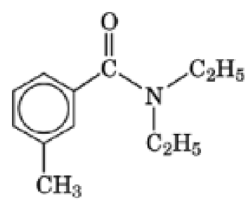
Kirk-Othmer Encyclopedia of Chemical Technology.

REPELLENTS

Repellents are materials that affect insects and other organisms by disrupting their natural behavior of bloodseeking through biting of humans and animals, and are the first line of defense that can be readily used for this purpose (1). The best overall standard repellent is *N*,*N*-diethyl-*m*-toluamide [134-62-3] (DEET), systematically named *N*,*N*-diethyl-3-methylbenzamide **(1)**.



(1)

Many other compounds are presently in use; a 1993 database search showed 27 active ingredients in 212 products registered by the U.S. EPA for human use as repellents or feeding depressants, including octyl bicycloheptene dicarboxamide (*N*-2-ethylhexyl bicyclo[2.2.1]-5-hepten-2,3-dicarboxamide), dipropyl isocinchomeronate (2,5-pyridine dicarboxylic acid, dipropyl ester), dimethyl phthalate, oil of citronella, cedarwood oil, pyrethrins, and pine tar oil (2). Repellent–toxicant or biting depressant systems are available which are reasonably comfortable for the user and can protect completely against a number of pests for an extended period of time (2).

Newer, cosmetically appealing formulations of chemical repellents have become popular in the United States since the mid-1980s, and interest in personal protection against biting arthropods has been renewed (3). Children and adults may be exposed daily to risks of Lyme disease, and those exposed should be particularly interested in reducing exposure to nymphs of the deer tick *Ixodes scapularis*. The tick, which carries the bacterium *Borellia burgdorferi*, is the same tick species previously called *I. dammini* by some entomologists. Destruction of ticks by spraying is expensive, works only locally, and is not very effective on a large scale. Not only is this disease difficult to diagnose and treat, but treatment of Lyme disease using expensive antibiotics has no effect on the next infective bite. In 1993, the Center for Disease Control (CDC) in Atlanta reported 9677 cases, with the foci in downstate New York and eastern Long Island (ca 3000 per year each). Although most cases are reported around Long Island Sound and in Wisconsin, all U.S. states except one have reported cases. The number of cases reported each year has been relatively constant since 1988, comprising 90% of all vector-borne diseases in the United States. Europe has also reported increased numbers of cases.

An exotic mosquito species, *Aedes albopictus*, the Asian tiger mosquito, has become established in many regions of the United States because viable eggs have been imported in shipments of used automobile tires from Asia that were placed in huge tire dumps all over the country and in the Caribbean islands. This species is a persistent, small but aggressive biter whose females bite any time of the day, are easily disturbed, and cause

Table 1. Anthropod-Borne Diseases in the United States, 1989–1993

Disease	Number of reported cases
malaria	2400[a]
encephalitis	1300
encephalitis Calif. serotype	100
sylvatic plague	10
Rocky Mountain spotted fever	100

[a]All but eight cases were imported.

multiple bites and allergic welts. Although the *Aedes aegypti* yellow-fever mosquito has been displaced from its habitat in Florida, it is not known whether this is helpful for disease transmission, because *A. albopictus* is also an effective carrier of the disease dengue fever. In addition, there are at least 170 other species of mosquitoes in North America, and repellents have been formally tested against only a few regarded as disease vectors (3).

The use of insecticides has led to the rise of widespread resistance in areas where residual insecticides were applied for malaria eradication (see also Insect-control technology), and in some locations that have widespread irrigation, as in California, or that practice flooding for rice production. Mosquito resistance to insecticides is prevalent in Southeast Asia, India, and East Africa, as is resistance of the malaria parasites, *Plasmodium falciparum*, also *P. malariae* and *P. vivax*, to prophylactic drugs. The number of cases of malaria is estimated at more than 250 million cases per year, resulting in as many as one million deaths; the goal of malaria eradication has been abandoned except in selected locations (4). The number of cases has stayed rather constant in the 1990s, but with increased danger of mortality on account of the declining effectiveness of drugs. Use of personal protection and repellents is recommended for travelers to malarious areas for avoiding serious health risks.

Disease cases reportable to the CDC of arthropod-borne diseases from 1989 to 1993 appear in Table 1. Arthropod-borne diseases not reportable are babesiosis, tularemia, relapsing fever, Colorado tick fever, leishmaniasis, ehrlichiosis, and LaCrosse virus. Also dengue fever, endemic in the islands of the Caribbean, is readily vectored by *Aedes aegypti* and *Aedes albopictus* (5). Worldwide disease-bearing mosquitoes that are day- or night-biters include the *Aedes* species, which often transmit viruses to humans. Of 435 arboviruses (arthropod-borne viruses) found in insects by 1980, 100 cause diseases in humans. The diseases include yellow fever, dengue haemorrhagic fever, and many forms of encephalitis, including Japanese B, Venezuelan, West Nile, Chikungunya, Ross River, and Rift Valley fever. More than 60 species of *Anopheles* mosquito are vectors of malaria, in particular the human-biting members of the *A. gambiae* species complex in Africa. The *Culex* species are vectors of several forms of encephalitis in the United States, including Western Equine, Eastern Equine, St. Louis, and California encephalitis. Other insect species that can be vectors of diseases are listed in Table 2.

It has been suggested that the U.S. military, during operations in southeast Asia in the 1960s and 1970s, evacuated more personnel because of vector-borne diseases, primarily malaria, than for combat injuries. Most of the malaria cases reported in the United States since 1990 are imported cases, but there are a few unexplained transmissions. Computer models indicate that disease transmission from mosquitoes in developed countries becomes less likely when there has been a change to Western lifestyles, such as the regular installation of window screens, air conditioning in houses and businesses, and prevalence of indoor television viewing. Thus, the problem of mosquito-borne disease in developed countries may be less serious than in Third World locations where these factors are unlikely to be encountered, and where serious arthropod-borne diseases are common.

Table 2. Insect Vectors of Disease[a]

Insect	Scientific name	Disease
biting midges	*Ceratopogonidae*	bluetongue virus
blackflies	*Simulium*	river blindness
sandflies	*Phlebotamus, Leptoconops*	leishmaniasis
tsetse flies	*Glossina*	African trypanosomiasis or sleeping sickness
tabanids or horseflies	*Tabanus*	
clegs	*Haemotopota*	
deerflies	*Chrysops*	
snipe flies and stableflies	*Stomoxys*	
cattle ticks	*Rhipicephalus*	heartwater fever and blackwater fever
soft ticks	*Dermacentor*, *Amblyomma*	Rocky Mountain and spotted fever
mites or chigger mites	*Trombidiidae*	scrub typhus
bedbugs	*Cimex*	
lice	*Pediculus*	typhus
kissing bugs	*Pentatomid*	Chagas disease
fleas	*Xenopsylla, Pulex*	plague

[a]Ref. 2.

1. Evaluation of Repellents

A critical review (6) of techniques for the evaluation of insect repellents describes many test methods, including the following.

1.1. Repellents on Skin

The candidate chemical is dissolved in ethanol and spread over one forearm of the human subject, as DEET **(1)** is similarly applied to the other forearm. Each arm is then exposed to 1500 avid *A. aegypti* female mosquitoes for 3 min at 30-min intervals. Effectiveness is based on complete protection, ie, the time until the first confirmed bite (one bite followed by another within 30 min).

1.2. Repellents on Cloth

Each candidate repellent is applied to a knit cotton stocking or cloth patch at 3.3 g/m^2 cloth, usually as a 1% solution of active ingredient (AI) in acetone. Two hours later, the stock or cloth patch is placed over an untreated nylon stocking on the arm of a subject, the hand covered, and the arm exposed to 1500 female mosquitoes for one minute. If fewer than five bites are counted, the test is repeated at 24 h, then weekly until failure, which is, by definition, five bites per minute. The standard mosquitoes used are *Aedes aegypti*, *Anopheles quadrimaculatus*, or *A. albimanus*. Candidate repellents in cloth tests are in one of the following classes: class 1, effective 0 d; class 2, 1–5 d; class 3, 6–10 d; class 4, 11–21 d; and class 5, >21 d.

1.3. Space-Borne Repellents

Air is drawn over a human arm through a 9.5-cm disk of cotton netting having 0.64-cm holes and treated with a solution of the candidate repellent; air is then drawn into an olfactometer cage containing 125 avid female *A. aegypti*. The number of days the repellent prevents $>10\%$ of the mosquitoes from passing through the netting constitutes effectiveness. Tests typically use 1.0–3.89 mg/g netting.

1.4. Skin Patch-Tested Repellents

Small areas of human forearms are marked and treated with small amounts of repellent on a unit area basis to ensure that the treatment rate is always the same between subjects (7). The patches are tested at 0 and 4 hours against small numbers (ca 15) of mosquitoes. This method does not consider creep, movement of repellent across the skin surface, or the interaction between two chemicals owing to such lateral movement of chemical.

1.5. Repellents Not Using Human Bait (No Attractant)

A treated strip of fabric and a control strip are lowered into a container of crawling arthropods such as ticks, fleas, and mites. After a predetermined time, the strips are lifted, the animals remaining are counted, and the percentage repellency is determined.

1.6. Repellents Tested with an Inanimate Attractant

Machines have been constructed by several groups to measure the intrinsic (initial) repellency of a compound when it is added to a warm, moist airstream to overcome the attractiveness of the airstream to mosquitoes. Such machines remove the factor of human odor in attempts to simplify the measurement of repellency.

1.7. Repellents Tested with Animal Attractants

Numerous methods have involved the use of animals as attractants, followed by evaluation of repellents as skin treatments or attached cloth treatments, often against crawling arthropods such as fleas, ticks, and mites. Animals such as gerbils, guinea pigs, camels, mice, shaved rabbits, and hairless dogs have been used, particularly when the toxicity is unknown.

