Proceedings of the Fifth International Conference on Urban Pests
Chow-Yang Lee and William H. Robinson (editors), 2005.
Printed by Perniagaan Ph'ng @ P&Y Design Network, Malaysia.

FIELD EFFICACY OF METOFLUTHRIN – A NEW MOSQUITO REPELLENT

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Abstract SumiOne® (common name metofluthrin, 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl (E,Z) (1R,3R)-2,2-dimethyl-3-(prop-1-enyl) cyclopropane carboxylate) is a novel vapor active pyrethroid that is effective against mosquitoes. Impregnated paper substrates have been shown to be effective at dispensing metofluthrin though passive evaporation at room temperature. The rate of evaporation has been studied and shown to decline gradually over time. Field trials were conducted in the United States to evaluate the repellent activity of paper substrates ("emanators") each treated with 200 mg metofluthrin. To determine the duration of protection treated emanators were pre-aged for 36 hours in a wind tunnel. Trials were conducted in Florida and Washington State, with 5 volunteers being used in each trial. Each volunteer was protected from biting by Tyvek® suits and head nets and was positioned between two paper emanators that were suspended 8 feet apart. Each emanator consisted of a folded piece of thin paper with a surface area of 4000 cm^2. (This measurement includes both sides of the device). Pre- and post-treatment landing counts were conducted at 2-minute intervals for a maximum of 30 minutes. In the Washington trials, where *Aedes vexans* was the dominant species, an average of 26 mosquito landings per minute were observed prior to treatment. Greater than 95% landing reductions were observed in all but 3 tests, where reductions were still greater than 85%. In the Florida trials, higher mosquito density (mostly *Ochlerotatus* spp.) was observed with an average of 32 landings per minute observed prior to treatment. Seven treatments failed to provide greater than 95% landing reductions, but overall mean reductions in these treatments were greater than 80%. Results demonstrate that metofluthrin treated emanators are effective at repelling mosquitoes under outdoor conditions.
Key Words Pyrethroid repellency, metofluthrin, *Ochlerotatus*, *Aedes*, SumiOne®

INTRODUCTION

Mosquitoes are the main vectors for the transmission of human diseases worldwide (Lehane, 1991). Preventing mosquito bites is therefore an important factor in reducing disease transmission. One of the major innovations in the control of mosquito borne diseases has been the development and introduction of insecticide treated mosquito nets. Long-lasting insecticide nets containing a repellent pyrethroid insecticide that can work for years and withstand multiple washings, offer one of the most promising tools for low cost and sustainable malaria control. However, while these nets offer excellent levels of protection while sleeping, users are still exposed to mosquitoes that bite earlier in the evening, both inside and outside the home.

Mosquito coils, vaporizing mats, and other formulation types have been developed and used successfully in many parts of the world to prevent indoor biting mosquitoes (Birley et al., 1987). Their widespread adoption as tools to control mosquito-borne diseases, however tends to be limited to the more wealthy individuals in a community. In North America, while mosquito transmitted diseases are less prevalent mosquitoes are still a significant cause of discomfort and distress. Since houses are largely air-conditioned and windows and doors fitted with insect proof screens, the indoor use of mat and coil products is limited, and products are largely used out of doors to prevent nuisance-biting mosquitoes. The recent outbreak of West Nile Virus which in 2004 caused 2470 cases of the disease and 88 human deaths, resulted in a significant increase in the use of mosquito repellent mats and coils in North America.

One limitation of these products is that they require a heat source to vaporize the active ingredient, commonly a synthetic pyrethroid such as d-allethrin or prallethrin. Coils, which produce a visible and sometimes unpleasant smoke when ignited also tend to be brittle and can break in transit and use. Vaporizing mat products generally use a plug in heater, although a candle-heated mat has been recently introduced in North America. SumiOne® (common name metofluthrin, 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl (E,Z)(1R,3R)-2,2-dimethyl-3-(prop-1-enyl) cyclopropanecarboxylate) is a novel vapor active synthetic pyrethroid that is highly effective against mosquitoes (Sugano et al., 2004; Ujihara et al., 2004). The vapor pressure of metofluthrin is significantly greater than d-allethrin or prallethrin and will vaporize readily at room temperature without heating. Paper substrates impregnated with metofluthrin have been shown to be effective at dispensing this compound though passive evaporation at room temperature. Using insect collections from human and animal baited nets, Kawada et al., (2004) reported the results of indoor and outdoor field efficacy trials of metofluthrin treated paper strips in Lombok Island, Indonesia, Argueta et al. (2004) demonstrated the outdoor spatial repellency of metofluthrin using CDC mosquito traps.

