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# A MILESTONE IN BOTANICAL MOSQUITO REPELLENTS: NOVEL PMD-BASED FORMULATION PROTECTS MORE THAN TWICE AS LONG AS HIGH-CONCENTRATION DEET AND OTHER LEADING PRODUCTS

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ABSTRACT. The use of skin-applied repellents is the primary method recommended by the Centers for Disease Control and Prevention for personal protection against biting mosquitoes. Historically, the majority of long-efficacy mosquito repellents have been *N*,*N* diethyl-3-methylbenzamide (deet)–based. Recently, a variety of new botanical formulations have been marketed, but their protection times generally continue to fall well short of high-concentration deet products. We present a laboratory arm-in-cage study of a Neo-Innova® repellent that has a prolonged action "NEO-PART®" (Prolonged Action Release Technology) formulation with 40% Citriodiol®. This formulation provides the botanical molecule *para*-menthane 3,8-diol (PMD) at 25% w/v of the total formulation. Against *Aedes aegypti*, Neo-Innova's mean complete protection time (CPT; 14.2 h) was approximately 2 to 3 times longer than that of 5 leading high-performance repellents marketed in the USA, including 25% deet and a 20% PMD ethanolic formulation. When testing Neo-Innova, 5 of the 6 subjects had no landings after 15 h. The 6th had single landings at 10 and 11 h (individual CPT of 10 h), but received no additional landings in further exposures made at 13 and 15 h. Neo-Innova repellency against *Culex quinquefasciatus* was similarly prolonged. The tremendous increment in repellency duration observed for the Neo-Innova product, when compared with both current standard and botanical repellent options, represents a milestone in repellent development and supports "once-a-day" applications as a practical strategy for personal protection against mosquitoes.

**KEY WORDS** *Aedes aegypti*, *Culex quinquefasciatus*, botanical, NEO-PART®, prolonged action

## INTRODUCTION

Mosquito-vectored diseases are a major cause of death and illness globally, particularly in the tropics (Guernier et al. 2004). Changing climates are supporting expansions in the actual or predicted geographic ranges of mosquito species important to public health, including *Aedes aegypti* (L.) and *Culex quinquefasciatus* Say (Morrison et al. 2008, Rochlin et al. 2013, Samy et al. 2016). In consequence, risks from mosquito-vectored pathogens are expanding into new human populations, including in countries in which topical mosquito repellents are already widely used for protection from seasonal nuisance biting. The primary methods recommended by the Centers for Disease Control and Prevention (CDC) for the prevention of mosquito-borne illnesses include wearing protective clothing, avoiding high-arthropod areas, and using skin-applied personal repellent products, the latter sometimes being the only feasible option, rendering efficacy duration of topical repellents a central aspect of disease prevention (Fradin and Day 2002, CDC 2016).

Topical mosquito repellents have been used for personal protection since the middle of the 20th century and are increasingly recognized as a primary tool for the prevention of mosquito-borne illness by both the CDC (2005) and the World Health Organization (WHO 2016). The discovery and commercial dissemination of *N*,*N* diethyl-3-methylbenzamide (deet) was a 1st milestone in topical repellent development, and was long the only AI for topical repellents recommended by the CDC. Despite its wide use and established efficacy in repelling a range of biting arthropods, some individuals prefer not to use deet for a variety of reasons, including dermal irritation and other perceived health concerns, and may instead turn to alternative products (Katz et al. 2008, Maia and Moore 2011). Moreover, deet may not be the best general repellent for all target arthropods, including *Anopheles* spp. (Moore et al. 2002) and biting midges (Trigg 1996). While a range of botanical compounds was developed and marketed as mosquito repellents recently, a majority may unfortunately be of little value with respect to their capacity to reliably repel their claimed target (Fradin and Day 2002, Rodriguez et al. 2015). Currently, no botanicals have yet become widely recognized as having the repellent value of high-concentration deet products in efficacy or duration of repellency (Maia and Moore 2011).

