GENERAL INFORMATION

N,N-Diethyl-*m*-toluamide, also known as DEET or *m*-DET, is an aromatic amide that is an effective insect repellent for control of biting flies, biting midges, black flies, chiggers, deer flies, fleas, gnats, horse flies, mosquitoes, no-see-ums, sand flies, small flying insects, stable flies, and ticks. DEET was first developed by the U.S. Department of Agriculture for military use in 1946 and was first registered in the United States in 1957. It has been estimated that approximately 38 percent of the U.S. population uses DEET-containing repellents annually (Veltri et al., 1994; Selim et al., 1995). As of September 1998, 225 DEET products were registered with the EPA; they are prepared in many different application types (e.g., aerosol and non-aerosol sprays, creams, lotions, sticks, foams, and towelettes) and have DEET concentrations ranging from approximately 4 percent to 100 percent (USEPA, 1998a).

Technical DEET is composed of more than 95 percent *m*-DET isomers. Ortho (*o*-DET) and para (*p*-DET) isomers are slightly more and less toxic than *m*-DET, respectively (Ambrose and Yost, 1965). The chemical identity of DEET is shown in Table 5.1, and Table 5.2 summarizes its physical and chemical properties.

Table 5.1

Chemical Identity of DEET

Characteristic	Information
Chemical class	Aromatic amide (*N,N*-dialkylarylamides); repellent
Chemical name	*N,N*-Diethyl-*m*-toluamide
Trade names	DEET, OFF, Delphene, MGK diethyltoluamide, Detamine, Metadelphene, Chemform, Chiggar-Wash, Muskol, Cutter, Repel, Old Time Woodsman
Chemical formulas	$C_6H_4CH_3CON(C_2H_5)_2$ $C_{12}H_{17}NO$
CAS Registry number	134-62-3

Table 5.2

Physical and Chemical Properties of DEET

Property	Information
Molecular weight	191.26
Color/form	Colorless to off-white, light-yellow, amber liquid
Odor	Nearly odorless
Water solubility at 25°C	Practically insoluble
Partition coefficient (K_{ow})	100
Soil sorption coefficient (K_{oc})	300
Vapor pressure at 20°C	5.6×10^{-3} mm Hg
EPA toxicity classification	Class III
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	NA
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	D
IARC	NA

NA = not available.

AVAILABILITY AND RECOMMENDED USE OF DEET DURING ODS/DS

DEET insect repellent is part of a complete repellent system used by U.S. military personnel that has shown excellent efficacy in preventing arthropod-borne disease (Young and Evans, 1998). Until 1989, the standard-issue insect repellent of the U.S. military consisted of 75 percent DEET in an alcohol base. By 1984, the 3M Company (St. Paul, Minnesota) had developed a slow-release, polymer-based product containing 33 percent DEET, which is now the repellent provided to all U.S. military personnel. This product is available to the general public from 3M as Ultrathon. Three DEET products were shipped to the Gulf area; these products are detailed in Table 5.3.

Table 5.3

Formulations of DEET Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Areas
6840-01-284-3982	3M insect/arthropod repellent	Cream	33	2-oz tube	Skin and clothing
6840-00-753-4963	Insect repellent, clothing and personal application	Liquid	75	2-oz bottle	Skin and clothing
6840-00-142-8965	Cutter insect repellent stick	Stick	33	1-oz stick	Skin and clothing

Source: Provided by OSAGWI.

POTENTIAL HEALTH EFFECTS OF DEET

DEET Metabolism/Pharmacokinetics

Carbon dioxide and lactic acid are among the most important cues mosquitoes use to locate a host. It is believed that DEET repels mosquitoes by inhibiting lactic acid receptors on their antennae (Davis and Sokolove, 1976).

DEET can enter the body through several exposure pathways, including dermal and ocular exposures, inhalation, and ingestion. Some consider DEET an ideal permeant of skin (Stinecipher and Shah, 1997), and it has been reported to accelerate the dermal penetration of pharmaceuticals (Windheuser et al., 1982), raising the concern that DEET may also increase dermal penetration of pesticides, since they are often used together (Moody et al., 1987). Several studies in animals and humans have shown that, following absorption, DEET is completely metabolized prior to elimination in the urine (Schmidt et al., 1959; Smith et al., 1963a; Selim et al., 1995).

