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PMD, A REGISTERED BOTANICAL MOSQUITO REPELLENT WITH DEET-LIKE EFFICACY

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ABSTRACT. *para*-Menthane-3,8-diol(PMD) is a monoterpene spent product of the distillation of leaves of the Australian lemon-scented gum tree (updated nomenclature *Corymbia citriodora* ssp. *citriodora*). In April 2005, the U.S. Centers for Disease Control and Prevention (CDC) endorsed two non-deet mosquito repellents, including PMD. However, few mosquito professionals have in-depth familiarity with the history and efficacy of PMD. In this article, we describe the origin and development of PMD as a repellent and offer a comprehensive review of its performance against *Aedes, Anopheles, Culex*, and *Ochlerotatus*. In addition, we present original data from field and laboratory studies involving large numbers of subjects and comparisons with high-concentration deet and other repellents. We conclude that not only is the CDC endorsement warranted but also that it probably underestimates the value of PMD as a deet alternative for public health applications.

KEY WORDS *Aedes*, *Anopheles*, *Culex*, *Ochlerotatus*, *Corymbia citriodora*, deet, lemon eucalyptus, malaria, *p*-menthane-3,8-diol, PMD, repellent

INTRODUCTION

Mosquito-transmitted disease continues to be a major source of illness and death. Most parasitic diseases are tropical, and intensifying globalization and climatic change are increasing the risk of contracting arthropod-borne illnesses (Brower and Chalk 2003, Guenier et al. 2004). One ongoing example is West Nile virus; current federal statistics indicate that it will be responsible for thousands of cases of neuroinvasive disease in North America over the next several years (CDC 2005a). Vector control and other public health initiatives may reduce danger of contracting disease, but persistent risk indicates that prevention of mosquito bites is a prudent strategy for immediate disease avoidance. Commercial insect repellents containing the active *N,N*-diethyl-*m*-methylbenzamide (deet) have been used for decades as highly effective and generally safe means of bite control (Osimitz and Grothaus 1995).

Despite its excellent repellency, many consumers do not use deet because of concerns about safety, comfort, and its plasticizing capacity. They may instead use other types of repellents, particularly botanicals, despite that most are of relatively low efficacy (Fradin and Day 2002). Hence, it is notable that in April 2005, the Centers for Disease Control and Prevention (CDC) added two non-deet products to their list of repellents of public health value (CDC 2005b). One of the newly recommended actives is the terpene *para*-menthane 3,8-diol (PMD), obtained from botanical sources or synthesized, and the other is picaradin (KBR3023), a synthetic marketed under the trade name Autan for several years in Europe, and beginning in 2005 as Cutter Advanced in the USA. Although their endorsement by CDC offers promise to programs and individuals needing deet alternatives, neither is well-known to professionals or the U.S. public.

This article focuses on PMD, its history of development, and its efficacy. Our treatment is divided into two sections. In the first section, we review all literature we could obtain on PMD pertaining to its utility as a mosquito repellent. In the second section, we augment what is known about the performance of PMD, particularly in the United States, with data from our own field and laboratory trials comparing Repel™ Brand PMD-based repellent against other commercial repellents, including high- and low-concentration deet and S.C. Johnson Off! Botanicals™, which uses synthetic PMD at a relatively low concentration.

PMD: DEVELOPMENT HISTORY, SOURCE, AND PERFORMANCE REVIEW

A variety of plant essential oils repel blood-feeding arthropods, and several are used in commercial repellent products (Curtis et al. 1991, Fradin and Day 2002).Volatile monoterpenoids are the active molecules in most such oils, and although their vapor pressure probably promotes their repellency, it also results in rapid dissipation of efficacy (Barasa et al. 2002). At high concentrations needed to enhance duration, dermatitis may result (Barnard 1999). As a monoterpene of relatively low volatility, PMD may be especially promising as a deet alternative (Barasa et al. 2002).

PMD was isolated from so-called ''lemon eucalyptus'' leaves as part of mass screenings of

plants for repellent properties undertaken in China beginning in 1960 (Curtis et al. 1991). Called quwenling ("effective mosquito repeller"), it is the principal waste material resulting from the hydrodistillation of the essential oil from the leaves (Curtis et al. 1990). Thus, the repellent is not "oil of lemon eucalyptus" but is instead the leftovers of that oil's distillation process.