Recognition of the potential for effective botanical repellents was primed by CDC's (2005) addition of the 1st botanical molecule, *para*-menthane 3,8-diol (PMD), to the list of recommended AIs for mosquito repellents. The PMD molecule is found in the distilled leaf oil of the Australian lemon-scented gum tree, *Corymbia citriodora* (Hook.) (Carroll and Loye 2006a). Supporting the CDC decision to list botanicals was a set of PMD efficacy studies published or in press at that time (Trigg 1996; Trigg and Hill 1996; Moore et al. 2002; Carroll and Loye

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2006a, 2006b; SP Carroll, personal observation). As a conservative gesture, CDC (2005) equated PMD protection to that of low-concentration deet products, despite evidence of similar or greater protection against both *Aedes* and *Anopheles* spp. (Carroll and Loye 2006a). Misconstruing PMD as fundamentally inferior to deet has been perpetuated in more recent reviews and guidelines (Lupi et al. 2013, Stanczyk et al. 2015).

Buescher et al. (1983) proposed that better knowledge of the physical properties of repellent persistence at the skin surface would allow improved repellent design. They found, for example, that the US Army 75% deet formulation achieved little added protection compared with, for example, a 50% concentration. Such studies led to the development of polymer-based fixatives to improve the temporal pattern of deet evaporation and achieve longer repellency with lower concentrations, resulting in the US Military adoption of the 34% deet 3M® "Ultrathon®" repellent lotion (reviewed by Carroll 2007). However, success in the pursuit of performance-extending fixatives has been elusive (Carroll 2007), with Schofeld et al. (2007), for example, reporting no increment in protection duration from Ultrathon and another polymerized deet formulation versus an ethanolic formulation with equivalent dosing of the AI.

Similar modifications in the formulations of botanical compounds to extend the duration of repellency have also been the focus of recent efforts (Maia and Moore 2011). For example, the use of large molecules such as vanillin as fixatives has been suggested for extending the repellency of botanicals (Carroll 2007, Lupi et al. 2013). In this study we measured laboratory complete protection time (CPT) for human subjects testing a novel "prolonged-release" pump-spray product formulated by Neo-Innova® Healthcare Ltd. The product contains the United States Environmental Protection Agency (US EPA) registered repellent active "Citriodiol®" at 40%, providing PMD at 25% w/v of the total compound, with 10% vanillin as a fixative. Within the same arm-in-cage test protocol, we compared Neo-Innova performance with 5 efficacious US commercial formulations in exposures to *Ae. aegypti* and *Cx. quinquefasciatus*.

## MATERIALS AND METHODS

We assessed the CPT of a Neo-Innova topical repellent against 5 high-performance commercial mosquito repellents currently marketed in the USA. Testing took place during 6 days at the Carroll-Loye Biological Research Laboratory in Davis, CA, and included the application and testing of these 6 mosquito repellent products on human participants in a laboratory setting. Schulman Associates Institutional Review Board reviewed and approved the protocol and Informed Consent forms on August 4, 2017.

### Study participants, mosquito species, and test materials

All participants were consenting adults recruited from the Davis, CA, area. Participants had substantial experience in college-level life sciences training and research. Treated participants included 5 males and 2 females, and 2 additional males served as untreated (negative) controls to verify mosquito avidity before each testing period.

Mosquitoes used in this study were laboratory-reared adult females from 2 disease-vectoring mosquito species, *Ae. aegypti* and *Cx. quinquefasciatus*, approximately 6–13 days posteclosion. On each test day, 4 groups of approximately 100 mosquitoes per species were placed individually into 25-cm cubic cages with aluminum frames and screening. The multiple cages meant that each group of 100 females was utilized only once per 4 h and returned to the insectary after 10 min of use to ensure continual avidity. The mosquito food source (10% sucrose in water) was removed 10 h prior to the 1st exposure for each cage to ensure avidity.

The Neo-Innova NEO-PART® (Prolonged Action Release Technology) formulation was a topical pump spray with AI Citriodiol 40%, providing the bioactive molecule PMD at 25% w/v of the total formulation. The 5 comparator products used were long-lasting repellent pump sprays in the US market, containing AIs including deet; 2,-(2-hydroxyethyl)-1-piperidine carboxylic acid 1-methylpropylester (picaridin); ethyl butylacetyl aminoproprionate (IR3535); geraniol; and PMD (Table 1).