After DEET is applied to the skin, it is partially absorbed, but some also evaporates[1] or is rubbed off by clothing, the latter accounting for the majority of loss (Smith et al., 1963b). Following absorption, DEET does not appear to accumulate in the superficial layers of the skin. In a definitive study, DEET was absorbed across the forearms of human volunteers within two hours of application, but the rate of elimination via excreta was more rapid than the rate of absorption (Selim et al., 1995). This is consistent with expected absorption patterns of low-molecular-weight, lipophilic chemicals (Scheuplein, 1967) such as DEET.

DEET has been shown to affect the cardiovascular and nervous systems. The mechanism of cardiovascular toxicity has been investigated in dose-response experiments with intraperitoneal injections of DEET in rats, studies of hypodynamic responses of dogs following intraperitoneal DEET injections, and studies of the effect of atropine in blocking DEET-induced hypotension and bradycardia (Leach et al., 1988). These experiments showed a significant effect of hypotension. In the dog study, there was a significant reduction in cardiac output but no change in stroke volume and total peripheral resistance, suggesting that the observed hypotension was a result of DEET-induced bradycardia.

Episodes of severe DEET toxicity in mammals are usually related to a direct action on the nervous system. Experimental animals that received large doses of DEET have manifested coma and death. Animal studies have suggested that

[1]There is some evidence, however, that there is little or no evaporation of DEET from the skin of rats (Schoenig et al., 1996) and humans (Selim et al., 1995).

DEET is not a selective neurotoxin (Osimitz and Grothaus, 1995; Schoenig et al., 1996).

Reported cases of severe DEET toxicity in humans have involved mainly encephalopathies in children. The vast majority of these cases occurred in female children exposed to topical DEET, so it was hypothesized that another mechanism of DEET toxicity that may occur with smaller systemic doses is perturbation of ammonia metabolism (Heick et al., 1988), resulting in hyperammonia. In this case, DEET would be especially toxic to individuals with genetic or acquired defects in ammonia metabolism, such as female carriers of ornithine carbamoyl transferase (OCT) deficiency (this condition is usually fatal in neonatal males). Heick et al. (1988) injected normal mice with DEET and observed acutely increased ammonia levels. While this result, as reported in case-study observations, suggests hyperammonia as a primary mechanism of acute DEET toxicity, the authors also point out several cases that suggest hypersensitivity reactions (Miller, 1982; Roland et al., 1985). Furthermore, cases of DEET-associated seizures in boys (MMWR 1989; Lipscomb et al., 1992) and men (MMWR, 1989; Veltri et al., 1994) may discredit the hypothesis that OCT deficiency is the predisposing factor for DEET CNS toxicity (Lipscomb et al., 1992), or may at least suggest that there is yet another responsible mechanism.

Exposure to DEET as Reviewed in the Scientific Literature

It is beyond the scope of this literature review to speculate about the magnitude of exposures to pesticides by individuals during ODS/DS. However, Robbins and Cherniack (1986) provide some exposure information that may prove useful. It should first be noted that limited information is available for estimating exposure from what these authors refer to as "conventional consumer use practices." Table 5.4 presents predictions based on limited mid-range data points for DEET exposure (USEPA, 1980). Robbins and Cherniack (1986) rightfully point out that considerable error may be associated with some of the estimates, which were made during the mosquito season and reflect 60 applications per year for military personnel and four days of use per week for Everglades biologists—the latter intended to represent high-dose use. It should also be noted that military personnel were using the old 75 percent DEET repellent. Although this formulation was available in limited quantities during ODS/DS, a 33 percent DEET extended-duration formulation was the primary DEET repellent used there. Robbins and Cherniack also included data from the preliminary report of a NIOSH Health Hazard Evaluation, based on survey data of Everglades Park Service employees. These data are not presented in Table 5.4 because of their preliminary nature and the fact that they included a range of DEET concentrations (15 percent to 75 percent) applied for a seven-month period (as opposed to six months in the EPA study). Nonetheless, this