In this paper we report the results of field efficacy studies to evaluate the repellency of pre-aged metofluthrin treated paper emanators using human volunteers.

MATERIALS AND METHODS

Paper Emanators. Metofluthrin impregnated paper emanators were supplied by Sumitomo Chemical Company Ltd. (Takarazuka, Hyogo, Japan). These consist of a multi-layer foldable structure (9 x 7 cm x 0.3 cm thick, unfolded: 9 x 7 x c.56 cm, Figure 1). Each was treated in the open state with 200 mg of metofluthrin diluted in acetone and uniformly applied to the paper surface (1.82% w/w). The acetone was then allowed to evaporate at ambient temperature before refolding. Blank emanators treated with acetone only served as controls. The total surface area of the unfolded paper was approximately 4000 cm^2.

Evolution Rate Assessments. Paper emanators were opened and suspended in a laminar flow fume hood, Model FHS 180 (Yamato Scientific Co. Ltd, Japan) at 25 ºC and 60% RH with the airflow set at 0.6 meters per second (1.4 mph) to simulate air movement during normal outdoor use. Devices were sampled fresh and after 6, 12, 24, 36 and 72 hours aging. Samples were cut into strips and extracted in acetone. Residual metofluthrin content was determined using an Agilent Model 6890N gas liquid chromatogram (Agilent Industries Co., California, USA). Based on evolution rate assessments (reported below) devices were aged before test for 36 h. Once aging was complete, emanators were folded and stored in heat sealed aluminum pouches.