Neo-Innova topical repellent was provided by the sponsoring agency, and the comparator products were purchased online within 1 month of testing and stored in their original containers in closed cabinets at 23°C until use.

### Study conduct and design

This study took place during 6 days over 2 wk at Carroll-Loye Biological Research Laboratory. Laboratory environmental conditions during all testing hours were kept relatively dark, warm, and humid (26–30°C and 42–61% RH) to promote mosquito avidity. Mosquitoes were sourced from Benzon Research Laboratories (Carlisle, PA) and were approximately 7 to 10 days posteclosion during the study.

In order to limit the amount of potential volatilized repellent in the test area, participants were kept in a different building and each individual occupied the laboratory only for the duration of each of their own test exposures. Negative pressure was also used to remove air from the test room, allowing gradual replacement by conditioned fresh air. Participants abstained from using scented products, smoking, or drinking alcohol on testing days.

On each of the 6 test days, a single repellent product was applied to 7 participants (one being an alternate) at the industry standard dosing rate of 1 g

Table 1. Summary of comparator formulations tested.

| Product name | AI % | Labeled CPT[1] (h) |
|---|---|---|
| Coleman Skinsmart | IR3535 20 | 8 |
| Guardian Wilderness | Geraniol 5 | 8 |
| Cutter Backwoods | Deet 25 | Long-lasting[2] |
| Repel Lemon Natural | PMD[3] 20 | 6 |
| Sawyer SP544 | Picaridin 20 | 12 |

[1] CPT, complete protection time.
[2] Labeled protection times for other ≥20% deet products are commonly ≥8 h.
[3] PMD, *para*-menthane 3,8-diol.

per 600 $cm^2$ of skin surface area on the forearms between the crease of the elbow and wrist. Individual doses were calculated in advance, based on the surface areas of each participant's forearms, measured by the average of 4 evenly spaced circumferences of each forearm multiplied by the length of the treatment area.

Before product application on each test day, both forearms were washed with fragrance-free soap, rinsed with water, rinsed again with 70% ethyl alcohol, and rinsed a 2nd time with water, then dried with clean unscented paper towels. Test material was applied to one of each participant's forearms (alternating forearms each test day) by a research assistant using a 3-ml syringe without a needle in drops and lines over the test area and then distributed evenly with 2 gloved fingertips until full coverage was achieved. Participants wore gloves on the hand of the designated testing arm and the test area of each participant was isolated using medical bandaging at the elbow and wrist. Participants were instructed to keep the test area free from contact with any surface for the duration of the testing period.

In order to limit excessive human exposure to mosquitoes and because all products being tested were labeled for at least 6 h of protection, 1st exposures of participants to mosquitoes began 5 h after application. Each exposure period began with a verification of mosquito avidity by exposing the test area of the untreated control participants in both the *Aedes* and *Culex* cages for 20–30 sec while 2 research assistants, positioned on each side of the cage, assessed "landings with intent to bite" (LIBes), defined as a mosquito alighting on the skin, ceasing locomotion, and proceeding to place the tip of the proboscis against the skin. This measure was used to keep attention on events significant to product performance while reducing the chance of skin penetration, which may reduce avidity through bloodfeeding before treated exposures. Feeding avidity of caged *Cx. quinquefasciatus* is relatively low compared with the yellow fever mosquito, *Ae. aegypti*, which is the more commonly used mosquito in arm-in-cage studies due to its ease of rearing and high avidity (Lupi et al. 2013). Reflecting the WHO (2009) topical repellent testing guideline, the minimum ambient biting pressure for *Ae. aegypti* was designated as 10 LIBes per 30 sec of exposure. The minimum ambient biting pressure for *Cx. quinquefasciatus*, which is less anthropophilic, was determined as 5 LIBes per 30 sec. Caged groups not attaining this rate at the beginning of each test interval were replaced by suitably avid groups before exposures of treated participants.