Table 5.4

Estimated Exposure to DEET During a Six-Month Mosquito Season

Group	Concentration *of DEET in Formulation* (%)	Estimated Exposure to Active Ingredient Reported	Exposure Quantity[a] (g)
Upper 1% of general population[b]	15	> 1.65 g/day	>214
	75	> 8.35 g/day	>1071
Military personnel	75	43 g/season[c] *(approximately 0.12 g/day)*	43
Everglades biologist[d]	28.7	4.25 g/day	442

Source: U.S. EPA (1980), in Robbins and Cherniack (1986). Italics indicate additions in the present report.

[a]Exposure quantity is estimated and assumes the active ingredient is applied to all exposed skin during May to October.

[b]Estimated from a survey of only 71 employees of one company.

[c]Annual exposure is based on the U.S. Army's estimated usage of 1 ml of a 75 percent formulation, 60 times per year.

[d]Exposure based on four-day use per week.

evaluation calculated an estimated exposure of >2 kg of DEET over seven months, which can be approximated as 9.5 g/day. The EPA provides some additional estimates of exposure to DEET, calculated assuming one application per day and standard body weights: 12.10 and 9.68 mg DEET/kg/day (USEPA, 1998a).

Skin Permeation and Absorption of DEET

Uncertainty about the degree of percutaneous absorption of DEET in humans complicates an objective assessment of effects. Generally, the amount of DEET that permeates the skin is closely related to the repellent formulation. Using commercially available products, Stinecipher and Shah (1997) found that the cumulative amount of DEET that permeated human skin in vitro ranged from approximately 6 percent to 100 percent, depending upon the repellent tested. Earlier research suggested that approximately 9 percent to 56 percent of applied DEET permeates the skin, although only approximately 15 percent is systematically absorbed (Robbins and Cherniack, 1986). However, in vitro studies involving infinite-dose applications of DEET to human skin have agreed closely: Stinecipher and Shah calculated the steady-state flux of DEET at from 21 to 63 $\mu g/cm^2/hr$ (Stinecipher and Shah, 1997), while Moody et al. calculated it to be from 20 to 60 $\mu g/cm^2/hr$ (Moody et al., 1995).

To determine DEET absorption accurately, it is necessary to recover all applied DEET, achieving mass balance. Few studies have been successful in this approach. One study that reports good mass balance (88.7 percent to 94.3 percent

of radioactivity from ^{14}C-labeled DEET accounted for, depending upon formulation applied) is that of Selim et al. (1995). In this study, ^{14}C-labeled DEET formulations of 100 percent and 15 percent in ethanol were applied to the forearms of two groups of six human volunteers. After eight hours, the skin was washed, and samples were taken by applying tape to the skin at one, 23, and 45 hours after rinsing. Serial blood, urine, and stool samples were also analyzed, and radioactivity was used as the marker to estimate biodistribution of DEET. Plasma radioactivity indicated absorption of DEET within two hours of application, but elimination was rapid and was complete four hours after the eight-hour exposure period. Most of the DEET was washed off the skin, and most of that which was absorbed was metabolized: Six major metabolites were observed in the urine, the primary route of excretion. These results definitively refute earlier suggestions (Bloomquist and Thorsell, 1977; Spencer et al., 1979; Snodgrass et al., 1982; Stinecipher and Shah, 1997) that the epidermis may serve as a depot for DEET, with subsequent slow release to the circulation. Based upon the percentage of applied DEET recovered in the total excreta, dermal absorption of DEET ranged from 3 percent to 8 percent (mean = 5.6 percent) of 100 percent DEET and 4 to 14 percent (mean = 8.4 percent) of the 15 percent DEET-in-ethanol formulation.

Table 5.5 compares dermal absorption in DEET reported in different studies and with different test subjects. However, these results may not accurately represent human exposure conditions, where individuals apply repeated doses of DEET to the skin without washing off previous doses.

Acute Effects

As with many pesticides, the majority of health effects reported to have been caused by DEET are acute. In fact, there appears to be no evidence in the literature that suggests chronic low-level exposure to DEET produces effects lasting months or years after exposure. DEET has been associated with a suite of symptoms, which are summarized in Table 5.6.