The source tree is native to eastern Queensland, Australia, and planted pantropically and subtropically. In Australia, it is called "lemon-scented gum," and its botanical name was until recently *Eucalyptus maculata* subsp. *citriodora*. Systematic reorganization of the genus *Eucalyptus* (Hill and Johnson 1995) led to its placement in the genus *Corymbia* as well as the elevation and further division of the subspecies. Lemon-scented gum, then, is *Corymbia citriodora* (Hook.) Hill & Johns. subsp. *citriodora* (Henderson 2002).

In China, the repellent properties of PMD were successfully commercialized, and it is widely used there in an ethanol base (Curtis et al. 1991). Li et al. (1974) (summarized in Curtis et al. 1991) reported high, long-lasting efficacy against *Aedes* spp. in the laboratory and field. In addition, Nishimura (unpublished data cited in Watanabe et al. 1993) observed high efficacy of both *cis*- and *trans*-isomers of PMD. In contrast, the first western studies showed mediocre-to-good performance of 10–30% PMD, but at a level normally below, and never exceeding, that of 10–20% deet in laboratory and field tests against *Aedes* and *Anopheles* mosquitoes (Schreck and Leonhardt 1991, Collins et al. 1993).

Collins et al. (1993) obtained their PMD in the form of a Chinese commercial repellent, and it seems that Schreck and Leonhardt (1991) did so as well. In reformulations by MASTA in the United Kingdom in the mid-1990s, PMD concentration was increased to 50%, and ethanol was replaced with more cosmetically sophisticated carriers (Trigg 1996a). The result was enhanced efficacy. In field evaluations against *An. funestus* and *An. gambiae*, MASTA Mosi-guard Natural gel, spray, and stick formulations gave "complete protection from biting" for 6–7.75 h, not different from a 50% deet spray, with similar results in the laboratory (Trigg and Hill 1996). These were the first studies to suggest that by altering formulation, the efficacy of PMD might be enhanced to reach that of a deet standard. These results were far superior to those obtainable from citronella, the best-known botanical active then (Trigg and Hill 1996) and now.

Subsequent studies in the laboratory and field have largely confirmed this positive assessment (Table 1). In general, PMD and deet have shown similar performance against mosquitoes of several species and genera. The studies listed in Table 1 found 90 or 95% repellency (relative to untreated or negative controls) for 4–8.5 h (minimum and maximum test durations were independent of repellent performance in some studies). In laboratory tests against species in three genera, Barnard and Xue (2004) ranked PMD first of 12 commercial repellents in a test that included potent synthetics: PMD (20%) > KBR3023 (10%) > deet (15%) > IR3535 (7.5%). Similarly, in our laboratory study, a 20% PMD product outperformed 10% deet and was only slight less repellent than 30% deet over 8 h (this study).

In the field, Moore et al. (2002) found 30% PMD superior to 15% deet in a 4-h test (97% vs. 85% repellency) (Table 1). In the study of Barnard et al. (2002), percentage of repellency did not differ statistically, but deet seemed to be consistently slightly superior. In our field study, artificially truncated at 6 h, 20% (lotion) and 26% (spray) PMD were at least as repellent as Deep Woods Off lotion (~20% deet).

MATERIALS AND METHODS

We measured degree and duration of protection with arm-in-cage tests and field trials. In cage testing, effects of potentially confounding environmental variables were reduced, whereas field tests provided complementary data under conditions resembling those of actual use. We recruited adult volunteers from the Life Science programs at the University of California–Davis. The institutional review board of the University of California–San Francisco School of Medicine and the Department of Pesticide Regulation of the California Environmental Protection Agency approved the study protocol. Wisconsin Pharmacal (also known as WPC Brands, Inc., Jackson, WI) supplied its lemon eucalyptus repellents by courier, and the other repellents were purchased over-the-counter in Davis, California. Materials were stored in the containers in which they were received, indoors in closed containers at room temperature. Application methods were based on the guidelines in ASTM E 939-94 (ASTM 1994).

Laboratory test

In February 2002, we conducted cage testing to compare four repellents: 1) WPC Brands Repel Oil of Lemon Eucalyptus (hereinafter 'Repel OLE') in lotion formulation (20% PMD); 2) SC Johnson Off! Botanicals™ lotion (10% synthetic PMD); 3) Cutter Outdoorsman lotion (30% deet); and 4) Off! Skintastic SPF 30 lotion (10% deet).

Test mosquitoes were the yellowfever mosquito, *Aedes aegypti*, reared in captivity. Approximately 200 unfed females were present in each of two test cages. Cages were 45-cm cubic screen enclosures. The females were 3–4 days posteclosion. Conditions during the test followed a stan-

Table 1. Comparison of relative protection times of recent formulations of PMD versus deet in tests of duration against mosquitoes. References are listed in chronological order.