Exposures of treated participants began with each participant placing their treated test arm in the *Aedes* and *Culex* cages consecutively, each for the duration of 60 sec. Two research assistants, one on each side of the cage, used red light to assess LIBes. Exposures were repeated every 60 min. Product failure was determined for each interval when participants received a 1st confirmed bite (FCB) that was followed by another bite in the next exposure (60 min later) or 2 LIBes in the same exposure, after which exposures were terminated for that participant. Due to reduced avidity of *Culex* at the beginning of the 13-h testing period, exposures to *Culex* were not continued past 12 h. In contrast, exposures to *Aedes* in most cases were continued until all participants received a confirming LIBe due to the continued avidity of *Aedes* throughout all test days. In the case of one repellent, the Study Director invoked the 16-h time limit for the duration of total daily study participation, stopping all further exposures after 15 h in order to comply with the consented study duration.

### Statistical analyses

In order to effectively compare products with each other, repellent performance was gauged by time of protection until confirmed bites rather than percent protection relative to the untreated controls. Repellent failure was scored independently for each individual participant and defined as the time that had elapsed after application at which the 1st bite occurred that was followed by another bite with approximately 60 min (time of FCB), which we designated as the measure of CPT.

We assessed means and standard deviations of CPTs for all products and assessed differences in the 6 products' CPTs with Wilcoxon rank-sum tests. Survival analyses were not used based on the outcomes showing that little important variation was detectable among products against *Culex* before this species' avidity dropped, while the important superiority of Neo-Innova against *Aedes* involved excessively truncated data due to the inability to continue work beyond the consented 16 h.

## RESULTS

Mean (± SD) CPTs for all products tested against *Ae. aegypti* and *Cx. quinquefasciatus* are found in Tables 2 and 3, respectively. It is important to note that due to necessity of cessation of testing for 5 of the 6 subjects testing Neo-Innova against *Ae. aegypti*

Table 2. *Aedes aegypti*: Mean complete protection times (CPTs) ± SD in hours of Neo-Innova® topical repellent and comparators in descending order. Exposures began 5 h after application. Groups differ at $P < 0.01$ or better based in multiple comparisons with Wilcoxon rank-sum tests.

| Product name | AI % | CPT (h) | Group |
|---|---|---|---|
| Neo-Innova | PMD[1] 25 | >14.2 ± 2.0 | A |
| Guardian Wilderness | Geraniol 5 | 7.5 ± 0.8 | B |
| Cutter Backwoods | Deet 25 | 6.7 ± 0.8 | B |
| Repel Lemon Natural | PMD 20 | 6.2 ± 1.0 | BC |
| Sawyer SP544 | Picaridin 20 | Approximately <5 | CD |
| Coleman Skinsmart | IR3535 20 | <5 | D |

[1] PMD, *para*-menthane 3,8-diol.

after 15 h, the mean presented likely underestimates the true mean CPT.

Neo-Innova topical repellent had a significantly longer CPT against *Ae. aegypti* than any other repellent tested (Wilcoxon rank-sum comparisons; $P < 0.004$ or better). Findings for this species are detailed in Table 2 and Fig. 1. Just 1 of the 6 subjects testing Sawyer picaridin was protected against *Ae. aegypti* when exposures commenced after the 5-h pre-exposure period, and none of those testing Coleman IR3535 was protected then, leading us to estimate their respective CPTs to likely or certainly be less than 5 h. For simplicity's sake, we assigned all failures at 1st exposure a CPT of 5 h. That handicap will tend to minimize any true differences between each of those 2 products and all others ("Group" column, Table 2).

Because exposures to *Cx. quinquefasciatus* could not be continued past 12 h due to loss of avidity, true mean CPTs are underestimated for all test materials (Table 3). The statistical comparisons given in Table 3 are therefore preliminary. Notably, both Neo-Innova PMD and Sawyer picaridin yielded no bites, Repel® PMD had 4 unconfirmed bites, Coleman IR3535 had 2 confirmed and 4 total bites, and the Cutter deet and Guardian geraniol both had 5 confirmed and 6 total bites.