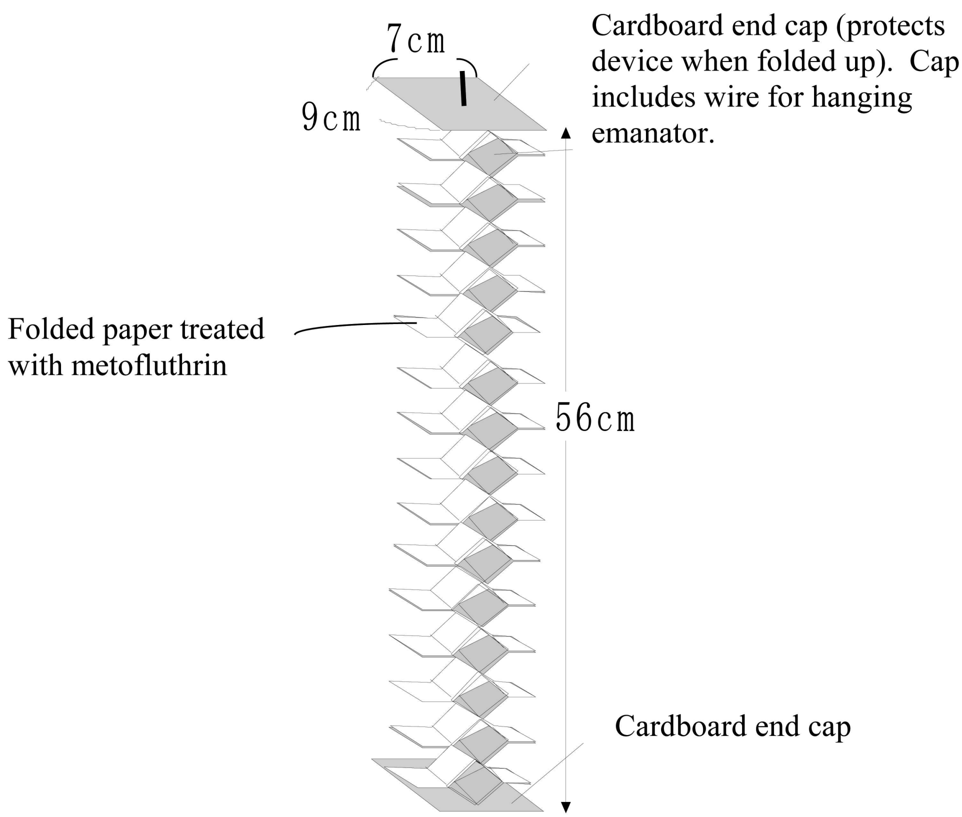

Figure 1. Metofluthrin Paper Emanator

Field Trials Sites. Field trials were conducted in the United States during June and July 2004 in Washington State and Florida. The predominant mosquito species in Washington State was *Aedes vexans*, while in Florida it was *Ochlerotatus* spp. Five human volunteers (who had each signed informed consent forms) were used at each trial location. Since evaluations used natural populations of mosquitoes, volunteers wore Tyvek® suits, with mosquito landing rates assessed rather than biting. Wind speed was measured using an anemometer, temperature and humidity measurements were taken using a sling psychrometer. At the beginning of each test, blank untreated emanators were placed four feet on either side of each volunteer. Where wind direction was detectable, one device was placed upwind and one downwind from the volunteer.

Mosquito landing assessments. Three one-minute landing rate counts were taken at consecutive 2-minute intervals. These counts were used to determine the pre-treatment or control landing rates of resident mosquitoes. The two untreated emanators were then replaced with two treated emanators, hung in the same position. Treated emanators were allowed to hang for two minutes before landing counts were once again taken. Counts continued to be taken at 2-minute intervals until 95% reduction in landings was achieved in three consecutive intervals, or when 30 minutes had elapsed, whichever occurred first. A total of three replicates were conducted for each volunteer. Counts were taken through the day from 8.00 pm to 11.30 pm (Washington State) and 10.00 am to 6.00 pm (Florida).

RESULTS AND DISCUSSION

Results demonstrate a gradual decline in the metofluthrin content of emanators over time, consistent with its relatively high volatility (Figure 2). From this data evaporation rates can be calculated. These show initial evolution in the range of 2.0 – 3.3 mg ai / hour, declining after 48 h to less than 1.0 mg ai / hour.

Earlier studies conducted by the Sumitomo Chemical Company indicated that an evolution rate of approximately 2.0 mg ai/hour/device, using two emanators, should provide good levels of mosquito repellent activity (unpublished Sumitomo internal report). Devices that had been aged in the wind tunnel for 36 h were therefore selected, as these should be evolving active ingredient at a rate greater than 2.0 mg ai / hour. Providing good efficacy was obtained with these aged devices, and based on the knowledge that evolution rate declines over time, it is possible to conclude that devices aged for less than 36 hours would also provide similar or better levels of protection. These findings differ from those of Kawada et al. (2004) who successfully demonstrated activity of paper emanators over a 6-week period. Kawada aged paper emanators in still air, which would significantly reduce the rate of metofluthrin evaporation and increase the length of time devices continue to work, compared with aging in a wind tunnel. While aging in still air provides a realistic means to assess the duration of protection indoors, use of a wind tunnel in these studies is more appropriate since it better simulates air movements that often occur out of doors.

