled DEET, 98.9%	Group I: single oral dose of 100 mg/kg (0.523 mmol/kg) Group II: single or repeated doses of 100 or 500 mg/kg (0.523 or 2.61 mmol/kg) orally, or 100 mg/kg (0.523 mmol/kg) dermally Group III: single oral dose of 500 mg/kg (2.61 mmol/kg)	Group I: Sampling (blood) up to 24 h post-application Group II: Sampling (tissues and excreta) up to 168 h post-application Group III: Sampling (excreta) up to 72 h post-application	Oral administration: 85-91% dose recovered in urine and 3-5% in feces. The fastest excretion rate was noted in the repeated low-dose group, followed by the single low-dose and the single high-dose groups. Dermal administration: 74-78% dose recovered in urine, 4-7% in feces, and 6.5% on the surface of the skin. No unchanged parent compound was detected in urine after either route; 2 major urinary metabolites were identified.	Schoenig et al. (1996)
Excised abdominal skin from 4 wk old Cotton rats	number and sex n.p.	DEET, >98.5%	<i>In vitro</i> , dermal: 0.15 g (0.78 μ mol)/formulation Formulations: 12% DEET solutions with 40, 50, 75, or 100% ethanol or PEG 400; gel emulsions containing 10 or 15% DEET and various polymers or humectants; gel emulsions containing 7.5% DEET, various polymers, and PEG 400 or ethanol	Sampling and HPLC analysis occurred at 0.5, 2, 4, 6, 8, and 10 h	40 and 50% aqueous ethanol solutions increased the steady-state penetration rate by 157 and 137%, respectively, while a 75% aqueous solution, neat ethanol, and PEG 400 decreased the rate by 67, 74, and 59%, respectively. Humectants had no significant effect. Polymers and 75% ethanol decreased rates up to 22.7%. A formulation incorporating PEG 400, Carbopol 940F, and Pemulen TR-2 was also effective in reducing DEET skin permeation.	Qiu et al. (1998)

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rabbit</i>						
New Zealand white, age n.p.	8 M	DEET, >95%	i.v.: 0.1 mL/kg of a 10% DEET solution in ethanol dermal: 1 g/kg (5 μ mol/kg) of 10% DEET in liposphere or ethanol solution	Blood and urine collected at various intervals up to 24 h, then daily for 7 d	The bioavailability of DEET from the ethanol solution was 45% and that from lipospheres was 16%. Approximately 74% of the i.v. dose was recovered in urine, versus 39 and 19%, respectively, of the dermal ethanolic and lipospheric formula-tions.	Domb et al. (1995)
<i>Dog</i>						
Adult beagles, age n.p.	4 M	DEET, >98.5%; formulation A: OFF! Skintastic II, 7.125% DEET; formulation B: gel emulsion, 7.5% DEET	i.v.: 2.5 mg/kg (0.013 mmol/kg) into the cephalic vein. After a 2-wk washout, 6.0 mg/kg (0.031 mmol/kg) given. dermal: 15 mg/kg (0.078 mmol/kg) Formulation A applied to anterior dorsal region along backline. After a 2-wk washout, formulation B was applied.	Blood sampling at various intervals for 15 min-18 h post-application	Linear pharmacokinetics was demonstrated after i.v. dosing. DEET underwent extensive extravascular distribution and rapid elimination. The transdermal absorption of DEET was faster from formulation A than from B. The bioavailabilities were 18.3% and 14.0%, respectively.	Qiu et al. (1997)
<i>Pig</i>						
Yorkshire, age n.p.	9 F	¹⁴ C-labelled DEET, \approx 98%	dermal: 4 μ g/cm ² (0.02 μ mol/cm ²)	48 h after application	Increasing the rate of air flow over the skin from 60 mL/min to 600 mL/min significantly increased evaporation from the skin surface, decreased the residues in the upper skin layer, and decreased the penetration of DEET in the epidermis.	Reifenrath et al. (1991)

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Cattle</i>						
Hereford, age n.p.	4 F	DEET, >97%	i.v.: 2.5 mg/kg (0.013 mmol/kg) dermal: 10 mg/kg (0.052 mmol/kg)	Blood samples were obtained 15-1440 min post-application	73% of the dermally applied dose was absorbed systemically, with peak plasma concentrations at 37.5 min. The elimination rate constants were 0.0046/min after i.v. dosing and 0.0035/min after dermal dosing. Linear pharmacokinetics was demonstrated after i.v. dosing.	Taylor et al. (1994)
9.1.2.3 Species Comparisons						
Sprague-Dawley rats and Rhesus monkeys (<i>Macaca mulatta</i>), ages n.p.	5-8 M rats and monkeys/group	¹⁴ C-labelled DEET, >98%	single dose: 44 µg; (0.23 µ mol) on shaved mid-dorsal region of rats and the forearm, forehead, and ventral and dorsal sides of the forepaw of monkeys repeated doses: three 33-µ L doses applied at 2-h (rat) or 0.5-h (monkey) intervals. Dose occluded for 24 h, then washed.	Urine samples collected at 4 and 8 h (Day 1), then at 24-h intervals for 7 d	Absorption in rats was 36%. The extent and rate of absorption in the monkey were highly dependent upon the anatomic site, with penetration of 14% from the forearm, 27% from the dorsal side of the paw, 33% from the forehead, and 68% from the ventral side of the forepaw. No significant difference was seen between the total percentage absorbed with single versus repeated doses for either species.	Moody et al. (1989)
Human and pig (strain and/or age n.p.)	Human abdominal or breast skin (sex n.p.) and pig skin (3-9, sex n.p.)	¹⁴ C-labelled DEET, 98% in the following formulations: A=silicone polymer B=acrylate polymer C=fatty acid D=proprietary polymer E=dimethyl phthalate Control=unformulated	dermal: 320-360 µ g/cm ² (1.67-1.88 µ mol/ cm ²); control: 10 µ g/cm ² (0.052 µ mol/cm ²)	Sampling occurred at various intervals up to 50 h	The evaporation and penetration of A, B, and C were not significantly different from those of the control. D showed significantly less evaporation and less penetration than the control. For E, the total evaporation and penetration of each repellent did not change, but the maximum evaporation and penetration rates were lower and extended over a longer period of time.	Reifenrath et al. (1989)