In summary, the Neo-Innova topical repellent provided longer complete protection than the 5 comparators against *Ae. aegypti* and provided the maximal duration of protection possible in this study against *Cx. quinquefasciatus*. Neo-Innova mean CPT against *Ae. aegypti* was at least 14.2 h, almost double of the next highest performer. While all products exhibited prolonged protection against *Cx. quinquefasciatus,* Neo-Innova again had the maximum possible CPT of 12 h, equaling 2 of the comparator products and outlasting the remaining 3.

Table 3. *Culex quinquefasciatus*: Mean complete protection times (CPTs) ± SD in hours of Neo-Innova® topical repellent and comparators in descending order. Exposures began 5 h after application. Against this species, all products protected at least some subjects fully, so mean CPTs are likely underestimated. Groups differ at $P < 0.003$ or better based in multiple comparisons with Wilcoxon rank-sum tests.

| Product name | AI % | CPT (h) | Group |
|---|---|---|---|
| Neo-Innova Mosquito | PMD[1] 25 | >12.0 ± 0.0 | AB |
| Repel Lemon Natural | PMD 20 | >12.0 ± 0.0 | AB |
| Sawyer SP544 | Picaridin 20 | >12.0 ± 0.0 | AB |
| Coleman Skinsmart | IR3535 20 | >11.7 ± 0.8 | BC |
| Guardian Wilderness | Geraniol 5 | >11.0 ± 1.3 | BC |
| Cutter Backwoods | Deet 25 | >10.7 ± 1.5 | C |

[1] PMD, *para*-menthane 3,8-diol.

## DISCUSSION

Our findings show that not only can a botanically based mosquito repellent provide prolonged protection against even particularly avid mosquito species, but also that it can be formulated to protect for much longer periods than deet-based and other recognized long-lasting repellent products currently available for consumer and military use. Historically, alternative mosquito repellents marketed in the USA have provided consumers with a variety of options with relatively short protection times, with no widely recognized botanical products labeled for efficacy equaling high-concentration deet products (Lupi et al. 2013). The expansion of the CDC's recommended mosquito repellents in the mid-2000s shifted the focus toward botanically based alternatives (Carroll and Loye 2006a), and consumer demand for alternative mosquito repellent products in the last decade has spurred the multiplication of US EPA minimum-risk consumer repellents, many of questionable efficacy (Lupi et al. 2013, Rodriguez et al. 2015). Marketing of short-duration botanical repellents both poses risks to users and potentially discredits biochemical repellents as a class of viable options for protection against mosquitoes.

However, plant oils with repellent qualities often have at least 1 monoterpenoid constituent, which have been repeatedly correlated with repellency. Among them, PMD is unusual in having 2 hydroxyl groups rather than 1, a structure that reduces volatility of the molecule and promotes its residence on the skin rather than quickly evaporating (Barasa et al. 2002). The PMD also exhibits low skin penetration compared with deet, such that more remains on the skin surface and aids in longer repellency (Reifenrath et al. 2009). "Citriodiol," the naturally sourced oil of lemon eucalyptus product containing approximately 65% PMD, is the EPA-registered AI