Type of test	Mosquito	% AI[1] and relative repellency			Dosing	Reference
		PMD	vs.	Deet		
Laboratory	*Anopheles gambiae*	50	=	20	0.68 vs. 0.48 g/cm^2	Trigg and Hill (1996)
Field	*An. funestus* and *An. gambiae*	50	=	50	"Adequate coverage"	Trigg (1996a)
Laboratory	*An. gambiae*	20[2]	>	7	"Small measured" PMD 25% lower[3]	Hill (1998)
Field	*An. arabiensis*	71	=	15	"Normal practice"	Govere et al. (2000)
Field	*Ochlerotatus taeniorhynchus*	20	=	25	1 g/650 cm^2	Barnard et al. (2002)[4]
Field	*An. darlingi*	30	>>	15	3 ml/lower leg	Moore et al. (2002)
Laboratory	*Aedes albopictus*	20	=	15	1 g/650 cm^2	Barnard and Xue (2004)
	Culex nigripalpus	20	=	15	1 g/650 cm^2	Barnard and Xue (2004)
	Oc. triseriatus	20	=	15	1 g/650 cm^2	Barnard and Xue (2004)
Laboratory	*Aedes aegypti*	20	≥	10	1 g/600 cm^2	This study
		20	≤	30	1 g/600 cm^2	This study
Field	*Oc. melanimon* and *Ae. vexans*	20/26	=	20	1 and 1.5 g/600 cm^2	This study

[1] AI, active ingredient; concentrations are rounded up to the integer.
[2] Presswell, personal communication.
[3] Based on ED90.
[4] Barnard et al. (2002) indicate that they tested Repel OLE lotion with PMD at 40%, but Barnard and Xue (2004) alter this value to 26% for both studies. However, our records and those of Wisconsin Pharmacal (Wundrock, personal communication) indicate that Repel OLE lotion was only produced with 65% PMD within a 30% OLE fraction, for an absolute concentration of 19.5% PMD (here rounded to 20%). Values of 40% would refer to the OLE concentration in the spray, in which PMD is again at 65%, for an absolute concentration of 26% PMD in the spray.

dard diel cycle, with air temperature 27 ± 0.2°C, 47 ± 3% RH, and light intensity of 290 ± 45 lux.

Subjects were 7 males and 3 females. Technicians wearing latex gloves applied repellents at 1.0 g/600 cm^2 skin surface area, spreading them evenly on arms between the bend of the elbow and the bend of the wrist. Nine subjects tested Repel OLE, and 8 subjects tested Off! Botanicals. One experienced male subject served as untreated control, 1 male tested 30% deet, and 1 female tested 10% deet. Allocation to test subjects was alphabetical and in that manner indiscriminate. Test materials were given anonymous code designations to blind the study subjects and staff during application and testing.

Subjects wore latex gloves to protect the hands from biting and exposed 1 limb at a time to mosquitoes for 1-min periods at 30-min intervals for 8 h. All exposures began 5–10 min after application. We divided subjects into 2 groups, each of which included those testing the PMD and deet, which alternated between the 2 cages in successive exposure periods. In addition, the order of subject and limb exposure was altered within each group from one exposure period to the next. Upon receiving 4 or more bites in a single exposure period (i.e., not necessarily after the first confirmed bite [FCB]; defined below), a subject arm was retired.

A foraging mosquito was considered to have bitten as soon as penetration of the subject epidermis began. Bites were counted by 2 observers per arm (1 observer on each side, and not the subject individual), and a 3rd assistant recorded the total number of bites after each exposure period. Counts were recorded on data sheets. The first exposure was designated as time 0.

Field test

We tested at the Gray Lodge State Wildlife Area in Butte County, California, in October 1999. This is an area of mixed woodland and marsh that does not use environmental mosquito control. Data were collected between 1000 and 1630 h, with temperature, humidity, light intensity, wind speed, and general weather conditions recorded at approximately 60-min intervals throughout the test. Repel OLE was in lotion (20% PMD) and pump spray (26% PMD) forms. The deet comparison was Deep Woods Off! lotion (approx. 20% deet) (hereinafter DW Off!).