Table 3. Absorption, Distribution, Metabolism, and Elimination of DEET (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Rhino mice (10 mo old), Sprague-Dawley rats (5 wk old), hairless Crl: IAF/HA (hr/hr)BR guinea pigs (9 mo), Yorkshire pig (8-9 wk old), and Caucasian human (33 yr old)	n=4 for each skin type M mouse, rats, and pig (back skin); F guinea pigs (back skin), and F human (abdominal skin); M Testskin (human foreskin)	¹⁴ C-ring-labelled DEET, >98%	<i>In vivo</i> and <i>in vitro</i> application of 50 µL at the following dose rates: Species Doses <u>(µg/cm²) (µmol/cm²)</u> mouse 33.3 0.174 rat 38.7 0.202 g. pig 12.5 0.0653 pig 19.4 0.101 human 44.7 0.234 Testskin 27.9 0.146	<i>In vitro</i> : sampling of the receiver fluid at various intervals up to 48 h; <i>in vivo</i> : urinary sampling at 24-h intervals for 14 d	<i>In vitro</i> : the total percentage of absorption were as follows: mouse (36%), human (28%), rat (21%), pig (15%), Testskin (15%), and guinea pig (11%). The <i>in vitro</i> procedure under-estimated the observed <i>in vivo</i> dermal penetration of DEET.	Moody and Nadeau (1993)
Sprague-Dawley rats (5 wk old), hairless guinea pig (9 mo old), Caucasian human (40 yr old)	n=4 for each skin type M rats (back skin), F guinea pigs (back skin), F human (abdominal skin)	OFF! (14.25% DEET); Deep Woods (23.75% DEET); Muskol (95% DEET)	<i>In vitro</i> : 14.5-97.3 mg/cm ² (0.076-0.509 mmol/cm ²) <i>In vivo</i> (rat only): same doses as above	Automated sampling at various intervals up to 48 h; 24-h soap wash	<i>In vitro</i> , the total percentage of absorbed DEET for OFF! , Deep Woods , and Muskol , respectively, were 50, 49, and 44% (rat), 46, 37 and 19% (guinea pig), and 48, 36, and 17% (human). Soap wash percentage recoveries increased for all species with the more concentrated DEET formulations. <i>In vivo</i> , DEET penetration through rat skin was significantly lower than <i>in vitro</i> penetration for each formulation.	Moody et al. (1995)

Abbreviations: concn. = concentration; d = day(s); GC = gas chromatography; h = hour(s); HPLC = high performance liquid chromatography; n = number; n.p. = not provided; PEG = polyethylene glycol; wk = week(s); yr = year(s).

9.1.3 Acute Exposure

Acute toxicity values for DEET are presented in **Table 4**. The details of studies discussed in this section are presented in **Table 5**.

Table 4. Acute Toxicity Values for DEET

Route	Species (sex and strain)	LD ₅₀ /LC ₅₀	Reference
dermal	mouse (sex and strain n.p.)	LD ₅₀ = 3,170 mg/kg (16.67 mmol/kg)	Lewis (1996)
	rat (sex and strain n.p.)	LD ₅₀ = 5,000 mg/kg (26.14 mmol/kg)	Lewis (1996); RTECS (1998)
	rabbit (sex and strain n.p.)	LD ₅₀ = 3,180 mg/kg (16.62 mmol/kg)	Lewis (1996); Mount et al. (1991)
inhalation	rat (sex and strain n.p.)	LC ₅₀ = 5,950 mg/m ³ (31.10 mmol/m ³ ; 760 ppm)	Lewis (1996)
oral	mouse (sex and strain n.p.)	LD ₅₀ = 1,170 mg/kg (6.116 mmol/kg)	RTECS (1998)
	rat (M and F; Female Lac:P Wistar derived)	LD ₅₀ : M = 891 mg/kg (4.66 mmol/kg), 11 d.o.; 2,000 mg/kg (10.45 mmol/kg) 25 d.o.; 1,782 (9.315 mmol/kg) 31-35 d.o.; and 3,564 (18.63 mmol/kg) 47-56 d.o. LD ₅₀ : F = 667 mg/kg (3.49 mmol/kg) 11 d.o.; 1,259 mg/kg (6.581 mmol/kg) 25 d.o.; 1,414 mg/kg (7.392 mmol/kg) 31-35 d.o.; and 3,429 mg/kg (17.92 mmol/kg) 47-56 d.o.	Verschoyle et al. (1992)
	rat (sex and strain n.p.)	LD ₅₀ = 1,950 mg/kg (10.19 mmol/kg)	Lewis (1996); RTECS (1998)
	rabbit (sex and strain n.p.)	LD ₅₀ = 1,584 mg/kg (8.280 mmol/kg)	Lewis (1996); Mount et al. (1991)

Abbreviations: d.o. = days old; F = female; LC₅₀ = concentration lethal to 50% of test animals; LD₅₀ = dose lethal to 50% of test animals; M = male; n.p. = not provided.

McCain et al. (1997) exposed male Sprague-Dawley rats to single oral doses of 2000-5010 mg/kg (10.45-26.19 mmol/kg) DEET. Animals were lethargic and displayed signs of respiratory distress. In a study of the neurotoxicity of DEET in CD rats, animals dosed orally with 50-500 mg/kg (0.26-2.61 mmol/kg) DEET exhibited no impairment of neurologic function or any other toxicity (Schoenig et al., 1993). In rats given single oral doses of 400-5000 mg/kg

(2.09-26.14 mmol/kg) DEET, toxicity decreased with age and females were more sensitive than males (Verschoyle et al., 1992). Doses of 2000-3000 mg/kg (10.45-15.68 mmol/kg) produced a severe rapid decrease in reactivity and muscle tone. Rats given 2500-4000 mg/kg (13.07-20.91 mmol/kg) died between 50 minutes and 24 hours, exhibiting progressive respiratory depression. Sprague-Dawley rats given i.p. doses of 56, 113 or 225 mg/kg (0.29, 0.591, or 1.18 mmol/kg) exhibited dose-related decreases in blood pressure and heart rate at the mid and high doses (Leach et al., 1988). No effects were observed at the low dose.

In guinea pigs, a single dermal application of 200 mL DEET occluded for 4 hours produced no signs of irritation when observed for 72 hours (Tenjarla et al., 1995). Dermal application of 75-100% DEET caused no sensitization (Harvey, 1987).