2. Arthropod Repellents

2.1. Mosquito Repellents

2.1.1. Insecticide-Impregnated Cloth

Clothing impregnants may be applied to socks, head nets, gloves, or conventional apparel by dipping into emulsions, manual application of liquid, or surface spraying with aerosols (qv). Repellents may be applied to cotton cloth using technical material dissolved in acetone, although this solvent may be unavailable or incompatible with some synthetic fabric blends. Repellents may be applied to clothing on a large scale using 10% of a nonionic emulsifier and 90% technical material at 5 wt % of the cloth. Repellent jackets made of 0.64-cm cotton mesh are impregnated with a repellent such as DEET **(1)**. There are several advantages in this. For instance, the repellent is applied to the mesh, not directly on skin. Repellents other than DEET may be used, such as repellents more effective than DEET, against biting flies or other mosquitoes. The jacket may be retreated as necessary simply by the addition of a measured quantity of concentrated repellent, such as 75 wt % DEET, to the jacket while in its storage pouch. An effective skin repellent such as DEET is lost much more slowly from the mesh jacket than from skin. This jacket has been added to the army supply system and is meant to be retreated with standard military-issue 75 wt % DEET. The DEET-treated jacket has been effective against mosquitoes in northern and southern states, blackflies in Maine, biting midges in Florida, and sandflies in Panama. The jacket is effective against heavy pressures of small insects that are capable of passing through mesh. Also, the jacket's wide spaces allow passage of air and moisture, making it a more comfortable alternative than either wearing long-sleeved, heavily repellent-treated clothing or having repellents applied to skin, particularly in warm, humid climates with heavy insect populations (8).

The standard clothing impregnant adapted by the U.S. Armed Services, M-1960, was intended for large-scale utilization in military laundries for protection from mosquitoes, fleas, ticks, and chigger mites (9). It contains equal parts of benzyl benzoate [120-51-4], *N*-butylacetanilide [91-49-6], 2-ethyl-2-butyl-1,3-propanediol [115-84-4], and a third of a part of Tween 80. The repellent also has disadvantages, including odor, and is less effective as a mosquito repellent than DEET, although benzyl benzoate is a good tick and mite repellent. The M-1960 formulation has been replaced in the U.S. Army system with aerosol formulation DEET for personal protection and clothing treatment or 75 wt % DEET and 25 wt % ethanol in plastic squeeze bottles especially for skin treatment. A formulation problem with aerosols is that chlorofluorocarbon propellants were first replaced with compressed flammable hydrocarbon gases; in the 1990s, however, water-base sprays are more common. Clothing treatments onto 100% cotton military uniforms using DEET have been shown to resist laundering better than treatments onto polyester–cotton blends, whereas 100% polyester retains repellents poorly (10).

Several studies of cloth treatment for toxicity and repellency have been conducted using impregnation with permethrin emulsifiable concentrate (EC), together with residue studies. Permethrin-treated military uniforms, treated by aerosol spray, pressurized spray, or impregnation during the washing process, have been found effective in tests (11). Tent material may be treated with permethrin or dimethyl phthalate for repelling mosquitoes (12). Alternatively, a cloth manufacturer (Graniteville Company) coats bulk cloth with permethrin either before or after the weaving operation. The effective treatment level of 0.125 mg/cm^2 of permethrin that is toxic to mosquitoes appears to be compatible with subsequent sewing operations, thus making unnecessary post-manufacture or field treatment. This material is commercially available for manufacture into tent fabric and ground cloths.

2.1.1.1. Bednets and Treated Bednets. Effective personal protection for sleeping can be provided by the use of bednets, of which many varieties are commercially available, including modern self-supported structures. Good information sources are available (2, 13). Studies suggest that chemical treatment of bednets at 2 g/m^2 active ingredient can reduce numbers of biting insects in the near vicinity of the bednet, even if the net is torn (14). Mosquitoes that contact a permethrin-toxicant-treated bednet may be killed if they rest on it or may be knocked down and therefore much less likely to bite (15).

2.1.2. Standard Mosquito Repellents

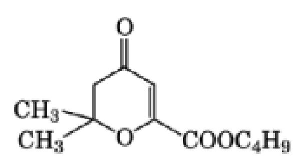
Since its initial report as a promising repellent in 1954, DEET has been considered the best all-around repellent having generally acceptable characteristics, despite a continuing search for a superior chemical. Improvements include many commercial products with added cosmetic agents that use slow release technology, such as the U.S. Armed Services slow release 35% DEET formulation (16). There were 35 EPA-registered repellent products in 1994 that contained only DEET under different trade names (2). DEET is present in 192 of the 212 products mentioned previously (2).

The mode of action of successful repellents is still unproven as of this writing (1996). Replacement of DEET with something better becomes even more remote because of the estimated $25 million cost of development and registration of a new material. DEET is the principal or only component in most of the effective mosquito repellents on the market, as can be seen from the commercial products listed in Table 3 (2). Muskol (100% DEET) and a number of other products containing 100% DEET were popular in the 1980s, with reports in outdoor magazines and *Consumer Reports* claiming that 100% DEET was perhaps more desirable, and had to be applied less often than more dilute formulations. However, the use of 100% DEET on skin is usually not justified because of the possibility of skin irritation, and not for reasons of better or worse repellent activity (2). Sales of DEET repellents were estimated at $50–$75 million/yr in the United States in 1984 (17). DEET costs ca $9/L ($34/gal) from a chemical manufacturer. A 30-cm^3 (1-oz) bottle that retails for $4–$5 and lasts the typical consumer a year contains $0.30 of chemical. More recent tests against *Anopheles albimanus* show good activity (2).

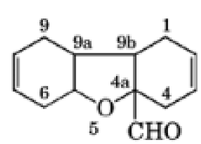
Dimethyl phthalate [131-11-3] (DMP) is a clear oil insoluble in water and soluble in organic solvents, and is synthesized from phthalic acid esterified with methanol. DMP is an effective repellent, used as a standard against *A. aegypti*, and is effective for 11–22 d on cloth. The famous repellent Rutgers 6–12, 2-ethyl-1,3-hexanediol [94-96-2], is a clear oil that is insoluble in water and miscible with organic solvents such as ethanol. Screened during World War II, this repellent is exceptionally effective against *A. aegypti*, lasting 196 d on cloth. Tests have been run against the newer pests *A. albopictus* and *A. aegypti*, including five repellents containing DEET (test standard), a controlled release formulation containing DEET, two dosages of DEET in ethanol, and Avon Skin-So-Soft. On the skin, the repellent chemicals provide significant protection from biting; however, *A. albopictus* is more sensitive to repellents than *A. aegypti*. Two experimental repellents provide 7-h protection, 25% DEET provides >8 h, a controlled release formulation with 35% DEET provides >10 h, but the Avon Skin-So-Soft provides only 0.6-h protection from bites. Permethrin-treated fabric provides complete protection through five washings. Repellent products containing more than 12% DEET can provide satisfactory protection against bites of this species (18). More recently, populations of the Asian tiger mosquito in Texas have been found to show malathion resistance and a tolerance for bendiocarb, which suggests that chemical management of this mosquito may prove to be difficult.

2.1.3. Experimental Mosquito Repellents

A comparison of nine commercial repellents has been made against *A. aegypti* using the skin patch test. At zero time (measuring intrinsic repellency), Stabilene [9003-13-8] and MGK Repellent 326 [136-45-8, 3737-22-2] are significantly inferior to DEET, dibutyl phthalate [84-74-2], indalone [532-34-3] **(2)**, dimethyl phthalate, MGK Repellent 11 [126-15-8] **(3)**, 2-ethyl-1,3-hexanediol [94-96-2], and citronellal [39785-81-4] **(4)**. Efficacy ranking by 4-h ED50 (50% biting rate on the treatment) was indalone, citronellal, 2-ethyl-1,3-hexanediol, and DEET, as the others had become ineffective. The relative superiority of DEET in comparison to other standard repellents has been discussed (19).



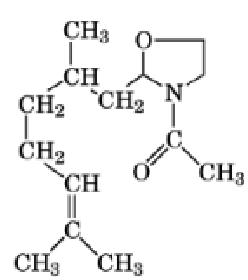
(2)



(3)

Table 3. U.S. Mosquito Repellents Containing DEET

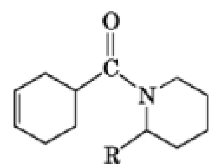
Company	Location	Product brand name	Form	Composition, %
AMREP, Inc.	Marietta, Ga.	Misty Insect Repellent	spray	7
		Misty Extra Strength	spray	25
ARI, Inc.	Griffin, Ga.	Bug Barrier 100%	lotion	100
		Bug Barrier	spray	7
		Bug Barrier II	spray	25
Bayer Inc.	Chicago, Ill.	Cutter Evergreen Scent	cream	35
		Cutter Insect Repellent	stick	33
		Cutter Insect Repellent	spray	18
		Cutter Maximum Strength Formula 100	lotion	100
		Cutter for Kids	spray	8
CCL Custom Manufacturing Inc.	Danville, Ill.	Personal Insect Repellent	spray	10.5
		CCL Quick Breaking Insect Repellent	foam	8.9
D-Con Co. Inc.	Montvale, N.J.	6-12 Super Strength Premium	spray	26.3
		6-12 Plus Sportsmate II	spray	5
		Premium	cream	45
Fuller Brush Co.	Great Bend, Kans.	Insect Repellent	gel	7
		Ful-Scat Insect Repellent	spray	8
Hysan Corp.	Chicago, Ill.	Adios Insect Repellent	spray	7
Littlepoint Corp.	Cambridge, Mass.	Littlepoint Insect Repellent	lotion	10
Olson Outdoor Laboratory	Freehold, N.J.	One + One	lotion	11.2
Pete Rickard Inc.	Cobleskill, N.Y.	Ole Time Woodsman Kampers	lotion	50
		Ole Time Woodsman Jungle Formula	spray	60
Reckitt & Coleman Household Products	Wayne, N.J.	Insect Repellent Spray for Personal Use	spray	7
S.C. Johnson & Son Inc.	Racine, Wis.	Off! Insect Repellent	spray	15
		Maximum Strength Deep Woods Off! 100	lotion	100
		Off! Towelette	wipe	25
		Off! Skintastic II	lotion	7.5
		Unscented Off!	spray	15
Schering-Plough Health Care Products Inc.	Liberty Corner, N.J.	Muskol Insect Repellent	lotion	100
		Muskol Insect Repellent	spray	25
Whitmire Research Laboratories, Inc.	St. Louis, Mo.	P/P Outdoor Lotion	lotion	19.4
		Whitmire Insect Repellent Stick No. 1	stick	14
Wisconsin Pharmacal Co.	Jackson, Wis.	Repel Insect Repellent Towelette	wipe	55
		Repel 100	lotion	100
		Repel Scented Family Formula	spray	35
		Repel Insect Aerosol	spray	55
Winsol Labs	Seattle, Wash.	Eddie Bauer Insect Formula	lotion	10
Woodland Products	Ormond Beach, Fla.	Woodlands Insect Repellent	lotion	10