Among a total of 24 subjects, 20 subjects tested Repel OLE, 2 subjects tested DW Off!, and 2 subjects were untreated controls. Each Repel OLE subject tested a single formula at 1 dose on 1

arm and the other dose on 1 leg. Other body areas were protected with clothing or netting as needed. For lotion, 7 subjects were male and 3 subjects were female. For spray, 6 subjects were male and 4 subjects were female. Two subjects, 1 male and 1 female, tested DW Off!. Two experienced male subjects served as untreated controls; they removed biting mosquitoes with mechanical aspirators. Blinding was the same as in the laboratory study.

Treatments were applied on the arms as described for laboratory testing, and also on legs between the bend of the knee and the ankle. Treatments were evenly distributed between the limbs. Lemon eucalyptus was applied at 2 dosages: low (1.0 g/600 cm^2 skin surface area) and high (1.5 g/600 cm^2 skin surface area). The low dosage is a standard rate for studies of deet-based repellents, and we used that dosage alone for DW Off!. The higher dosage is more typical for studies of botanical repellents and sunscreens and was included to test for a dosage effect on the efficacy of Repel OLE.

Subjects counted and recorded bites in a series of approximately 72 consecutive 5-min periods. Counts were recorded on data sheets. One hundred and five biting mosquitoes aspirated from untreated control limbs throughout the test were collected for identification. Sixty-seven (64%) mosquitoes were *Ochlerotatus melanimon*, 34 (32%) mosquitoes were *Aedes vexans*, and 3 (3%) mosquitoes were *Oc. increpitus*, all pest species. During data collection, air temperature ranged from 26.9–32.6°C, relative humidity from 16–22%, light incidence from 571–1,200 lux, and wind speed from 0.2–4.4 kph.

Statistical analysis

Treatment mean biting rates are from subject means and were calculated as 100(1 – mean of treatment/mean of untreated control). Treatments were compared with nonparametric 2-way Wilcoxon rank sum tests. Complete protection time (CPT) is estimated as the time from the onset of exposure to mosquitoes until the first confirmed bite (FCB). The FCB is the first bite to be followed by another bite within 30 min (i.e., in the subsequent exposure in the laboratory test). Treatment mean ± SD CPTs are calculated across subjects for each treatment.

RESULTS

In tests in cages and in the field, the efficacy of Repel OLE closely matched that of high-concentration deet products and exceeded that of both low-concentration deet products and the low-concentration, synthetic PMD product Off! Botanicals.

Laboratory test

From first exposure through time of failure (arms were retired after the first exposure period with 4 or more bites), all test repellents reduced biting rate by at least 95% in comparison with the untreated control (Table 2). Repel OLE reduced biting by approximately 99%, similar to 30% deet, but for a briefer period on average. Five of the 9 OLE subjects persisted through the full 8 h, and all of these subjects experienced fewer total bites than did the 30% deet subject. Repel OLE was significantly more repellent than Off! Botanicals ($z = 2.74$, $P = 0.012$), and its average performance was superior to that of 10% deet (Table 2). Biting pressure on the untreated control ranged from 27 to 60 bites/min (mean ± SD; cage 1, 48 ± 9; cage 2, 50 ± 13; cages were tested in alternate exposure periods, beginning with cage 1; Table 2).

CPT from Repel OLE averaged >5 h (307 ± 144 min), almost 2.5 times the mean CPT from Off! Botanicals (124 ± 108 min). Two of the 9 subjects testing Repel OLE did not receive a confirming bite, such that the CPT exceeded the 8-h test duration (and so the treatment mean CPT value for Repel OLE underestimates the actual mean CPT). The CPT for 10% deet was 2 h, whereas for 30% deet, 3 bites occurred during the exposure at 8 h, so that its CPT was exactly 8 h.

Field test

Almost all of the subjects treated with the PMD repellents and the 20% deet repellent were completely protected throughout the field exposure (Table 3). Ambient biting rates averaged nearly 1.5/min on the untreated arm (range 0–2.4), and 3/min on the untreated leg (range 0.8–10.3). All Repel OLE treatments reduced mean biting rates by more than 1,000-fold in comparison with the untreated limbs (Table 3). Efficacy of Repel OLE was equally high at both low and high doses. The 20% deet subjects received similar protection, with an approximately 500-fold reduction on the leg, and prevention of all bites on the arm (Table 3).