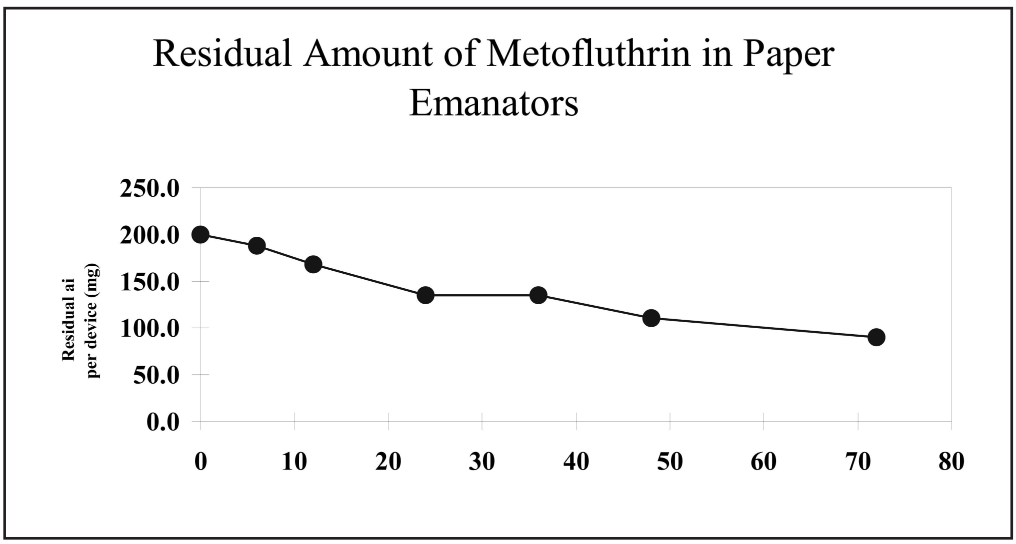

Figure 2. Residual amount of metofluthrin in paper emanators.

Table 1. Time to 95% reduction in mosquito landings, Washington State.

Volunteer	A1	A2	A3	B1	B2	B3	C1	C2	C3	D1	E1	E2	Average (mins)
Minutes to 95% reduction	4	8	16	4	14	4	8	6	6	4	12	16	8.5

("Time" defined as the first of the three observations where 95% or greater was recorded).

Table 2. Time to 95% reduction in mosquito landings, Florida.

Volunteer	A2	A3	B2	D2	D3	E1	E2	E3	Average (mins)
Minutes to 95% reduction	4	10	8	10	14	10	10	4	8.8

("Time" defined as the first of the three observations where 95% or greater was recorded).

Table 3. Average % reduction where 95% not reached, Washington State.

Volunteer	D2	D3	E3	Average (%)
Minutes to 95% reduction	87.8	85.4	82.7	85.3

Table 4. Average % reduction where 95% not reached, Florida.

Volunteer	A1	B1	B3	C1	C2	C3	D1	Average (%)
Minutes to 95% reduction	73.9	73.5	86.6	91.2	72.0	85.6	80.6	80.5

In the Washington State trials, there was almost no detectable air movement. Humidity was high (80% RH) and temperatures ranged between 16 and 27 ºC. An average of 26 mosquito landings per minute were observed prior to treatment with the majority being *Aedes vexans.* In the Florida trials, wind speeds up to 1.4 mph were recorded. Humidity was 80% RH and higher temperatures were recorded (30-34 ºC). A mean of 32 mosquito landings per minute were observed pre-treatment (mostly *Ochlerotatus* spp.).

The individual pre- and post-treatment replicated landing counts for each of the 5 volunteers and the two respective trials are recorded on Figures 3 and 4. These data have then been averaged for each trial and the percentage reductions in landings calculated.

A difficulty of attempting to graphically present this data is that, once 95% reduction or greater was observed, further counts were not taken. A simple assumption has been made: once 95% or greater protection was recorded and observations ceased, the level of protection observed in the final landing count continued to be observed until the end of the test. Examination of data where 95% or greater protection was not achieved indicated that in all but one case landing rates did not increase significantly once a level of protection was established. This approach may in some cases be understating the actual levels of protection that might have occurred had