(**4**)

Seventy-one *N,N*-dimethylcarboxamides have been tested on cloth against three species of mosquitoes: *A. aegypti*, *A. quadrimaculatus*, and *A. albimanus*. The amides are prepared via the acid chloride by treatment of the appropriate carboxylic acid with thionyl chloride, which is then added to a cold mixture of ether–water containing excess *N,N*-dimethylamine plus sodium hydroxide. Extraction and vacuum distillation give materials that are used as distilled, with 95–98% purity. Nine of 38 *N,N*-dimethylbenzamides, three of 17 *N,N*-dimethylphenylacetamides, two *N,N*-dimethylphenylcarboxamides, and three *N,N*-dimethylalkanamides are class 5 repellents against all three species of mosquitoes. Typically, *N,N*-dimethylundecanamide [6225-09-8] provided 71-d, 132-d, and 59-d protection against *A. aegypti*, *A. quadrimaculatus*, and *A. albimanus*, respectively (20). Several of these materials have been tested and found to be effective against blackflies in Maine.

Excellent personal protection is afforded by controlled-release topical repellents and permethrin-treated clothing against natural populations of *Aedes taeniorhynchus* (21). Again the increased protection is afforded by use of skin repellents with clothing treatment to avoid all bites. Two of the substituted piperidines, 1-(3-cyclohexen-1-ylcarbonyl)-2-methylpiperidine (AI3-37220) [69462-43-7] (**5**, $R = CH_3$) and 1-(3-cyclohexen-1-ylcarbonyl)piperidine (AI3-22872) [52736-58-0] (**5**, $R = H$), have been the most promising in tests against mosquitoes; this piperidine family looks like the only promising group to be discovered in some years (18).



(**5**)

Tests against *Aedes albopictus* mosquitoes using either piperidine compound have shown these compounds to be nearly as good as DEET. Subsequent tests in southeast Asia suggest repellency about the same as DEET against the resistant *A. dirus* malaria vector species, but poor repellency against *A. albimanus* and *A. quadrimaculatus*; against *A. taeneorhynchus* it shows activity about equal to DEET (22). Further tests of toxicological properties are pending for these two compounds but are suspended at U.S. Army Environmental Health Agency (AEHA) because of lack of funds.

More recently the cis and trans isomers of the mosquito repellent CIC-4, a mixture of citronella isomers, have been separated by preparative hplc and bioassayed for effectiveness (23). Chiral-phase capillary gas chromatography and mosquito repellent activity of some oxazolidine derivatives of (+)- and (−)-citronellal have been studied to find structure–activity relationships (24). Several 2-alkyl-*n*-acetyloxalidines have been synthesized and tested against mosquitoes, with further efforts using nmr to determine the rotational isomers of the more active *N*-acetyl-2,2-dimethyloxazolidine (25).

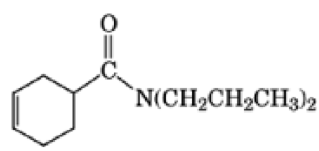
2.1.4. Natural Mosquito Repellents

Thousands of exotic and native natural botanicals, plant extracts, and 12,000 synthesized compounds have been collected worldwide and tested for activity during and after World War II in Orlando and Gainesville, Florida by the U.S. Department of Agriculture (USDA). A USDA review of plants of possible insecticidal value lists 1182 species, and is followed by two other compilations of botanicals tested on a large scale by USDA from 1940 to 1964 (9). The review includes tests against 15 species of insects. A further study of synthetic compounds has been published (26). Natural and synthetic repellents have been reviewed in a comparison with synthetic repellents (14), which include common materials such as pyrethrum and Vitamin B_1, as well as many essential oils, including citronella, *Artemesia*, lemon, eucalyptus, mint, and *Clausena*. Cedarwood oil and citronella have been tested against four African species of mosquitoes in Tanzania in competitive tests with

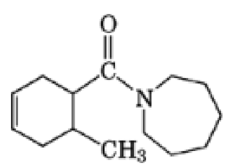
DEET, dimethyl phthalate, ethylhexanediol, and permethrin (14). A Chinese lemon eucalyptus oil formulation, Qwenling, received some attention and was found to have effectiveness but only for a short (10–20 min) time compared to a standard DEET treatment, which can last for several hours (27). This is typical for repellent materials described as natural and obtained from plant essential oils that must be reapplied often.

2.2. Biting Midge Repellents

The genus *Culicoides* is found in fresh water, salt water, and tide water environments in the southeastern United States and Caribbean, where they may be properly called biting midges, or more commonly sandflies, sand fleas, sand gnats, punkies, no-see-ums, or flying teeth. Because of their small size, they can pass easily through ordinary mosquito screens. Commonly used repellents are of varying effectiveness, depending on the species involved (28). In paired field tests, topically applied candidate carboxamide repellents have been compared to DEET at Parris Island, South Carolina, against *C. hollensis*, and on the Gulf coast of Florida against *C. mississippiensis* (29). Repellency has been determined three ways, ie, by biting rates, length of protection, and coefficient of protection. DEET averaged 61 times greater protection than the untreated check, and all others averaged 130 times greater protection at Parris Island. In Florida, DEET averaged 28 times greater protection than an untreated check, whereas all other materials averaged 190 times greater protection. DEET was considered an effective repellent when applied to exposed skin as a 25 wt % formulation, but four novel alicyclic piperidines (carboxamides) have been found more effective than DEET: *N*,*N*-dipropylamino-3-cyclohexenecarboxamide [68571-08-4] **(6)**, bp 93°C (60 Pa (0.45 mm Hg)); 2-methyl-1-piperidyl-3-cyclohexenecarboxamide [69462-43-7] (**5**, R = CH_3), bp 110°C (103 Pa (0.77 mg Hg)); 1-piperidyl-3-cyclohexenecarboxamide [52736-58-0] (**5**, R = H), bp 108°C (60 Pa (0.45 mm Hg)); and 1-(hexahydro-1*H*-azepinyl)2-methylcyclohexenecarboxamide [67013-96-1] **(7)**, bp 115°C (120 Pa (0.9 mm Hg)). The first two were substantially more effective against *Culicoides* species.



(6)



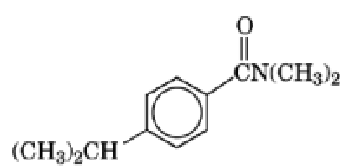
(7)

Among the 117 compounds synthesized, structures that have been found especially active include the 1-piperidyl- **(5)** and 1-[hexahydro-1*H*-azeipinyl] **(7)** derivatives where the cyclohexenyl ring can either be monounsaturated or have methyl branches such as in the 2-position (30). The use of Avon Skin-So-Soft, a scented mineral oil cosmetic, has been claimed to repel biting midges at Parris Island, South Carolina, and it is reportedly widely used for mosquitoes as well (28). When applied liberally, it apparently traps the midges or fouls their mouthparts and thus inhibits biting. Tests of several commercial mineral oil preparations, both scented and unscented, show interference with biting behavior and therefore a repellent effect. This is because when applied thickly to skin, the small biting midges tend to become thickly coated and drown in the oil (28).

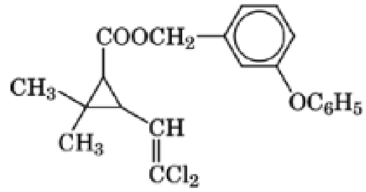
2.3. Phlebotomine Sandfly Repellents

Because military and civilian personnel were potentially exposed to biting insects during involvement of Allied military in the Persian Gulf and Middle East in the 1980s, U.S. personnel had access to DEET and permethrin clothing treatment through the military supply system. Phlebotomine sandflies are found primarily in relatively underdeveloped tropical and subtropical regions of the world. They are vectors of the various forms of leishmaniasis, bartonellosis, and numerous arboviruses, including the medically important sandfly fever group. However, personal protection against phlebotomine sandflies has had little attention as compared to repellents for mosquitoes. Only a few tests of repellents for Old World phlebotomine flies have been documented, but none in the 1990s.