Federal law requires pesticides that were first registered before November 1, 1984, to be re-registered to ensure that they meet evolving, more stringent health standards. DEET was subjected to this process in 1998. The EPA concluded that DEET is generally of low acute toxicity, and on the basis of the available toxicological data, the agency stated that normal use of DEET does not present a health concern to the general U.S. population (USEPA, 1998a). It should be noted that the EPA assumes that the general population receives “subchronic exposure” to DEET; that is, users are expected to be exposed to DEET intermittently for only days or weeks.

Table 5.5

In Vivo and In Vitro Dermal Absorption of DEET

Reference	Species	Dose ($\mu g/cm^2$)	Solvent of Application	Collection Period (days)	Percent Absorbed
Feldman and Maibach, 1974	Human[a]	4	Acetone	5	16.17 ± 5.10
Moody and Nadeau, 1993)	Human[b]	44.7	Acetone	2	27.7 ± 4.24
Selim et al., 1995	Human[a]	625[c]	Technical-grade DEET	5	5.6 (range 3–8)
Selim et al., 1995	Human[a]	500[d]	Ethanol	5	8.4 (range 4–14)
Reifenrath et al., 1981	Hairless dog[a]	4	Ethanol	5	12.8 ± 4.6
Reifenrath et al., 1980	Hairless dog[a]	320	Ethanol	5	9.4 ± 3.6
Moody and Nadeau, 1993	Pig[b]	19.4	Acetone	2	15.3 ± 0.82
Reifenrath et al., 1984	Weanling pig[a]	4	Ethanol	5	9.4
Moody and Nadeau, 1993	Guinea pig[a]	12.5	Acetone	14	30.0 ± 5.96
Moody and Nadeau, 1993	Guinea pig[b]	12.5	Acetone	2	10.9 ± 1.40
Moody and Nadeau, 1993	Rat[a]	38.7	Acetone	14	41.0 ± 10.51
Moody and Nadeau, 1993	Rat[b]	38.7	Acetone	2	21.4 ± 2.17
Moody and Nadeau, 1993	Mouse[b]	33.3	Acetone	2	36.2 ± 27.5

Source: Stinecipher and Shah (1997), with additions and re-ordering in the present report.
[a]In vivo studies.
[b]In vitro studies.
[c]Approximation; the authors reported applying approximately 15 mg of 98.8 percent DEET to a 4 x 6-cm area.
[d]Approximation; authors reported applying approximately 12 mg of 15 percent DEET formulation in ethanol to a 4 x 6-cm area.

Table 5.6

Reported Signs and Symptoms of DEET Toxicity

Affected Area	Sign or Symptom
Cardiovascular	Hypotension
	Bradycardia
Dermatologic/allergic	Erythema
	Bullous eruptions
	Contact urticaria
	Anaphylaxis
Nervous system	Ataxia
	Confusion
	Slurred speech
	Muscle cramping
	Insomnia
	Tremor
	Clonic jerking
	Psychosis
	Seizures
	Coma

Source: Clem et al. (1993).

In studies using laboratory animals, DEET generally has been found to be of low acute toxicity. It is slightly toxic by the eye, dermal, and oral routes and has been placed in the EPA's Toxicity Category III (the second lowest of four categories) because of these effects (USEPA, 1998a).

Generally, neurotoxic symptoms dominate at near-lethal doses of DEET in rats and other animals. The rat oral LD_{50} is 2 to 4 g DEET/kg (Ambrose and Yost, 1965).[2] Rats given a single oral dose of 500 mg DEET/kg displayed increases in thermal response time and possible decreased rearing activity (Schoenig et al., 1993).