On the other hand, dermal application of 75-100% DEET to the abraded skin of rabbits caused mild irritation (Harvey, 1987). Rabbits experienced edema of the nictitating membrane, lacrimation, conjunctivitis, purulent discharge, and occasional corneal cloudiness when exposed ocularly to 10-100 μ L of 100% DEET (MacRae et al., 1984). Eyes returned to normal within 1 week and no permanent damage was observed. Nine New Zealand white rabbits exposed ocularly to 0.1 mL of 50% DEET developed mild opacity lasting 7-10 days (Kellner et al., 1981). Two rabbits developed iritis lasting 4-6 days, while three rabbits developed conjunctivitis within 24 hours after dosing. In a related study, rabbits exposed ocularly to 0.1 mL of 75% DEET developed corneal injury, iritis, and conjunctival irritation; eyes returned to normal after 7 days (Topper and Weeks, 1981).

Dogs and cats given either oral or dermal doses of 0.089-7.128 g/kg (0.46-37.26 μ mol/kg) of a flea and tick spray containing 9% DEET experienced ataxia, seizures, muscle tremors, hypersalivation, restlessness, depression, and incoordination (Mount et al., 1991). Dogs treated i.p. with 225 mg/kg (1.18 mmol/kg) of 75% DEET had a significant decrease in blood pressure and heart rate compared to controls (Leach et al., 1988).

Table 5. Acute Exposure to DEET

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Rat						
Adult Sprague-Dawley, age n.p.	10 M/dose	DEET, 98.5%	Oral: 2000, 2510, 3160, 3980, and 5010 mg/kg (10.45, 13.12, 16.52, 20.81, and 26.19 mmol/kg)	Single dose, 14- d observation period	Animals were lethargic and showed signs of respiratory distress.	McCain et al. (1997)
CD, 12 wk old	10 M and F/dose	DEET, 98%	Oral: 50, 200, and 500 mg/kg (0.26, 1.04, and 2.61 mmol/kg)	Single dose, 14- d observation period	Treatment had no effect on body weights, food consumption, incidence of gross lesions, systemic effects, or motor activity.	Schoenig et al. (1993)
Lac:P Wistar derived, 7-9 wk old	M and F, numbers n.p.	DEET, 98%	Oral: 400-5000 mg/kg (2.09-26.14 mmol/kg)	Single dose, 8- d observation period	Toxicity decreased with age and was greater in females than males. Doses of 2000-3000 mg/kg produced a severe rapid decrease in stimulus reactivity and muscle tone. Rats given 2500-4000 mg/kg died between 50 minutes and 24 hours, exhibiting progressive respiratory depression.	Verschoyle et al. (1992)
Sprague-Dawley, age n.p.	5 M/dose	DEET, 75%	i.p.: 56, 113, and 225 mg/kg (0.29, 0.591, and 1.18 mmol/kg)	Single injection, observation period n.p.	No effects observed at 56 mg/kg. Dose-related decrease in blood pressure and heart rate seen with higher doses.	Leach et al. (1988)
Guinea Pig						
Charles River hairless, age n.p.	6 M	DEET, concn. n.p.	Dermal: 200 mL	Single application occluded for 4 h, 72-h observation period	No irritation was observed.	Tenjarla et al. (1995)
Hartley albino, age n.p.	Number and sex n.p.	DEET, 75-100%	Dermal: dose n.p.	Exposure and observation period n.p.	Dermal application caused no sensitization.	Harvey (1987)

Table 5. Acute Exposure to DEET (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rabbit</i>						
New Zealand white, age n.p.	Number and sex n.p.	DEET, 75-100%	Dermal: dose n.p.	Exposure and observation periods n.p.	Dermal application caused mild irritation to abraded skin.	Harvey (1987)
New Zealand albino, age n.p.	Number and sex n.p.	DEET, 100%	Ocular: 10, 30, 100 µL	Single application, 168-h observation period	Signs of irritation included edema of the nictitating membrane, lacrimation, conjunctivitis, purulent discharge, and occasional corneal cloudiness. Eyes returned to normal within 1 wk and no permanent damage was observed.	MacRae et al. (1984)
New Zealand white, young adults	9 M or F	DEET, 50%	Ocular: 0.1 mL	Single exposure, 13-d observation period	DEET-treated animals showed mild opacity lasting 7-10 d after dosing. Two rabbits developed iritis lasting 4-6 d. Three rabbits developed conjunctivitis within 24 h after dosing.	Kellner et al. (1981)
New Zealand white, age n.p.	9, sex n.p.	DEET, 75%	Ocular: 0.1 mL	Single exposure, 21-d observation period	Animals developed corneal injury, iritis, and conjunctival irritation, all of which were reversible within 7 d.	Topper and Weeks (1981)
<i>Dog</i>						
Hound, Setter, Shepherd, Pitbull, and mixed breeds, 3 mo to 2 yr old	4 M, 6 F	DEET, 9%	Oral or dermal: 0.089-7.128 g/kg (0.46-37.26 µ mol/kg)	Single dose or application, observation period up to 72 h	Symptoms of toxicity included ataxia, seizures, muscle tremors, hypersalivation, restlessness, depression, and incoordination.	Mount et al. (1991)
Beagles, age n.p.	6 M	DEET, 75%	i.p.: 225 mg/kg (1.18 mmol/kg)	Single injection, observation period n.p.	Significant decrease in blood pressure and heart rate.	Leach et al. (1988)

Table 5. Acute Exposure to DEET (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Cat</i>						
DSH and Siamese, 3 mo to 5 yr old	2 M, 8 F	DEET, 9%	Oral or dermal: 0.089-7.128 g/kg (0.46-37.26 μ mol/kg)	Single dose or application, observation period up to 72 h	Symptoms of toxicity included ataxia, seizures, muscle tremors, hypersalivation, restlessness, depression, and incoordination.	Mount et al. (1991)

Abbreviations: d = day(s); DSH = Domestic Short Hair; F = female; h = hour(s); i.p. = intraperitoneal injection; M = male; mo = month(s); n.p. = not provided; wk = week(s); yr = year(s).

9.1.4 Short-Term and Subchronic Exposure

The details of these studies are presented in **Table 6**.