In tests done in the 1940s, dimethyl phthalate and pyrethrum cream were found to be partially protective on skin against *Phlebotomus papatasi* for 6 h (31). Tests with laboratory-reared *P. papatasi* show that the duration of complete protection (no bites) provided by DEET, *o*-ethoxy-*N,N*-diethylbenzamide, *o*-chloro-*N,N*-diethylbenzamide, or *N*-butyryl-1,2,3,4-tetrahydroquinoline, averages at least 4 h, but perspiration contributes to a high rate of repellent loss (32). Investigations using repellent-treated netting indicate that DEET-treated bednets provide complete protection throughout the night (33). In Panama, phlebotomine sandflies are responsible for the transmission of *Leishmania braziliensis panamensis*, the causative agent of cutaneous leishmaniasis, a human disease among people living in close association with the forests. Cutaneous leishmaniasis and arboviruses affect locals and U.S. military personnel who train in jungle areas. A more recent study shows that 1.6% of U.S. Army personnel who took part in the jungle warfare training course during a three-week period contracted leishmaniasis (34). Personal protection methods have been evaluated against phlebotomine sandflies in the bush in Panama. Arms are treated with 2 mL of 12 wt % max of the following repellents in paired tests with DEET, which was applied to the other forearm in the same manner: hexahydro-1-((2-methylcyclohexyl)carbonyl)-1*H*–azepine [52736-62-6] (**7**, saturated six-membered ring); 4-isopropyl-*N,N*-dimethylbenzamide [6955-06-2] **(8)**; DEET **(1)**; and *N,N*-dipropylcyclohexanecarboxamide [67013-94-9] (**6**, saturated ring). Skin applications of the five selected repellents including DEET provide a mean coefficient of protection (CP) of 99.2% against the attack of at least three species of *Lutzomyia*. All of these repellents tested at the highest dosage give good protection from the bites of at least three species of phlebotomine sandflies, two of which are important vectors of leishmaniasis. However, the azepine (**7**, saturated) gives complete protection and warrants further study (28).



(8)

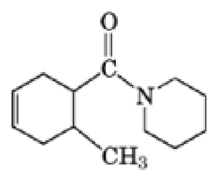


(9)

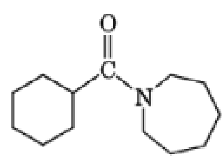
DEET-treated net jackets also provide good protection, but an additional application of 10–25% solutions of repellent to the unprotected face is necessary for maximum protection. Clothing treated with permethrin [52645-53-1] **(9)** does not provide the protection expected against these insects. Because sandfly behavior and resistance to quick knockdown are responsible for the numbers of bites recorded, maximum protection from bites thus requires application of DEET or another suitable repellent to the exposed skin when wearing permethrin-treated clothing (35).

2.4. Horseflies, Greenheadflies, Deerflies, Stableflies

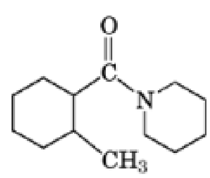
Field trials of permethrin-treated clothing against highly susceptible tsetse flies have shown good effectiveness (36). There are no published tests exhibiting the effectiveness of clothing treatments against North American species of horseflies and deerflies. Bath oils are commonly used by lifeguards on the Florida Gulf Coast for protection against biting stableflies, and have been used effectively on horses; however, as usual, repellents fail at high fly populations. This repellent effect is difficult to demonstrate in cage tests with stableflies, where biting attacks occur despite treatment with this material (37). It is likely that use of repellent-treated mesh jackets and hats for mosquitoes and sandflies would be most effective against these large biting flies. Table 4 compares the effectiveness of eight repellents to DEET.



(10)



(11)



(12)

2.5. Tick and Chigger Repellents

Prevention of tick attachment is possible by mechanically preventing access of the ticks to bare skin bordering or beneath the clothing, such as zippered long pants with bloused cuffs tucked into boot or sock tops and a long-sleeved shirt tucked into the pants (2). Repellents are best impregnated into clothing, on wrist skin under the sleeve, on and above the socks, and around the neck on the exposed skin and under the collar. DEET products are available as a 50% liquid and may be mixed with isopropyl alcohol (59 mL DEET and 1 L 2-propanol)

Table 4. Relative Effectiveness[a] Compared to DEET[b]

Priority	Structure number	Name	CAS Registry Number	*Aedes aegypti*	*Aedes taeniorhynchus*	*Anopheles quadrimaculatus*	*Stomoxys calcitrans*	*Chrysops atlanticus*	Black-flies	*Culicoides* (sandflies)
1	(**5**, R = H)	1-(3-cyclohexen-1-ylcarbonyl)piperidine	[52736-58-0]	<	>	=	>	>	>	>
2	(**6**, satu-rated ring)	*N,N*-dipropylcyclohexanecarboxamide	[67013-94-9]	<	>	<	>	>	<	>
3	(**7**, satu-rated ring)	hexahydro-1-((2-methylcyclohexyl)-carbonyl)-1*H*-azepine	[52736-62-6]	<	=	<	>	>	=	>
4	(**7**, no methyl)	1-(3-cyclohexen-1-yl-carbonyl)hexahydro-1*H*-azepine	[52736-59-1]	<	<	=	>	=	>	
5	**(8)**	*p*-isopropyl-*N,N*-dimethylbenzamide	[6955-06-2]	<	=	=	=	=	<	>
6	**(10)**	1-((6-methyl-3-cyclohexen-1-yl)carbonyl)pyrrolidine	[67013-95-0]	<	=	<	=	=	=	
7	**(11)**	1-(cyclohexylcarbonyl)-hexahydro-1*H*-azepine	[68571-09-5]	<	=	<	<	=	=	
8	**(12)**	1-((2-methylcyclohexyl)-carbonyl)pyrrolidine	[52736-60-4]	=	<	=	=		=	

[a] $>$, $<$, or $=$ indicates statistically significant differences of greater than, less than, or equal to DEET, respectively.
[b] Ref. 38.

to produce sufficient material to impregnate clothing with a 5% solution and, depending on tick density, give 80–98% protection.

Permethrin was developed as a clothing impregnant for military use by several countries worldwide, including the United States. It first became available in 1982 as a clothing treatment under EPA label 24C in an aerosol formulation called Permanone Tick Repellent. The same formulation is widely available in products registered with approved labeling under such trade names as Duranon Tick Repellent and Coulston's Permethrin Arthropod Repellent. A topical permethrin treatment of clothing has shown good effectiveness against crawling insects when applied as a water-based formulation of 0.5 wt % permethrin (38). It gives extremely effective protection against ticks. Permethrin-treated cloth is practically odorless; a single treatment of ca 20-s spray (ca 0.2 g/m^2) adsorbs to the outer surface of clothing, does not contact skin, and is long lasting (38). Permethrin as a clothing treatment acts more as a toxicant than as a repellent, and though ticks may crawl on the clothing, the visit is only temporary and usually fatal within a few minutes. The lethal barrier provided has been shown to give 100% protection in tests against ticks in Oklahoma, Kentucky, and Florida (38). The materials named above are likewise effective repellents against chigger mites (*Trombiculidae*), also called chiggers or redbugs.

2.6. Body and Head Lice

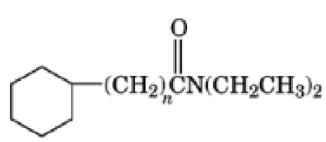
The human body louse, *Pediculus humanus* L., is an important health threat in gyms and schools of the United States and in many areas of the world. There are no licensed vaccines for typhus or relapsing fever. Even if vaccines were available, protection of military personnel would not prevent epidemics in refugee or POW camps under U.S. military control. Lindane was the standard U.S. military pediculicide for over 20 years, used as a delouser during the Korean conflict and on Iraqi troops in early 1991 (22). However, it is believed by some to be obsolete, and is considered a possible oncogen by the U.S. EPA. Also, most populations of body lice are resistant to the organochlorine insecticides, including lindane. The all-purpose clothing impregnant, M-1960, was developed for the U.S. Department of Defense (DOD) and introduced in 1953. It had poor user acceptance on account of its plasticizing properties, disagreeable odor, and irritation to sensitive skin, and is no longer manufactured.

Alternatively, fabric patches treated with permethrin have been evaluated against natural and laboratory strains of human body lice in Peru. Permethrin-treated fabric is toxic to lice on contact and quickly affects feeding behavior, even when washed up to 20 times. Thus permethrin-treated clothing interrupts disease transmission, and offers a passive louse control not previously feasible (39).

Permethrin, under consideration by DOD as a candidate pediculicide for emergency louse control, is marketed as a 1% cream rinse for head louse control. It has been successfully used as a dust formulation against body lice in Egypt. During World War II, studies were done in the United Kingdom, the former Soviet Union, and the United States on the use of various chemicals for impregnating underwear to prevent louse infestations. Pyrethrins have been found effective, but only at high rates of application, and are mostly removed by laundering (39).

2.7. Cockroach Repellents

General information on cockroach control, including repellents and toxicants, is available (40). Transport of goods and materials also provides rapid transport of cockroaches in corrugated cardboard boxes, empty beer and soft-drink bottles, cases in recycling locations, and commercial trucks used for transporting commodities such as bananas, laundry, dry cleaning, and paper bags. Personal automobiles also helped in the rapid dispersal of a newly introduced pest, the flying Asian cockroach, across central Florida in the late 1980s. Repellents may be helpful in preventing transport of cockroaches into uninfested areas. Some logical uses of repellents are on cardboard cartons for food and soft drinks, on beer crates, and in coin-operated vending machines, all of which provide excellent shelter and food for cockroaches (40). Recycling of beer cans and soft-drink containers offers cockroaches another opportunity for shelter and transport, and control is probably difficult. A good repellent can be used either alone or in conjunction with an insecticide as a residual treatment in business establishments or homes. Such effective, long-term repellents can become more useful in the future if the only toxicants available are short-term biodegradable materials. This is especially problematic when retreatment is expensive and rapidly becomes ineffective. Also, the cockroach's opportunistic nature of feeding and shelter-finding permits survival and flourishing when most but not all sites are treated. Similarly, the use of slow-acting toxicants such as borax and boric acid is not effective for long unless insects can be confined to dry, treated surfaces. This tends to describe a laboratory environment and is not applicable to the real world in which cockroaches may quickly leave an effectively treated area and fully recover from the sublethal effects. Many repellents are found among amides, sulfonamides, cyanoacetic acids, and carboxamides, but two good ones are *N,N*-diethylcyclohexaneacetamide (**13**, $n = 1$) and *N,N*-diethylcyclohexanepropaneamide (**13**, $n = 2$), both better than fencholic acid when tested against the common North American cockroaches, *Blattella germanica* and *Periplaneta americanica* (41).