Most reports of severe DEET adversity in humans describe neurologic symptoms, and most of the severe adverse reactions occur in children (Veltri et al., 1994; Osimitz and Murphy, 1997; Fradin, 1998). Reports of DEET adversity have described manic psychosis, cardiovascular events, anaphylaxis, and several cases of contact urticaria and irritant contact dermatitis. These are included in Table 5.7, which summarizes reports of health effects on humans attributed to DEET exposure. It is possible that examples of DEET sensitivity may be missed, especially in children, as cases may easily be misdiagnosed as a viral encephalitis (Zadikoff, 1979). Deaths in adults have occurred following large doses, and blood levels of DEET in fatal systemic poisonings have ranged from 168 mg/L to 240 mg/L (Tenenbein, 1987). In contrast, a blood concentration of 3 mg/L was measured after routine application of a repellent to a 30-year-old male volunteer (Wu et al., 1979).

Manic psychosis occurred in a 30-year-old man who, for a period of three weeks, applied DEET daily and then sat in a light-bulb-heated box, apparently for self-medication to treat a rash. Sedation and incoherence were noted for short periods after each application session, and the man was admitted to a hospital after displaying aggressiveness and psychotic ideation. Clinical improvement (haloperidol) was complete within six days, atypical for classic endogenous mania. The authors point out the structural similarities between DEET and certain CNS-active drugs such as *N,N*-dimethyl acetamide and doxapram hydrochloride (Snyder et al., 1986).

A cardiovascular event occurred in a 61-year-old woman who applied a DEET-containing repellent (unknown concentration) "liberally" to all exposed skin prior to gardening. She suffered bradycardia and hypotension but recovered without sequelae (Clem et al., 1993). Other reports of cardiovascular DEET toxicity have included two cases of apparent suicide via ingestion of DEET-

[2] LD_{50} is the median lethal dose. This is a statistically derived single dose that can be expected to cause death in 50 percent of test animals when administered by the route indicated. It is expressed as the weight of a substance per unit weight of animal.

Table 5.7

Reported Health Effects in Humans Following the Topical Application of DEET

Reference	Affected Area	Sex/Age (yr); Possible Predisposition	DEET Concentration (%)	Pattern of Use (dermal unless otherwise noted)	Symptoms	Outcome
Heick et al., 1980	CNS	F/6; OCT heterozygote	15	≥10 occasions	Headaches, ataxia, disorientation, cerebral edema	Death
de Garbino and Laborde, 1983	CNS	F/1.5	20	Frequent	"Acute encephalopathy"	Death
Zadikoff, 1979	CNS	F/5	10	Nightly for 3 mo	Headaches, ataxia, seizures, agitation, opisthotonos, generalized edema	Death
Tenenbein, 1987	CNS	F/1	47.5	Ingested ≈25 mL	Seizures, opisthotonos	Recovery
Hall et al., 1975	CNS	F/7.5	10	Application and ingestion	Opisthotonos	Recovery
Zadikoff, 1979	CNS	F/1.5	10	Ingestion of unknown but probably small amount	Opisthotonos, ataxia	Recovery
Gryboski et al., 1961	CNS	F/3	15	Daily for 2 wk	Ataxia, encephalopathy	Recovery
Roland et al., 1985	CNS	F/8	15 & 100	Copious for 4 days	Seizures, rash, restlessness	Recovery
Edwards and Johnson, 1987	CNS	F/1.5	20	3 mo	Ataxia, movement disorder, drooling, opisthotonos, opsoclonus, myoclonus	Recovery
Lipscomb et al., 1992	CNS	M/5	100 & 15	Brief	Seizures	Recovery
MMWR, 1989	CNS	4 cases: M/3-7	NA	NA	Seizures	Recovery
Tenenbein, 1987	CNS	F/14	95	Ingested 50 mL	Unconsciousness, seizures	Recovery
MMWR, 1989	CNS	M/29	NA	NA	Seizures	Recovery
Veltri et al., 1994	CNS	M/17	17.9	Saturated clothing	Ataxia, possible seizure or unconsciousness	Recovery, incomplete follow-up
Veltri et al., 1994	CNS	M/adult; ingested phenothiazine drug same day	20.9	Sprayed entire body	Dystonia	Recovery

Table 5.7 (continued)