Charles River CD rats were given daily oral doses of 125, 250, and 750 mg/kg (0.653, 1.31, and 3.92 mmol/kg) DEET for 21 days (Schoenig et al., 1994). Animals in the high-dose group exhibited signs of toxicity including hypoactivity, ataxia, decreased muscle tone, foot splay, urine stains, perinasal encrustation, and perioral wetness. No signs were observed in the mid- and low-dose groups. Sprague-Dawley rats were exposed s.c. to 0.3-1.80 mL/kg (1.6-9.4 mmol/kg) DEET (Wright et al., 1992). No female rats survived more than 10 days; liver and kidney weights were elevated in all DEET-treated groups. Male rats developed skin lesions at the injection site and showed gait disturbance followed by eating of the toes on the affected feet. Autopsy revealed grossly distended, urine-filled bladders. Rats exposed to 250-1500 mg/m³ (1.31-7.841 mmol/m³; 31.9-191.7 ppm) DEET by inhalation 5 days per week for 13 weeks had a significant increase in weight and size; no significant signs of toxicity were seen (Sherman, 1979).

Decreased body weight and food consumption were observed in New Zealand white rabbits given 325 mg/kg/day (1.70 mmol/kg/day) DEET orally for 29 days (Schoenig et al., 1994). No mortality or other signs of toxicity were observed. In another study, rabbits were given 132-528 mg/kg (0.690-2.76 mmol/kg) DEET orally for 15 days (Haight et al., 1979). Those in the high-dose group showed decreased body weight and increased kidney weight. Furthermore, serum calcium levels decreased while cholesterol and triglyceride levels increased. No other signs of toxicity were observed. Rabbits exposed dermally to a commercial insect repellent containing DEET (purity and dose n.p.) for 14 days had increased foldings and indentations on the skin surface, epidermal thinning, and cystic dilations of the dermis containing eosinophilic fluid (Wong and Yew, 1978).

Abou-Donia et al. (1996b) exposed adult Leghorn laying hens to 500 mg/kg (2.61 mmol/kg) DEET s.c. for 5 days per week for 8 weeks. Hens showed decreased activity, diarrhea, and shortness of breath, but recovered within 24 hours after dosing. Neuropathological examination revealed a slight increase in the frequency of enlarged axons.

Table 6. Short-Term and Subchronic Exposure to DEET

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rat</i>						
Charles River CD, age n.p.	25 F/dose	DEET, 98.3%	Oral: 125, 250, and 750 mg/kg (0.653, 1.31, 3.92 mmol/kg)	Daily doses for 21 d, 21-d observation period	High-dose group experienced hypoactivity, ataxia, decreased muscle tone, foot splay, urine stains, perinasal encrustation, and perioral wetness. No symptoms observed in the mid- and low-dose groups.	Schoenig et al. (1994)
Sprague-Dawley, age n.p.	12 F/dose	DEET, 97-98%	s.c.: 0.50, 0.62, 0.78, 0.96, or 1.2 mL/kg (2.6, 3.2, 4.1, 5.0, or 6.3 mmol/kg)	10-d exposure, 20-d observation period	No females survived 10 d of dosing with 1.2 mL/kg. No deaths occurred in 0.50 mL/kg group. Liver and kidney weights were elevated in all treated groups.	Wright et al. (1992)
	20 M/dose		s.c.: 0.30, 0.46, 0.73, 1.15, or 1.80 mL/kg (1.6, 2.4, 3.8, 6.0, or 9.4 mmol/kg)	Exposed 5 d/wk for 9 wk, 9-wk observation period	Most developed skin lesions at one or several injection sites attributed to scratching after dosing. Gait disturbance accompanied by eating of the toes on affected feet was observed. Upon death, autopsies revealed grossly distended, urine-filled bladders.	
Strain and age n.p.	10 M, 10 F	DEET, concn. n.p.	Inhalation: 250, 750, and 1500 mg/m ³ (1.31, 3.92, and 7.841 mmol/m ³ ; 31.9, 95.9, and 191.7 ppm)	Exposed 6 h/d, 5 d/wk, for 13 wk, 13-wk observation period	Considerable increase in weight and size was observed; no significant signs of toxicity were seen.	Sherman (1979)

Table 6. Short-Term and Subchronic Exposure to DEET (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rabbit</i>						
New Zealand white, age n.p.	16 F/dose	DEET, 98.3%	Oral: 30, 100, and 325 mg/kg/day (0.16, 0.523, and 1.70 mmol/kg/day)	Daily doses for 13 d, 29-d observation period	Decreased body weight and food consumption were observed in the high-dose group. No mortality or signs of toxicity were observed in any group.	Schoenig et al. (1994)
New Zealand white, age n.p.	6 M/group	DEET, 95%	Oral: 132, 264, and 528 mg/kg (0.690, 1.38, and 2.76 mmol/kg)	15-d exposure and observation period	Rabbits in the high-dose group showed decreased body weight and increased kidney weight. Serum calcium levels decreased while cholesterol and triglyceride levels increased. No other signs or symptoms were observed in any group.	Haight et al. (1979)
Albino, species and age n.p.	Number and sex n.p.	DEET in a commercial repellent, concn. n.p.	Dermal: dose n.p.	Applied to ears for 14 d, observation period n.p.	Increased foldings and indentations on skin surface, thinning of the epidermis, and cystic dilations (containing eosinophilic fluid) of the dermis were observed.	Wong and Yew (1978)
<i>Chicken</i>						
Leghorn laying hens, 18 mo old	5 F	DEET, 97%	s.c.: 500 mg/kg (2.61 mmol/kg)	Exposure 5 d/wk for 8 wk, 8-wk observation period	Hens showed decreased activity, diarrhea, and shortness of breath, but recovered within 24 h after dosing. Neuropathological examination revealed a slight increase in frequency of enlarged axons.	Abou-Donia et al. (1996b)

Abbreviations: concn. = concentration; d = day(s); F = female; h = hour(s); M = male; mo = month(s); n.p. = not provided; s.c. = subcutaneous injection; wk = week(s).

9.1.5 Chronic Exposure

The details of studies discussed in this section are presented in **Table 7**.