(13)

(14)

$HOCH_2CH_2S(CH_2)_7CH_3$

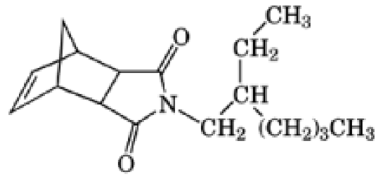
(15)

Dibutyl succinate or Tabutrex [141-03-7]; R-11; R-55 [23885-27-0] **(14)**; and R-874 [3547-33-9] **(15)** have been available for industry as cockroach repellents since the 1960s. Tabutrex (Glenn Chemical Company) is formulated as an emulsion concentrate (20%) and an oil spray (2%). The oral LD_{50} (rat) is 8000 mg/kg. Treated surfaces remain 100% repellent to *B. germanica* for three weeks. In laboratory tests, cockroaches are repelled from wooden beverage crates for 15 weeks (42). Hexahydrodibenzofurancarboxaldehyde–butadienefurfural copolymer, MGK R-11 **(3)** (Phillips Petroleum Company) is a pale yellow liquid having a fruity odor, miscible with many organic solvents, and compatible with most insecticides. A typical formulation contains 0.075% pyrethrins, 0.15% piperonyl butoxide, and 1% R-11. For treating the inside of cartons, R-11 is applied as a 1% emulsion incorporating 2% of the synergist MGK 264. On beer cartons, R-11 gives $>$80% repellency for two months, reducing to 60% at six months. MGK R-11 has been used in pet sprays and in repellents for personal use. Of all the materials evaluated for odor, this repellent is the most pleasant (43). The acute oral LD_{50} (rat) is 2500 mg/kg; the dermal LD_{50} is $>$2000 mg/kg.

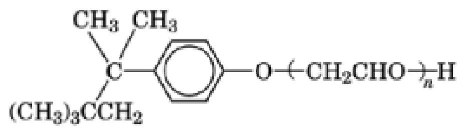
t-Butyl *N,N*-dimethyldithiocarbamate **(14)** or MGK R-55 (McLaughlin Gormley King Company) is a rodent and insect repellent. It repels *B. germanica* from treated cartons for 90 d (at 2%) and for 63 d (at 1%). It is more odorous and toxic than MGK R-11 and MGK R-874. However, 2-hydroxyethyl *n*-octyl sulfide **(15)** or MGK R-874 (Phillips Petroleum Company), the only commercially available repellent, is a light amber liquid having a mild mercaptan-like odor, slightly soluble in water but miscible with most organic solvents (40). The label indicates that it may be used near food (40). It is used with MGK 264, a pyrethrins synergist. Formulations commercially available are an EC diluted with water and applied at 1–5% by automatic spraying equipment and an oil solution used at one gram of active material per square meter. R-874 tested against German cockroaches is marginally more effective than R-55 and lasts twice as long as R-11. Toxicity is low; the acute oral LD_{50} (rat) is 8530 mg/kg; dermal LD_{50} is 13,590 mg/kg.

A listing of compounds evaluated in the laboratory as cockroach repellents summarizes 872 synthetic compounds out of 901 bioassayed from 1953 to 1974 (43). Fencholic acid [512-77-6] (3-isopropyl-1-methylcyclopentanecarboxylic acid) has been used as a standard repellent in tests conducted by placing 20 cockroaches in a glass crystallizing dish without food and water and offering them a choice of two cardboard shelters, one of which was treated with 1 or 2 mL of a 1% solution of the candidate in acetone. Counts were made daily for seven days.

Another problem lies in the overlap of repellent–toxicant definition, in that many toxicants are known to have repellent effects (43). Pyrethrins are often used on ships to flush cockroaches from harborages during a treatment with another, less activating toxicant. In a survey of the components, eg, toxicants, synergists, solvents, flushing agents, and emulsifiers, making up commercially available formulations of insecticides for cockroach control in the United States, 121 different materials were examined (44). Tests show that pyrethrins which have been considered repellents for some years, MGK 264 [113-48-4] **(16)** and the emulsifier Triton X100 [9002-93-1] **(17)**, are noticeably repellent to both German and American cockroaches (44).

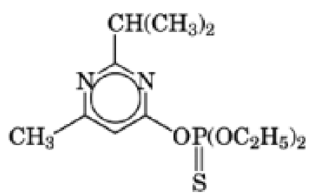


(16)

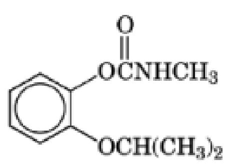


(17)

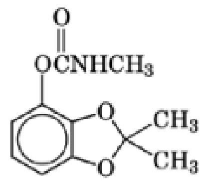
The list of repellent materials also includes a number of surfactants (wetting agents) and deodorants, but in no case are solvents implicated (45). In laboratory studies for repellency, some formulations containing 0.5% organophosphates did not function as repellents, but diazinon [333-41-5] **(18)** (0.5%), propoxur [114-26-1] **(19)** (1%), synergized pyrethrins (1%), some synthetic pyrethroids, and bendiocarb [22781-23-3] **(20)** (1%) were repellent for a week or more (46). In an extensive testing program of many insecticides, avoidance of treated surfaces has been observed more frequently with diazinon than with any of the other materials (47). Diazinon **(18)** is commonly used in Florida for household treatments, although chlorpyriphos, permethrin, cypermethrin, and hydroprene are widely used for cockroach control.



(18)



(19)

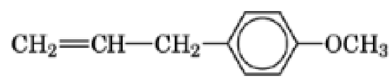


(20)

Sixty-two novel experimental carboxamides of 1,2,3,6-tetrahydropyridine have been tested as repellents of German cockroaches, and five provided 100% repellency for 17 d in a stringent test (48).

2.8. Other Insects

Bark beetle management in European forests has been successful using combinations of sex pheromones and tree volatiles. Repellents that were tested in Louisiana to deter attacks of the southern pine beetle afforded protection of high value loblolly pines by using the host tree compound 4-allylanisole [140-67-0] (49). The aggregation inhibitor 4-allylanisole **(21)** eliminated tree deaths for the length of the 30-d test by placing nine vials with wicks containing 20 g each of repellent vertically on the lower trunk of each tree being protected, using the tree as a flagpole. A patent has been issued on this technology (49).



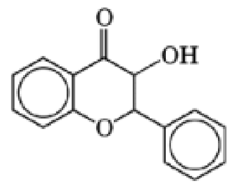
(21)

3. Bird Repellents

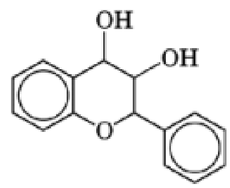
Blackbirds, starlings, and sparrows are North American birds that cause serious damage to growing crops, costing at least $40 million/yr. Nonchemical techniques using repelling devices such as propane cannons, shiny Mylar ribbons, scarecrows, metallic pinwheels, and recorded distress calls give temporary results, but when the birds become accustomed to the devices, the effect is generally lost (50). However, when reflective tapes were stretched at close intervals over entire fields of a high value sweet corn crop, losses of corn ears to blackbirds were one-sixth to one-third of losses in untaped fields; goldfinches and deer were not deterred (50).

Millet is a grain-yielding sorghum, a vital staple food crop occupying 44×10^6 ha (10.9×10^7 acres) in the Third World, including India, southern Asia, Latin America, the Sahelian zone of Africa, the Near East, and the Middle East. The main bird pest in Africa is *Quelea quelea*, a weaver finch. In many of these areas where control measures are necessary for the preservation of the crop (51), chemical repellents are expensive and difficult to obtain, require special application equipment, and therefore in some situations are an unlikely consideration. For these areas, it seems practical to breed the ability to resist bird depredation into the physical characteristics of the plants (52) or the genetic composition of the plants, and much effort has been so directed since 1960 (53). High content of tannins is the characteristic most often associated with bird resistance in sorghum because these polyphenolics (tannins) produce astringency and thus repellency. Unfortunately, the palatability, digestibility, and nutritional quality of foods may also be reduced in tannin-loaded food products. Hydrolyzable tannins are present in small quantities in sorghum, and condensed tannins are responsible for coagulation of proteins of the saliva and mucous membranes, resulting in the astringent taste response.

Polyphenolic condensed tannins or proanthocyanidins are a series of complex condensed 4-ketoflavan-3-ol [577-85-5] **(22)** and flavan-3,4-diol [5023-02-9] **(23)** molecules of 500–3000 mol wt (54). The subject of polyphenolic tannins has been reviewed (55); however, application of natural tannins onto crops failed to show efficacy.



(22)

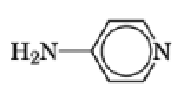


(23)

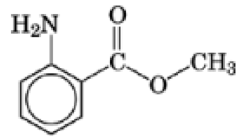
Some bird repellents are composed of viscous, sticky materials that birds dislike having on their feet (17). These compounds, eg, Tanglefoot, Roost-No-More, and TackTrap, are often based on incompletely polymerized isobutylene and thinned with aromatic solvents. They should be formulated to have the proper blend of tackiness and viscosity for the weather, method of application, and pest species. They are applied to leave sticky residues on perching locations in buildings and roosts in trees. Because these materials do not have an obnoxious odor, the birds must land on and learn its location in order to avoid it, as there are no long-range cues in the treatment itself for conditioning.