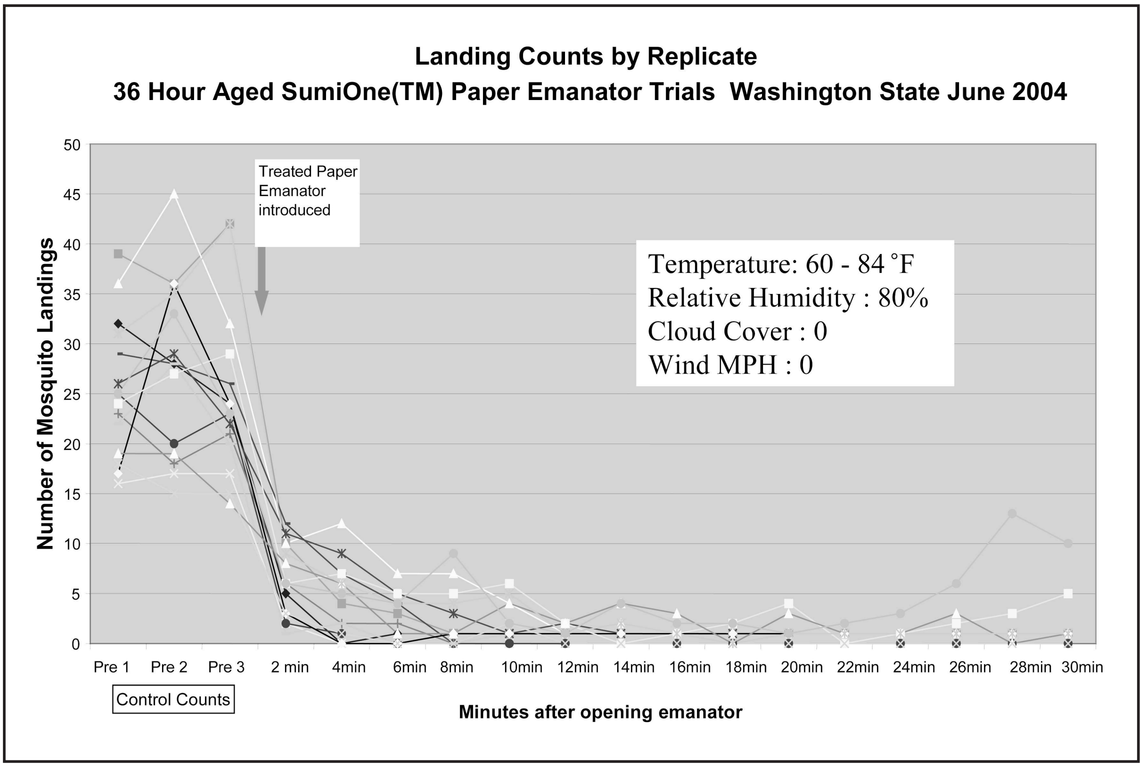

Figure 3. Landing counts by replicate, 36-hour aged paper emanator trials, Washington State.

observations continued for 30 minutes, and in others may be overstating this protection. Overall, however, extrapolated data should be close to actual observations had they been taken.

The results (Figures 5 and 6) demonstrate a dramatic decline in mosquito landing rate in both trials immediately after the treated emanator was opened. Landing rates continued to decline for a further 8–10 minutes after which the number of landings stabilized at a very much lower rate, corresponding to 92–97% protection when compared with pre-treatment counts. The speed at which the greatest levels of protection were achieved appears to be faster in the Washington State trials (where there was no detectable wind movement) compared to the trials in Florida.

The time taken for 95% or greater reduction in landings to occur in each test replicate is presented in Tables 1 and 2. Where 95% reduction was not recorded, the overall average percent reduction for all post treatment observations has been calculated (Tables 3 and 4). In the Washington State trials, 95% or greater reduction in landing rates was observed in twelve out of the fifteen tests, with devices taking an average of 8.5 minutes to achieve this level of control. Of the three tests where less than 95% reduction was observed, overall average protection was still over 85%. In the Florida trials, greater than 95% reductions were observed in eight out of the fifteen tests, with devices taking an average of 8.8 minutes to achieve control. In the remaining tests, overall average protection was over 80%.

As with other pyrethroids, the spatial repellency of metofluthrin paper strips observed here is caused by the disruption of mosquito host finding and orientation activity. Wind tunnel tests using volunteers who exposed bare skin to laboratory-reared mosquitoes (publication in preparation) indicate that in the presence of airborne metofluthrin, significant disruption in host finding occurs. However, even when landings did occur, the majority of insects were still inhibited from biting. This sub-lethal effect results from pyrethroid induced neural hyper-excitation, which can occur at much lower doses than those required for insect knockdown and mortality. Winney (1975) for example reported that female *Aedes aegypti* exposed for a few minutes to the smoke of pyrethrum coils although not knocked down, still did not bite. From this it can be presumed that had bite inhibition rather than the more practical measure of landing inhibition been measured, the levels of protection observed in these field trials would have been significantly higher.