Five of the 10 subjects testing lotion and 6 of the 10 subjects testing spray received no bites. Only 1 of the 10 subjects testing each PMD formula (spray or lotion) received a confirming bite (i.e., 2nd bite within 30 min of the 1st bite). Four subjects terminated their exposures prematurely for reasons unrelated to bites, and 3 subjects tested for 370 or 375 min, making the average exposure time for the PMD formulae 350 rather than 360 min. Average CPT for the high lotion dosage on the arm was 331 min and for the high spray dosage on the leg was 326 min. All other PMD treatments protected for the entire

Table 2. Laboratory test showing bite incidence for each subject for up to 8 h. Subject arms were withdrawn after 4 bites were received in an exposure. CPT is complete protection time, i.e., the interval between first exposure and the first bite that was followed by another within 30 min (first confirmed bite [FCB]). FCBs are in bold.

Treatment	Subject	Exposure period × 30^{-1} min																	CPT (min)
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Deet (30%) Cutter	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	**3**	480
Deet(10%) Off! Skintastic	10	0	0	0	0	**2**	3	0	2	2	1	0	2	4	—	—	—	—	120
PMD (20%) Repel OLE[1]	5	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	480+
	8	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	480+
	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**3**	1	455
	9	0	0	0	0	0	0	0	0	0	0	**1**	1	0	0	0	0	1	300
	2	0	0	0	0	0	0	0	0	0	0	**1**	1	2	0	0	0	0	300
	4	0	0	0	0	0	0	1	0	0	0	0	**1**	2	3	9	—	—	330
	6	0	0	0	0	0	0	**3**	0	0	0	0	0	6	—	—	—	—	180
	3	0	0	0	0	**1**	5	—	—	—	—	—	—	—	—	—	—	—	120
	7	0	0	0	0	**6**	—	—	—	—	—	—	—	—	—	—	—	—	120
PMD (10%) Off! Botanicals[2]	5	0	0	0	0	0	0	0	0	0	**1**	1	1	2	3	4	—	—	270
	2	0	0	0	0	0	1	0	**3**	0	1	3	6	—	—	—	—	—	210
	4	0	0	0	1	0	0	**2**	0	1	2	2	8	—	—	—	—	—	180
	7	0	0	0	0	**1**	4	—	—	—	—	—	—	—	—	—	—	—	120
	6	**2**	0	1	1	1	4	—	—	—	—	—	—	—	—	—	—	—	0
	9	0	0	0	**1**	17	—	—	—	—	—	—	—	—	—	—	—	—	90
	3	0	**2**	0	7	—	—	—	—	—	—	—	—	—	—	—	—	—	30
	8	**6**	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Untreated control	1	27	33	46	33	45	60	55	60	50	46	59	68	49	57	49	46	49	0

[1] PMD naturally derived.
[2] PMD synthesized.

Table 3. Mean and SD of biting rate per 5-min sampling period for the untreated controls, Repel LE, and Deep Woods Off!, by limb. Percentage of reduction in biting rate over the test period is calculated relative to the untreated controls, by limb.

Treatment	*n*	$\bar{x}$	SD	Mean[1] total bites	% reduction[2] in biting
Untreated					
Arm	1	7.3	4.0	546	—
Leg	1	14.1	10.6	1,055	—
Repel OLE lotion					
Arm @ 1 g	5	0.003	0.006	0.6	99.9
Arm @ 1.5 g	5	0.011	0.018	0.8	99.9
Leg @ 1 g	5	0.005	0.012	0.6	99.9
Leg @ 1.5 g	5	0	0	0	100.0
Repel OLE spray					
Arm @ 1 g	5	0.008	0.012	0.6	99.9
Arm @ 1.5 g	5	0.003	0.006	0.2	99.9
Leg @ 1 g	5	0	0	0	100.0
Leg @ 1.5 g	5	0.008	0.013	0.6	99.9
DW Off! lotion					
Arm @ 1 g	1	0	0	0	100.0
Leg @ 1g	1	0.031	0.25	2	99.8

[1] In the untreated and DW Off! Rows, $n = 1$, so values are raw numbers rather than means.
[2] Calculated by limb as 100(1 – mean of treatment/untreated control).

period. One deet subject was protected throughout the period, and the other subject withdrew at 317 min upon receiving a confirming bite.

DISCUSSION

The use of repellents is recommended for protection against biting arthropods and consequently the diseases they transmit (Curtis 1992, Gupta and Rutledge 1994). Among the many synthetic and botanical insect repellents currently available, only deet-based formulations have been widely recommended by the medical community to reduce the risk of contracting disease (Fradin and Day 2002). By expanding the list of recommended repellents to include PMD and picaridin, CDC (2005b) is effectively shifting some attention away from deet and toward these lesser known actives. Our review of PMD literature as well as our test results support and extend the CDC recommendations from an efficacy standpoint.