Intoxicating chemicals are those that are not necessarily lethal (see Pesticides) but operate as primary repellents or secondary repellents, eg, emetics causing sickness or distress. Primary bird repellents are those whose mode of action is having a bad taste; immediate rejection of food is the desired result. However, they are effective only if other foods are available; they are not effective in times of food shortages, because large flocks of migrating birds would be forced to feed or starve. Bird repellents have been discussed in reviews (51, 56).

Avitrol [504-24-5] (4-aminopyridine) **(24)**, mp 155–158°C, bp 273°C, has repellent–toxicant properties for birds and is classed as a severe poison and irritant. This secondary bird repellent can be used as a broadcast bait, causing uncoordinated flight and distress calls and escape responses in nearby birds (57). A reevaluation shows lack of effectiveness of 1% baits but better control of blackbirds with 3% baits (58). Suspected contamination of drinking water with 4-aminopyridine has been reported in toxicosis of Brahman cattle and horses (59).

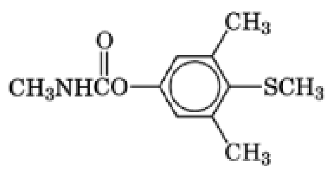


(24)



(25)

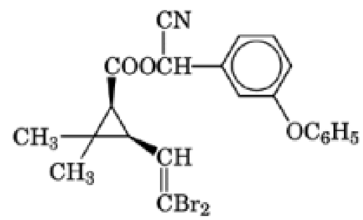
Methyl anthranilate [140-20-3] **(25)**, the grape flavoring used in food products, has been shown effective as a waterfowl repellent when applied at 90–169 kg/ha (8–15 lb/acre). Research has shown statistically significant reduction of activity compared to untreated water with 0.06–0.5% solutions applied onto shallow standing water next to airport runways (60). In more recent efforts, a free-flowing powder formulation was added to 1-m dia children's wading pools (at 0.075% g/g) and showed significant reduction of activity (94–96% less activity) against free-ranging gulls for 4–11 days, compared to untreated water. Overall gull activity has been reduced even when all water was treated (61). A surfactant-containing formulation was tested against mallard ducks in 1-m dia wading pools at 0.02% AI, and both pool entry and bill dipping were measured and found to be significantly reduced (61). These materials demonstrated repellency at concentrations of 0.038% vol/vol, which are 10–60 times lower than concentrations needed to repel red-winged blackbirds and European starlings from solid livestock feed (61). Also, data collected support evidence of long-lasting effects and suggest learned avoidance of anthranilate compounds by birds (62), a further indication that these compounds may be useful in reducing damage to newly planted rice fields and to reduce losses at fish hatcheries.



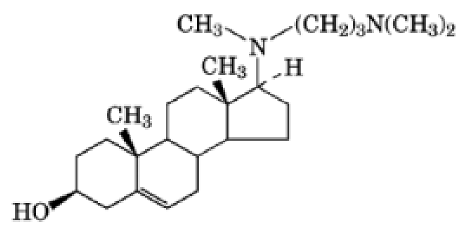
(26)

Methiocarb [2032-65-7] (3,5-dimethyl-4-(methylthio) phenol methylcarbamate) **(26)** is classed as an insecticide and acaricide and is used as a slug and snail bait, but is no longer registered for use as a bird repellent in the United States. Its uses on field and horticultural crops for bird repellency as an emetic have been reviewed (63). It was found to reduce bird damage in treatments of sweet corn (64). Methiocarb has been applied to wine grapes in Ohio, California, and Oregon (65), and to blueberries in New Zealand (66). Residues in wine (qv), as well as its effect on the composition and flavor of the bottled wine, were reported (67). Its efficacy in ripening sorghum in Canada and Senegal were also reported (51, 68), as were its residues and its sulfoxide and sulfone metabolites during efficacy studies against starlings in cherry orchards (69). Sorghum hybrids were treated with methiocarb, and grain yield and predation were studied (70). The conditioning response acquired is effective against red-winged blackbirds and persists in the laboratory up to 16 weeks (71). More recent studies to answer EPA queries show lack of methiocarb toxicity to birds and mammals in the laboratory and during field studies in fruit and sweet corn using labeled treatment levels. Based on estimates from 26 studies, treated plantings average 15% loss of fruit to birds compared to 36% for nearby orchards; it has been concluded that methiocarb has efficacy in repelling birds from fruit crops when applied at 1.7 kg/ha, a level that does not adversely affect birds (71). Calcium carbonate has been added to methiocarb in an effort to increase its effectiveness as a visual cue, but failed to enhance bird repellency in ripening sorghum (72).

Anthrahydroquinones have been patented in Japan as bird repellents (73), and anthraquinone [84-65-1](qv) is used widely in Europe as a spray to protect growing crops and as a wood dressing. The synthetic pyrethroid deltamethrin [52918-63-5] **(27)** was evaluated (74), as were other materials, including bendiocarb **(20)** (75) and 20,25-diazocholesterol dihydrochloride [1249-84-9] (Ornitrol) **(28)**, a steroid that inhibits embryo development when adsorbed or ingested as a seed treatment of bait corn (55, 76).



(27)



(28)

4. Mammalian Pests

The concept of employing a nonlethal repellent to control wildlife depredation on crops arose early in agricultural history and has been pursued vigorously ever since. Although the continued interest in repellents may reflect public opinion about the impact on endangered or protected species, feeding inhibitors and modern lethal treatments remain practical solutions. A food repellent has been defined as "a compound or combination of compounds that, when added to a food source, acts through the taste system to produce a marked decrease in the utilization of that food by the target species" (50). The action can be primary, where the animal reacts to the taste of the repellent alone, or secondary, where the animal uses the taste of the repellent as a cue to later adverse effects. A useful repellent is meant to stop a hungry animal from feeding on a readily accessible, abundant, and palatable food, forcing the pest animal to leave the area or make a change in food habits, both unlikely choices. The feeding activity of deer has become an increasingly important problem in the U.S. Pacific Northwest, where black-tailed deer and Roosevelt elk browse Douglas fir seedlings. Nonlethal repellents to protect crops from vertebrate pests, together with some considerations for their use and development, have been reviewed (50, 77).

Evaluations have been conducted using deer, a multiple-choice preference-testing apparatus, and tetramethylthiuram disulfide [137-26-8] (TMTD) **(29)** or the fungicide thiram as a standard repellent for competitive tests with repellent-treated food (78).

(29)

A fermented-egg product (FEP), patented as an attractive bait for synanthropic flies, has been shown to be attractive to coyotes and repellent to deer (79). Its components are variable, with relative concentrations of 77% fatty acids, 13% bases, and 10% (primarily) neutrals composed of at least 54 volatiles such as ethyl esters, dimethyl disulfide, and 2-mercaptoethanol. Synthetic formulations have been evaluated to find a replacement for a patented fermented-egg protein product that attracts coyotes and repels deer. Ten aliphatic acids (C-2 to C-8), four amines (pentyl, hexyl, heptyl, and trimethyl), dimethyl disulfide, 2-mercaptoethanol, and 54 more volatiles (C-1 to C-5 esters of C-1 to C-8 acids) have been tested as synthetic fermented egg (SFE) (80) in approximately the same proportions that are present in FEP. Weathering was a problem that caused decreased efficacy, which suggests trials of controlled-release formulations. Fourteen repellents have been examined against white-tail deer in Pennsylvania in choice tests when treated onto shelled corn (81).

Hinder or Repel, registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 24C, a state registration for special local need only, repels deer and rabbits from fruit trees, vines, vegetables, field crops, forage and grain crops, ornamentals, nursery stock, and noncrop areas. It is best applied before damage occurs as an aqueous spray or by painting and is claimed to last 3–8 weeks. Hinder contains 15% ammonium soaps of higher fatty acids (1.5% ammonia and 13% mixed rosin and fatty acids) and 85% inert ingredients (81). The material is sold in the western United States as Hinder and in the eastern United States as Repel or Sticker-spreader 268. Chaperone is the only material as of this writing (1996) approved by EPA in Florida as a repellent for deer, mice, and rabbits. About 10 materials have been registered in Georgia in 1982, usually containing 4–22% thiram **(29)** (82).

Although no consistently effective chemical repellent has been developed for vertebrate pests, some promising materials have been tested as repellents that are based on predator avoidance, specifically compounds from the secretions of predators. In 1995, synthetic sulfur compounds (two thietanes, a thiolane, and a substituted methyl sulfide, which were originally identified from the anal glands of the stoat, ferret, and red fox) suppressed browsing by the introduced Australian brush-tail opossum in New Zealand about as well as FEP (83). Suggestions were made that these compounds can be made more effective by the use of bitter compounds in a cocktail.

Area repellents are materials that are intended to keep animals away from a broad area. They include predator scent such as lion or tiger manure, blood meal, tankage such as putrefied slaughterhouse waste, bone tar oil, rags soaked in kerosene or creosote, and human hair (84). Although few controlled tests have been run on these materials in the past, more recent investigations of predator odors have shown promise (85).