In a two year study, mice, rats, and dogs were given 10-1000 mg/kg/day (0.052-5.23 mmol/kg) DEET orally for 1 to 2 years (Schoenig et al., 1999). Mice and rats in the high dose groups had decreases in body weight and food consumption; female rats also had an increase in serum cholesterol. Dogs in the high dose group had incidences of vomiting, reduced hemoglobin and hematocrit levels, decreased cholesterol, and increased potassium; males also had increased alkaline phosphatase. (Carcinogenic effects are discussed in **Section 9.3**)

The F₂ offspring of CD rats administered 500, 2000, or 5000 ppm (3.91, 15.66, or 39.12 g/m³; 20.4, 81.86, or 204.5 mmol/m³) DEET in the diet continuously during a two-generation reproductive study were given the same dietary concentrations of DEET for nine months (Schoenig et al., 1993). They exhibited no neurotoxic effects other than a slight increase in exploratory locomotor activity at the high dose level. (Reproductive effects are discussed in **Section 9.2**)

Table 7. Chronic Exposure to DEET

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Mice, CD-1, age n.p.	60 M and 60 F/group	DEET, 98%	Oral: 250, 500, or 1000 mg/kg (1.31, 2.61, or 5.23 mmol/kg)	Daily in diet for 18 mo; 18-mo observation period	Decreased body weight and food consumption in the high dose group.	Schoenig et al. (1999)
Rats, CD, age n.p.	60 M and 60 F/group		Oral: 10, 30 or 100 mg/kg (M) (0.052, 0.16, or 0.523 mmol/kg); 30, 100, or 400 mg/kg (F) (0.16, 0.523, or 2.09 mmol/kg)	Daily in diet for 2 yr; 2-yr observation period	Decreased body weight and food consumption, and increased serum cholesterol (F only) in high the dose group.	
Dogs, beagle, age n.p.	4 M and 4 F/group		Oral: 30, 100, or 400 mg/kg (0.16, 0.523, or 2.09 mmol/kg)	Daily in gelatin capsules for 1 yr; 1-yr observation period	Vomiting, reduced hemoglobin and hematocrit levels, increased alkaline phosphatase (M only); decreased cholesterol, increased potassium in the high dose group. One M dog in high dose group exhibited ataxia, tremors, and/or convulsions on several occasions.	
F ₂ offspring of exposed rats, CD, 40 wk old	80 M and 80 F	DEET, 98%	Oral: 500, 2000, or 5000 ppm (3.91, 15.66, or 39.12 g/m ³ ; 20.4, 81.86, or 204.5 mmol/m ³)	Daily in diet for 9 mo; 8-wk observation period	Slight increase in exploratory locomotor activity at the high dose level.	Schoenig et al. (1993)

Abbreviations: concn. = concentration; n.p. = not provided; M = male; F = female; yr = year(s); mo = month(s); wk = week(s).

9.2 Reproductive and Teratological Effects

Several studies, the details of which are presented in **Table 8**, have reported the reproductive and teratological effects of DEET in humans, rats, rabbits, and chick embryos.

Although effects including mental retardation, muscular hypotonia, hearing loss, and coarctation of the aorta have been observed in infants whose mothers used insect repellents containing DEET during pregnancy, a direct relationship between the use of DEET and birth defects has not been demonstrated (Schaefer and Peters, 1992; Hall et al., 1975).

In female rats, oral administration of 125, 250, and 750 mg/kg/day (0.653, 1.31, and 3.92 mmol/kg/day) on gestational days 6-15 caused no external, visceral, or skeletal malformations; however, reduced fetal weight was observed at 750 mg/kg (Schoenig et al., 1994). No reproductive or developmental effects were observed in the fetuses of female and male rats given 0.30 mL/kg (1.6 mmol/kg) DEET s.c. (Wright et al., 1992). No effects on sperm count, morphology, or viability were seen in male rats treated dermally with 100, 300, and 1000 mg/kg (0.523, 1.57, and 5.227 mmol/kg) DEET (Lebowitz et al., 1983).

In female rabbits treated orally or dermally with 30-325 mg/kg (0.16-1.70 mmol/kg) DEET on gestational days 6-18, no treatment-related effects were observed (Schoenig et al., 1994). Female rabbits exposed dermally to 50-1000 mg/kg (0.26-5.227 mmol/kg) on gestational days 1-29, had no reproductive or teratological effects (Angerhofer and Weeks, 1981).

Gross malformations, including ventricular septal defects, anomalous aortic arch patterns, absence of a rump, absence of or malrotated limbs, and CNS malformations, were seen in chick embryos exposed to 1.27 μ mol (243 μ g) DEET by topical application to the chorioallantoic membrane on the second day of incubation (Kuhlmann et al., 1981, abstract). One-third of the 41% of embryos that survived to day 15 showed malformations.

Table 8. Reproductive and Teratological Effects of DEET

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Humans						
Child, 4 yr old	1 M	DEET, 25%	Dermal: dose n.p.	Application to arms and legs of mother once or twice/d during pregnancy	Statomotor retardation, muscular hypotonia, central hearing loss, and strabismus were observed during first month of life. A causal relationship between these effects and prenatal exposure to DEET was not certain.	Schaefer and Peters (1992)
Infants, age n.p.	2 M	DEET, concn. n.p.	Dermal: dose n.p.	Application to mother during first trimester of pregnancy	Both infants developed coarctation of the aorta. A causal relationship with exposure to DEET was not certain.	Hall et al. (1975)
Rats						
Charles River CD, age n.p.	25 F/dose	DEET, 98.3%	Gavage: 125, 250, and 750 mg/kg (0.653, 1.31, and 3.92 mmol/kg)	Exposure on gd 6-15, sacrificed on gd 21	Reduced fetal weight was observed at 750 mg/kg. No treatment-related effects, such as external, visceral, or skeletal malformations or effects on gestational parameters, were observed.	Schoenig et al. (1994)
Sprague-Dawley, age n.p.	35-37 F	DEET, 97-98%	s.c.: 0.30 mL/kg (1.6 mmol/kg)	Exposure on gd 6-15, half of the animals sacrificed on gd 20 and the remaining half observed on pd 3, 9, and 14	No evidence of reproductive or developmental toxicity reported. Sporadic malformations and variations were observed, but no significant differences existed between fetuses of treated group and controls. No signs of adverse effects on reproductive success in rats exposed <i>in utero</i> .	Wright et al. (1992)
	20 M/dose		s.c.: 0.30 and 0.73 mL/kg (1.6 and 3.8 mmol/kg)	Exposure 5 d/wk for 9 wk, observation period n.p.	No effects noted on sperm or evidence of induced dominant lethal mutations. No effect observed on survival of fetuses sired from male treated rats or on neonatal growth or development.	
Sprague-Dawley, age n.p.	80 M/dose	DEET, 98.34%	Dermal: 100, 300, and 1000 mg/kg (0.523, 1.57, and 5.227 mmol/kg)	Exposure 5 d/wk for 9 wk, 96-d observation period	No effect on sperm count, morphology, or viability at any dose level observed.	Lebowitz et al. (1983)