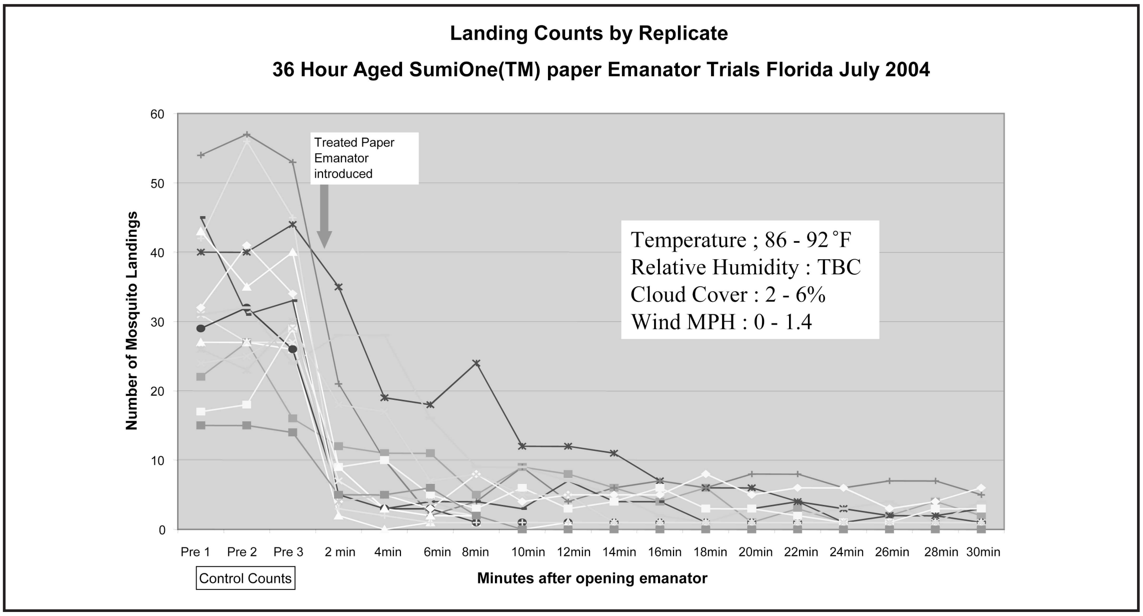

Figure 4. Landing counts by replicate, 36-hour aged paper emanator trials, Florida State.

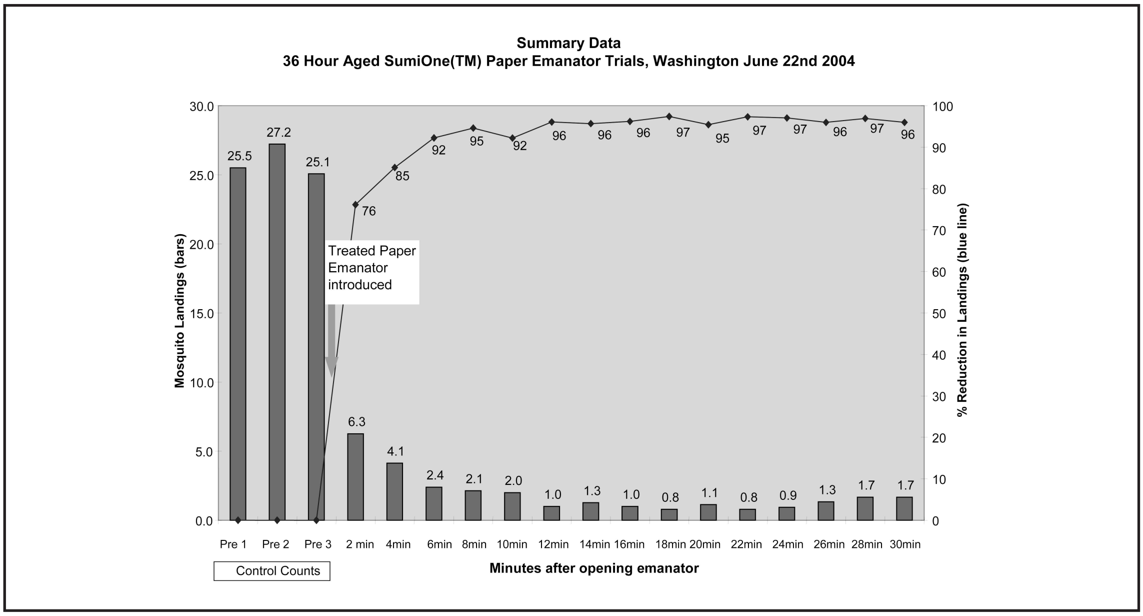

Figure 5. Summary data, 36-hour aged paper emanator trials, Washington State.