Reference	Affected Area	Sex/Age (y); Possible Predisposition	DEET Concentration (%)	Pattern of Use (Dermal Unless Otherwise Noted)	Symptoms	Outcome
Snyder et al., 1986	CNS	M/30	70	Daily application followed by dry sauna, 3 wk	Aggressiveness, psychotic ideation, psychomotor hyperactivity, rapid and pressured speech, tangentiality, flight of ideas, grandiose delusions, auditory hallucinations	Recovery
Veltri et al., 1994	Cardiovascular, CNS	M/33	NA	Intentionally ingested 8 oz of DEET repellent	Cardiorespiratory arrest, hyperglycemia (day 2), seizures, intravascular coagulopathy, cerebral edema	Death
Tenenbein, 1987	Cardiovascular, CNS (plus bowel)	F/33	95	Ingestion of up to 50 mL	Hypotension, seizure, coma, bowel infarction	Death
Veltri et al., 1994	Cardiovascular, CNS	M/33; self-reported diagnosis of Raynaud's Disease	NA (6-yr-old repellent product)	NA (potential inhalation during application 1 wk prior to symptoms)	Numbness, dizziness, vomiting, hypotension	Recovery, incomplete follow-up
Clem et al., 1993	Cardiovascular	F/61	NA	Liberal application, frequency NA	Bradycardia, hypotension	Recovery
Miller, 1982	Cutaneous or allergic reaction	F/42	52	Touched companion who had just applied repellent	Anaphylaxis	Recovery
Maibach and Johnson, 1975; von Mayenburg and Rakoski, 1994; Wantke et al., 1996	Cutaneous or allergic reaction	3 cases: 2 M + 1 F/4-35	NA	Urticaria developed 10-30 min after application	Wheals	Recovery
Reuveni and Yagupsky, 1982	Cutaneous or allergic reaction	10 cases: M/18-20	33-50	Military, applied to skin and then slept	Hemorrhagic bulla and erosions, confined to antecubital fossa	Recovery in 9 of 11; scarring in 2 of 11

Source: Adapted from Osimitz and Murphy (1997) and Fraden (1998).

CNS = central nervous system; NA = not available; OCT = ornithine carbamoyl transferase.

containing repellents (Tenenbein, 1987; Veltri et al., 1994). The case of anaphylaxis listed in Table 5.7 was a woman with brief exposure to DEET; her symptoms returned when she was re-exposed to DEET in an emergency room, indicating a possible hypersensitivity (Miller, 1982).

A particularly important study examined 9,086 human exposures to DEET-containing insect repellents that were reported to 71 Poison Control Centers (PCCs) between 1985 and 1989 (Veltri et al., 1994).[3] In these cases, most of the adverse effects were related to the route of exposure, rather than the age or gender of the patient or the concentration of DEET in the repellent formulation. Symptoms were most likely to occur following inhalation or ocular exposures, and these accounted for 2.0 percent and 31.9 percent of the total cases handled by the PCCs, respectively. Ingestion and multiple-route exposures accounted for 49.4 percent and 12.6 percent of all cases, respectively. Of all cases, 39.8 percent of the patients had symptoms that were considered related to DEET exposure; 54 percent of the patients were asymptomatic. After the study, 74.8 percent of the patients were followed long enough to determine a definitive outcome; of these, 98.9 percent either experienced no effects or had symptoms that were transient, resolved rapidly, and usually involved the skin or mucous membranes. Of 889 patients who were evaluated in a health care facility, 81.4 percent were discharged after initial treatment and 4.9 percent were admitted for medical care. (The remainder were lost to follow-up.) The authors suggest that in most patients, symptoms, if present, were not serious and resolved quickly. Sixty-six patients experienced more pronounced or prolonged symptoms, but these resolved without apparent sequelae. Five patients (all male) were reported to have suffered serious health effects. One had a dystonic reaction. He had ingested prochlorperazine (known to cause distonia) earlier in the day, so a synergistic reaction with DEET was not excluded. Two of the patients experienced eye irritation, which was treated at home. Two other patients were treated and released from an emergency room: A 17-year-old male who saturated his clothing with repellent (17.9 percent DEET) was ataxic and possibly suffered a seizure; a 33-year-old male experienced diminished sensation and hypotension one week after using repellent.