Table 8. Reproductive and Teratological Effects of DEET (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rabbits</i>						
New Zealand white, age n.p.	16 F/dose	DEET, 98.3%	Gavage: 30, 100 and 325 mg/kg (0.16, 0.523, and 1.70 mmol/kg)	Exposure on gd 6-18, sacrificed on gd 29	No treatment-related effects, such as external, visceral, or skeletal malformations of offspring or effects on gestational parameters, were observed.	Schoenig et al. (1994)
New Zealand white, age n.p.	20 F/dose	DEET, 95%	Dermal: 50, 100, 500 and 1000 mg/kg (0.26, 0.523, 2.61, 5.227 mmol/kg)	Daily exposure on gd 1-29, sacrificed on gd 30	No reproductive or teratological effects observed.	Angerhofer and Weeks (1981)
<i>Chickens</i>						
White Leghorn embryo	number and sex n.p.	DEET, concn. n.p.	Topical to chorioallantoic membrane: 1.27 μ mol (243 μ g)	Exposure during second incubation d, 15-d observation period	Of 41% of embryos that survived to day 15, 33% had gross malformations including ventricular septal defects, anomalous aortic arch patterns, absence of a rump, amelia, malrotated limbs, and CNS malformations.	Kuhlmann et al. (1981), abstract

Abbreviations: concn. = concentration; CNS = central nervous system; d = day(s); F = female; gd = gestational day(s); M = male; n.p. = not provided; pd = postnatal day(s); s.c. = subcutaneous injection; wk = week(s); yr = year(s).

9.3 Carcinogenicity

The details of studied discussed in this section are presented in **Table 9**.

No treatment-related tumors were observed in male or female mice and rats administered 10-1000 mg/kg/day (0.052-5.23 mmol/kg) DEET orally for 1 to 2 years (Schoenig et al., 1999).

Swiss mice (female) and New Zealand rabbits (male and female) were exposed dermally to 0.02 mL (0.02 g; 0.1 mmol) of 10, 50, and 100% concentrations of DEET twice a week for up to 160 weeks (Stenbäck, 1977). There were no significant differences in the number of tumors in DEET-treated animals compared to controls.

9.4 Genetic Toxicity

The details of these studies are presented in **Table 10**.

9.4.1 Prokaryotic Systems

DEET (10-3333 μ g/plate; 0.052-17.42 μ mol/plate) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98, with or without induced rat or hamster liver S9, when tested in a preincubation assay (Zeiger et al., 1992).

9.4.2 Lower Eukaryotic Systems

Exposure of *Tradescantia paludosa* pollen mother cells in early prophase I to 1-3 sprays of the commercial insect repellent OFF! , did not induce micronuclei in later stages of pollen maturation (early tetrad stage) (Ma et al., 1984).

Table 9. Carcinogenicity of DEET

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
CD-1 mice, CD rats; ages n.p.	60 M, 60 F mice/group; 60 M, 60 F rats/group	DEET, 98%	Oral: 10-1000 mg/kg (0.052-5.23 mmol/kg)	Daily doses in diet or via gelatin capsule; 1-yr to 2-yr observation periods	No tumors were observed.	Schoenig et al (1999)
Mice, Swiss, 7 wk old	50 F/group	DEET, 10, 50, and 100%	Dermal: 0.02 mL (0.02 g; 0.1 mmol)	Twice weekly on the back, up to 160-wk observation period	Tumors of various organs, including skin, ovary, and mammary gland, were observed; however, the incidence was not increased compared to controls.	Stenbäck (1977)
Rabbits, New Zealand, 8 wk old	5 M or F/group			Twice weekly on the left ear, up to 160-wk observation period	No tumors or mortality were observed in either treated animals or controls.	

Abbreviations: concn. = concentration; F = female; M = male; n.p. = not provided; wk = week(s); mo = month(s); yr = year(s).

Table 10. Genetic Toxicity of DEET

Test System	Biological Endpoint	+/- S9	Chemical Form, Concentration	Dose	Endpoint Response	Reference
9.6.1 Prokaryotic Systems						
<i>Salmonella typhimurium</i> strains TA100, TA1535, TA97, and TA98	<i>his</i> gene mutations	+/-	DEET, concn. n.p.	10-3333 μ g/plate (0.052-17.42 μ mol/plate)	Negative	Zeiger et al. (1992)
9.6.2 Lower Eukaryotic Systems						
<i>Tradescantia paludosa</i> Sax, early prophase I pollen mother cells	micronuclei	-	OFF! , concn. of DEET n.p.	1 to 3 sprays; 6-h exposure duration in a glass chamber	Negative	Ma et al. (1984)

Abbreviations: concn. = concentration; h = hour(s); n.p. = not provided; "+" = positive; "-" = negative.

9.5 Immunotoxicity

The details of these studies are presented in **Table 11**.

DEET causes a hypersensitivity response in the immune system (Brooks et al., 1992). Gryboski et al. (1961) suggested that hypersensitivity to DEET was a significant factor in the development of toxic encephalopathy in a 3.5-year-old girl. A woman exposed to DEET developed contact urticaria by an immunologic mechanism (Maibach and Johnson, 1975). This type of reaction is identical to other types of immediate hypersensitivity in that specific IgE molecules on the surface of basophils and mast cells join with absorbed antigens, resulting in the typical weal-and-flare appearance due to histamine release. Anaphylactic shock can occur, but this response is only generated for substances which either provoke strong hypersensitivity or are abundantly absorbed through the skin (Harvell et al., 1994). A case of anaphylactic hypersensitivity was reported in a woman who developed generalized pruritis after touching a person who had been sprayed with DEET (Miller, 1982).