The studies of PMD efficacy conducted since its formulation was first modernized in the mid-1990s differ widely in details of study design, goals, setting, and conduct. For example, our own studies have too few deet subjects for great statistical power, because deet was used as a standard rather than for statistical comparison. Despite such scientific and environmental variation, PMD has shown unprecedented repellency and consistency for a botanical (Table 1). As formulated, the PMD repellents have outperformed lower concentration (<20%) deet comparators, and they typically approach and sometimes equal the performance of well-known, higher concentration (≥20%) deet products. Foundational studies indicate that repellent susceptibility often varies widely among mosquito species and genera (reviewed by Carroll, in press), but positive results for PMD span the 4 genera tested—*Anopheles, Aedes*, Culex, and *Ocherlotatus*—and include malaria vectors from Africa and South America, and yellow fever and encephalitis vectors. At least 5 h of protection, on average, is evidenced in the studies that were conducted for that long.

In our own laboratory trials, for example, Repel OLE lotion (20% PMD) was substantially more effective against *Ae. aegypti* than either a 10% deet formula or a 10% synthetic PMD formula. For a majority of subjects, its performance slightly exceeded that of 30% deet across an 8-h period, but some subjects were protected less well (Table 2). Given that *Ae. aegypti* seems particularly repelled by deet (compared with congeners; Barnard 1998), these results are encouraging. The great increase in repellency of PMD at 20% versus 10% implies a more than linear positive affect of higher concentration. Other differences between these two formulations, including probable differences in stereoisomer constituency, may be less important than the concentration of the active (Barasa et al. 2002), but it would be especially valuable to compare natural and synthetic PMD within a concentration.

Results were perhaps more impressive in our field study, a 6-h challenge in which an untreated limb received more than 1,000 bites. The 20 PMD

subjects received on average 1/3 (0.34) bite. For comparison, 1 deet subject received 2 bites, and the other subject no bites. High PMD performance was consistent across the 20 volunteers: the majority of volunteers was unbitten, and none received more than 3 bites on a limb. Protection was equivalent for spray and lotion delivery systems, at high and low dosing. Our study protocol called for 6 h of exposure because we assumed a botanical would fail by that time. The high level of protection experienced means that data collection ended while almost all subjects were still well protected.

The CDC (2005b) endorsement of PMD equates its efficacy with that of lower concentration deet products currently on the market. In general, these less effective deet products have been designed to address consumer concerns about the safety and cosmetic properties of this active ingredient. However, their shorter lived protection, like that of non-PMD botanicals reviewed by Fradin and Day (2002) and the synthetic PMD tested here, indicate that their use is most appropriate for brief periods of exposure or when biting is mainly a nuisance rather than a health risk. In addition, the same CDC bulletin states that the "oil of lemon eucalyptus has not been tested against mosquitoes that spread malaria and some other diseases that occur internationally."

Although we appreciate CDC's long-standing conservative approach to endorsing new repellents in the context of public health, our findings address or refute both of the foregoing qualifiers to the recommendation. First, PMD formulations are generally equal or superior in performance to lower concentration deet. In no studies were PMD formulations less repellent, and in several they were as efficacious as high-concentration deet. In addition, Barnard and Xue (2004) found PMD to be more effective than their picaridin (KBR3023) comparator, although CDC (2005b) has endorsed picaridin without qualification. In cases where more secure, longer term protection is required, commercially available PMD-based repellents from a botanical source are probably both more efficacious than low concentration deet repellents, and reasonable alternatives to high concentration deet repellents. They are superior to other botanical alternatives that individuals who avoid deet might choose.

Second, five published studies have shown PMD to be effective against chief malaria vectors on two continents. In addition, cage tests show excellent performance against *Ae. aegypti*.

PMD also repels ixodid ticks in the laboratory (Trigg and Hill 1996; Carroll and Loye, unpublished data), and *Culicoides* biting midges in laboratory and nature (Trigg 1996b, Trigg and Hill 1996), *Stomoxys* stable flies in the laboratory (Trigg and Hill 1996), and *Leptoconops* biting midges in nature (Carroll and Loye, in press). This broad-spectrum efficacy suggests that botanical PMD repellents may have wide applicability for protection against arthropod-vectored human diseases. A closely related compound isolated from *Eucalyptus camaldulensis* shows similar repellent activity (Watanabe et al. 1993, Satoh et al. 1995), suggesting that there may be a trove of potential repellent actives in this group of plants. Relatively unknown, unstudied and undeveloped, PMD repellents deserve additional attention as tools in the prevention of vector-borne disease.

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