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[3] As the authors point out, the data analyzed were voluntarily reported to a national database by the PCCs. These data are useful but not without limitations: "The data included in this report were not obtained from a sample that is generalizable to the population of the US. The data represent those persons who have an exposure and report that exposure to a PCC. It is unknown how those persons differ from those who do not call a PCC." However, the cases reported do provide some insight into the common routes of exposure associated with specific health outcomes and some measure of the severity of effects.

Chronic, Reproductive, Genetic, and Carcinogenic Effects

As mentioned above, DEET underwent scrutiny during an EPA re-registration process in 1998 (USEPA, 1998a) which concluded that human exposure to DEET was usually brief, and long-term exposure was not to be expected. Based on laboratory animal studies, the EPA concluded that DEET is of low acute toxicity (Toxicity Category III). Further, DEET has been classified as an EPA Group D carcinogen (not classifiable as a human carcinogen), and mutagenicity tests for DEET (Ames assay, chromosomal aberration assay, and unscheduled DNA synthesis assay) were all negative, indicating that DEET is not mutagenic.

No reports were found of long-term effects in humans from chronic exposures to DEET (with the exception of rare reports of scarring), so there is no evidence to suggest such a scenario is of great concern in predicting the potential health effects of DEET in PGWV. As seen in Table 5.7, there have been some reports of subacute, subchronic, or possibly chronic human exposures to DEET; but with the exception of three deaths in children (at least one of whom was confirmed to have had a predisposing condition), these exposures resulted in no long-term effects. The following summarizes some of the animal studies considered by the EPA in the re-registration of DEET (USEPA, 1998a).

In a two-year chronic toxicity/carcinogenicity study in rats, 60 rats of each sex received 98.3 percent DEET in their diet. No toxicity was seen in male rats at the highest dose (100 mg/kg/day), but female rats displayed decreases in food consumption and body weight and an increase in cholesterol levels at their highest dose (400 mg/kg/day). At this same dietary concentration, 400 mg DEET/kg/day, beagle dogs in a separate one-year study displayed decreases in food consumption and body weight, an increase in the incidence of ptyalism, and a decrease in cholesterol levels. No compound-related effects on reproduction (e.g., fertility, gestation, or viability) were noted in rats given DEET in their diet at up to 5,000 ppm for two consecutive generations.

SYNTHESIS

Most reviews of DEET toxicity have concluded that the risk of adverse effects from DEET-containing repellents used as directed by the label appears low (Veltri et al., 1994; Osimitz and Grothaus, 1995; Fradin, 1998; Goodyer and Behrens, 1998). This conclusion is based on reviews of reported effects in humans, animal toxicology, and possible alternate etiologies for symptoms reported in most patients. In fact, hypersensitivity may be required for severe acute toxic effects to occur, and a suite of data from animal studies generated to support DEET registration provides no evidence of adverse long-term effects related to DEET exposure.

No correlation between the concentration of DEET in a repellent and the frequency or severity of effects is supported by the literature. Further, it is difficult to quantify consistently the temporal relationship between the onset of CNS symptoms and exposure to DEET, but the reaction is generally rapid, as is the resolution in most cases. There have been a relatively small number of severe adult effects related to DEET exposure. While a pattern of potentially severe neurotoxicity in children who have been exposed to DEET is emerging, the total number of reported cases is very small compared with the population exposed. This pattern has not been observed in adults. The reasons for this disparity are unknown but may be related to the fact that children have a different surface-area-to-volume ratio than adults. Generally, patients who are reported to present severe health effects related to DEET use recover without reported sequelae.

Concern about the interactive effect of DEET with other chemicals may be warranted (see Chapter Eight), but the available literature is not complete enough to allow definitive conclusions to be drawn at this point. It is difficult to extrapolate the results of animal studies to long-term human effects, and the possibility of chemical interactions compounds the uncertainty inherent in the process. This is not to say, however, that further research should not be undertaken. A prudent approach may be to, first, more accurately determine the exposures that warrant further study. If it is determined that coexposures warrant further investigation, it may be sensible to examine common routes of exposure for resulting bioavailability before investigating specific toxicological endpoints. In addition to this area for potential research, efforts to explain the broad variety of outcomes associated with DEET exposure may be warranted, especially for cases of hypersensitivity.