There are very few reports that confirm the efficacy of anti-mosquito products out of doors. Jensen et al. (2000) in studies evaluating the performance of a variety of products including citronella candles and ultrasonic repellers reported that only pyrethroid based mosquito coils and DEET products significantly reduced mosquito landing rates when compared with untreated controls.

The results from both trials demonstrate the ability of aged metofluthrin paper emanators to rapidly reduce mosquito landings out of doors despite heavy initial insect pressure. Since the metofluthrin evolution rate data demonstrates an overall pattern of decline over time, it is reasonable to infer that devices aged for less than 36 hours would provide similar or better levels of protection than those observed in these trials.

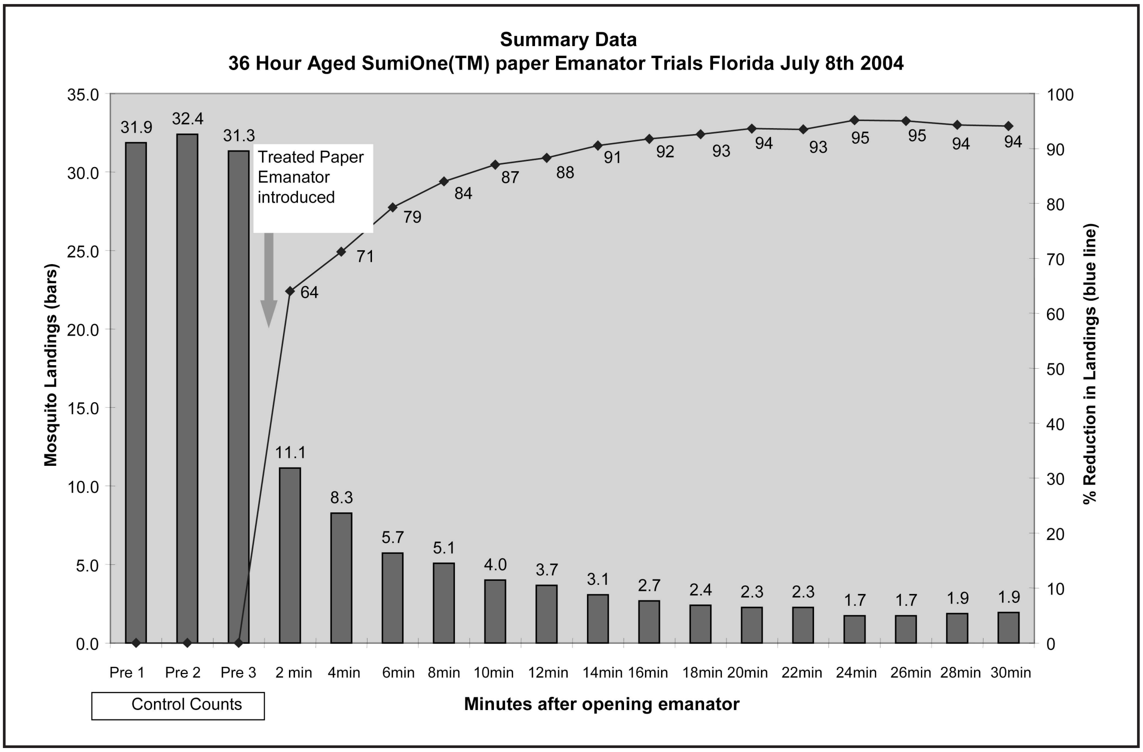

Figure 6. Summary data, 36-hour aged paper emanator trials, Florida State.

The benefits of this ambient temperature technology compared to mosquito mats and coils include ease and duration of use, low cost, ease of handling, no requirement for a heat source or electricity, no fire risk and no smoke. These findings further confirm the potential for metofluthrin passive emanators as a valuable and cost effective tool in providing protection from biting mosquitoes.

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