9.6 Other Data

9.6.1 Inhibition of the Urea Cycle and Gluconeogenesis

In a study by Brini and Tremblay (1991), 20 mM (3.8 mg/mL) DEET inhibited the synthesis of urea from ammonia and the production of glucose from lactate in male COBS-CD rat liver hepatocytes after 1 hour of incubation. Both inhibitions were reversed when hepatocytes were washed and resuspended in DEET-free medium.

9.6.2 Effect on Pentobarbital Activity

A single oral dose of 0.4 g/kg (2 mmol/kg) DEET given to rats 1, 2, or 6 hours prior to the i.p. administration of 25 mg/kg pentobarbital increased sleeping times by 2- to 6-fold, which was associated with an increase in liver microsomal pentobarbital hydroxylase activity (Liu et al., 1984, abstract). Conversely, DEET administered 12, 24, 48, 36, or 72 hours prior to administration of pentobarbital markedly decreased the sleeping time and hydroxylase activity.

Table 11. Immunotoxicity of DEET

Sex and Age of Individuals	Chemical Form and Concentration	Route/Dose	Exposure	Results/Comments	Reference
F, 3.5 yr old	DEET, 15%	Dermal: 180 mL	Child, bedding, and nightclothes sprayed with OFF! for 2 wk	Hypersensitivity to DEET was suggested as a significant factor in the development of toxic encephalopathy.	Gryboski et al. (1961)
F, 35 yr old	DEET, concn. n.p.	Dermal: ~0.1 mL	Application of a commercial insect repellent containing DEET	Subject developed contact urticaria, which suggested an immunologic response (immediate hypersensitivity).	Maibach and Johnson (1975)
F, 42 yr old	DEET, 52%	Dermal: dose n.p.	Touching someone who had been sprayed with DEET	Symptoms were attributed to anaphylactic hypersensitivity.	Miller (1982)

Abbreviations: concn. = concentration; F = female; n.p. = not provided; wk = week(s); yr = year(s).

9.6.3 Effect on the Percutaneous Absorption of Other Chemicals

Details of these studies are presented in **Table 12**.

Human Studies

A study was conducted in 16 healthy male volunteers (18-80 years old) to determine the effect of DEET on the dermal penetration of 2,4-D-amine from either palmar or forearm regions (Moody et al., 1992). Application of ^{14}C -2,4-D-amine ($0.5 \mu\text{Ci}$ in $7 \mu\text{g}/10 \mu\text{L}$ water or acetone) was made to either the left palmar region or the left ventral forearm to a 4.2-cm^2 area, with or without prior application of $10 \mu\text{L}$ of DEET, and occluded with a polypropylene cover. In general, the presence of DEET tended to decrease palmar penetration of 2,4-D-amine in water. Penetration of 2,4-D-amine through the palmar region was approximately twice that observed from forearm sites (14% versus 7%).

The dermal absorption and excretion of the insect repellent MGK 326 (di-*n*-propyl isocinchomeronate), either alone or formulated with 17.5% DEET and MGK 264 (*N*-octyl bicycloheptene dicarboximide), was studied following a single topical application of each of these formulations to the forearms of healthy male volunteers (Selim et al., 1994). DEET inhibited the penetration of MGK 326 up to 8-fold. In a similar study, DEET decreased the absorption of MGK R11 (Selim et al., 1995). About 8% of the MGK R11 was recovered when administered alone compared to 3% from the DEET-MGK 211 formulation.

DEET (4%, applied neat to a 1.13-cm^2 area) increased the amount of methotrexate (MTX) that accumulated in the stratum corneum of the human forearm (Lu et al., 1996, abstract).

Animal Studies

DEET (15%) significantly reduced carbaryl absorption from acetone, but not from dimethyl sulfoxide (DMSO) mixtures, in a study of the *in vitro* percutaneous absorption of carbaryl through pig skin (Baynes and Riviere, 1998).

In an *in vivo* study conducted using 5 male Sprague-Dawley rats and 5 male rhesus monkeys to determine the effect of DEET ($0.005\text{-}1000 \mu\text{g}$; $0.03 \text{ nmol-}5.227 \mu\text{mol}$) on the dermal persistence of fenitrothion (Moody et al., 1987), greater fenitrothion persistence occurred in both

rats (15% without DEET and 31.5% with DEET) and monkeys (1.5% without DEET and 6.0% with DEET).

A comparative study was conducted to determine the effect of DEET in solutions of ethanol, DMSO, and acetone on the penetration of permethrin and carbaryl across rat, mouse, and pig skin (Baynes et al., 1997). Administration of permethrin plus DEET resulted in penetration of DEET, but not permethrin. Permethrin was detected only when applied alone to mouse skin in solutions of DMSO or acetone, indicating that DEET may be decreasing its absorption. DEET also inhibited carbaryl absorption in acetone but not in DMSO. Of the chemicals tested, only DEET had sufficient penetration to induce toxicity when used with pesticides.

DEET (4%) (applied neat to a 1.13-cm² area) increased the amount of MTX that accumulated in the stratum corneum of the rabbit ear (Lu et al., 1996, abstract).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

No data on structure-activity relationships were located.

Table 12. Effect of DEET on the Percutaneous Absorption of Other Chemicals

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Human Studies</i>						
Human volunteers, 18-80 yr old	16 M, 4/dose	DEET, >98%; ¹⁴ C-2,4-D-amine, >99%	Dermal (occluded) to palm or forearm: ¹⁴ C-2,4-D-amine: 0.5 μCi in 7 μg/10 μL in water or acetone Formulation with DEET: 10 μL	24-h exposure, urine samples collected at 24-h intervals for 5 d post-application	Approximately 14% of the applied palmar 2,4-D-amine dose was absorbed versus 10% of palmar 2,4-D-amine dose with DEET, 7% of forearm 2,4-D-amine dose in water, and 13% of forearm 2,4-D-amine dose in acetone. Up to 34% of the applied dose was recovered.	Moody et al. (1992)
Human volunteers, ages n.p.	8 M, 4/formulation	DEET, 98.8%; MGK 326, 99.7%; ¹⁴ C-MGK 326, >98%; MGK 264, 100%	Single topical application to forearms: ¹⁴ C-MGK 326 alone: 0.012 mg/kg Formulation with 17.5% DEET: 0.014 mg/kg	8-h exposure; blood and urine samples collected at various intervals up to 120 h post-application	Incorporation of DEET inhibited the penetration of MGK 326 up to 8-fold.	Selim et al. (1994)
Human volunteers, ages n.p.	8 M, 4/formulation	DEET, 98.8%; ¹⁴ C-MGK R11, 93.8%	Single topical application to forearms: ¹⁴ C-MGK R11 alone: 0.014 mg/kg Formulation with 17.5% DEET: 0.014 mg/kg	8-h exposure, blood and urine samples collected at various intervals up to 120 h post-application	Dermal absorption of the MGK R11 was poor, regardless of the formulation, with only about 8% recovered in the urine when administered alone versus about 3% from the DEET-MGK formulation.	Selim et al. (1995)
Human volunteers, ages n.p.	6, sex n.p.	DEET and MTX, concn. n.p.	4% DEET in a gel containing 28 μg/cm ² MTX	Samples collected 2 and 4 h post-application	DEET enhanced the percutaneous absorption of MTX in the stratum corneum of the human forearm.	Lu et al. (1996, abstract)