5. Health and Safety Factors

5.1. Toxicology

Toxicological testing has been carried out on many of the older, widely used materials, all of which require re-registration with the EPA (86). This accounts for the disappearance from the U.S. market of 2-ethylhexane-1,3-diol [94-96-2]. Few of the newer compounds have been submitted for extensive toxicological testing because of cost, problems of registration (87), and a necessity to be competitive in the marketplace with every new product. As a result of EPA regulations, many of the materials submitted as cloth repellents since 1970 have been tested at the USDA Agriculture Research Service, Medical and Veterinary Entomology Research Laboratory in Gainesville, Florida. Effective compounds, after further testing, are then submitted to the U.S. Army Environmental Health Agency for extensive toxicological testing. Compounds are tested as repellents on human skin only after passing the four standard toxicological tests: rabbit eye irritation, rabbit skin dermal, rat inhalation, and rat acute ingestion. All of these, plus EPA regulations in the United States classifying repellents as pesticides, have drastically reduced the number of candidate chemicals submitted to the USDA laboratory in Gainesville (2) for general screening since about 1975, and virtually eliminated chemicals submitted as candidate repellents. As a result, this function of the USDA may be eliminated. Some materials of either private or public origin continue to be tested in the 1990s under a Cooperative Research and Development Agreement (CRADA) system (88). Canada Health and Welfare and Occupational Health have tested DEET for skin penetration on the forehead of monkeys and claimed that it was toxic (89). As a result, most products having high concentrations of active ingredients are either canceled in Canada, or require warning labels against application to bare skin.

5.2. Hazard Assessment of Chemical Repellents

Labels for repellent products sold in the United States are recommended for purposes of efficacy and safety of use. Newer products containing DEET may contain less active ingredient but feature a cosmetic that makes the compound less objectionable on the skin and more acceptable to use (2). Even though such a treatment may last for less time, it may help decrease exposure and potential adverse effects, especially on children and/or adults with sensitive skin. NIOSH has recommended for National Park Service employees of the Everglades National Park in Florida that DEET use should not exceed the amount absolutely necessary for repellency (90). Serious adverse reactions are rare to DEET (91) unless used to drastic excess. Since 1954, six female children under the age of eight have been reported with toxic encephalopathy associated with use of products containing DEET. Generally the children had been excessively overtreated from three days to three months, thus resulting in three deaths; however, the causes of death have not been resolved.

The dermal adsorption of DEET in humans has been studied in the Netherlands by application of [^{14}C] DEET as undiluted technical material or as 15% solutions in alcohol. Labeled material was recovered from the skin, and absorption of DEET was indicated by the appearance of label in urine after two hours of skin exposure. About 5–8% of the applied treatments was recovered as metabolites from urine, and excretion of metabolites in the urine came to an end four hours after exposure ended. DEET did not accumulate in the skin, and only a small (less than 0.08%) amount ended up in feces. Curiously, less has been absorbed through skin from 100% DEET application (3–8%, mean of 5.6%) than from 15% alcohol application (4–14%, mean of 8.4%). These results have been described as consistent with previous absorption/metabolism studies using guinea pigs, rats, and hairless dogs. Other publications on DEET toxicology have been cited (92).

Dog repellents available commercially in the 1990s have been generally unsuccessful in laboratory tests. For example, lithium chloride treatments were usually rejected immediately with no ingestion, and bone oil treatments that contained up to 0.1% of the active ingredient were still consumed (93). Oleoresin capsicum [8023-77-6], the essence of red pepper, did have an extended effect on coyotes, even though the deer repellents mentioned above were attractive to coyotes (93). Although a capsicum-base aerosol repellent has been described as potentially harmful (94), pepper spray is commercially available in the United States to repel humans, as is Mace.

Numerous articles in the popular press have stated that heavy consumption of vitamin B_1 (thiamine) can stop attacks of biting and stinging insects on the thiamine-loaded human (see Vitamins, thiamine). This was investigated during World War II, in post-war tests (95), and as recently as 1992 at Gainesville (22). There is no scientific evidence that thiamine has any effect whatsoever on the attraction of *A. aegypti* to humans in olfactometer tests, whether taken internally to excess or applied externally, during scientific tests in 1944, 1952, 1969, and 1973 (2). The same results have been noted for garlic by the U.S. Food and Drug Administration, which concluded that, because of the lack of adequate data to establish the effectiveness of this or any other ingredient for over-the-counter (OTC) internal use as an insect repellent, labeling claims for OTC orally administered insect repellent drug products are either false, misleading, or unsupported by scientific data (96).

6. Mechanical Noisemakers

Claims of effects of repelling or disrupting ultrasonic devices on selected rodent species (97) have been extended by some producers of such devices to include repelling of cockroaches, mosquitoes, fleas, and other insects. There is replicated scientific evidence that shows no effect of several sonic and ultrasonic frequencies (1,000–60,000 Hz) on German cockroaches in choice boxes, because the cockroaches were neither killed nor repelled (98). No effect was seen on fleas or cockroaches (99). Experiments with human arms in olfactometers showed no effect on the attraction of *A. aegypti* when sonic devices were used. Mosquito attraction was statistically the same whether or not any of several makes of small portable sonic devices (600–1000 Hz) reputed to repel mosquitoes were activated (100), regardless of the claims for the production of wavelengths of sound produced by male mosquitoes (98, 101). Warnings were sent in the spring of 1993 to some distributors of ultrasonic pest-control devices, which noted that "statements that pertain to the efficacy of the product have not been substantiated and when used in connection with the product could be in violation of the FIFRA" (27).

7. Extension of Repellent Effectiveness

Attempts to extend repellent effectiveness involve chemical bonding of the repellent molecule to dermophilic compounds that then bind to the skin. Compounds containing 1,3-dihydroxyacetone and pendent repellent molecules were investigated until 1972 (102), as were amino acid analogues of 2-ethyl-1,3-hexanediol, but results were not outstanding (103). Effective cosmetics formulation technology is available in the 1990s to extend the effective length of DEET on skin (2). These materials use extenders and odor-masking agents to make the use of DEET more pleasant.

BIBLIOGRAPHY

"Repellents" in *ECT* 3rd ed., Suppl. Vol., pp. 786–805, by D. A. Carlson, University of Florida.

Cited Publications

1. C. F. Curtis and co-workers, *Med. Vet. Entomol.* **1**, 109 (1987).
2. C. E. Schreck, in P. S. Auerbach, ed., *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*, Mosby Co., St. Louis, Mo., 1995.
3. C. E. Schreck, in J. Adams, ed., *Insect Potpourri: Adventure in Entomology*, Sandhill Press, Inc., Gainesville, Fla., 1992, p. 79.
4. *World Health*, 10 (Apr. 1982); E. A. Smith, *Mosq. News*, **42**, 510 (1982).
5. *Biology and Control of Aedes aegypti, Vector Topics No. 4* and *Dengue Surveillance Survey No. 9*, U.S. Public Health Service, Centers for Disease Control and Prevention, Atlanta, Ga., 1979 and 1983.
6. C. E. Schreck, *Ann. Rev. Entomol.* **22**, 101 (1977).
7. F. E. Kellog and co-workers, *Can. Entomol.* **100**, 763 (1968).
8. C. E. Schreck and co-workers, *Mosq. News*, **37**, 455 (1977).
9. W. V. King, *Chemicals Evaluated as Insecticides and Repellents at Orlando, Fla.*, Ag. Handbook 69, USDA, Washington, D.C., 1954.
10. C. E. Schreck and co-workers, *Soap Cosmet. Chem. Special.*, 36 (Sept. 1982).
11. C. E. Schreck and co-workers, *Am. J. Trop. Med. Hyg.* **31**, 1046 (1982).
12. C. E. Schreck, *J. Am. Mosq. Control Assoc.* **7**, 533 (1991).
13. Long Road Travel Supplies, Berkeley, Calif., (800) 359-6040; Epco Design, Juneau, Ark., (907) 586-1622.