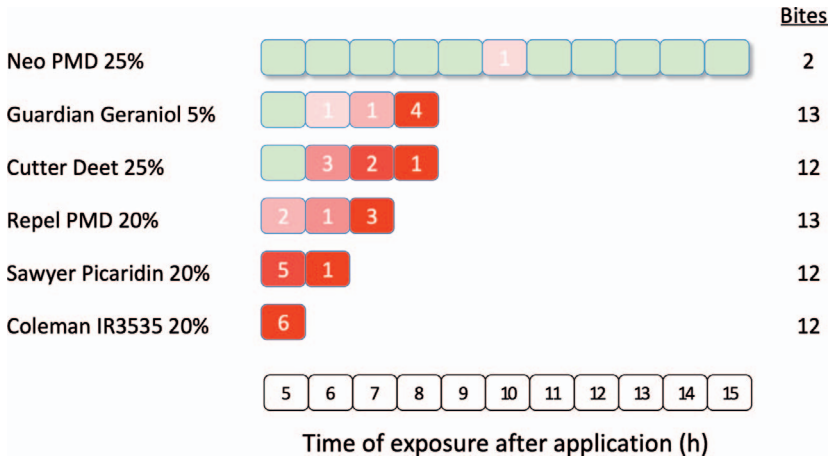


Fig. 1. Protection from *Aedes aegypti*: when did bites occur? The 6 repellents studied are labeled with their AI concentrations. The same 6 subjects tested each repellent, with only 1 repellent tested per study day. Exposures commenced 5 h after repellents were applied. The number of subjects with confirmed bites in a given hourly 1-min exposure is given in the colored boxes. Green boxes indicate exposure periods in which no bites were observed, while pink-to-red indicates the growing proportion of the 6 total subjects per test material with confirmed bites across progressive exposures. The total number of bites across all subjects is 1 higher for both Guardian and Repel® than the other 3 comparators because each experienced a single early bite that was not confirmed.

in both the Neo-Innova formulation and the ethanolic comparator tested in this study.

Neo-Innova's NEO-PART prolonged-action technology has greatly extended the repellency window of plant compounds and of insect repellents in general. The CPTs afforded by prolonged-release Neo-Innova repellent against *Ae. aegypti* were likely at least double those of 5 leading high-performance repellents on the US market. All subjects testing all comparator products experienced CPTs between >5 and 8 h. In contrast, 5 of 6 subjects testing Neo-Innova's PMD product experienced no bites (or landings) throughout the entire 15-h test period. The dramatically longer protection time can be attributed to a formulation specificity of the PMD-based Neo-Innova product. Neo-Innova is formulated with vanillin (10%), a large molecule that when added to many botanical oils has shown to reduce evaporation of plant compounds (Tawatsin et al. 2001), including those that repel mosquitoes (Maia and Moore 2011, Lupi et al. 2013).

In this regard, it is instructive to compare the protection times afforded by the 25% PMD Neo-Innova product with those we observed for the EPA-registered Repel product that dilutes the same Citriodiol AI in ethanol to achieve an approximately 20% PMD concentration. By combining the 2 botanical molecules with the novel NEO-PART technology, a 25% increment in PMD concentration is associated with approximately 250% extension of protection time. While declining avidity in the *Culex* studied precluded further discrimination of the test materials with reference to that genus, Neo-Innova nonetheless exhibited unsurpassed full protection over 12 h of testing in this species as well. The extended protection times offered by this product further suggest that formulation and specifically, the combination of certain botanical molecules may together provide dramatically better results than either constituent alone.

The results against *Ae. aegypti* are notable because this species is highly anthropophilic and tolerates many botanical compounds that repel other mosquitoes (Lupi et al. 2013). Interestingly, results from past studies have suggested that there may be a strongly positive relationship between PMD concentration and repellency. For example, the mean CPT of 20% PMD Repel was approximately 250% more prolonged than that of a 10% PMD product (Carroll and Loye 2006a). Field studies have also suggested that concentration, in addition to formulation and stereoisomer constituency (Barasa et al. 2002), may be very important to PMD performance (Barnard and Xue 2004).

The increasing consumer demand for botanical repellents in the USA highlights the necessity of finding, testing, and marketing effective and long-lasting botanical mosquito repellents in the USA and globally (Maia and Moore 2011). Because some individuals may avoid the use of deet for personal reasons, and due to the low efficacy and short protection times of many currently marketed botanical alternatives, there are currently few long-lasting repellent options for this group of consumers. Moreover, extremely long-lasting repellents may be especially important as tools for personal protection from disease-vector species in vector-borne disease endemic regions. The discovery of a higher-concentration and novel PMD topical repellent could encourage wider and more effective use of repellents

by the consumer base, rendering once-a-day application effective and convenient for vector-borne disease prevention. This study complements and augments the existing endorsement of PMD by the CDC and underscores that PMD is a compound of high importance in the continuing research and development of effective long-lasting botanical arthropod repellents.

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