Table 12. Effect of DEET on the Percutaneous Absorption of Other Chemicals (Continued)

Species, Strain, and Age	Number and Sex	Chemical Form and Concentration	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Animal Studies</i>						
Yorkshire pigs (weanlings)	14 F	DEET and carbaryl, concn. n.p.	<i>In vitro</i> : 10 µL carbaryl with or without 15% DEET in acetone or DMSO	Samples collected at various intervals up to 8 h	DEET significantly reduced carbaryl absorption from acetone (0.44-0.59% versus 6.51-9.46%) but not from DMSO (2.27-3.34% versus 2.14-2.94%).	Baynes and Riviere (1998)
Sprague-Dawley rats, ages n.p.	5 M	¹⁴ C-ring-labelled DEET, >98%; fenitrothion (FT), concn. n.p.	<i>In vitro</i> : FT in 0.005-1000 µg (0.03 nmol-5.227 µmol) DEET <i>In vivo</i> : 5 µL FT in acetone or DEET	Urine collected at 4 and 8 h (Day 1), then at 24 h intervals for 7 d post-application	DEET enhanced fenitrothion persistence (98.6% versus 1.9%). DEET increased dermal persistence of fenitrothion in rats (32% versus 15%)	Moody et al. (1987)
Rhesus monkeys, age n.p.	5 M				DEET increased dermal persistence of fenitrothion in monkeys (9.7% versus 3.2%)	
CH3 mice (age n.p.); albino rats (strain and age n.p.); Yorkshire pigs (weanling)	F pigs; for other species, sex n.p.; number of animals n.p.	DEET, 98%; permethrin and carbaryl, concn. n.p.	Dose volume: 10 µL Permethrin: 500 µg/cm ² Carbaryl: 40 µg/cm ² 15% DEET for pig; 35% DEET for rat and mouse	Samples were collected hourly for 8 h (rat and pig), and at 2, 4, 6, 8, 12, 16, and 24 h (mouse)	Application of DEET + permethrin resulted in the absorption of DEET but not permethrin. DEET inhibited carbaryl absorption in acetone but not in DMSO.	Baynes et al. (1997)
Rabbit, strain and age n.p.	sex and number n.p.	DEET and MTX, concn. n.p.	<i>In vitro</i> : DEET (dose n.p.) and 57.5 µg/cm ² MTX	Samples collected at 1, 2, and 4 h post-application	DEET enhanced the percutaneous absorption of MTX in the stratum corneum of the rabbit ear.	Lu et al. (1996, abstract)

Abbreviations: concn. = concentration; d = day(s); FT = fenitrothion; DMSO = dimethyl sulfoxide; F = female; h = hour(s); M = male; MGK 264 = *N*-octylbicycloheptene dicarboximide; MGK 326 = di-*n*-propyl-isocinchomerate; MGK R11 = 2,3:4,5-bis(2-butylene) tetrahydro-2 furaldehyde; MTX = methotrexate; n.p. = not provided; yr = year(s).

11.0 ONLINE DATABASES AND SECONDARY REFERENCES**11.1 Online Databases**Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Chemical Economics Handbook (CEH)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS

EMBASE

Registry

CANCERLIT

HSDB

RTECS

CAPLUS

MEDLINE

TOXLINE

CHEMLIST

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSH TIC	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet

ChemFinder. Website: <http://chemfinder.camsoft.com/cgi-win/cfserver.exe/>. (6/17/98).

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In-House Databases

CPI Electronic Publishing Federal Databases on CD

Current Contents on Diskette

The Merck Index, 1996, on CD-ROM

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APPENDIX A UNITS AND ABBREVIATIONS

°C = degrees Celsius

μg/cm² = micrograms per square centimeter

μg/L = micrograms per liter

μg/m³ = micrograms per cubic meter

μg/mL = micrograms per milliliter

μM = micromolar

AAPCC = American Association of Poison Control Centers

d = day(s)

EPA = U. S. Environmental Protection Agency

F = female

FEMA = Federal Emergency Management Agency

FIFRA = Federal Insecticide, Fungicide, and Rodenticide Act

g = gram(s)

g/mL = grams per milliliter

GC = gas chromatography

GC/MS = gas chromatography/mass spectrometry

h = hour(s)

HPLC = high performance liquid chromatography

i.p. = intraperitoneal injection

i.v. = intravenous injection

kg = kilograms

LC₅₀ = concentration lethal to 50% of test animals

LD₅₀ = dose lethal to 50% of test animals

LIP = Label Improvement Program

M = male

mg/kg = milligrams per kilogram

mg/m³ = milligrams per cubic meter

mg/mL = milligrams per milliliter

mL/kg = milliliters per kilogram

mm = millimeters

mm Hg = millimeters of mercury

mM = millimolar

mmol = millimoles

mmol/kg = millimoles per kilogram

min = minute(s)

mo = month(s)

mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute for Occupational Safety and Health

NOES = National Occupational Exposure Survey

NOHS = National Occupational Hazard Survey

nm = nanometer

n.p. = not provided

N/A = not applicable

NYDEC = New York Department of Environmental Conservation

OPP = Office of Pollution Programs

OPPT = Office of Pollution Prevention and Toxics

PAI = pesticide active ingredient

PCC = Poison Control Center

ppb = parts per billion

ppm = parts per million

RED = Reregistration Eligibility Decision

s.c. = subcutaneous injection

wk = week(s)

yr = year(s)

y.o. = years old