14. C. F. Curtis and co-workers, in C. F. Curtis, ed., *Appropriate Technology in Vector Control*, CRC Press, Boca Raton, Fla., 1989, p. 75.
15. M. I. Hossaine and C. F. Curtis, *Med. Vet. Entomol.* **3**, 367 (1989); C. E. Schreck and L. S. Self, World Health Organization, *Vector Biological Control, 85.914*, 1–6 (1985).
16. C. E. Schreck and D. L. Kline, *J. Am. Mosq. Control Assoc.* **5**, 91 (1989).
17. *Pest Control, Retail Producers Guide*, 20 (Mar. 1983).
18. C. E. Schreck and T. P. McGovern, *J. Am. Mosq. Control Assoc.* **5**, 247 (1989).
19. M. D. Buescher and co-workers, *Mosq. News* **42**, 428 (1982).
20. U.S. Pat. 4,291,041 (Sep. 22, 1981); U.S. Pat. 4,356,180 (Oct. 26, 1982); and U.S. Pat. 4,298,612 (Nov. 3, 1981), T. P. McGovern and C. E. Schreck (to USDA).
21. C. E. Schreck and D. L. Kline, *J. Am. Mosq. Control Assoc.* **5**, 77 (1989).
22. C. E. Schreck, personal communication, Gainesville, Fla., June 2, 1995.
23. J. D. Warthen and co-workers, *J. Chromatogr. Sci.* **590**, 133 (1992).
24. W. G. Taylor and C. E. Schreck, *J. Pharmaceut. Sci.* **74**, 534 (1985).
25. W. G. Taylor and C. E. Schreck, *Pesticide Sci.* **33**, 1 (1991); W. G. Taylor and co-workers, *Can. J. Chem.* **70**, 165 (1992).
26. N. E. McIndoo, ed., “Plants of Possible Insecticidal Value,” USDA, Washington, D.C., 1945; “Materials Evaluated as Insecticides, Repellents and Chemosterilants, Orlando and Gainesville, Fla., 1952–1964,” USDA, Washington, D.C., 1967.
27. C. E. Schreck and B. A. Leonhardt, *J. Am. Mosq. Control Assoc.* **7**, 433 (1991).
28. C. E. Schreck and D. L. Kline, *Mosq. News*, **41**, 7 (1981).
29. C. E. Schreck and co-workers, *J. Med. Entomol.* **16**, 524 (1979).
30. T. P. McGovern and C. E. Schreck, *Mosq. News*, **40**, 394 (1980); U.S. Pat. 4,530,935 (July 25, 1985), T. P. McGovern and C. E. Schreck.
31. A. B. Sabin and co-workers, *J. Am. Med. Assoc.* **125**, 693 (1944).
32. M. L. Schmidt and J. R. Schmidt, *J. Med. Entomol.* **6**, 79 (1969).
33. V. M. Safyanova, *Med. Parazitol. Parazit. Bolezni*, **35**, 549 (1963).
34. E. T. Takafugi and co-workers, *Am. J. Trop. Med. Hyg.* **29**, 516 (1980).
35. R. H. Grothaus and co-workers, *Mosq. News*, **36**, 11 (1976).
36. L. L. Sholdt and co-workers, *Med. Vet. Entomol.* **3**, 153 (1989).
37. J. Hogsette, personal communication, USDA, Gainesville, Fla., Nov. 1, 1995.
38. C. E. Schreck and co-workers, *J. Econ. Entomol.* **75**, 1059 (1982); C. E. Schreck and co-workers, *J. Med. Entomol.* **19**, 143 (1982).
39. L. L. Sholdt and co-workers, *Military Med.* **154**, 90 (1989).
40. P. B. Cornwell, *The Cockroach*, Vol. **II**, Associated Business Programmes, Ltd., London, 1976, 157–190; L. D. Goodhue and G. L. Tissol, *J. Econ. Entomol.* **45**, 133 (1952); P. G. Koehler and co-workers, in K. Storey, ed., *Handbook of Pest Control*, 7th ed., p. 100.
41. B. E. Hagenbuch and co-workers, *J. Econ. Entomol.* **80**, 1022 (1987); U.S. Pat. 4,621,143 (Nov. 4, 1986), T. P. McGovern and G. C. Burden (to USDA).
42. *Pest Control*, **25**, 22 (1957).
43. *Laboratory Evaluations of Compounds as Repellents to Cockroaches, 1953–1974*, Production Research Report No. 64, Agricultural Research Service, USDA, Washington, D.C., Oct. 1976.
44. B. J. Smittle and co-workers, *Pest Control*, **36**, 9 (1968).
45. NPCA Tech. Release No. 15-69, National Pest Control Association, Vienna, Va., 1969.
46. G. S. Burden, *Pest Control*, **43**, 16 (1975).
47. J. M. Grayson, *Pest Control*, **44**, 30 (1976).
48. T. P. McGovern and G. S. Burden, *J. Med. Entomol.* **22**, 381 (1985).
49. J. L. Hayes and co-workers, *J. Chem. Ecol.* **20**, 1595 (1994); U.S. Pat. 5,403,836 (Apr. 4, 1995) (to USDA).
50. J. G. Rogers, Jr., in R. W. Bullard, ed., *Flavor Chemistry of Animal Foods*, ACS Symposium Series No. 67, Washington, D.C., 1978, p. 150.
51. R. L. Bruggers, in R. L. Bruggers, *Quelea quelea: Africa’s Bird Pest*, R. L. Bruggers and C. C. H. Elliot, eds., Oxford Press, U.K., 1989, p. 262.
52. R. A. Dolbeer and co-workers, *Crop Protection*, **14**, 39 (1995).

53. R. W. Bullard and B. Gebrekidan, in Ref. 51, p. 281.
54. R. W. Bullard and co-workers, *J. Agric. Food Chem.* **28**, 1006 (1980).
55. R. W. Bullard and D. J. Elias, *Proc. Inst. Food Technol.* 43 (June 1979).
56. E. N. Wright, ed., *Bird Problems in Agriculture*, British Crop Protection Council 23, BCPC Publications, Croydon, U.K., 1980, p. 164.
57. J. F. Besser, *Proceedings of the 7th Vertebrate Pest Control Conference*, Monterey, Calif., 1976, p. 11.
58. P. P. Woronecki and co-workers, *J. Wildlife Manage.* **43**, 184 (1979).
59. S. S. Nicholson and C. J. Prejean, *J. Am. Vet. Med. Assoc.* **173**, 1277 (1981); G. A. Van Gelder, in P. W. Pratt, ed., *Equine Medicine and Surgery*, 3rd ed., American Veterinary Publications, Santa Barbara, Calif., 1982, p. 197.
60. R. A. Dolbeer, *USDA–APHIS Denver Wildlife Center Animal Repellents Report*, U.S. Armed Forces Pest Management Board, Washington, D.C., 1990, 1996.
61. J. L. Belant and co-workers, *Crop Protect.* **14**, 171 (1995).
62. J. F. Gelahn and co-workers, *Wild. Soc. Bull.* **17**, 313 (1989).
63. F. T. Crase and R. W. Dehaven, in Ref. 57, p. 46.
64. P. P. Woronecki and co-workers, *J. Wildlife Manage.* **35**, 693 (1981).
65. R. L. Hothem and co-workers, *Am. J. Enol. Vitic.* **32**, 150 (1981); *Proc. Bird Cont. Semin.* **8**, 59 (1982).
66. *Proc. N. Z. Weed Pest Control Conf.* **33**, 125 (1980).
67. A. C. Noble, *Am. J. Enol. Vitic.* **31**, 98 (1980).
68. R. R. Duncan, *Can. J. Plant Sci.* **60**, 1129 (1980); G. Gras and co-workers, *Bull. Environ. Contam. Toxicol.* **26**, 393 (1981).
69. *Phytoparasitica*, **8**, 95 (1979).
70. *Argon. J.* **73**, 290 (1981).
71. R. A. Dolbeer and co-workers, *Pestic. Sci.* **40**, 147 (1994).
72. R. A. Dolbeer and co-workers, in R. A. Dolbeer and co-workers, *Chemical Signals in Vertebrates*, Plenum Press, New York, 1992, p. 323.
73. Jpn. Kokai Tokyo Koho 8183408 (July 8, 1981).
74. *Poult. Sci.* **60**, 1149 (1981).
75. *Res. Discl.* **211**, 420 (1981).
76. R. W. Bullard, in T. E. Acree and D. M. Soderlund, eds., *Semiochemistry: Flavors and Pheromones*, W. de Gruyter & Co., New York, 1985, p. 65.
77. D. Muller-Schwartze, in D. W. McDonald, D. Muller-Schwartz, and S. E. Natynzuk, eds., *Chemical Signals in Vertebrates*, Oxford Press, U.K., 1990, p. 585; R. L. Bruggers and co-workers, *Wild. Soc. Bull.* **14**, 161 (1986); R. A. Dolbeer, *Wild. Soc. Bull.* **14**, 418 (1986).
78. D. L. Campbell and R. W. Bullard, *Proceedings of the 5th Vertebrate Pest Conference*, Fresno, Calif., 1972.
79. U.S. Pat. 3,846,557 (Nov. 5, 1974), M. S. Mulla and Y.-S. Hwang (to 3M Co.).
80. R. W. Bullard and co-workers, *J. Agric. Food Chem.* **26**, 155 (1978).
81. W. Palmer, *Deer-Away Technical Report*, International Reforestation Suppliers, Eugene, Oreg., 1980.
82. J. Jackson, *Deer and Rabbit Repellents*, Dept. of Forest Resources, University of Georgia, Athens, Ga., 1982.
83. *Extension Publication 18*, No. 11, Dept. of Natural Resources, NYSC Agriculture and Life Sciences, Cornell University, Ithaca, N.Y., 1980; *Supplement No. 120*, Extension Wildlife and Sea Grant, University of California, Davis, Calif., Oct. 1979; *Extension Information Bull. No. 146*, Cornell University, Ithaca, N.Y., 1978.
84. A. D. Woolhouse and D. R. Morgan, *J. Chem. Ecol.* **21**, 1571 (1995).
85. R. A. Bruggers, personal communication, Denver, Colo., Jan. 15, 1996.
86. M. L. Leng, in G. J. Marco, R. M. Hollingsworth, and J. R. Plimmer, eds., *Regulation of Agrochemicals: A Driving Force in their Evolution*, ACS Non-Symposium Series, American Chemical Society, Washington, D.C., 1991, p. 26.
87. EPA: *N,N*-Diethyl-m-toluamide (DEET), Pesticide Registration Standard, U.S. EPA, Washington, D.C., 1980.
88. D. R. Zimmer, personal communication, USDA, ARS, Athens, Ga., Jan. 15, 1996.
89. R. P. Moody and co-workers, *J. Toxicol. Environ. Health* **26**, 137 (1989).
90. R. McConnell and co-workers, HETA 83-085-1757, U.S. Dept. Health and Human Services, CDC, Cincinnati, Ohio, 1986.
91. E. H. Roland and co-workers, *Can. Med. Assoc. J.* **132**, 155 (1985).
92. S. Selim and co-workers, *Fund. Appl. Toxicol.* **25**, 95 (1995).

93. Personal communication, R. Teranishi, USDA Western Regional Laboratory, Albany, Colo., 1983.
94. *Vet. Human Toxicol.* **22**, 18 (1980).
95. H. J. Maasch, *Tropenmed. Parasitol.* **4**, 119 (1973).
96. *Federal Register* 8:26987, Part III, Dept. Health and Human Services, June 10, 1983.
97. A. V. Scalingi, *Pest Control*, **48**, 26 (1980).
98. C. E. Schreck, J. C. Webb, and G. S. Burden, *J. Environ. Sci. Health A*, **19**, 521 (1984).
99. P. G. Koehler and co-workers, *J. Econ. Entomol.* **79**, 1027 (1986).
100. W. A. Foster and K. R. Lutes, *J. Amer. Mosq. Control. Assoc.* **1**, 199 (1985).
101. D. J. Lewis and co-workers, *Can. Entomol.* **114**, 699 (1982).
102. R. P. Quintana and co-workers, *J. Econ. Entomol.* **65**, 66 (1972).
103. R. P. Quintana and co-workers, *J. Med. Chem.* **15**, 1073 (1972).

D. A. CARLSON
University of Florida

Related Articles

Insect control technology